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CONTINUOUS REMOTE MONITORING
AND POINT-OF-CARE LUNG ULTRASOUND
TO DETECT CLINICAL DETERIORATION AND
POSTOPERATIVE COMPLICATIONS

Hugo Rutger Willem Touw

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POSTOPERATIVE COMPLICATIONS

H.R.W. Touw, Dissertation, Vrije Universiteit, Amsterdam

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VRIJE UNIVERSITEIT

**CONTINUOUS REMOTE MONITORING
AND POINT-OF-CARE LUNG ULTRASOUND
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POSTOPERATIVE COMPLICATIONS**

ACADEMISCH PROEFSCHRIFT

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List of abbreviations

ACS	acute chest syndrome
ACS NSQIP	American College of Surgeons national surgical quality improvement program
AIS	alveolar interstitial syndrome
ARISCAT	assess respiratory risk in surgical patients in Catalonia
ARDS	acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
AT	atelectasis
AUC	area under the curve
AUROC	area under the receiver operating characteristics
BA	Bland-Altman
BIS	bispectral index spectrometry
BLUE	bedside lung ultrasound in emergency
BMI	body mass index
brpm	breaths per minute
bpm	beats per minute
CABG	coronary artery bypass graft
COPD	chronic obstructive pulmonary disease
crPPC	clinically relevant postoperative pulmonary complications
CRP	C-reactive protein
CPAP	continuous positive airway pressure
CXR	chest X-ray
CT	computed tomography
ECG	electrocardiogram
ERAS	enhanced recovery after surgery
ED	emergency department
EDI	early deterioration indicator
EPR	electronic patient record
EWS	early warning score
eCART	electronic cardiac arrest risk triage
FiO ₂	fraction of inspired oxygen
HR	heart rate
HSROC	hierarchical summary receiver operating characteristic
HU	houndsfield units
IBW	ideal bodyweight
ICARUS	intensive care ultrasound
ICU	intensive care unit
IQR	interquartile range
KG	kilograms
LC	lung contusion
LoA	limits of agreement
LOS	length of stay
LP	lung point
LR	likelihood ratio

LUS	lung ultrasound
MCU	medium care unit
MEWS	modified early warning score
mg	milligram
mm	millimeter
mmHg	millimetre of mercury
MV	minute ventilation
NEWS	national early warning score
NIBP	non-invasive blood pressure
NIV	non-invasive ventilation
NPV	negative predictive value
NVIC	Netherlands society of intensive care
PaO ₂	partial pressure of oxygen in arterial blood at sea level
P/F	PaO ₂ /FiO ₂
PEEP	positive end-expiratory pressure
PE	pulmonary embolism
PIE	pleural effusion
PICUD	post intensive care unit day
PLAPS	posterolateral alveolar and/or pleural syndrome point
PNA	pneumonia
PPC	postoperative pulmonary complication
PPG	photoplethysmography
PPV	positive predictive value
POSPOM	preoperative score to predict postoperative mortality
POD	postoperative day
PSA	procedural sedation and analgesia
PTX	pneumothorax
QUADAS	quality assessment of diagnostic accuracy studies
remMEWS	remote modified early warning score
RR	respiratory rate
RRc	capnography respiratory rate
RRp	plethysmography respiratory rate
RIT	rapid intervention team
RRT	rapid response team
ROC	receiver operating characteristics
SD	standard deviation
SN	sensitivity
SOFA	sequential organ failure assessment
SpO ₂	peripheral oxygen saturation
SP	specificity
PLAPS	posterolateral alveolar and/or pleural syndrome
TCI	target controlled infusion
UGI	upper gastrointestinal

Chapter 1

General introduction

Perioperative care

More than 230 million surgical procedures are undertaken worldwide each year, with more than 15 million procedures in the Netherlands.^{1,2} Fortunately, the mortality risk for patients undergoing surgery have decreased tremendously due to improved management of perioperative patients.³ In particular, the Netherlands is one of the safest countries in the world for patients to be operated, with an estimated total perioperative mortality of up to 2%.^{2,4}

Recently, the preoperative score to predict postoperative mortality (POSPOM) was validated predicting postoperative mortality.⁵ The score combines patient factors, such as age, heart disease, and pulmonary disease, with the procedural risk. The POSPOM score showed that perioperative mortality risks vary widely for individual patients, due to the combination of patient and procedural factors.^{4,5} For example, a low-risk procedure like breast surgery is associated with the lowest adjusted mortality incidence, while patient-specific comorbidities may increase the risk for perioperative mortality.^{5,6} Moreover, high-risk surgery is increasingly performed in the growing elderly population, while these patients typically suffer from cardiopulmonary comorbidities.⁶ Consequently, in Western-Europe, 80% of postoperative deaths are among the 10% of patients at the highest risk of postoperative mortality.^{4,7}

Postoperative patients frequently develop complications and adverse events, increasing morbidity, mortality and costs.^{8,9,10,11} Postoperative complications and mortality are related; but they are not consequently linked. Interestingly, despite similar incidence rates of postoperative complications across hospitals in the United States, surgical death rates varied widely across these hospitals.¹² The ability to rescue patients after the development of complications differed among these hospitals, leading to different mortality rates. The term failure-to-rescue is used to describe the failure to treat patients once postoperative complications have occurred.¹² The Dutch authorities for good clinical practice included failure-to-rescue as a standard indicator to evaluate Dutch hospitals since 2016.¹³ Hospitals are expected to rescue patients once complications have occurred, and failure-to-rescue rates are therefore an important parameter for surveillance of good clinical care.

Our major challenge is to improve the quality of postoperative care and to reduce failure-to-rescue rates. Because of economic constraints, the resources for postoperative care are limited. For initial surveillance, patients are frequently admitted to special post-anesthesia care or intensive care units after surgery with continuous, invasive and non-invasive patient monitoring for the early detection of clinical deterioration. Contrary, monitoring is performed intermittently on the surgical wards. Patients who are clinically deteriorating on the ward

should be detected, recognized and re-admitted to the intensive care unit to prevent further harm.

Currently, patient care by nurses and physicians on the surgical ward has an intermittent character, and clinical deterioration is easily missed. Postoperative pneumonia and other potentially lethal complications have a fairly slow onset. Subtle changes in vital signs are often present 8 to 24 hours before the development of adverse events.¹⁴⁻¹⁷ Therefore, a time window of opportunity might exist for the early detection and treatment of these complications. Continuous remote monitoring could detect patients who are clinically deteriorating early to prevent adverse events and improve patient outcome.^{18,19} Remarkably, the majority of postoperative patients (without do-not-resuscitate orders) die in a normal ward.^{4,20} This seems to be counter-intuitive, as patients who die are most likely to be critically ill. These observations support the failure-to-rescue phenomenon, indicating that critically ill patients are not detected, inadequately recognized or undertreated after surgery.

Anesthesia

Over the last decades, the direct or attributable intraoperative mortality due to anesthesia-related complications has almost disappeared. The adverse effects of anesthesia and mechanical ventilation are more apparent in the postoperative period when postoperative pulmonary complications develop. General anesthetics change respiration mechanics and inhibit respiratory drive. Most anesthetics also reduce functional residual capacity because of loss of muscle tone. The drop in functional residual capacity may lead to atelectasis, by promoting airway closure and gas resorption behind occluded airways, using high inspired oxygen gas fractions.²¹ Partly due to these physiological changes, undesirable respiratory events following anesthesia and surgery typically start with atelectasis, diaphragmatic dysfunction and the inability to clear secretions. Additionally, other factors may further contribute to the development of postoperative pulmonary complications, such as insufficient pain management, decreased mobilization and decreased vital lung capacity.

Postoperative pulmonary complications

Postoperative pulmonary complications are among the most common complications after major surgery; up to 40% of the patients develop at least one postoperative pulmonary complication after general surgery.²²⁻²⁶ The definition of a postoperative pulmonary complication varies among different studies. Furthermore, there are heterogeneous assessment procedures across studies to score these complications, complicating the comparison and interpretation of different study results.²⁷ In order to overcome these problems, Canet *et al.* defined different postoperative pulmonary complications in 2010.²⁸

They defined respiratory failure (postoperative PaO₂ < 60 mmHg in room air, a PaO₂ to FiO₂ ratio < 300, or SpO₂ < 90% that required oxygen therapy); pulmonary infection (requiring antibiotics treatment with at least one additional criterion (new or changed sputum, new or changed lung opacities on a clinically indicated radiograph, temperature > 38.3°C, leukocyte count >12.000 mm³); bronchospasm (newly detected expiratory wheezing treated with bronchodilators) and (radiological signs of) pleural effusion; atelectasis; pneumothorax. Postoperative pulmonary complications and definitions detailed in Table 1.²⁸

Table 1. Definitions of postoperative pulmonary complications according to Canet *et al.*

Complication	Definition
Respiratory infection	When a patient received antibiotics for suspected respiratory infection and met at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count >12,000/ μ (12 10 ⁹ /L)
Respiratory failure	When postoperative PaO ₂ <60 mmHg on room air, a ratio of PaO ₂ to inspired oxygen fraction <300 or arterial oxyhemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy
Pleural effusion	Chest x-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in an upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

In 2014, the PROVE Network Investigators further defined postoperative pulmonary complications as hypoxemia (like respiratory failure according to Canet *et al.*), severe hypoxemia (need for non–invasive or invasive mechanical ventilation or a PaO₂ < 60 mmHg or SpO₂ < 90% despite supplemental oxygen (excluding hypoventilation)), radiological signs of pulmonary infiltrate, aspiration pneumonitis, development of acute respiratory distress syndrome and pulmonary edema caused by cardiac failure.²⁹ Most recently, Bhagat *et al.* defined the clinically most meaningful postoperative pulmonary complications: pneumonia and/or septic shock, unplanned intubation and prolonged intubation >48 hours according to the reported data in the database of the American College of Surgeons national surgical

quality improvement program (ACS NSQIP).²² Gupta created a risk calculator predicting the need for mechanical ventilation to treat postoperative respiratory failure based on data from the ACS NSQIP. This model included the type of surgery, emergency status, functional status, sepsis, and physical status according to the American Society of Anesthesiologists (ASA) score.²⁵

Not only operation-related factors but also pre-existing patient characteristics are associated with the development of postoperative pulmonary complications. Arozullah *et al.* identified the type of surgery (neurosurgical, thoracic, abdominal aortic aneurysm, upper abdominal and peripheral vascular, emergency surgery); albumin < 30 g L⁻¹; urea > 11 mmol L⁻¹; partial or full dependency; COPD and age as risk factors for the development of PPCs.³⁰ Recently, the assess respiratory risk In surgical patients in Catalonia (ARISCAT) risk score was developed and validated to predict the risk for postoperative pulmonary complications.³⁰ This score typically included patient characteristics as risk factors. Seven independent risk factors were identified: age; pre-operative oxygenation saturation; respiratory infection in the last month; preoperative anemia (hemoglobin concentration < 100 g.l⁻¹); upper abdominal or thoracic surgery; surgical duration > 2 h; and whether the surgery was an emergency procedure.²⁸

Preventing complications requires a continuum of preoperative, intraoperative as well as postoperative interventions. Multiple optimizations were proposed in the last decades to decrease the number of postoperative complications. For example, the introduction of enhanced recovery after surgery (ERAS) concepts reduced postoperative complications rates and improved quality of life.³¹ ERAS protocol includes counseling such as no prolonged fasting, no selective bowel preparation, thromboprophylaxis, mid-thoracic epidural, short-acting anesthetics, normothermia, avoidance of salt and water overload, prevention of postoperative nausea and vomiting, early mobilization and nutrition. These interventions also reduce the amount of postoperative pulmonary complications.³² Furthermore, lung protective ventilation strategies are used to protect the lung and to prevent postoperative pulmonary complications.²⁴ These strategies include a low tidal volume and low positive end-expiratory pressure (PEEP), without recruitment maneuvers.²⁹ The optimal positive end-expiratory pressure level has yet to be established and is probably patient, operation site and technique specific.³¹

Although calculating the risk for postoperative complications is essential for informed consent and weighing the potential consequences of planned surgical procedures, it is also an attempt to create awareness among physicians and potentially prevent postoperative

pulmonary complications. Anesthesiologists are increasingly involved in prehabilitation strategies, including the start of preventive and therapeutic strategies before surgery. Smoking cessation before surgery reduces the incidence of postoperative pulmonary complications.³² Furthermore, physiotherapy interventions with inspiratory muscle training are effective to reduce postoperative pulmonary complications and length of hospital stay after major surgery and should start preoperatively.³⁴ Prevention is the most elegant strategy in medicine. However, to improve postoperative patient outcome, early detection and immediate treatment of postoperative pulmonary complications is essential.

Early Warning Scores

Early warning scores consist of vital parameters in a weighted scoring system including heart rate, respiratory rate, blood pressure, urinary output, temperature and level of consciousness. In our hospital, nurses routinely monitor patients and the modified early warning score (MEWS) is calculated (Table 2 and 3). For example, a patient with a respiratory rate of 28 breaths per minute with a SpO₂ below <90%, already has a critical MEWS score of ≥ 3 points. The MEWS is a validated early warning score, and a high MEWS is associated with admission to the intensive care unit, cardiac arrest and mortality on the general ward.¹¹

Early warning and intervention systems integrate early warning scores with an algorithm to plan clinical action. These systems are adopted in hospitals in Western Europe, Australia and the USA.³⁵ The beneficial impact of early warning and intervention systems on risk postoperative failure-to-rescue rates has however not yet been proven.³⁶ Detecting at-risk patients early in their disease course requires regular and systematic assessment. Ideally, this should be done frequently to identify patients at a time when intervention can make a clinical difference.¹⁸ The intermittent character of the early warning score and non-adherence to monitoring frequencies on the ward could be limiting factors of current early warning scores.³⁷

Table 2. Scoring system for the modified early warning score.

Score	3	2	1	0	1	2	3
Respiratory rate (breaths min ⁻¹)		< 9		9-14	15-20	21-30	> 30
SpO ₂ (with therapy) (%)	< 90						
Pulse rate (beats min ⁻¹)		< 40	40-50	51-100	101-110	111-130	>130
Systolic blood pressure (mmHg)	<70	70-80	81-100	101-200			
Temperature (°C)		<35.1	35.1-36.5	36.5-37.5	>37.5		
Consciousness				A	V	P	U
Urine production			<75mL in the last 4 hours				
Nurse being worried				1 point			

SpO₂ = peripheral oxygen saturation; A=Alert; V=Response to verbal stimulation; P=Response to painful stimulation; U=Unresponsive

Table 3. Rapid intervention team protocol

RIT protocol
1. Determine MEWS → MEWS ≥ 3 contact clinician on duty
2. Clinician on duty assess patient < 30 min and draft a plan for treatment
3. Effect of treatment is analyzed < 60 min
4. If no effect of treatment → clinician on duty contracts RIT
5. If not complied with 2,3,4 → clinician on duty or nurse contacts RIT
6. Document aberrant parameters in the patient' charts

Traditionally, paper-based observation charts have been used to identify deteriorating patients. Nowadays electronic patient records assist in data registration and early warning score calculations. With emerging patient data managing systems, electronic algorithms can be implemented to detect patients who are clinically deteriorating and even automatically contact the attending physician on a smartphone or pager.

For example, the electronic cardiac arrest risk triage (eCART) score is a multi parameter score which includes patient data registered in the electronic medical records to predict cardiac arrest.³⁸ These systems integrate vital signs with other patient information such as laboratory results, when sending out automated triggers to clinicians on duty. The electronically generated eCART score was more accurate for predicting in-hospital cardiac arrest, transfer to an intensive care unit and death compared to the MEWS in general ward patients.³⁹ Integrating technology can contribute to detect patients who are clinically

deteriorating, showing current early warning and intervention systems can be further improved.

Although recent systematic reviews and meta-analysis in a general population might point to a positive effect on the implementations of early warning systems on patient outcome.^{19,40} Untangling the different components of the early warning system, for example the afferent and efferent limb, might give insight into the beneficial effect of specific elements or could give insight in potential further improvements. This thesis focuses on the potential of improving the monitoring of vital signs to detect patients who are clinically deteriorating. Detecting clinically deteriorating patients as early as possible might limit the impact of complications, resulting in less serious adverse events, therefore improve individual patient outcome, shown in figure 1.

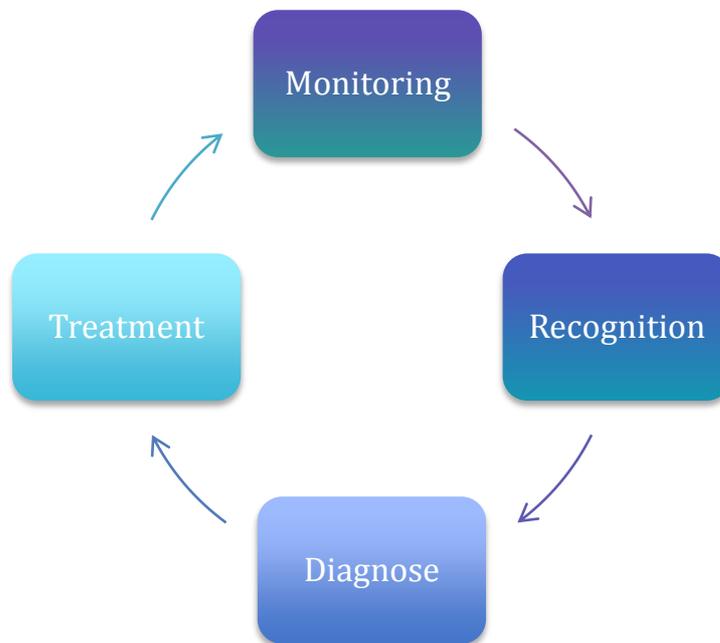


Figure 1. Continuum of actions to limit the impact of pulmonary postoperative complications.

Continuous remote monitoring

Recently, wireless wearable devices have become available that enable continuous remote monitoring of vital signs at the general ward. Recently, Subbe *et al.* reported decreased mortality and cardiac arrest rates in a prospective before-and-after study incorporating continuous remote monitoring within an automated notification system.⁴¹ However, in this study continuous remote monitoring remained only optional and was used according to the discretion of treating clinicians. Of the 2263 patients in the study only 278 (12%) had at least one cable-less sensor attached.⁴¹ Despite many potential advantages, wearable devices may also have disadvantages caused by technical dysfunction, increase in false positive alarms and experienced patient discomfort.

Furthermore, the cost-effectiveness and evaluating possible unintended consequences (e.g. over diagnostics and treatment) should be evaluated. Ideally, the early warning and intervention systems could assess “real-time” data to identify patients who are clinically deteriorating. This could eventually lead to a significant effect on mortality reduction.

Detection of postoperative pulmonary complications

The stethoscope was invented in 1816 by the French physician Laënnec and has been used as a diagnostic tool for the pulmonary system for over 200 years.⁴² Chest auscultation remains the first diagnostic tool in the clinical evaluation of patients. Chest X-ray is the second most used diagnostic tool especially in the detection of postoperative pulmonary complications after surgery.⁴³ However, there are major limitations in performing chest X-ray in postoperative and intensive care patients. First of all, patients tend to have complex radiological appearances due to several cardiopulmonary disorders.⁴⁴ Secondly, the suboptimal supine anterior-posterior radiograph setting is used in postoperative patients. Both are resulting in a low diagnostic accuracy, with a sensitivity in the detection of pleural effusion of 39%, alveolar consolidation 68% and pulmonary edema 60% compared with the gold standard CT scan.⁴⁵ Thirdly, use of chest X-ray comes with extensive use of resources, costs and exposure to radiation.⁴⁶ However, CT has an even higher radiation burden and requires patient transportation to the radiology department. Therefore, accurate bedside diagnostics of postoperative pulmonary complications is warranted.

An alternative in diagnostic chest imaging is lung ultrasound. Lung ultrasound is bedside available, fast, non-invasive, reproducible and enables the physician to monitor disorders and responses to treatment over time.^{45,47,48} Lung ultrasound provides real-time, accurate and relevant information and therefore avoids possible delay in diagnosis and treatment initiation. Furthermore, operator-dependence with lung ultrasound is minimal due to a high inter-observer agreement.⁴⁴ The bedside lung ultrasound in emergency (BLUE)-protocol is a

validated and widely used protocol to diagnose the cause of a respiratory failure in the emergency department.⁴⁵ Therefore, the use of lung ultrasound has earned popularity mainly in the emergency department and intensive care unit.⁴⁹

Different lung ultrasound profiles have been defined to distinguish between the most common causes of respiratory failure (pneumonia, congestive heart failure, chronic obstructive pulmonary disease (COPD), asthma, pulmonary embolism, and pneumothorax). Therefore lung ultrasound could also be used in postoperative care once clinical deterioration is detected to narrow down the differential diagnosis and guide further diagnostic and possible therapeutic interventions. Despite all studies investigating the usefulness of lung ultrasound in critically ill patients, only a few studies investigated lung ultrasound in the cardiothoracic surgery setting and no studies have been performed after abdominal surgery.^{50,51}

Outline of this thesis

This thesis investigates the feasibility and diagnostic value of new technologies for the detection of clinical patient deterioration and postoperative pulmonary complications. First, detecting clinical deterioration with continuously remotely monitored respiratory rate, peripheral oxygen saturation, heart rate and MEWS was studied in postoperative patients admitted to, and intensive care unit patients discharged to the general ward. Second, point-of-care lung ultrasound was evaluated for the diagnosis of postoperative pulmonary complications, potentially leading to adverse events after surgery. We hypothesized that the use of novel techniques like continuous remote monitoring and point-of-care lung ultrasound are of added value in the detection of (1) patients who are clinically deteriorating and (2) postoperative pulmonary complications.

In the first part of this thesis, in **chapter 2**, we give an overview of the current evidence for continuous remote monitoring in postoperative patients and its integration in an automated early warning score strategy. In **chapter 3** we study continuous remote monitoring of the respiratory rate, SpO₂ and pulse rate for four postoperative days after major abdominal surgery. We calculated a remote MEWS based on remotely measured vital parameters. In **chapter 4** we also studied the incidence of a critical remote MEWS in intensive care unit patients discharged to the general ward. In **chapter 5** we studied hypoxemic events during procedural sedation for upper gastrointestinal procedures. We compared photoplethysmography respiratory rate monitoring with capnography as the gold standard for respiratory rate monitoring for the detection of hypoventilation.

The second part of the thesis focuses on the feasibility, clinical effectiveness and diagnostic accuracy of lung ultrasound in postoperative patients. In **chapter 6** we describe the impact and implications of adopting point-of-care lung ultrasound as a diagnostic imaging technique for future physicians. In **chapter 8** we performed a meta-analysis to evaluate the diagnostic accuracy of chest X-ray, and when concomitantly studied lung ultrasound for adult critically ill patients with respiratory symptoms, in comparison with the gold standard CT. In **chapter 9** we studied lung ultrasound and chest X-ray in the detection of clinically relevant postoperative pulmonary complications in patients undergoing cardiac surgery. In **chapter 11**, lung ultrasound was used in the postoperative ward as a diagnostic imaging technique for the detection of postoperative pulmonary complications after major abdominal surgery. We studied a protocol for daily screening for postoperative pulmonary complications with lung ultrasound according to the BLUE protocol.

References

1. Weiser TG, Regenbogen SE, Thompson KD. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*. 2008;372: 139–144.
2. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FAG, Boersma E; Postoperative Mortality in The Netherlands: A Population-based Analysis of Surgery-specific Risk in Adults. *Anesthesiology* 2010;112: 1105-1115.
3. Findlay G, Goodwin A, Protopappa K, Smith N, Mason M. Knowing the risk: a review of the peri-operative care of surgical patients. National Confidential Enquiry into Patient Outcome and Death; London: 2011.
4. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet*. 2012; 380: 1059-1065.
5. Le Manach Y, Gary Collins, Reitze Rodseth, Christine Le Bihan-Benjamin, Bruce Bicccard, Bruno Riou, P.J. Devereaux, Paul Landais; Preoperative Score to Predict Postoperative Mortality (POSPOM): Derivation and Validation. *Anesthesiology* 2016; 124:570-579.
6. Boehm O, Baumgarten G, Hoeft A. Epidemiology of the high-risk population: perioperative risk and mortality after surgery. *Curr Opin Crit Care*. 2015; 21:322-7.
7. Pearse RM, Harrison DA, James P. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care*. 2006; 10:R81.
8. Ahmad T, Bouwman RA, Grigoras I, Aldecoa C, Hofer C, Hoeft A, Holt P, Fleisher LA, Buhre W, Pearse RM: Use of failure-to-rescue to identify international variation in postoperative care in low-, middle- and high-income countries: A 7-day cohort study of elective surgery. *British Journal of Anaesthesia* 2017; 119:258-266.
9. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, Howard KM, Weiler PC, Brennan TA: Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care* 2000, 38:261-271.
10. Vincent C, Neale G, Woloshynowych M: Adverse events in British hospitals: preliminary retrospective record review. *BMJ* 2001, 322:517-519.
11. van Galen LS, Dijkstra CC, Ludikhuizen J, Kramer MH, Nanayakkara PW. A Protocolised Once a Day Modified Early Warning Score (MEWS) Measurement Is an Appropriate Screening Tool for Major Adverse Events in a General Hospital Population. *PLoS One*. 2016;11:e0160811.
12. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med*. 2009; 361:1368–1375.
13. Basisset kwaliteitsindicatoren ziekenhuizen 2016. www.IGJ.nl
14. Schein RM, Hazday N, Pena M, Ruben BH, Sprung CL. Clinical antecedents to in-hospital cardiopulmonary arrest. *Chest* 1990; 98:1388–92.
15. Kause J, Smith G, Prytherch D, Parr M, Flabouris A, Hillman K. A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia and New Zealand, and in the United Kingdom- theACADEMIA study. *Resuscitation* 2004; 62:275–82.

16. Taenzer AH, Pyke JB, McGrath SP, Blike GT. Impact of pulse oximetry surveillance on rescue events and intensive care unit transfers: a before-and-after concurrence study. *Anesthesiology*. 2010; 112:282–7.
17. Ludikhuizen J, Smorenburg SM, de Rooij SE, de Jonge E. Identification of deteriorating patients on general wards; Measurement of vital parameters and potential effectiveness of the Modified Early Warning Score. *J Crit Care* 2012; 27:424.e7-424.13.
18. DeVita, M. a. et al. 'Identifying the hospitalised patient in crisis'-A consensus conference on the afferent limb of Rapid Response Systems. *Resuscitation* 2010; 81:375–382.
19. Maharaj R, Raffaele I, Wendon J Rapid response systems: a systematic review and meta-analysis. *Crit Care* 2015; 19:254.
20. Mazo V, Sabate S, Canet J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. *Anesthesiology* 2014; 121:2.
21. G. Hedenstierna, L. Edmark. Effects of anesthesia on the respiratory system *Best Practice & Research Clinical Anaesthesiology* 2015; 29:273e284.
22. Bhagat R, Bronsert MR, Juarez-Colunga E, Weyant MJ, Mitchell JD, Glebova NO, Henderson WG, Fullerton D, Meguid RA. Postoperative Complications Drive Unplanned Readmissions after Esophagectomy for Cancer. *Ann Thorac Surg*. 2018; 105:1476-1482.
23. Fernandez-Bustamante A, Frenzl G, Sprung J, Kor DJ, Subramaniam B, Martinez Ruiz R, Lee J, Henderson WG, Moss A, Mehdiratta N, Colwell MM, Bartels K, Kolodzie K, Giquel J, Vidal Melo MF. Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery A Multicenter Study by the Perioperative Research Network Investigators. *JAMA Surg*. 2017; 152:157–166.
24. LAS VEGAS investigators. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS – an observational study in 29 countries. *European Journal of Anaesthesiology* 2017; 34:492–507.
25. Gupta H, Gupta PK, Fang X, et al. Development and validation of a risk calculator predicting postoperative respiratory failure. *Chest* 2011; 140:1207–15.
26. Stens J, Hering JP, van der Hoeven CWP et al. The added value of cardiac index and pulse pressure variation monitoring to mean arterial pressure-guided volume therapy in moderate-risk abdominal surgery (COGUIDE): a pragmatic multicentre randomised controlled trial. *Anaesthesia* 2017; 72:1078-1087.
27. Mills G. H. Respiratory complications of anaesthesia *Anaesthesia* 2018, 73 (Suppl. 1), 25–33
28. Canet J, Gallart L, Gomar C et al. ARISCAT Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010; 113:1338-50.
29. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet*. 2014; 384:495-503.

30. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. *Annals of Surgery* 2000; 232: 242–53.
31. Liu VX, Rosas E, Hwang J, Cain E, Foss-Durant A, Clopp M, Huang M, Lee DC, Mustille A, Kipnis P, et al. Enhanced Recovery After Surgery Program Implementation in 2 Surgical Populations in an Integrated Health Care Delivery System. *JAMA Surg*. 2017; 152:e171032.
32. Jurt J, Hübner M, Pache B, Hahnloser D, Demartines N, Grass F. Respiratory Complications After Colorectal Surgery: Avoidable or Fate? *World J Surg*. 2018: [Epub ahead of print]
33. Lugg ST, Tikka T, Agostini PJ, et al. Smoking and timing of cessation on postoperative pulmonary complications after curative-intent lung cancer surgery. *Journal of Cardiothoracic Surgery*. 2017; 12:52.
34. Kendall F, Oliveira J, Peleteiro B, Pinho P, Bastos PT. Inspiratory muscle training is effective to reduce postoperative pulmonary complications and length of hospital stay: a systematic review and meta-analysis. *Disabil Rehabil*. 2018; 40:864-882
35. Lyons PG, Edelson DP, Churpek MM: Rapid response systems. *Resuscitation* 2018; 128:191-197.
36. Hollis RH, Graham LA, Lazenby JP, Brown DM, Taylor BB, Heslin MJ, Rue LW, Hawn MT: A role for the early warning score in early identification of critical postoperative complications. *Annals of surgery* 2016; 263:918-923.
37. Petersen JA. Early warning score challenges and opportunities in the care of deteriorating patients. *Dan Med J*. 2018; 65:B5439.
38. Churpek MM, Yuen TC, Winslow C, Robicsek AA, Meltzer DO, Gibbons RD, Edelson DP. Multicenter development and validation of a risk stratification tool for ward patients. *Am J Respir Crit Care Med*. 2014; 190:649-55.
39. Green M, Lander H, Snyder A, Hudson P, Churpek M, Edelson D. Comparison of the Between the Flags calling criteria to the MEWS, NEWS and the electronic Cardiac Arrest Risk Triage (eCART) score for the identification of deteriorating ward patients. *Resuscitation*. 2018; 123:86-91.
40. Maharaj R, Stelfox HT. Rapid response teams improve outcomes: no. *Intensive Care Med* 2016; 42:596–598.
41. Subbe CP, Duller B, Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Crit Care* 2017; 21:52.
42. Solomon SD, Saldana F. Point-of-care Ultrasound in Medical Education — Stop Listening and Look. *N Engl J Med*. 2014; 370:1083–5.
43. Tolsma M, Kröner A, van den Hombergh CLM, Rosseel PMJ, Rijpstra TA, Dijkstra HAJ, et al. The clinical value of routine chest radiographs in the first 24 hours after cardiac surgery. *Anesth Analg*. 2011; 112:139–42.
44. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby J-J. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology*. 2004; 100:9–15.
45. Lichtenstein DA. Lung ultrasound in the critically ill. *Clinical Intensive Care*. 2014. p. 1–12.

46. Khan A, Hamdan A-J, AL-Ghanem S, Alaa G. Reading chest radiographs in the critically ill (Part II): Radiography of lung pathologies common in the ICU patient. *Ann Thorac Med.* 2009; 4:149.
47. Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest* 2015; 147:1659-1670.
48. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest* 2008; 134: 117-25.
49. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med.* 2012; 38:577-91.
50. Vezzani A, Manca T, Brusasco C, Santori G, Valentino M, Nicolini F, et al. Diagnostic value of chest ultrasound after cardiac surgery: a comparison with chest X-ray and auscultation. *J Cardiothorac Vasc Anesth.* 2014; 28:1527-32.
51. Alsaddique A, Royse AG, Royse CF, Mobeirek A, El Shaer F, AlBackr H, et al. Repeated Monitoring With Transthoracic Echocardiography and Lung Ultrasound After Cardiac Surgery: Feasibility and Impact on Diagnosis. *Journal of Thoracic and Cardiovascular Anesthesia.* 2016; 30:406-12.

Chapter 2

Postanesthesia care by remote monitoring of vital signs in surgical wards

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Current Opinion Anesthesiology 2018; 31:716-722.

Abstract

Purpose of review

This narrative review summarizes recent insights into the role of remote monitoring of vital signs in the postoperative period in surgical wards.

Recent findings

Despite recent improvements in the safety of anesthesia and surgical procedures, postoperative complication rates are still unacceptably high. This is partly attributable to the intermittent provision of personal care to patients by nurses and ward physicians. Continuous remote monitoring of vital functions in the early postoperative period may reduce these complication rates. There are several medical-grade remote monitoring platforms available that integrate a biosensor signal with electronic patient records, enabling automated prediction or notification of patient deterioration. Most available platforms have technical limitations with respect to the accuracy of respiratory rate measurements. Of note, although the implementation of automated notifications of patient deterioration is associated with a reduced activation of acute response teams, the involvement of ward physicians in the early diagnosis and treatment of subtle changes in vital functions is increased.

Summary

Remote monitoring of vital signs in the surgical ward may contribute to prevention of severe complications and reduction in failure-to-rescue rates, although evidence for this association is still lacking. Anesthesiologists should contribute their knowledge and skills with respect to perioperative abnormalities in vital functions to improve patient safety during the postoperative period.

Key points

- Postoperative monitoring of vital signs in surgical patients using spot check monitors has an intermittent character, and early signs of patient deterioration may therefore be missed.
- Continuous remote monitoring of vital signs with wireless biosensors facilitates automated notification of patient deterioration and early diagnostic and therapeutic interventions.
- Implementation of automated notifications of patient deterioration is associated with reduced activation rates of rapid response teams, but increased involvement of ward physicians in the early treatment of postoperative complications.
- Anesthesiologists should use remote monitoring of vital signs to intensify their involvement in post-anesthesia care of surgical patients.

Introduction

Despite major improvements in the safety of anesthesia and surgery, the number of postoperative complications is still unacceptably high. Postoperative complications vary among surgical procedures but rates up to 25-40% are reported, with readmission rates of 16-22% following high risk procedures.^{1,2} Postoperative complications are therefore a tremendous burden on hospital logistics, health care costs and the quality of life of surgical patients. Anesthesiologists are highly qualified to identify relevant changes of vital functions in an early phase, and their contribution to the monitoring of surgical patients may therefore lead to improved outcome.

There is increased awareness that early recognition and timely management of mild or moderate abnormalities in the patients' condition, once they have occurred, may improve the quality and outcomes of postoperative care.³ However, the organization of postoperative care is frequently inadequate to detect these mild and moderate abnormalities, leading to the development of severe complications and unplanned intensified care, also known as failure-to-rescue. Ghaferi et al. showed that failure-to-rescue rates can particularly be attributed to the inconsistency in the structure and quality of postoperative care among hospitals and the age of patients.⁴ Moreover, personal care for patients by nurses and physicians has an intermittent character, and early signs of deterioration of health may therefore easily be missed. While hospitals try to limit staffing costs, new technological innovations such as continuous telemetric monitoring of vital parameters, so-called remote monitoring or automated notifications, may be introduced to fill this gap in surgical wards.

The goal of this review is to give an overview of the concept of remote monitoring of vital signs in the postoperative period in surgical wards, and to summarize existing evidence for the added value of this monitoring concept.

The use of early warning scores in postoperative care

Preoperative risk scores constructed from patient risk profiles, the type of surgery and intraoperative events, have a moderate accuracy in the prediction of surgical risk and complications.⁵ The addition of changes in postoperative dynamic clinical parameters, such as heart rate (HR), respiratory rate (RR), blood pressure and SpO₂ values, may increase the accuracy of these risk scores. Subtle changes in these parameters, such as an increased respiratory rate or heart rate may be indicative for the development of, e.g., pneumonia or hypovolaemia.⁶

In an attempt to assess variations in vital functions, institutions implemented (modified) early warning scores ((M)EWS) to guide activation of rapid response teams (RRT) in case of patient deterioration.⁷ This score is usually measured by nurses using spot check monitors

and permits segregation of normal physiological changes from pathologic variation. An EWS that exceeds 3 points leads to intensification of monitoring, the initiation of a diagnostic work-up and/or the start of therapeutic interventions.

While the EWS can be used to identify and treat aberrations in vital functions in a protocolized fashion, a beneficial impact on risk reduction in postoperative failure-to-rescue rates has not yet been proven.⁷ Moreover, it has been shown that a manual EWS has superior discriminative performance compared to an automated EWS using continuous data obtained from bedside monitors, mainly due to differences in the chosen thresholds for manually charted and digitally recorded respiratory rates.^{8,9} However, manually charted EWS files are frequently incomplete and may be biased by opinionated health professionals.¹⁰ An important limitation of the EWS is a low discriminative power for early and mild abnormalities in vital functions. These scores are therefore mostly used for activation of response teams in case of severe patient deterioration.

Remote technologies and automated notification systems may help to improve the appropriateness, reliability, and speed of diagnosis and therapeutic interventions in deteriorating surgical patients.^{11,12} The use of continuous remote monitoring of single parameters to detect mild deviations in vital signs of surgical patients is only one piece of the puzzle. Figure 1 shows a step-up monitoring model that starts with spot check monitoring of vital signs by nurses, followed by continuous wireless monitoring of vital signs in a remote fashion. More advanced steps include the automated calculation of early warning scores using remote monitoring signals, the automated notification of patient deterioration through tablets and smartphones and prediction rules for patient deterioration, which are discussed below.

Remote monitoring devices used in the surgical ward

Although there are many digital applications available that are embedded in smartphone and tablet interfaces to measure vital functions like heart rate or activity,^{13,14} this review only reports on remote monitoring devices using medical-grade biosensors. For medical-grade systems, the signal is transferred from a cable-less biosensor to a central receiver that is preferably connected to an electronic patient record (EPR) database. Ideally, remote monitoring systems allow free movement of the patient. Figure 2 shows an example of implementation of remote monitoring in perioperative care. Using e-Health applications, patients are monitored and prehabilitated before surgery. After hospital admission, patients with an indication for postoperative hospital stay receive a biosensor that transfers vital sign recordings to a dedicated monitor and software platform. This software platform integrates

the received signals with the electronic patient record database and provides automated early warning scores. Deviations in vital functions or early warning scores are notified to health care professionals in order to initiate diagnostic or therapeutic interventions.¹⁵

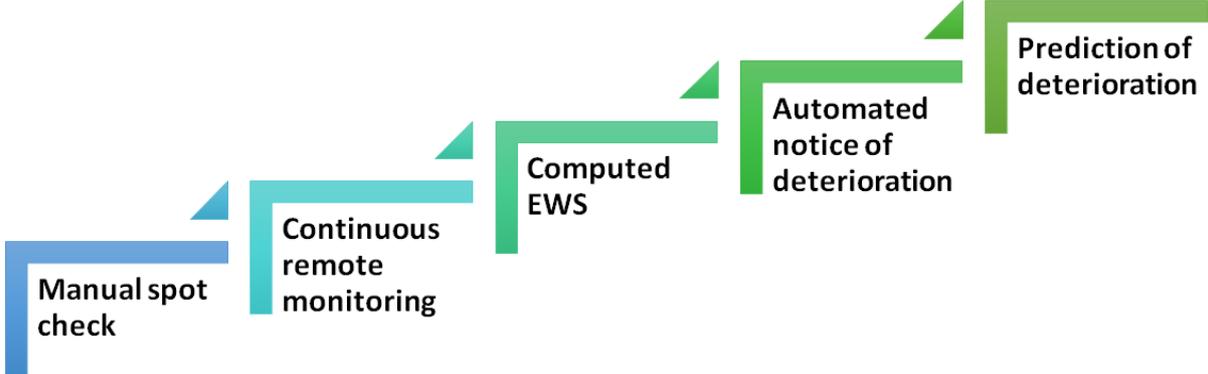


Figure 1. Step-up monitoring model for vital signs in hospital wards. EWS = early warning score

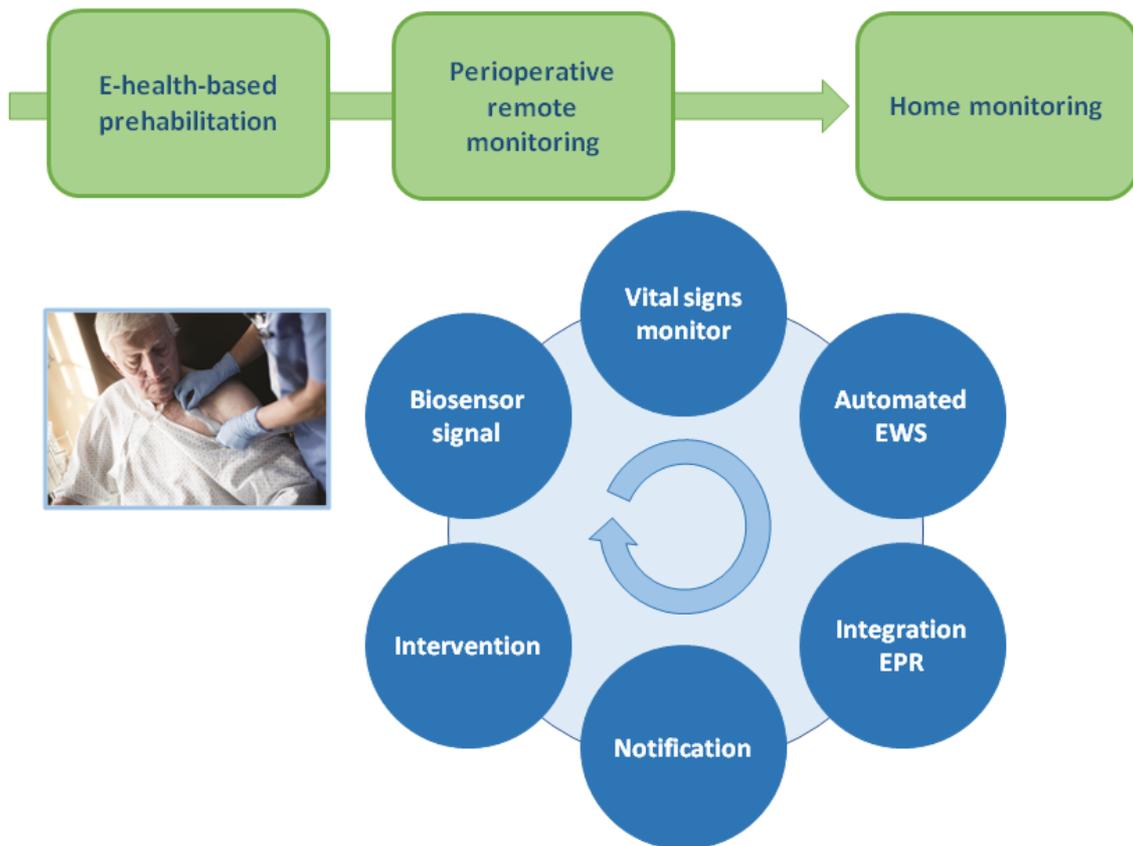


Figure 2. Example of the use of remote monitoring in the perioperative period. Using e-health interventions, patients are prehabilitated before surgery. During hospital admission, patients receive a biosensor that transfers information about vital signs by WIFI or radiofrequency signals to a dedicated monitor depicting automated EWS calculations. The vital sign monitor is linked to the hospital electronic patient record system. Abnormalities in vital signs or the early warning score are automatically notified to health care professionals using a computer terminal, tablet or mobile phone, supporting early interventions to improve patient health. Example of the wireless Intellivue Guardian[®] biosensor (published with courtesy of Philips Healthcare).

Table 1 summarizes the remote monitoring devices with WIFI or radiofrequency connectivity platforms that were studied in the context of the surgical ward. While there are systems that use a wireless biosensor or patch with data storage capacity (VitalPatch[®], Intellivue Guardian[®], Sensium[®]), other systems still require some wiring between the measurement sensors and wearable remote monitor device (ViSi Mobile System[®], Radius-7 / Patient Safetynet[®]). Most systems are able to communicate with an electronic patient record platform, pagers, tablets and mobile phones. Patients perceived remote monitoring as helpful tool to alleviate the nursing staff, and to reduce nightly interruptions for charting reasons.¹⁶ but cannot replace the benefits of face-to-face nursing contact.¹⁶

Table 1. Remote monitoring devices with WIFI or radiofrequency connectivity platforms that were studied in the context of the surgical ward

Product	Remote vital signs	Automated EWS	Wireless biosensor
HealthPatch[®]	Single-lead ECG, HR, HR variability, RR,	Yes	Yes
MD / VitalPatch[®]	temperature, activity		
Intellivue Guardian[®]	HR, RR, posture	Yes	Yes
Sensium[®]	HR, RR, temperature	Yes	Yes
ViSi Mobile System[®]	HR, PR, RR, SpO ₂ , blood pressure, temperature	Yes	No
Radius-7 / Patient Safetynet[®]	HR, RR, SpO ₂	Yes	No

ECG=electrocardiogram, HR=heartrate, RR=respiratory rate and SpO₂= peripheral oxygen saturation

Technical limitations

The remote monitoring systems that are currently available still exert technical limitations. A comparison between a wireless heart rate and respiratory rate sensor with a routine intensive care monitoring system in high-risk postoperative patients showed that for different biosensors heart rate was accurate, while the respiratory rate was outside the accuracy limit range compared to standardized monitoring^{17,18} or manual respiratory rate measurements.¹⁹ ²⁰ Photoplethysmography respiratory rate using an SpO₂ biosensor also showed a low agreement with routine capnography during procedural sedation for endoscopy.²¹ The addition of end-tidal CO₂ to an automated MEWS was investigated in a patient population undergoing elective surgery with a history of obesity, sleep apnea or receiving patient-controlled analgesia or epidural narcotics.²² It was shown that the addition of etCO₂ alarms to an automated MEWS was feasible but resulted in high false-positive alarm rates. Despite the low agreement between some remotely recorded vital signs and manual or spot check measurements, the continuous trend analysis that is enabled by remote monitoring devices has the potential as addition to current postoperative care.

Automated calculation of early warning score deviations and notifications

The need for automated systems for the recognition of patient deterioration was demonstrated in a cohort of non-cardiac surgery patients, showing that nurses only detected 5% of the hypoxemic episodes that were recorded by pulse-oximetry.²³ The unawareness of vital sign aberrations may cause an avoidable risk for the development of more severe complications. Two before-after clinical studies investigated the impact of an automated notification system for patient deterioration.^{24,25} Patient deterioration was assessed by an EWS calculated from a combination of bed-side observations and a 15-minute automated evaluation of vital signs including heart rate, respiratory rate, SpO₂ and blood pressure. Abnormal vital signs were send to an automated paging device. Local protocols recommended escalation of health care intensity or activation of a rapid response team in case of exceeding a specific EWS. In the study of Subbe et al.²⁴ it was shown that the number of RRT notifications increased by 30%, resulting in more interference in fluid therapy, the use of bronchodilators and antibiotics. The mortality of patients referred to the ICU was 50% lower after the implementation of automated notifications. However, the extrapolation of these results to the general surgical ward was limited, since the patient cohort included patients at a general ward with a moderate-to-high risk for severe complications.²⁴ In a similar fashion, Heller et al. implemented automated notifications in a surgical ward.²⁵ In this study population, the number of medical emergency calls and unplanned ICU admissions was lower in the intervention cohort, whereas the number of critical notifications increased in this cohort. In particular, deterioration of patient health was more frequently treated by the

physician in charge on the ward without activation of a rapid response team.²⁵ These findings suggest that the introduction of automated notifications of deterioration in vital signs leads to enhanced involvement of ward physicians, rather than increased activation rates of specialized response teams. Similar findings were observed in the setting of neurological and neurosurgical patients. Implementation of a vital signs monitor with automated nursing notification of alarms via smartphones was associated with a reduction in the rapid response team call rate, but the study was not powered to show changes in intensive care admission rates.²⁶ Another study showed that the implementation of an electronic dashboard with MEWS values of non-surgical and surgical patients resulted in a higher rate of first rapid response team activations, while the overall rapid response team activation rate decreased.²⁷ An explanation for this observation was the higher awareness among ward physicians of patient deterioration after the first rapid response team activation. From these small number of studies, it can be concluded that the introduction of an automated EWS with notification system leads to a reduction in rapid response team activation in case of severe patient deterioration and increase in diagnostic and therapeutic interventions for subtle changes in the condition of the patients.

Machine-learning algorithms for impending patient deterioration

Machine learning and data mining allow the construction of models that detect deviation of normal early warning scores.²⁸ A next step in automated detection of patient deterioration is the development of patient-specific predictive algorithms using large datasets containing information of vital signs. Ghost et al. developed the Early Deterioration Indicator (EDI) algorithm using spot-check data of vital signs as recorded in electronic patient files, and subsequently performed a validation study.²⁹ The EDI scoring algorithm was based on data of stable and unstable patients and provides continuous probabilities of instability ranging from zero to 1. EDI had a higher sensitivity and was a better discriminator of patient deterioration than a 5-point and 7-point EWS. The further development of EDI using data from wireless remote monitoring devices will further support early prediction of patient deterioration and may contribute to a reduction in the postoperative complication rate.

Remote monitoring after hospital discharge

The introduction of the surgical home concept and home telemedicine systems may be supportive in the reduction of postoperative length of stay. Currently, most home-based telemedicine systems for postoperative patients are limited to mobile applications that monitor the quality of recovery. In the first feasibility studies, patients used a mobile phone daily to complete a quality of recovery scale and took photographs of the surgical site.^{30, 31} In a second feasibility study, it was shown that a smartphone text message-based algorithm to

monitor patient health following colorectal surgery was acceptable to patients and reduced the number of postoperative telephone consultations.³² However, vital functions like blood pressure and heart rate were manually measured by patients or relatives, and not by remote monitoring devices. Both studies showed that patient cooperation is an important prerequisite for the use of mobile applications that require active input. Biosensor-based monitoring devices may alternatively be used to guarantee patient compliance and to reveal early signs of patient deterioration. These systems are currently under development or became recently available, and feasibility and efficacy studies are lacking. In specialties like cardiology there is extensive experience with home-based remote monitoring of patients with arrhythmias or heart failure, but with the footnote that these systems are also at risk for cybersecurity issues and hacking, warranting a collaboration between stakeholders to set a standard for the level of security of these systems.³³

Where anesthesiologists can fill the gaps in postoperative care

In a continuous effort to improve patient outcome, anesthesiologists should contribute to improvements in the structure and quality of postoperative care. Some suggest that this niche should particularly be filled by anesthesiologist-intensivists, who are increasingly involved in preoperative risk reduction, extracorporeal and mechanical support teams and RRTs.³⁴ However, from the studies that implemented automated notification systems in surgical wards one may conclude that remote monitoring of postoperative patients will lead to a shift from the activation of rapid response teams to smaller interventions in case of mild abnormalities in vital functions.²⁴⁻²⁷ In 2015, the American Society of Anesthesiologists introduced the concept of perioperative surgical homes in order to reduce the variability in perioperative practice. The perioperative surgical home is still in its infancy and may not be fully adapted by other continents.³⁵ The concept of perioperative medicine, rather than anesthesiology, promotes the commitment of anesthesiologists to the outcome of surgical procedures and broader collaboration of anesthesiologists with other healthcare providers. This also requires specific educational programs to increase the knowledge and competencies of anesthesiologists in the postoperative period.³⁵ Remote monitoring of vital signs may be a helpful tool in this transition of anesthesiologists to perioperative physicians.

Conclusion

Despite improvements in the quality and safety of anesthesia, postoperative care in moderate-to-high risk patients is still dominated by high complication rates. Intermittent monitoring of patients in the surgical ward by nurse staff and physicians is insufficient to detect mild aberrations in vital functions that could be the first sign of the development of severe complications. The introduction of continuous remote monitoring of vital functions in the postoperative period, with automated calculation of early warning scores and notification of health care providers, could lead to a shift from recognizing mild instead of severe disturbances in the condition of a patient.³⁶ This will not only result in a reduced activation rate of rapid response teams but can also pave a path for anesthesiologists in the field of perioperative medicine. While awaiting the evidence for a beneficial impact of remote monitoring and automated notifications on postoperative complication rates, anesthesiologists should bring in their knowledge and skills with respect to perioperative abnormalities in vital functions to increase the safety of patients in the postoperative period. Anesthesiology resident programs should emphasize the importance of the early postoperative period beyond the recovery ward and prepare them for their role as perioperative physicians.

References

1. Ahmad T, Bouwman RA, Grigoras I, et al. Use of failure-to-rescue to identify international variation in postoperative care in low-, middle- and high-income countries: a 7-day cohort study of elective surgery. *British journal of anaesthesia* 2017; 119:258-266.
2. Jacobs BL, He C, Li BY, et al. Variation in readmission expenditures after high-risk surgery. *The Journal of surgical research* 2017; 213:60-68.
3. Walston JM, Cabrera D, Bellew SD, et al. Vital Signs Predict Rapid-Response Team Activation Within Twelve Hours of Emergency Department Admission. *The western journal of emergency medicine* 2016; 17:324-30.
4. Ward ST, Dimick JB, Zhang W, Cet al. Association Between Hospital Staffing Models and Failure to Rescue. *Annals of surgery* 2018.
5. Talmor D and Kelly B. How to better identify patients at high risk of postoperative complications? *Current opinion in critical care* 2017; 23:417-423.
6. Taenzer AH, Pyke JB, McGrath SP and Blike GT. Impact of pulse oximetry surveillance on rescue events and intensive care unit transfers: a before-and-after concurrence study. *Anesthesiology* 2010; 112:282-7.
7. Hollis RH, Graham LA, Lazenby JP, et al. A Role for the Early Warning Score in Early Identification of Critical Postoperative Complications. *Annals of surgery* 2016; 263:918-23.
8. Watkinson PJ, Pimentel MAF, Clifton DA et al. Manual centile-based early warning scores derived from statistical distributions of observational vital-sign data. *Resuscitation* 2018.
9. Subbe CP and Duller B. Continuous Monitoring of Respiratory Rate on General Wards What might the implications be for Clinical Practice? *Acute medicine* 2018; 17:5-9.
10. Pedersen NE, Rasmussen LS, Petersen JA, et al. A critical assessment of early warning score records in 168,000 patients. *Journal of clinical monitoring and computing* 2018; 32:109-116.
11. Lyons PG, Edelson DP and Churpek MM. Rapid response systems. *Resuscitation* 2018; 128:191-197.
12. Downey CL, Chapman S, Randell R, et al. The impact of continuous versus intermittent vital signs monitoring in hospitals: A systematic review and narrative synthesis. *International journal of nursing studies* 2018; 84:19-27
13. Michard F. A sneak peek into digital innovations and wearable sensors for cardiac monitoring. *Journal of clinical monitoring and computing* 2017; 31:253-259.
14. Michard F, Gan TJ and Kehlet H. Digital innovations and emerging technologies for enhanced recovery programmes. *British journal of anaesthesia* 2017; 119:31-39.
15. da Costa CA, Pasluosta CF, Eskofier B, det al. Internet of Health Things: Toward intelligent vital signs monitoring in hospital wards. *Artificial intelligence in medicine* 2018.
16. Downey CL, Brown JM, Jayne DG et al. Patient attitudes towards remote continuous vital signs monitoring on general surgery wards: An interview study. *International journal of medical informatics* 2018; 114:52-56.

17. Breteler MJMM, Huizinga E, van Loon K, et al. Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in the Netherlands: a clinical validation study. *BMJ open* 2018; 8:e020162.
18. Churpek MM, Snyder A, Twu NM et al. Accuracy Comparisons between Manual and Automated Respiratory Rate for Detecting Clinical Deterioration in Ward Patients. *Journal of hospital medicine* 2018.
19. Weenk M, van Goor H, Frietman B, et al. Continuous Monitoring of Vital Signs Using Wearable Devices on the General Ward: Pilot Study. *JMIR mHealth and uHealth* 2017; 5:e91.
20. Granholm A, Pedersen NE, Lippert A, et al. Respiratory rates measured by a standardised clinical approach, ward staff, and a wireless device. *Acta anaesthesiologica Scandinavica* 2016; 60:1444-1452.
21. Touw HRW, Verheul MH, Tuinman PR, et al. Photoplethysmography respiratory rate monitoring in patients receiving procedural sedation and analgesia for upper gastrointestinal endoscopy. *Journal of clinical monitoring and computing* 2017; 31:747-754.
22. Blankush JM, Freeman R, McIlvaine J, et al. Implementation of a novel postoperative monitoring system using automated Modified Early Warning Scores (MEWS) incorporating end-tidal capnography. *Journal of clinical monitoring and computing* 2017; 31:1081-1092.
23. Sun Z, Sessler DI, Dalton JE, et al. Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. *Anesthesia and analgesia* 2015; 121:709-15.
24. Subbe CP, Duller B and Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Critical Care* 2017; 21:52.
25. Heller AR, Mees ST, Lauterwald B, et al. Detection of Deteriorating Patients on Surgical Wards Outside the ICU by an Automated MEWS-Based Early Warning System With Paging Functionality. *Annals of surgery* 2018.
26. Weller RS, Foard KL and Harwood TN. Evaluation of a wireless, portable, wearable multi-parameter vital signs monitor in hospitalized neurological and neurosurgical patients. *Journal of clinical monitoring and computing* 2018;32:945-951.
27. Fletcher GS, Aaronson BA, White AA, et al. Effect of a Real-Time Electronic Dashboard on a Rapid Response System. *Journal of medical systems* 2017; 42:5.
28. Petit C, Bezemer R and Atallah L. A review of recent advances in data analytics for post-operative patient deterioration detection. *Journal of clinical monitoring and computing* 2018; 32:391-402.
29. Ghosh E, Eshelman L, Yang L, et al. Early Deterioration Indicator: Data-driven approach to detecting deterioration in general ward. *Resuscitation* 2018; 122:99-105.
30. Semple JL, Sharpe S, Murnaghan ML, et al. Using a mobile app for monitoring post-operative quality of recovery of patients at home: a feasibility study. *JMIR mHealth and uHealth* 2015; 3:e18.
31. Semple JL and Armstrong KA. Mobile applications for postoperative monitoring after discharge. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2017; 189:E22-e24.

32. Bragg DD, Edis H, Clark S, Parsons SL, et al. Development of a telehealth monitoring service after colorectal surgery: A feasibility study. *World journal of gastrointestinal surgery* 2017; 9:193-199.
33. Baranchuk A, Refaat MM, Patton KK, et al. Cybersecurity for Cardiac Implantable Electronic Devices: What Should You Know? *Journal of the American College of Cardiology* 2018; 71:1284-1288.
34. Bennett S, Grawe E, Jones C, et al. Role of the anesthesiologist-intensivist outside the ICU: opportunity to add value for the hospital or an unnecessary distraction? *Current opinion in anaesthesiology* 2018; 31:165-171.
35. King AB, Alvis BD and McEvoy MD. Enhanced recovery after surgery, perioperative medicine, and the perioperative surgical home: current state and future implications for education and training. *Current opinion in anaesthesiology* 2016; 29:727-732.
36. McGillion MH, Duceppe E, Allan K, et al. Postoperative Remote Automated Monitoring: Need for and State of the Science. *The Canadian journal of cardiology* 2018; 34:850-862.

Chapter 3

Continuous remote monitoring to detect critical early warning scores in patients after abdominal surgery

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Submitted

Abstract

Background

Patients who are clinically deteriorating can be detected too late by early warning and intervention systems due to its intermittent character. We studied the feasibility of a critical modified early warning score (MEWS) detection with continuously remotely monitoring of vital signs in patients after abdominal surgery. Secondly, we related our findings to the development of postoperative pulmonary complications (PPCs).

Methods

This explorative observational feasibility study included patients undergoing major abdominal surgery with an increased preoperative risk for PPCs. The respiratory rate, SpO₂ and pulse rate were continuously remotely monitored for four postoperative days, and a remote MEWS was calculated according these vital signs. Critical remote MEWS (≥ 3) detected patients who were clinically deteriorating according to the MEWS protocol. Findings were related to predefined PPCs, retrospectively scored using patient records.

Results

Overall, 112 patients were included prospectively, of whom 12 met exclusion criteria. Overall, continuous remote monitoring feasible in 97 out of 100 eligible patients (97%, 95% CI: 91 to 99%). Critical remote MEWS was detected in 11.6% (0.8-20.8) of the monitoring time in patients with a PPC compared to 0.44% (0.1-2.7) in patients without a PPC ($P < 0.001$). Thirty-nine patients (40%, 95% CI: 30 to 51%) developed one or more PPC in POD 0-4.

Conclusion

This study shows that continuously remotely monitoring of MEWS is highly feasible after major abdominal surgery and frequently detects clinical deterioration in these patients. In the future, randomized controlled trials should evaluate the effect of continuous remote monitoring on the postoperative ward on patient outcome.

Introduction

Up to 40% of the patients undergoing major abdominal surgery develop a complication during their hospital stay causing patient morbidity and mortality.¹⁻³ Such complications are often preceded by deviations in respiratory rate (RR), heart rate (HR) and peripheral oxygen saturation (SpO₂), and deteriorations of vital signs are predictive for cardiopulmonary arrest and transfer to the intensive care unit in medical and perioperative patients.⁴⁻⁹ Early detection of such deteriorations and timely management of developing complications may therefore improve patient outcomes and failure-to-rescue rates.^{4,10-12}

Early warning scores (EWS), such as the National EWS (NEWS) and modified EWS (MEWS), which are composite scores calculated based on vital signs measured by medical personnel on the ward, are increasingly used in hospitals to detect deteriorating patients.^{12,13} Scores above certain cut-off thresholds commonly trigger escalating emergency responses, ranging from increased intensity of patient monitoring to immediate activation of an emergency medical intervention team. However, no high quality evidence has yet confirmed the improvement of patient outcome with early warning and intervention systems in postoperative care.¹³

A plausible explanation for the discrepancy between theoretical benefit and measurable improvement of outcomes is that routine point-check EWS have an intermittent character and known low protocol adherence, limiting their clinical usefulness.^{14,15} Furthermore, continuous monitoring of SpO₂ showed that postoperative hypoxemia was common at the surgical ward but often stayed undetected with routine manual point-check pulse oximetry measurements by nurses.¹⁶

We hypothesize that continuous remote monitoring of vital signs may overcome these limitations and could be useful to detect patients who are clinically deteriorating. In this explorative proof-of-concept study, we studied the feasibility of a remote MEWS (remMEWS) to identify clinical deterioration. Moreover, we evaluated the diagnostic ability of the remMEWS to detect the development of postoperative pulmonary complications (PPCs), as PPCs are particularly frequent after abdominal surgery and significantly contribute to postoperative morbidity.

Methods

Study population

This single center, prospective, observational cohort study was performed in the department of Anaesthesiology of the VU University Medical Center (VUmc, Amsterdam, the Netherlands). The study was approved by the Human Subjects Committee of VUmc (PulMONIC study; 2015.496) and written informed consent was obtained from all participants. Patient inclusion started February 2016 and ended December 2016.

The study included consecutive adult patients (age ≥ 18 years) scheduled for elective major abdominal (e.g. gastro-intestinal, vascular or renal surgery) with a high or intermediate risk for the development of postoperative pulmonary complications according to the Assess Respiratory risk In Surgical patients in CATalonia (ARISCAT) risk score ≥ 26 .¹⁷ Exclusion criteria were trauma and emergency surgery.

Remote monitoring of vital functions

RR, SpO₂ and PR were continuously remotely monitored after surgery upon admission to the ward for a maximum of four consecutive postoperative days (PODs) or until hospital discharge or unexpected intensive care unit admission. In case no research team member was available after late discharge from the post-anaesthesia care unit, the patient was connected to the monitor on the first postoperative day. A dedicated member of the research team attended every patient several times per day to check the correct position of the sensors. The sensors were disconnected and reconnected so patients could shower, bathe and make visits outside the postoperative ward. As this inevitably leads to missing data, a percentage of missing data of less than 30% was considered acceptable. More than 30% missing data was considered evidence for technical issues with the monitoring device or patient noncompliance. Doctors, nurses and investigators were blinded for the measurements obtained by the remote monitor, and remote monitoring data were not used for diagnostic and therapeutic interventions.

Continuous remote monitoring of vital signs was performed using the Radius-7[®] (Masimo Corporation, California, USA). RR was measured through Rainbow[™] acoustic monitoring by a sensor attached to the neck of the patient (Masimo Corporation, California, USA).¹⁸ PR and SpO₂ were measured by the SET[®] measure-through motion and low perfusion pulse oximetry fingertip sensor (Masimo Corporation, California, USA). Sensors were connected to the Radius-7[®] worn around the upper arm.

The Radius-7[®] display was covered with tape to keep patient and hospital personnel blinded for the continuous remote monitored signs. Data for all signs were recorded every two seconds and sent to the Root[®] main dock by a secured Bluetooth connection. The Root was placed near the bed of the patient in a black box, and was daily connected to a dedicated

and secured laptop to transfer the raw data. Data were transferred by an encrypted USB memory stick to a secured desktop computer for further analysis.

The remMEWS was calculated according to the averaged minute values for RR, SpO₂ and PR according to the weighted and aggregated MEWS scoring system (Table 1).⁴ In the validated MEWS protocol a score of ≥ 3 indicates a doctor referral and is therefore a remMEWS score of ≥ 3 was also certainly considered critical since it is based on only 3 parameters compared to 8 parameters in the original MEWS. Normal vital sign values were defined as 9-20 breaths min⁻¹ for RR, >90% for SpO₂, 51-100 beats min⁻¹ for PR.^{4,12}

Table 1. Remote modified early warning score according respiratory rate (RR), peripheral oxygen saturation (SpO₂) and pulse rate (PR) continuously remotely monitored.

Score	3	2	1	0	1	2	3
RR (breaths min ⁻¹)		< 9		9-14	15-20	21-30	> 30
SpO ₂ (%)	< 90						
PR (beats min ⁻¹)		< 40	40-50	51-100	101-110	111-130	> 130

Postoperative pulmonary complications

The incidence of PPCs was retrospectively retrieved by a research team member from the patient data managing system (EPIC). PPCs were assessed using registered vital signs, laboratory results and reported findings by the radiologist of diagnostic imaging studies performed during daily clinical practice. PPCs were defined as previously described: respiratory failure (postoperative PaO₂ < 7.98 kPa in room air, a PaO₂ to FiO₂ ratio < 39.9 kPa, or SpO₂ < 90% that required oxygen therapy), pulmonary infection (respiratory infection requiring antibiotics treatment with at least one additional criterion (new or changed sputum, temperature > 38.3°C, leukocyte count >12.000 mm³, new or changed lung opacities on chest radiography), pleural effusion (blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemi diaphragm), atelectasis (lung opacification with shift of the mediastinum, hilum or hemi diaphragm towards the affected area and compensatory over-inflation in the adjacent non-atelectatic lung), pneumothorax (air in the pleural space with no vascular bed surrounding the visceral pleura) and bronchospasm (newly detected expiratory wheezing treated with bronchodilators).¹⁷

Other study parameters

Patient characteristics were retrieved from the electronic patient file and included age, gender, weight, length and body mass index (BMI), vital signs, preoperative haemoglobin

level, American Society of Anesthesiologists (ASA) classification, the ARISCAT risk score, Metabolic Equivalent of Task score,¹⁹ comorbidities, alcohol use and smoker status. Perioperative parameters were also retrieved and included type of surgery, type of incision, intensive care unit (ICU) referral and total in-hospital length of stay.

Statistical analysis

For this explorative feasibility study, the sample size target was empirically set at 100 patients to detect 20-40 PPCs based on incidence rates of PPCs after major abdominal surgery.¹⁷ The course of continuously remotely monitored vital signs is presented as averaged minute values. RR, SpO₂ and PR were also converted to means per hour values. The incidence of deviating vital signs per hour were reported for patients without PPCs (no PPC group) and patients with PPCs (PPC group) in POD 0-4. The time that a patient had a remMEWS of ≥ 3 was calculated according to average minute values and presented as a percentage of total monitoring time. Data was collected using Castor EDC.²⁰

Statistical analyses were performed using SPSS (Version 22.0, IBM, Armonk, NY). The Kolmogorov-Smirnov test was used to assess the distribution of continuous data. Normally distributed data are presented as mean (standard deviation) and not normally distributed data are expressed as median with quartiles. Categorical data are presented as frequencies and percentages. Patients were divided into groups: patients without PPCs in POD 0-4 (no PPC group) and the patients with ≥ 1 PPCs in POD 0-4 (PPC group). Categorical data are presented as frequencies and percentages, including their 95% confidence intervals. Data were compared between groups using a Student's T-test, Mann-Whitney U test or Chi square test as appropriate. A two-tailed P-value of <0.05 was considered significant.

The diagnostic ability of remote monitoring on POD 1 to detect patients who are developing a PCC and where diagnosed with a PPC on POD2, was evaluated using receiver operating characteristics (ROC) curves. Herein, the relative cumulative duration of measurements of deviated vital signs, or the relative duration of a remMEWS score of ≥ 3 , (both expressed as percentage of total monitoring time on POD 1), rather than single observations of deviated vital signs, were considered as potential indicator of a PPC. This choice was made because single, short deviations are not uncommon during continuous monitoring and may often represent artifacts rather than true deviations. In contrast, consistent measurements of deviations over a longer time period likely indicate a patient-related problem. Cut-points for percentage monitoring time with deviating vital signs were chosen applying the Youden index.²¹

Results

Patient characteristics and technical feasibility of remote monitoring

Overall, 112 eligible patients were included in the study, of whom 8 patients were excluded due to withdrawal of informed consent or cancelled surgery (Figure 1). Patients were further excluded when their total monitoring time was below 8 hours (n=4). Of the remaining 100 patients, missing data comprised more than 30% in 3 patients, who were excluded from further analysis. Main reasons for missing data were loosened sensors and technical problems with the Root device. Overall, remote monitoring was successfully performed in 97 out of 100 eligible patients (97%, 95% CI: 91 to 99%), indicating technical feasibility of remotely monitoring the vast majority of patients on the postoperative ward after abdominal surgery.

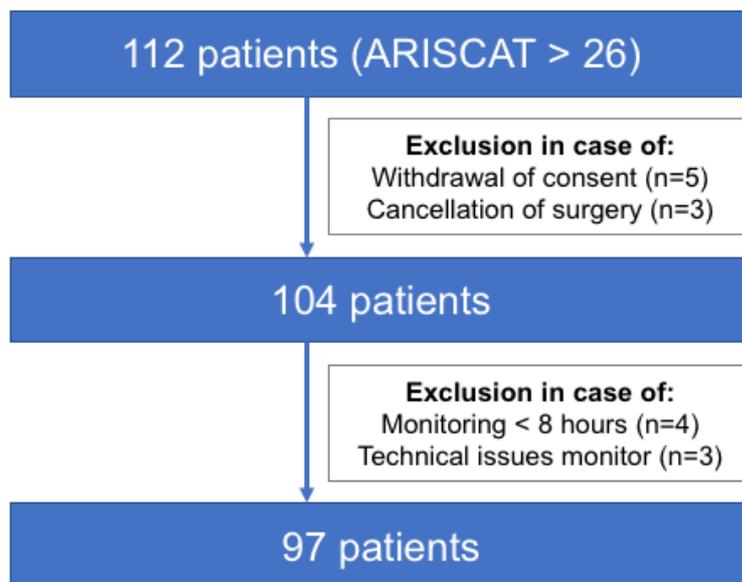


Figure 1. Study flow chart

Of 97 patients in whom monitoring was successful and who entered in the final data analysis, continuous remote monitoring started in 23 patients on POD 0, and in 74 patients on the early morning of POD 1. The total number of patients was 97, 90, 72 and 41 for POD 1, POD 2, POD 3 and POD 4, respectively.

Table 2 shows the preoperative patient characteristics, further stratified in the patients without a PPC in POD 0-4 (no PPC group) and the patients with ≥ 1 PPCs in POD 0-4 (PPC group). Patients in the PPC group were not significantly older (68 [27-84] vs. 63 [19-86]; $P=0.05$) but had a higher BMI (27.3 (4.7) vs. 25.0 (3.6); $P=0.01$) compared to patients in the

no PPC group. Median ARISCAT scores, preoperative SpO₂ and haemoglobin levels were not significantly different between groups.

Table 2. Preoperative patients characteristics grouped for patients without and with a postoperative pulmonary complication (PPC).

Variable	All patients	No PPC	PPC	P-value
N	97	58 (59.8%)	39 (40.2%)	
Age (years [range])	66 [19-86]	63 [19-86]	68 [27-84]	0.05
Males	58%	57%	61%	0.64
Median ASA classification	2 (2-3)	2 (2-3)	2 (2-3)	0.02 *
Body Mass Index (kg m⁻²)	26.1 (4.3)	25.0 (3.6)	27.3 (4.7)	0.01 *
Smoking	58%	52%	65%	0.22
Surgical procedure				
<i>Gastrointestinal</i>		34%	52%	0.07
<i>Hepatobiliary</i>		43%	39%	0.64
<i>Nephrology</i>		17%	2%	0.02 *
<i>Urology</i>		2%	7%	0.22
<i>Other</i>		4%	0%	0.06
Endoscopic procedures (%)	28%	26%	30%	0.73
Median ARISCAT score	41 (35-49)	41 (34-47)	41 (38-49)	0.33
Preoperative SpO₂ (%)	97 (3.0)	97 (3.0)	97 (3.0)	0.77
Haemoglobin levels (mmol L⁻¹)	8.1 (0.9)	8.1 (0.9)	8.2 (0.9)	0.63
COPD	16%	11%	20%	0.20
OSAS	8%	4%	14%	0.08

ASA = American Society of Anesthesiologists score; COPD = chronic obstructive pulmonary disease; OSAS = obstructive sleep apnea syndrome. Data are presented as mean (standard deviation), median with interquartile range or frequencies. * P<0.05

Thirty-nine out of 97 patients (40%, 95% CI: 30 to 51%) developed one or more PPCs during POD 0-4. Respiratory failure, atelectasis and pleural effusion were the most prevalent PPCs

among the study population. Table 3 shows the incidence of PPCs during the postoperative study period. Hospital length of stay was longer in the PPC group compared to the no PPC group, respectively (12 ± 2 days vs. 9 ± 1 days; $P=0.001$).

Table 3. Incidence of postoperative pulmonary complications (PPCs).

Day	N	≥ 1 PPC	Respirat ory failure	Respirat ory infection	Atelec tasis	Pleural effusion	Pneumo -thorax	Broncho- spasm
Day 0	97	N=22 (23%)	13	0	5	8	4	2
POD 1	97	N=21 (22%)	14	0	3	2	2	1
POD 2	90	N=7 (7%)	5	0	2	2	0	0
POD 3	71	N=9 (13%)	3	0	6	4	2	1
POD 4	40	N=0	0	0	0	0	0	0

Day 0 = day of surgery; POD = postoperative day.

Postoperative feasibility of remote monitoring to track the course of RR, SpO₂ and PR.

Figure 2 shows the course of the continuously remotely monitored RR (panel A), SpO₂ (panel B) and PR (panel C) for all patients in the no PPC and the PPC group during POD 0-4. Visual inspection of the graphs suggest that the RR and PR tended to be higher in patients with PCCs, while the SpO₂ tended to be lower in the PCC group compared to patients in the no PCC group. Vital signs changed during day and night time, with the lowest values for respiratory rate, SpO₂ and pulse rate during the night (10:00 p.m. to 05:00 a.m.). These observations suggest the feasibility of remote monitoring to track changes of vital signs over time.

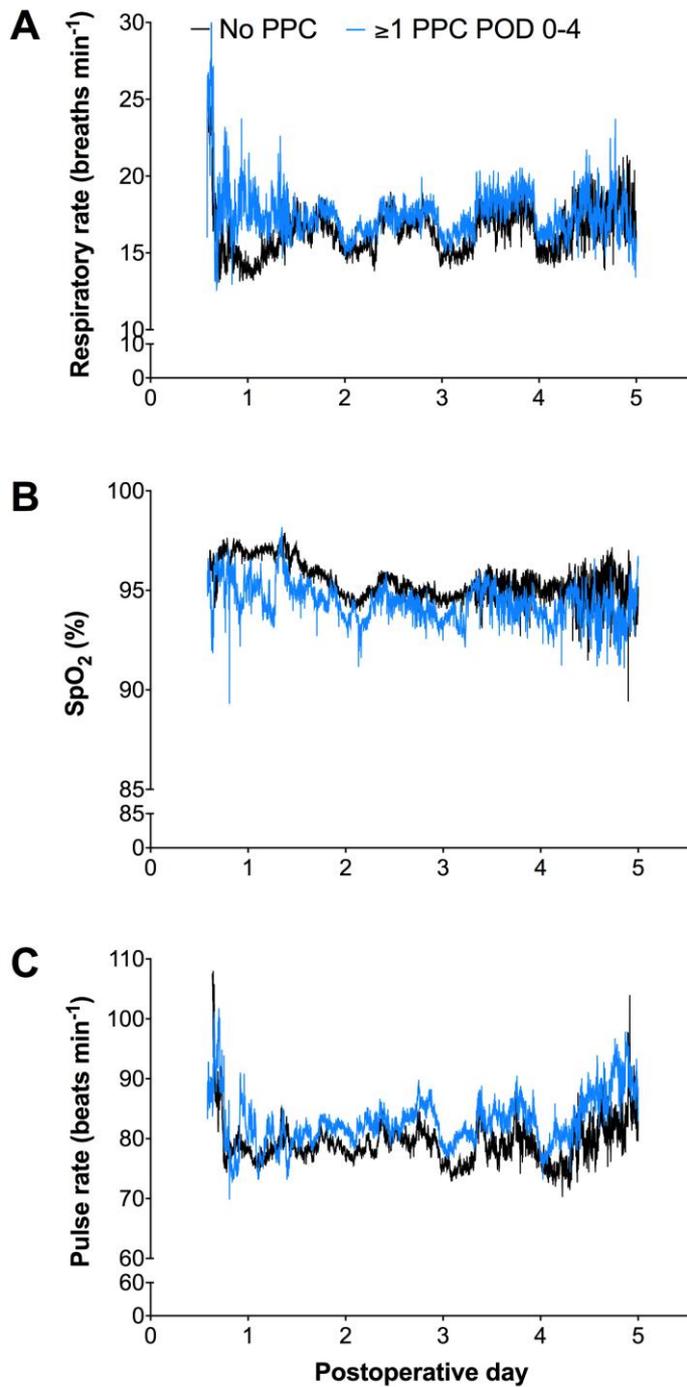


Figure 2. The course of the continuously remotely monitored respiratory rate (panel A), peripheral oxygen saturation (SpO₂) (panel B) and pulse rate (panel C) over the first 4 postoperative days (PODs) for patients without (black line (n=53)) and with (blue line (n=44)) a postoperative pulmonary complication (PPC) in POD 0-4. Graphs are based on average minute values. The total number of patients was 97, 90, 72 and 41 for POD 1, POD 2, POD 3 and POD 4, respectively.

Figure 3 shows the relative time (percentage of total monitoring time) that the RR (panel A), SpO₂ (panel B) and PR (panel C) deviated from normal values. The median relative time that patients showed a RR >21 breaths per minute or PR >111 beats per minute was not significantly different between patients in the PPC and the no PPC group. However, patients in the PCC group more frequently showed an SpO₂ on POD1 of <95% (55% (23-68) vs. 18% (3-54); P=0.004), <90% (2.9% (0-15.3) vs. 0.17% (0-1.5); P=0.03) and <85% (0% (0-2.9) vs. 0% (0-0.1); P=0.04) compared to the no PPC group. The differences in SpO₂ values between patients with or without a PPC continued over the subsequent PODs.

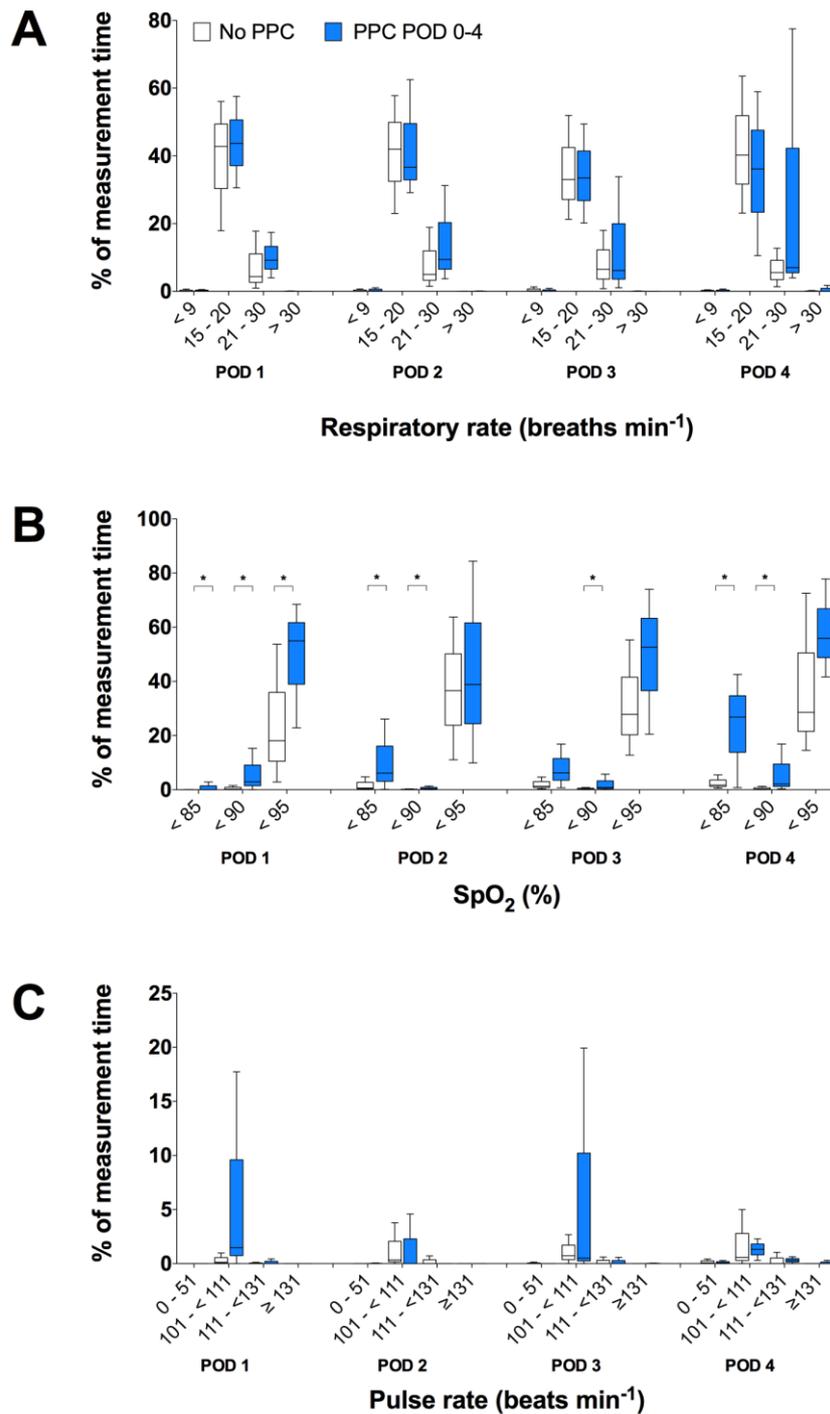


Figure 3. Incidences of deviating respiratory rates (A), peripheral oxygen saturation levels (B) and pulse rates (C) per postoperative day (POD) and grouped for patients without and with postoperative pulmonary complications (PPC) in POD 0-4. Data represent median with interquartile range and were analyzed by a Mann-Whitney-U tests. The total number of patients was 97, 90, 72 and 41 for POD 1, POD 2, POD 3 and POD 4, respectively. * P<0.05.

Remote MEWS

Figure 4 represents the median percentage time per patient that a remMEWS ≥ 3 was scored in the no PPC and the PPC group, respectively, in POD 0-4. In the PPC group, patients more frequently had a remMEWS ≥ 3 on POD1 compared to the no PPC group (11.6% (0.8-20.8) vs. 0.44% (0.1-2.7); $P < 0.001$).

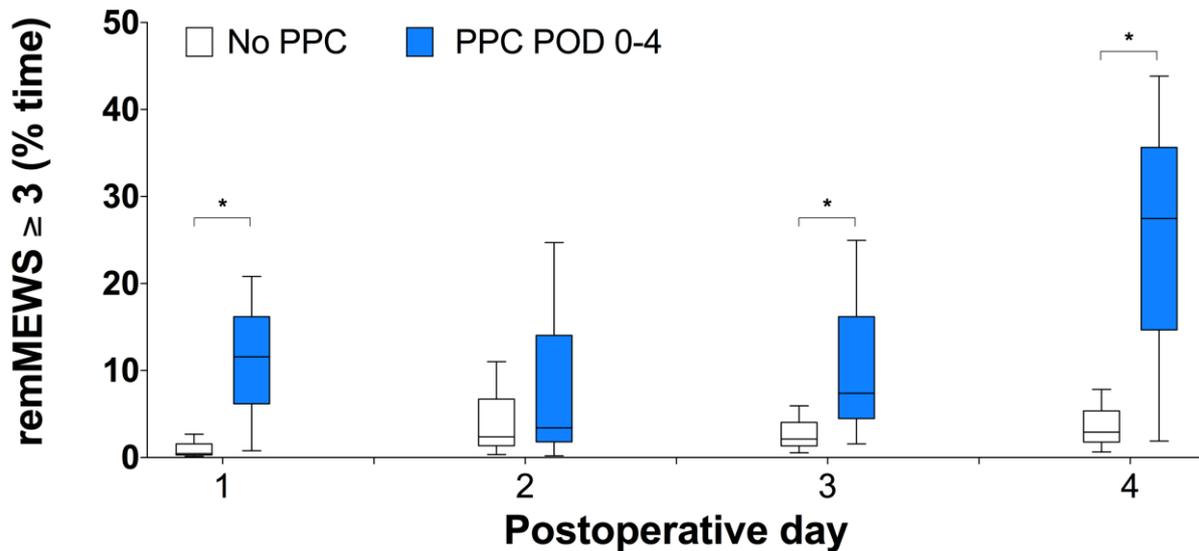


Figure 4. The median percentage time of a remote modified early warning score ≥ 3 in patients on different postoperative days (POD) stratified for the occurrence of a postoperative pulmonary complication (PPC). Data represent median with interquartile range and were analyzed by a Mann-Whitney-U tests. The total number of patients was 97, 90, 72 and 41 for POD 1, POD 2, POD 3 and POD 4, respectively. * $P < 0.05$.

Diagnostic ability of deviating vital signs for PPCs

Table 4 shows the AUC values and Figure 5 the ROC curves of the diagnostic ability of vital signs and remMEWS on POD1 for the development of new PPCs on POD2. Percentage time with deviating vital signs showed subsequent diagnostic ability: RR > 21 breaths per minute was found to have fair diagnosing ability for new PPCs diagnosed on POD 2 (AUC=0.79 [95% CI 0.68 to 0.91]) and a cut-point at 12,5% yielded a sensitivity of 86%, a specificity of 73%, a negative predictive value (NPV) of 0.98 and a positive predictive value (PPV) of 0.20. RemMEWS ≥ 3 and SpO₂ $< 90\%$ were found to have moderate diagnostic ability (AUC=0.66 [95% CI 0.43 to 0.89] and a cut-point at 1.4% yielded a sensitivity of 71%, specificity of 59%, NPV of 0.96, PPV of 0.12) and (AUC=0.65 [95% CI 0.46 to 0.84] and a cut-point at 0.3% yielded a sensitivity of 86%, specificity of 53%, NPV of 0.98 and PPV of 0.13) respectively. Time percentage PR > 100 beats per minute was found to have poor

diagnostic ability (AUC 0.52 [0.27-0.77] cut-point 0.1% yielded a sensitivity of 57%, specificity of 57%, NPV of 0.93 and PPV of 0.08).

Table 4. Area under the curve and subsequent sensitivity, specificity, negative and positive predictive value at the cut-point of continuously remotely monitored vital signs on postoperative day 1 for diagnostic ability for new postoperative pulmonary complications on postoperative day 2.

Parameter	AUC [CI]	Sensitivity (%)	Specificity (%)	NPV	PPV
RR>21 (breaths min⁻¹)	0.79 [0.68-0.91]	86	73	0,98	0,20
RR<9 (breaths min⁻¹)	0.71 [0.56-0.87]	86	55	0,98	0,13
SpO₂<90%	0.65 [0.46-0.84]	86	53	0,98	0,13
PR>100 (beats min⁻¹)	0.52 [0.27-0.77]	47	57	0,93	0,08
remMEWS≥3	0.66 [0.43-0.89]	71	59	0,96	0,12

*AUC = area under the curve, NPV = negative predictive value, PPV = positive predictive value, RR = respiratory rate, SpO₂ = peripheral oxygen saturation, PR = pulse rate, remMEWS = remote modified early warning score. * P<0.05*

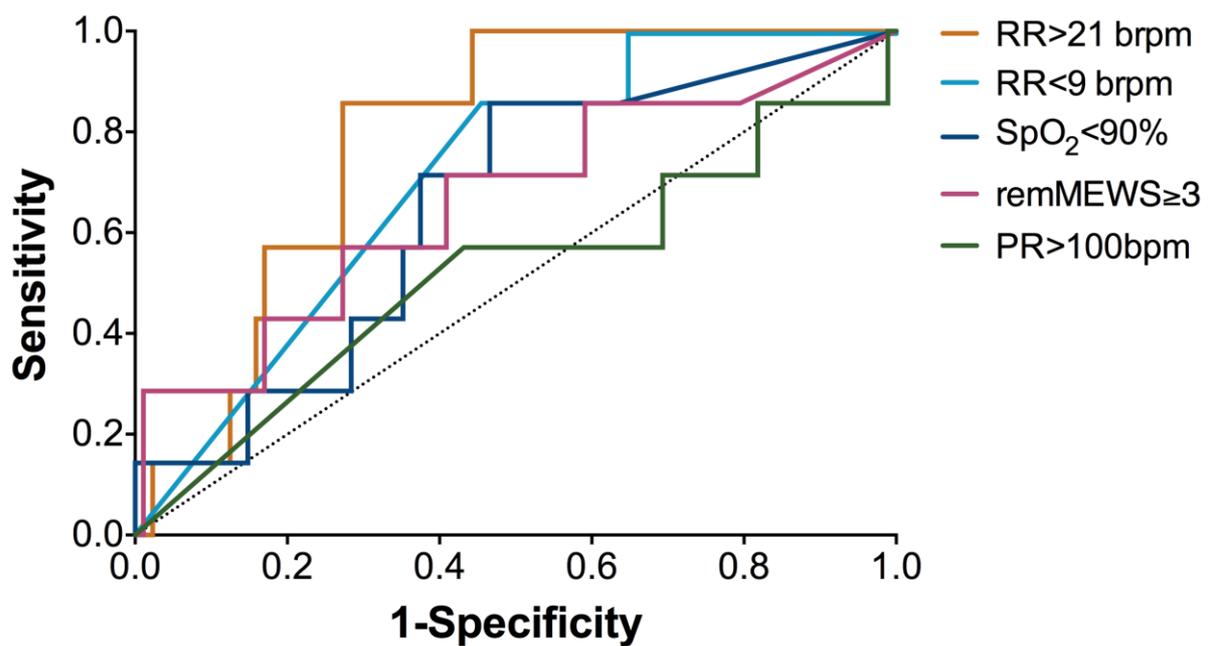


Figure 5. Receiver operating characteristic for diagnostic ability of deviating vital signs and remote modified early warning score on postoperative day 1 for the development of postoperative pulmonary complications on postoperative day 2.

Legend: RR >21 breaths per minute (AUC=0.79 [95% CI 0.68 to 0.91] cut-point a 12,5% yielded sensitivity of 86%, specificity of 73%, NPV of 0.98 and PPV of 0.20). SpO₂<90% (AUC=0.65 [95% CI 0.46 to 0.84] and a cut-point at 0.3% yielded sensitivity 86%, specificity 53%, NPV 0.98 and PPV 0.13) and remMEWS≥3 (AUC=0.66 [95% CI 0.43-0.89] and a cut-point at 1.4% yielded sensitivity 71%, specificity 59%, NPV 0.96 and PPV 0.12). PR >100 beats per minute (AUC 0.52 [95% CI 0.27-0.77] and a cut-point at 0.1% yielded sensitivity 47%, specificity 57%, NPV 0.93 and PPV 0.08)

Discussion

This study shows the feasibility of continuous remote monitoring MEWS to detect patients who are clinically deteriorating on the postoperative ward after abdominal surgery. Furthermore, the remote MEWS detected differences between patients who developed a PPC compared to patients who did not developed a PPC, and may be useful to detect PPCs. Our findings suggest that implementation of continuous remote monitoring on the postoperative ward after abdominal surgery might result in more frequent detection of patients who are deteriorating, and could be useful to trigger emergency responses according to the MEWS protocol.

An early warning score is the afferent limb of a early warning and intervention system, which has been introduced in many institutions for the early detection clinical deterioration to prevent adverse events.²² A recent systematic review did not show that implementation of early warning and intervention system effectively reduce failure-to-rescue rates, and this might be explained by the lack of standardization of the early warning system and its use in different populations.²² Another possible reason for the limited value of early warning systems in the prevention of adverse events is the intermittent measurement of the score by attending nurses. Furthermore, previous research showed that monitoring frequency is not adhered to in 81% of patients unexpectedly admitted to the ICU from the general ward and in 42% of the cases the doctors were not notified about patients' condition.^{23,24}

In this context, remote continuous monitoring of vital signs may overcome some of the shortcomings of current point-check monitoring by medical personnel on the ward. Continuously measured vital signs could be used to automatically calculate a warning score and to activate medical response teams. A recent study in general ward patients suggests benefit of an implementation of continuous monitoring with an automated advisory and notification system.²⁵ However, similar data on remote warning scores in surgical patients are lacking.

Previous studies have examined the role of non-remote continuous monitoring of distinct vital paramters on surgical wards. Sun et al. reported a high incidence of hypoxemia in a general non-cardiac surgery population.¹⁶ In agreement with these findings, we found that more than 50% of the patients developing PPCs had an event of reduced oxygen levels ($SpO_2 < 95\%$), and some patients even encountered oxygen levels below 85%.¹⁶ Previous research also showed that continuous SpO_2 monitoring contributed to a reduction in intensive care admissions for treatment of PPCs after cardiac and thoracic surgery,²⁶ suggesting that SpO_2 should be an integral component of a postoperative remote warning score.

Decreases or increases in RR have both been described as predictors for complications, as they might be early signs of hypoxemia, hypercapnia and metabolic acidosis.²⁷ Our findings seem to indicate that the diagnostic ability of RR might have a higher sensitivity and specificity to detect for PPCs compared with SpO₂. However, confidence intervals of both AUC values were wide and therefore statistical analysis of significant difference is not indicated.

Continuous monitoring of vital signs will most likely increase the detection of clinical deterioration in current practice and therefore will require doctor referral more frequently. Although the performance of an EWS is mostly described in terms of the AUROC, the clinical practical clinical value is better expressed as the nonevent rate (proportion of early warning alarm signals that are not followed by an adverse event) and the missed event rate (proportion of adverse events not detected by an early warning alarm).¹³ The nonevent rate depends more on the adverse event rate than on the discriminatory power of the EWS.¹³ Therefore, we do think that the EWS could also be helpful in identifying patients who may benefit from increased attention from medical personnel which is not directly measured in prevention of adverse events. Improvement of patient outcome should possibly be measured in soft endpoints: length of hospital stay or experienced quality of life. This could decrease the current very high nonevent rate of current EWS found in the largest validation cohorts in postoperative patients (82-94% of critical MEWS were not followed by an adverse event in the postoperative patients).¹³

The pathogenesis of PPCs depends on patient-related risk factors, the type of surgery performed and anaesthetic technique, including mechanical ventilation and fluid therapy.^{28,29} In a cohort of 293 postoperative patients with respiratory failure after abdominal surgery, atelectasis was the main cause of respiratory failure in 64% of the patients, compared to 32% in our study.³⁰ Atelectasis might be indirectly caused by diaphragm dysfunction due to the impact of abdominal surgery, and might be furthermore underreported in our study which used imaging techniques just on indication according to daily clinical practice.^{31,32}

Limitations of our study were the possible biases. Patients who suffered from complications and on the other hand patients who recovered soon, more frequently were disturbed by the sensors and decided to stop the study. The used neck sensor for continuous remote monitoring of RR, which was frequently experienced as uncomfortable by participating patients. Finally, we encountered some technical issues with the monitoring device, for which monitoring was not possible in 3 patients. Strengths of the current study were its prospective

cohort design, and attending physicians, nurses and participants were blinded for the monitoring data.

Monitoring by itself is not therapeutic and should be followed by adequate actions and treatments, including the initiation of pain management, goal directed fluid therapy, restrictive blood transfusion management, physiotherapy, O₂ suppletion, treatment of infections and respiratory support. Strategies aimed to detect postoperative respiratory failure early may contribute in avoiding reintubation and invasive mechanical ventilation which are associated with higher mortality and increased health care utilization.³³ Among patients with hypoxemic respiratory failure following abdominal surgery, the use of non-invasive ventilation (NIV) compared with standard oxygen therapy has shown to reduce the risk of tracheal reintubation within 7 days, and support the use of NIV in this setting.³⁴ Other studies showed benefits in treatment of hypoxemic failure in nonsurgical patients with high-flow oxygen cannulas.³⁵ In contrast, in a recent study among patients undergoing major abdominal surgery, early preventive application of high-flow nasal cannula oxygen therapy after extubation did not result in improved pulmonary outcomes compared with standard oxygen therapy.³⁶ More studies in large, multicenter settings are required to proof the benefits of NIV or high-flow oxygen cannulas in the post-operative setting.

Our study suggests that continuous remote monitoring on the postoperative ward is highly feasible and may be useful in the early detection of patients who are clinically deteriorating after abdominal surgery. However, future research is needed. Continuous remote monitoring should not only detect clinical deterioration but should also contribute to improved outcome. Whether continuous remote monitoring will limit the the impact of postoperative complications and improve patient outcome can only be determined by large randomized controlled trials since firm evidence is still lacking.³⁷

References

1. Stens J, Hering JP, van der Hoeven CWP et al. The added value of cardiac index and pulse pressure variation monitoring to mean arterial pressure-guided volume therapy in moderate-risk abdominal surgery (COGUIDE): a pragmatic multicentre randomised controlled trial. *Anaesthesia* 2017; 72:1078-1087.
2. Cannesson M, Ramsingh D, Rinehart J et al. Perioperative goal-directed therapy and postoperative outcomes in patients undergoing high-risk abdominal surgery: a historical-prospective, comparative effectiveness study. *Crit Care* 2015; 19:261.
3. Pestaña D, Espinosa E, Eden A et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). *Anesth Analg* 2014; 119 : 579-87.
4. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. *Quarterly Journal of Medicine* 2001; 94:521-526.
5. Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation* 2004; 62:137-41.
6. Kyriacos U, Jelsma J, Jordan S. Record review to explore the adequacy of post-operative vital signs monitoring using a local modified early warning score (mews) chart to evaluate outcomes. *PLoS One*. 2014; 31:9
7. McGain F, Cretikos MA, Jones D et al. Documentation of clinical review and vital signs after major surgery. *Medical journal of Australia* 2008; 189:380-383.
8. Cutbertson BH, Boroujerde M, McKie L, Aucott L, Prescott G. Can physiological variables and early warning scoring systems allow early recognition of the deteriorating surgical patient? *Crit Care Med* 2007; 35:402-409.
9. Fieselmann JF, Hendryx MS, Helms CM, Wakefield DS. Respiratory rate predicts cardiopulmonary arrest for internal medicine patients. *J Gen Intern Med* 1993; 8 : 354-60.
10. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. *Ann Surg* 2009; 250:1029-34.
11. Ghaferi AA, Dimick JB. Importance of teamwork, communication and culture on failure-to-rescue in the elderly. *Br J Surg* 2016; 103:e47-51
12. van Galen LS, Dijkstra CC, Ludikhuizen J, Kramer MH, Nanayakkara PW. A Protocolised Once a Day Modified Early Warning Score (MEWS) Measurement Is an Appropriate Screening Tool for Major Adverse Events in a General Hospital Population. *PLoS One*. 2016 ;5:11.
13. de Grooth H-J, Girbes AR, Loer SA. Early warning scores in the perioperative period: applications and clinical operating characteristics. *Current Opinion in Anesthesiology*: 31:732-738
14. Hollis RH, Graham LA, Lazenby JP, et al. A Role for the Early Warning Score in Early Identification of Critical Postoperative Complications. *Ann Surg* 2016 ; 263 : 918-923.

15. Van Galen LS, Struik PW, Driesen BE et al. Delayed Recognition of Deterioration of Patients in General Wards Is Mostly Caused by Human Related Monitoring Failures: A Root Cause Analysis of Unplanned ICU Admissions. *PLoS One* 2016; 11 : e0161393.
16. Sun Z, Sessler DI, Dalton JE, Devereaux PJ, Shahinyan A, Naylor AJ, Hutcherson MT, Finnegan PS, Tandon V, Darvish-Kazem S, Chugh S, Alzayer H, Kurz A. Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. *Anesth Analg*. 2015; 121 : 709-15.
17. Canet J, Gallart L, Gomar C et al. ARISCAT Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010 ; 113 : 1338-50.
18. Ramsay MA, Usman M, Lagow E, Mendoza M, Untalan E, De Vol E. The accuracy, precision and reliability of measuring ventilatory rate and detecting ventilatory pause by rainbow acoustic monitoring and capnometry. *Anesth Analg* 2013; 117 : 69-75.
19. Ainsworth BE, Haskell WL, Herrmann SD et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011; 43 : 1575-81.
20. Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2018
21. Vetter TR, Schober P, Mascha EJ. Diagnostic Testing and Decision-Making: Beauty Is Not Just in the Eye of the Beholder. *Anesth Analg*. 2018; 127 :1085-1091.
22. Ochroch EA, Russell MW, Hanson WC et al. The Impact of Continuous Pulse Oximetry Monitoring on Intensive Care Unit Admissions from a Postsurgical Care Floor. *Anesth Analg* 2006; 102 : 868-875.
23. Cretikos MA, Bellomo R, Hillman K, Chen J, Finfer S, Flabouris A. Respiratory rate: The neglected vital sign. *Med J Austral* 2008; 188 : 657-659.
24. Alam N, Hobbelink EL, van Tienhoeven AJ, van de Ven PJ, Jansma EP, Nanayakkara PWB. The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. *Resuscitation* 2014; 85 : 587-594.
25. Subbe CP, Duller B, Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Crit Care* 2017; 21 : 52.
26. Petersen JA. Early warning score challenges and opportunities in the care of deteriorating patients. *Dan Med J*. 2018; 65 : B5439.
27. Petersen JA, Mackel R, Antonsen K, Rasmussen LS. Serious adverse events in a hospital using early warning score – What went wrong? *Resuscitation* 2014; 85 : 1699-1703
28. Arozullah A, Khuri S, Henderson W, et al. Development and Validation of a Multifactorial Risk Index for Predicting Postoperative Pneumonia after Major Noncardiac Surgery. *Ann Intern Med* 2001; 135 : 847.
29. Simonneau G, Vivien A, Sartene R et al. Diaphragm dysfunction induced by upper abdominal surgery. Role of postoperative pain. *Am Rev Respir Dis* 1983; 128 : 899-903.
30. Jaber S, Lescot T, Futier E et al. Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. *JAMA* 2016; 315 : 1345-53.

31. Hedenstierna G, Edmark L. Mechanisms of atelectasis in the perioperative period. *Best Pract Res Clin Anaesth* 2010; 24 : 157-69.
32. Ali J, Weisel RD, Layug AB, Kripke BJ, Hechtman HB. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg* 1974; 128 :376-82.
33. Serpa Neto A, Hemmes SN, Barbas CS et al; PROVE Network Investigators. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med*. 2014; 2 : 1007-1015.
34. Jaber S, Lescot T, Futier E et al.; NIVAS Study Group. Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. *JAMA*. 2016; 315 : 1345-53.
35. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015; 372 : 2185-2196.
36. Futier E, Paugam-Burtz C, Godet T et al. OPERA study investigators. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). *Intensive Care Med* 2016; 42 : 1888.
37. Boer C, Touw HR, Loer SA. Postanesthesia care by remote monitoring of vital signs in surgical wards. *Curr Opin Anaesthesiol* 2018; 31:716-722.

Chapter 4

Continuous remote monitoring to detect critical early warning scores after intensive care unit discharge: an explorative observational study

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Submitted

Summary

Patients discharged from an ICU face a decrease in intensity of vital signs monitoring. Due to the routine and intermittent character of the modified early warning score (MEWS), clinical deterioration can be missed or detected too late in these patients. The primary aim of this study was to report the incidence of critical MEWS detected with continuous remote monitoring on a general ward in patients after ICU discharge. Secondly, we compared the detected critical MEWS episodes with continuous remote monitoring (≥ 3 for ≥ 1 hour) with detected MEWS according routine point-check assessments by nurses according daily clinical practice.

This exploratory study included adult patients discharged from an ICU or medium care unit to the general ward. The respiratory rate, peripheral oxygen saturation and pulse rate were continuously remotely monitored for four days. A remote MEWS was calculated according to these vital signs. The detected critical remote MEWS episodes were compared with the detected MEWS.

Forty-four patients were included in this study. The most common reason for ICU admission was respiratory failure (31.8%) and median duration of ICU stay was 4.0 (1.8-8.5) days. Critical remMEWS was detected in 10.2% (2.5-23.6) of total monitored time and 21 patients (47.7%) developed a total of 28 critical remote MEWS episodes. Seventeen out of 28 critical remote MEWS episodes (60.7%) were not detected by MEWS and in 5 out 28 critical remote MEWS episodes (18%) the MEWS detected a critical MEWS with a delay of >2 hours.

To conclude, this explorative observational study shows that continuous remote monitoring frequently detects critical remote MEWS episodes at the general ward in patients after ICU discharge, which were not detected in more than half of these episodes by current MEWS assessments.

Introduction

Patients discharged from an ICU to a general ward face a decrease in vital signs monitoring. However, (re)-admission to the ICU and cardiac arrest, are mostly preceded by detectable changes in vital parameters in the hours before these events.^{1,2} Early warning and intervention systems have been introduced to systematically detect and manage clinically deteriorating patients on the ward to prevent patient morbidity and mortality. A recent meta-analysis showed that early warning and intervention system implementation is indeed associated with a reduction in hospital mortality and cardiopulmonary arrest.³ The early recognition of patients with vital signs in jeopardy seems desirable and the use early warning systems (EWS) is therefore still propagated.⁴

The modified early warning score (MEWS) is a validated screening tool to detect clinical deterioration in patients within an early warning and intervention system.^{5,6} MEWS was critical, defined as a score of ≥ 3 , in up to 80% of the patients 48 hours prior to unexpected ICU admission and readmission to the ICU occurred in up to 9.6% of post-ICU patients.⁷⁻⁹ Limitations of the current MEWS practice on the ward are the point-check and routine character of this bedside monitoring tool: checks are done intermittently at a prefixed moment. Furthermore, in a single centre retrospective study, the protocol adherence and correct calculation of the MEWS were found to be relatively low: 89% and 71%, respectively.⁶ In general, half of the unplanned ICU admissions from the general ward were related to failures in monitoring patients adequately.¹⁰ To overcome these limitations and current inadequacies in patient monitoring, recently introduced continuous remote monitoring strategies enable continuous vital sign monitoring at the general ward beyond the ICU.

The primary aim of this exploratory study was to report the incidence of critical MEWS episodes detection using continuous remote monitoring (remMEWS) in patients admitted to the ward after ICU or medium care unit (MCU) discharge. Secondly, we compared the detection of critical remMEWS episodes with the detection of critical MEWS with routine time point-check MEWS assessments by the nurses according to daily clinical practice.

Methods

Study design and patient population

This single centre, prospective, observational cohort study was conducted in the Amsterdam UMC, VU University Medical Centre, Amsterdam, The Netherlands. The Amsterdam UMC, VU University Medical Centre, is an academic 733-bedded medical centre with 18-22 ICU beds and 8-10 MCU beds. The study was approved by the Human Subjects Committee of VUmc (METc 2016.201), and written informed consent was obtained from all participants. Patient inclusion started October 2016 and ended March 2017. The study included consecutive patients (age > 18 years) with a minimum ICU stay of 1 day. ICU stay included MCU stay as well. Exclusion criteria were ICU discharge after elective surgery, delirium, inability to wear a neck sensor (e.g. patients wearing a neck brace) and/or restricted policy concerning readmission to the ICU for medical reasons.

Continuous remote monitoring

Respiratory rate (RR), peripheral oxygen saturation (SpO₂) and pulse rate (PR) were continuously and remotely monitored. Monitoring started on the day of ICU discharge to the ward (post ICU day (PICUD) 0) and lasted for a total maximum of four consecutive days or until unexpected ICU readmission. Doctors, nurses and investigators were blinded for the measurements obtained by the remote monitor. Furthermore, continuous remote monitored data were not used to initiate diagnostic and therapeutic interventions. Continuous monitoring of the vital signs was performed with a remote wireless monitor, the Radius-7® (Masimo Corporation, California, USA). RR was measured through Rainbow™ acoustic monitoring by a sensor placed lateral to the cricoid cartilage in the neck of the patient (Masimo Corporation, California, USA). PR and SpO₂ were measured by the SET® measure-through motion and low perfusion pulse oximetry fingertip sensor (Masimo Corporation, California, USA). Sensors were connected to the Radius-7® worn around the upper arm. A dedicated member of the research team attended every patient several times per day to check the correct position of the sensors. The sensors were only disconnected and reconnected so patients could shower or bathe.

The Radius-7® transmitted the collected data every 2 seconds to the Root® main dock by a secured Bluetooth connection. According agreements with the Human Subjects Committee of VUmc Wifi was not used to transfer data. The Root was placed near the bed of the patient in a black box, and was daily connected to a dedicated and secured laptop to transfer the raw data. Data were daily transferred by an encrypted USB memory stick to a secured desktop computer for further analysis.

Remote modified early warning score

remMEWS was defined as the MEWS according three weighted and aggregated continuously remotely monitored parameters: RR, SpO₂ and PR (Table 1).^{5,6} Averaged minute values of RR, SpO₂ and PR were used to calculate remMEWS per minute. Critical remMEWS episodes were defined as remMEWS ≥3 for ≥1 hour.

Modified early warning score

According to the hospital wide protocol 3 times a day (every morning, afternoon and evening) nurses determined the MEWS using vital parameter measurements at the bedside recorded in the electronic system (Table 1). MEWS measurements could be repeated according to the protocol any time during the day on indication by doctors. Score values were also calculated retrospectively based on the measurements taken by the nurses for each time point at which one or more vital signs were recorded. Missing parameters were considered normal.

Table 1. Scoring system of the remote MEWS and MEWS. Remote MEWS is only scored according the first three parameters; continuously and remotely monitored respiratory rate, peripheral oxygen saturation and pulse rate. MEWS is scored according all eight parameters.

Score	3	2	1	0	1	2	3
RR (breaths min⁻¹)		<9		9-14	15-20	21-30	>30
SpO₂ (with therapy) (%)	<90						
PR (beats min⁻¹)		<40	40-50	51-100	101-110	111-130	>130
Systolic blood pressure (mmHg)	<70	70-80	81-100	101-200			
Temperature (°C)		<35.1	35.1-36.5	36.5-37.5		>37.5	
Consciousness				A	V	P	U
Urine production				<75mL in the last 4 hours			
Nurse being worried				1 point			

RR = respiratory rate; SpO₂ = peripheral oxygen saturation; PR = pulse rate; A=Alert; V=Response to verbal stimulation; U=Unresponsive

Data collection

Patient characteristics were retrieved from the electronic patient file and included age, gender, co-morbidities, reason for admission to ICU/MCU and Sequential Organ Failure Assessment (SOFA) score (on admission and on discharge). Data regarding follow-up including length of stay and the occurrence of complications (readmission to the ICU/MCU,

unexpected re-admission to the hospital within 30 days and mortality) were also retrieved from the electronic patient file. Data was collected using Castor EDC.¹¹

Statistical analysis

Within a 6 months time frame, in which continuous remote monitoring devices were available to perform this exploratory study, we wanted to include 50 patients in our exploratory observational trail, to find 2-5 patients to be re-admitted to the ICU according to known re-admission rates.⁸ Continuous monitoring could only be done during the presence hours of the researcher and consecutive patients were included. Statistical analysis was performed using SPSS (Version 22.0, IBM, Armonk, NY). This study reports the course of continuously remotely monitored vital signs and remMEWS. Data are presented as averaged minute values of all patients. The percentage of the total monitoring time detecting deviating vital signs (RR >30 per minute, SpO₂ <90% and PR > 100 per minute) and critical remMEWS episodes (remMEWS ≥ 3 of ≥ 1 hour) were calculated during the study period. This explorative study was too small and not designed to determine the impact of a critical MEWS on patient outcome. Diagnostic accuracy of percentage of total monitoring time with deviating vital signs and critical remMEWS were calculated for prolonged length of hospital stay, defined as >14 days. The Kolmogorov-Smirnov test was used to test for normality. Normally distributed data were presented as mean ± standard deviation and non-parametric data were expressed as median with interquartile range or frequencies. Data were analyzed using a Student's T-test, Mann-Whitney U test or Chi square test when appropriate. A P-value of <0.05 was considered significant.

Results

Patient characteristics

Eighty-eight patients were assessed for eligibility and 45 patients gave informed consent to participate in the study (Figure 1). One patient was lost to follow-up, because the monitoring duration was less than 8 hours due to technical device problems. Forty-four patients were included for the final data analysis. Table 2 shows the patient characteristics. The mean age was 63 (13) years and 66 % were men. The most common reason for admission to the ICU was respiratory failure, followed by traumatic injury. The median length of ICU stay was 4.0 (1.8-8.5 [1-126]). SOFA scores on ICU admission and discharge were 10 (7-12 [3-17]) and 5 (4-7 [3-10]) respectively.

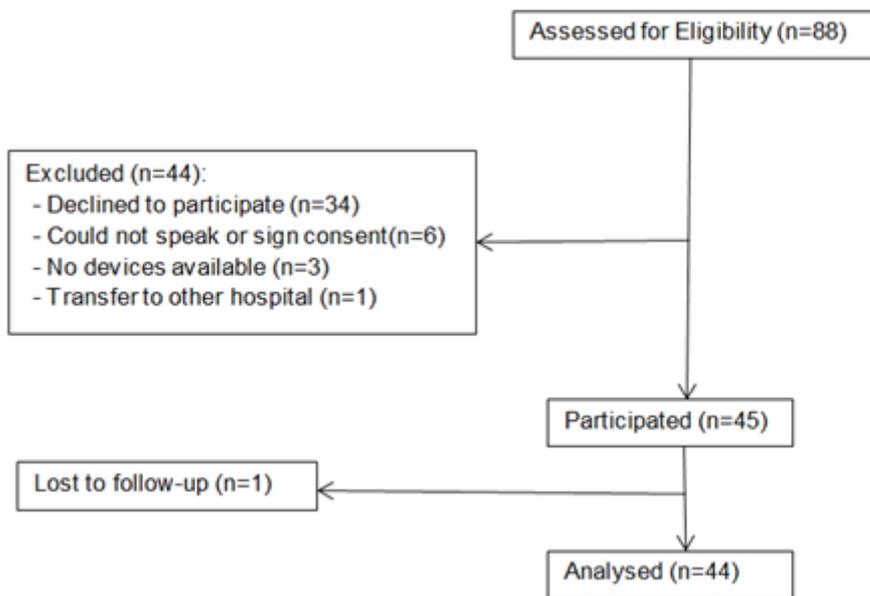


Figure 1. Study flow chart.

Table 2. Characteristics of patients receiving continuous remote monitoring on the ward after ICU discharge.

Characteristic	Participated subjects (n=44)
Age, years	63 (13)
Gender	
Male	29 (66%)
Female	15 (34%)
Body Mass Index, kg/m²	27.8 (5.5)
Smoking	20 (45.5%)
Comorbidities	
Hypertension	19 (42.2%)
Cardiovascular disease	18 (40.0%)
Diabetes Mellitus	10 (22.2%)
COPD	11 (24.4%)
Chronic Kidney Disease	5 (11.1%)
Critical care unit admission cause	
Respiratory failure	14 (31.8%)
Traumatic injury	8 (18.2%)
Sepsis	5 (11.4%)
Post cardiac arrest/heart failure	5 (11.4%)
Gastro-intestinal bleeding	3 (6.8%)
Vascular surgery	3 (6.8%)
Metabolic disorder/ Kidney failure	3 (6.8%)
Other	3 (6.8%)
Length of stay ICU, days	4.0 (1.8-8.5 [1-126])
SOFA score at ICU admission	10.0 (7.0-12.2 [3-17])
SOFA score at ICU discharge	5.0 (4.0-7.0 [3-10])
Recent surgery	19 (42.2%)
Total in-hospital LOS, days	13 (8-29 [3-152])

Data are represented by n(%), mean (standard deviation), median (IQR [range]) or number (proportion). COPD = chronic obstructive pulmonary disease; ICU=intensive care unit (including medium care unit) SOFA = Sequential Organ Failure Assessment; LOS = Length of stay.

Vital signs, remMEWS and MEWS

Continuous remote monitoring started directly after ICU discharge on the ward. Figure 2 shows the course of the continuously and remotely monitored RR (panel A), SpO₂ (panel B), PR (panel C) and remote MEWS (panel D) during PICUD 0-3. The number of patients that was followed up in the study was 45, 41, 30 and 16 for day 0, day 1, day 2 and day 3 respectively. Vital signs changed during day and night time, with the lowest values during the night (between 10:00 p.m. and 05:00 a.m.). The median time that patients showed deviating vital signs according a RR >30 p/m, SpO₂ <90% and HR > 100 p/m was 7.5 (0-52) min, 74 (11-329) min and 48 (3-384) min, respectively. The percentage of total monitoring time that a critical remMEWS was detected varied from 2.5 – 23.6% per patient, with a median value of 10.2%. Figure 3 represents the aggregated time that a critical remMEWS was detected per patient compared to the total monitored time. A total of 28 critical remMEWS episodes were detected in 21 patients (47.7%) during continuous remote monitoring. The median duration of a critical remMEWS episode was 235 minutes, with a minimal duration of 61 minutes and a maximum duration of 1360 minutes.

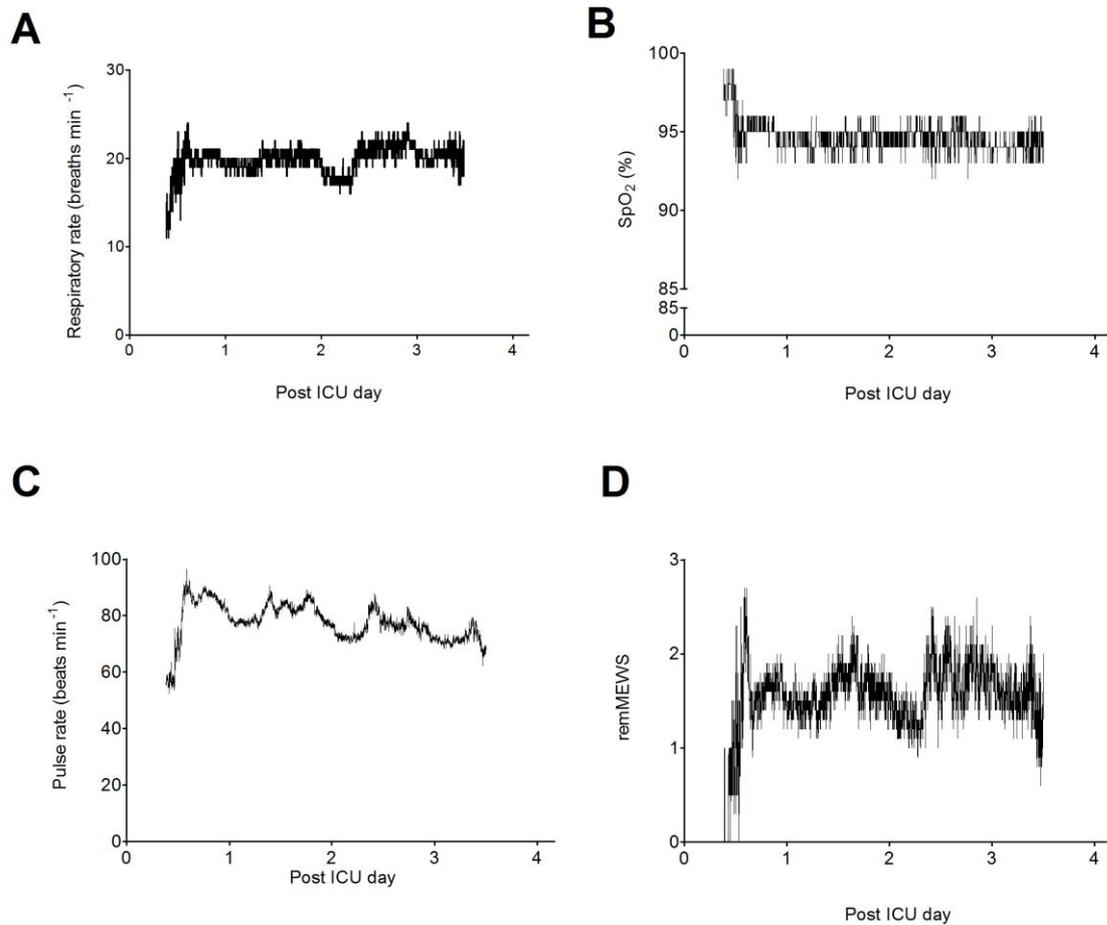


Figure 2. The course of the continuous remote monitored respiratory rate (panel A), SpO₂ (panel B), pulse rate (panel C) and remote MEWS (panel D) over 4 days on the general ward after critical care unit discharge. Graphs are based on average minute values. The number of patients was 45, 41, 30 and 16 for day 0, day 1, day 2 and day 3 respectively.

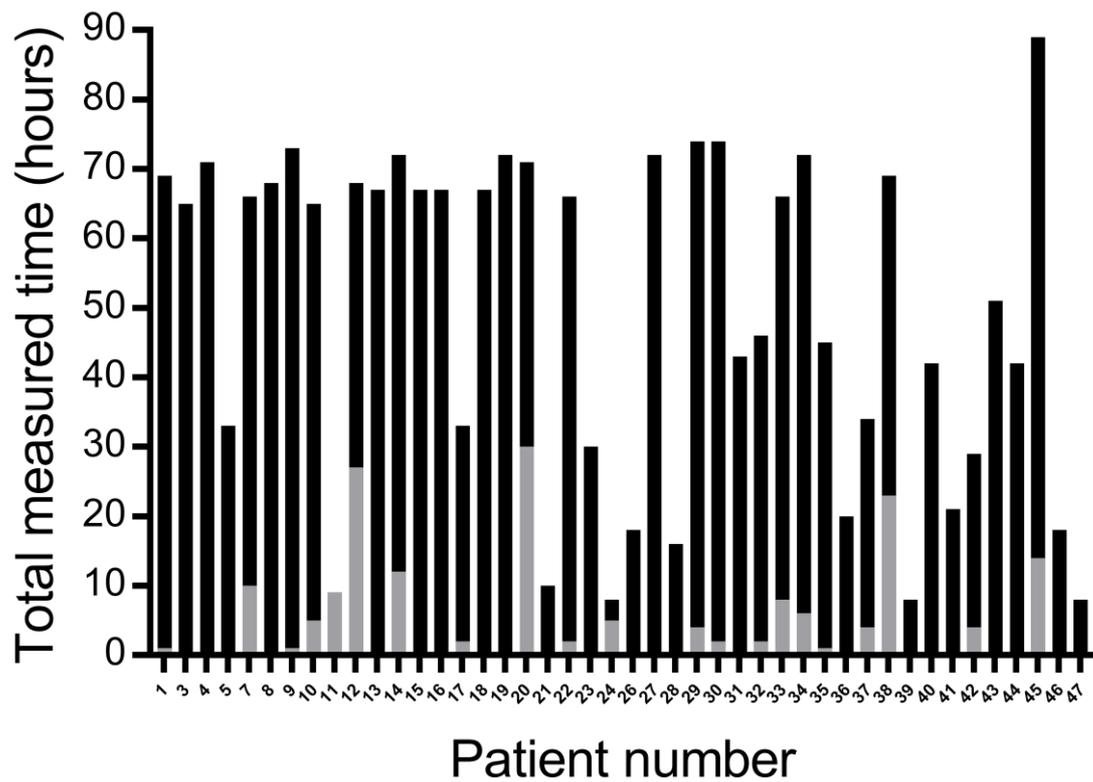


Figure 3. Time per patient that a critical remote MEWS (≥ 3) was detected compared to the total continuous remote monitored time. Time (hours) remote MEWS ≥ 3 was detected (), total monitoring time ().

Critical remMEWS was also detected with MEWS in 11 (39.3%) of the episodes. Six episodes (55%) were detected within 2 hours and 5 episodes (45%) were detected with a delay > 2 hours (2 episodes were detected with a delay of 2-6 hours and 3 episodes were detected with a delay of >6 hours). Seventeen of these critical remMEWS episodes (60.7%) were not detected by the routine point-check MEWS assessments. Data are shown in Table 3.

Table 3. Critical remote MEWS episodes detection with continuous remote vital sign monitoring compared to reported critical MEWS detection during routine point-check MEWS assessments by the nurses according to daily clinical practice.

		Time interval****			
		<2 hrs	2 - 6 hrs	>6 hrs	Total
Number of episodes of critical remMEWS*	Detected by routine point-check MEWS**	6 (21.4%)	2 (7.1%)	3 (10.7%)	11 (39.3%)
	Not detected by routine point-check MEWS***	4 (14.3%)	5 (17.8%)	8 (28.6%)	17 (60.7%)
	Total	10 (35.7%)	7 (10.7%)	11 (14.3%)	28 (100%)

* critical remMEWS episode: remMEWS \geq 3 for \geq 1 hour

** Subsequent MEWS measured by nurse was \geq 3

*** Subsequent MEWS measured by nurse was $<$ 3

**** Time interval from start critical remMEWS until subsequent MEWS measured by nurse

An example of patient readmission to the ICU and the predictive value of deviating vital signs and remMEWS for prolonged length of stay.

As an example of detecting clinical deterioration in patients with continuous remote monitoring, the vital signs and remMEWS of a patient who has been readmitted to the ICU is presented in Figure 4. This figure shows that the readmission was preceded by deterioration in vital signs and a detected critical remMEWS. Table 4 represents the AUC, CI, sensitivity, specificity, NPV and PPV of different deviating vital signs and critical remMEWS for a prolonged hospital length of stay of \geq 14 days. RR above 30 breaths/min was found to be a fair predictor for prolonged length of hospital stay with an area under the curve (AUC) of 0.762 (CI, 0.622-0.903). The diagnostic accuracy of remMEWS \geq 3 was moderate for predicting prolonged length of hospital stay with an AUC of 0.660 (CI, 0.497-0.823).

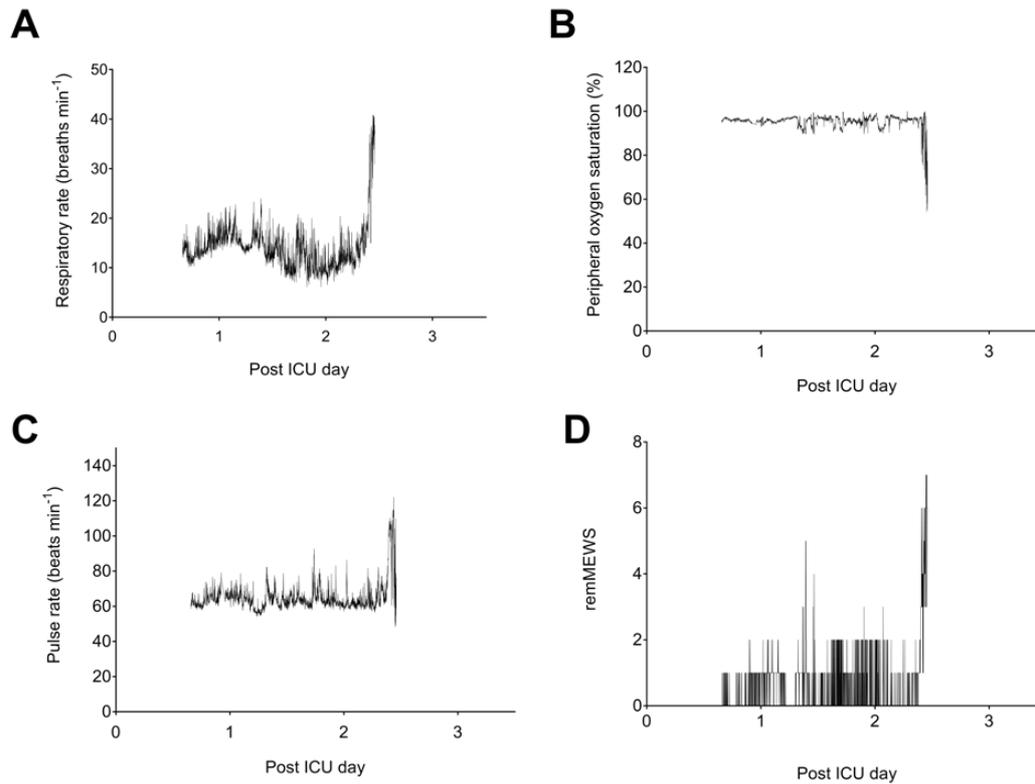


Figure 4. The course of the respiratory rate (panel A), peripheral oxygen saturation (panel B), pulse rate (panel C) and remote MEWS (panel D) in a study patient that was readmitted to the intensive care unit from the general ward on the second day after intensive care unit discharge.

Table 4. Area under de curve for deviated vital signs and critical remote MEWS detected with continuous remote monitoring for diagnostic accuracy prolonged length of stay (>14 days).

Vital signs	AUC	95% CI		Sensitivity (%)	Specificity (%)	NPV	PPV
		Lower bound	Upper bound				
RR >30 p m ⁻¹	0.762	0.622	0.903	86.4	55.5	0.95	0.30
RR >20 p m ⁻¹	0.731	0.579	0.882	1	34.6	1	0.25
SpO ₂ <85%	0.603	0.433	0.773	68.2	50.0	0.88	0.23
SpO ₂ <90%	0.583	0.408	0.758	77.8	46.2	0.90	0.24
PR >100 p m ⁻¹	0.641	0.470	0.812	50	80.8	0.88	0.37
remMEWS ≥3	0.660	0.497	0.823	72.7	54.5	0.90	0.26

NPV; negative predictive value, PPV; positive predictive value, RR; respiratory rate, PR; pulse rate, remMEWS; remote MEWS.

Discussion

This study shows that continuous remote monitoring of vital signs detects critical MEWS episodes frequently on the general ward in patients discharged from the ICU, which were not detected in more than half of these episodes by routine point check MEWS assessment by the nurses according daily clinical practice. Furthermore, MEWS detected critical scores with a significant delay (>2 hours) in 45% of the detected critical remMEWS episodes.

Early warning and intervention systems have been introduced in many institutions for the early recognition and management of clinical deteriorating patients to prevent adverse events.³ Although evidence is pointing in the direction of potential effectiveness, firm evidence for early warning and intervention systems implementation is still lacking. Looking for reasons for this lack of evidence, the afferent limb lacks EWS standardization, includes heterogeneous patient populations and has a known low protocol adherence.⁴ Another plausible reason for unproven value on patient outcome is the current intermittent point-check assessments of the EWS by nurses, which also leads to a delay and even under detection of clinical patient deterioration as shown in our study.

The frequently detected critical MEWS episodes in our study on the ward by continuous remote monitoring would have resulted in referral of the attending physician. Subbe et al. recently showed that continuously monitoring of the EWS, in combination with an automated advisory and notification system, was associated with significant improvement in mortality and a reduction in cardiac arrests in patients on the ward.¹² Furthermore, the effect of continuous remote monitoring might be underestimated since only 12% of the studied patients were continuously remotely monitored. In this trail remote monitoring was only optional and was used according to discretion of treating clinicians.¹²

Petersen et al. recently reported that in patients who were unexpectedly admitted to the ICU from the general ward, monitoring frequency was indeed not adhered to in 81% of the cases.^{13,14} In addition, in 42% of the critical EWS scores the doctors were not notified about patients' condition.^{13,14} These problems could be overcome by the use of continuous remote monitoring and automatically notification of the physicians by sending an alarm on a pager or mobile phone when deterioration is detected. Furthermore we hypothesise that continuous remote monitoring potentially saves time monitoring patients, time which could be spend in other ways to improve patient care.

Despite having many potential advantages, wearable devices may also have disadvantages, e.g. technical dysfunction, increase in false positive alarms and patient discomfort. To

prevent a high (false) alarm rates we choose to detect critical MEWS episodes lasting a hour. For higher critical MEWS scores other time frames could be chosen to detect patients who are clinically deteriorating in clinical practice. Furthermore cost-effectiveness and unwanted effects on patient outcome (e.g. over diagnostics and unfavourable side effects of initiated treatment) should be evaluated in future randomized controlled studies.

The workload for attending physicians on the ward might increase, considering the reported incidence of critical remMEWS episodes that were currently missed by point-check MEWS assessments. Although the performance of an EWS is mostly described in terms of the AUROC, the clinical practical clinical value is better expressed as the non-event rate (proportion of early warning alarm signals that are not followed by an adverse event) and the missed event rate (proportion of adverse events not detected by an early warning alarm). The non-event rate depends more on the adverse event rate than on the discriminatory power.¹⁵ We do think that an EWS could also be used to identify patients who may benefit from increased attention from medical personnel, which makes the current non-event rate more relative. Despite the high non-event rate for adverse events of early warning systems, van Galen et al. showed that doctor referral did lead to an intervention (mainly adjusting treatment and performing diagnostics) in 41% of the episodes when a doctor was informed of a critical MEWS score.⁶ Therefore, we do believe that an increase in doctor referral could lead to improvement of patient care beyond the prevention of direct adverse events.

A limitation of this study is that the results might not be generalizable to all patients discharged from the ICU, due to possible bias. Thirty-one patients decided not to participate in this study due to the high burden they experienced from their illness and the ongoing treatment. This could have resulted in a selection bias, since the patients who experienced the most burden possibly more frequently did not give informed consent for study participation.

Strengths of this study are its exploratory, prospective and observational nature. Furthermore, Attending physicians, nurses and participants were blinded for the continuously remotely monitored data. Therefore it was possible to monitor patients, detect deviating vital signs and critical remMEWS on the ward after ICU discharge and compare detected episodes with routine point-check MEWS assessments by nurses according to daily clinical practice.

Clinical consequence of introducing continuous remote monitoring in patients after ICU discharge on the general ward was beyond the scope of this study and still has to be

determined. Furthermore, the effect of introducing continuous remote monitoring on patient outcome in other settings, for example the postoperative setting, has not yet been determined.¹⁶ It has to be further investigated in large controlled trials whether detection of a critical MEWS by continuous remote monitoring could improve patient outcome within a early warning and intervention system.

In conclusion, our study suggests that remote monitoring is useful for the detection of critical MEWS episodes, which were not detected by point-check MEWS assessments by nurses in more than 50% of critical remMEWS episodes.

References

1. Schein RM, Hazday N, Pena M, Ruben BH, Sprung CL. Clinical antecedents to in-hospital cardiopulmonary arrest. *Chest* 1990; 98: 1388-92.
2. Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation* 2004; 62: 137-141.
3. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. *Critical Care* 2015; 19: 254.
4. Alam N, Hobbelenk EL, van Tienhoeven AJ, van de Ven PJ, Jansma EP, Nanayakkara PWB. The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. *Resuscitation* 2014; 85: 587-594.
5. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. *Quarterly Journal of Medicine* 2001; 94: 521-526.
6. van Galen LS, Dijkstra CC, Ludikhuizen J, Kramer MH, Nanayakkara PW. A Protocolised Once a Day Modified Early Warning Score (MEWS) Measurement Is an Appropriate Screening Tool for Major Adverse Events in a General Hospital Population. *PLoS One* 2016; 11 e0160811
7. Ludikhuizen J, Smorenburg SM, de Rooij SE, de Jonge E. Identification of deteriorating patients on general wards; Measurement of vital parameters and potential effectiveness of the Modified Early Warning Score. *Journal of Critical Care* 2012; 27: 424.e7-424.13.
8. Kareliusson F, De Geer L, Tibblin AO. Risk prediction of ICU readmission in a mixed surgical and medical population. *Journal of intensive care* 2015; 3:1.
9. Rosenberg AL, Hofer TP, Hayward RA, Strachan C, Watts CM. Who bounces back? Physiologic and other predictors of intensive care unit readmission. *Critical care medicine* 2001; 29: 511-8.
10. van Galen LS, Struik PW, Driesen BE, Merten H, Ludikhuizen J, van der Spoel JI, Kramer MH, Nanayakkara PW. Delayed Recognition of Deterioration of Patients in General Wards Is Mostly Caused by Human Related Monitoring Failures: A Root Cause Analysis of Unplanned ICU Admissions. *PloS one* 2016; 11: e0161393.
11. Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2018
12. Subbe CP, Duller B, Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Critical Care* 2017; 21: 52.
13. Petersen JA. Early warning score challenges and opportunities in the care of deteriorating patients. *Danish Medical Journal* 2018; 65 : B5439.
14. Petersen JA, Mackel R, Antonsen K, Rasmussen LS. Serious adverse events in a hospital using early warning score – What went wrong? *Resuscitation* 2014; 85 : 1699-1703
15. de Grooth HJ, Girbes AR, Loer SA. Early warning scores in the perioperative period: applications and clinical operating characteristics. *Current Opinion in Anesthesiology* 2018; 31:732-738.
16. Boer C, Touw HR, Loer SA. Postanesthesia care by remote monitoring of vital signs in surgical wards. *Current Opinion Anesthesiology* 2018; 31:716-722.

Chapter 5

Photoplethysmography respiratory rate monitoring in patients receiving procedural sedation and analgesia for upper gastrointestinal endoscopy

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Abstract

Background

The value of capnography during procedural sedation and analgesia (PSA) for the detection of hypoxaemia during upper gastrointestinal (UGI) endoscopic procedures is limited. Photoplethysmography respiratory rate (RRp) monitoring may provide a useful alternative, but the level of agreement with capnography during PSA is unknown. We therefore investigated the level of agreement between the RRp and capnography RR (RRc) during PSA for UGI endoscopy.

Methods

This study included patients undergoing PSA for UGI endoscopy procedures. Pulse oximetry (SpO₂) and RRc were recorded in combination with Nellcor 2.0 (RRp) monitoring (Covidien, USA). Bland-Altman analysis was used to evaluate the level of agreement between RRc and RRp. Episodes of apnoea, defined as no detection of exhaled CO₂ for minimal 36 seconds, and hypoxaemia, defined as an SpO₂<92%, were registered.

Results

A total of 1054 minutes of data from 26 patients were analysed. Bland Altman analysis between the RRc and RRp revealed a bias of 2.25 ± 5.41 breath rate per minute (brpm), with limits of agreement from -8.35 to 12.84 brpm for an RR \geq 4 brpm. A total of 67 apnoea events were detected. In 21% of all apnoea events, the patient became hypoxaemic. Hypoxaemia occurred 42 times with a median length of 34 (19-141) s, and was preceded in 34% of the cases by apnoea and in 64% by an RRc \geq 8 brpm. In 81% of all apnoea events, photoplethysmography registered an RRp \geq 4 brpm.

Conclusion

We found a low level of agreement between capnography and the plethysmography respiratory rate during procedural sedation for UGI endoscopy. Moreover, respiratory rate derived from both the capnogram and photoplethysmogram showed a limited ability to provide warning signs for a hypoxaemic event during the sedation procedure.

Introduction

Upper gastrointestinal (UGI) endoscopy is frequently performed under procedural sedation and analgesia (PSA) to facilitate the procedure and enhance patient comfort. However, PSA might be associated with intraprocedural sedation-related cardiovascular and respiratory events, such as depressed minute ventilation and eventually hypoxaemia defined as an $SpO_2 < 92\%$, especially in patients with a higher ASA classification and body mass index.^{1,2} Pulse oximetry is the most commonly used monitoring parameter for the detection of hypoxaemic episodes during PSA, but it is a late indicator of hypoventilation, especially in patients that receive supplemental oxygen.³⁻⁵ Alternatively, it has been suggested that capnography during PSA may identify respiratory depression before the onset of hypoxaemia.⁶⁻⁸ However, while capnography is currently considered the gold standard of respiratory rate monitoring in perioperative medicine, its usefulness during PSA for UGI is under debate. Although capnography might reduce hypoxaemic events by early detection of ventilation abnormalities Quadeer et al. also reported that capnography erroneously displayed a flat line for at least 50 seconds without a concomitant decrease in oxygen saturation with normal chest excursions on subsequent clinical examination in 13% of patients during PSA for UGI endoscopy.⁸ Concordantly, 25% of patients who develop hypoxaemia show normal ventilation patterns according to capnography⁹, and 46% of patients with capnography monitoring developed hypoxaemia.⁸ This inaccuracy is mainly caused by a diminution of airflow due to the presence of the oral scope in a narrow oropharyngeal inlet, interference of the CO₂ suction pump with capnographic CO₂ detection, or blockage of the nasal cannula by residual moisture accumulation.⁸ Respiratory rate is considered as a proxy of minute ventilation^{10,11}, and the introduction of monitors that enable continuous registration of respiration rate, including transthoracic impedance plethysmography or bioacoustical sensor technology, may broaden the monitoring spectrum during PSA. The recently introduced Nellcor™ photoplethysmography (PPG) waveform analysis calculates the respiratory rate from the respiratory variation in the pulse oximetry signal.¹²⁻¹⁴ The added value of the use of PPG-based respiratory rate (RRp) monitoring technology during PSA has however not yet been evaluated. In this study we therefore investigated the level of agreement between respiratory rate monitoring based on photoplethysmography or capnography during PSA for UGI endoscopic procedures and evaluated the ability of RRp to predict hypoxaemia in this setting.

Methods

Subjects

This prospective, observational clinical study was conducted in the VU University Medical Centre (Amsterdam, The Netherlands), a tertiary hospital. The local Human Subjects Committee of the VUmc approved the study (METc14/489), and written informed consent was obtained from all subjects. Patients were included in case of procedural sedation and analgesia (PSA) for upper gastrointestinal (UGI) endoscopy. Patients were excluded from enrolment if they met any of the following exclusion criteria: <18 years of age, mechanical ventilation, atrial fibrillation and the presence of an implanted pacemaker.

PSA

PSA was conducted according to the national guideline and local protocols for the administration of PSA outside the operating room. Propofol was administered via a target controlled infusion (TCI) system (120-185 microgram·kg⁻¹·min⁻¹). The dosage of propofol, (s)-ketamine (Ketanest, Pfizer, the Netherlands) and alfentanil (Rapifen, Janssen-Cilag BV, the Netherlands) was individualized and titrated to the desired clinical effect by a certified registered nurse anaesthetist specialized in PSA with a supervising anaesthetist available for assistance. Standard in all procedures 3 L/min of supplemental oxygen was administered via a nasal cannula.

Standard respiratory monitoring

Pulse oximetry (SpO₂), heart rate (HR) and intermittent non-invasive blood pressure (NIBP) were monitored with an IntelliVue MX450 and capnography with an M3015B module (Koninklijke Philips NV®, Eindhoven, the Netherlands). A sidestream and/or microstream® CO₂ filter Smart CapnoLine Guardian™ (Covidien, Mansfield, MA, USA) was used for measuring CO₂ via a combined nasal and oral cannula. The IntelliVue system displays respiratory rate (RRc), end-tidal CO₂ levels and a continuous capnographic waveform during the UGI endoscopic procedure. The RRc that was recorded consists of the average breath rate per minute (brpm) calculated every 12 seconds, and is able to reflect an RR from 0 to 40 brpm. The capnometer was set to alarm when there was no CO₂-detection.

Plethysmography-based respiration rate monitoring

The Nellcor™ bedside patient monitoring system version 2.0 (Covidien, Mansfield, MA, USA) was used to measure the respiratory rate derived from the photoplethysmogram (RRp). The finger cuff of the Nellcor was wrapped around the finger and placed ipsilateral to the NIBP. The hand was subsequently placed in a supine position. Every 5 seconds, the Nellcor calculates a current respiratory rate based on a 45-second photoplethysmogram. This RRp is averaged further with the previously displayed rate, and passes through additional logic before displayed as a final RRp reported to the user. The Nellcor has a reference range of 4

to 40 brpm and therefore suppresses the display of respiratory rates <4 brpm. The entire algorithm is reset (returns to NO POST) if the oximeter algorithm reports a pulse rate or SpO₂ of zero (i.e. a dropout) or the sensor is disconnected [15]. No alarms were set on the Nellcor device.

Data extraction

RRc and RRp measurements were performed simultaneously in sedated patients who underwent UGI endoscopy. Data recording started when medication was administered. For every patient, respiratory rates were converted into a mean RR per minute for both capnography (average of 5 measurements) and photoplethysmography (average of 60 measurements). The two parameters were matched exactly with respect to the time point and time frame. SpO₂ and heart rate data were recorded every second in the offline IntelliVue data report. NIBP values were collected every 5 minutes.

A hypoxaemic episode was defined as any timeframe with an SpO₂ value below 92%. Episodes of hypoxaemia were counted and the average length was calculated. The episodes of hypoxaemia were categorized according to the registered RR prior to hypoxaemia: non-registration, normopnoea, bradypnoea and apnoea. Bradypnoea was defined as an RRc of 1-7 brpm or RRp of 4-7 brpm. The number and average length of detected bradypnoea episodes was calculated for both RRc and RRp. When a hypoxaemic episode was preceded by bradypnoea, the elapsed time between the occurrence of bradypnoea and the signalling of a SpO₂ below 92% was calculated for both monitors.

Episodes of apnoea captured by capnography were defined as a time lapse exceeding 36 seconds, or no detection of exhaled CO₂. The performance quality of monitoring was registered by calculating the percentage and average duration of non-registration during the procedure, and defined as the inability to calculate the respiratory rate per minute.

Other study procedures

All interventions performed by the sedation nurse when inadequate ventilation or oxygenation was recognized were recorded. These interventions included basic life support, airway manoeuvres (e.g. jaw-thrust, head-tilt and chin-lift) and ventilator support with a manual resuscitator.

Other study parameters, patient characteristics, comorbidities, medical history, ASA classification and type of procedure were recorded on a case record form. Relevant changes in blood pressure, heart rate, hand movement and surrounding noise were marked as an event on the Nellcor monitor. After removal of the endoscopic device, the total amount of administered propofol, s-ketamine and alfentanil were recorded.

Statistical analysis

Statistical data analyses were carried out using a SPSS statistical software package version 19.0 (IBM, New York, NY, USA). Standard descriptive statistics were used to describe the patient characteristics and respiratory data and expressed as mean \pm standard deviation (SD), median with interquartile range (IQR) or frequencies.

The bias and limits of agreement (LoA) between the RR_c and RR_p were analysed using Bland–Altman analysis for repeated measurements using MedCalc version 12.7.4. (MedCalc Software, Ostend, Belgium). Bland–Altman analysis provided the bias, SD of the bias, and limits of agreement between both methods for an RR \geq 4brpm. The 95% limits of agreement refer to the bias \pm 1.96 SD.

Furthermore, the relation between the RR_c and the RR_p was evaluated by linear regression analysis using $(RR_p+RR_c)/2$ as the independent variable and RR_p-RR_c as the dependent variable. Regression analysis was used to quantify whether the difference between measurements for both monitors was related to the average measured RR. This analysis was not corrected for multiple measurements.

Additionally, Bland-Altman analyses were performed in case of an RR \geq 12 brpm, which is considered as the lower limit of a normal breathing frequency. A statistical significant difference was defined as a *p*-value <0.05 .

Results

Patient characteristics

Twenty-eight patients were assessed for eligibility and included in the study. One patient was excluded from the final analysis due to the development of atrial fibrillation de novo during the procedure. A second patient was excluded, as pulse oximetry data could not consistently be recorded. A total of 1054 minutes of capnography and photoplethysmography data points were obtained. Figure 1 shows the capnography, photoplethysmography and pulse oximetry data of a representative patient receiving PSA during UGI endoscopy.

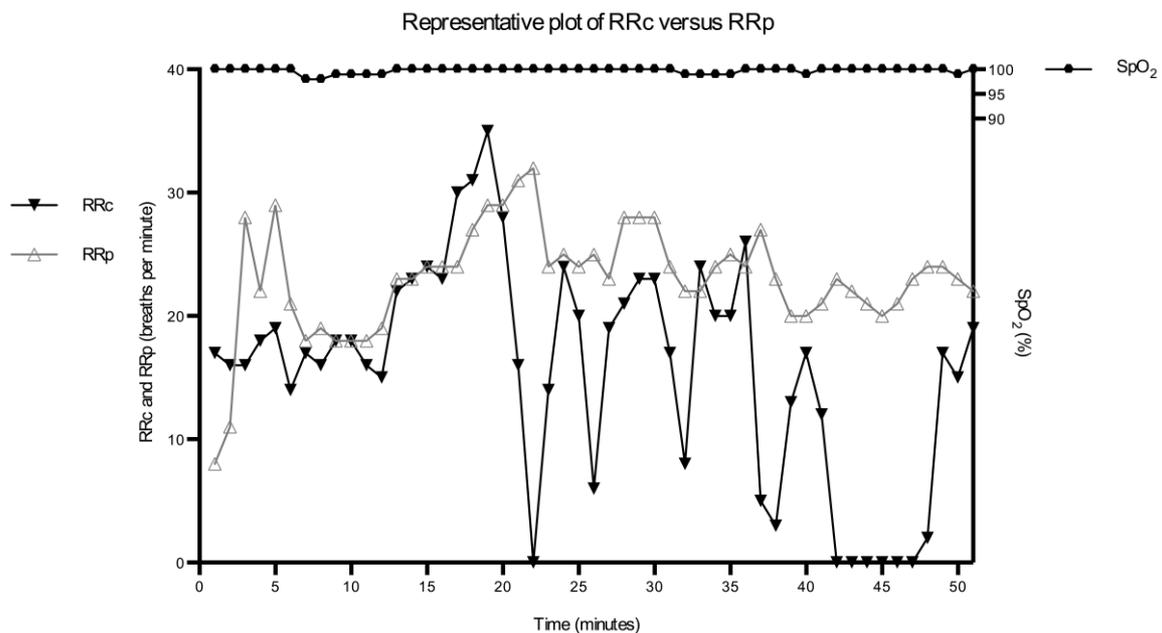


Figure 1. Capnography, photoplethysmography and pulse oximetry data of a representative patient receiving PSA during UGI endoscopy.

Table 1 shows the characteristics of the included patients. The patient population consisted of 16 males and 10 females, they were 59 ± 16 years old and had a median ASA classification of 2 (1-3).

Table 1. Characteristics of the study population

Patient characteristics	Values
N	26
Males / females	16 / 10
Age (years)	59 ± 16
Body Mass Index (kg/m²)	23.1 ± 4.8
ASA score	2 (1-3)
Alcohol use [n]/(%)	8 (31)
History of smoking [n]/(%)	9 (35)
Comorbidities [n]/(%)	
<i>Chronic obstructive pulmonary disease</i>	3 (12)
<i>Obstructive sleep apnoea</i>	1 (4)
<i>Hypertension</i>	8 (31)
<i>Cardiomyopathy</i>	1 (4)
<i>Heart failure</i>	1 (4)
<i>Renal failure</i>	2 (8)
<i>Cirrhosis</i>	1 (4)
<i>Diabetes mellitus</i>	3 (12)

Data represent mean ± standard deviation, median with interquartile range or frequencies. ASA = American Society of Anaesthesiologists.

Procedural characteristics

The characteristics of the procedural sedation and anaesthesia are detailed in Table 2. Most patients underwent oral double balloon enteroscopy (35%) or endoscopic retrograde cholangiopancreatography (31%). The median procedural duration was 36 (25-64) minutes. The average respiratory rate during the procedure was 12 ± 8 breath rate per minute (brpm) with a SpO₂ of 97 ± 3%. Propofol was administered in combination with alfentanil (85% of the patients) and/or S-ketamine (77% of the patients). The RRc and RRp ranged from 0-36 brpm and 4-32 brpm, respectively.

Table 2. Upper gastrointestinal endoscopy procedural characteristics

Procedural and patient characteristics	Values
Type of procedure [n]/(%)	
<i>Oral double balloon enteroscopy</i>	9 (35)
<i>Endoscopic retrograde cholangiopancreatography</i>	8 (31)
<i>Gastroscopy</i>	5 (19)
<i>Oesophageal dilatation</i>	1 (4)
<i>Upper endoscopic ultrasound</i>	1 (4)
<i>Percutaneous endoscopic gastrostomy</i>	1 (4)
Procedural duration (minutes)	36 (25-64)
Manual resuscitation, n (%)	1 (4)
Median heart rate (bpm)	77 (71-97)
Mean respiratory rate (brpm)	12 ± 8
Mean SpO₂ during procedure (%)	97 ± 3
TCI propofol (mg)	365 (245-521)
TCI propofol (mg·kg⁻¹·h⁻¹)	8.3 (7.1-10.5)
Alfentanil use (µg)	196 (100-300)
S-ketamine use (mg)	15 (0-25)

Data represent mean ± standard deviation, median with interquartile range or frequencies. Bpm = beats per minute; brpm = breaths per minute; TCI = target controlled infusion.

Episodes of hypoxaemia and apnoea

Hypoxaemia was detected 42 times in 11 patients (39%), with a median episode length of 34 (19-141) seconds. Thirty-seven out of 42 (88%) hypoxaemic episodes occurred in the first 10 minutes of the sedation procedure.

In 14 (34%) cases, the hypoxaemic episode was preceded by apnoeas detected by capnography, with a delay of 40 seconds between apnoea and the development of hypoxaemia. In 10 cases (24% of all hypoxic events), the RRp could not be measured or display of the RRp was suppressed by the Nellcor algorithm in the period preceding a hypoxaemic period. Bradypnoea before a hypoxaemic episode was detected in 1 and 2 cases by capnography and photoplethysmography, respectively. A respiratory rate ≥8 brpm preceded a hypoxaemic episode in 64% (RRc) and 71% (RRp) of the cases. Table 3 shows the characteristics of episodes of apnoea as detected by capnography. A total of 67 apnoeas were detected by capnography with an incidence of 36% for the total patient cohort and a median length of 159 (68-198) seconds.

Table 3. Characteristics of apnoea detection by capnography

Apnoea episodes	Values
Total of detected episodes of apnoea	67
Episode length (s)	159 (68-198)
Number of apnoeas per patient	2.5 (2-5.75)
Number of apnoea episodes where an RRc could be calculated [n, % of total detected apnoea episodes)	54 (81)
Number of apnoea episodes resulting in hypoxaemia [n]/(%)	14 (21)
Elapsed time until hypoxaemic episode (s)	40.3 (29.0-94.0)

Data represent median with interquartile range or frequencies. Apnoea= RRc 0 brpm for >36 seconds. Hypoxaemia= SpO₂ <92%. RRc = respiratory rate for capnography; RRp = respiratory rate for plethysmography.

Level of agreement between RRc and RRp

The photoplethysmography device did not report an RRp in 15.5% of all recorded minutes. The level of agreement between the RRc and RRp was evaluated using Bland-Altman (BA) analysis corrected for repeated measurements in case of a minimal RR of ≥ 4 brpm (Figure 2, panel A) of RR of ≥ 12 brpm (panel B). Panel A shows in 690 paired observations of RR data a bias of 2.25 brpm (SD 5.41), with 95% limits of agreement from -8.35 to 12.84 brpm.

Linear regression analysis revealed a slope of -1.026 ($P < 0.0001$) for the relation between the difference between RRc and RRp for every mean RR, suggesting that the difference between RR measurements decreases as the average respiratory rate increases, until a point where this difference becomes negative (Figure 3). Using a cut-off of an RR ≥ 12 brpm, 495 paired observations revealed a bias of 0.50 brpm (SD 3.18) with 95% limits of agreement from -5.72 to 6.73 brpm (Figure 2 panel B).

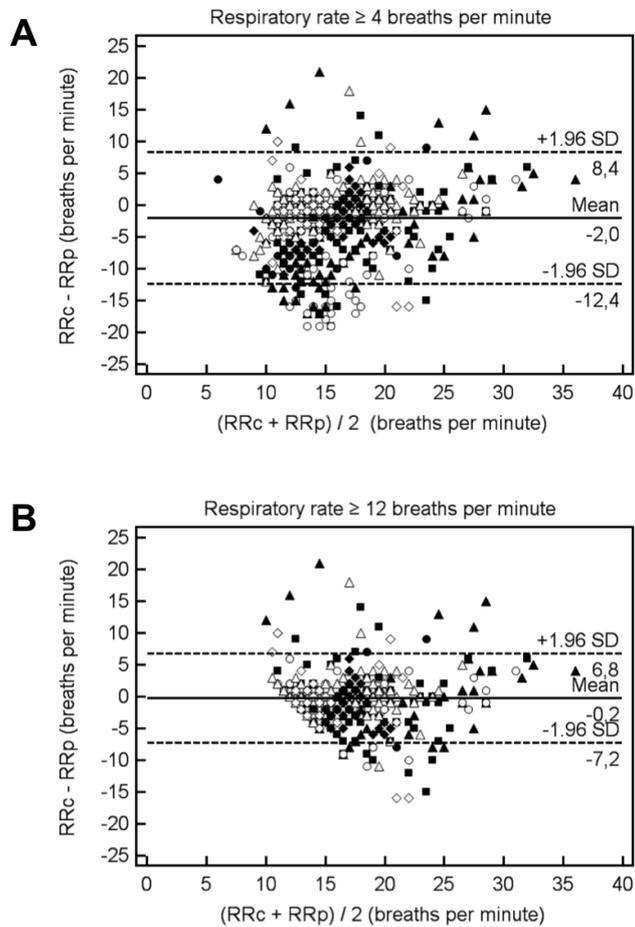


Figure 2. Bland-Altman analysis corrected for repeated measures of capnography respiratory rate (RRc) versus plethysmography respiratory rate (RRp) in case of an RR ≥ 4 breaths per minute (brpm) (Panel A) or an RR ≥ 12 brpm (Panel B).

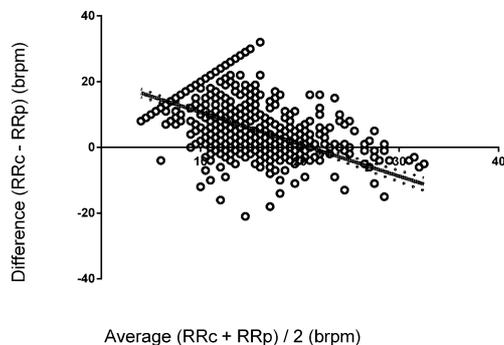


Figure 3. Linear regression analysis using $(RRc + RRp) / 2$ as independent variable and RRc-RRp as the dependent variable represented as separate dots.

Discussion

The present study investigated the level of agreement between the respiratory rate as calculated from the respiratory variation during photoplethysmography with capnography as gold standard during procedural sedation and analgesia for upper gastrointestinal endoscopic procedures. Our study showed a low level of agreement between photoplethysmography and capnography respiratory rate (RR), even when the analysis was limited to normal breathing frequencies (RR \geq 12 brpm).

Respiratory rate monitoring might be used for the early detection of respiratory depression and prevention of hypoxaemic episodes. We therefore studied the added value of photoplethysmography respiratory rate to capnography in the detection of hypoxaemia during sedation. As the photoplethysmography device is unable to detect apnoea, we evaluated the occurrence of bradypnoea before a hypoxaemic event, and found a low incidence rate for both devices. Our findings suggest that the addition of a photoplethysmography respiratory rate to standard capnography in procedural sedation does not increase the chance to detect apnoea or bradypnoea before the occurrence of hypoxaemia. The clinical implications of our findings should however be further tested in a randomized controlled setting.

In contrast to our findings, Addison and colleagues recently reported a good level of agreement between the RR as measured by plethysmography and capnography.¹³ One explanation for these different findings is the removal of capnography waveforms with poor quality in their study, while we choose to keep all capnography recordings in the final analysis to mimic routine clinical practice. Moreover, in contrast to other studies we included patients with comorbidities and high median ASA scores,^{1,16} and consequently reported a relatively high number of hypoxaemic episodes. Age, male sex, comorbidities, fentanyl use, ASA classification, and BMI were previously reported as independent risk factors for respiratory events during UGI endoscopy.^{1,2,16,17} In contrast, Goudra et al. found no increased risk for hypoxaemia in patients with a higher ASA classification or BMI when patients were pre-oxygenated with 100% oxygen prior to drug administration and received an airway device to maintain a patent airway.¹⁸ Our study shows that a hypoxaemic episode was preceded by apnoea in only in 34% of the cases, with a delay of about 40 seconds between apnoea and the development of hypoxaemia. This delay was comparable as reported by van Loon and colleagues.¹⁹ However, in the study of van Loon et al., supplemental oxygen was only provided in case of disturbed oxygenation or ventilation, which makes these findings incomparable with our report.¹⁹

As the depth of sedation is of influence on the occurrence of hypoxaemia, we compared anaesthesia infusion rates with other studies. Unfortunately, most studies lack information with respect to anaesthesia infusion rates, which makes a close comparison with our findings unfeasible. A limitation of our study was that the degree of sedation could not be objectified with bispectral index spectrometry (BIS) because s-ketamine would have reduced its value in predicting moderate sedation levels.²⁰

Although capnography is recommended in the guidelines during PSA for UGI endoscopy, it may be difficult to use capnography as a diagnostic tool by itself, and it should be used in conjunction with accompanying data, such as heart rate, blood pressure and photoplethysmography. The value of capnographic recordings might be enhanced if the shape of the capnogram, the P_{ETCO_2} , and respiratory rate are added to algorithms for clinical decision-making.²¹ Deitch et al. reported 100% sensitivity for hypoxia detection with capnography while supplemental oxygen was administered.²² Respiratory depression was set as a P_{ETCO_2} of >50 mmHg, an absolute increase or decrease from baseline P_{ETCO_2} of 10% or greater, or loss of the CO_2 waveform for >15 sec. In this study, 50% of respiratory depression events were caused by an P_{ETCO_2} >10% below baseline, suggesting that the prognostic value of capnography might be enhanced by evaluation of more advanced indices. However, extrapolation of these indices to the setting of UGI endoscopy might be difficult, as the endoscope disables airflow in a narrowed airway, especially in case of obesity, and PSA-related decreases in cardiac output may influence the P_{ETCO_2} . Moreover, as we studied the routine clinical setting instead of a controlled setting where a dedicated healthcare provider could act on disturbed capnographic values,^{8,22} our data are difficult to compare with other reports.

Our data showed that the Nellcor 2.0 was able to register the respiratory rate in 81% of the apnoea episodes detected by capnography. However, the Nellcor did not improve hypoxaemia prediction as surrogate end-point of patient outcome, when compared to capnography. The analysis of respiration-induced variations in the plethysmography waveform requires frequency analysis of the PPG baseline.²³ As breathing movements disappear during central apnoea, the phasic PPG respiratory signal vanishes, while the PPG signal can additionally be influenced by autonomic nerve activity.²⁴ Nilsson et al. additionally compared different PPG techniques at different anatomical sites for synchronous measurement of heart rate, respiratory rate and oxygen saturation, and showed that the location of the finger is the least favourable for RR detection.²⁵ Although there may be a timing deviation between different sensor location, this deviation was considered as clinically insignificant in the present study. Moreover, the largest respiration-induced variations in the

PPG signal were observed at high tidal volumes, absence of abdominal breathing and low respiratory rates.²⁴ During propofol-induced procedural sedation, tidal volume is probably more suppressed than respiration rate.²⁶⁻²⁸ Although abdominal respiration is diminished during spontaneous breathing in sedation,²⁹ we showed that the difference between RRc and RRp changes with distinct respiration rates. A more accurate RRp due to the increase in respiratory effort and thoracic expansion with high inspiration rates might explain this.³⁰

Our study is pragmatic by nature, and we aimed to include all measured waveforms in our final analysis in order to allow conclusions that are relevant to daily clinical practice. Although this might have contributed to a lower level of agreement between methods, our final conclusions are better implementable in the clinical setting.

The question that arises from the current study is whether capnography as gold standard for respiration rate during UGI with procedural sedation is the most appropriate methodology as comparator. While the Nellcor device was unable to detect low respiration rates, the capnogram was frequently disturbed by the endoscope and alterations in airflow. Additionally, Holley et al. recently performed a study with the ExSpirom bio-impedance-based respirator volume monitor, showing that low RR values do not represent episodes of respiratory depression, and the association of respiration rates with minute ventilation in upper endoscopic procedures was very low.¹⁰ This manufacturer-supported trial included 51 patients to simulate a variety of RR alarm conditions. The study showed that a substantial fraction of low minute ventilation (MV) measurements (MV <40 % of MV baseline) went undetected at 8 brpm (>70% low MV measurements were missed), but no hypoxemic event analysis was performed. In addition, Ebert. et al described a -48% reduction of minute ventilation by bioimpedance following sedation.³¹ Future studies should investigate whether other measurements, like respiratory minute volume, are superior to detect respiratory compromise and prevent hypoxemia in sedated patients when compared to available techniques, such as respiration rate monitoring or capnography.

References

1. Berzin TM, Sanaka S, Barnett SR, Sundar E, Sepe PS, Jakubowski M, Pleskow DK, Chuttani R, Sawhney MS (2011) A prospective assessment of sedation-related adverse events and patient and endoscopist satisfaction in ERCP with anesthesiologist-administered sedation. *Gastrointest Endosc* 73:710-7.
2. Coté GA, Hovis RM, Ansstas MA, Waldbaum L, Azar RR, Early DS, Edmundowicz SA, Mullady DK, Jonnalagadda SS (2010) Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. *Clin Gastroenterol H* 8:137-42.
3. Gross JB, Bailey PL, Caplan RA, Connis RT, Coté CJ, Davis FG et al (2002) Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 96:1004-17.
4. Niesters M, Mahajan RP, Aarts L, Dahan A (2013) High-inspired oxygen concentration further impairs opioid-induced respiratory depression. *Brit J Anaesth* 110:837–41.
5. Fu ES, Downs JB, Schweiger JW, Miguel RV, Smith RA (2004) Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. *Chest* 126:1552–1558.
6. Vargo JJ, Zuccaro G Jr, Dumot JA, Conwell DL, Morrow JB, Shay SS (2002) Automated graphic assessment of respiratory activity is superior to pulse oximetry and visual assessment for the detection of early respiratory depression during therapeutic upper endoscopy. *Gastrointest Endosc* 55:826-31.
7. Waugh JB, Epps CA, Khodneva YA (2011) Capnography enhances surveillance of respiratory events during procedural sedation: a meta-analysis. *J Clin Anesth* 23:189-96.
8. Qadeer MA, Vargo JJ, Dumot JA, Lopez R, Trolli PA, Stevens T, Parsi MA, Sanaka MR, Zuccaro G (2009) Capnographic monitoring of respiratory activity improves safety of sedation for endoscopic cholangiopancreatography and ultrasonography. *Gastroenterology* 136:1568-76.
9. Qadeer MA, Lopez AR, Dumot JA, Vargo JJ (2011) Hypoxemia during moderate sedation for gastrointestinal endoscopy: causes and associations. *Digestion* 84:37-45.
10. Holley K, MacNabb CM, Georgiadis P, Minasyan H, Shukla A, Mathews D (2016) Monitoring minute ventilation versus respiratory rate to measure the adequacy of ventilation in patients undergoing upper endoscopic procedures. *J Clin Monitor Comp* 30:33-39.
11. Atkins JA, Mandel JE (2014) Performance of Masimo rainbow acoustic monitoring for tracking changing respiratory rates under laryngeal mask airway general anesthesia for surgical procedures in the operating room: a prospective observational study. *Anesth Analg* 119:1307-1314.
12. Høiseth LØ, Hoff IE, Hagen OA, Kirkebøen KA, Landsverk SA (2015) Respiratory variations in the photoplethysmographic waveform amplitude depend on type of pulse oximetry device. *J Clin Monitor Comp* 2015 jun 12 [Epub a head of print].
13. Addison PS, Watson JN, Mestek ML, Ochs JP, Uribe AA, Bergese SD (2015) Pulse oximetry-derived respiratory rate in general care floor patients. *J Clin Monitor Comp* 29:113-120.
14. Schlag C, Wörner A, Wagenpfeil S, Kochs EF, Schmid RM, von Delius S (2013) Capnography improves detection of apnea during procedural sedation for percutaneous transhepatic cholangiodrainage. *Can J Gastroenterol* 27:582-6.

15. Addison PS, Watson JN, Mestek ML, Mecca RS (2012) Developing an algorithm for pulse oximetry derived respiratory rate (RR(oxi)): a healthy volunteer study. *J Clin Monit Comput* 26:45-51.
16. Heuss LT, Schnieper P, Drewe J et al (2003) Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients - a prospective, controlled study. *Am J Gastroenterol* 98:1751-1757.
17. Wani S, Azar R, Hovis CE, Hovis RM, Cote GA, Hall M, Waldbaum L, Kushnir V, Early D, Mullady DK, Murad F, Edmundowicz SA, Jonnalagadda SS (2011) Obesity as a risk factor for sedation-related complications during propofol-mediated sedation for advanced endoscopic procedures. *Gastrointest Endosc* 74:1238-47.
18. Goudra BG, Singh PM, Sinha AC (2013) Outpatient endoscopic retrograde cholangiopancreatography: Safety and efficacy of anesthetic management with a natural airway in 653 consecutive procedures. *Saudi J Anaesth* 7:259-65.
19. Van Loon K, van Rheineck Leyssius AT, van Zaane B, Denteneer M, Kalkman CJ (2014) Capnography during deep sedation with propofol by non-anesthesiologists: a randomized controlled trial. *Anesth Analg* 119:49-55.
20. De Oliveira GS Jr, Kendall MC, Marcus RJ, McCarthy RJ (2015) The relationship between the Bispectral Index (BIS) and the Observer Alertness of Sedation Scale (OASS) scores during propofol sedation with and without ketamine: a randomized, double blinded, placebo controlled clinical trial. *J Clin Monitor Comp* 2015 jul 29 [Epub a head of print].
21. Kodali BS (2013) Capnography outside the operating rooms. *Anesthesiology* 118:192-201.
22. Deitch K, Miner J, Chudnofsky CR, Dominici P, Latta D (2010) Does end tidal CO₂ monitoring during emergency department procedural sedation and analgesia with propofol decrease the incidence of hypoxic events? A randomized, controlled trial. *Ann Emerg Med* 55:258-64.
23. Meredith DJ, Clifton D, Charlton P, Brooks J, Pugh CW, Tarassenko L (2012) Photoplethysmographic derivation of respiratory rate: a review of relevant physiology. *J Med Eng Technol* 36:1-7.
24. Nilsson LM (2013) Respiration signals from photoplethysmography. *Anesth Analg* 117:859-65.
25. Nilsson LM, Goscinski T, Kalman S, Lindberg LG, Johansson A (2007) Combined photoplethysmographic monitoring of respiration rate and pulse: a comparison between different measurement sites in spontaneously breathing subjects. *Acta Anaesth Scand* 51:1250-7.
26. Krauss B, Hess DR (2007) Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 50:172-181.
27. Burton JH, Harrah JD, Germann CA et al (2006) Does end-tidal carbon dioxide monitoring detect respiratory events prior to current sedation monitoring practices? *Acad Emerg Med* 13:500-504.
28. Miner JR, Heegaard W, Plummer D (2002) End-tidal carbon dioxide monitoring during procedural sedation. *Acad Emerg Med* 9:275.
29. Aliverti A, Kostic P, Lo Mauro A, Andersson-Olerud M, Quaranta M, Pedotti A, Hedenstierna G, Frykholm P (2011). Effects of propofol anaesthesia on thoraco-abdominal volume variations during spontaneous breathing and mechanical ventilation. *Acta Anaesthesiol Scand* 55:588-96.

30. Sluiter ER, Rowaan CJ, Dorlas JC, Nijboer JA, Jorritsma FF, Blom JA, Beneken JE (1981) Peak-to-peak detector for the arterial pulsations in the plethysmogram. II: results of its use during anaesthesia. *Med Biol Eng Comput* 19:267-70.
31. Ebert TJ, Middleton AH, Makhija N (2015) Ventilation monitoring during moderate sedation in GI patients. *J Clin Monitor Comp* [Epub ahead of print].

Chapter 6

Lung ultrasound: routine practice for the next generation of internists

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Abstract

Background

The lung is at the crossroads of ventilation and circulation and can provide a wealth of diagnostic information. In the past, lung ultrasound (LUS) was considered impossible. However, the interplay between air, fluid and pleurae creates distinctive artefacts. Combinations of these artefacts can help differentiate between various pathological processes, including pulmonary oedema, pneumonia, pulmonary embolism, obstructive airway disease and pneumothorax. LUS, when used by experienced physicians, is superior to chest X-ray and comparable to computed tomography for establishing a diagnosis in acutely dyspnoeic patients. LUS allows for rapid, non-invasive and bedside patient assessment. It is therefore unfortunate that unlike many other medical specialists in the Netherlands, internists have not yet incorporated LUS into their daily practice.

Objectives

This review aims to be the starting point for internists wanting to acquire competence in LUS.

Review content

This narrative review describes the principles of ultrasound equipment, LUS artefacts, gives practical guidance to perform LUS and provides a road map towards LUS competence. Furthermore, it presents a decision tree to differentiate between causes of acute dyspnoea.

Authors conclusions

LUS is a promising diagnostic technique that can be of great help for the internist. It can be applied directly at the bedside and can also be used to follow up on disease progression and therapy. It is our belief that it will replace the stethoscope and that it will be the most used imaging technique in the near future, especially in dyspnoeic patients.

Introduction

The lungs can provide a wealth of diagnostic information, as they represent the crossroads of respiration and circulation. However, physical examination of the lungs remains a significant challenge. This is largely due to the poor acoustical performance of the stethoscope. Even seasoned physicians may fail to become experts at this 19th century technique.¹ For example, for detecting congestive heart failure or pneumonia, auscultation has a low sensitivity.² Clinical decision-making entered another era when the chest X-ray was introduced, followed by computed tomography (CT). Due to its superior sensitivity, the CT scan is now the gold standard in the diagnosis of community acquired pneumonia.^{3,4} But CT scanning requires transportation of a potentially critically ill patient, which is not without risk.^{5,6} In addition CT scanning is associated with significant costs, radiation and contrast burden, which should not be taken lightly.^{6,7} Lung ultrasonography (LUS) is the answer to these limitations. LUS enables physicians to differentiate between causes of acute dyspnoea within minutes at the bedside, and as such is particularly helpful in the emergency department and on the ward.^{8,9} LUS is not only superior to the physical examination and chest X-ray, but even comparable to CT for many diagnoses.¹⁰⁻¹² Pneumonia, pulmonary oedema, pulmonary embolism, asthma, chronic obstructive pulmonary disease and pneumothorax can be assessed with sensitivity and specificity ranging from 90 to 100% (*table 1*).

Table 1. Performance of ultrasound compared with computer tomography scan as gold standard

	Sensitivity (%)	Specificity (%)
Pleural effusion¹³	94	97
Alveolar consolidation¹⁴	90	98
Interstitial syndrome¹⁵	93	93
Complete pneumothorax¹⁶	100	95
Occult pneumothorax¹⁷	79	100

LUS yields important diagnostic information within minutes and is able to answer important binary questions.¹⁸ The examination can easily be repeated to evaluate the progress of the disease or the effect of initiated therapy. And importantly, LUS avoids radiation, transport and excessive cost. We have extensive experience with LUS, as it is an essential component of our intensive care ultrasound (ICARUS) curriculum and protocol. It is against this background that we see great potential for LUS in the daily practice of internists. In this narrative review, we therefore aim to provide guidance for internists wishing to adopt LUS.

Development of LUS

In medicine, ultrasound frequencies between 1 and 15 MHz are used, to allow for non-invasive visualisation of tissue structures. Ultrasound physics have been extensively reviewed elsewhere.^{19,20} In short, ultrasound beams travel through tissues until they are reflected when acoustic impedance of the adjacent tissue is different. Ultrasound cannot penetrate bone and is fully reflected by air. Therefore, the lung was considered unsuitable for ultrasound in the past.^{21,22}

However, LUS creates artefacts through the interplay of air, lung tissue, pleurae, fluid and bone. Through reflection, scatter and absorption of ultrasound beams, physiological and pathological processes generate distinctive combinations of artefacts and these speak a language of their own. This was studied in detail by Lichtenstein and colleagues who named many of these artefacts and showed their reproducibility.²³ In fact, virtually all acute life-threatening respiratory disorders about the pleural line, generating artefacts that unveil the great potential of LUS.

Machine and probe selection

For LUS, virtually any ultrasound machine will do, even legacy equipment. Handy features include a supporting trolley, fast start-up time and a small width, allowing bedside use. Most importantly, as LUS relies on artefacts, it should be possible to suppress all software artefact reduction, such as harmonics, filters and other image optimisation. Higher beam frequency yields higher resolution, but less maximum depth. In practice, linear vascular probes, cardiac phased array probes, or even abdominal probes may be used.

Systematic scanning

LUS is a trade-off between diagnostic speed and extensive scanning. A reasonable approach is to scan at least three different zones of the lung: anterior, anteromedial and posterior. We recommend the approach suggested by Lichtenstein in his BLUE protocol.⁸ Figure 1 shows how to find these points.

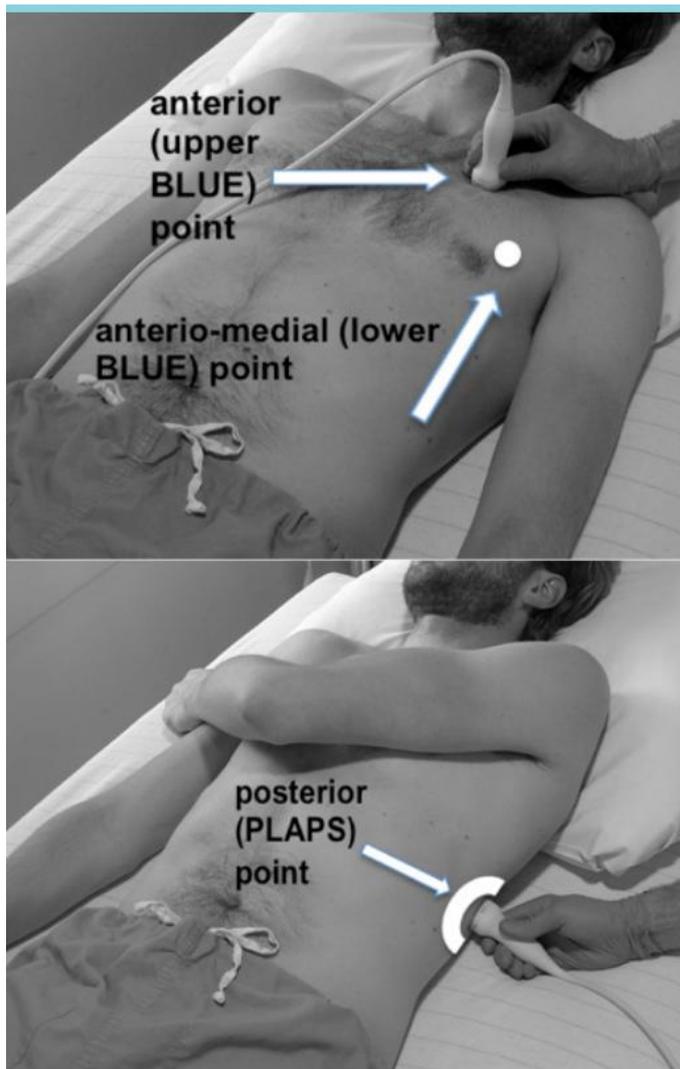


Figure 1. BLUE and PLAPS points

The anterior points are called upper BLUE points and the anteromedial points lower BLUE points, after the protocol. The posterior points are called the ‘posterolateral alveolar and/or pleural syndrome point’, or PLAPS point. In addition, the protocol includes optional identification of the ‘lung point’ and scanning for lower extremity venous thrombosis to aid diagnosis. Table 2 shows the proposed compulsory and optional views for LUS. As discussed in detail below, these views enable discrimination between acute causes of dyspnoea. LUS does not require any cardiac ultrasound imaging, as a cardiac cause of dyspnoea can be diagnosed from lung imaging only.

Table 2. The standard lung ultrasound (LUS) views, including the optional lung point identification and venous analysis. At our institute, these LUS views are embedded in the Intensive Care Ultrasound (ICARUS) Protocol, which consists of 22 compulsory views and includes echocardiography

LUS views as embedded in the ICARUS protocol

1. Upper BLUE point, left
2. Upper BLUE point, left, M-mode
2. Lower BLUE point, left
4. Lower BLUE point, left, M-mode
5. Upper BLUE point, right
6. Upper BLUE point, right, M-mode
7. Lower BLUE point, right
8. Lower BLUE point, right, M-mode
9. PLAPS point – left
10. PLAPS point – right
11. Lung point (optional)
12. Venous analysis (optional)

BLUE= bedside lung ultrasound in emergency; PLAPS= posterolateral alveolar and/or pleural syndrome

LUS artefacts

There are many LUS artefacts, but for daily practice only a few of these need to be remembered. It is essential to first identify the pleural line, as most pathology abuts it. To do so, the probe should be positioned perpendicular to the ribs. A rib is easily recognised as a shadow, caused by absorption of ultrasound by bone tissue. The pleural line is horizontal and hyperechoic, situated slightly beneath the two ribs. This yields a characteristic image called the ‘bat sign’ (*figure 2a*). Under normal circumstances, the parietal pleura and visceral pleura are seen as one line.

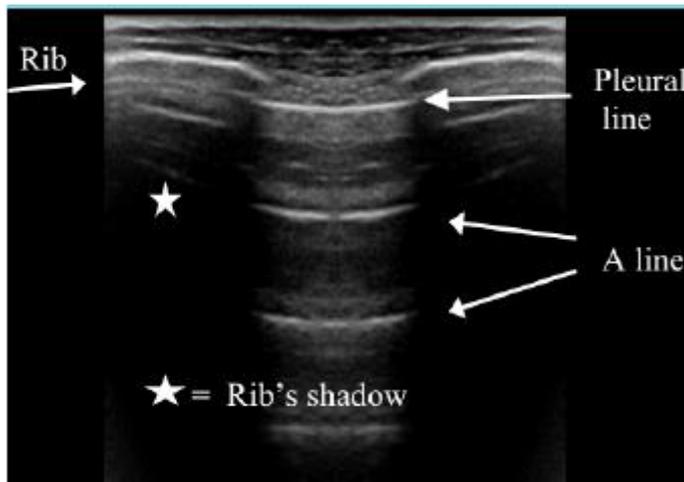


Figure 2a. Normal lung ultrasound image with the *bat sign* and A-lines

Lung sliding

Although visualised as one, respiration causes visceral pleura to slide relative to the parietal pleura. This causes a subtle sparkling to-and-fro movement artefact called lung sliding. Lung sliding indicates that both pleura are adjacent, ruling out pneumothorax at that point.²⁴ Lung sliding is so characteristic that it takes only a few seconds to recognise. Lung sliding can be confirmed using the M-mode. This setting essentially repeats one line of the screen over time. In the presence of lung sliding, the 'seashore phenomenon' occurs (*figure 2b*). If lung sliding is absent, the 'stratosphere sign' appears (*figure 2c*). Of note, abolished lung sliding is far from specific: pneumothorax is the classic example, but a motionless pleural line can also be caused by inflammatory or chronic adhesences, fibrosis and atelectasis.

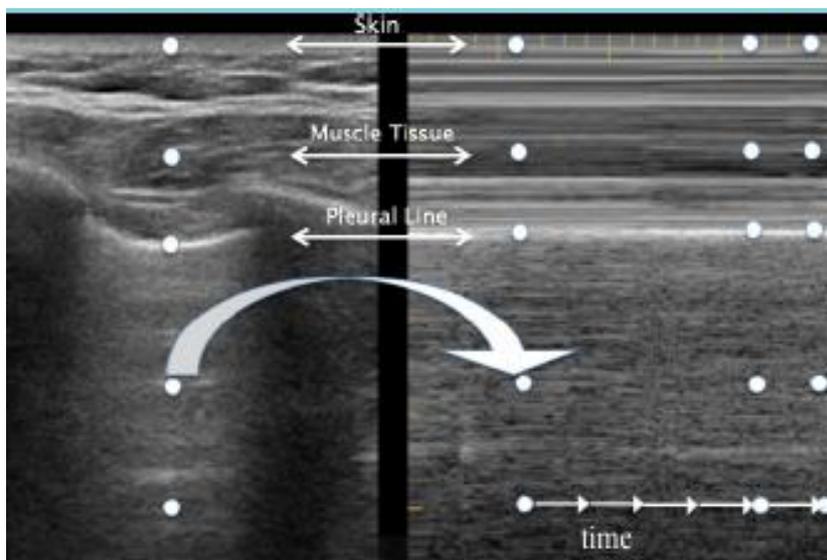


Figure 2b Normal lung ultrasound with normal M-mode scanning (seashore phenomenon)

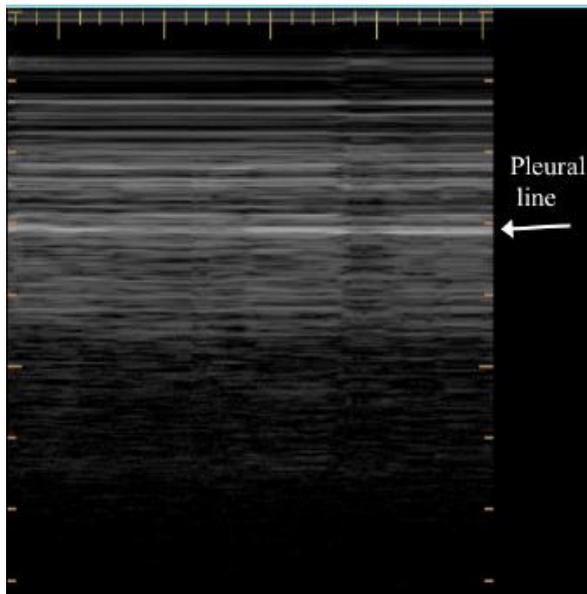


Figure 2c. M-mode scanning in pneumothorax (stratosphere sign)

A-lines

An A-line is the main horizontal artefact and a repetition of the pleural line. If ultrasound beams encounter a tissue-air interface, they are reflected back to the probe. However, the probe itself reflects them once again. This causes the beams to travel through the soft tissue a second time. This is called reverberation and causes the visualisation of A-lines (*figure 2a*). The depth at which an A-line is displayed is always equal to the distance of the pleural line to the probe and can be used to differentiate A-lines from other artefacts. It follows that A-lines represent the presence of air at the pleural line. This can be alveolar air and therefore normal lungs yield A-lines. However, it can also be air outside the alveoli, such as the air between the visceral and parietal pleura in pneumothorax.

B-lines

B-lines are the main vertical artefacts and are reminiscent of helicopter search spotlights. They are sometimes referred to as lung rockets or comet tail artefacts. However, strictly speaking, B-lines are a specific subtype of these. Interstitial oedema first appears in the subpleural interlobular septa which are surrounded by alveolar gas. Ultrasound beams entering this small pleural line-fluid-air system are reflected again and again, essentially being trapped. This results in many to-and-fro moments, generating a long vertical hyperechoic artefact, the B-line. Thus, by definition, B-lines arise from the pleural line. They erase A-lines and immediately rule out pneumothorax. B-lines are hyperechoic and narrow, span across the whole ultrasound image without fading and move with lung sliding. More than two anterior B-lines are pathological and indicate interstitial syndrome.¹⁵ Although

semantically unrelated, B-lines correlate with Kerley B-lines on chest X-ray (*figure 2d*). Any disease affecting the pulmonary interstitium can cause an interstitial syndrome. The commonest cause is pulmonary oedema. The number of B-lines per screen or the distance between B-lines allows assessment of severity. It has been suggested that very dense B-lines, i.e. more than 10 per screen or only 3 mm apart, favour the diagnosis of ARDS.^{8,23}

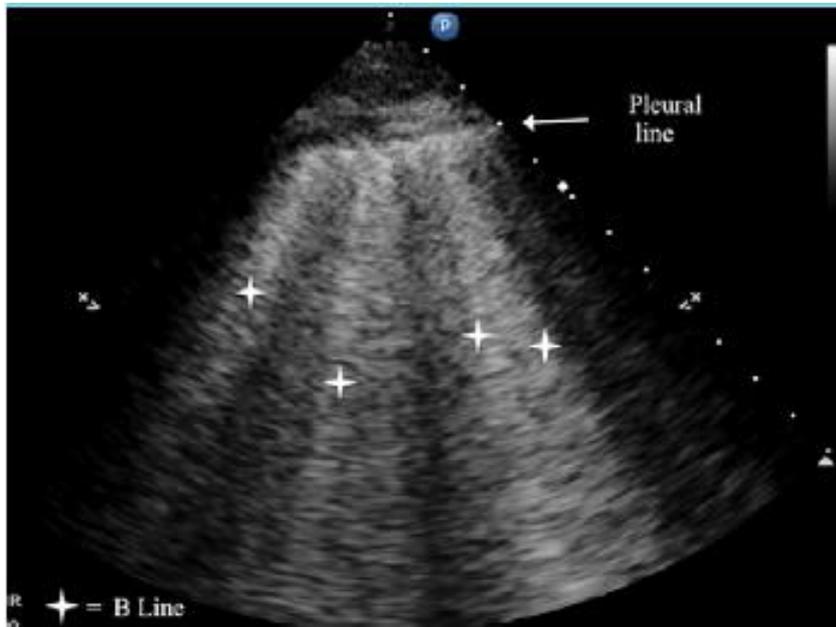


Figure 2d. B-lines

C-lines, air bronchogram, shred sign and pleural effusions

Alveolar consolidation causes typical ultrasound patterns at the different scanning points. At the anterior points, this yields C-lines, identified by a curvilinear aspect of the pleural line (*figure 2e*). This is caused by adjacent consolidated tissue.²³ Pulmonary consolidations are fluid disorders. The non-aerated lung tissue is therefore easily traversed by ultrasound beams and creates an image comparable with that of liver tissue (*figure 3a and b*). Virtually all consolidations touch the pleural line. However, because of gravity, consolidation usually appears first at the PLAPS point.¹⁴



Figure 2e. C-line

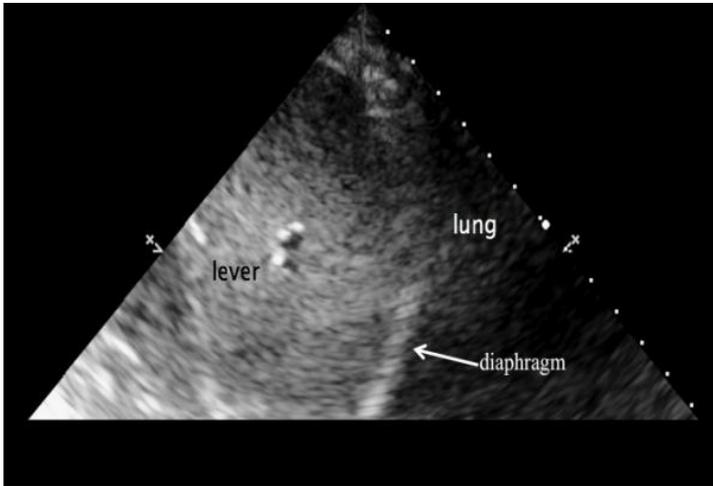


Figure 3a. Normal lung in posterolateral alveolar and/or pleural syndrome point.



Figure 3b. Consolidated lung and pleural effusion in posterolateral alveolar and/or pleural syndrome point with air bronchogram and shred sign

For similar reasons, pleural effusions also first appear at the PLAPS point (*figure 3b*). They can be hypoechoic or hyperechoic with particles. Hyperechoic effusions are associated with exsudate, but accuracy is not perfect.[25] Hyperechoic effusions in combination with consolidated lung tissue at the PLAPS point are associated with the diagnosis of pneumonia. Consolidations can be further analysed by looking for air bronchograms or the shred sign (*figure 3b*). An air bronchogram is caused by reflection of ultrasound beams in the air-filled bronchi surrounded by consolidated tissue. The shred sign appears when the border of aerated lung and consolidated lung is not sharp. Both are suggestive of pneumonia. Furthermore LUS will identify the presence, size, and nature of an effusion and can be used to guide thoracocentesis (*figure 3b*).

The decision tree

We propose a decision tree for a structured approach of the dyspnoeic patient using LUS. This is based on the original data from the BLUE study.⁸ This landmark investigation related combinations of ultrasound signs to final diagnosis in acutely dyspnoeic patients presenting at the emergency department. Our decision tree consists of binary questions. Answering these rapidly narrows the differential diagnosis with impressive accuracy (*figure 4*).

In addition, *table 3* gives a number of combinations of findings that either directly point to a certain diagnosis or directly exclude it. This may be useful in hyperacute settings.

The protocol starts by scanning the anterior BLUE points. The first step in our decision tree is to identify line artefacts. These determine the BLUE profile, depending on the predominance of anterior artefacts. Thus, A and B profiles are distinguished. If one lung shows A-predominance and the other B-predominance, this is called the A/B profile. If any anterior C-line is noted, the C-profile is said to be present, regardless of other artefacts. In case of A or B profiles, the decision tree calls for further analysis based on combinations of lung sliding, findings at the PLAPS point, identification of a lung point and/or venous analysis.

Imaging both PLAPS points again aims to answer a binary question. PLAPS is said to be positive if any sign of alveolar consolidation is seen or if any pleural effusion is seen. If not, PLAPS is said to be negative. Of course, more information can be deducted from the exact findings, but for application of the decision tree, this simple yes or no will suffice.

Table 3. Using only the anterior BLUE points for lung ultrasound, certain ultrasound profiles may directly rule in or out various conditions. On further scanning, other profiles show this behaviour as well. These include the lung point, which immediately rules in pneumothorax, and various combinations of findings (*figure 4*). Data based on the original BLUE protocol study

Finding	Rules out	Rules in
A/B profile		PNA* (100%)
C profile		PNA* (90%)
Lung sliding	PTX (0%)	
B profile	PTX (0%), OBS (3%), PE (0%)	
B profile AND lung sliding		EDE (87%)
B profile WITHOUT lung sliding		PNA* (100%)

* denotes that the diagnosis of ARDS is also possible for that finding. PNA = pneumonia; EDE = cardiogenic pulmonary oedema; PTX = pneumothorax; OBS = chronic obstructive pulmonary disease or asthma; PE = pulmonary embolism.

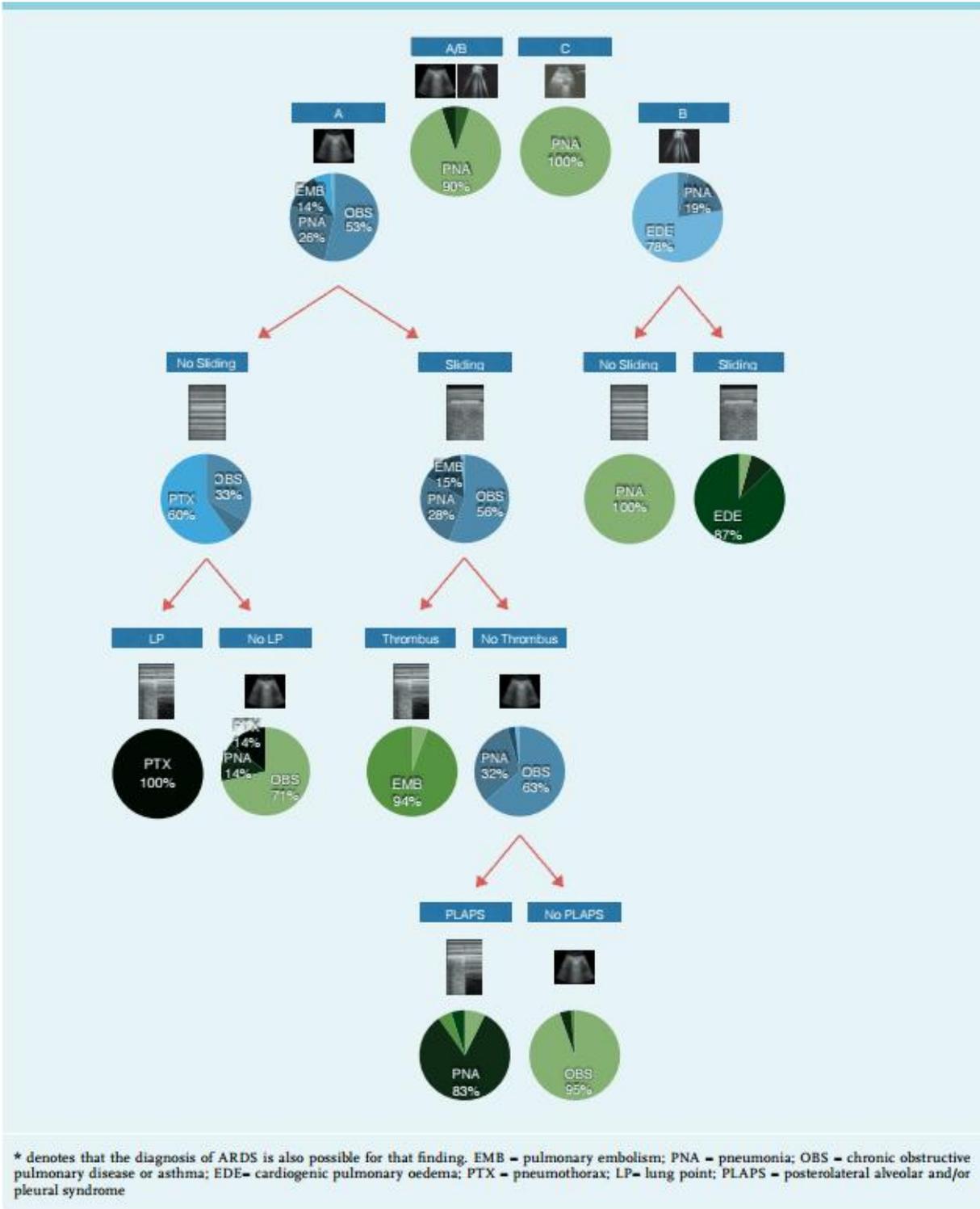


Figure 4. Schematic overview to guide physicians in using lung ultrasound. A step-by-step approach is provided including typical ultrasound findings. Pie graphs represent the differential diagnosis at each step, including percentages of incidence. Green pie graphs indicate the end of the protocol, as only one likely diagnosis remains. All data based on the original BLUE study. Confirmatory findings for the various diagnosis groups include the following: Cardiogenic pulmonary oedema – cardiac ultrasound for left ventricular systolic and diastolic dysfunction and atrial dimensions, NT-pro BNP^{26,27}; Pulmonary embolism –

cardiac ultrasound for right heart dimensions, D-dimer²⁸; Pneumonia – shred sign, air bronchogram, infection parameters such as white blood cell count and differential, C-reactive protein and procalcitonin; ARDS – very dense B-lines, abolished lung sliding, shred sign, air bronchogram

Identification of the lung point to confirm the presence of pneumothorax becomes necessary if an A-profile is present without lung sliding. Starting at the BLUE point where lung sliding was found to be absent, the operator moves the probe down the chest, while staying at the same intercostal space to search for the lung point. This is the point on the thorax where the visceral pleura is sliding in and out of the ultrasound image, due to respiratory movement (*figure 5a*). This implies that M-mode imaging at the lung point will yield a pattern that alternates between the seashore sign and the stratosphere sign. Interestingly, LUS was shown to be superior to bedside chest radiographs for the detection pneumothorax.[12] In addition, the size of the pneumothorax may be estimated from the distance between the lung point and the sternum, as the pneumothorax extends anteriorly from this point.

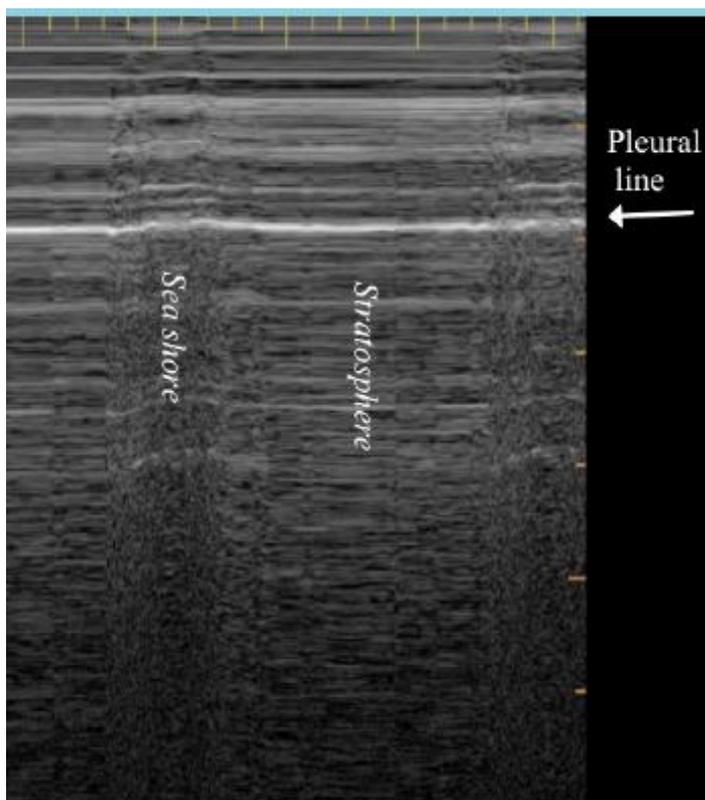


Figure 5a. M-mode scanning at the lung point in pneumothorax

Venous analysis is not performed routinely for LUS, but can be of great help in the setting of A-lines with lung sliding. Presence of thrombus in the large veins of the lower extremity strongly suggests pulmonary embolism as the final diagnosis in this situation. Subtle

compression manoeuvres starting from the femoral vein can distinguish thrombus from patent veins. Veins can usually be followed up to the popliteal fossa with relative ease. However, venous analysis is not an absolute requirement to narrow down the differential diagnosis.

Using the diagnostic tree is fairly straightforward. For example: the presence of lung sliding, bilateral A-lines but without evidence of PLAPS leads to the diagnosis of COPD/asthma.

Become an early adapter

There are limited data on the efficiency of LUS education. Lichtenstein suggests that short sessions, with a total duration of 90 minutes, focusing on lung sliding (yes/no) and searching for B-lines (yes/no), yield an average accuracy of 95%.[23] Medical students using ultrasound identified abnormalities more accurately than certified specialists who performed physical examination.[29] This stresses that it is not difficult to learn point-of-care LUS. Recently, an international expert group recommended at least 30 studies to achieve global competency in basic critical care echocardiography and we think the same holds true for LUS.[30] Recently, it was suggested to incorporate ultrasound training in standard undergraduate training.[31] Ultrasound can also be used for other parts of the body, for example the abdomen, but this is beyond the scope of this review.

Our experience

At VU University Medical Center (VUmc), we have developed the Intensive Care Ultrasound (ICARUS) protocol and curriculum. The protocol consists of 22 compulsory views (*table 2*). Eight views are devoted to LUS. The other views are dedicated to echocardiography. This can provide further evidence for the BLUE diagnosis, for example in pulmonary embolism (enlarged right heart) or cardiogenic pulmonary oedema (decreased ventricular function).

The program is open to fellows in intensive care medicine and anaesthesiology residents. Intensivists, anaesthesiologists, internists and emergency medicine physicians from the Netherlands and abroad can also take part. Following a two day hands-on introductory course, candidates perform the ICARUS protocol on 50 patients in their own hospital. After 5-10 patients, external candidates return to VUmc for hand-on refinement of their technique on VUmc patients. Following a practical and theoretical exam, candidates become ICARUS certified and are able to perform LUS for clinical purposes. Endorsement of the ICARUS certification program by the Netherlands Society for Intensive Care Medicine and other ultrasound courses may facilitate widespread dissemination of ultrasound knowledge amongst physicians, including those specialising in internal medicine, in all hospitals in the Netherlands.

Limitations

Performing a LUS examination and interpreting the acquired images correctly requires formal training. The reliability of LUS is therefore dependant on the experience of the ultrasonographer. It is important to note that point-of-care ultrasound does not replace specialised ultrasound examinations by comprehensively trained physicians, such as an echocardiography by a cardiologist. Also patient-dependent factors such as obesity, the presence of subcutaneous emphysema and wound dressings alters the transmission of ultrasound beams and makes ultrasound a challenge in some patients. Most of the studies validated ultrasound for acute dyspnoeic patients in the emergency department and ultrasound has yet to be validated for other indications.⁸ Acquired images should be uploaded to a hospital server so they can be reviewed by more experienced ultrasonographers, discussed with colleagues and used to compare with newer images to evaluate the effect of initiated therapy or progress of the disease over time.

Conclusion

LUS is a rapid diagnostic bedside tool that is easily accessible for internists and should therefore be considered an extension of physical examination and used in combination with laboratory tests and when needed other imaging techniques. Answering clinical questions with LUS enables immediate therapy for potentially lethal conditions. LUS will give the internist an advantage in clinical care in the near future.

References

1. Laennec RTH, Forbes J. A treatise on the diseases of the chest and on the mediate auscultation. S. Wood & Sons; 1830.
2. Butman SM, Ewy GA, Standen JR, Kern KB, Hahn E. Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. *J Am Coll Cardiol.* 1993 Oct;22(4):968-74.
3. Hagaman JT, Rouan GW, Shipley RT, Panos RJ. Admission chest radiograph lacks sensitivity in the diagnosis of community-acquired pneumonia. *Am J Med Sci.* 2009 Apr;337:236-40.
4. Esayag Y, Nikitin I, Bar-Ziv J et al. Diagnostic Value of Chest Radiographs in Bedridden Patients Suspected of Having Pneumonia. *Am J Med.* 2010;123:88.e1–88.e5.
5. Greenbaum DM, Marschall KE. The value of routine daily chest x-rays in intubated patients in the medical intensive care unit. *Crit Care Med.* 1982;10:29-30.
6. Bekemeyer WB, Crapo RO, Calhoun S, Cannan CY, Clayton PD. Efficacy of Chest Radiography in a Respiratory Intensive-Care Unit - a Prospective-Study. *Chest.* 1985;88:691-6.
7. Mayo JR, Aldrich J, Müller NL. Radiation Exposure at Chest CT: A Statement of the Fleischner Society. *Radiology.* 2003;228:15-21.
8. Lichtenstein DA, Mézière GA. Relevance of Lung Ultrasound in the Diagnosis of Acute Respiratory Failure. *Chest.* 2008;134:117-25.
9. Lichtenstein DA. Lung ultrasound in the critically ill. *Ann Intensive Care.* 2014;4:1.
10. Mouratev G, Howe D, Hoppmann R et al. Teaching medical students ultrasound to measure liver size: comparison with experienced clinicians using physical examination alone. *Teach Learn Med.* 2013;25:84-8.
11. Liebo MJ, Israel RL, Lillie EO, Smith MR, Rubenson DS, Topol EJ. Is pocket mobile echocardiography the next-generation stethoscope? A cross-sectional comparison of rapidly acquired images with standard transthoracic echocardiography. *Ann Intern Med.* 2011;155:33-8.
12. Alrajab S, Youssef AM, Akkus NI, Caldito G. Critical Care | Abstract | Pleural ultrasonography versus chest radiography for the diagnosis of pneumothorax: review of the literature and meta-analysis. *Crit Care.* 2013;17:R208.
13. Lichtenstein D, Hulot JS, Rabiller A, Tostivint I. Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. *Intens Care Med.* 1999;25:955-8.
14. Lichtenstein DA, Lascols N, Mézière G, Gepner A. Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intens Care Med.* 2004;30:276-81.
15. Lichtenstein DA, Mézière G, Biderman NP, Gepner A, Barré O. The Comet-tail Artifact. *Am J Respir Crit Care Med.* 1997;156:1640-6.
16. Lichtenstein DA, Mézière G, Biderman P, Gepner A. The comet-tail artifact: an ultrasound sign ruling out pneumothorax. *Intens Care Med.* 1999;25:383-8.
17. Lichtenstein DA, Mézière G, Lascols N et al. Ultrasound diagnosis of occult pneumothorax. *Crit Care Med.* 2005;33:1231-8.
18. Bosch FH, Maaten ter JC, Geers A, Gans R. Binary ultrasonography for the internist: yes or no, that's the question! *Neth J Med.* 2012;70:473-5.

19. Goldstein A. Overview of the physics of US. *Radiographics*. 1993;13:701-4.
20. Lawrence JP. Physics and instrumentation of ultrasound. *Crit Care Med*. 2007;35:S314-22.
21. Weinberger SE, Drazen JM. Diagnostic procedures in respiratory diseases. In: Kasper DL, Braunwald E, Fauci AS et al., editors. *Harrison's Principles of Internal Medicine*. 16th edition. New York: McGraw-Hill; 2005:1505-8.
22. Desai SR, Hansell DM. Lung imaging in the adult respiratory distress syndrome: current practice and new insights. *Intens Care Med*. 1997;23:7-15.
23. *Whole Body Ultrasonography in the Critically Ill*. Springer Berlin Heidelberg; 2010.
24. Lichtenstein DA, Menu Y. A Bedside Ultrasound Sign Ruling Out Pneumothorax in the Critically Ill: Lung Sliding. *Chest*. 1995;108:1345-8.
25. Barillari A, Fioretti M. Lung ultrasound: a new tool for the emergency physician. *Intern Emerg Med*. 2010;5:335-40.
26. Bataille B, Riu B, Ferre F, et al. Integrated use of bedside lung ultrasound and echocardiography in acute respiratory failure: a prospective observational study in ICU. *Chest*. 2014;14-0681.
27. Mant J, Doust J, Roalfe A, Barton P, Cowie MR. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. *Health Technol Assess*. 2009;13:1-207.
28. Tick LW, Nijkeuter M, Kramer MHH et al., High D-dimer levels increase the likelihood of pulmonary embolism. *J Intern Med*. 2008;264:195-200.
29. Kobal SL, Trento L, Baharami S et al., Comparison of Effectiveness of Hand-Carried Ultrasound to Bedside Cardiovascular Physical Examination. *Am J Cardiol*. 2005;96:1002-6.
30. Expert Round Table on Ultrasound in ICU. International expert statement on training standards for critical care ultrasonography. *Intens Care Med*. 2011;37:1077-83.
31. Solomon SD, Saldana F. Point-of-care ultrasound in medical education--stop listening and look. *New Engl J Med*. 2014;370:1083-85.

Chapter 7

Lung ultrasound: the need of an adequate training for next generation of internists.

Letter to the editor from F.M. Trovato and G. Musumeci
&
Response to the letter to the editor

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Letter to the editor

We read with interest the review by Touw *et al.*¹ and the related editorial,² which warmly warrant the use of ultrasound for internists. We would respectfully remark that an adequate comprehensive training is needed to teach and learn the uses and limitations of ultrasound.³ An optimal ultrasound examination of a dyspnoeic patient should be done in sitting position, since it is unlikely that a dyspnoeic patient can lie in a supine position. Moreover, differently from what was suggested,¹ the pleural surface is most accessible from the back with longitudinal and transversal intercostal and paravertebral scans.³ The lung ultrasound (LUS) artifacts arise from the difference in acoustic impedance in the pleural spaces and have been classified as simple reverberation (horizontal A-line), 'comet-tail' and 'ring-down' (vertical B-line) artifacts, but some confusion of these terms is apparent,¹ (that 'comet tail' is considered to be a synonym of B-line).⁴ Although Touw *et al.*¹ suggested suppressing all software artefact reduction and image optimisation and prefer the high frequency and high resolution linear probe, which reduces the number of artifacts, most of the images shown in the paper¹ are taken by a sector probe, useful to scan between the ribs, but with poor near-field resolution to evaluate pleural line and useless for LUS. It is unrealistic to suppose that LUS allows us to distinguish easily between pulmonary oedema, COPD, asthma, pulmonary embolism, pneumothorax and pneumonia with sensitivities and specificities ranging from 81 to 100%, since even large lung consolidations, easily detectable by X-ray, can only be evaluated by ultrasound if no air is obstructing the beam's passage and their nature is not identifiable by the sole ultrasound imaging, since cancer, atelectasis and pneumonia have similar aspect.³ Moreover alveolar consolidations, in contrast to pleural effusion, do not appear first on a postero-basal scan; only aspiration pneumonia of mechanically ventilated patients arises in this way.⁶ Regarding diffuse lung disease the statement 'LUS does not require any cardiac ultrasound imaging, as a cardiac cause of dyspnoea can be diagnosed from lung imaging only',¹ is quite hazardous. The certainty that more than two anterior B-lines are pathological and indicate interstitial syndrome and thus pulmonary oedema, and that the number of B-lines per screen or the distance between B-lines allows assessment of severity is quite odd due to the variability related to different probes and setting, particularly in a moving dyspnoeic patient. The protocol proposed is not a good way to spread the use of ultrasound in the daily clinical practice since formal training incorporating ultrasound in adequate curricula is crucial for physicians,⁵ avoiding simplistic numeric rules, since medicine is not arithmetic.

References

1. Touw HR, Tuinman PR, Gelissen HP, et al. Lung ultrasound: routine practice for the next generation of internists. *Neth J Med.* 2015;73:100-7.
2. Alsmas J, Bosch FH. Ultrasound for internists: changing bedside examination. *Neth J Med.* 2015;73:98-9.
3. Sperandio M, Rotondo A, Guglielmi G, Catalano D, Feragalli B, Trovato GM. Transthoracic ultrasound in the assessment of pleural and pulmonary diseases: use and limitations. *Radiol Med.* 2014;119:729-40.
4. Trovato GM, Sperandio M. Sounds, ultrasounds, and artifacts: which clinical role for lung imaging? *Am J Respir Crit Care Med.* 2013;187:780-1.

Response to the letter to the editor

We would like to thank Trovato and Musumeci for their letter. We share their opinion that comprehensive training is required for lung ultrasound (LUS). This is exactly why we designed our Intensive Care Ultrasound (ICARUS) curriculum as described in our paper.[1] Alisma *et al.* even recommend this program in their editorial.[2] ICARUS includes basic cardiac ultrasound but this was beyond the scope of our review. However, LUS can differentiate between most causes of dyspnoea,[1,3] although Bataille *et al.* described significant advantages of an integrative cardiopulmonary ultrasound approach.[4] We have chosen to follow the BLUE protocol, with its impressive sensitivity and specificity. Of course it should be remembered that this study was performed in dyspnoeic patients in the emergency room. However, the physiological principles of ultrasound artifacts are universal. Lung consolidations may arise at any point, but touch the pleural surface in 98% of cases. Of course, this implies that LUS sensitivity will depend on the extent of scanning. However, most cases (90%) include findings at the PLAPS point,[5] which is part of the BLUE protocol. When choosing the optimal probe, bedside trade-offs need to be made between form factor, ergonomics, scanning depth and resolution. For speed and simplicity we tend to use only one probe (1-5 Mhz sector array), generating the obvious artifacts seen in our figures. Its shape allows satisfactory scanning of the intercostal spaces and facilitates cardiac imaging as well. Of course, the vascular probe (10+ Mhz, curved array) and the abdominal probe (1-5 Mhz, curved array) are also useful.[1]

Answering clinical questions with LUS enables immediate therapy for potentially lethal conditions. We therefore continue to feel that LUS should be standard practice.

References

1. Touw HR, Tuinman PR, Gelissen HP, et al. Lung ultrasound: routine practice for the next generation of internists. *Neth J Med.* 2015;73:100-7.
2. Alisma J, Bosch FH. Ultrasound for internists: changing bedside examination. *Neth J Med.* 2015;73:98-9.
3. Lichtenstein DA, Mézière GA. Relevance of Lung Ultrasound in the Diagnosis of Acute Respiratory Failure. *Chest.* 2008;134:117-25.
4. Bataille B, Riu B, Ferre F, et al. Integrated Use of Bedside Lung Ultrasound and Echocardiography in Acute Respiratory Failure A Prospective Observational Study in ICU. *Chest* 2014;146:1586-93.
5. Lichtenstein D, Lascols N, Mezière G, et al. Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive Care Med.* 2004;30:276-81.

Chapter 8

Diagnostic Accuracy of Chest Radiograph, and When Concomitantly Studied Lung Ultrasound, in Critically Ill Patients With Respiratory Symptoms: A Systematic Review and Meta-Analysis.

Michiel H. Winkler, Hugo R.W. Touw, Peter M. van de Ven, Jos W. Twisk and Pieter R. Tuinman.

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Abstract

Objective

Chest X-ray (CXR) is considered the first line diagnostic imaging modality for patients presenting with pulmonary symptoms in the intensive care unit (ICU).

In this meta-analysis we aim to evaluate the diagnostic accuracy of CXR, and when concomitantly studied lung ultrasound (LUS), in comparison to the gold standard Computed Tomography (CT) for adult critically ill patients with respiratory symptoms.

Data Sources

PubMed, Embase and Grey literature.

Study Selection

Studies comparing CXR, and if performed LUS, to CT for adult ICU patients with respiratory symptoms.

Data Extraction

Quality was scored with QUADAS-2 and study setting, test characteristics and study design were extracted.

Data Synthesis

In the meta-analysis we included 10 full text studies, including 543 patients and found that CXR has an overall sensitivity of 49% [95% CI 40-58%] and specificity of 92% [86-95%]. In seven studies, where also LUS was studied, LUS had an overall sensitivity of 95% [92-96%] and specificity of 94% [90-97%]. Substantial heterogeneity was found. A planned subgroup analysis for individual pathologies was performed. The results of four abstract only studies, included in the systematic review, were considered unlikely to significantly influence results of our meta-analysis. Study limitations were that most studies were of low power combined with methodological limitations.

Conclusion

This meta-analysis demonstrates that CXR has a low sensitivity and reasonable specificity compared to CT for detecting lung pathology in critically ill patients. The studies also investigating LUS, showed LUS to be clearly superior to CXR in terms of sensitivity with similar specificity, thereby opting to be the first line diagnostic tool in these patients.

Introduction

Chest X-ray (CXR) is considered the first line diagnostic imaging modality for almost all patients presenting with pulmonary symptoms.^{1,2} However, studies showed that diagnostic accuracy of CXR is relatively low. This leads to frequent false negative or false positive interpretations and hence inadequate therapy.^{3,4} In addition, CXR has several technical limitations that further jeopardise accurate diagnosis, especially in intensive care unit (ICU) patients.⁵

Exact accuracy has not been studied in a meta-analysis in adult critically ill patients however. Chest computed tomography (CT) is considered the gold standard for detecting respiratory pathology in acute dyspneic patients.⁶ Although accuracy of diagnosis is higher, CT has considerable limitations of its own, such as the transport of critically ill patients, contrast fluid and radiation exposure, and high cost.⁷

Multiple studies on the use of LUS in the ICU and emergency department have been published.

Especially in the ICU, when dealing with critically ill patients, LUS has potential advantages over CT and CXR as it can be performed at the bedside and without the described limitations of CT.⁸

Despite the aforementioned, CXR is still the first line of diagnostic chest imaging for patients with pulmonary symptoms in the ICU.

In this systematic review and meta-analysis we aim to investigate the diagnostic accuracy of CXR, and when concomitantly investigating LUS, compared to the gold standard CT in critically ill adult patients with respiratory symptoms.

Objectives

Primary Objective

To evaluate the diagnostic accuracy of CXR compared to CT in critically ill adult patients (≥ 18 years) with respiratory symptoms.

Secondary objectives

To evaluate the diagnostic accuracy of LUS compared to CT in critically ill patients with pulmonary symptoms, when also investigated in the included studies.

Material and Methods

Study design

This is a systematic review and meta-analysis. To improve the quality of our systematic review, PRISMA-guidelines were followed. The protocol was registered: PROSPERO CRD42016041448.

Selection of studies

Studies: randomized controlled trials, cross-sectional case control and observational studies.

Population: patients ≥ 18 years admitted to the ICU, with pulmonary symptoms (diagnosis included are among others: pneumothorax, pleura effusion, pulmonary edema, pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), who have an indication for CT.

Index test: CXR for the diagnosis of pulmonary symptoms; data on accuracy of LUS were also collected from studies that also investigated LUS.

Outcome: all data concerning diagnostic accuracy (sensitivity (SN), specificity (SP), positive predictive value (PPV) and/or negative predictive value (NPV)).

Reference standard: CT.

Exclusion criteria

- 1) *Measurements:* CXR for other reason than cardiopulmonary pathology.
- 2) Outcome: unable to determine accuracy, only determination of inter-observer agreement, no CT for comparison.
- 3) No abstract available.
- 4) Language: Abstract not in English.
- 5) Articles with only an abstract, but no full-text available or full-text in English were excluded from qualitative assessment and meta-analysis but were included in the systematic review for separate quantitative analysis when enough data was available regarding sensitivity, specificity and diagnostic accuracy.

These exclusion criteria were modified after screening of the abstracts. Several abstracts were identified without (English) full text that provided sufficient data on accuracy. Some studies were excluded based on more than one exclusion criteria. These studies are mentioned in one of the exclusion groups.

Literature search strategy

After consulting a medicine literature search specialist, we searched EMBASE and Pubmed for relevant articles up until April 2016. The selected articles were checked for backward and forward citations by hand search. We used Mendeley Software. Finally we searched for Grey

literature at OpenGrey (www.opengrey.eu), BASE (www.base-search.net) and at the National Library of Medicine's clinical trial registry (www.clinicaltrials.gov). Full search strategy was added as an appendix (n° 1).

Data extraction

Selection of studies and data extraction were performed by two independent reviewers (MW and PRT). Disagreement was resolved by consensus meetings with a third reviewer (HT).

Characteristics of data collected: setting, time between index test and reference test, test characteristics, study design.

Results: 2 x 2 table, SN, SP, PPV, NPV. Results were categorized according to the diagnosis investigated.

Quality assessment

The QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies) was used (9). Quality assessment was done by two independent reviewers (MW and PRT) and disagreement was resolved with a third reviewer (HT). Quality assessment was only performed on the full-text studies that were included in the meta-analysis

Statistical analysis and data synthesis

Pooled estimates of sensitivity and specificity were obtained by fitting a bivariate model on the raw study data. In the bivariate model pairs of sensitivity and specificity are jointly analyzed and the correlation that exists between these two measures obtained in a single study is then taken into account through the inclusion of a random effect for study in the model.

Results are presented with a 95% Confidence Interval [CI]. The models were estimated in STATA version 14. The Midas module for STATA was used to make forest plots and to estimate heterogeneity. Hierarchical summary receiver operating characteristic (HSROC)-curves for CXR and LUS, respectively, were made.

For studies with repeated measurements per patient (e.g. on different lung field or different regions of the hemothorax) the numbers of true/false negatives and true/false positives were reweighted in such a way that the total number matched the number of patients in the study. Publication bias was assessed using the Egger test for funnel plot asymmetry.

Results

Details regarding the study selection are presented in Figure 1. The search yielded 9230 articles. We included 10 studies, involving 543 patients, that underwent qualitative assessment. Additionally, we included two of the evaluated 617 non English articles studies^{10,11} with only their abstract written in English and two studies^{12,13} of which we were unable to get a full text, resulting in 323 extra patients.

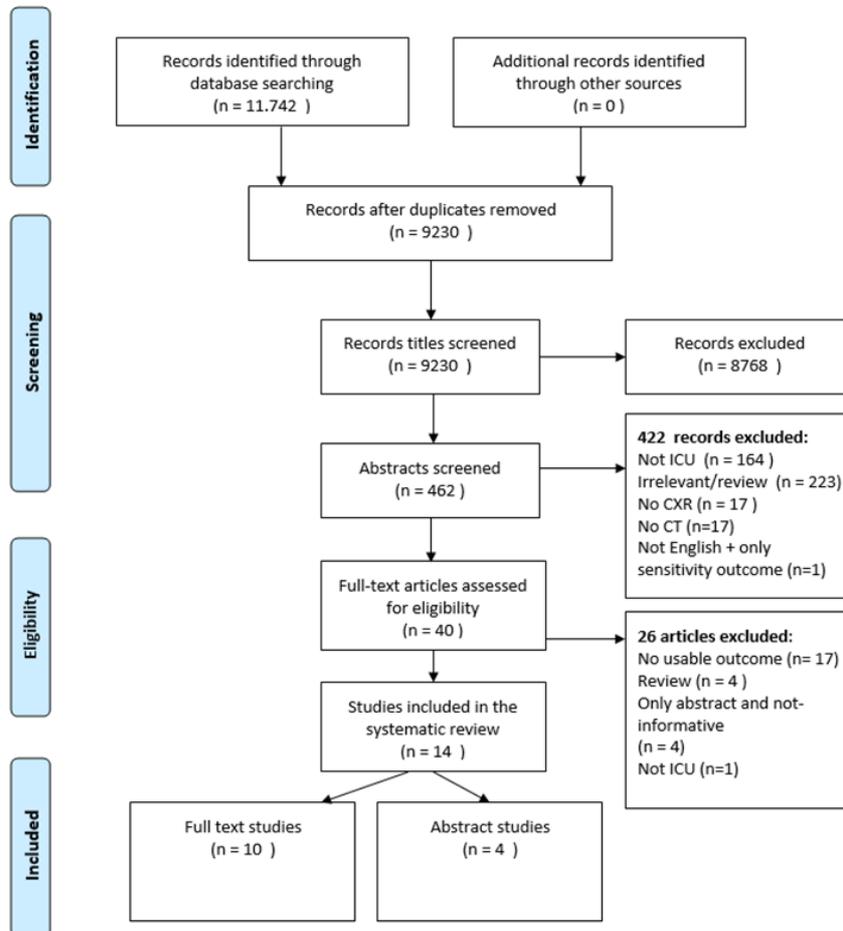


Figure 1 - PRISMA flow diagram

In table 1 study characteristics are summarized. The last four articles¹⁰⁻¹³ are abstract-only studies. In two studies it was unclear who evaluated the CXR^{14,15} and in three it was unclear how many reviewers evaluated the CXR.^{14,16,17} Two studies selected patients retrospectively.^{16,18} There were seven full-text and three abstract-only, who also evaluated the diagnostic accuracy of LUS compared to CT.^{5, 11-15, 17, 19-21}

Table 1. Characteristics of included studies.

AUTHOR	STUDY DESIGN	DEPARTMENT, PERIOD	PATIENTS WITH... (n) and CXR/LUS protocol	INVESTIGATOR (n)
Full text				
Lichtenstein <i>et al</i> (5)	Observational	ICU, unknown	ARDS (n=32) and healthy controls (n=10): total lung regions (n=384); CXR: 12 regions, according to Fleischner society(33) and lung pathology according to ARDS criteria(34, 35); LUS: 12 regions, 5MHz probe. AIS: >2 B lines in a given region. CS: air bronchogram. PIE: a dependent collection limited by the diaphragm and the pleura.	CXR: Radiologist (n=1) LUS: operator(n=1) CT: radiologist (n=1)
Xirouchaki <i>et al</i> (21)	Observational	ICU, unknown	Mechanical ventilation (n=42): total of hemi-thoraces (n=84) CXR: 12 regions, according to Fleischner society(33) LUS: 12 regions, probe not reported. Same protocol Lichtenstein(5)	CXR by: radiologist (n=1) LUS: operator(n=1) CT: radiologist (n=2)
Kitazono <i>et al</i> (18)	Observational; retrospective	ICU, Oct 2007 to Nov 2007	Critical illness at the surgical ICU (n=100): total of 200 hemi-thoraces CXR: According to 5 point likelihood scale(18) ¹⁶ .	CXR: radiologist of varying experience (n=4) CT: most experienced radiologist (n=1)
Figueroa-casas <i>et al</i> (20)	Observational; retrospective	ICU, Mar 2009 to Oct 2011	Clinically suspected ARDS (n=90). CXR: According to Fleischner society(33)	CXR/ CT: fellow radiologist (n=2)
Rocco <i>et al</i> (22)	Observational	ICU, Feb 2006 to Jan 2007	Trauma, requiring mechanical ventilation (n=15): total lung regions (n=180); CXR PE: generalized increased opacity. LC: homogenous hazy parenchymal consolidation/interstitial form of irregular infiltration; LUS: 12 regions, 3.5MHz probe. PE: a dependent collection either anechoic or echoic. LC: hypoechoic blurred lesion/ multiple vertical hyperechogenic lines.	CXR: Radiologist (n=?) LUS: operators (n=2) CT: unclear

Voggenreiter <i>et al</i> (24)	Observational	ICU, 40 months period	Multiple injuries and intubation because of respiratory insufficiency (n=39): total of 101 CT; CXR: PTX: air collection without signs of lung parenchyma. HT: (30-100 HU); PIE (0-30 HU); AT: opacities within anatomical limits. CS: circumscribed opacities with air bronchograms;	CXR: investigators (n=3) CT: unclear
Nafae <i>et al</i> (16)	Observational	Respiratory-ICU, Sep 2011- Dec 2012	Clinically suspected of PNA (n=100). CXR: unclear; LUS: 10 regions total, 5MHz probe. PNA: air- and fluid bronchogram(16).	Unclear for CXR/CT LUS: physician (n=1)
Bilotta <i>et al</i> (19)	Observational	Neurocritical care unit, Jan 2003 to May 2004	Neurological symptoms (n=34) screened on admission and received CT: total of 272 lung regions; CXR: 8 regions, According to Fleischner society(33); LUS: 5-10MHz probe, Devided in 8 regions and search for 'B-line' diagnosis(36).	CXR: radiologist (n=?) LUS: 'operator' (n=1) CT: unclear
Razazi <i>et al</i> (23)	Observational	ICU, Jun 2011 to Apr 2014	ACS (n=41); CXR: 12 regions according to Fleischner society(33); LUS: 12 regions, 3-5Mhz probe. Same protocol LUS(5)	CXR/CT: radiologist (n=1) LUS: operator (n=1)
Helmy <i>et al</i> (17)	Observational	ED and ICU, unknown	Isolated blunt trauma or poly-trauma with chest involvement (n=50) CXR: unclear; LUS: 5Mhz probe. According to blue protocol(37)	Unclear for CXR, LUS and CT
Abstracts				
Vaghasia <i>et al</i> (14)	Observational	ICU, unknown	MV patients (n=13) at the ICU, CXR and LUS protocol unknown	Radiologist (n=1)
Agmy <i>et al</i> (15)	Observational	ICU, unknown	MV patients (n=200) at the ICU, CXR and LUS protocol unknown	Unclear
Schäfer <i>et al</i> (12)	Observational	ICU, unknown	ICU patients (n=32) at the ICU, CXR and LUS protocol unknown	Radiologist (n=3)
Wang <i>et al</i> (13)	Observational	ICU, Jun 2010 to Dec 2011	Patients with MV more than 48 hours (n=78), at the ICU, CXR and LUS protocol unknown	Unclear

ACS: acute chest syndrome; AIS: alveolar interstitial syndrome; AT: atelectasis; CS: consolidations; CXR: chest radiograph; ED: Emergency Department; HT: hemothorax; HU: houndsfield units. ICU: Intensive Care Unit; MV: mechanically ventilation; LC: lung contusion; PIE: pleural effusion; PNA: Pneumonia; PTX: pneumothorax.

Figure 2 shows a forest plot for the individual study- and pooled results for the primary outcome, sensitivity and specificity of CXR. Figure 3 shows a forest plot for the secondary outcome, sensitivity and specificity of LUS. Pooled results of CXR and LUS accuracy for the different pathologies investigated, are presented in Table 2. All individual study results for CXR and LUS accuracy are presented in Appendix 2 (Table S1) and 3 (Table S2). HSROC curves showing study heterogeneity for both CXR and LUS are presented in Figures 4a and 4b, respectively.

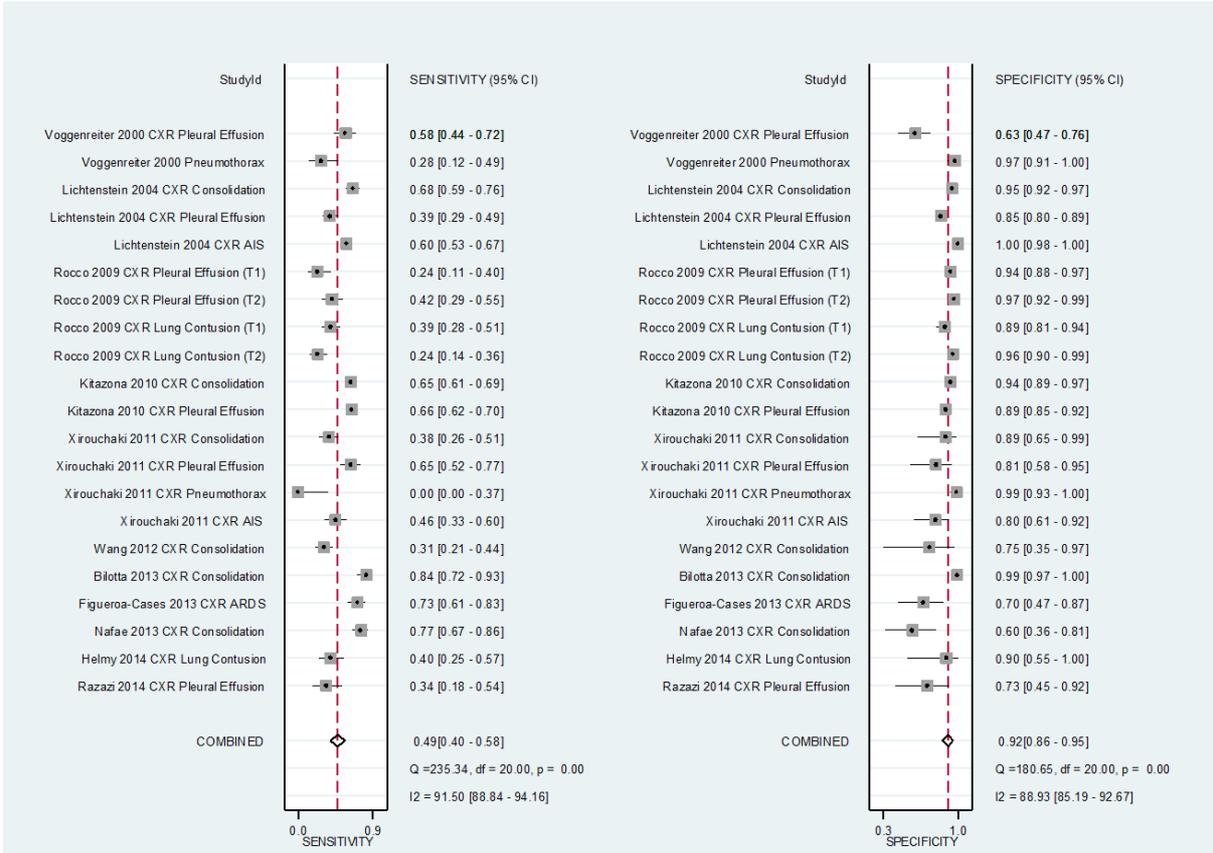


Figure 2. Forest plot of the sensitivity and specificity of chest X-ray compared to computed tomography in critically ill patients

Several studies used repeated measurements per patient (e.g. measurements on different regions of hemothorax, different ACS episodes or different lung fields). For these studies the numbers of FP, FN, TP and TN were reweighted in such a way that the total number matched the total number of patients in the sample. This yields conservative estimates of the confidence intervals (which would have been too narrow if repeated measurements were not accounted for). Voggenreiter consolidation sensitivity (92.3%, 95% CI: [0.84 – 1.00]) was not presented as mentioned in the text.



Figure 3. Forest plot of the sensitivity and specificity of lung ultrasound compared to computed tomography in critically ill patients

Several studies used repeated measurements per patient (e.g. measurements on different regions of hemothorax, different ACS episodes or different lung fields). For these studies the numbers of FP, FN, TP and TN were reweighted in such a way that the total number matched the total number of patients in the sample. This yields conservative estimates of the confidence intervals (which would have been too narrow if repeated measurements were not accounted for). Voggenreiter consolidation sensitivity (92.3%, 95% CI: [0.84 – 1.00]) was not presented as mentioned in the text.

Table 2. The pooled estimates of sensitivity and specificity of chest X-ray and lung ultrasound compared to computed tomography for each pathology investigated in critically ill patients.

Diagnosis	CXR Pooled sensitivity [95% CI]	CXR Pooled specificity [95% CI]	LUS Pooled sensitivity [95% CI]	LUS Pooled specificity [95% CI]
Overall accuracy	49% [CI 40, 58%]	92% [CI 86, 95%]	95% [CI 92, 96%]	94% [CI 90, 97%]
Consolidations	69% CXR: ns=7, np=349 LUS: ns=5, np=249 [49%, 84%]	90% [75%, 96%]*	97% [91%, 99%]	91% [79%, 96%]
Pleural effusion	55% CXR: ns=6, np=276 LUS: ns=4, np=137 [42%, 66%]	82% [73%, 89%]	98% [87%, 100%]	94% [79%, 99%]
Pneumothorax	21% CXR: ns=2, np=81 LUS: ns=1, np=42 [42%, 66%]	100% [0%, 100%]	-	-
Interstitial syndrome	53% CXR: ns=2, np=74 LUS: ns=2, np=74 [35%, 69%]	91% [75%, 97%]	95% [83%, 99%]	91% [75%, 97%]
Lung contusion	38% CXR: ns=2, np=65 LUS: ns=2, np=65 [25%, 51%]	90% [72%, 97%]	98% [87%, 100%]	90% [72%, 97%]

*CXR: Chest X ray; LUS: lung ultrasound; ns= number of studies; np= number of patients; 95% CI: confidence interval; *Voggenreiter specificity was excluded for consolidation. For pneumothorax LUS sensitivity and specificity are left blank because there was only one study and there was not enough data to determine study heterogeneity.*

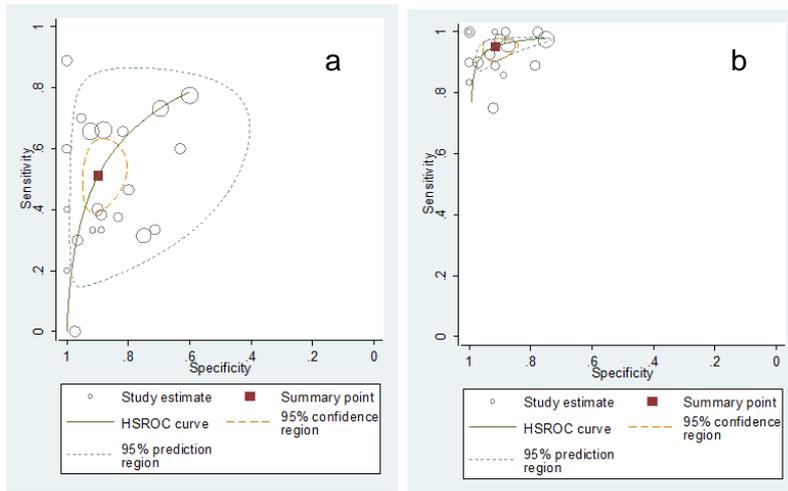


Figure 4. Hierarchical summary receiver operating characteristic (HSROC)-curves for chest radiograph (a) and lung ultrasound (b).

Consolidations

From Voggenreiter et al. data for specificity of CXR for diagnosis of consolidation was excluded because only one observation was available for the estimation of the specificity.²² Sensitivity from same study was not mentioned in Figure 2 because specificity was missing and the forest plot procedure requires both to be filled in. Razazi et al. did not report raw data for consolidations and was therefore also excluded.²¹ In addition, from three abstract-only studies^{11–13}, including 291 patients, the ranges of CXR sensitivity and specificity were 22-40% and 75%-100%, respectively. LUS sensitivity and specificity were 32-100% and 87-100%, respectively.

Pleural effusion/hemothorax

We excluded T2 data from Rocco et al. because they involved the same patients at T1.²⁰ Three abstract-only studies, including 245 patients, found a CXR sensitivity and specificity which ranged from 34-69% and 54-100%, respectively. Two out of these three studies, including 213 patients, reported LUS accuracy with a sensitivity from 47-100% and specificity 82-100%

Pneumothorax

There was not enough data to determine study heterogeneity. One additional abstract-only study, which investigated the presence of pneumothorax in 200 patients, reported a CXR sensitivity of 40% and specificity of 96% and for LUS a sensitivity and specificity of both 100%.¹³

Interstitial syndrome

Two additional, abstract-only, studies were included resulting in an extra 213 patients. Their range for CXR sensitivity were 42-100% and for specificity 82-100%. LUS sensitivity and specificity were 50-95% and 83-95%, respectively.

Other pulmonary pathology

Lung contusion was investigated in two full-text studies including 65 patients.^{15,20} There was one study investigating patients with ARDS including 90 patients.¹⁸ It did not consider LUS. Results from this study were used in the overall sensitivity and specificity of CXR. The CXR sensitivity was 73% [CI 61-83%] with a specificity of 70% [CI 47-87%].

Quality assessment

The risk of bias and applicability concerns are summarized in Table 3. Most studies lacked in some way information about blinding to the reference standard while evaluating the index results or the other way around. Sometimes this was mentioned, but mostly it was simply not presented in the study.

In appendix 4 shows the risk of bias and applicability concerns for each study are further described.

Figure 5 presents the funnel plot with no sign of publication bias found (p=0.69).

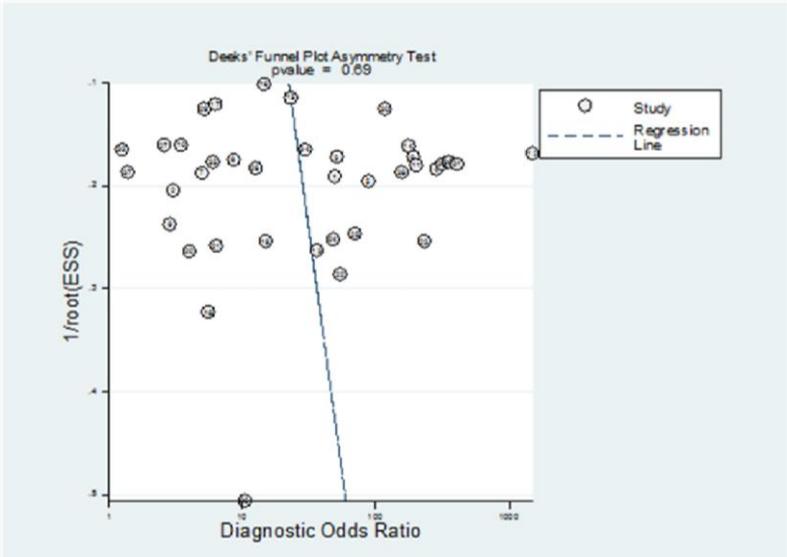


Figure 5. Funnel plot for assessing publication bias.

Table 3. Risk of bias and applicability concerns studies.

Study	Risk of bias					Applicability concerns				
	Patient selection	Index test CXR	Index test US	Reference standard	Flow and timing	Patient selection	Index test CXR	Index test US	Reference standard	
Lichtenstein <i>et al</i> (5)	-	+	+	+	+	+	+	+	+	+
Xirouchaki <i>et al</i> (21)	?	+	+	+	+	+	+	+	+	+
Kitazono <i>et al</i> (18)	?	+	NA	-	-	?	+	NA	-	-
Figuroa-casas <i>et al</i> (20)	-	+	NA	+	?	+	+	NA	+	+
Rocco <i>et al</i> (22)	+	+	+	?	-	+	+	+	+	+
Voggenreiter <i>et al</i> (24)	?	+	NA	-	?	+	+	NA	+	+
Nafae <i>et al</i> (16)	?	?	+	?	?	+	+	+	+	+
Bilotta <i>et al</i> (19)	+	+	+	?	-	+	+	+	?	?
Razazi <i>et al</i> (23)	+	+	+	+	-	-	+	+	+	+
Helmy <i>et al</i> (17)	?	?	+	?	?	-	+	+	+	+

+ low risk; - high risk; ? uncertain risk; NA non available.

Discussion

This meta-analysis on diagnostic accuracy of CXR compared to CT in ICU-patients with respiratory symptoms, found that CXR has an overall low sensitivity of 49% [CI 40-58%] and a good specificity 92% [CI 86-95%]. The seven studies that also compared LUS to CT demonstrated that LUS was clearly superior to CXR in terms of sensitivity 95% [CI 92-96%], with similar specificity 94% [CI 90-97%]. The results of four abstract-only studies, were considered unlikely to significantly influence the results of our meta-analysis because of similar characteristics in terms of study population and accuracy. All studies included had limitations in their design.

Our results contradict the widely held belief that CXR should be the primary thoracic imaging modality in the ICU, considering its significantly low sensitivity for the investigated lung pathologies. Of course, not only test characteristics should influence a physician's decision for diagnostic modality. Clinical suspicion and pre-test probability will also guide the diagnostic process to rule in or out several conditions with high accuracy. Thereby, the potency of CXR in ICU patients with respiratory symptoms to diagnose between different pulmonary conditions is further limited when the prevalence of a condition is low. Since prevalence of pulmonary pathology is lower in patients without symptoms, the additional value of CXR is further impaired.

In stark contrast, LUS sensitivity was above 95% for all four lung pathologies, with a specificity for all pathologies of similar accuracy as CXR. Therefore, LUS seems like a very good alternative in these patients, also because of its bedside availability and fewer downsides over CXR and CT.

Although, the accuracy of CXR for lung pathology is questioned in this meta-analysis, there are situations in which, in an ICU patient with pulmonary symptoms, it might be preferable to use CXR instead of LUS. For example: CXR is considered the gold standard for the detection of nasogastric tube- and central venous line (miss) placement and complication.^{23,24} One should note that LUS is operator dependent and can only be used to its full potential when the clinician masters the technique. By this we emphasize the importance to adjust the choice of diagnostic modality on individual patient level. Moreover, all modalities should be used in guidance with the clinic (e.g. history, laboratory results and setting) and the ability of the physician to adequately use all the data to construct a diagnosis. CT has additional value compared to LUS in situations where higher resolution or quantification of abnormalities is required, e.g. when to aid in difficult diagnosis or to advance our understanding of the pathogenesis and pathophysiology of a disease.²⁵

To our knowledge this is the first systematic review on the diagnostic accuracy of CXR and partly LUS, compared only to the gold standard CT in patients admitted primarily to the ICU and with respiratory symptoms, in which a variety of common lung pathologies were evaluated. Ashton-Cleary et al. also explored the diagnostic performance of LUS and CXR in a critical care population, however they emphasized on LUS and compared it to different kinds of reference standards, including CXR.²⁶ We conducted an extensive search strategy and put emphasis on CXR, with addition of LUS when concomitantly studied, since this is potentially the new first line diagnostic tool in these patients.

As with all systematic reviews, our review was sensitive for publication bias. We could not identify the effect of publication bias on results of a meta-analysis on diagnostic accuracy in the literature, but in meta-analysis on treatment effect, the effect could be overstated by an average 12%.²⁷ To minimize publication bias, we searched in multiple grey-literature databases.

Our meta-analysis was subject to substantial heterogeneity for several reasons. First of all we investigated various pathologies and these were all used in the forest plot (Fig. 2 and 3) as if they were equal to one another. Therefore, we also performed individual sensitivity and specificity analysis for each pathology to reduce heterogeneity (Table 1). Previous meta-analyses on LUS accuracy found also substantial heterogeneity, due to heterogeneity in study population, setting and reference standard, among others.²⁸⁻³⁰ Therefore, in our methods we used strict exclusion criteria for these factors to reduce heterogeneity.

Secondly, our systematic review included a limited number of studies of which only two studies had a study population of 100 participants or more.^{14,16} A study investigating the effect of small trials in 13 meta-analysis, found that small studies tend to have a more beneficial treatment effect.³¹ The authors advise to be careful with the interpretation of small trials especially when they lack high methodological quality.³² The same may hold true for studies on diagnostic accuracy with limited number of patients and cases, where a false negative or positive result can affect accuracy more strongly than with larger studies. In addition, the included studies had methodological shortcomings. Lastly, the number of radiologists who evaluated CXR or physicians who performed LUS were different for many studies. A few studies only used one reader for CXR and one performer for LUS. Most studies did not mention the operator's degree of experience. The unclear and varying level of experience between the operators, is a potential form of bias. The aforementioned makes it difficult to draw firm conclusions.

In this systematic review we primarily focused on the diagnostic accuracy of CXR and LUS versus the gold standard CT in varying lung pathology for patients admitted to the ICU to

assess its use in clinical practice. However, Bossuyt et al. stressed the importance of the clinical utility, ease of implementation and cost-effectiveness next to the accuracy of a diagnostic tool when evaluating its overall performance.³¹ Indeed, we found a better accuracy of LUS compared to CXR but we, and most studies included, did not look at the above-mentioned factors, which might lead to incorrect conclusions about the usefulness of CXR and LUS in clinical practice. One study looked at how diagnostic information influenced therapeutic consequences based on CT results. In over half of their participants, interventions were performed based on CT results and these results were not evident from the CXR.²² In another study, LUS also showed to change patient management in almost half of patients.³³ To our knowledge, there are no studies that contradict the utility of LUS.

There is a need for larger (multicenter) trials to compare CXR and LUS accuracy to the gold standard CT, but also to investigate the cost effectiveness, the ease of implementation and how it affects patient's outcome and performed interventions. However, it is challenging to perform clinical research on patient-centered outcome for a diagnostic modality as isolated variable, as they are often combined with other modalities. Lastly, because different LUS protocols were used in the included studies, it is important to determine if LUS protocols are comparable or one protocol is superior to another.

Conclusions

This study demonstrates that CXR has a low sensitivity and good specificity in critically ill patients with respiratory symptoms when CT is the gold standard. LUS was found to be superior to CXR in these patients as estimates of sensitivity were much higher than for CXR while LUS showed similar (or even higher) specificity. These results question the current use of CXR as the first line diagnostic modality for critically ill patients with respiratory symptoms. LUS seems to be a good alternative. Larger trials are needed that compare CXR to LUS not only for accuracy, but also for effects on outcome, clinical utility, ease of implementation and cost-effectiveness.

References

1. Bourcier J-E, Paquet J, Seinger M, et al.: Performance comparison of lung ultrasound and chest x-ray for the diagnosis of pneumonia in the ED. *Am J Emerg Med* 2014; 32:115–118
2. Chardoli M, Hasan-Ghaliiae T, Akbari H, et al.: Accuracy of chest radiography versus chest computed tomography in hemodynamically stable patients with blunt chest trauma. *Chinese J Traumatol = Zhonghua chuang shang za zhi / Chinese Med Assoc* 2013; 16:351–354
3. Nazerian P, Volpicelli G, Vanni S, et al.: Accuracy of lung ultrasound for the diagnosis of consolidations when compared to chest computed tomography. *Am J Emerg Med* 2015;
4. Henschke CI, Yankelevitz DF, Wand A, et al.: Accuracy and efficacy of chest radiography in the intensive care unit. *Radiol Clin North Am* 1996; 34:21–31
5. Lichtenstein D, Goldstein I, Mourgeon E, et al.: Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004; 100:9–15
6. Bouhemad B, Zhang M, Lu Q, et al.: Clinical review: Bedside lung ultrasound in critical care practice [Internet]. *Crit Care* 2007; 11:7
7. Beckmann U, Gillies DM, Berenholtz SM, Wu AW PP: Incidents relating to the intra-hospital transfer of critically ill patients. An analysis of the reports submitted to the Australian Incident Monitoring Study in Intensive Care. *Intensive Care Med* 2004; 30:1579–85.
8. Touw HRW, Tuinman PR, Gelissen HPMM, Lust E EP: Lung ultrasound: routine practice for the next generation of internist. *Neth J Med* 2015; 73:100–7.
9. Whiting PF1, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA BPQ-2 G: QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155:529–36.
10. Schäfer C, Sokiranski R, Bartzsch OM, et al.: Diagnosis of pleural effusions in intensive-care patients via digital recumbent chest x-ray. A study of CT-validated cases [Internet]. *Anesthesiol Intensivmed Notfallmedizin Schmerztherapie* 1997; 32:109–114.
11. Wang X, Liu D, Zhang H, et al. The value of bedside lung ultrasound in emergency-plus protocol for the assessment of lung consolidation and atelectasis in critical patients. *Zhonghua nei ke za zhi* 2012; 51:948–951.
12. Vaghasia P, Saini P, Bansal R, et al.: Chest xrays versus lung ultraound in mechanically ventilated critical care patients [Internet]. *Am J Respir Crit Care Med* 2014; 189.
13. Agmy G, Mohamed S, Gad Y: Transthoracic chest ultrasound in critically ill patients: Comparison with bedside chest radiography [Internet]. *Eur Respir J* 2014; 44.
14. Nafae R, Eman SR, Mohamad NA, et al.: Adjuvant role of lung ultrasound in the diagnosis of pneumonia in intensive care unit-patients [Internet]. *Egypt J Chest Dis Tuberc* 2013; 62:281–285.
15. Helmy S, Beshay B, Abdel Hady M, et al.: Role of chest ultrasonography in the diagnosis of lung contusion [Internet]. *Egypt J Chest Dis Tuberc* 2015; 64:469–475.
16. Kitazono MT, Lau CT, Parada AN, et al.: Differentiation of pleural effusions from parenchymal opacities: Accuracy of bedside chest radiography. *Am J Roentgenol* 2010; 194:407–412.

17. Bilotta F, Giudici LD, Zeppa IO, et al.: Ultrasound imaging and use of B-lines for functional lung evaluation in neurocritical care: a prospective, observational study. *Eur J Anaesthesiol* 2013; 30:464–468
18. Figueroa-Casas JB, Brunner N, Dwivedi AK, et al.: Accuracy of the chest radiograph to identify bilateral pulmonary infiltrates consistent with the diagnosis of acute respiratory distress syndrome using computed tomography as reference standard. *J Crit Care* 2013; 28:352–357.
19. Xirouchaki N, Magkanas E, Vaporidi K, et al.: Lung ultrasound in critically ill patients: comparison with bedside chest radiography. *Intensive Care Med* 2011; 37:1488–1493
20. Rocco M, Carbone I, Morelli A, et al.: Diagnostic accuracy of bedside ultrasonography in the ICU: feasibility of detecting pulmonary effusion and lung contusion in patients on respiratory support after severe blunt thoracic trauma. *Acta Anaesthesiol Scand* 2008; 52:776–784
21. Razazi K, Deux J-F, de Prost N, et al.: Bedside Lung Ultrasound During Acute Chest Syndrome in Sickle Cell Disease. *Medicine (Baltimore)* 2016; 95:e2553
22. Voggenreiter G, Aufmkolk M, Majetschak M, et al.: Efficiency of chest computed tomography in critically ill patients with multiple traumas. *Crit Care Med* 2000; 28:1033–1039.
23. Venugopal A, Koshy R, Koshy S: Role of chest X-ray in citing central venous catheter tip: A few case reports with a brief review of the literature [Internet]. *J Anaesthesiol Clin Pharmacol* 2013; 29:397.
24. Pillai JB: Thoracic complications of nasogastric tube: review of safe practice [Internet]. *Interact Cardiovasc Thorac Surg* 2005; 4:429–433.
25. Pesenti A, Musch G, Lichtenstein D, et al.: Imaging in acute respiratory distress syndrome [Internet]. *Intensive Care Med* 2016; 42:686–698.
26. Ashton-Cleary DT: Is thoracic ultrasound a viable alternative to conventional imaging in the critical care setting? *Br J Anaesth* 2013; 111:152–160.
27. Moher D1, Cook DJ, Eastwood S, Olkin I, Rennie D SD: Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses*. *Lancet* 1999; 354:1896–900.
28. Ebrahimi A, Yousefifard M, Kazemi HM, et al.: Diagnostic accuracy of chest ultrasonography versus chest radiography for identification of pneumothorax: A systematic review and meta-analysis. *Tanaffos* 2014; 13:29–40.
29. Alzahrani SA, Abdulatief M, Salamah A, et al.: Systematic review and meta - analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. *Crit Ultrasound J* 2017;
30. Chavez MA. b, Shams N., Ellington LE., et al.: Lung ultrasound for the diagnosis of pneumonia in adults: A systematic review and meta-analysis [Internet]. *Respir Res* 2014; 15.
31. Bossuyt PMM, Reitsma JB, Linnet K, et al.: Beyond diagnostic accuracy: The clinical utility of diagnostic tests. *Clin Chem* 2012; 58:1636–1643.
32. Nuesch E, Trelle S, Reichenbach S, et al.: Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study [Internet]. *Bmj* 2010; 341:c3515–c3515
33. Xirouchaki N1, Kondili E, Prinianakis G, Malliotakis P GD: Impact of lung ultrasound on clinical decision making in critically ill patients. *Intensive Care Med* 2014; 40:57–65.

Appendix 1.

PubMed search strategy

"Lung"[Mesh] OR "Lung Diseases"[Mesh] OR "Pleural Diseases"[Mesh] OR pulmonar*[tiab] OR bronchopulmon*[tiab] OR bronchopath*[tiab] OR bronchi*[tiab] OR alveol*[tiab] OR bronchu*[tiab] OR pneumoni*[tiab] OR pneumothora*[tiab] OR atelectas*[tiab] OR lung[tiab] OR lungs[tiab] OR pleura*[tiab] OR wet lung*[tiab]

"Radiography, Thoracic"[Mesh] OR ((radiograph*[tiab] OR xray*[tiab] OR x ray*[tiab] OR imagin*[tiab]) AND (thorac*[tiab] OR thorax[tiab] OR chest*[tiab]))

"Tomography, X-Ray Computed"[Mesh] OR computed tomograph*[tiab] OR ct[tiab] OR cts[tiab] OR cat scan*[tiab] OR computer assisted tomograph*[tiab] OR computerized tomograph*[tiab] OR computed x ray tomograph*[tiab] OR computed xray tomograph*[tiab]

("Sensitivity and Specificity"[MeSH] OR specificit*[tw] OR screening[tw] OR accura*[tw] OR reference value*[tw] OR false positive[tw] OR false negative[tw] OR predictive value*[tw] OR roc[tw] OR likelihood*[tw] OR likelihood*[tw])

Embase search strategy

'lung'/exp OR 'lung disease'/exp OR 'pleura disease'/exp OR pulmonar*:ab,ti OR bronchopulmon*:ab,ti OR bronchopath*:ab,ti OR bronchi*:ab,ti OR alveol*:ab,ti OR bronchu*:ab,ti OR pneumoni*:ab,ti OR pneumothora*:ab,ti OR atelectas*:ab,ti OR lung:ab,ti OR lungs:ab,ti OR pleura*:ab,ti OR 'wet lung*':ab,ti

'thorax radiography'/exp OR ((radiograph* OR xray* OR x ray* OR imagin*) AND (thorac* OR thorax OR chest*)):ab,ti

'computer assisted tomography'/exp OR 'computed tomography scanner'/exp OR (compute* NEAR/3 tomograph*):ab,ti OR ct:ab,ti OR cts:ab,ti OR 'cat scan*':ab,ti

'sensitivity and specificity'/exp OR 'screening'/exp OR 'reference value'/exp OR 'diagnostic error'/exp OR 'predictive value'/exp OR 'receiver operating characteristic'/exp OR specificit*:ti,ab OR screening:ti,ab OR accura*:ti,ab OR 'reference value*':ti,ab OR 'false positive':ti,ab OR 'false negative':ti,ab OR 'predictive value*':ti,ab OR roc:ti,ab OR likelihood*:ti,ab OR likelihood*:ti,ab

Appendix 2.

Supplement Table 1. All individual study results for chest radiography and lung ultrasound accuracy.

Author, country	Index	Reference standard	Outcome	SN (%)	SP (%)	Acc (%)	PPV (%)	NPV (%)	LR+, [CI]	LR-	Prevalence (%)
Lichtenstein <i>et al</i> (5) 2004, France	CXR	CT	Consolidation	68	95	75	86	87	13.9	0.34	31
			Pleural effusion	39	85	47	48	80	2.6	0.72	26
	LUS	CT	Alveolar-interstitial syndrome	60	100	72	100	73	-	0.40	48
			Consolidation	93	100	97	100	97	-	0.07	31
			Pleural effusion	92	93	83	82	97	13.0	0.09	26
			Alveolar-interstitial syndrome	98	88	95	88	98	8.2	0.02	48
Xirouchaki <i>et al</i> (21) 2011, Greece	CXR	CT	Consolidations	38	89	49	93	28	3.4	0.70	79
			Pleural effusion	65	81	69	91	44	3.4	0.43	75
			Pneumothorax	0	99	89	0	90	0	1.01	10
			Interstitial syndrome	46	80	58	81	45	2.3	0.67	64
	LUS	CT	Consolidations	100	78	95	94	100	4.5	0	79
			Pleural effusion	100	100	100	100	100	-	0	75
			Pneumothorax	75	93	92	55	97	11.4	0.27	10
			Interstitial syndrome	94	93	94	96	90	14.2	0.06	64
Kitazona <i>et al</i> (18)2010, USA	CXR	CT	Parenchymal opacities	65	89	72	94	49 65	6.1	0.39	73
			Pleural effusion	66	89	76	90		6.0	0.38	59
Figuroa-casas <i>et al</i> (20) 2013, USA	CXR	CT	ARDS	73	70	72	88	47	2.4	0.39	74
Rocco <i>et al</i> 2009(22), Italy	CXR	CT	Pleural effusion (T1)	23	94	81	49	82	3.8	0.81	21
			Pleural effusion (T2)	42	97	87	88	76	14.0	0.59	33
			Lung contusion (T1)	39	89	67	72	66	3.7	0.68	42
			Lung contusion (T2)	24	96	71	76	70	6.0	0.79	35
	LUS	CT	Pleural effusion (T1)	92	95	94	83	98	18.6	0.08	21
			Pleural effusion (T2)	94	99	98	95	99	94	0.06	33
			Lung contusion (T1)	89	89	90	86	92	8.5	0.12	42
			Lung contusion (T2)	86	97	93	94	93	28.6	0.14	35
Voggenreiter <i>et al</i> (24) 2000, Germany	CXR	CT	Atelectasis/Infiltration	93	0	92	99	0	0.9	-	99
			Pleural effusion/hemothorax	58	63	60	63	58	1.6	0.66	52
Nafae <i>et al</i> (16) 2013, Egypt	CXR	CT	Pneumothorax	28	97	80	78	80	10.6	0.74	25
	LUS	CT	Consolidations	78	60	74	89	40	1.9	0.38	80
Bilotta <i>et al</i> (19) 2013, Italy	CXR	CT	Consolidations	97.5	75	93	94	88	3.9	0.03	80
	LUS	CT	Consolidations	84	99	96	96	96	90.5	0.16	21
	LUS	CT	Consolidations	93	98	97	91	98	40.0	0.07	21

Razazi et al(23) 2014, France	CXR	CT	Consolidation	44	95	?	?	?	?	0.91	?
			Pleural effusion	33	73	62	32	74	1.2		
	LUS	CT	Consolidation	72	89	?	?	?	?	0.11	?
			Pleural effusion	91	81	84	65	96	4.8		
Helmy et al(17) 2014, Egypt	CXR	CT	Lung contusion	40	90	50	94	27	4.0	0.67	80
	LUS	CT	Lung contusion	98	90	96	98	90	9.8		

Abbreviations: CT: Computed Tomography; CXR: chest radiograph; US: ultrasound; SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; Acc: accuracy; LR: likelihood ratio; [-]: Confidence Interval;

Appendix 3.

Supplement Table 2. All individual study (abstract-only) results for chest radiography and lung ultrasound accuracy.

Author, country	Index	Reference standard	Outcome	SN (%)	SP (%)	Acc (%)	PPV (%)	NPV (%)	LR+, [CI]	LR-
Abstracts										
Vaghesia et al(14) 2014; USA	CXR	CT	Consolidation/atelectasis	22	100	?	100	11	-	0.78
			Pleural effusion	34	100	?	100	53	-	0.66
			Interstitial syndrome	100	63	?	19	100	2.7	0
	LUS	CT	Consolidation/atelectasis	32	100	?	100	9	-	0.68
			Pleural effusion	47	82	?	78	53	2.6	0.65
			Interstitial syndrome	50	83	?	27	96	2.9	0.60
Agmy et al(15) 2014, unknown	CXR	CT	Consolidations	40	85	50	?	?	2.7	0.71
			Pleural effusion	55	84	65	?	?	3.4	0.54
			Pneumothorax	40	96	88	?	?	10	0.63
			Interstitials syndrome	42	82	60	?	?	2.3	0.71
	LUS	CT	Consolidations	100	87	95	?	?	7.7	0
			Pleural effusion	100	100	100	?	?	-	0
			Pneumothorax	100	100	100	?	?	-	0
			Interstitial syndrome	95	95	95	?	?	19	0.05
Schafer et al(12) 1997, Germany	CXR	CT	Pleural effusion	69	54	65	81	34	1.5	0.57
Wang et al(13) 2012, China	CXR	CT	Consolidation/atelectasis	31	75	38	?	?	1.3	0.92
	LUS	CT	Consolidation/atelectasis	96	88	95	?	?	7.7	0.05

Appendix 4

The risk of bias and applicability concerns for each study are described.

Lichtenstein et al.⁵ 2004

Selection: there was a low risk of bias because of the prospective design and consecutive enrolling of patients. Applicability concerns were low because included patients match the review question.

Index test: it is unclear if the CXR was interpreted without knowledge of the indexes or reference. Applicability concerns were low.

Reference standard: An independent radiologist analyzed the reference and was blinded to all the indexes, so risk of bias and applicability concerns were low.

Flow and timing: The risk of bias is low because all the indexes were performed immediately before transportation to the CT scanner.

Xirouchaki et al.²¹ 2011

Selection: Unclear risk of bias because it is unclear if patients were randomly or consecutively enrollment in the study. Applicability concerns were low because included patients match the review question.

Index test: Low risk of bias because while evaluating the CXR, reference standard results were blinded. Applicability concerns were low.

Reference standard: Low risk of bias because while evaluating the reference, index results were blinded. Applicability concerns were low.

Flow and timing: CT was performed prior to the index test, but the time interval between these are unclear risk. Therefore unclear risk of bias.

Kitazono et al.¹⁸ 2010

Selection: unclear risk of bias because it is unclear if patients were consecutively recruited or randomly included. Applicability concerns were low because included patients match the review question.

Index test: low risk of bias because index results were evaluated in a separate session from reference evaluation. Also the index was evaluated by four reviewers. Applicability concerns were low.

Reference standard: unclear risk of bias because the reference standard was evaluated in a separate session after all the index results were evaluated, but it is not stated if these results were blinded.

Applicability concerns were low.

Flow and timing: High risk of bias because the study involves patients with pleural effusion and the interval between index and reference was within 24 hours.

Figuroa-casas et al.²⁰ 2013

Selection: High risk of bias because this was a retrospective study and an intensivist selected patients based on medical records information. Exclusion criteria were reasonable.

Applicability concerns were low because included patients match the review question.

Index test: Low risk of bias because evaluation of the index was by two independent radiologist and blinded to clinical information, prior imaging and interpretation. Radiologist were aware of the study and inclusion criteria. Applicability concerns were low because.

Reference standard: Low risk of bias because the reference standard was interpreted 4-6 weeks after the interpretation to eliminate recall bias . Applicability concerns were low.

Flow and timing: Unclear risk of bias because the interval between index and reference is not stated. All patients received the same reference.

Rocco et al.²² 2008

Selection: Low risk of bias because patients were consecutively enrolled to the study, with reasonable exclusion criteria. Applicability concerns were low because included patients match the review question.

Index test: Low risk of bias because the CXR were read by radiologist unaware of the reference standard findings. It is not stated if the other index results were blinded. Applicability concerns were low.

Reference standard: Unclear risk of bias because it is not stated if the index was blinded while evaluating the reference standard. Applicability concerns were low.

Flow and timing: Low risk of bias because the maximal interval between index and reference standard was 1 hour. All included patients received the same reference standard.

Voggenreiter et al.²⁴ 2000

Selection: It is unclear if patients were randomly or consecutively enrolled in the study. Also the exclusion criteria are not reported. Therefore high risk of bias. Applicability concerns were low because it involves patients with pulmonary symptoms.

Index: low risk of bias because the index is blinded to the reference standard. Interpretation of index results was performed by three reviewers and final diagnosis was by consensus. Applicability concerns were low.

Reference standard: High risk of bias because the reference standard was evaluated together with index results. Applicability concerns were low.

Flow and timing: the interval between index and reference is not stated, but the corresponding index was always evaluated the same day as the reference standard.

Because the study not only involves patients with pneumonia but also pneumothorax and pleural effusion it is rated as high risk of bias.

*Nafae et al.*¹⁶ 2013

Selection: Unclear risk of bias because it is not stated if patients were consecutively or randomly enrolled in the study. Applicability concerns were low because it involves patients with pulmonary symptoms.

Index: it is unclear for both indexes whether they were blinded to the reference standard. So unclear risk of bias. Applicability concerns were low.

Reference standard: unclear risk of bias because it is not stated if the reference was blinded to index results. Unclear risk of bias. Applicability concerns were low.

Flow and timing: Unclear risk of bias because the interval between index and reference is not stated.

*Bilotta et al.*¹⁹ 2013

Selection: patients were prospectively and consecutively enrolled in the study. Low risk of bias. Applicability concerns were low because it involves patients suspected of having pulmonary consolidations.

Index: Both indexes were evaluated without knowledge of reference standard. Therefore low risk of bias. Applicability concerns were low.

Reference standard: The reference standard was evaluated without knowledge of the indexes. Therefore low risk of bias. Applicability concerns were low.

Flow and timing: Patients were screened at admission by LUS and this was repeated every 48 hours. Because it involves consolidations, it is rated as low risk of bias.

*Razazi et al.*²³ 2014

Selection: patients were consecutively enrolled with acceptable exclusion criteria. Therefore low risk of bias. Applicability concerns were low because patients had pulmonary symptoms, but it involves patients with sickle- cell disease.

Index: both indexes were blinded to reference results. Therefore low risk of bias. Applicability concerns were low.

Reference standard: the index results were blinded while evaluating the reference. Low risk of bias. Applicability concerns were low.

Flow and timing: Time interval was <24 hours between index and reference. For consolidations this is acceptable, but for pleural effusion this might lead to false conclusion. Therefore high risk of bias.

*Helmy et al.*¹⁷ 2015

Selection: Unclear risk of bias because it is not stated if patients were randomly or consecutively enrolled in the study. Reasonable exclusion criteria were used. Applicability concerns were high because the study also involves patients admitted to the ED.

Index: it is unclear if the CXR was interpreted without knowledge of the indexes or reference. Applicability concerns were low.

Reference standard: Unclear risk of bias because it is not stated if the index was blinded while evaluating the reference standard. Applicability concerns were low.

Flow and timing: There is a low risk of bias because the time interval between index and reference was less than 24 hours and the study population involves lung contusion.

Chapter 9

Lung ultrasound compared with chest X-ray in diagnosing postoperative pulmonary complications following cardiothoracic surgery: a prospective observational study

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Anaesthesia 2018; 73:946-954.

Summary

Postoperative pulmonary complications are common after cardiothoracic surgery and are associated with adverse outcomes. The ability to detect postoperative pulmonary complications using chest X-rays is limited, and this technique requires radiation exposure. Little is known about the diagnostic accuracy of lung ultrasound for the detection of postoperative pulmonary complications after cardiothoracic surgery, and we therefore aimed to compare lung ultrasound with chest X-ray to detect postoperative pulmonary complications in this group of patients. We performed this prospective observational single-centre study in a tertiary intensive care unit treating adult patients who underwent cardiothoracic surgery. We recorded chest X-ray findings upon admission and on postoperative days two and three, as well as rates of postoperative pulmonary complications and clinically-relevant postoperative pulmonary complications that required therapy according to the treating physician as part of their standard clinical practice. Lung ultrasound was performed by an independent researcher at the time of chest X-ray. We compared lung ultrasound with chest X-ray for the detection of postoperative pulmonary complications and clinically relevant postoperative pulmonary complications. We also assessed inter-observer agreement for lung ultrasound, and the time to perform both imaging techniques. Subgroup analyses were performed to compare the time to detection of clinically relevant postoperative pulmonary complications by both modalities. We recruited a total of 177 patients in whom both lung ultrasound and chest X-ray imaging were performed. Lung ultrasound identified 159 (90%) postoperative pulmonary complications on the day of admission compared with 107 (61%) identified with chest X-ray ($p < 0.001$). Lung ultrasound identified 11/17 patients (65%) and chest X-ray 7/17 patients (41%) with clinically-relevant postoperative pulmonary complications ($p < 0.001$). The clinically-relevant postoperative pulmonary complications were detected earlier with lung ultrasound compared with chest X-ray ($p = 0.024$). Overall inter-observer agreement for lung ultrasound was excellent ($\kappa = 0.907$, $p < 0.001$). Following cardiothoracic surgery, lung ultrasound detected more postoperative pulmonary complications and clinically-relevant postoperative pulmonary complications than chest X-ray, and at an earlier time point. Our results suggest lung ultrasound may be used as the primary imaging technique to search for postoperative pulmonary complications after cardiothoracic surgery and will enhance bedside decision-making.

Introduction

Postoperative pulmonary complications (PPCs), including atelectasis, pneumonia and pulmonary oedema, are common after cardiothoracic surgery, and are associated with adverse outcomes [1,2,3]. Early recognition of PPCs might be important for intervention and/or monitoring as these patients often have compromised physiological reserves. The time from surgery until PPC detection is approximately three days using the most commonly used diagnostics such as chest auscultation, chest X-ray (CXR), arterial oxygen pressure, PaO₂/F₁O₂ (P/F) ratio, leucocytes and temperature [4]. The current standard diagnostic imaging technique to detect PPCs in the intensive care unit (ICU) setting remains CXR [5,6]. However, the diagnostic accuracy of CXR is limited and CXR requires radiation exposure and considerable costs [6].

Bedside lung ultrasound, an alternative imaging modality with a high sensitivity and specificity, is increasingly considered for the diagnosis of pulmonary pathology in the ICU. Lung ultrasound is without the downside of radiation exposure, and creates distinctive artefacts through the interplay between fluid, air and pleurae [7]. Combinations of these artefacts can help differentiate between various pathological processes and are combined and deciphered in the bedside lung ultrasound in emergency (BLUE)-protocol. In the BLUE-protocol, profiles have been designed for the main pulmonary complications (pneumonia, congestive heart failure, COPD, asthma, pulmonary embolism and pneumothorax) and have been validated with an accuracy > 90%, and are therefore extensively used in daily critical care [8]. For example, the lung-sliding artefact, which is a 'twinkling' visible at the pleural line during inspiration, excludes a pneumothorax and is part of definition of a normal lung surface (Video S1). A lines are the main horizon artefact and represent a reverberation of the pleural line, indicating air at the pleural line. B lines are the result of many to-and-fro moments of ultrasound beams between air and fluid, generating this long vertical hyper-echoic artefact (Fig S1). More than two anterior B-lines are pathological; this is the definition of a B-profile in the BLUE protocol, indicating interstitial syndrome or pulmonary oedema. Furthermore, detection of pleural effusions and consolidation are part of the postero-lateral alveolar and/or pleural syndrome (PLAPS) (Fig S2). At the PLAPS-point, a disorder can be described when an anechoic pleural effusion is visible or a disorder within the lung tissue is seen; for example, a shredded deep border immediately indicates lung consolidation [8].

Cardiac ultrasound has been shown to be valuable in the peri-operative assessment and therapeutic management of patients undergoing surgery [9]. In non-cardiothoracic surgery patients lung ultrasound performed better than CXR in diagnosing pneumonia, pulmonary oedema, pneumothorax and pleural effusion [10,11,12,13]. Until now, however, there have

been limited data available for the diagnostic value of lung ultrasound in cardiothoracic surgical patients. In addition, to date it is unknown whether repeated lung ultrasound is able to detect PPCs at an earlier stage compared with routine CXR. The primary outcome measure of this study was to compare the performance of lung ultrasound with CXR after cardiothoracic surgery in detecting PPCs and clinically-relevant PPCs, defined as PPCs that required treatment. We hypothesised that lung ultrasound would detect more PPCs and clinically-relevant PPCs than CXR. Secondary outcome measures were to evaluate the time to detection of clinically relevant PPCs by lung ultrasound and CXR, and to assess the relationship between lung ultrasound findings and outcome parameters.

Methods

We conducted this prospective, observational cohort study in the VU University Medical Center Amsterdam (VUmc Amsterdam, The Netherlands), a tertiary hospital. The local Human Subjects Committee of the VUmc approved the study (METc 15/270), and waived the requirement for informed consent. We included consecutive adult patients (≥ 18 years old) who had undergone cardiothoracic surgery upon their admission to the ICU during the period April 2015 - January 2016. Patients were not included if there was no investigator available to perform lung ultrasound examination upon ICU admission. Cardiothoracic procedures included coronary artery bypass grafting and/or valve surgery, Bentall procedures or pulmonary endarterectomy. All patients admitted to the ICU had their tracheas intubated and were receiving general anaesthesia following surgery. They were extubated according to local protocol, followed by the administration of supplemental oxygen via nasal cannulae. Monitoring, including pulse oximetry, heart rate, electrocardiographic, invasive blood pressure and CXR was performed according to standard clinical practice.

Anteroposterior bedside CXRs were obtained using a DRX-Revolution mobile X-ray unit (Carestream Health, Inc. © Toronto, Canada) upon admission to the ICU, and at post-operative days two and three, according to local protocol. We retrieved CXR findings, assessed by a radiologist blinded to the lung ultrasound findings, from the electronic patient data management system. The Nomenclature Committee of the Fleischner Society recommended terminology was used to describe pathological entities according to the diagnostic criteria for bedside CXR [14,15].

A trained member of the research team ($n=5$), which consisted of two investigators, one ICU physician and two intensivists, performed lung ultrasound upon admission to the ICU on day 0, and at postoperative days two and three. All ultrasonographers were trained according to the Netherlands Society of Intensive Care Programme for Intensive Care Ultrasound (NVIC ICARUS) training course (www.nvic.nl). The level of experience of lung ultrasound varied from three months to over five years. The ultrasonographer was blinded to clinical details and CXR findings, and did not contribute to the diagnostic and treatment strategy of the patient. Lung ultrasound was performed immediately before or after CXR. We used a CX50 ultrasound machine (Koninklijke Philips NV[®], Eindhoven, the Netherlands) with both the cardiac phased array (1-5 MHz) and the linear vascular probe (>10 MHz). The ultrasonographer could choose a particular probe for a particular view in a particular patient, according to individual preference. Lung sliding was determined using the vascular probe. Lung ultrasound views were obtained according to the BLUE protocol [16,17,18].

In short, we determined the BLUE profile for each BLUE point and BLUE profile per hemithorax (BLUE 1 and 2) as follows: A; B A'; B'; or C-profile. A profile means predominantly A lines (Fig 1). B profile means predominantly multiple (>2) anterior diffuse B lines. A' or B' means the corresponding BLUE profile with absence of, or abolished lung sliding. C profile means anterior alveolar consolidation. Furthermore, we determined the postero-lateral alveolar and/or pleural syndrome (PLAPS) on each side at the lateral sub-posterior ultrasound examination and scored this as positive or negative (Fig 2). When positive, consolidation and/or pleural effusion were scored separately and the diagnosis of atelectasis was added to the flowchart. The final conclusion was made according to the flow chart of the modified BLUE protocol after cardiothoracic surgery (Fig 3). For differentiation between pneumonia and atelectasis, the ultrasonographer was allowed to look for fever and C-reactive protein (CRP) in the medical chart of the patient.

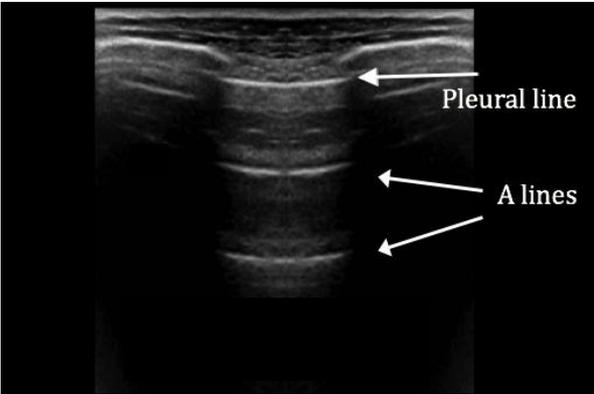


Figure 1. Lung ultrasound of the pleural line at anterior position demonstrating A line artefacts.

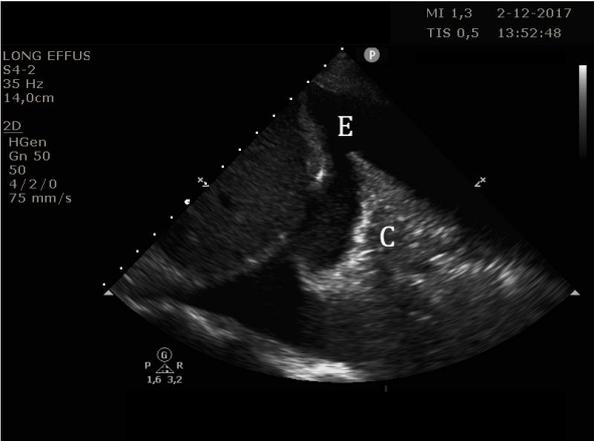


Figure 2. Lung ultrasound at the lateral sub-posterior position and detecting the postero-lateral alveolar and/or pleural syndrome. C=consolidated lung E=pleural effusion

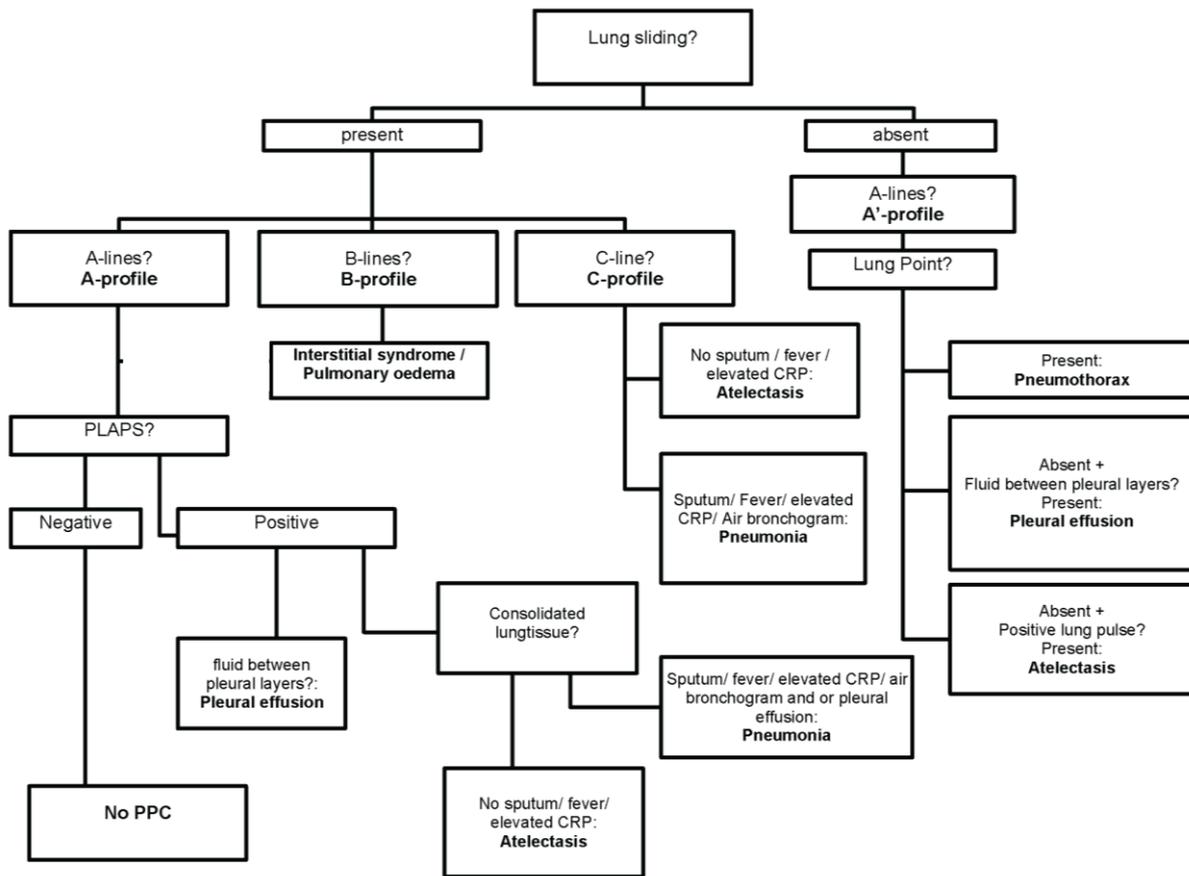


Figure 3. Bedside lung ultrasound in cardiothoracic surgery protocol.

The BLUE profile for each BLUE point and BLUE profile per hemithorax (BLUE 1 and 2) is to be determined as: A, B, A', B' or C-profile. First lungsliding is determined. An A-profile consists of predominant A-lines, a reverberation of the pleural line, indicating air at the pleurae. Absent lungsliding and visualization of A-lines indicates an A' profile. B-lines are the result of many to-an-fro moments of ultrasound beams between air and fluid, generating the long vertical hyper echoic artefact. More than two anterior B-lines are pathological and is the definition of a B-profile indicating interstitial syndrome or pulmonary oedema. If any anterior C-line is noted, a curvilinear aspect of the pleural line caused by consolidated lungtissue, the C-profile is present, regardless of other artefacts. Furthermore, the postero-lateral alveolar and/or pleural syndrome (PLAPS) was determined on each side and scored as positive or negative. If one lung shows A-predominance and the other B-predominance, this is called the A/B profile and indicates lungtissue consolidation at hemithorax with the B-profile.

We retrieved patient characteristics from the electronic patient data management system. These included: sex; age; body mass index (BMI); surgery type; and relevant cardiopulmonary comorbidities. Peri-operative data consisted of extracorporeal circulation and aortic clamp time, total peri-operative blood loss, and blood product transfusions. Respiratory data at time of lung ultrasound included: arterial oxygen saturation; mode of ventilation; positive end-expiratory pressure (PEEP); O₂ supplementation; P/F- ratio; and

hours of mechanical ventilation during ICU stay. Parameters retrieved from the documentation by the treating ICU-physician included: chest auscultation findings; conclusions/diagnoses concerning pulmonary status; and/or treatments. Routine data collection during ICU and medium care unit (MCU) stay included: temperature; fluid balance; drains; drain production; haemoglobin levels; white blood cell count; lactate; CRP levels; and ICU/MCU stay in hours, corrected for prolonged stay due to delayed transfer to the ward due to capacity problems.

Postoperative pulmonary complications were defined as previously described by Canet et al. as respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax and bronchospasm, and scored accordingly [1]. A distinction was made between PPCs and clinically-relevant PPCs, defined as a PPC that required treatment, as judged by the treating physician. We considered the following to be clinically-relevant treatments for PPCs: high flow oxygen therapy; a higher PEEP level or recruitment manoeuvres; continuous positive airway pressure (CPAP); re-intubation; bronchoscopy; extra bronchodilator therapy; thoracic drain placement; and the use of diuretics and/or antibiotics, in addition to local antibiotic protocols for cardiothoracic surgery. Scoring of clinically-relevant PPCs was based on the documentation by the treating ICU physician. The physician who diagnosed clinically-relevant PPCs was taking into account physical examination, conventional monitoring, laboratory results and CXR. This reflected daily clinical practice. The treating ICU physician was blinded to lung ultrasound findings. Clinically-relevant PPCs were considered the composite reference standard. The diagnostic accuracy of CXR alone is debated and is therefore an imperfect reference standard for lung ultrasound. The diagnostic accuracy of the reference standard was improved by using a composite reference standard, including multiple tests, one of which was CXR.

To assess the relationship between lung ultrasound findings and patient outcome parameters, we compared the number of B-lines, depth (cm) of pleural effusion and total atelectasis (cm²) between patients with clinically-relevant PPCs and patients without clinically-relevant PPCs. Furthermore, we compared P/F ratio and length of ICU stay between both groups.

We performed a predefined subgroup analysis of patients in whom all lung ultrasound and CXR examinations were successfully completed on both the day of surgery and admission to ICU (day 0), and days 2 and 3. This allowed for comparison of the time to detection of PPC and clinically-relevant PPC using both techniques. Not all patients could be included in this subgroup, as sometimes no researcher was available to perform lung ultrasound, mostly at

weekends. In addition, CXRs were not always performed for logistical reasons or at the discretion of the treating physician, bypassing the departmental protocol.

We assessed the inter-observer agreement in a random subset of the study population. We calculated that a sample size of 70 measurements would be required, according to a difference in overall agreement and change-probability of 0.6, and an accepted relative error of 20%. Seventy lung ultrasound points (BLUE points and PLAPS) were assessed to determine inter-observer agreement. Lung ultrasound was performed by two research team members (HT and KP). Both investigators were blinded to mutual lung ultrasound findings. Agreement between the findings was assessed at ten different points per patient, per hemi thorax (BLUE profile per BLUE point), PLAPS (positive or negative), atelectasis (positive or negative) and pleural effusion (positive or negative).

The time to perform CXR and lung ultrasound, after CXR was ordered, was compared. We hypothesised that lung ultrasound would detect an incidence of PPCs of 80% and that CXR would detect an incidence of 60% (our primary endpoint). We calculated that a sample size of 162 subjects would be required with an alpha of 0,05 and a power of 80%. With an anticipated 10% lost to follow-up, we set our sample size at 180 patients [1]. We carried out statistical data analyses using SPSS statistical software package version 19.0 (IBM, New York, NY, USA). We used the Chi Square test to compare unpaired categorical data, and the McNemar test for paired data. The accuracy of lung ultrasound and CXR for the detection of clinically relevant PPC was expressed as sensitivity, specificity, positive and negative predictive values and diagnostic accuracy.

We used the Wilcoxon Signed-Rank test for paired ordinal data (repeated measures) in order to analyse earlier detection of clinically-relevant PPCs with lung ultrasound versus CXR. Detection of day 0 PPCs was ranked as 1, detection of day 2 PPCs as 2, detection of day 3 PPCs as 3, and undetected PPCs were ranked as 4. To assess the inter-observer agreement for lung ultrasound, Cohen's kappa (κ) statistics were used with κ values < 0.40 indicating low agreement, 0.40 to 0.75 low-to-good agreement, and > 0.75 good-to-perfect agreement.

Results

During the study period, 360 patients underwent cardiothoracic surgery, and we recruited 177 of these patients to the study. The other patients were not included because no member of the research team was available to perform lung ultrasound on admission. Table 1 shows the demographic and clinical characteristics of included patients.

Table 1 Peri-operative characteristics of patients after cardiothoracic surgery.

Patient and operation characteristics (n = 177)	Values
Males / females	125 / 52
Age (yr)	68 (10)
Body Mass Index (kg.m⁻²)	27.5 (4.9)
Type of surgery	
<i>CABG</i>	69 (40%)
<i>Valve surgery</i>	54 (31%)
<i>CABG and valve surgery</i>	32 (18%)
<i>Pulmonary endarterectomy</i>	10 (5.7%)
<i>Bentall surgery</i>	11 (6.2%)
Type of comorbidity	
<i>Obstructive pulmonary airway disease</i>	11 (6.2%)
<i>Heart failure</i>	49 (28%)
ECC duration (min; n = 166)	129 (68)
Aortic clamp time (min; n = 166)	94 (47)
Mechanical ventilation time on ICU (hours)	6.5 (4.5-9.0 [0.5-263])
ICU stay (hours)	24 (22 – 46 [8-264])

Values are mean (SD), number (proportion) or median (IQR[range]).

Lung ultrasound identified more patients with a PPC compared with CXR ($p < 0.001$) upon ICU admission. The PPCs identified were pulmonary oedema, consolidation, pneumothorax, atelectasis and pleural effusion. The incidence of PPCs on day 0, day 2 and day 3, as detected by CXR and lung ultrasound, are shown in Table 2. The prevalence of pleural effusion increased during the postoperative course for both groups, but there was a higher prevalence detected using lung ultrasound compared with CXR, with rates of 44% and 71% on day 2 ($p < 0.001$) and 71% and 90% on day 3 ($p = 0.013$) for CXR and lung ultrasound, respectively. Lung ultrasound on admission mainly detected more cases of atelectasis (87% vs. 41%, $p < 0.001$) and pulmonary oedema (20% vs. 15%, $p = 0.143$) when compared with CXR.

Table 2 Presence of postoperative pulmonary complications based on lung ultrasound and chest X-ray and on day 0, day 2 and day 3 after cardiothoracic surgery.

PPC	Day 0 (n=177)			Day 2 (n=99)			Day 3 (n=58)		
	lung ultras ound	chest X-ray	p value	lung ultras ound	chest X-ray	p value	lung ultras ound	chest X-ray	p value
Total PPCs	159 (89.8%)	107 (60.5%)	<0.001*	90 (90.9%)	80 (80.8%)	0.031*	58 (100%)	52 (89.7%)	-
Pulmonary oedema	36 (20.3%)	26 (14.7%)	0.143	14 (14.1%)	9 (9.1%)	0.383	20 (34.5%)	11 (19.0%)	0.049*
Consolidation	14 (7.9%)	0 (0%)	-	16 (16.2%)	2 (2.0%)	0.001*	16 (27.6%)	0 (0%)	-
Pneumothorax	7 (4.0%)	2 (1.1%)	0.180	0 (0%)	2 (2.0%)	-	3 (5.2%)	3 (5.2%)	1.000
Atelectasis	154 (87.0%)	72 (40.6%)	<0.001*	84 (84.8%)	65 (65.7%)	0.002*	57 (98.3%)	39 (67.8%)	<0.001*
Pleural effusion	60(33.9 %)	51 (28.8%)	0.328	70 (70.7%)	44 (44.4%)	<0.001*	52 (89.7%)	41 (70.7%)	0.013*

*Values are number (proportion). PPC, postoperative pulmonary complication. * p value < 0.05 is considered significant.*

The incidence of clinically-relevant PPCs on day 0, 2 and 3 are shown in Table 3. Seventeen patients out of 177 patients (10%) developed a clinically-relevant PPC at day 0. The incidence of clinically relevant PPCs increased over the days, with fifteen patients out of 99 patients (15%) on day 2 and thirteen patients out of 58 patients (22%) on day 3.

Table 4 shows the sensitivity, specificity, PPV and NPV and diagnostic accuracy for lung ultrasound and CXR in detecting clinically relevant PPCs. Pulmonary oedema and atelectasis were the two clinically-relevant PPCs that occurred sufficiently commonly to allow us to calculate the sensitivity and specificity of diagnosis by lung ultrasound and CXR. The sensitivity was higher and specificity was lower for lung ultrasound for detecting clinically-relevant atelectasis compared with CXR. The diagnostic accuracy for detecting pulmonary oedema was comparable during the study period.

Table 3 Presence of clinically relevant postoperative pulmonary complications on day 0, 2 and 3 after cardiothoracic surgery.

Clinically relevant PPC	Day 0 (n=177)	Day 2 (n=99)	Day 3 (n=58)
Total clinically relevant PPC	17 (9.6%)	15 (15.2%)	13 (22.4%)
Pulmonary oedema	2 (1.1%)	8 (8.1%)	10 (17.2%)
Bronchospasm	4 (2.3%)	2 (2.0%)	1 (1.7%)
Pneumonia	0 (0.0%)	1 (1.0%)	1 (1.7%)
Pneumothorax	0 (0.0%)	0 (0.0%)	1 (1.7%)
Atelectasis	11 (6.2%)	4 (4.0%)	0
Pleural effusion	0	0	0

Values are number (proportion); PPC, postoperative pulmonary complication.

Table 4 Diagnostic accuracy of lung ultrasound and chest X-ray in detecting clinical relevant postoperative pulmonary complications on day 0, day 2 and day 3 post cardiothoracic surgery.

Lung ultrasound	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Pulmonary oedema (day 0)	0.42	0.85	0.95	0.17	0.86
Pulmonary oedema (day 2)	0.25	0.87	0.93	0.14	0.82
Pulmonary oedema (day 3)	0.50	0.83	0.89	0.38	0.78
Atelectasis (day 0)	0.82	0.13	0.91	0.06	0.17
Chest X-ray	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Pulmonary oedema (day 0)	0.27	0.84	0.95	0.10	0.81
Pulmonary oedema (day 2)	0.13	0.91	0.92	0.11	0.85
Pulmonary oedema (day 3)	0.30	0.83	0.85	0.27	0.74
Atelectasis (day 0)	0.45	0.59	0.94	0.07	0.58

PPV, positive predictive value; NPV, negative predictive value.

In total, lung ultrasound identified 26 (58%) clinically-relevant PPCs and CXR identified 17 (38%) clinically-relevant PPCs out a total of 45 clinically-relevant PPCs on day 0, 2 and 3 ($p=0.021$). On day 0 lung ultrasound identified 11/17 (65%) patients with a clinically-relevant PPC while detected CXR 7/17 (41%) patients, respectively ($p=0.125$). On day 2 lung ultrasound identified 8/15 (53%) patients with a clinically-relevant PPC and CXR identified

5/15 (33%) patients ($p=0.250$). On day 3 lung ultrasound identified 7 (54%) patients and CXR identified 5 (39%) patients out of 13 patients with clinically-relevant PPCs ($p=0.625$).

In a subgroup of 42 patients, clinically-relevant PPCs were detected earlier with lung ultrasound than with CXR ($p=0.024$) (Figure 4). Overall inter-observer agreement for lung ultrasound showed excellent agreement ($\kappa=0.907$, $p<0.001$). Lung ultrasound was performed within a mean (SD) of 15 (5) minutes compared with 42 (16) minutes for CXR ($p<0.001$).

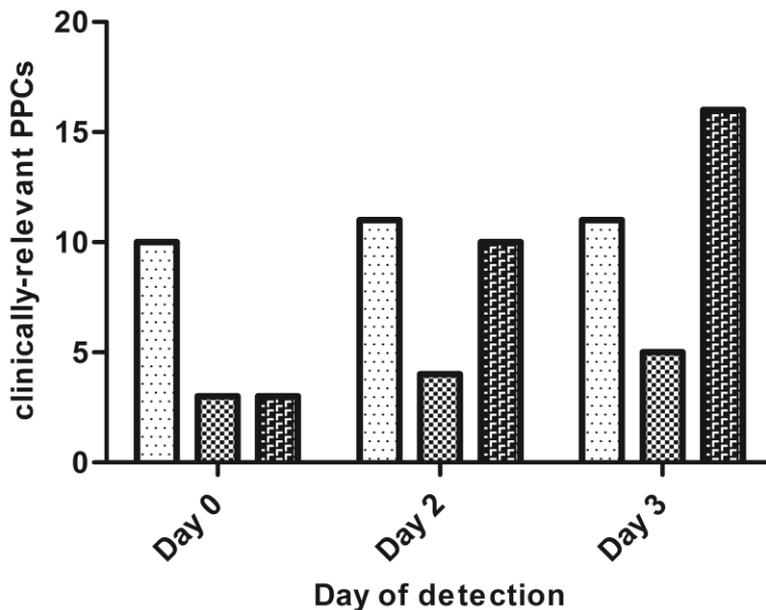


Figure 4. Cumulative number and time to detection of clinically relevant postoperative pulmonary complications after cardiothoracic surgery in a subgroup of patients with both lung ultrasound and chest X-ray findings available on day 0, 2 and 3 ($n=42$).

Bars represent number of cases of clinically relevant postoperative pulmonary complications, or future clinically relevant postoperative pulmonary complications detected with lung ultrasound (▨), chest X-ray (▩), and actual clinically relevant postoperative complications (▧).

Patients with a clinically-relevant PPC had a lower P/F ratio compared with patients without clinically-relevant PPCs on day 1 (188 (58) vs 250 (72) mmHg $p = 0.001$) and on day 2 (273 (71) mmHg vs 190 (84) mmHg $p=0.001$), respectively. Furthermore, ICU stay differed significantly between both groups ($p=0.083$) (Table 5). The total number of B-lines and pleural effusion (in cm) did not differ between patients with and without clinically-relevant PPCs. The degree of atelectasis (in cm^2) was smaller only on day 2 in patients with clinically-relevant PPCs compared with the non-clinically relevant PPC group (12.8 (6.4) cm^2 vs 7.7 (7.1) cm^2 , $p=0.045$). (Table 5)

Table 5. Lung ultrasound and clinical findings in patients without clinical relevant postoperative pulmonary complications compared to patients with clinical relevant postoperative pulmonary complications after cardiothoracic surgery.

lung ultrasound / clinical findings	day	without clinically relevant PPC	n	with clinically relevant PPC	n	p - value
Number of B-lines	0 (n=177)	(0.0 – 5.0[0.0-23.0])	160 (90.4%)	5.0 (0.5 – 9.5[0.0-18.0])	17 (9.6%)	0.038*
	2 (n=99)	(0.0 – 6.0[0.0-22.0])	84 (84.8%)	3.0 (0.0 – 9.0[0.0-16.0])	15 (15.2%)	0.332
	3 (n=58)	4.0 (2.0 – 7.8[0.0-17.0])	45 (77.6%)	9.0 (2.5 – 10.8[[0.0-16.0])	13 (22.4%)	0.779
Pleural effusion, cm	0 (n=177)	0.0 (0.0 – 0.0[0.0-4.2])	160 (90.4%)	0.4 (0.0 – 1.1[0.0-1.2])	17 (9.6%)	0.032*
	2 (n=99)	1.0 (0.0 – 7.0[0.0-6.7])	84 (84.8%)	(0.0 – 1.8[0.0-3.5])	15 (15.2%)	0.942
	3(n=58)	1.8 (1.3)	45 (77.6%)	2.1 (1.9)	13 (22.4%)	0.477
Atelectasis, cm ²	0 (n=177)	5.9 (4.8)	160 (90.4%)	11.0 (14.2)	17 (9.6%)	0.214
	2 (n=99)	7.7 (7.1)	84 (84.8%)	12.8 (6.4)	15 (15.2%)	0.045*
	3 (n=58)	7.8 (4.5)	45 (77.6%)	9.7 (6.6)	13 (22.4%)	0.323
P/F ratio, mmHg	0 (n=177)	249.9 (72.1)	160 (90.4%)	187.7 (58.3)	17 (9.6%)	0.001*
	2 (n=99)	273.2 (70.8)	84 (84.8%)	190.3 (84.0)	15 (15.2%)	0.001*
	3 (n=19)**	276 (87.5)	13 (68.4%)	211.2 (78.3)	6 (31.6%)	0.138

Data represent mean (SD), median (IQR [range]) or frequencies (%); P/F ratio= PaO₂/FiO₂ ratio *P value <0.05 is considered significant. ** small number due to removal of arterial line on day 2 postoperatively.

Discussion

This study demonstrates that lung ultrasound detects more PPCs and clinically-relevant PPCs, and at an earlier time point, when compared with CXR in patients following cardiothoracic surgery. In addition, time to perform lung ultrasound was significantly shorter than for CXR, and lung ultrasound had excellent inter-observer agreement. Lung ultrasound outperformed CXR in diagnosing clinically-relevant PPCs following cardiothoracic surgery and may potentially replace CXR as the primary imaging technique in these patients.

The PPC rate found in our study is in line with previous research, which showed that 54-73% of patients had atelectasis, pleural effusion or both after cardiothoracic surgery when detected by CXR.^{2,15,19} Of interest, we found a higher incidence of atelectasis and pleural effusions detected by lung ultrasound in these patients. This finding could be explained by the higher sensitivity and specificity of lung ultrasound in detecting pleural effusion and atelectasis compared with CXR, when compared to the gold standard for thoracic imaging, computed tomography (CT) scans.^{5,7,13,18} Furthermore, our results are comparable with the reported incidence of atelectasis of 90% found with thoracic CT scan in anaesthetised patients.²⁰ The incidence of clinically-relevant PPCs found in our study was comparable with rates described before, making our results generalisable to the postoperative population.^{2,4,21} Of note, more clinically-relevant PPCs were detected by lung ultrasound, despite the fact that this clinically-relevant composite reference standard was based on CXR findings, among others. This suggests that lung ultrasound would have performed even better when used as the primary imaging technique to screen for clinically-relevant PPCs. Previous research comparing CXR with lung ultrasound in patients after cardiothoracic surgery found that lung ultrasound identified most of the PPCs detected by CXR. Unfortunately, they reported the diagnostic value of lung ultrasound compared with CXR as the reference standard.²² By using a reference standard with potentially worse accuracy (CXR) than the index test (lung ultrasound) in the study, it is difficult to interpret their results.

Early detection of PPCs may lead to improved outcomes. Previous research showed that although PPC rates did not differ among hospitals, mortality rates did due to failure to rescue, a term coined by Silber et al.^{23,24} In a predefined subgroup analysis we found that lung ultrasound identified clinically-relevant PPCs at an earlier timepoint than CXR. In addition, lung ultrasound had superior sensitivity and almost comparable specificity in detecting PPCs, and thereby improves detection of PPCs. However, in the BLUE protocol we used, the extent of the complication was not determined, but only assessed as dichotomous: either a complication was present or not.¹⁷ An approach in which the extent of the PPC is quantified might be preferable. For assessing pleural effusions, considerable work has been done to

quantify the volume of effusion according to lung ultrasound imaging, but not to determine the clinical significance.²⁵ Our study found only that atelectasis in cm² differed significantly on day 2 for patients with clinically-relevant PPCs compared with patients without clinically-relevant PPCs. Of note, quantification of PPCs detected by lung ultrasound should be evaluated in future studies, because our study was underpowered to detect such a difference.

Considering the great variability in imaging strategies after cardiothoracic surgery in current practice, an optimal imaging strategy is still warranted [26]. Daily routine CXR performance has been largely abandoned in ICU patients whose lungs are ventilated, and has been replaced by an 'on demand' strategy.²⁷ This has led to a significant decrease in the number of CXRs without any increase in adverse events.^{6,26} Studies comparing a daily routine with an on 'demand strategy' using primarily CXR or lung ultrasound as imaging technique are lacking in the cardiothoracic population.

Our data suggest that lung ultrasound might be a key modality to optimise the post-operative imaging strategy in these patients. Lung ultrasound potentially facilitates prompt diagnosis of PPCs, thereby enabling treatment to start early. In addition, lung ultrasound can be used to evaluate the efficacy of therapies initiated for PPCs, since lung ultrasound offers an accurate, non-invasive, easily reproducible bedside evaluation. Alsaddique et al. found that repeated imaging with lung ultrasound after cardiothoracic surgery frequently altered diagnosis and management of PPCs.²⁸ Considering the aforementioned, we suggest using lung ultrasound as an extension of the physical examination in patients after cardiothoracic surgery. The use of stethoscopes and CXRs for the detection of PPCs, with their debatable accuracy and downsides such as radiation exposure, may be superseded,²⁹ although CXR remains the standard for confirmation of the position of central venous catheters, as well as endotracheal tube placement.

Our study has some important limitations. Firstly, we could not report sensitivity and specificity of lung ultrasound and CXR compared with the gold standard for lung imaging, the thoracic CT scan, since this was not performed in our study. Therefore, we used clinically-relevant PPCs as a clinically-relevant composite reference standard, to minimise imperfect reference standard bias. However, a disadvantage is the introduction of the subjectivity of the treating physician.³⁰ Secondly, lung ultrasound was not studied as the primary imaging technique following cardiothoracic surgery and compared with CXR in a blinded, randomised controlled trial. Possible variations in therapy initiated, and the incidence rate of detection of clinically-relevant PPCs for lung ultrasound compared with CXR could not be studied.

Theoretically, should therapy have been initiated according to more sensitive lung ultrasound findings, it could introduce an element overtreatment of clinically-irrelevant PPCs. However, the positive effects of early treatment and potentially faster recovery were not studied either. Thirdly, the BLUE protocol was validated for patients in respiratory distress presenting to the emergency department.¹⁷ Strengths of the current study are the large sample size compared with previous studies in non-cardiothoracic surgery, and the fact that this is the first study to show that lung ultrasound can detect PPCs at an earlier stage than CXR. Furthermore, lung ultrasound was performed by multiple investigators, with different levels of experience, thus mirroring daily clinical practice. In addition, lung ultrasound showed a high inter-observer agreement, in concordance with previously reported findings, and was performed faster than CXR.²² Lastly, we have shown that lung ultrasound is feasible in patients after cardiothoracic surgery, who are considered less accessible to lung ultrasound, e.g. due to wound dressings and thoracic drain tubes, again in accordance with previous studies.^{22,28} There is a need for larger (multicenter) trials investigating the cost effectiveness, the ease of implementation and the effects on patient outcomes and interventions performed when lung ultrasound is used a primary imaging technique, compared with CXR. Since different lung ultrasound protocols were used in previous studies, it would be of interest to determine if lung ultrasound protocols are comparable, or if one protocol is superior to another. In addition, we suggest quantification of lung ultrasound findings.

In conclusion, lung ultrasound detected more (clinically-relevant) PPCs and at an earlier time point than CXR following cardiothoracic surgery. Our results suggest lung ultrasound can be used as primary imaging technique to search for PPCs after cardiothoracic surgery, and will enhance bedside decision-making. The next step is to test lung ultrasound as the primary imaging technique in these patients, and further quantify the extent of PPCs.

References

1. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010;113: 1338–50.
2. Weissman C. Pulmonary complications after cardiac surgery. *Seminars in Cardiothoracic and Vascular Anesthesia* 2004;8: 185-211.
3. Marseu K, Slinger P. Peri-operative pulmonary dysfunction and protection. *Anaesthesia*. 2016;71: 46-50.
4. Mazo V, Sabaté S, Canet J, Gallart L, de Abreu MG, Belda J, et al. Prospective External Validation of a Predictive Score for Postoperative Pulmonary Complications. *Anesthesiology* 2014;121: 219–31.
5. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby J-J Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004;100: 9–15.
6. Tolsma M, Rijpstra TA, Rosseel PM, Scohy TV, Bentala M, Mulder PG, van der Meer NJ Defining indications for selective chest radiography in the first 24 hours after cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery* 2015;150: 225-9.
7. Touw HR, Tuinman PR, Gelissen HP, Lust E, Elbers PW. Lung ultrasound: routine practice for the next generation of internists. *Netherlands Journal of Medicine*. 2015;73: 100-7.
8. Lichtenstein, DA. BLUE-Protocol and FALLS-Protocol *CHEST* 2015;147: 1659-1670.
9. Barber RL, Fletcher SN. A review of echocardiography in anaesthetic and peri-operative practice. Part 1: impact and utility. *Anaesthesia*. 2014;69: 764-76.
10. Ye X, Xiao H, Chen B, Zhang S. Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis. *PLOS One* 2015;10: e0130066.
11. Martindale JL, Noble VE, Liteplo A. Diagnosing pulmonary edema: lung ultrasound versus chest radiography. *European Journal of Emergency Medicine* 2013;20: 356-60.
12. Alrajab S, Youssef AM, Akkus NI, Caldito G. Pleural ultrasonography versus chest radiography for the diagnosis of pneumothorax: review of the literature and meta-analysis. *Critical Care* 2013;17: R208.
13. Ashton-Cleary DT. Is thoracic ultrasound a viable alternative to conventional imaging in the critical care setting? *British Journal of Anaesthesia* 2013;111: 152-60.
14. Tuddenham WJ. Glossary of terms for thoracic radiology: recommendations of the Nomenclature Committee of the Fleischner Society. *American Journal of Roentgenology*. 1984;143: 509-17.
15. Rubinowitz AN, Siegel MD, Tocino I. Thoracic imaging in the ICU. *Critical Care Clinics*. 2007;23: 539-73.
16. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest* 2008;134: 117-25.
17. Lichtenstein D. Lung ultrasound in acute respiratory failure an introduction to the BLUE-protocol. *Minerva Anestesiologica* 2009;75: 313-7.

18. Lichtenstein D. Whole Body Ultrasonography in the Critically Ill .Berlin, Germany: Springer-Verlag; 2010.
19. Jain U, Rao TL, Kumar P, Kleinman BS, Belusko RJ, Kanuri DP, et al. Radiographic pulmonary abnormalities after different types of cardiac surgery. *Journal of Thoracic and Cardiovascular Anesthesia*. 1991;5: 592-5
20. Hedenstierna G, Edmark L Mechanisms of atelectasis in the perioperative period. *Best Practice and Research in Clinical Anaesthesiology*. 2010;24: 157-69.
21. Jindani A, Aps C, Neville E, Sonmez B, et al: Postoperative cardiac surgical care: An alternative approach. *British Heart Journal* 1993;69: 59-64.
22. Vezzani A, Manca T, Brusasco C, Santori G, Valentino M, Nicolini F, et al. Diagnostic value of chest ultrasound after cardiac surgery: a comparison with chest X-ray and auscultation. *Journal of Thoracic and Cardiovascular Anesthesia* 2014;28: 1527-32.
23. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. *Annals of Surgery*. 2009;250: 1029-34.
24. Silber JH, Williams SV, Krakauer H, Schwartz JS. Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. *Medical Care* 1992;30: 615-29.
25. Balik M, Plasil P, Waldauf P, Pazout J, Fric M, Otahal M, Pachtl J. Ultrasound estimation of volume of pleural fluid in mechanically ventilated patients. *Intensive Care Medicine*. 2006;32: 318-21.
26. Lee J, Geyer B, Naraghi L, Kaafarani HM, Eikermann M, Yeh DD, Bajwa EK, Cobb JP, Raja AS. Advanced imaging use in intensive care units has decreased, resulting in lower charges without negative effects on patient outcomes. *Journal of Critical Care*. 2015;30: 460-4.
27. Hejblum G, Chalumeau-Lemoine L, loos V, Boëlle PY, Salomon L, Simon T, Vibert JF, Guidet B. Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised, two-period crossover study. *Lancet*. 2009;374: 1687-93.
28. Alsaddique A, Royse AG, Royse CF, Mobeirek A, El Shaer F, AlBackr H, et al. Repeated Monitoring With Transthoracic Echocardiography and Lung Ultrasound After Cardiac Surgery: Feasibility and Impact on Diagnosis. *Journal of Thoracic and Cardiovascular Anesthesia*. 2016;30: 406-12.
29. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology*. 2004;100: 9-15.
30. Naaktgeboren CA, Bertens LC, de Groot JA, Moons KG, Reitsma JB. Value of composite reference standards in diagnostic research. *British Medical Journal* 2013;25: 347:5605.

Chapter 10

Ultrasound for detecting postoperative pulmonary complications.

Letter to the editor from C. Rivett and N. Broughton
&

Response to the letter to the editor

Hugo R.W. Touw, Krista L. Parlevliet, Mo Beerepoot and Pieter R. Tuinman

Anaesthesia 2018; 73:1442-1443.

Letter to the editor

We congratulate Touw et al. for their pragmatic study evaluating lung ultrasound for detecting postoperative pulmonary complications (PPC) following cardiac surgery [1](#). We agree with their overall conclusion that lung ultrasound shows great promise and might replace chest radiography as a routine imaging modality. We accept the limitations of the study acknowledged by the authors and agree that further research is necessary.

The authors listed common PPCs, and defined these as relevant where a change in management was necessary after PPC detection. This is a reasonable and pragmatic definition, but makes the quoted rate of 'relevant PPCs' subjectively based on previous management. For instance, some units engage in alveolar recruitment manoeuvres routinely, rather than responsively. This pragmatic study design limits the applicability of findings to other centres – particularly the quoted figures for sensitivity and specificity, positive and negative predictive values, and diagnostic accuracy.

We think that double counting may have affected the 'relevant PPC rate'. For example, wheeze might result from either bronchospasm or pulmonary oedema, and patients may receive treatment for both conditions, generating two 'relevant PPCs' from one pathological process. We would be interested to know how the authors controlled for this possibility and whether the results might have been affected by this potential bias?

An important question to consider is what is considered 'normal' in this context? For example, while healthy patients should not have small pleural effusions and/or mild atelectasis, these findings are not abnormal for patients whose lungs are ventilated on ITU when discovered by computed tomography (CT). While intensivists have come to accept a different range of normality for CT findings, we do not consider a similar consensus has emerged for lung ultrasound findings in this cohort.

The authors quote a PPC rate of 90% at day 0 and 2, and 100% at day three. These are defined as postoperative pulmonary complications, but could be considered pulmonary consequences. If these are truly complications, do the authors consider that patients should be quoted the 90–100% complication rate during the consent process before surgery?

As advocates of lung ultrasound, we look forward to further research in this field and hope for greater clarity over contextual-based definitions of 'normality' and 'abnormality', as we consider this an important step towards an evidence-based and rational adoption of widespread lung ultrasound scanning in critical care.

References

1. Touw HR, Parlevliet KL, Beerepoot M, et al. Lung ultrasound compared with chest x-ray in diagnosing postoperative pulmonary complications following cardiothoracic surgery: a prospective observational study. *Anaesthesia* 2018; 73: 946–54.

Response to the letter to the editor

We thank Rivett and Broughton for their interest in our research.^{1,2} We chose a pragmatic approach for evaluating lung ultrasound in the postoperative cardiothoracic setting by focusing on postoperative pulmonary complications (PPC) that required treatment. We agree that the specific diagnostic accuracy we quoted is centre specific, as postoperative patient management strategies that differ between centres and treatments for PPCs are multifactorial. We used the final diagnosis determined by the treating physician to avoid double counting. Rivett and Broughton raise an interesting point about distinguishing consequences from complications. We suggest that the unavoidable pulmonary consequences of cardiothoracic surgery, for example, limited atelectasis or pleural effusion, lead to clinically-relevant complications. We believe this continuum warrants a seamless postoperative lung ultrasound imaging strategy to objectively monitor postoperative pulmonary status, and should be studied in future research. We tried to quantify postoperative lung ultrasound findings, but that was not straightforward, as described by our results and in our discussion. We think that atelectasis or pleural effusion should be contextualised according to patients' symptoms, performance and rehabilitation status, before deciding whether to start specific treatment. Further research is required to clarify those treatment algorithms.

References

1. Touw HR, Parlevliet KL, Beerepoot M, et al. Lung ultrasound compared with chest x- ray in diagnosing postoperative pulmonary complications following cardiothoracic surgery: a prospective observational study. *Anaesthesia* 2018; 73: 946–54.
2. Rivett C, Broughton N. Ultrasound for detecting postoperative pulmonary complications. *Anaesthesia*. 2018;73:1442

Chapter 11

Routine lung ultrasound to detect postoperative pulmonary complications following major abdominal surgery: a prospective observational feasibility study

Hugo R.W. Touw, Aniek E. Schuitemaker, Freek Daams, Donald L. van der Peet, Ewald M. Bronkhorts, Patrick Schober, Christa Boer and Pieter R. Tuinman

Submitted

Abstract

Introduction

Postoperative pulmonary complications (PPCs) after major abdominal surgery are associated with adverse outcome. The diagnostic accuracy of chest X-rays (CXR) to detect pulmonary disorders is limited. Alternatively, lung ultrasound (LUS) is an established evidence based point-of-care diagnostic modality which outperforms CXR in critical care. However, its feasibility and diagnostic ability for PPCs following abdominal surgery are unclear.

Methods

In this prospective observational feasibility study, we included consecutive patients undergoing major abdominal surgery with an intermediate or high risk for the development of PPCs according to the ARISCAT score. LUS was routinely performed on postoperative days (PODs) 0-3 by a researcher blinded for CXR or other clinical findings. CXRs were performed on demand according daily clinical practice. Feasibility of LUS and detection rates of PPCs were reported for LUS. Secondly, we compared LUS and CXR findings.

Results

A total of 98 consecutive patients with a ARISCAT score of 41 (34-49) were included in the study. LUS was feasible in all patients. LUS detected in 94 (95%) of patients one or more PPCs during the first four PODs. On POD 0, LUS detected 31 out of 43 patients (72.1%) with 1 or more PPCs, compared to 13 out of 36 patients (36.1%) with 1 or more PPCs detected with CXR ($p=0.004$) RR 2.0 (95 CI [1.24-3.20]). The number of discordant observations with both modalities was high for atelectasis 23 (43%) and pleural effusion 29 (54%), but not for pneumothorax, respiratory infection and pulmonary edema 8 (15%), 3 (5%) and 5 (9%) respectively.

Conclusion

This pilot study shows that LUS is highly feasible and frequently detects PPCs after major abdominal surgery. Discordant observations in atelectasis and pleural effusions for LUS and CXR can be explained by a superior diagnostic ability of LUS in detecting these conditions. The effects of LUS as primary imaging modality on patient outcome should be evaluated in future studies.

Introduction

There is increasing interest in early detection of postoperative pulmonary complications (PPCs) to reduce patient morbidity and mortality.¹ Furthermore, in patients unsuspectedly admitted to the intensive care unit (ICU), insufficient diagnostic imaging was performed on the general ward and inadequate treatments were initiated.² Early PPC detection would enable the physician to start treatment on time and therefore prevent its negative impact on patient outcome.

Respiratory failure following anaesthesia and surgery typically start with atelectasis, due to diaphragmatic dysfunction, inability to clear secretions and immobility. Chest auscultation and Chest X-ray (CXR) are frequently used as diagnostic modalities to detect PPCs, but have limited diagnostic accuracies.³⁻⁶ Moreover, ideally radiography requires an upright position of the patient, and multiple concomitant lung abnormalities further complicate its two-dimensional interpretation.⁷⁻⁹ Computed Tomography (CT) is the gold standard for pulmonary pathology but requires significant ionizing radiation and the need for transfers within the hospital, which is not without risk.³

Alternatively, lung ultrasound (LUS) is a quick, bedside technique and is radiation free. It has an excellent diagnostic accuracy for atelectasis, pulmonary effusions, pulmonary edema and/or pneumonia in critically ill patients compared to the gold standard CT.^{3,4,6} Therefore, LUS is well established in these patients and practical approaches to perform LUS have been described extensively elsewhere.^{10,11} We previously showed that in cardiothoracic surgery patients LUS compared to CXR detected more (clinically-relevant) PPCs and at an earlier time point.¹² Following major abdominal surgery dressings, chest drains or subcutaneous emphysema could limit the feasibility of lung ultrasound in this setting.

Due to its limitations daily routine CXR performance has been largely abandoned in ICU and cardiothoracic patients, and has been replaced by an on demand strategy. This has led to a significant decrease in the number of CXRs without any increase in adverse events in ICU patients.¹³ Studies comparing on demand strategies with routine strategies are lacking in patients after major abdominal surgery. However, performing CXR on demand after a clinical suspicion causes a potential delay in detection. Potentially, routine LUS can detect PPCs early and with higher accuracy to improve perioperative management in major abdominal surgery patients.^{4,10,14}

The aim of this pilot study was to test the feasibility of routine LUS following major abdominal surgery and to report the detected PPCs with LUS in these postoperative patients. Secondly, PPC detection rates for LUS and CXR were compared.

Methods

We conducted this prospective, observational feasibility study in the Amsterdam UMC - VU University Medical Center Amsterdam (VUmc Amsterdam, The Netherlands), a tertiary hospital. The local Human Subjects Committee of the VUmc approved the study (METc 16/128), and written informed consent was obtained from all participants. Patient inclusion started June 2016 and ended March 2017. The study included consecutive adult patients (age ≥ 18 years) scheduled for elective major abdominal (e.g. gastro-intestinal, vascular or renal surgery) with an intermediate or high risk for the development of postoperative pulmonary complications according to the Assess Respiratory risk In Surgical patients in CATalonia (ARISCAT) risk score ≥ 26 .^{15,16} Exclusion criteria were trauma or emergency surgery.

Patient characteristics

Patient characteristics were retrieved from the patient data management system and included age, gender, weight, length and body mass index (BMI), American Society of Anesthesiology (ASA) classification, the ARISCAT score, co morbidities, alcohol use and smoker status. Perioperative parameters were also retrieved and included type of surgery, intensive care unit (ICU) referral and total in-hospital length of stay. Patient and laboratory data included: arterial oxygen saturation, mode of ventilation, O₂ supplementation, sputum cultures, temperature and leukocyte count.

Chest X-Ray

CXR was performed according to standard clinical practice (e.g. after placement of chest tube or central venous line placement) and when demanded by the treating physician for clinical reasons. Anteroposterior bedside CXRs were obtained using a DRX-Revolution mobile X-ray unit (Carestream Health, Inc. © Toronto, Canada). We retrospectively retrieved CXR findings, assessed by a radiologist blinded to the LUS findings, from the PDMS. The Nomenclature Committee of the Fleischner Society recommended terminology was used to describe pathological entities according to the diagnostic criteria for bedside CXR.^{17,18}

Lung ultrasound

A trained member of the research team (n=3), which consisted of two dedicated investigators and one ICU Fellow, performed 'routine' LUS upon admission after surgery on postoperative day (POD) 0, and on all consecutive PODs 1-3. LUS was only performed when a researcher was available, e.g. during weekdays and working hours. All ultrasonographers were trained according to the Netherlands Society of Intensive Care Programme for Intensive Care Ultrasound (NVIC ICARUS) training course (www.nvic.nl). The ultrasonographer was blinded

to clinical details and CXR findings, and did not contribute to the diagnostic and treatment strategy of the patient. We used a CX50 ultrasound machine (Koninklijke Philips NV[®], Eindhoven, the Netherlands) with both the cardiac phased array (1-5 MHz) and the linear vascular probe (>10 MHz). The ultrasonographer could choose a particular probe for a particular view in a particular patient, according to individual preference. Lung sliding was determined using the vascular probe. LUS views were obtained according to the BLUE protocol.^{13,19}

In short, as described before¹², we determined a BLUE profile for each BLUE point and BLUE profile per hemithorax (BLUE 1 and 2) as follows: A; B; A'; B'; or C-profile. A profile means predominantly A lines. B profile means predominantly multiple (>2) anterior diffuse B lines indicating interstitial syndrome. A' or B' means the corresponding BLUE profile with absence of, or abolished lung sliding. C profile means anterior alveolar consolidation. Furthermore, we determined the postero-lateral alveolar and/or pleural syndrome (PLAPS) on each side at the lateral sub-posterior side of the chest and scored this as positive or negative. When positive, consolidation and/or pleural effusion were scored separately and the diagnosis of atelectasis was added to the flowchart. The final conclusion was made according to the bedside LUS protocol in cardiothoracic patients, as published in previous research.¹² For differentiation between pneumonia and atelectasis, the ultrasonographer was further allowed to look for fever, leukocyte count and possibly C-reactive protein (CRP) in the PDMS.

Postoperative pulmonary complications

The incidence of PPCs detected with CXR were retrospectively retrieved by a research team member using the PDMS. PPCs were scored according to reported radiology findings of on demand CXR studies ordered by the treating physician at the ward. PPCs were scored as previously defined by others: respiratory infection defined as treatment with antibiotics for a suspected respiratory infection and at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count >12,000/mm³; pleural effusion defined by blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows; atelectasis defined by lung opacification with shift of the mediastinum, hilum or hemi diaphragm towards the affected area and compensatory over-inflation in the adjacent non-atelectatic lung; and pneumothorax defined by air in the pleural space with no vascular bed surrounding the visceral pleura, all demonstrated by the CXR.^{15,16}

Clinically relevant postoperative pulmonary complications

Clinically-relevant PPCs, defined as a PPC that required treatment, as judged by the treating physician, were also reported.¹² We considered the following to be treatments initiated for clinically-relevant PPCs: high flow oxygen therapy; a higher positive end-expiratory pressure (PEEP) level or recruitment maneuvers; continuous positive airway pressure (CPAP); re-intubation; bronchoscopy; extra bronchodilator therapy; thoracic drain placement; and the use of diuretics and/or antibiotics. Scoring of clinically relevant PPCs were retrospectively retrieved from the PDMS according to initiated treatment by the treating physicians for a PPCs at the ward. The physician who diagnosed clinically relevant PPCs took the following into account: physical examination, conventional monitoring, laboratory results, CXR and/or CT scan results when available. This reflected daily clinical practice. The treating physicians were blinded to LUS findings.

Statistical analysis

We included as many consecutive patients as possible in the study period. We planned to include more than 90 patients to detect around 30 PPCs based on incidence rates of PPCs after surgery.¹⁶ Results of this study will be used to plan a larger study on the effects of LUS on patient outcome after major abdominal surgery. We carried out statistical data analyses using SPSS statistical software package version 22.0 (IBM, New York, NY, USA). Feasibility was reported as percentage of patients in which LUS was possible. Detection rates of PPCs during the study period were reported as frequencies. In addition, detection rates were compared according to both imaging modalities. Furthermore, an aggregated analysis was performed to compare the detection of PPCs in patients who had both; CXR and LUS performed the same day during the study period. Relative risk was calculated comparing PPC detection with LUS and CXR. Discordant observations were compared for PPCs detected with LUS and CXR.

Results

Overall, 98 consecutive patients were included in the study. Table 1 shows the patient characteristics of included patients.

Table 1. Perioperative patient characteristics.

Patient characteristics	Values
N	98
Males / females (n)	59 / 39
Age (years)	64 ± 11.7
Body Mass Index (kg/m²)	26.1 ± 4.6
Median ASA physical status	2 [2 - 3]
Median ARISCAT score	41 [34-49]
Types of surgery, n(%)	
<i>Esophageal</i>	14 (14.3)
<i>Gastric</i>	9 (9.2)
<i>Hepatic</i>	19 (19.4)
<i>Pancreatic</i>	12 (12.2)
<i>Vascular</i>	6 (6.1)
<i>Renal</i>	16 (16.3)
<i>Other gastrointestinal</i>	22 (22.4)

Data represent mean ± standard deviation, median with [interquartile range] or number of cases (percentage). ASA = American Society of Anesthesiologists; ARISCAT = Assess Respiratory risk In Surgical patients in CATalonia.

Routine Lung Ultrasound: feasibility and incidence of PPCs

In 100% of patients LUS was feasible. LUS examinations performed and incidence rates of PPCs detected with LUS are shown in Table 2. In total, routine LUS detected in 94 out of 98 patients (96%) a PPC in the study period.

Table 2. Incidence rates of postoperative pulmonary complications detected with ‘routine’ lung ultrasound after major abdominal surgery.

Day	LUS (routine)	N ≥ 1 PPC	Respiratory infection	Pneumo- thorax	Pulmonary edema	Atelectasis	Pleural effusion
POD 0 (n=98)	43 (45%)	31 (72%)	2	2	1	29	10
POD 1 (n=98)	92 (94%)	64 (70%)	0	2	2	55	31
POD 2 (n=98)	87 (89%)	21 (24%)	4	0	1	9	9
POD 3 (n=92)	56 (61%)	8 (14%)	1	0	2	1	5

Data represent number of cases (percentage). LUS= lung ultrasound, PPC=postoperative pulmonary complication, POD=postoperative day. N ≥ 1 PPC (percentage of total LUS examinations performed on POD x).

Lung ultrasound compared with Chest X-ray

CXR examinations performed and incidence rates of PPCs detected are shown in Table 3. In total on demand CXR detected in 36 out of 98 patients (37%) a PPC in the study period. *On POD 0, lung ultrasound detected 31 out of 43 patients (72.1%) with 1 or more PPCs, compared to 13 out of 36 patients (36.1%) with 1 or more PPCs detected with CXR (p=0.004) RR 2.0 (95% CI [1.24-3.20]).* LUS and CXR mainly identified atelectasis and pleural effusion as shown in Table 2 en Table 3. The number of discordant observations for the 54 cases where both LUS and CXR were performed, for pneumothorax, respiratory infection and pulmonary edema were 8, 3 and 5 (15%, 5% and 9%) respectively. For atelectasis and pleural effusion the number of discordant pairs was much higher: 23 and 29 (43% and 54%) respectively.

Table 3. Incidence rates of postoperative pulmonary complications detected with ‘on demand’ chest X-ray after major abdominal surgery according to daily clinical practice. Data represent number of cases (percentage).

Day	CXR (on demand)	N ≥ 1 PPC	Respiratory infection	Pneumo-thorax	Pulmonary edema	Atelectasis	Pleural effusion
POD 0 (n=98)	36 (37%)	13 (36%)	0	2	3	9	4
POD 1 (n=98)	19 (19%)	13 (72%)	0	4	3	9	6
POD 2 (n=98)	13 (13%)	7 (54%)	0	2	0	3	5
POD 3 (n=92)	9 (10%)	3 (33%)	0	1	1	1	3

CXR= chest X ray, PPC=postoperative pulmonary complication, POD=postoperative day. N ≥ 1 PPC (percentage of total number of total CXR examinations performed on POD x).

The incidence of clinically relevant postoperative pulmonary complications

The incidence of clinically relevant PPCs during the study period POD 0-4 are shown in Table 4. The incidence of clinically relevant PPCs increased over the first 4 days, with a maximal of 10 patients out of 98 patients on POD 3. For 8 patients incidence of respiratory infection could be followed up to 30 days postoperatively. LUS detected consolidations in 7 out of 8 patients treated for respiratory infection and CXR detected consolidations in 5 out of 8 patients during the study period.

Table 4. Presence of clinically relevant postoperative pulmonary complications on day 0, 1, 2, 3 and 4-30 in 98 patients after abdominal surgery.

Clinically relevant PPCs	Day 0	Day 1	Day 2	Day 3	Day 4-30
Total	0 (0%)	3 (3%)	6 (6%)	10 (10%)	13 (13%)
Pneumonia	0 (0%)	0 (0%)	0 (0%)	3 (3%)	5 (5%)
Pneumothorax	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Pulmonary edema	0 (0%)	1 (1%)	3 (3%)	3 (3%)	0 (0%)
Atelectasis	0 (0%)	0 (0%)	2 (2%)	1 (1%)	0 (0%)
Pleural effusion	0 (0%)	2 (2%)	1 (1%)	2 (2%)	2 (2%)

Data represent number of cases (percentage). PPCs = postoperative pulmonary complications.

Discussion

This pilot study demonstrates that routine LUS is highly feasible and frequently detects PPCs in patients following major abdominal surgery. Secondly, LUS detected more PPCs when compared to CXR when both modalities were performed on POD 0. Importantly the discordant observations for LUS and CXR were highest for atelectasis and pleural effusion.

We confirm that LUS is highly feasible in postoperative patients.^{12,20,21} Goudy *et al.* found that lung ultrasound was feasible in 97% of the hemi thoraxes in 252 ultrasound examinations after cardiothoracic surgery despite the presence of chest drainage tubes or applied dressings.²¹ To the best of our knowledge we are the first to report highly feasibility following major abdominal surgery. Following major abdominal surgery dressings, chest drains or subcutaneous emphysema or limited patient mobility could have prohibited the feasibility in this setting.

To our knowledge, we are the first to report PPC rates detected by LUS following major abdominal surgery. The rates found with LUS are high in comparison with PPC rates previously reported with other diagnostic modalities.¹⁵ However, in the cardiothoracic surgery population, it was previously reported that the rate of PPCs detected with LUS were up to 100%.^{12,22} Detection of PPCs with CXR in our study (37%) is in line with preoperative risk scores.¹⁶ Also, Mazo *et al.* recently showed incidence rates of PPCs ranging from 38-50% in a large validation study in Western Europe in a comparable study population.¹⁶

We found that LUS and CXR, when performed at the same time, identified pleural effusion and atelectasis in different patients (discordant pairs) following major abdominal surgery. These discordant pairs were detected in up to 50% of the patients who had both imaging modalities performed on the same day. This difference can be explained by a higher sensitivity and specificity of LUS in detecting pleural effusion and atelectasis compared to CXR.^{3,6,20} In a recent systematic review and meta-analysis, LUS had an overall sensitivity of 95% (92–96%) and specificity of 94% (90–97%) compared to CT in adult critically ill patients with respiratory symptoms.⁶ CXR had an overall sensitivity of 49% (40-58%) and specificity of 92% (86-95%) in the same systematic review and meta-analysis. Therefore, LUS is being considered by others as the bedside gold standard for pulmonary pathology in critically ill patients with respiratory symptoms.^{4,14}

In a recent pilot study performed in cardiothoracic surgery evaluating effectiveness of LUS as the primary diagnostic imaging technique; LUS was exhaustive in up to 80% of the patients. Subsequent CXR was not required in the postoperative management of these patients to assist decision making in this study and LUS was considered effective in perioperative

patient management. Furthermore, LUS allowed further discrimination of lung abnormalities mainly between atelectasis and pleural effusions.^{22,23}

Other advantages of LUS are that the time to perform LUS was significantly shorter than for CXR in the postoperative setting¹² and LUS had excellent inter-observer agreement.^{4,12} Furthermore, LUS can be used to guide central venous catheter placement and position,²⁴ thoracosynthesis and the management of fluid administration in acute circulatory failure.¹¹ However, if routine LUS findings are inconclusive in patients with respiratory symptoms additional imaging is warranted; we do suggest using additional CXR or CT imaging to make a final diagnosis.

Our study has important limitations. LUS examinations could not be performed on all postoperative days; on POD 0 patients were frequently admitted after working hours and POD 3 was most frequently during weekends, so researchers were not always available to perform LUS. Therefore, the predictive value of detected complications to become clinically-relevant PPCs could not be analyzed. Another important limitation is the absence of the gold standard (computed tomography) for lung pathology to relate our lung ultrasound findings to. We choose to use and adjust the most practical, succinct, but well validated and accurate lung ultrasound protocol (BLUE protocol).^{14,19} However, also a method for further quantifying B-lines and to scan eight or even 28 separate intercostal spaces instead of four has been described which could increase the detection rate even more.²⁵ It is unknown what the clinical importance is of detecting PPCs with LUS that do not require therapy according to the treating physician. This should be studied in further studies. We strongly believe that not all atelectasis nor pleural effusion need treatment, but LUS findings, like other clinical findings, should always be seen in light of patient's symptoms and health status. Our findings indicate to further study LUS as primary screening tool for detecting PPCs in major abdominal surgery patients. Future studies should focus on patient outcome and cost effectiveness.

Strengths of this study is we show that LUS is indeed feasible and frequently detects PPCs in patients following major abdominal surgery. The protocol we propose is easy to use, also for physicians newly trained in LUS. The protocol is based on limited, standardized signs, a major advantage of LUS, because the risk of wrong interpretations is thereby decreased.

Developing competence in LUS is considered straightforward. Surgeons and anaesthesiologists active in the postoperative period should consider training in LUS as part of their point-of-care ultrasound skills. Furthermore, adding this useful tool into resident training would parallel its broader use in other medicine specialties. Learning the basics of

LUS to perioperative physicians and residents would be fairly easy. For example, in nephrology, a 4-h course that includes pre-course cognitive preparation, a didactic lecture and training in image acquisition/interpretation are sufficient to give the learner a strong foundation in LUS. However, the course alone is not sufficient to provide competence.²⁶ Competence in LUS requires additional bedside scanning of patients under the supervision of capable faculty as outlined before.¹⁰

In conclusion, this pilot study shows that LUS is highly feasible and detects PPCs frequently in patients after major abdominal surgery. Lung ultrasound findings should be evaluated in combination with all available clinical data when considering initiating treatment. Closely monitoring patients and detecting PPCs with lung ultrasound could create a window of opportunity to limit the impact of PPCs on patient outcome. This needs to be studied in future trials.

References

1. Ricciardi R, Roberts PL, Read TE, Hall JF, Marcello PW, Schoetz DJ. Which adverse events are associated with mortality and prolonged length of stay following colorectal surgery? *J Gastrointest Surg.* 2013;17:1485-93
2. Van Galen LS, Struik PW, Driesen BE et al. Delayed Recognition of Deterioration of Patients in General Wards Is Mostly Caused by Human Related Monitoring Failures: A Root Cause Analysis of Unplanned ICU Admissions. *PLoS One* 2016; 11 : e0161393.
3. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004; 100:9–15.
4. Lichtenstein DA. Lung ultrasound in the critically ill. *Clinical Intensive Care.* 2014. p. 1–12.
5. Hammon M, Dankerl P, Voit-Hohne HL, Sandmair M, Kammerer FJ, Uder M, et al. Improving diagnostic accuracy in assessing pulmonary edema on bedside chest radiographs using a standardized scoring approach. *BMC Anesthesiol* 2014;14:94.
6. Winkler MH, Touw HR, van de Ven PM, Twisk J, Tuinman PR. Diagnostic Accuracy of Chest Radiograph, and When Concomitantly Studied Lung Ultrasound, in Critically Ill Patients With Respiratory Symptoms: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2018;46:e707-e714.
7. Self WH, Courtney DM, McNaughton CD, Wunderink RG, Kline JA. High discordance of chest X-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. *Am J Emerg Med* 2013;31: 401–5.
8. Halperin BD, Feeley TW, Mihm FG, Chiles C, Guthaner DF, Blank NE. Evaluation of the portable chest roentgenogram for quantitating extravascular lung water in critically ill adults. *Chest* 1985;88:649–52.
9. Tasci O, Hatipoglu ON, Cagli B, Ermis V. Sonography of the chest using linear-array versus sector transducers: correlation with auscultation, chest radiography, and computed tomography. *J Clin Ultrasound* 2016;44:383–9.
10. Touw HR, Tuinman PR, Gelissen HP, Lust E, Elbers PW. Lung ultrasound: routine practice for the next generation of internists. *Neth J Med.* 2015 Mar;73:100-7. Review.
11. Miller A; Practical approach to lung ultrasound, *BJA Education*, Volume 16, Issue 2, 1 February 2016, Pages 39–45.
12. Touw HR, Parlevliet KL, Beerepoot M, Schober P, Vonk A, Twisk JW, Elbers PW, Boer C, Tuinman PR. Lung ultrasound compared with chest X-ray in diagnosing postoperative pulmonary complications following cardiothoracic surgery: a prospective observational study. *Anaesthesia.* 2018; 73:946-954
13. Hejblum G, Chalumeau-Lemoine L, Ioos V, Boëlle PY, Salomon L, Simon T, Vibert JF, Guidet B. Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised, two-period crossover study. *Lancet.* 2009;374: 1687-93.

14. Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest*. 2015 ;147:1659-1670.
15. Canet J, Gallart L, Gomar C et al. ARISCAT Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010; 113 : 1338-50
16. Valentín Mazo, Sergi Sabaté, Jaume Canet, Lluís Gallart, Marcelo Gama de Abreu, Javier Belda, Olivier Langeron, Andreas Hoeft, Paolo Pelosi; Prospective External Validation of a Predictive Score for Postoperative Pulmonary Complications. *Anesthesiology* 2014;121:219-231.
- Tuddenham WJ. Glossary of terms for thoracic radiology: recommendations of the Nomenclature Committee of the Fleischner Society. *AJR Am J Roentgenol*. 1984; 143: 509-17.
17. Rubinowitz AN, Siegel MD, Tocino I. Thoracic imaging in the ICU. *Crit Care Clin*. 2007; 23: 539-73.
18. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest* 2008; 134: 117-25.
19. Vezzani A, Manca T, Brusasco C, Santori G, Valentino M, Nicolini F, et al. Diagnostic value of chest ultrasound after cardiac surgery: a comparison with chest X-ray and auscultation. *J Cardiothorac Vasc Anesth* 2014;28: 1527-32.
20. Goudie E, Bah I, Khereba M, Ferraro P, Duranceau A, Martin J, Thiffault V, Liberman M. Prospective trial evaluating sonography after thoracic surgery in postoperative care and decision making. *Eur J Cardiothorac Surg* 2012; 41: 1025–1030.
21. Chiappetta M, Meacci E, Cesario A, Smargiassi A, Inchingolo R, Petracca Ciavarella L, Lopatriello S, Contegiacomo A, Congedo MT, Margaritora S. Postoperative chest ultrasound findings and effectiveness after thoracic surgery: A pilot study. *Ultrasound Med Biol*. 2018; 44:1960-1967.
22. Jip Nooitgedacht, Mark Haaksma, Hugo R. W. Touw, Pieter R. Tuinman. Perioperative care with an ultrasound device is as Michael Jordan with Scotty Pippen: at its best! *J Thorac Dis* 2018;10):6436-6441.
23. Smit JM, Raadsen R, Blans MJ, Petjak M, Van de Ven PM, Tuinman PR. Bedside ultrasound to detect central venous catheter misplacement and associated iatrogenic complications: a systematic review and meta-analysis. *Crit Care*. 2018; 22:65.
24. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, Dean A, Tsung JW, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby JJ, Arbelot C, Liteplo A, Sargsyan A, Silva F, Hoppmann R, Breikreutz R, Seibel A, Neri L, Storti E, Petrovic T, International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012; 38:577-91.
25. Ross DW, Abbasi MM, Jhaveri KD, Sachdeva M, Miller I, Barnett R, Narasimhan M, Mayo P, Merzkani M, Mathew AT. Lung ultrasonography in end-stage renal disease: moving from evidence to practice-a narrative review. *Clin Kidney J*. 2018;11:172-178.

Chapter 12

General conclusions, discussion and future perspectives

General conclusions

Up to forty percent of the patients after major surgery develop postoperative complications, causing a tremendous socio-economic burden.^{1,2} Death after treatable complications (failure to rescue) is an important cause of mortality.³ Early detection and immediate appropriate treatment of mild to moderate clinical deterioration, occurring once complications arise, could prevent the incidence of these serious adverse events.^{3,4} Current practice encompasses intermittent point-check monitoring of vital signs and routine calculation of Early Warning Score (EWS) by nurses to detect these mild to moderate clinical deteriorations.⁵⁻⁸ When the EWS exceeds a critical threshold, a doctor should be called who initiates diagnostic work-up and/or therapeutic interventions. However, early signs of clinical deterioration may be missed. The impact of continuous monitoring of vital signs in postoperative and post-intensive care unit (ICU) patients on the detection rate of clinical deterioration and sequelae is largely unknown.

The most frequent and clinically important complications in the postoperative period are pulmonary complications. The detection of these complications is currently mainly based on chest radiography. Routine chest radiography is not without controversies; this imaging modality has limited diagnostic accuracy, comes with radiation exposure and considerable costs.⁹ Alternatively, lung ultrasound is a fast, low-cost, non-invasive and radiation-free imaging technique for the diagnosis of various pulmonary conditions.¹⁰ The diagnostic accuracy of lung ultrasound has been demonstrated to be superior to chest radiography when both are compared to the gold standard (computed tomography) for lung consolidation, pleural effusion, pneumothorax and pulmonary oedema in critically ill patients.^{10,11} However, the clinical significance of detecting pulmonary complications with lung ultrasound in the postoperative setting is also largely unknown.

The first aim of this thesis was to evaluate continuous remote monitoring of vital signs to detect clinical deterioration in postoperative patients admitted to and intensive care unit patients discharged to the general ward. Our second aim was to study point-of-care lung ultrasound in patients after major surgery to detect pulmonary complications. In order to achieve these goals, we performed multiple observational trials in the clinical setting.

In the first part of this thesis (**chapter 2-5**) we demonstrated that aberrant vital signs are well detected by continuous remote monitoring in postoperative patients (**chapter 3**) admitted to and intensive care unit patients (**chapter 4**) discharged to the general ward. In **chapter 3** we found that continuous remote monitoring of acoustical respiratory rate, peripheral oxygen saturation and heart rate in patients after major abdominal surgery results in the frequent

detection of remote modified early warning score (MEWS) values that were critical. Critical remote MEWS were seen in 11.6% of the monitoring time in patients with postoperative pulmonary complications compared to 0.44% of the monitoring time in patients without postoperative pulmonary complications. Early detection and recognition of clinical deterioration in these postoperative patients should prompt immediate doctor referral, in line with the MEWS protocol for escalation of care, to evaluate and initiate appropriate adjustment in patient management. In **chapter 4**, we also found that the remote MEWS was critical in 10% of the total monitored time in ICU patients discharged to the general ward. Importantly, in this study we compared remote MEWS with current practice point-check MEWS performed by nurses. More than half of the detected critical remote MEWS episodes were not detected by current practice point-check MEWS. We conclude in **chapter 4** that the continuous remote monitoring of MEWS would lead to increased doctor referral and may contribute to the prevention of developing severe complications.

In **chapter 5** we studied non-invasive respiratory rate monitoring in the challenging field of procedural sedation and analgesia in upper gastrointestinal endoscopic procedures. We found a low level of agreement between the detected respiratory rate with plethysmography versus the gold standard capnography in this setting. Non-invasive respiratory rate monitors are also available as a remote monitors. Most currently available non-invasive respiratory rate monitoring devices also have technical limitations with respect to the accuracy of continuous remote monitoring respiratory rate monitoring.¹² In our studies (**chapter 3 and 4**) we evaluated continuous remote monitoring by means of an acoustical respiratory rate. Ramsey *et al.* found acceptable limits of agreement between acoustical respiratory rate and capnography in detecting respiratory rate in patients in the postoperative care unit.¹³ However, it is possible that remote monitoring of acoustical respiratory rate in postoperative clinical deteriorating patients admitted to the general ward is less accurate. When clinical deterioration is detected with continuous remote monitoring a point-check verification should be performed by nurses.

From the first part of this thesis and available literature (**chapter 2**), we conclude that firm evidence for the clinical significance of continuous remote monitoring of vital signs in postoperative patients discharged to the general ward is still lacking. Our results do show potential to improve current practice of detecting patients who are clinically deteriorating. Future studies should evaluate the full extent of the possibilities of continuous remote monitoring in postoperative patients.

In the second part (**chapter 6-11**) of this thesis, we investigated the detection of postoperative pulmonary complications in cardiothoracic (**chapter 9**) and major abdominal surgery patients (**chapter 11**) with point-of-care lung ultrasound. In **chapter 6** we describe the principles of lung ultrasound and give a practical guidance how to adopt lung ultrasound in clinical practice to diagnose lung pathology. Based on our meta-analysis and systematic review in **chapter 8**, we conclude that lung ultrasound is clearly superior to chest radiography in terms of sensitivity and is similar in terms of specificity for detecting lung pathology in critically ill patients when compared to the gold standard, computed tomography.

In a prospective observational study (**chapter 9**), we studied the detection of postoperative pulmonary complications with point-of-care lung ultrasound in patients undergoing cardiothoracic surgery in whom, according to protocol daily chest radiography was performed. Lung ultrasound detected more postoperative pulmonary complications and also more postoperative pulmonary complications that required therapy compared to chest radiography. These complications were detected at an earlier point in time and also with excellent interobserver variability. Our results suggest that point-of-care lung ultrasound may be used as the primary imaging technique to screen for postoperative pulmonary complications after cardiothoracic surgery. Point-of-care lung ultrasound also increases the identification of clinical irrelevant findings. In patients where lung ultrasound acquisition is limited or is inconclusive, for example in case of subcutaneous emphysema or large thoracic dressings, the use of other diagnostic modalities such as chest radiography or computed tomography is warranted.

In another prospective observational study (**chapter 11**), we studied the detection of postoperative pulmonary complications with point-of-care lung ultrasound in patients undergoing major abdominal surgery and compared our results to chest radiography. We found that lung ultrasound was highly feasible following major abdominal surgery to detect postoperative pulmonary complications. Chest radiography only detected in 44 out of 98 patients (45%) one or more postoperative pulmonary complications. Lung ultrasound detected in 95 out of 98 patients (95%) one or more postoperative pulmonary complications in our pilot study. Importantly the detection of pleural effusion and atelectasis was different in the subgroup of patients who had both imaging modalities performed on the same day during the total study period. This can easily be explained by the superior diagnostic accuracy of lung ultrasound we confirmed in **chapter 8**.

We conclude that point-of-care lung ultrasound is a promising diagnostic technique that can be of great value to the perioperative physician. It can be applied directly at the bedside and can also be used to follow up on disease progress and therapy. It is our belief that point-of-care lung ultrasound will be the most used diagnostic imaging technique in the near future and should be considered as an indispensable extension of routine physical examination. However, future research is needed and must focus on lung ultrasound as a primary diagnostic tool and correlate its findings to patient outcome.

Discussion

Less than 50% of the critical remote MEWS episodes detected with continuous remote monitoring are witnessed by nurses with routine point-check MEWS assessments.

A recent meta-analysis showed that early warning and intervention system implementation is associated with a reduction in hospital mortality and cardiopulmonary arrest.⁴ However, from a recent systematic review it was concluded that there is insufficient evidence to support the hypothesis that early warning and intervention systems improve patient outcome.¹⁴ Potentially preventable serious adverse events continue to occur in different patient populations, despite wide spread use of early warning and intervention systems.¹⁵⁻¹⁹ Importantly, current practice point-check MEWS assessments have an intermittent character, are manually charted by nurses, are frequently incomplete and may be biased by the opinion of the healthcare professional.^{20,21} In spite of this lack of clear evidence and limitations in current practice, the potential yield of early recognition of patients who are clinically deteriorating in the general ward cannot be denied. Furthermore, early warning and intervention systems are endorsed by hospital management and required by overseeing bodies (Health and Youth Care Inspectorate, NICE). The first aim of this thesis was to evaluate continuous remote monitoring of vital signs to detect clinical deterioration in postoperative patients admitted to the general ward, and intensive care unit patients discharged to the general ward. We hypothesized that continuous remote monitoring improves the detection of deviating vital signs.

In **chapter 4**, we have shown that point-check MEWS assessments by nurses not only have a delay in detecting clinically deteriorating patients, but also miss critical MEWS episodes in 50% of the cases. This is in line with research by Petersen *et al.*^{21,22} Ideally, an early warning and intervention system alerts clinicians at the first sign of clinical deterioration, includes appropriate risk stratification and minimizes false alarms.²³ Early intervention can entail to monitor patients more closely, to run diagnostics, to adjust treatment or even to transfer patients to an intensive care unit in an effort to improve outcome.²⁴⁻²⁶ Heller *et al.* indeed found that implementation of continuous remote monitoring and automated notifications of clinical deterioration in the early stages of postoperative care is associated with increased involvement of ward physicians.²⁷

The choice of Early Warning Score may be of influence on the detection of critically ill patients.

There are multiple early warning scores, all based on vital signs and other physiological parameters.²⁸ These early warning scores were originally developed and validated in general ward patients. However, they appear to perform equally well in postoperative patients.²⁹ The effectiveness of an early warning score is mostly described in terms of the area under the receiver operator characteristics curve (AUROC). Alternatively the practical clinical value of an early warning system is better expressed in the non-event rate (proportion of early warning alarm signals that are not followed by an adverse event) and the missed event rate (proportion of adverse events not detected by an early warning alarm).²⁹

We cannot rule out the possibility that the use of another early warning score system in our studies would have resulted in the detection of different critical remote EWS episodes. We choose to study the validated 7-item MEWS currently in use in our hospital to be able to compare remote MEWS with point-check MEWS.²⁰ One study compared the 6-item MEWS with the National Early Warning score (NEWS) in postoperative patients and found it to have similar diagnostic accuracy for serious adverse events (AUROC of 0.75 (95% CI: 0.73-0.76) and 0.76 (95% CI: 0.75-0.78) respectively).³⁰ The 7-item MEWS is only slightly different from the NEWS which is endorsed by the Royal College of Physicians in the UK and more frequently studied.²³ More advanced early warning scores have been developed showing even better diagnostic accuracy in detecting postoperative patients at risk of adverse events. The 16-item electronic cardiac arrest triage score (eCART) incorporates not only vital signs but also laboratory results.³⁰ The eCART had a better diagnostic accuracy in postoperative patients (AUROC 0.79 (95% CI: 0.78–0.81)) compared to the 6-item MEWS and the NEWS.³¹ Furthermore, de Groot *et al.* showed that the non-event and the missed event rate in the study of Bartkowiak *et al.* for MEWS, NEWS and eCART in postoperative patients was: 94% and 19%, 95% and 25% and 89% and 25% respectively.^{29,31} These findings suggest that a more advanced early warning score including multiple parameters, can improve the clinical effectiveness of an early warning and intervention system.

We choose to continuously remotely monitor peripheral oxygen saturation, pulse rate and respiratory rate (with acoustical non-invasive respiratory rate monitoring). There was no access to devices which could continuously remotely monitor other vital signs such as blood pressure and body temperature. We choose not to score the other point-check MEWS parameters to complement the remote MEWS. It is reasonable to assume that this omission has resulted in fewer detected critical remote MEWS episodes.

Accurate respiratory rate monitoring is of key importance in the MEWS. Respiratory rate, after all, is the vital sign with the highest predictive value for serious adverse events.³¹ In **chapter 3** we confirmed this and found respiratory rate to have the best diagnostic ability to detect postoperative pulmonary complications. The continuous remote monitoring devices that are currently available have technical limitations.¹² Low level of agreement has been reported between remotely recorded vital signs and point-check measurements.¹² However, Ramsey *et al.* found in a study performed in a population of postoperative patients, that remote monitoring of acoustical respiratory rate corresponded to true respiratory rate.¹³ In another trial comparing acoustic respiratory rate monitoring with capnography, the bias and limits of agreement were 0 (95% CI of -1.4-1.4) breaths per minute in patients admitted to the postoperative care unit.³² In our studies patients frequently experienced the acoustical respiratory rate sensor as uncomfortable. Limited patients, those who developed complications, but also those who made an unremarkable and quick recovery, decided to withdraw from the study prematurely. Therefore our remote MEWS dataset was incomplete. There is no way to ascertain what the net effect has been. It is possible that clinical deterioration detected by remote MEWS was underestimated. Patient compliance is one of the determining factors for feasibility and successful application of continuous remote monitoring. In contrast, we encountered only a few technical issues; monitoring was not feasible in 3 out of 98 patients studied in **chapter 4**. The medical staff (including doctors and nurses) should also completely embrace continuous remote monitoring. However we did not evaluate these factors since all remote alarms were suppressed in our observational study.

The detection of subtle deviations in vital signs may contribute to the prevention of severe and clinically relevant complications.

Serious adverse events (cardiac arrest, death, unexpected ICU admission) are relatively rare in postoperative care resulting in very high non-event rates of the early warning score.²⁹ The effectiveness of MEWS improves when aimed at detecting less serious adverse events in postoperative patients, for example major postoperative complications with end-organ failure.³³ We believe that MEWS, as all other medical interventions, should not only be judged on its effectiveness to reduce mortality. We must also consider soft endpoints like experienced quality of life or length of hospital stay. Although not evidence based it is logical to assume, that identifying patients who may benefit from closer nurse observations, performing diagnostics and adjusting therapeutic management improves patient outcome. We must realize that interventions are initiated in 41% (including diagnostics and treatment adjustments) of the patients when a critical point-check MEWS was detected by nurses.²⁰ These interventions may not translate to reduced mortality but may lead to better

experienced quality of life and functional status after hospital discharge. Our conclusion is that continuous remote monitoring of the vital signs to detect clinical deterioration could improve patient care and outcome. The full potential and impact of remote MEWS should be studied in large randomized controlled trials.

Continuous remote monitoring is the best way to overcome the intermittent character of point-check MEWS in current practice. In our studies we looked at the average of continuous remote MEWS of each patient per hour. We aimed at detecting prolonged episodes of clinical deterioration in an effort to prevent high non-event rates. Remote MEWS protocols should incorporate different clinical thresholds weighing both sample time and absolute MEWS to trigger interventions. It is imperative to identify patients who are clinically deteriorating at a time when an intervention can make a difference, in other words to eliminate failure to rescue. To guarantee early identification of patients who are clinically deteriorating our detection of critical remote MEWS episodes (sample time one hour) could still be insufficient. One can argue that a high remote MEWS for 15 minutes might relate to a higher chance of (serious) adverse events than a moderate remote MEWS for 30 minutes. Future (machine learning) algorithms should be designed to detect these patients with higher diagnostic accuracy. It is important to realize that the full potential of continuous remote monitoring is not explored in this thesis.

Compared to point-check MEWS assessments, Tirkkonen *et al.* found that correct vital sign registration seems to improve when continuous remote monitoring is implemented. Unfortunately, potential benefit of continuous monitoring on patient outcome was lost due to inappropriate and delayed interventions.³⁴ Furthermore, Blankush *et al.* reported that continuous remote monitoring in postoperative patients combined with an automated warning system resulted in high alarm rates (3.3 alarms and pagers sounded per hour) when no delay (sample time) was used.³⁵ A consequence of these high alarm rates is the risk of alarm fatigue.³⁶ Alarm fatigue is an important patient safety hazard and can seriously undermine all efforts to improve (point-check) MEWS in current practice.

Hence it is important to find the right balance between patient safety, available local resources and workflow in the general ward. Weller *et al.* performed a study involving continuous remote monitoring in hospitalized neurological and neurosurgical patients. They reported an average alarm rate of 2.3 alarms/patient/day for all alarms.³⁷ In their study, alarm settings were adjusted to limit false alarm rates (non event rates) in an attempt to balance improved detection of episodes of postoperative hypoxemia and increased workload. Herein indeed lies the challenge. Is it possible to design a device and MEWS protocol that is

sensitive enough to identify patients who are clinically deteriorating and also specific enough to eliminate false alarms?

All technological innovations, such as continuous remote monitoring, should have potential to improve patient outcome and/or to decrease total healthcare costs. Considering the hospital staff required for point-check MEWS, continuous remote monitoring could potentially decrease the workload of nursing staff. Hospital staff should focus on actual patient care. As evidence will arise and models to evaluate continuous remote monitoring will evolve, we shall need to perform an evaluation including all aspects.

Training programmes for medical staff should focus on recognizing and treating patients who are clinically deteriorating. Despite recent improvements in the safety of anaesthesia and surgical procedures, postoperative complication rates are still unacceptably high. Patients are approximately 1000 times more likely to die in 30 days after surgery than during surgery itself.³⁸ Specialists in critical and perioperative care should be involved in the postoperative phase. Aiming at improving patient outcome, it is way better to prevent a cardiac arrest than to treat a patient with a cardiac arrest.

To summarize, continuous remote monitoring by itself is not the solution, early recognition of clinical patient deterioration and initiation of adequate and effective interventions is. It is our belief that continuous remote monitoring will have a central role in the ultimate early warning and intervention system of the future. Future research should evaluate if the detected critical remote MEWS episodes indeed improves the recognition of patients who are clinically deteriorating and if the subsequent clinical interventions or escalation of care results in improved patient outcome.

Lung ultrasound detects more (clinically relevant) postoperative pulmonary complications at an earlier point in time compared to chest radiography.

Preoperative risk scores to identify patients who are at risk of postoperative pulmonary complications have a moderate accuracy in predicting postoperative pulmonary complications.³⁹ We choose to use the definitions for postoperative pulmonary complications stated by Canet *et al.*⁴⁰ These definitions combine pulmonary pathology diagnosed with chest radiography (atelectasis and pleural effusions) and clinical diagnoses like respiratory failure (peripheral oxygen saturation of 90% requiring oxygen therapy).

In **chapter 8** we present a systematic review and meta-analysis of diagnostic imaging with chest radiography and lung ultrasound in critically ill patients. Lung ultrasound is clearly superior in terms of sensitivity and has similar specificity to chest radiography when both are compared to computed tomography. Although lung ultrasound is an evidence-based practice in emergency medicine and critical care, evidence for the use of lung ultrasound in postoperative care is very limited.⁴¹

In **chapter 9** (cardiothoracic patients) **and chapter 11** (major abdominal surgical patients) we have shown that lung ultrasound detects more postoperative pulmonary complications compared to chest radiography. This is in line with the reported higher diagnostic accuracy of lung ultrasound in critically ill patients. To be more specific, we found that lung ultrasound yields a higher incidence of atelectasis and pleural effusions in both groups of patients. The incidence of atelectasis, pleural effusions or both following cardiothoracic surgery, diagnosed with chest radiography, was 54-73% corresponding with previous research.⁴²⁻⁴⁴ The incidence of atelectasis, pleural effusions or both following cardiothoracic surgery, diagnosed with lung ultrasound was 159 out of 177 patients (90%). It is of vital importance to emphasize that pulmonary complications visualized by lung ultrasound must be interpreted with great caution. They do not always require (invasive) treatment. Lung ultrasound findings need to be interpreted in conjunction with clinical symptoms.

It is also important to address another issue. Chest radiography is considered to be an imperfect reference standard for lung ultrasound.^{45,46} If the reference standard, chest radiography, does not perfectly correspond to true diagnosis of postoperative pulmonary complications estimates of the accuracy of lung ultrasound, such as sensitivity and specificity, can be biased. All studies reporting about the diagnostic accuracy of lung ultrasound while using chest radiography as a reference standard are therefore inherently flawed.^{47,48}

In our observational studies (**chapter 9 and 11**), we did not have a single error-free reference test available. Computed tomography, in literature generally accepted as the gold standard, is not performed routinely in daily clinical practice to detect postoperative pulmonary complications. The method we used to tackle this issue was to introduce a composite reference standard. A composite reference standard improves the diagnostic accuracy of the reference standard and strongly resembles existing diagnostic rules (daily practice). Results of several imperfect tests (physical examination, chest radiography, overall judgment of the attending physician) were combined to diagnose clinically relevant postoperative pulmonary complications. Clinically relevant complications were defined as complications that require treatment according to the attending physician on the postoperative ward. In **chapter 9** we found that point-of-care lung ultrasound increased the incidence of recognized clinically relevant postoperative pulmonary complications. This finding confirms the growing evidence of the superiority of the diagnostic accuracy of lung ultrasound compared to chest radiography.

To date there are not many studies on the detection of pulmonary pathology with lung ultrasound in postoperative patients. In a prospective observational study by Alsaddique *et al*, 91 patients following cardiac surgery were included. Transthoracic echocardiography and lung ultrasound were performed at three time points (day after surgery, after extubation and at discharge to the general ward).⁴⁹ Interestingly, the initial diagnosis, based on conventional diagnostic tools, physical examination and chest radiography, had been changed in 67% of patients after incorporating the ultrasound findings. Vezzani *et al*. reported about lung ultrasound findings compared to chest radiography in patients immediate upon admission to the intensive care unit following cardiac surgery. Lung ultrasound identified most of the pathological abnormalities with a diagnostic accuracy comparable to chest radiography.⁴⁷ In this study, as in ours, lung ultrasound played an important role differentiating pleural effusions from atelectasis. Lung ultrasound more adequately differentiated between different postoperative pulmonary complications. It may be time to update current practice and to start using lung ultrasound as the first diagnostic imaging modality in postoperative care. Chiapetta *et al*. already reported on the results of an interesting prospective observational pilot study evaluating lung ultrasound as the primary imaging modality in thoracic surgery patients. In the vast majority of cases (79%) ultrasound (echocardiography and lung ultrasound) was sufficient and chest radiography was only essential in a minority of patients to detect clinically relevant complications.⁵⁰

Regrettably lung ultrasound is not always highly feasible in postoperative care (**chapter 9 and 11**). In some situations, insurmountable technical restrictions like subcutaneous

emphysema and/or large thoracic dressings are present. In these cases the use of other diagnostic modalities such as chest radiography and/or computed tomography is warranted. In our observational studies most of the lung ultrasound images and their interpretations were made by medical students. These students had received the training course we currently still provide in our hospital, the Amsterdam UMC, location VUmc. The course focuses on the known challenges in lung ultrasound, such as detecting pneumothorax. Pneumothorax is a rare but potentially life-threatening postoperative complication. The students all learned only to diagnose a pneumothorax when the lung point could be detected in absence of lungsliding (this is at the boundary of the pneumothorax) and to rule out a pneumothorax when lungsliding was found.^{46,51}

It is clear that point-of-care lung ultrasound needs to be studied in future research. Is lung ultrasound viable as the primary imaging modality in postoperative patients? What is the impact on patient outcome? What the true value of the potential of lung ultrasound to differentiate between clinically relevant and irrelevant findings? All this (and more) is necessary to answer the final question: what is the ideal diagnostic follow-up of postoperative patients to detect clinically relevant pulmonary complications in order to maximize patient outcome? Lung ultrasound could prove to be an essential part of the answer.

Point-of-care lung ultrasound in the perioperative setting requires specific training programs.

In order to integrate point-of-care lung ultrasound into daily routine practice, several issues must be addressed to optimize and accelerate this process. Firstly, point-of-care lung ultrasound needs to be considered as the fifth pillar of clinical examination next to inspection, palpation, percussion and auscultation. Secondly, point-of-care lung ultrasound must be distinguished from conventional (lung) ultrasound, which is specialized ultrasound performed by radiologists, cardiologists or intensivists who received standard certified training. In addition, implementation of point-of-care ultrasound asks for clear agreements between point-of-care ultrasound performers and ultrasound experts.⁵² Thirdly, training must be adopted into clinical practice by other specializations outside intensive care and emergency medicine, such as anaesthesiology, (cardiothoracic) surgery, cardiology and pulmonology. Everybody has to speak the same 'diagnostic language'. As described in **chapter 6** and in the literature several educational programs on lung and cardiac ultrasonography have been developed.⁵³ Point-of-care ultrasound should be implemented in the curriculum of the medical student to prepare the physician of the future. An impressive nine-year investigation on effectiveness of point-of-care ultrasound education for medical students showed promising results. Medical students seem to be quick learners.⁵⁴⁻⁵⁶ Fourthly, some important logistical steps must be undertaken and legal aspects should be addressed. Consensus on documentation must be reached regarding which images should be reviewed and how to store them in patient records. Technical development is fast, with devices getting smaller, significantly cheaper and with improved image quality. It's time to build momentum to persuade hospital management to purchase ultrasound machines for the general ward.⁵⁷

Final conclusion

Our observational studies show that less than 50% of the critical remote MEWS episodes detected with continuous remote monitoring are witnessed by nurses with routine point-check MEWS assessments. It is our belief that patient outcome can significantly improve through the development of continuous remote MEWS combined with a fully automated intervention system tailored to local requirements. Further research is needed to evaluate each step in this process and guide us through this gigantic undertaking.

Our observational studies show that lung ultrasound detects more clinically relevant postoperative pulmonary complications at an earlier point in time compared to chest radiography. It is our belief that lung ultrasound is an essential imaging modality in the ideal diagnostic follow-up of postoperative patients to detect clinically relevant pulmonary complications in order to maximize patient outcome. Future research is needed to ascertain its proper place in perioperative care.

References

1. Ahmad T, Bouwman RA, Grigoras I, Aldecoa C, Hofer C, Hoeft A, Holt P, Fleisher LA, Buhre W, Pearse RM: Use of failure-to-rescue to identify international variation in postoperative care in low-, middle- and high-income countries: A 7-day cohort study of elective surgery. *British Journal of Anaesthesia* 2017; 119:258-266.
2. Mazo V, Sabate S, Canet J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. *Anesthesiology* 2014; 121:2.
3. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med.* 2009; 361: 1368–1375.
4. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. *Critical Care* 2015; 19: 254.
5. Jones DA, DeVita MA. Bellomo R. Rapid-Response Teams. *N. Engl. J. Med.* 2011; 365, 139–146.
6. Bell MB., Konrad D., Granath F., Ekbom A. Martling CR. Prevalence and sensitivity of MET-criteria in a Scandinavian University Hospital. *Resuscitation* 2006; 70, 66–73.
7. Correia, N. et al. Improving recognition of patients at risk in a Portuguese general hospital: results from a preliminary study on the early warning score. *Int. J. Emerg. Med.* 2014; 7, 22.
8. Ludikhuijze J. et al. Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands. *Crit. Care Med.* 2015 43, 2544–51.
9. Tolsma M, Kröner A, van den Hombergh CLM, Rosseel PMJ, Rijpstra TA, Dijkstra HAJ, et al. The clinical value of routine chest radiographs in the first 24 hours after cardiac surgery. *Anesth Analg.* 2011;112:139–42.
10. Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest* 2015; 147:1659-1670.
11. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med.* 2012; 38:577-91.
12. Van Loon, K.; van Zaane, B.; Bosch, E.J.; Kalkman, C.J.; Peelen, L.M. Non-Invasive Continuous Respiratory Monitoring on General Hospital Wards: A Systematic Review. *PLoS ONE* 2015; 10, e0144626.
13. Ramsay MA, Usman M, Lagow E, Mendoza M, Untalan E, De Vol E. The accuracy, precision and reliability of measuring ventilatory rate and detecting ventilatory pause by rainbow acoustic monitoring and capnometry. *Anesth Analg* 2013; 117 : 69-75.
14. Alam N, Hobbelenk EL, van Tienhoeven AJ, van de Ven PJ, Jansma EP, Nanayakkara PWB. The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. *Resuscitation* 2014; 85: 587-594.
15. Nolan, J. P. et al. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation* 2014; 85:987–92.

16. Chen, J. et al. Delayed Emergency Team Calls and Associated Hospital Mortality: A Multicenter Study. *Crit. Care Med.* 2015; 43: 2059–65.
17. Andersen, L. W. et al. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation* 2016; 98:112–117.
18. Herod R, Frost SA,, Parr M, Hillman K, Aneman A. Long term trends in medical emergency team activations and outcomes. *Resuscitation* 2014; 85: 1083–7.
19. Astroth, K. S., Woith, W. M., Stapleton, S. J., Degitz, R. J. & Jenkins, S. H. Qualitative exploration of nurses' decisions to activate rapid response teams. *J. Clin. Nurs.* 22, 2876–82 (2013).
20. Van Galen LS, Struik PW, Driesen BE et al. Delayed Recognition of Deterioration of Patients in General Wards Is Mostly Caused by Human Related Monitoring Failures: A Root Cause Analysis of Unplanned ICU Admissions. *PLoS One* 2016; 11 : e0161393.
21. Petersen JA, Mackel R, Antonsen K, Rasmussen LS. Serious adverse events in a hospital using early warning score – What went wrong? *Resuscitation* 2014;85:1699-1703
22. Petersen JA. Early warning score challenges and opportunities in the care of deteriorating patients. *Dan Med J.* 2018; 65: B5439.
23. Royal College of Physicians. National Early Warning Score (NEWS) - Standardising the assessment of acute-illness severity in the NHS. Report of a working party. (2012).
24. Devita, M. a et al. Findings of the first consensus conference on medical emergency teams. *Crit. Care Med.* 2006; 34:2463–2478.
25. Smith, G. B. In-hospital cardiac arrest: is it time for an in-hospital 'chain of prevention'? *Resuscitation* 2010; 81:1209–11.
26. DeVita, M. a. et al. 'Identifying the hospitalised patient in crisis'-A consensus conference on the afferent limb of Rapid Response Systems. *Resuscitation* 2010: 81:, 375–382.
27. Heller AR, Mees ST, Lauterwald B, et al. Detection of deteriorating patients on surgical wards outside the ICU by an automated MEWS-based early warning system with paging functionality. *Ann Surg* 2018. [Epub ahead of print]
28. Smith GB., Prytherch DR., Schmidt PE., Featherstone PI. Review and performance evaluation of aggregate weighted 'track and trigger' systems. *Resuscitation* 2008; 77: 170–9.
29. de Grooth HJ, Girbes AR, Loer SA. Early warning scores in the perioperative period: applications and clinical operating characteristics. *Current Opinion in Anesthesiology* 2018; 31: 732-738.
30. Churpek MM, Yuen TC, Park SY, et al. Using electronic health record data to develop and validate a prediction model for adverse outcomes in the wards. *Crit Care Med* 2014; 42:841–848.
31. Bartkowiak B, Snyder AM, Benjamin A, Schneider A, Twu NM, Churpek MM, Roggin KK, Edelson DP. Validating the Electronic Cardiac Arrest Risk Triage (eCART) Score for Risk Stratification of Surgical Inpatients in the Postoperative Setting: Retrospective Cohort Study. *Ann Surg.* 2018 Jan 12. doi: 10.1097/SLA.0000000000002665. [Epub ahead of print]
32. Mimoz O., Benard T., Gaucher A., Frasca D., Debaene B. Accuracy of Respiratory Rate Monitoring using a Non-Invasive Acoustic Method after GeneralAnaesthesia. *Br J Anaesth.* 2012; 108:872-5.

33. Hollis RH, Graham LA, Lazenby JP, et al. A role for the early warning score in early identification of critical postoperative complications. *Ann Surg* 2016; 263:918–923.
34. Tirkkonen, J. et al. Factors associated with delayed activation of medical emergency team and excess mortality: an Utstein-style analysis. *Resuscitation* 2013; 84: 173–8.
35. Blankush JM, Freeman R, McIlvaine J, et al. Implementation of a novel postoperative monitoring system using automated modified early warning scores (MEWS) incorporating end-tidal capnography. *J Clin Monit Comput* 2017; 31:1081–1092.
36. Winters, D. B. , Cvach, M. M. , Bonafide, P. C. , Hu, X. , Konkani, A. , O'Connor, F. M. , Rothschild, M. J. , Selby, M. N. , Pelter, M. M. , McLean, B. & Kane-Gill, L. S.. Technological Distractions (Part 2). *Critical Care Medicine* 2018; 46:130–137.
37. Weller RS, Foard KL, Harwood TN. Evaluation of a wireless, portable, wearable multiparameter vital signs monitor in hospitalized neurological and neurosurgical patients. *J Clin Monit Comput* 2018; 32:945-951.
38. Sessler DI, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med* 2018; 44:811–822.
39. Talmor D, Kelly B. How to better identify patients at high risk of postoperative complications? *Curr Opin Crit Care* 2017; 23:417–423.
40. Canet J, Gallart L, Gomar C, Paluzie G, Valles J, Castillo J, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 2010; 113:1338-50.
41. Volpicelli, G., Elbarbary, M., Blaivas, M. et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* 2012; 38: 577.
42. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby J-J Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004; 100: 9–15.
43. Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest* 2015; 147:1659-1670.
44. Vezzani A, Manca T, Benassi F, Galligani A, Spaggiari I, Brusasco C, et al. Diagnostic value of chest ultrasound after cardiac surgery: a comparison with chest Radiograph and auscultation. *Critical Care*. 2014; 18:P130.
45. Goudie E, Bah I, Khereba M, Ferraro P, Duranceau A, Martin J, et al. Prospective trial evaluating sonography after thoracic surgery in postoperative care and decision making. *European Journal of Cardio-Thoracic Surgery*. 2011; 41:1025-30.
46. Weissman C. Pulmonary complications after cardiac surgery. *Seminars in Cardiothoracic and Vascular Anesthesia* 2004; 8:185-211.
47. Rubinowitz AN, Siegel MD, Tocino I. Thoracic imaging in the ICU. *Critical Care Clinics*. 2007; 23: 539-73.
48. Jain U, Rao TL, Kumar P, Kleinman BS, Belusko RJ, Kanuri DP, et al. Radiographic pulmonary abnormalities after different types of cardiac surgery. *Journal of Thoracic and Cardiovascular Anesthesia*. 1991;5: 592-5

49. Alsaddique A, Royse AG, Royse CF, Mobeirek A, El Shaer F, AlBackr H, et al. Repeated monitoring with transthoracic echocardiography and lung ultrasound after cardiac surgery: feasibility and impact on diagnosis. *Journal of cardiothoracic and vascular anesthesia*. 2016; 30:406-12.
50. Chiappetta M, Meacci E, Cesario A, Smargiassi A, Inchingolo R, Ciavarella LP, et al. Postoperative chest ultrasound findings and effectiveness after thoracic surgery: A pilot study. *Ultrasound in medicine & biology*. 2018; 44:1960-7.
51. Blanco P, Volpicelli G. Common pitfalls in point-of-care ultrasound: a practical guide for emergency and critical care physicians. *Crit Ultrasound J*. 2016;8(1):15.
52. Elbers P, Kamp O, Lely R, Tuinman P. Should every doctor be allowed to use ultrasound? Dilemmas surrounding broad application of ultrasound in clinical practice. *Nederlands tijdschrift voor geneeskunde*. 2017; 161:D1063-D.
53. Mahmood F, Bortman J, Amir R, Mitchell J, Wong V, Feng R, et al. Training Surgical Residents for Ultrasound-Guided Assessment and Management of Unstable Patients. *Journal of surgical education*. 2018.
54. Hoppmann RA, Rao VV, Bell F, Poston MB, Howe DB, Riffle S, et al. The evolution of an integrated ultrasound curriculum (iUSC) for medical students: 9-year experience. *Critical ultrasound journal*. 2015; 7:1.
55. Andersen GN, Viset A, Mjølstad OC, Salvesen Ø, Dalen H, Haugen BO. Feasibility and accuracy of point-of-care pocket-size ultrasonography performed by medical students. *BMC medical education*. 2014; 14:156.
56. See K, Ong V, Wong S, Leanda R, Santos J, Taculod J. Lung ultrasound training: curriculum implementation and learning trajectory among respiratory therapists. *Intensive Care Medicine*. 2016; 42: 63.
57. Jip Nooitgedacht, Mark Haaksma, Hugo R. W. Touw, Pieter R. Tuinman. Perioperative care with an ultrasound device is as Michael Jordan with Scotty Pippen: at its best! *J Thorac Dis* 2018; 10:6436-6441.

English summary

Chapter 1 provides a general introduction describing the postoperative patient population and the impact of postoperative pulmonary complications including its pathophysiology. Death after treatable complications (failure to rescue) is an important cause of mortality. An overview is given on currently used point-check patient monitoring strategies to detect clinical deterioration in an early stage. Diagnostic imaging of postoperative patients for pulmonary pathology is also described, including point-of-care lung ultrasound.

In general, the **first part (chapters 2-5)** of this thesis focuses on continuous remote monitoring. We monitored respiratory rate, peripheral oxygen saturation and heart rate in postoperative patients admitted to and intensive care unit patients discharged to the general ward. We hypothesized that early detection of aberrant vital parameters in these patients indicates clinical deterioration. Furthermore, early detection may enable the medical team to limit the impact of postoperative complications and save lives. Its current practice to use modified early warning scores on regular intervals to detect clinical deterioration of ward patients to prevent adverse events. Therefore, we proposed to use modified early warning score based on continuous remote monitoring of vital parameters to overcome this intermittent character.

The **second part (chapters 6-11)** of this thesis focuses on point-of-care lung ultrasound. We first performed a systematic review and meta-analysis of the value of chest radiograph, the current first-line diagnostic imaging modality for pulmonary symptoms in critically ill patients, and the value of lung ultrasound, the emerging and possibly the first-line diagnostic imaging modality in the near future. To expand the growing evidence, we performed multiple studies with lung ultrasound in the postoperative setting. We introduced lung ultrasound to physicians willing to adopt this imaging modality and studied point-of-care lung ultrasound to detect postoperative pulmonary complications in cardiothoracic and major abdominal surgery patients. We hypothesized that lung ultrasound could detect more (clinically-relevant) postoperative pulmonary complications than chest radiograph.

In more detail, in **chapter 2** we wrote a narrative review summarizing the current technical possibilities for continuous remote monitoring and the evidence for its application in the postoperative period. There are several medical grade continuous remote monitoring platforms available that integrate a biosensor signal with electronic patient records, allowing for automated notification of patients clinical deterioration. We conclude that continuous remote monitoring of vital signs in the surgical ward may contribute to prevent severe

complications and subsequently reduces failure-to-rescue rates, but evidence for this association is still lacking.

In **chapter 3** we studied the incidence of deviating vital signs and clinical deterioration detected by continuous remote monitoring. For this purpose, we included patients undergoing major abdominal surgery with an increased preoperative risk for the development of postoperative pulmonary complications. The respiratory rate, peripheral oxygen saturation and pulse rate were continuously remotely monitored for four postoperative days. A remote MEWS was calculated. Overall, continuous remote monitoring feasible in 97 out of 100 eligible patients (97%, 95% CI: 91 to 99%). Thirty-nine patients (40%) developed one or more postoperative pulmonary complications during the study period. We frequently found aberrant postoperative vital parameters. The remote MEWS was critical in 11.6% (0.8-20.8) of the study period in patients with postoperative pulmonary complications. Our findings suggest that continuous remote monitoring of vital signs may be useful in early detection of patients who are clinically deteriorating after major abdominal surgery.

In **chapter 4** we studied continuous remote monitoring in ICU patients discharged to the general ward. It is known that these patients are at risk for adverse events and are frequently re-admitted to the intensive care unit. We studied the incidence of aberrant vital signs measured with continuous remote monitoring and subsequently the incidence of critical MEWS. The remote MEWS was critical in 10% of the study period in these patients. Twenty-one out of 44 patients (47.7%) developed a critical remote MEWS episode. Seventeen out of 28 critical remote MEWS episodes (60.7%) were not detected by current practice of MEWS assessments. Patients with a critical remote MEWS for more than 1 hour had a prolonged hospital length of stay. We concluded that continuous remote monitoring frequently detects critical remMEWS episodes in ICU patients discharged to the general ward which were not detected with current practice MEWS assessments in more than 50%.

In **chapter 5** we studied respiratory rate monitoring during procedural sedation and analgesia in upper gastrointestinal endoscopic procedures. At present, capnography is considered the gold standard of respiratory rate monitoring but the diagnostic accuracy during these procedures is limited. Inadequate ventilation and hypoxemic events are preferentially prevented during these procedures since they could lead to serious adverse events. We evaluated photoplethysmography as a possible alternative for respiratory rate monitoring and its diagnostic accuracy in predicting hypoxemic events since respiration rate is a proxy of ventilation. We found a low level of agreement between capnography and plethysmography respiratory rate during procedural sedation in upper gastrointestinal endoscopic procedures.

Furthermore, respiratory rate derived from both capnography and photoplethysmography showed a limited ability to provide for an early warning sign in order to prevent hypoxemic events.

In the **second part, chapter 6** details a narrative review about point-of-care lung ultrasound. The goal of the review was to serve as an introduction, starting point for physicians willing to adopt lung ultrasound as an imaging modality. We describe the principles of the ultrasound equipment, lung ultrasound artefacts and how to perform lung ultrasound. A decision tree is presented to differentiate between causes of acute dyspnoea. We state that point-of-care lung ultrasound is a promising diagnostic modality that can be of great assistance to the physician. It is applied directly at the bedside and can be used to follow up on disease progression and effect of therapy. It is our belief that lung ultrasound will be the most used diagnostic imaging technique in the near future and should be considered an essential extension of routine physical examination.

Chapter 8 is about, a systematic review and meta-analysis of the diagnostic value of chest radiography and lung ultrasound, when concomitantly performed, as an imaging modality for pulmonary symptoms in critically ill patients. Chest radiography is considered the first line imaging modality. However, the diagnostic accuracy is possibly limited in this setting. We aimed to evaluate the diagnostic accuracy of both imaging modalities. The imaging techniques were compared to the gold standard for evaluating respiratory pathology: computed tomography. We demonstrated that chest radiography has a low sensitivity and a reasonable specificity compared to computed tomography for detecting lung pathology in critically ill patients. When lung ultrasound was performed concomitantly, lung ultrasound proved to be vastly superior to chest radiography in terms of sensitivity with similar specificity. Lung ultrasound opts to be the first-line diagnostic tool in these patients.

In **chapter 9** we investigate the detection of postoperative pulmonary complications with lung ultrasound for following cardiothoracic surgery in a prospective observational study. Postoperative pulmonary complications are common after cardiothoracic surgery and are associated with adverse outcomes. However, little is known about the diagnostic accuracy of lung ultrasound for the detection of postoperative pulmonary complications after cardiothoracic surgery. We recruited patients undergoing cardiothoracic surgery in whom, according to standard postoperative protocol daily chest radiography was performed. Each patient underwent standardized point-of-care lung ultrasound examinations. These findings were blinded for the treating physician. Lung ultrasound detected, at an earlier point in time, more clinically relevant postoperative pulmonary complications compared to chest

radiography. Our results suggest that point-of-care lung ultrasound may be used as the primary imaging technique to screen for postoperative pulmonary complications after cardiothoracic surgery. It will probably boost bedside decision-making.

In **chapter 11**, we compared detection rates of postoperative pulmonary complications following major abdominal surgery with routine point-of-care lung ultrasound, to on demand chest radiography in a prospective observational study. Early detection of pulmonary complications in postoperative patients to prevent serious adverse events and failure to rescue piques growing interest in the literature. We describe a well defined protocol for point-of-care lung ultrasound following major abdominal surgery to detect postoperative pulmonary complications. Lung ultrasound detected more patients with postoperative pulmonary complications. The number of discordant observations with both modalities was high for atelectasis and pleural effusion, but not for pneumothorax, respiratory infection and pulmonary edema. Future research is needed to evaluate a possible role for point-of-care lung ultrasound in perioperative management of major abdominal surgery patients. Another interesting question is whether lung ultrasound can stratify the frequently detected postoperative pulmonary complications appropriately to the required treatment and thereby limit its impact.

Chapter 12 contains a general conclusion of our findings and a discussion including future perspectives. Continuous remote monitoring of vital signs frequently detects clinical deterioration in patients (defined by MEWS), that otherwise would not have been detected by standard MEWS assessments in current practice. Lung ultrasound frequently detects postoperative pulmonary complications. Future research is needed to evaluate the impact on patient outcome of all these findings.

Nederlandse samenvatting

Na een operatie ontwikkelen veel patiënten een complicatie en in sommige gevallen overlijden zij aan deze complicatie. Om complicaties eerder te kunnen herkennen en te behandelen zijn de huidige methoden om patiënten te bewaken niet altijd toereikend. Door de introductie van nieuwe technologieën, zoals het bewaken van de vitale functies van een patiënt op afstand (telemonitoring, remote monitoring) en het in beeld brengen van de gezondheid van de longen met behulp van echografie, is het mogelijk om complicaties eerder op te sporen of misschien zelfs wel te voorkomen. Het centrale doel van dit proefschrift was om te onderzoeken wat de waarde is van deze nieuwe technologieën bij patiënten die een operatie hebben ondergaan of van de intensive care unit naar de gewone afdelingen worden ontslagen.

In **hoofdstuk 1** geven wij een overzicht van de postoperatieve patiëntenpopulatie en beschrijven wij de gevolgen van postoperatieve complicaties van de longen (pulmonale complicaties). Vervolgens wordt er een overzicht gegeven van de momenteel gebruikte strategieën van patiëntbewaking om klinische verslechtering in een vroeg stadium te detecteren. Daarnaast worden de diagnostische technieken die gebruikt kunnen worden om afwijkingen in de longen beschreven.

Over het algemeen richt het eerste deel van dit proefschrift (**hoofdstuk 2-5**) zich op de continue bewaking van patiënten op de verpleegafdeling. Deze continue bewaking werd uitgevoerd met behulp van verschillende apparaten die door middel van elektrodes de hartfunctie en longfunctie kunnen meten. Met deze apparatuur wordt de ademhalingsfrequentie, de perifere zuurstofsaturatie en de hartfrequentie gemeten bij patiënten die na een operatie of behandeling op de intensive care afdeling werden opgenomen op de verpleegafdeling. Wij veronderstelden hierbij dat detectie van afwijkende vitale parameters bij deze patiënten een vroeg teken van klinische verslechtering was. Vroege detectie van klinische verslechtering kan het medische team vervolgens in staat stellen de gevolgen van postoperatieve complicaties te beperken waardoor zelfs levens gered zouden kunnen worden. Op dit moment wordt klinische verslechtering van patiënten gedetecteerd door verpleegkundigen door op regelmatige tijdstippen, aan het bed van de patiënt, vitale functies te meten en de modified early warning score (MEWS) te berekenen. Om dit intermitterende karakter van de huidige praktijk te overbruggen hebben wij in ons onderzoek gekozen voor continue monitoring van vitale functies. Wij hebben deze data vervolgens gebruikt om continu de Modified Early Warning Score te berekenen.

Het tweede deel van dit proefschrift (**hoofdstuk 6-11**) richt zich op de echografie van de longen. Ten eerste hebben wij een systematische review en meta-analyse uitgevoerd om de diagnostische waarde van de standaard gebruikte röntgenopnames van de borstkas en van de nieuwe techniek longechografie bij intensive care patiënten vast te stellen. Daarnaast voerden wij meerdere onderzoeken uit met longechografie in de postoperatieve zorg. wij introduceerden longechografie bij artsen die deze beeldvorming techniek zouden willen gaan gebruiken en bestudeerden de waarde van longechografie om postoperatieve pulmonale complicaties bij patiënten te detecteren. Wij stelden de hypothese dat longechografie meer (klinisch relevante) postoperatieve pulmonale complicaties zou kunnen detecteren dan röntgenopnames van de borstkas.

In **hoofdstuk 2** presenteren wij een huidig overzicht van de technische mogelijkheden voor continue patiëntbewaking op de chirurgische verpleegafdeling. Daarin presenteren wij het wetenschappelijk bewijs voor deze bewakingstechniek in de postoperatieve periode. Er zijn tevens verschillende continue bewakingsplatformen voor medische doeleinden beschikbaar waarin sensoren signalen doorsturen naar het elektronische patiëntendossiers. Dit maakt het mogelijk dat gedetecteerde klinische verslechtering van de patiënt automatisch kan worden doorgegeven aan medisch personeel in het ziekenhuis. wij concluderen dat continue bewaking van vitale parameters op afstand zou kunnen bijdragen aan het voorkomen van ernstige gevolgen van complicaties. Echter ontbreekt sluitend bewijs voor deze associatie nog steeds.

In **hoofdstuk 3** bestudeerden wij de incidentie van afwijkende vitale parameters en klinische verslechtering die werden gedetecteerd door continue bewaking. Voor dit doel hebben wij patiënten die een grote buikoperatie ondergingen met een verhoogd preoperatief risico voor de ontwikkeling van postoperatieve pulmonale complicaties in onze studie geïnccludeerd. De ademhalingsfrequentie, de perifere zuurstofsaturatie en de polsfrequentie werden continu met monitors gemeten gedurende vier postoperatieve dagen. Een MEWS werd berekend op basis van deze continue data. Continue bewaking op afstand bleek mogelijk bij 97 van de 100 patiënten. Negenendertig patiënten (40%) ontwikkelden een of meer postoperatieve pulmonale complicaties tijdens de onderzoeksperiode. Bovendien vonden wij vaak afwijkende postoperatieve vitale parameters. De continue MEWS was kritisch verhoogd in 11,6% van de onderzoeksperiode bij patiënten met postoperatieve pulmonale complicatie. Onze bevindingen suggereren dat continue bewaking op afstand van vitale functies nuttig kan zijn bij vroege detectie van patiënten die klinisch achteruitgaan na een grote buikoperatie.

In **hoofdstuk 4** bestudeerden wij continue bewaking op afstand van intensive care patiënten die werden ontslagen naar de algemene verpleegafdeling. Het is bekend dat deze patiënten risico lopen op complicaties en vaak opnieuw worden opgenomen op de intensive care afdeling. wij bestudeerden de incidentie van afwijkende vitale parameters gemeten met continue monitoring en berekenden vervolgens de incidentie van kritische verhoogde MEWS. De continue MEWS was kritisch verhoogd in 10% van de onderzoeksperiode bij deze patiënten. Eenentwintig van de 44 patiënten (47,7%) ontwikkelden een kritieke MEWS episode op basis van de continue data. Zeventien van de 28 kritieke continue MEWS episodes (60,7%) werden niet gedetecteerd in de huidige klinische praktijk van MEWS berekeningen door de verpleegkundige aan het bed van de patiënt tijdens driemaal daagse routine controles. Patiënten met een kritieke verhoogde MEWS (met een duur langer dan 1 uur) hadden een langere opnameduur in het ziekenhuis. wij concluderen dat continue bewaking frequent kritiek verhoogde MEWS episodes detecteert bij intensive care patiënten die naar de algemene afdeling worden ontslagen. Deze kritiek verhoogde episodes werden met de huidige MEWS beoordelingen door de verpleegkundige aan het bed in meer dan 50% niet gedetecteerd.

In **hoofdstuk 5** bestudeerden wij de ademhalingsfrequentie monitoring tijdens procedurele sedatie en analgesie bij endoscopische procedures in het bovenste deel van het maag-darmkanaal. Op dit moment wordt capnografie beschouwd als de goudstandaard voor het meten van de ademhalingsfrequentie, maar de diagnostische nauwkeurigheid van deze techniek is tijdens deze procedures beperkt. Incidenten van verminderde ademhaling en verminderde zuurstofsaturatie worden bij voorkeur voorkomen tijdens deze procedures, omdat ze kunnen leiden tot ernstige complicaties. Wij evalueerden plethysmografie als een mogelijk alternatief voor de monitoring van de ademhalingsfrequentie. wij onderzochten de diagnostische nauwkeurigheid van plethysmografie bij het voorspellen van deze gebeurtenissen. Wij vonden een laag overeenstemming niveau tussen capnografie en plethysmografie ademhalingsfrequentie tijdens procedurele sedatie in endoscopische procedures van het bovenste deel van het maag-darmkanaal. Verder toonde de ademhalingsfrequentie afgeleid van zowel capnogram als plethysmogram een beperkt vermogen om te voorzien in een vroegtijdige waarschuwing voor een naderende daling van de zuurstofsaturatie.

In het tweede deel wordt in **hoofdstuk 6** een beschrijvend overzicht gegeven van de echografie van de longen. Het overzicht dient als een inleiding en een uitgangspunt voor artsen die in de toekomst longechografie willen toepassen als beeldvormende techniek. wij beschrijven ondermeer de principes en de artefacten van echografie. Een beslisboom wordt

gepresenteerd om met behulp van echografie onderscheid te maken tussen oorzaken van acute dyspneu. Wij stellen dat echografie van de longen een veelbelovende diagnostische techniek is die van grote waarde kan zijn voor arts en patiënt. Echografie kan direct naast het bed van de patiënt worden toegepast ter diagnostiek. Vervolgens kan men de evolutie en het effect van de therapie op het ziekteproces vervolgen. Het is onze overtuiging dat longechografie in de nabije toekomst de meest gebruikte diagnostische beeldvormende techniek zal zijn en moet worden beschouwd als een essentiële uitbreiding van het lichamenlijk onderzoek.

In **hoofdstuk 8** beschrijven wij de uitgevoerde systematische review en meta-analyse van de diagnostische waarde van röntgenopnames van de borstkas en longechografie voor de detectie van pulmonale pathologie bij intensive care patiënten. De röntgenopname van de borstkas wordt op dit moment beschouwd als de beeldvormingstechniek van eerste keuze. De diagnostische nauwkeurigheid is echter mogelijk beperkt in deze patiëntengroep. Beide technieken werden vergeleken met de goudstandaard voor respiratoire pathologie: computertomografie (CT). wij hebben aangetoond dat de röntgenopname van de borstkas een lage sensitiviteit en een redelijke specificiteit heeft in vergelijking met computertomografie voor het detecteren van longpathologie bij intensive care patiënten. Wanneer in de onderzoeken longechografie gelijktijdig werd uitgevoerd, bleek longechografie veel beter dan röntgenopnames van de borstkas qua sensitiviteit en met vergelijkbare specificiteit. Daarom lijkt longechografie in deze patiëntencategorie de aangewezen eerste keus diagnostisch techniek te zijn.

In **hoofdstuk 9** onderzoeken wij de detectie van postoperatieve pulmonale complicaties met longechografie in een prospectieve observationele studie in patiënten na cardiothoracale chirurgie. Postoperatieve pulmonale complicaties komen vaak voor na cardiothoracale chirurgie en zijn geassocieerd met ongunstige uitkomsten. Er is echter weinig bekend over de diagnostische nauwkeurigheid van longechografie voor de detectie van postoperatieve pulmonale complicaties. Wij includeerden patiënten die een cardiothoracale operatie ondergingen waarbij, volgens het standaard postoperatieve protocol, dagelijkse röntgenopnames van de borstkas werden uitgevoerd. Elke patiënt onderging gestandaardiseerde longechografie onderzoeken. Deze longechografie bevindingen waren geblindeerd voor de behandelende arts. Longechografie detecteerde, op een eerder tijdstip, meer klinisch relevante postoperatieve pulmonale complicaties in vergelijking met röntgenopnames van de borstkas.

Onze resultaten suggereren dat longechografie kan worden gebruikt als primaire beeldvormende techniek voor het screenen op postoperatieve pulmonale complicaties na cardiothoracale chirurgie. Het zal waarschijnlijk de besluitvorming aan het bed van de patiënt verbeteren.

In **hoofdstuk 11** vergeleken wij de detectie van postoperatieve pulmonale complicaties na een grote abdominale operatie met longechografie in een prospectieve observationele studie. Wanneer op aanvraag van de dokter of volgens het postoperatieve protocol, röntgenopnames van de borstkas werden gemaakt. Werden deze bevindingen vergeleken met de bevindingen gevonden met longechografie. Wij beschrijven een protocol voor longechografie om postoperatieve pulmonale complicaties te detecteren. Detectie van de eerste verschijnselen van pulmonale complicaties kan dienen om ernstige complicaties te voorkomen. Voorkoming van de gevolgen van complicaties na operatie heeft in toenemende mate de aandacht in wetenschappelijke literatuur. Longechografie detecteerde meer patiënten met postoperatieve pulmonale complicaties dan röntgenopnames van de borstkas. Het aantal verschillende waarnemingen met beide modaliteiten in patiënten was groot voor atelectase en pleurale effusie, maar niet voor pneumothorax, respiratoire infectie en longoedeem. Toekomstig onderzoek is nodig om een mogelijke rol van longechografie te evalueren in perioperative behandeling van patiënten na grote buikoperaties. Een andere interessante vraag is of longechografie de veelvuldig gedetecteerde postoperatieve pulmonale complicaties kan onderscheiden in klinisch relevante complicaties en klinisch irrelevant complicaties. Wanneer echografie kan bepalen welke complicaties behandeling vereisen kan daardoor de uitkomst voor patiënten verder verbeteren.

Hoofdstuk 12 bevat een algemene conclusie, een discussie en de toekomstperspectieven van onze bevindingen. Continue bewaking van vitale functies detecteert vaak klinische verslechtering van patiënten (gedefinieerd door MEWS). Het gaat om klinische verslechtering van patiënten die anders niet zouden zijn gedetecteerd door de standaard MEWS beoordeling aan het bed van de patiënt door de verpleegkundige. Longechografie detecteert vaak postoperatieve pulmonale complicaties. Toekomstig onderzoek is nodig om de impact van deze bevindingen voor de uitkomsten van patiënt te evalueren.

List of publications

1. Piers LH, Touw HR, Gansevoort R, Franssen CF, Oudkerk M, Zijlstra F, Tio RA. Relation of aortic valve and coronary artery calcium in patients with chronic kidney disease to the stage and etiology of the renal disease. *Am J Cardiol.* 2009; 103:1473-7.
2. Touw HR, Tuinman PR, Gelissen HP, Lust E, Elbers PW. Lung ultrasound: routine practice for the next generation of internists. *Neth J Med.* 2015;73:100-7.
3. Touw HR, Tuinman PR, Gelissen HP, Lust E, Elbers PW. Response tot the letter of Trovato et al. *Neth J Med.* 2015; 73:306.
4. Touw HRW, Verheul MH, Tuinman PR, Smit J, Thöne D, Schober P, Boer C. Photoplethysmography respiratory rate monitoring in patients receiving procedural sedation and analgesia for upper gastrointestinal endoscopy. *J Clin Monit Comput.* 2017; 31:747-754.
5. Touw HRW, Oudemans-van Straaten HM. When to start renal-replacement therapy in critically ill patients? *Neth J Crit Care* 2017; 25:183-4.
6. Winkler MH, Touw HR, van de Ven PM, Twisk J, Tuinman PR. Diagnostic Accuracy of Chest Radiograph, and When Concomitantly Studied Lung Ultrasound, in Critically Ill Patients With Respiratory Symptoms: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2018; 46:707-714.
7. Touw HR, Parlevliet KL, Beerepoot M, Schober P, Vonk A, Twisk JW, Elbers PW, Boer C, Tuinman PR. Lung ultrasound compared with chest X-ray in diagnosing postoperative pulmonary complications following cardiothoracic surgery: a prospective observational study. *Anaesthesia* 2018; 73:946-954.
8. Touw HR, Parlevliet KL, Beerepoot M, Tuinman PR. Ultrasound for detecting postoperative pulmonary complications: a reply. *Anaesthesia* 2018; 73:1443.
9. Boer C, Touw HR, Loer SA Postanesthesia care by remote monitoring of vital signs in surgical wards. *Curr Opin Anaesthesiol.* 2018; 31:716-722.
10. Jip Nooitgedacht, Mark Haaksma, Hugo R. W. Touw, Pieter R. Tuinman. Perioperative care with an ultrasound device is as Michael Jordan with Scotty Pippen: at its best! *J Thorac Dis* 2018; 10:6436-6441.
11. Tuinman PR, van Westerloo D, Slot S, Touw HRW. The 'blinking frog' ultrasound sign establishes the presence of pretracheal vasculature. *Intensive Care Med.* 2019; 45:261-262.

Biography

Hugo Touw was born on May 25, 1984 in Vianen, the Netherlands. After graduating from the Utrechts Stedelijk Gymnasium in 2002, he first studied Industrial Engineering & Management at the University of Groningen. After one year however, he discovered where his true passion lied. He switched to Medicine at the same University and he graduated in 2009. Hugo followed electives in Intensive Care Medicine (Hamilton), Anaesthesiology (Gisborne) and Emergency Medicine (Gisborne) in New Zealand. In 2011 he became a resident in Anaesthesiology and combined this in 2016 with a fellowship Intensive Care Medicine at the VU University Medical Center in Amsterdam (Chairs: Prof. S.A. Loer and Prof. A.R.J. Girbes). During his residency he started his PhD program at the Department of Anesthesiology under supervision of Prof. C. Boer and co-supervision of Dr. P.R. Tuinman and Dr. P. Schober. After completing his fellowship he joined the Department of Intensive Care at the Radboud University Medical Center (Chair: Prof. J.G. van der Hoeven) in Nijmegen in 2017.

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