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## Sepsis, mechanical ventilation and the heart

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## List of abbreviations

|        |  |
|--------|--|
| AECC   | American-European consensus conference |
| AGE    | advanced glycation end                 |
| ALI    | acute lung injury                      |
| AP     | activator protein                      |
| ARDS   | acute respiratory distress syndrome    |
| ATP    | adenosine tri-phosphate                |
| Bcl    | B-cell lymphoma                        |
| BPM    | beats per minute                       |
| CEBP   | CCAAT-enhancer-binding proteins        |
| CLP    | cecal ligation and puncture            |
| CML    | carboxymethyl-lysine                   |
| CO     | cardiac output                         |
| COX    | cyclooxygenase                         |
| COX IV | cytochrome C oxidase IV                |
| CPAP   | continuous positive airway pressure    |
| CsA    | ciclosporin A                          |
| cTnI   | cardiac troponin I                     |
| cTnT   | cardiac troponin T                     |
| CVP    | central venous pressure                |
| CXCL   | chemokine (C-X-C motif) ligand         |
| DAB    | 3,3-diaminobenzidine                   |
| DAPI   | 4',6-diamidino-2-phenylindole          |
| DNA    | deoxyribonucleic acid                  |
| dP/dt  | deltaPressure/deltaTime                |
| EDG    | electron dense granules                |
| EM     | electron microscopy                    |
| eMax   | maximum elastance                      |
| ES     | enrichment score                       |
| Et-1   | endothelin-1                           |
| FAC    | fractional area change                 |
| FDR    | false discovery rate                   |

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|                               |   |
|-------------------------------|---|
| F <sub>i</sub> O <sub>2</sub> | fraction of inspired oxygen                 |
| FITC                          | fluorescein isothiocyanate                  |
| FOXO                          | forkhead box O                              |
| FS                            | fractional shortening                       |
| GAPDH                         | glyceraldehyde-3-phosphate dehydrogenase    |
| GEE                           | generalizes estimated equations             |
| GSEA                          | gene set enrichment analysis                |
| HR                            | heart rate                                  |
| HR-QoL                        | health-related-quality of life              |
| Hsp-70                        | heat shock protein 70                       |
| HVt                           | high tidal volume                           |
| i.m.                          | intramuscular                               |
| i.p.                          | intraperitoneal                             |
| i.t.                          | intratracheal                               |
| i.v.                          | intravenous                                 |
| ICAM-1                        | intercellular adhesion molecule -1          |
| ICU                           | intensive care unit                         |
| IL                            | Interleukin                                 |
| IPA                           | ingenuity pathway analysis                  |
| LPS                           | lipopolysaccharide                          |
| LV                            | left ventricle / left ventricular           |
| LVEDA                         | left ventricular end diastolic area         |
| LVEDD                         | left ventricular end diastolic diameter     |
| LVEF                          | left ventricular ejection fraction          |
| LVEF                          | left ventricular ejection fraction          |
| LVESA                         | left ventricular end systolic area          |
| LVESD                         | left ventricular end systolic diameter      |
| LVEVDI                        | left ventricular end diastolic volume index |
| LVt                           | low tidal volume                            |
| MAP                           | mean arterial pressure                      |
| MEF                           | myocyte enhancing factor                    |

|                               |  |
|-------------------------------|--|
| MMP                           | matrix metalloproteinase                         |
| MPO                           | myeloperoxidase                                  |
| mPTP                          | mitochondrial permeability transition pores      |
| mRNA                          | messenger ribonucleic acid                       |
| mtDNA                         | mitochondrial deoxyribonucleic acid              |
| MV                            | mechanical ventilation                           |
| NES                           | normalised enrichment score                      |
| NF- $\kappa$ B                | nuclear factor- $\kappa$ beta                    |
| NO                            | nitric oxide                                     |
| NRF-1                         | nuclear respiratory factor 1                     |
| NRF-2                         | nuclear factor erythroid-derived 2-like-2        |
| PAF                           | platelet activating factor                       |
| PAF                           | platelet activating factor                       |
| P <sub>a</sub> O <sub>2</sub> | partial pressure of oxygen in arterial blood     |
| PEEP                          | positive end expiratory pressure                 |
| PEEPi                         | intrinsic positive end-expiratory pressure       |
| PGC                           | proliferator-activator gamma coactivator         |
| PMN                           | polymorphonuclear neutrophils                    |
| PRR                           | pattern recognition receptor                     |
| qRT-PCR                       | quantitative real-time polymerase chain reaction |
| RAGE                          | advanced glycation end receptor                  |
| ResV                          | resveratrol                                      |
| RNA                           | ribonucleic acid                                 |
| ROS                           | reactive oxygen species                          |
| RV                            | right ventricle / right ventricular              |
| s.c.                          | subcutaneous                                     |
| SAM                           | significant analysis of microarray               |
| SEM                           | standard error of the mean                       |
| SIRS                          | systemic inflammatory response syndrome          |
| SVR                           | systemic vascular resistance                     |
| TF                            | transcription factors                            |

|               |  |
|---------------|--|
| TFAM          | mitochondrial transcription factor A                         |
| TLR           | toll-like receptor   |
| TNF-R         | tumor necrosis factor $\alpha$ - receptor                    |
| TNF- $\alpha$ | tumor necrosis factor $\alpha$                               |
| TUNEL         | terminal deoxynucleotidyl transferase dUTP nick end labeling |
| VCAM-1        | vascular cell adhesion molecule -1                           |
| VILI          | ventilator-induced lung injury                               |
| Vt            | tidal volume   |
| WGA           | wheat germ agglutinin  |





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## List of publications

## Full papers

**Smeding L**, Kuiper JW, Plotz FB, Kneyber MCJ, ABJ Groeneveld. Aggravation of myocardial dysfunction by mechanical ventilation is mediated through a calcium-independent mechanism in LPS-induced pneumonia in rats. *Shock* [submitted]

Kuiper JW, Plotz FB, Groeneveld J, Haitsma JJ, **Smeding L**, Begieneman MPV, Jothy S, Vaschetto R, Zhang H, Slutsky AS. High tidal volume mechanical ventilation during sepsis causes kidney apoptosis and decreased kidney function without significant lung injury. *Crit Care* [submitted]

**Smeding L**, Plotz FB, Lamberts RR, van der Laarse RR, Kneyber MCJ, Groeneveld ABJ. Mechanical ventilation with high tidal volumes attenuates myocardial dysfunction by decreasing cardiac edema in a rat model of LPS-induced peritonitis. *Resp Res* 2012 [in press]

**Smeding L**, Plötz FB, Groeneveld ABJ, Kneyber MCJ. Structural alterations in sepsis-induced myocardial dysfunction. *Shock* 2012;37:449-456.

**Smeding L**. Leong-Poi H, Hu P, Shan Y, Haitsma JJ, Horvath E, Furmli S, Masoom H, Kuiper JW, Slutsky AS, Parker TG, Plötz FB, dos Santos CC. Salutary effects of Resveratrol in sepsis-induced myocardial depression. *Crit Care Med* 2012 [in press]

**Smeding L**, van der Laarse WJ, van Veelen TA, Lamberts RR, Niessen HW, Kneyber MC, Johan Groeneveld AB, Plötz FB. Early myocardial dysfunction is not caused by mitochondrial abnormalities in a rat model of peritonitis. *J Surg Res* 2011 [in press]

Bouwman RA, Vreden MJ, Hamdani N, Wassenaar LE, **Smeding L**, Loer SA, Stienen GJ, Lamberts RR. Effect of bupivacaine on sevoflurane-induced preconditioning in isolated rat hearts. *Eur J Pharmacol* 2010;647:132-8.

**Smeding L**, Lust E, Plötz FB, Groeneveld AB. Clinical implications of heart-lung interactions. *Neth J Med* 2010;68:56-61.

dos Santos CC, Gattas DJ, Tsoporis JN, **Smeding L**, Kabir G, Masoom H, Akram A, Plotz F, Slutsky AS, Husain M, Sibbald WJ, Parker TG. Sepsis-induced myocardial depression is associated with transcriptional changes in energy metabolism and contractile related genes: a physiological and gene expression-based approach. *Crit Care Med* 2010;38:894-902.

Groeneveld AB, **Smeding L**, van der Heijden M. What is new in Shock, July 2009?: from bench to bedside. *Shock* 2009;32:1-3.

## Submitted abstracts

### Oral presentations

- 8<sup>th</sup> World Congress on Trauma Shock Inflammation and Sepsis 2010  
**Smeding L**, van der Laarse W, van Veelen T, Kneyber M, Groeneveld J, Plotz F. Mitochondria seem not involved in the onset of myocardial depression in a rat acute sepsis model. *Inflamm Res* 2010;59:S72

### Poster presentations

- American Thoracic Society International Conference 2011  
**Smeding L**, Kneyber MCJ, Groeneveld ABJ. Direct measurement of stroke volume variations is not correlated with systolic or pulse pressure variations in the rat during vena cava occlusion. *Am J Respir Crit Care Med* 2011; 183: A4745.
- 22<sup>nd</sup> Annual Congress European Society Intensive Care Medicine 2009  
**Smeding L**, Lamberts RR, van der Laarse WJ, Plotz FB, Groeneveld ABJ, Kneyber MCJ. High tidal volume ventilation partly prevents sepsis induced myocardial depression by decreasing cardiac edema. *Int Care Med* 2009;35:S78
- 29<sup>th</sup> International Symposium Intensive Care and Emergency Medicine 2009  
**Smeding L**, van Veelen TA, van der Laarse WJ, Lamberts RR, Groeneveld J, Plötz FB, Kneyber MC. Cytochrome C is not released in the heart during sepsis-induced myocardial depression. *Crit Care* 2009;13:S150
- Society of Critical Care Medicine's 37<sup>th</sup> Critical Care Congress 2008  
**Smeding L**, Haitsma JJ, Slutsky AS, Zhang H, dos Santos CC, Leong Poi H, Tsoporis J, Parker T, Kuiper JW, Plötz FB. Resveratrol prevents sepsis induced myocardial depression. *Crit Care Med* 2007;35:A51



## **Awards**

2009 - Derde prijs Jonge Fysiologendag; mondelinge presentatie

2008 - Jonge Fysiologenprijs; Beste Poster Presentatie

## **Grants**

2010 - Tebu-bio's Researchers Travel Grant

2008 - Reisbeurs W. Stiggelbout programma Nederlandse Hartstichting

2007 - Studenten Beurs E. Dekkerprogramma Nederlandse Hartstichting

2007 - Studentenreisbeurs Dittmerfonds

## Curriculum Vitae

Lonneke Smeding was born on the August 19 1984 and grew up in Wijk bij Duurstede and IJsselstein. In 2002 she graduated from high school at the Cals College in Nieuwegein. She obtained her Bachelor degree in Biomedical Sciences at the University of Utrecht in 2005 and started her Masters training at the VU University in Amsterdam with a specialization in cardiovascular diseases and extra courses on science journalism and communication science. She did an internship with the Physiology department at the VU University in 2006 and with the Critical Care department of the St. Michaels Hospital in Toronto, Canada in 2007. After obtaining her Masters degree in August 2007, she prolonged her internship and in November 2007 she started as a PhD student under the supervision of Prof.Dr. A.B.J. Groeneveld, Dr F.B. Plötz and Dr M.C.J. Kneyber. She gave presentations at national and international conferences and obtained several travel grants. In 2008 she won the Young Physiologist Award for best poster presentation. In 2010 she organised the Young Physiologist Day and she was board member of the Dutch Physiological Society. The results of her research are presented in this thesis.



Lonneke Smeding is geboren op 19 augustus 1984 in Utrecht en groeide op in Wijk bij Duurstede en IJsselstein. In 2002 heeft ze haar gymnasiumdiploma gehaald aan het Cals College in Nieuwegein. In datzelfde jaar is ze begonnen met de opleiding Biomedische wetenschappen aan de Universiteit Utrecht. Na het behalen van haar bachelor-diploma in 2005 heeft ze de master-opleiding Biomedical Sciences gevolgd aan de Vrije Universiteit in Amsterdam met een differentiatie in hart- en vaatziekten en als extra vakken o.a. wetenschapjournalistiek en communicatiewetenschappen. Binnen het kader van deze opleiding heeft ze in 2006 stage gelopen op de afdeling Fysiologie van de Vrije Universiteit Amsterdam en in 2007 op de afdeling Critical Care Medicine in het St. Michael's Hospital in Toronto, Canada. Deze laatste stage heeft zij, na het afronden van haar opleiding in augustus 2007, verlengd met enkele maanden, waarna zij in november 2007 met haar promotie-onderzoek is gestart onder begeleiding van prof.dr. A.B.J. Groeneveld, dr. F.B. Plötz en dr. M.C.J. Kneyber. In deze periode heeft zij presentaties gehouden op nationale en internationale congressen waarvoor zij een aantal beurzen heeft verworven. In 2008 won zij de Jonge Fysiologenprijs voor de beste posterpresentatie. In 2010 heeft zij de Jonge Fysiologendag georganiseerd en zat zij in het bestuur van de Nederlandse Vereniging voor Fysiologie. De resultaten van haar promotie-onderzoek staan beschreven in dit proefschrift.