Assessment of cardiovascular autonomic function in the anaesthesia population

Keet, S.W.M.

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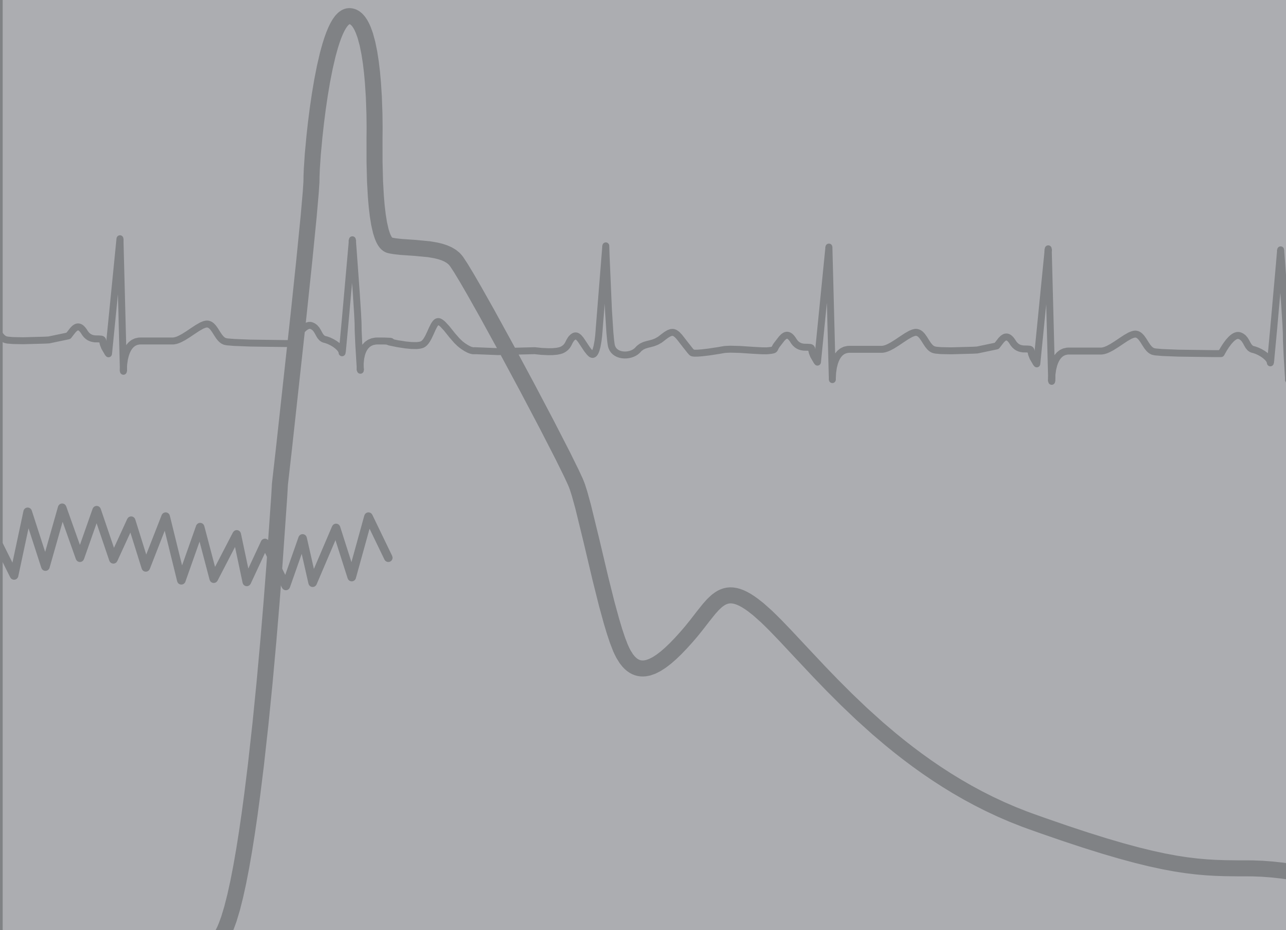
Chapter 10

General conclusions and discussion



GENERAL CONCLUSIONS

General anaesthesia has a marked effect on autonomic function, which may lead to unexpected haemodynamic instability during surgery. Moreover, general anaesthesia may increase the incidence of perioperative complications in patients with pre-existing autonomic dysfunction due to health risk factors and/or diseases such as diabetes mellitus or heart failure. However, autonomic function is not evaluated in the perioperative setting routinely because of the complexity of standardised autonomic function tests.

This thesis shows that health risk factors are highly prevalent in the anaesthesia population. The most prevalent factors are overweight, smoking and hypertension. Of particular importance, patients are often unaware of these risk factors and tend to under-report risk factors when asked by physicians. However, as these lifestyle-related risk factors contribute to the development of autonomic dysfunction, it is very likely that impaired autonomic regulation is silently prevalent in many patients.

We evaluated the use of a simplified (non-standardised) test sequence for the detection of autonomic dysfunction in volunteers and patients. Interestingly, the results of these simplified tests correlated very well with the standardised tests (under specific test conditions such as overnight fasting, refraining from smoking, alcohol or caffeine and measurements during morning hours) in healthy, diabetic and cardiovascular patients. In addition we observed that short-term pulse rate variability (PRV) derived from non-invasive continuous blood pressure waveforms represents a valuable alternative for traditional short-term heart rate variability (HRV) derived from ECG-recordings in healthy, diabetic and cardiovascular patients. Using pulse rate variability eliminates or substantially decreases artefacts caused by movement or electrical interference during surgery. In conclusion, we established simple tools to evaluate cardiovascular autonomic function in ambulatory and perioperative patients to identify patients at risk for cardiovascular complications.

In subsequent measurements we addressed the preoperative recognition of patients at risk for haemodynamic instability, with the scope to optimise conditions and thereby reduce cardiovascular risks. We showed that preoperative disturbances in autonomic function, as reflected by a depressed short-term PRV, are predictive for intraoperative hypotension. From these findings we conclude that a routine PRV assessment in the preoperative period is not only feasible to perform, but may also contribute to improved perioperative care.

Finally, we also studied autonomic function in surgeons. We observed that robot-assisted laparoscopic surgery leads to a stronger decrease in mean heart rate and an increase in heart rate variability of the surgeon when compared to laparoscopic surgery without robot-assistance. These findings also suggest that the susceptibility to stress of surgeons is reflected by alterations in autonomic function.

CLINICAL IMPLICATIONS

Cardiovascular autonomic neuropathy results in more perioperative cardiovascular events

Cardiac complications remain one of the main causes of perioperative mortality and morbidity in all patients undergoing a surgical procedure each year in the Netherlands (1.400.000 operations) [1-3]. It is very likely that impaired autonomic innervation of the heart and blood vessels results in perioperative haemodynamic instability, which may therefore contribute to cardiovascular morbidity and mortality [2, 4-9]. It is well recognised that perioperative morbidity and mortality are significantly increased in patients with diabetes mellitus [10]. It is also known that diabetes mellitus represents one of the main causes of cardiovascular autonomic neuropathy. Consequently, the early identification of patients with impaired cardiovascular autonomic function may be valuable in increasing awareness of cardiovascular risk profiles (**Chapter 2**).

High prevalence of health risk factors in the anaesthesia population

Health risk factors are increasingly prevalent in the general anaesthesia population and may lead to a delayed patient recovery and a prolonged hospital stay [4-5, 11-12]. Almost half of our study population (in a tertiary hospital) suffered from overweight or obesity, which is in accordance with prevalence in the general Dutch population (**Chapter 3**) [13]. Since lifestyle-related risk factors may increase the chance for perioperative cardiovascular complications, anaesthetists must be aware of these factors, both during the preoperative screening and in the perioperative period. Moreover, in 30% of the patients that reported a normal weight in a survey, the anaesthetist diagnosed a body mass index exceeding 25 kg/m^2. This finding suggests unawareness of patients of their weight and health condition.

Pulse rate variability is a useful substitute for heart rate variability to evaluate cardiovascular autonomic function

An impaired autonomic function may be reflected in a decreased heart rate variability [14-15]. Heart rate variability analysis might however be hindered in the intraoperative setting by movement artefacts and electrical interferences which may disturb R-wave detection by electrocardiography. Instead of R-R intervals from ECG-recordings also interbeat intervals derived from continuous non-invasive blood pressure measurements can also be used to calculate pulse rate variability [16-17]. We investigated whether the interbeat intervals derived from a Nexfin HD monitor, a device for non-invasive, beat-to-beat blood pressure measurements [18-19], may substitute for R-R intervals from electrocardiography recordings (**Chapter 4** and **Chapter 7**). We observed a high correlation of pulse and heart rate variability in healthy subjects and patients with diabetes mellitus and therefore suggest that pulse rate variability is a useful substitute for heart rate variability in evaluating cardiovascular autonomic function. This finding is consistent with previous observations on the agreement between pulse and heart rate variability using other non-invasive blood pressure measurement devices [16-17].

Parameters of heart rate variability are influenced by gender, not by age
We determined normal ranges for short-term heart rate variability for young and middle-aged adults, which were lacking in current scientific literature (**Chapter 5**). In our population, aged between 18 and 50 years, we observed significant differences between men and woman for most studied parameters of heart rate variability. In accordance with earlier studies in older subjects, males showed significantly higher values [20-22]. The differences in heart rate variability parameters may be due to differences in resting heart rate, which was significantly lower for men in our population [23]. A decline in heart rate variability with aging has previously been described before in patients aged between 50 and 75 years [21-22, 24]. In contrast to these reports we found no differences in our study population when we compared those in the 18 - 30 age-group with those in the 31 - 50 year age-group. This observation may be explained by the fact that we included a relatively young study population. With the use of reference values for heart rate variability, a diagnostic algorithm can be developed for the detection of autonomic dysfunction in patients undergoing anaesthesia and surgery.

Cardiovascular autonomic function tests to evaluate autonomic function can be performed during non-standardised measurements
Traditional Ewing tests (deep breathing, Valsalva manoeuvre, sustained handgrip, quick standing) and heart rate variability analysis are internationally used to identify patients with an impaired autonomic function [21-22, 25-26]. Nevertheless, standardised test conditions, such as environmental factors and abstention from smoking eating and drinking, are described in the literature as study preconditions for these tests [21, 25-26].
In this dissertation we presented two studies which advocate that standardised test conditions for cardiovascular autonomic function tests are not required for the diagnosis of autonomic dysfunction (**Chapter 6** and **Chapter 7**). We observed in healthy volunteers that the results and reproducibility of non-standardised test conditions were comparable to those of standardised conditions with regard to cardiovascular autonomic function

tests. The same observations were made in patients with diabetes mellitus and cardiovascular comorbidity. Thus non-standardised cardiovascular autonomic function tests can be used to evaluate cardiovascular autonomic function in the ambulatory and perioperative setting. As these tests are much easier to implement, we advocate the development of a guideline for autonomic function testing in patients undergoing anaesthesia and surgery.

Ewing tests for evaluation of sympathetic function are questionable

The Ewing tests based on heart rate responses (deep breathing, Valsalva manoeuvre, quick standing) were developed to analyse parasympathetic function, whereas the Ewing tests to analyse sympathetic function (sustained handgrip, quick standing) are based on blood pressure responses [26]. However, in healthy individuals, the reproducibility of the quick standing test for both heart rate and blood pressure responses were poor during standardised as well as non-standardised test conditions (**Chapter 6**), whereas other autonomic function tests showed a moderate-to-good reproducibility (deep breathing, Valsalva manoeuvre, sustained handgrip). Furthermore, in diabetic patients the reproducibility of sympathetic autonomic function tests, such as blood pressure responses to sustained handgrip and quick standing was poor (**Chapter 7**). In contrast, the parasympathetic tests demonstrated a moderate-to-good reproducibility during standardised as well as non-standardised test conditions in diabetic subjects. These data are in concordance with Gerritsen et al., who also observed a low reproducibility for the quick standing test [22]. In agreement with our data, Kolwalewski et al. showed a questionable reproducibility for the sustained handgrip [27]. Moreover, the performance of the sustained handgrip is sensitive to bias [27-28]. From our findings and the studies by others it might be concluded that Ewing tests for the assessment of sympathetic autonomic function are unreliable, and should preferably be removed from the autonomic function test battery.

Interestingly, recent literature suggests that the best Ewing test to determine cardiovascular autonomic neuropathy is the deep breathing test, with the Valsalva manoeuvre as second best [29]. The deep breathing test as well as the Valsalva manoeuvre demonstrated the best reproducibility in our data. Therefore, we propose to use the deep breathing test and Valsalva manoeuvre, in combination with heart or pulse rate variability analysis, which are discussed below (**Chapter 2** and **Chapter 8**), to determine cardiovascular autonomic neuropathy.

Short-term pulse rate variability is a feasible tool to evaluate the cardiovascular autonomic function in the anaesthesia population

Traditionally, the diagnosis of autonomic dysfunction requires a battery of tests for parasympathetic and sympathetic function [22-26]. This battery of tests is however difficult to enrol in the preoperative setting. Increasing evidence shows that these autonomic function tests may be replaced by sole measurements of heart rate variability as a valuable predictor for cardiovascular events in the perioperative setting and as an outcome predictor in the intensive care setting [21, 25].

As described in the previous section, pulse rate variability may replace heart rate variability. In **Chapter 8** we gained more insight into the relationship between preoperative pulse rate variability and intraoperative haemodynamic stability. We showed that an impaired autonomic function reflected by depressed short-term pulse rate variability in the preoperative phase, might be used as a predictor for intraoperative hypotension.

Interestingly, recent evidence suggests adverse outcome when intraoperative hypotension is present during anaesthesia and surgery [30-31]. Therefore, when an impaired autonomic function is diagnosed, this information has to be considered when planning the anaesthetic and surgical procedures. Prophylactic treatment in patients with depressed autonomic function through administration of vasopressors or fluids may reduce the risk of intraoperative hypotension.

Robot-assistance in laparoscopic surgery leads to a reduction in intraoperative mental strain for the surgeon

The demanding nature of surgery poses significant physical and mental strain on surgeons [32]. Perioperative cardiovascular autonomic function testing may be valuable for physicians as well [33]. Indeed, mental strain is acknowledged as a risk factor for the development of cardiovascular diseases [34-37]. Heart rate variability is impaired during mental strain since it leads to a more regular heart rhythm [14-15, 38]. Intraoperative measurements in surgeons performing general or thoracic surgery showed an increased heart rate and decreased variability of heart rate [39-40]. Laparoscopic procedures may contribute to increased mental strain compared to conventional open surgery, which is less exhausting [41]. However, laparoscopic surgery is beneficial for patients in terms of postoperative pain, convalescence and duration of hospital admission [41]. We demonstrated in **Chapter 9** that robot-assistance in laparoscopic surgery leads to a decrease in mean heart rate and an increase in heart rate variability, which suggests a reduction in mental strain for the surgeon. Robotic assistance in laparoscopic surgery could potentially lead to faster, more accurate and less exhausting surgery and may therefore reduce operative mental strain which might be beneficial for the patient as well [42-43].

METHODOLOGICAL CONSIDERATIONS

Limitations of pulse rate variability measurements

Current guidelines recommend performance of spectral analysis under resting conditions for optimal systematic evaluation [21]. We studied the agreement and reliability of pulse rate variability during rest. Therefore, extrapolation of our results to exercise conditions is a limitation for instance during 24-hour measurements.

The pulse rate variability was derived with the non-invasive Nexfin device, which measures arterial blood pressure waveforms based on the volume clamp method using a specific finger cuff [18-19]. Although this method has been previously established in autonomic function testing, its intraoperative use under different clinical conditions is still not well validated. Additional studies using non-invasive blood pressure devices for the assessment of pulse rate variability are necessary to standardise the use of these devices in preoperative autonomic function testing and intraoperative blood pressure measurements. Moreover, Nexfin blood pressure measurement is impaired in patients with perfusion disturbances of their fingers due to hypothermia or vasopressor therapy. It has to be underlined that these limitations of the Nexfin technology may be especially pronounced in patients with cardiovascular disease and/or at risk of intraoperative haemodynamic instability. Future studies should further elaborate on the applicability of non-invasive continuous blood pressure measurements for the detection of pulse rate variability in the clinical setting.

The use of medication during autonomic function testing

In the studies for this dissertation, patients continued with their prescribed medication. However, the use of diuretic, antihypertensive or tricyclic medication can affect the autonomic nervous system, and the results of cardiovascular autonomic function tests may therefore be biased [21, 44-47]. In particular, autonomic function test results may be misleading, incorrectly showing either normal or depressed function of the autonomic system [21, 44-47]. Nevertheless, as we aimed to study the true clinical situation, the use of medication was not an exclusion criterion. Moreover, we showed that the value of pulse rate variability to predict intraoperative hypotension is still present despite the use of cardiovascular medication. From these findings we propose that a diagnostic guideline for preoperative autonomic dysfunction should contain information about the potential interference effect of pharmacological agents on autonomic function.

FUTURE DIRECTIONS

Our findings show that preoperative cardiovascular autonomic function tests using simplified test conditions are a valuable instrument to identify patients at risk of perioperative cardiovascular complications. Since cardiovascular autonomic neuropathy in surgical patients can markedly affect perioperative haemodynamics and postoperative recovery, the addition of autonomic function testing to preoperative screening is feasible. In order to bring this concept into practice, two conditions have to be fulfilled. Firstly, we have to develop a diagnostic algorithm and guideline for patients undergoing anaesthesia and surgery, that describes reference values, a description of the test conditions, the influence of pharmacological interventions on autonomic function and a treatment algorithm where autonomic dysfunction is diagnosed. Secondly, the diagnosis of autonomic dysfunction in the preoperative setting requires an on-line spectral analysis of R-R or pulse rate intervals. Recently, automated devices became available that allow the measurement of heart rate variability in the ambulatory or clinical setting. Interestingly, heart rate variability is currently promoted as an optimal parameter to guide cardio-fitness training using a PDA-based non-invasive measurement technique. This type of remote monitoring may be used in the near future for patient monitoring in preoperative holding or upon admission to a general ward. In addition to remote monitoring systems, devices have become available for the professional medical use, which can be used for on-line monitoring of heart rate variability in patients at risk. In relation to our findings, these developments may promote the entry of autonomic testing in high risk patients in anaesthesia practice.

FINAL CONCLUSIONS

The findings in this thesis support our central hypothesis that simple preoperative cardiovascular autonomic function tests during non-standardised test conditions, with specific emphasis on pulse or heart rate variability may be a valuable tool to identify patients at risk for perioperative cardiovascular complications. Since cardiovascular autonomic neuropathy in surgical patients can markedly affect perioperative haemodynamics and postoperative recovery, the addition of autonomic function testing to preoperative patient risk assessment may contribute to the recognition of patients at risk for postoperative complications.

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