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DOI (link to publication from Publisher):
10.5278/VBN.PHD.MED.00049

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

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BY
MICHAEL DAHL

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

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Dissertation submitted

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PhD Series:	Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-450-7

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2015

CURRICULUM VITAE

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PREFACE AND ACKNOWLEDGEMENTS

This dissertation is based on studies carried out during my employment at the Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital, Denmark from 2010 to 2015. However, Study I was carried out in the animal research facility at Aarhus University Hospital, Skejby, some years earlier. Studies II and III took place in cooperation with the Department of Anesthesia at Rigshospitalet, Copenhagen where Professor Niels H. Secher has established an international laboratory for human cardiovascular research – a wonderful place where even a researcher from Jutland is taken well care of.

The idea of the project was to identify a method for assessment of fluid responsiveness in spontaneously breathing patients in the emergency department or in a pre-hospital setting and remains valid even though the project has been delayed. I do hope that this project will lead to improved bedside monitoring of fluid responsiveness, but I am aware that it takes years to disseminate knowledge to the medical community and my studies will only represent small pieces to the puzzle.

This work has only been made possible by help from others. First, I would like to express my sincerest gratitude to my supervisors: Professor Bodil Steen Rasmussen, M.D., Ph.D. for valuable input, positive attitude and not least persistent belief and encouragement despite temporal challenges. Professor Anders Larsson, M.D., med. dr. is thanked for bringing the idea to my attention, encouraging me to start this Ph.D. project, and providing constructive criticism and evaluation of my work despite the geographic distance. I thank Professor Else Tønnesen, M.D., dr. med. for guidance, and of course for the coffee. Special thanks goes to Professor Niels H. Secher, M.D., dr. med. for letting me use his laboratory and for patiently teaching me the art of scientific writing with unremitting enthusiasm and a positive attitude, and for believing in my project and me – your constructive criticism and evaluation of my work have been essential.

In addition, I wish to acknowledge the contribution of the volunteers in the tilt table experiments. Without these enthusiastic persons, this work would not have been possible.
Special thanks goes to former Clinical Director, Consultant Flemming Knudsen, M.D., dr. med. for introducing me to research and pre-hospital emergency care and for enthusiastically encouraging me to start this Ph.D. project. Moreover, I express my gratitude to Resident Chris F. Hays, M.D. for his enormous work with graphic measurements and for being a co-author; to Resident Lonni Nielsen, M.D. for valuable support during the laboratory work; to IT support manager Klaus Larsen for

priceless technical support; to Consultant Finn Vestergaard M.D. for language proofreading; to Head of Department, Consultant Odd Ravlo M.D., planner of working time Consultant Martin Herløw, M.D. and all colleagues at the Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital who have contributed so much to this time-consuming process.

I wish to address a very special thanks to statistician María Rodrigo Domingo for priceless help with Stat and patiently answering my never-ending questions.

Also, I acknowledge the contribution of my co-authors: Jacob Koefoed-Nielsen, M.D, Ph.D. and Simon T. Vistisen, engineer, Ph.D.

Finally and yet importantly, this work was made possible through financial support from the Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital and I am deeply grateful to former Clinical Director, Consultant Frank Brøgger, M.D., who realized the need to establish economic support for research in the department. Furthermore, I acknowledge the financial support from The Laerdal Foundation for Acute Medicine and Speciallæge Heinrich Kopps Foundation.

However, not everything has been without problems. My Ph.D. project has been somewhat complicated due to enrollment as part-time Ph.D. student. This soon proved to be unrealistic due to clinical work in an understaffed department. Also, I switched from being enrolled at Aarhus University to being enrolled at Aalborg University when the Faculty of Medicine was established there in 2013.

So in many ways, it has been turbulent years. Therefore, my warmest thanks go to my amazing Tina who jumped into the chaos and provided me with endless support, understanding and patience. You have always kept up the good spirit and reminded me of the true values in life. I am eternally grateful!

Michael Dahl
December 2015.

ENGLISH SUMMARY

Introduction

Initial treatment of arterial hypotension includes intravenous administration of fluid to support the circulation. To define the volume to administer, there is increasing focus on so-called goal-directed fluid therapy (GDT). GDT methods seem superior to a clinical estimate of a volume deficit as during major surgery, GDT appears to be associated with reduced postoperative complications, fewer hypotensive events and reduced length of stay in hospital. One GDT strategy takes advantage of that positive pressure ventilation increases the intrathoracic pressure during inspiration, thereby reducing venous return to right atrium, e.g. reduces cardiac preload. Due to the transit time through the pulmonary circulation, the reduced preload generated during inspiration reduces cardiac stroke volume (SV) and hence arterial pressure a few heartbeats later. These ventilator-induced dynamic arterial pressure variations can be used to detect a (central) volume deficit and thus fluid responsiveness during mechanical ventilation.

In this dissertation it was considered whether a similar approach addressing blood pressure variation in relation to ventilation could guide fluid therapy during spontaneous breathing. Because oscillations in intra-thoracic pressure are small during spontaneous breathing, expressions of ventilatory-related variations in arterial function as pulse pressure variation (PPV), systolic pressure variation (SPV) and stroke volume variation (SVV) are also small and cannot detect a central volume deficit.

We hypothesized that by using an inspiratory and/or expiratory resistor, these ventilator-related variations in expressions of arterial function would be amplified to such an extent that they could detect central hypovolemia and consequently whether a patient would demonstrate “fluid responsiveness”. Because the perspective was to use these methods in awake patients, we also considered whether the non-invasive variations in peak height of pulse oximetry plethysmography waveform (ΔPH_{POP}) and a continuous estimate (PVI®; Pleth Variability Index; Masimo Comp. CA, USA), which detects functional hypovolemia during mechanical ventilation could be applied during spontaneous breathing with the use of the in- and/or expiratory resistances to detect central hypovolemia.

The aim of the studies was to examine, during spontaneous breathing, whether inspiratory and/or expiratory resistance could enhance the intrathoracic pressure oscillations, hence induce large arterial pressure variations during hypovolemia but only small variations during normovolemia and mild hypervolemia. The second aim

of the study was to examine whether SPV and PPV as well as ΔPH_{POP} and PVI® predict fluid responsiveness during experimentally induced central hypovolemia.

Methods

We developed an inspiratory resistor, an expiratory resistor, a combined in- and expiratory resistor and a control "resistor" with no resistance, each with a threshold resistance of 7.5 cm H_2O. Since this devise was new, it was evaluated in an animal study and subsequently in a study involving healthy volunteers.
Eight prone anesthetized and spontaneously breathing 20 to 25 kg pigs were subjected to 30% hypovolemia, normovolemia, and 20% and 40% hypervolemia. At each volume load, the pigs breathed, in a randomized order through the different resistors. Hemodynamic and respiratory variables were measured and pulse contour analysis determined SV. Fluid responsiveness was defined as a 15% increase in SV following fluid loading.
In the human study, 13 healthy volunteers were exposed to central hypovolemia by 45° head-up tilt while breathing through a facemask fitted with the four resistor configurations in randomized order. Hemodynamic variables were measured, including PPV, SPV and SVV. Pulse contour analysis determined SV and thus CO, and we evaluated whether SPV, PPV and SVV could detect a 10% decrease in CO when the subjects were exposed to the head-up tilt challenge. With the same setup, we evaluated ΔPH_{POP} and PVI® as a non-invasive approach to detect head-up tilt-induced central hypovolemia.

Results

In the animals, SV was significantly lower during hypovolemia (24 (±5) mL; mean ±SD) compared with normovolemia (65 (±11)), but no differences were found between normovolemia and 20% or 40% hypervolemia. Breathing through the different resistors enhanced the airway and esophageal (pleural) pressures, while only the combined in- and expiratory resistor configuration enhanced the transpulmonary pressure. Compared with breathing through no resistors, SPV was amplified by all resistors during hypovolemia, whereas there were no changes during normovolemia and hypervolemia. PPV was amplified by the inspiratory resistor and the combined in- and expiratory resistor configuration. Regression analysis between SPV or PPV and SV showed the highest r^2 (0.83 for SPV and 0.52 for PPV) when the expiratory resistor was applied. The corresponding sensitivity and specificity for the prediction fluid responsiveness were 100% and 100%, respectively, for SPV and 100% and 81%, respectively, for PPV.
When the healthy volunteers' position was changed from supine to 45° head-up tilt, SV decreased from 91 (±46) to 55 (±24) mL and CO from 5.8 (±2.9) to 4.0 L/min (±1.8) ($P < 0.05$), while heart rate increased (65 (±11) to 75 (±13) bpm; $P < 0.05$). During head-up tilt, SPV tended to be enhanced by the resistors (from 17% (±11%) to 28% (±14%) and a SPV ≥ 37% predicted a decrease in CO ≥ 10% with a sensitivity

and specificity of 78% and 100%, respectively.
For the non-invasive approach, ΔPH_{POP} was not enhanced by any respiratory resistor. However, during head-up tilt, PVI® was 24 (±10) with no resistor applied, and with an inspiratory resistor, an expiratory resistor, and with the combined in- and expiratory resistors applied, PVI increased ($P < 0.05$) to 29 (±9), 32 (±8) and 35 (±7), respectively. Also, no significant correlation was found between ΔPH_{POP} or PVI® and variation in pulse pressure, systolic pressure or SV. Based on an area under the curve analysis between 0.43 and 0.68, neither ΔPH_{POP} nor PVI® detected central hypovolemia.

Conclusion

Inspiratory and/or expiratory threshold resistors enhance intrathoracic pressure oscillations and hence amplify SPV and PPV in spontaneously breathing pigs during hypovolemia. Use of the expiratory resistor allowed SPV and PPV to predicted fluid responsiveness with high sensitivity and specificity.
In spontaneously breathing healthy volunteers, combined in- and expiratory resistors enhances SPV during head-up tilt-induced central hypovolemia and allows for identification of a 10% reduction in CO with acceptable sensitivity and specificity. Thus, breathing through combined in- and expiratory resistors could identify a fluid deficit in spontaneously breathing patients. Variation in peak height of the pulse oximetry plethysmography waveform was however not enhanced by breathing through the inspiratory or expiratory resistors and therefore did not detect head-up tilt-induced central hypovolemia.

DANSK RESUMÉ

Introduktion

Når patienter er hypotensive, er den primære symptomatiske behandling administration af intravenøs væske med henblik på at understøtte cirkulationen. For at øge nøjagtigheden af denne væsketerapi er der stigende fokus på målrettet væsketerapi, såkaldt goal-directed therapy (GDT). GDT synes at være overlegen i forhold til en klinisk vurdering, da postoperative komplikationer og hypotensive hændelser samt indlæggelsestid er reducerede, når GDT er anvendt til at retlede væsketerapi til patienter, der gennemgår større kirurgiske indgreb.

Én GDT metode anvender det forhold, at mekanisk overtryksventilation (respiratorbehandling) øger det transpulmonale tryk under inspiration, hvilket reducerer det venøse tilbageløb til højre atrium, altså inducerer et nedsat pre-load til hjertet. På grund af transittiden gennem lungekredsløbet ses denne pre-load reduktion nogle hjerteslag senere (sammenfaldende med eksspirationen) som en reduktion i hjertets slagvolumen (SV) og dermed i arterietrykket. Disse ventilationsinducerede dynamiske, arterielle trykvariationer kan detektere central hypovolæmi og dermed "fluid responsiveness" under respiratorbehandling.

Her undersøges det, om væsketerapi til hypotensive patienter kan gennemføres på tilsvarende måde under spontan vejrtrækning. Vurderingen af central hypovolæmi og "fluid responsiveness" er vanskelig, da de dynamiske variationer i blodtrykket, som anvendes til at vurdere væskestatus under respiratorbehandling, ikke er tilstrækkelige store hos patienter, der selv trækker vejret. Dette skyldes, at de intrathorakale tryksvingninger er små, og dermed er de dynamiske parametre som pulstryk variation (PPV), systolisk tryk variation (SPV) og slagvolumen variation (SVV) tilsvarende små og ikke i stand til at detektere central hypovolæmi. Da patienter med spontan vejrtrækning oftest er vågne, var målet for undersøgelsen at etablere en non-invasiv metode til GDT baseret på pulsoximeterets plethysmografikurve, da den har lighed med arterietrykskurven. Således ses der også vejrtrækningsinducerede variationer i plethysmografikurven (ΔPH_{POP}), og en kontinuerlig beregning af disse variationer er kommercielt tilgængelig (PVI®; Pleth Variability Indeks; Masimo Comp CA, USA). Disse non-invasive dynamiske parametre kan detektere hypovolæmi hos patienter under respiratorbehandling, men ikke når patienterne trækker vejret spontant.
Vores hypotese var, at ved at lade patienter trække vejret gennem en inspiratorisk og eksspiratorisk modstand, forstærkes de intrathorakale tryksvingninger og dermed forstærkes også de vejrtrækningsinducerede arterielle trykvariationer under hypovolæmi, men ikke under normovolæmi eller hypervolæmi. Efter forstærkning af de vejrtrækningsinducerede arterielle trykvariationer med sådanne respiratoriske modstande, undersøgte vi, om SPV og PPV kan detektere central hypovolæmi og

dermed ”fluid responsiveness”. Tilsvarende undersøgtes, om de non-invasive parametre ΔPH_{POP} og PVI® kan detektere betydende central hypovolæmi.

Metode

Vi udviklede en inspiratorisk modstand, en eksspiratorisk modstand, en kombineret in- og eksspiratorisk modstand og en kontrol "modstand" uden modstand. Hver af disse havde en modstand på 7,5 cm H_2O. Da dette er nyt udstyr, undersøge vi effekten i et dyreeksperimentelt studie og på raske frivillige forsøgspersoner.

Otte bedøvede grise, der vejede 20 til 25 kg, var på spontan respiration. Alle grise gennemgik et forløb, hvor de først blev gjort 30% hypovolæme, så normovolæme og derefter 20% og 40% hypervolæme. På hvert volumenniveau trak de vejret igennem de forskellige modstande i randomiseret rækkefølge. Hæmodynamiske og respiratoriske variable blev målt, og SV blev bestemt ved pulskonturanalyse. ”Fluid responsiveness” blev defineret som en stigning på mindst 15% i SV fra 30% hypovolæmi til normovolæmi.

Tilsvarende blev tretten raske frivillige forsøgspersoner udsat for central hypovolæmi under 45° head-up tilt på et vippeleje, mens de trak vejret gennem en ansigtsmaske udstyret med de fire modstande i randomiseret rækkefølge. Hæmodynamiske variable blev målt, herunder PPV, SPV og SVV og SV og CO blev bestemt med pulskontur analyse. Vi vurderede om SPV, PPV og SVV kunne detektere et fald i CO på mindst 10%, når lejet blev vippet fra liggende til head-up tilt. I samme opsætning vurderede vi, om de non-invasive parametre ΔPH_{POP} og PVI® kunne detektere den head-up tilt inducerede centrale hypovolæmi.

Resultater

Det dyreeksperimentelle studie viste, at SV var lavere ved hypovolæmi (24 (±5) ml; middelværdi ±SD) i forhold til normovolæmi (65 (±11) ml), mens der ikke var forskel mellem SV under normovolæmi og 20% eller 40% hypervolæmi. Vejrtrækning gennem modstande gav en forstærkning af variationerne i luftvejs- og øsofagustrykkene, mens kun den kombinerede in- og eksspiratoriske modstand forstærkede det transpulmonale tryk. Sammenlignet med spontan vejrtrækning uden modstand blev SPV forstærket af alle modstande, når grisene var centralt hypovolæme, hvorimod der ikke var nogen forstærkning under normovolæmi og hypervolæmi. Også under hypovolæmi blev PPV forstærket af den inspiratoriske modstand og den kombinerede in- og eksspiratoriske modstand. Regressionsanalyse af SPV eller PPV versus SV viste de højeste r^2 (0,83 til SPV og 0,52 for PPV), når den eksspiratoriske modstand blev anvendt. Den tilsvarende sensitivitet og specificitet for at detektere ”fluid responsiveness” var henholdsvis 100% og 100% for SPV og 100% og 81% for PPV.

Når vi ændrede lejets position fra liggende til 45° head-up tilt hos forsøgspersonerne, blev SV reduceret fra 91 (±46) til 55 (±24) ml og CO fra 5,8 (±2,9) til 4,0 (±1,8) l/min (P <0,05), mens hjertefrekvensen steg (65 (±11) til 75 (±13) bpm; P <0,05). Under head-up tilt induceret central hypovolæmi blev SPV øget fra 17 (±11)% uden modstand til 28 (±14)% med den kombinerede in- og eksspiratoriske modstand. Således kunne SPV ≥ 37% detektere et fald i CO ≥ 10% med en sensitivitet og specificitet på henholdsvis 78% og 100%. For de non-invasive parametre var ΔPH_{POP} ikke forstærket af de forskellige modstande, hvorimod PVI® under 45° head-up tilt blev forstærket fra 24 (±10) uden modstand til 29 (±9), 32 (±8) og 35 (±7), med henholdsvis den inspiratoriske modstand, den eksspiratoriske modstand, og den kombinerede in- og eksspiratoriske modstand (P <0,05). Der blev ikke fundet en signifikant sammenhæng mellem ΔPH_{POP} eller PVI® og PPV, SPV eller SVV. Baseret på "Area Under the Curve" beregning mellem 0,43 og 0,68 kunne hverken ΔPH_{POP} eller PVI® anvendes til at detektere central hypovolæmi.

Konklusion

Inspiratoriske og/eller eksspiratoriske modstande forstærker de intra-thorakale tryksvingninger og forstærker dermed SPV og PPV under spontan vejrtrækning hos hypovolæme grise. Efter denne forstærkning kan SPV og PPV anvendes til at detektere "fluid responsiveness" med god sensitivitet og specificitet. Tilsvarende ses hos raske personer under 45° head-up tilt induceret central hypovolæmi og spontan vejrtrækning, at den kombinerede in- og eksspiratoriske modstand forstærker SPV og gør det muligt at detektere centrale hypovolæmi med acceptabel sensitivitet og specificitet. De non-invasive parametre kunne imidlertid ikke forstærkes tilstrækkeligt til at detektere central hypovolæmi.

PUBLICATIONS

This Ph.D. dissertation is based on the following papers referred to in the text by their Roman number.

I Dahl MK, Vistisen ST, Koefoed-Nielsen J, Larsson A: **Using an expiratory resistor, arterial pulse pressure variations predict fluid responsiveness during spontaneous breathing: an experimental porcine study.** *Crit Care* 2009, **13**:R39

II Dahl M, Hayes CF, Rasmussen BS, Larsson A, Secher NH: **Can a central blood volume deficit be detected by systolic pressure variation during spontaneous breathing?** Submitted.

III Dahl M, Hayes CF, Rasmussen BS, Larsson A, Secher NH: **Ventilatory variation in pulse oximetry plethysmography peak height does not detect central hypovolemia during spontaneous breathing.** Draft.

ABREVIATIONS

AC = alternating current

ANOVA = analysis of variance

AUC = Area under the curve

CI = cardiac index

CO = cardiac output

CPAP = continuous positive airway pressure

CVP = central venous pressure

DC = direct current

DO_2 = oxygen delivery

ECG = electrocardiogram

Fr. = French

GDT = goal-directed therapy

HR = heart rate

ID = inside diameter

ITBV = intrathoracic blood volume

MSFP = mean systemic filling pressure

$OP_{CIRC.}$ = operating point of the circulation

PAWP = pulmonary artery wedge pressure

PEP = positive expiratory pressure

PH = peak height

PI = perfusion index

PP = pulse pressure

PPV = pulse pressure variation

PPV_{PiCCO} = pulse pressure variation obtained by the PiCCO device

PVI® = Pleth variability index

Q_{RV} = venous return to the right ventricle

R = the ratio AC over DC

RAP = right atrial pressure

ROC = receiver operation characteristic

R_V = venous vascular resistance

$ScvO_2$ = central venous oxygen saturation

SP = systolic pressure

SpO_2 = arterial oxygen saturation measured by pulse oximetry

SPV = systolic pressure variation

SV = stroke volume

SVV = stroke volume variation

VO_2 = oxygen consumption

ΔPH_{POP} = pulse oximetry plethysmographic waveform peak height variation

ΔPOP = pulse oximetry plethysmographic waveform amplitude variation

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CHAPTER 1. INTRODUCTION AND BACKGROUND

Detecting a central volume deficit is clinically important. Whether it is caused by direct hypovolemia or more indirectly by distributive, cardiogenic or obstructive pathologies clinical signs as pale and mottled skin and, altered consciousness and reduced blood pressure are late signs. If not detected or treated insufficient, there will be an increasing imbalance between oxygen consumption (VO_2) and oxygen delivery (DO_2) to the tissues. This imbalance causes cellular hypoxia and compromised mitochondrial function, with a switch towards anaerobic metabolism resulting in acidosis and increased lactate. This pathophysiological response further deteriorates the circulatory function (Gómez et al., 2012; Pawelczyk et al., 1994; Secher & Van Lieshout, 2011; Vincent & De Backer, 2013). Initial symptomatic treatment intending to correct the oxygen consumption/delivery mismatch should be established by intravenous fluid therapy. This treatment should be guided by the cardiac output (CO) in order to maintain DO_2 (Donati et al., 2007). Concurrently, correction of the underlying condition is of course mandatory.

It can be difficult to evaluate how much fluid should be administered, i.e. to find a balance between a compromised circulation and fluid retention with the development of edema and hence impaired exchange of gases and nutrients (Doherty & Buggy, 2012). If cardiac function is hampered, pulmonary edema with further deteriorating oxygenation may occur. Both hyper-and hypo-hydration can induce multiple organ failure and increased morbidity (Grocott et al., 2005; Holte et al, 2002; Lowell et al, 1990).

To increase the accuracy of fluid therapy, focus is on goal-directed therapy (GDT) to guide fluid administration. Different objective methods have been suggested; e.g. estimation of stroke volume (SV) or peak aortic flow velocity by esophageal Doppler (Futier et al., 2010; Gan et al., 2002); calculation of oxygen extraction (Donati et al., 2007); analysis of stroke volume variation (SVV) by uncalibrated pulse contour analysis (Benes et al., 2010; Goepfert et al., 2013); analysis of pulse pressure variation (PPV) (Salzwedel et al., 2013); measurement of global end-diastolic volume index (Goepfert et al., 2013); or cardiac index (CI) (Goepfert et al., 2013; Salzwedel et al., 2013). These methods to guide fluid administration seem to be superior to the clinical judgment of the anesthesiologist (Benes et al., 2010; Donati et al., 2007; Salzwedel et al., 2013). In patients undergoing major abdominal, orthopedic or cardiac surgery, these methods reduce postoperative complications, number of hypotensive events, length of hospital stay, but whether mortality is improved remains uncertain (Benes et al., 2010; Donati et al., 2007).

1.1. FRANK–STARLING CURVE AND THE RESPONSIVENESS TO FLUID

When fluid is administrated the increased preload and hence filling of the heart increases the interaction between actin and myosin filaments in the cardiac myocytes and thus contractility and SV.

Otto Frank and Ernest H. Starling are the "fathers" of the Frank–Starling relationship that describes the interaction between right atrial pressure (RAP) and CO (Braumwald et al, 1960; Patterson & Starling, 1914; Sarnoff & Berglund, 1954). Placing the central venous pressure (CVP) or pulmonary artery wedge pressure (PAWP) on abscissa of the Frank–Starling curve has induced clinicians to presume that fluid resuscitation of patients with reduced CVP would increase SV and hence CO (Berlin & Bakker, 2015). However, these static variables do not predict the response of CO to a fluid bolus in patients in the intensive care unit, operating room or in the emergency department (Cecconi et al., 2015; Marik et al, 2008; Marik & Cavallazzi, 2013). Moreover, for the individual patient, it is not possible to predict where on the Frank–Starling curve the heart is operating. Therefore, it cannot be determined whether a patient is fluid responsive (Bendjelid & Romand, 2003; Cecconi et al., 2015; Marik et al., 2008; Michard & Teboul, 2002). Consequently, fluid therapy is often administered using a "trial and error" principle.

Understanding this interaction between fluid therapy and the Frank–Starling relationship is essential when fluid responsiveness should be predicted or to detect a central volume deficit. When intravenous fluid is provided for circulatory support, it predominantly fills the veins, i.e. the capacitance vessels. In a state of normal vascular compliance, the veins contain about 2/3 of the total blood volume (Feihl & Broccard, 2009a; Feihl & Broccard, 2009b). Increasing the volume in the capacitance vessels, including the vena cava, increases mean systemic filling pressure (MSFP). MSFP is the pressure that determines venous return to the right ventricle via the right atrium (Q_{RV}). Q_{RV} also depends on the pressure in the right atrium (RAP) and the venous vascular resistance (R_v) and can be expressed as $Q_{RV} = (MSFP - RAP) / R_v$ (Feihl & Broccard, 2009a; Feihl & Broccard, 2009b). The added volume of fluid will increase MSFP more than RAP and therefore increase Q_{RV}. This increases the filling of the heart and leads to an inotropic response with increased SV, according to the Frank–Starling relationship, and an increased CO (CO = heart rate (HR) x SV) (Magder, 2011). Graphically Q_{RV} and CO can be related to RAP by a combination of the venous return curve and the Frank–Starling curve (Figure 1-1). This curve shows that fluid administration shifts the venous return curve to the right. Since the circulation is serially connected, Q_{RV} is equal to CO, which is illustrated by the point where the venous return curve and the Frank–Starling curve intersect. This point is referred to as the operating point of the circulation ($OP_{CIRC.}$) (Feihl & Broccard, 2009a; Magder, 2011)

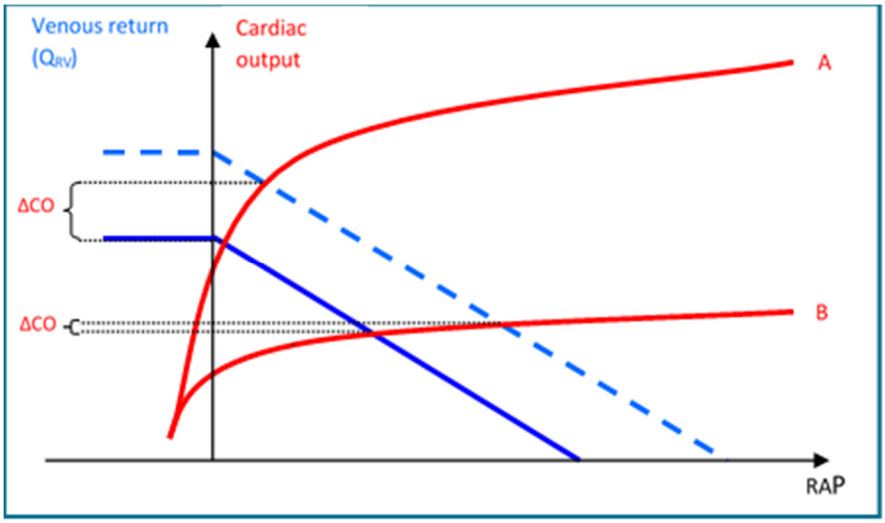

Figure 1-1. Combination of the venous return curve and the Frank–Starling curve. See text for details.

Figure 1-1 shows that the effect of fluid administration depends on where the heart is operating on the Frank–Starling curve. If the heart is operating on the steep part, a given fluid load leads to significant increase in CO (Figure 1-1, curve A). Otherwise, if the heart is operating on the horizontal part of the curve, an equal volume gives an insignificant change of CO (Figure 1-1, curve B). Exactly where the heart is operating on the Frank-Starling curve is normally not known, but from intensive care patients, we know that only approximately 50-60% respond to volume therapy with a resultant increase in CO, i.e. show fluid responsiveness (Feihl & Broccard, 2009; Magder, 2006; Michard et al., 2000; Michard & Teboul, 2002).
In these studies fluid responsiveness was defined as an increase in the cardiac index (CI) (CO/ body surface area) ≥ 15% by 500 ml of isoosmolar colloid fluid (Michard et al., 2000).

1.2. RESPIRATORY PRESSURE – CIRCULATORY INTERACTION

During mechanical ventilation, airflow is forced into the alveoli by positive pressure (typical by 16–20 cm H_2O), while expiration is passive by the elastic recoil of the lungs as opposed by any positive end-expiratory pressure (typical 5–10 cm H_2O). The increased transpulmonary pressure during inspiration reduces venous return to the right atrium, i.e. reduces preload to the heart. Due to the transit time through the

pulmonary circulation, the reduced preload generated during inspiration reduces SV and hence the arterial pressure a few heartbeats later. Thus, it coincides with expiration. Therefore, the smallest arterial pressure amplitudes are found during expiration (but generated during inspiration) and the largest during inspiration (Feihl & Broccard, 2009a; Feihl & Broccard, 2009b; Pinsky, 2007).

However, due to minor and opposite intrathoracic pressure oscillations it is not possible to transfer this observation to patients breathing spontaneously. Here inspiration is caused by actively expanding the thoracic cage, resulting in negative transpulmonary pressure (typically -8 cm H_2O), while expiration is passive and with a slightly positive transpulmonary pressure. Thus, during spontaneous breathing intrathoracic pressure oscillations are minimal. Consequently, the ventilation-induced alteration of Q_{RV} is correspondingly minor, and the hemodynamic interaction is not immediately reflected in arterial pressure variations (Cohn et al., 1967; Dornhorst et al., 1952). Therefore, it is not possible to use the dynamic parameters to predict fluid responsiveness during spontaneous breathing (Coudray et al., 2005).

However, the normal respiratory variations in arterial pressure may be enhanced creating a pulsus paradoxus in pathological situations in which the filling of the left heart is hampered during inspiration, such as during cardiac tamponade, or when right heart filling is reduced during expiration by high intrathoracic pressure, for example, during an acute exacerbation of chronic obstructive lung disease or asthma (Dornhorst et al., 1952; Feihl & Broccard, 2009b). In addition, pulsus paradoxus has been reported as a sign of severe hemorrhagic shock (Cohn et al., 1967).

1.3. PREDICTING FLUID RESPONSIVENESS

As mentioned, evidence has emerged that favors the use of GDT in the perioperative setting. However, one of the challenges of the use of GDT is predicting where on the Frank–Starling curve the patient's heart is operating, and thus whether fluid therapy will improve circulation (Coudray et al., 2005; Magder, 2006). Static parameters, e.g. invasive pressure measurements like CVP or PAWP, are of limited value (Cecconi et al., 2015; Marik et al., 2008; Marik & Cavallazzi, 2013). Correspondingly, echocardiographic assessment of the end-diastolic ventricular volumes such as right and left ventricular end-diastolic volume do not provide information as to whether cardiac output is preload dependent, i.e. that the $OP_{CIRC.}$ is on the steep part of the Frank–Starling curve (Bendjelid & Romand, 2003; Marik et al., 2008; Marik & Cavallazzi, 2013; Michard & Teboul, 2002).

Dynamic variations in arterial pressure might be more useful than the static pressures (Bendjelid & Romand, 2003; Benes et al., 2010; Michard & Teboul, 2002; Michard, 2005). These variations are caused by the reduced Q_{RV} due to increased intrathoracic pressure during the inspiratory phase of mechanical ventilation (Feihl & Broccard, 2009a, 2009b; Magder, 2004; Pinsky, 2007). If the $OP_{CIRC.}$ is located on the upper

horizontal part of the Frank–Starling curve, the ventilation-induced Q_{RV} reduction results only in a small change in SV (Figure 1-1, curve B) and thus in arterial pressure. Conversely, if OP_{CIRC} is located on the steep part of the Frank–Starling curve, a corresponding Q_{RV} reduction will provide a significant reduction in SV (Figure 1-1, curve A). In other words, if the $OP_{CIRC.}$ is on the steep part of the Frank–Starling curve, as can be seen in hypovolemia, SV and hence arterial pressure will vary significantly during mechanical ventilation as an expression of fluid responsiveness.

During mechanical ventilation with the patient sedated and muscle-relaxed, the ventilation-induced variations in SV are reflected in the arterial pressure variations. Different estimates of these fluctuations like PPV, systolic pressure variation (SPV), SVV and pressure variation in the right atrium predicts fluid responsiveness (Bendjelid & Romand, 2003; Michard, 2005; Perel et al. 1987; Perel, 1998). Michard et al. found a difference of more than 12% between pulse pressure during inspiration and during expiration (PPV ≥ 13%) is an indicator of fluid responsiveness in mechanically ventilated septic patients with circulatory collapse (Michard, 2005).

Thus, in mechanically ventilated patients, using relatively large tidal volumes with the patient deeply sedated and muscle-relaxed without initiating breaths or spontaneously breathing, the more respiratory-induced variation in the arterial pulse pressure, the more intense intravascular volume depletion (Bendjelid & Romand, 2003; Michard, 2005; Perel, 1998). However, if the patient is breathing spontaneously, or with spontaneous trigger activity while being mechanically ventilated in support mode, the arterial pressure variations will not provide information about fluid responsiveness (Heenen, et al. 2006). Thus, in spontaneously breathing, hemodynamically unstable patients, Soubier et al. found sensitivity and specificity for predicting the effect of a subsequent fluid administration to be 63% and 92%, respectively, for PPV, and 47% and 92% for SPV (Soubrier et al., 2007).

1.4. PLETHYSMOGRAPHIC WAVEFORM TO PREDICT HYPOVOLEMIA

A non-invasive monitoring of arterial oxygen saturation became available when the Japanese engineer Takuo Aoyagi developed pulse oximetry in late 1973 (Severinghaus, 1987; Severinghaus, 2007). Pulse oximetry is now considered a crucial part of standard of care of acute and perioperative patients (Jubran, 2015).

Arterial oxygen saturation is measured by a spectrophotometric methodology. This technique illuminates the tissue by two different light wavelengths (660 nm: red light and 940 nm: infrared light) and measures the absorption of oxygenated and de-oxygenated blood at each wavelength. Assuming that only arterial blood pulsates, each absorption is divided into a pulsatile component (alternating current (AC)) and a non-pulsatile component (direct current (DC)). While AC represents the absorption of the pulsating arterial blood, the DC represents the absorption of the skin, other

tissues and non-pulsatile venous blood. The ratio (R) is based on the calculation of AC/DC for each wavelength: $R = (AC_{660}/DC_{660})/(AC_{940}/DC_{940})$. The pulse oximeter software calibrates R to display arterial oxygen saturation.

To assist identify any artifacts of the pulse oximetry, most pulse oximeters display the plethysmographic waveform representing the AC, which closely resembles the arterial blood pressure curve (Jubran, 1999, 2015) and hence reflects the arterial blood pulsation. There is a correlation between respiratory-induced variations in arterial pressure and variations in the pulse oximetry plethysmographic waveform (Alian & Shelley, 2012; Cannesson et al, 2005; Natalini et al., 2006; Partridge, 1987; Solus-Biguenet et al., 2006). Therefore, the respiratory-induced variations registered on the pulse oximetry plethysmographic waveform have the ability to predict a central volume deficit (Alian et al., 2011; Chan et al., 2008; Genderen et al, 2013; McGrath et al., 2011; Pizov et al., 2010), and fluid responsiveness (Bendjelid, 2008; Cannesson et al., 2008; Cannesson et al., 2007; Chen et al. 2010; Natalini et al., 2006; Solus-Biguenet et al., 2006) in mechanically ventilated patients.

Respiratory-induced variations in the pulse oximetry plethysmographic waveform are often expressed as the difference in either the amplitude of the AC curve (pulse oximetry plethysmographic waveform amplitude variation (ΔPOP)) (Cannesson et al., 2005) or the difference in the peak height variations of the AC curve (ΔPH_{POP}) (Chen et al., 2010). These expressions are most often calculated retrospectively on printouts of the curves and therefore of limited value for clinical decision-making. Another expression is the Pleth Variability Index (PVI®) (Masimo Comp., Irving, CA, USA), which allows automated and continuous bedside calculation. This algorithm is different because PVI® calculates the perfusion index for infrared light ($PI_{940} = (AC_{940}/DC_{940}) \times 100$) and expresses respiratory-induced variations. $PVI® = ((PI_{940}(max) - PI_{940}(min))/PI_{940}(max)) \times 100$. PVI® has also shown the ability to predict central hypovolemia and fluid responsiveness during mechanical ventilation (Cannesson et al., 2008; Loupec et al., 2011; Wajima et al., 2010).

However, as described, the intrathoracic pressure oscillations during spontaneous breathing are opposite and minor compared to those in mechanically ventilated patients. Therefore, ΔPOP, ΔPH_{POP} and PVI® do not seem to be able to predict central hypovolemia or fluid responsiveness in awake, spontaneously breathing patients (Nilsson et al., 2010; Nilsson et al., 2013; Schoonjans et al., 2010).

CHAPTER 2. HYPOTHESIS AND AIM

We hypothesized that central hypovolemia, defined as a decrease in CO ≥ 10%, could be predicted during spontaneous breathing by amplification of intrathoracic pressure swings using inspiratory and expiratory resistance.

The following intermediate objectives were defined:

- To examine whether arterial pressure variations would be amplified by in- and expiratory resistors during hypo-, normo- and hypervolemia.

- To examine whether arterial pressure variations would predict the hemodynamic effect of subsequent fluid loading.

- To identify which expression of blood pressure variation is most sensitive to a significant reduction of the central blood volume.

- To identify whether ΔPH_{POP} and PVI® can detect a significant reduction in the central blood volume defined as a 10% reduction in CO by exposing subjects to head-up tilt

CHAPTER 3. METHODS AND METHODOLOGICAL CONSIDERATIONS

This dissertation is based on three papers that report and discuss the findings in two experimental studies. The first experimental setup was an animal study (Paper I) and the second was a study in healthy volunteers (Paper II and Paper III).

3.1. THE RESISTORS

To predict central hypovolemia during spontaneous breathing, we must be able to amplify the respiratory-induced intrathoracic pressure oscillations. For this purpose, we considered to use the PEP (positive expiratory pressure) flute used to prevent atelectasis and the facemask applied CPAP (continuous positive airway pressure) used to improve oxygenation and treat atelectasis. However, these devices only amplify the pleural pressure during expiration. We were not aware of any commercial device that amplifies the pleural pressure during inspiration, but a closer look at the CPAP resistor (CPAP; Philips Respironics, Herrshing, Germany) revealed a spring valve that rectifies the airflow, resulting in a threshold resistance of 7.5 cm H_2O. It would also be necessary to overcome the same threshold resistance if breathing took place through the outflow tract. Using a T-piece connector, we developed a combined in- and expiratory resistor with inspiratory flow the "wrong" way through the CPAP resistor and expiratory flow the "right" way. To make devices with only

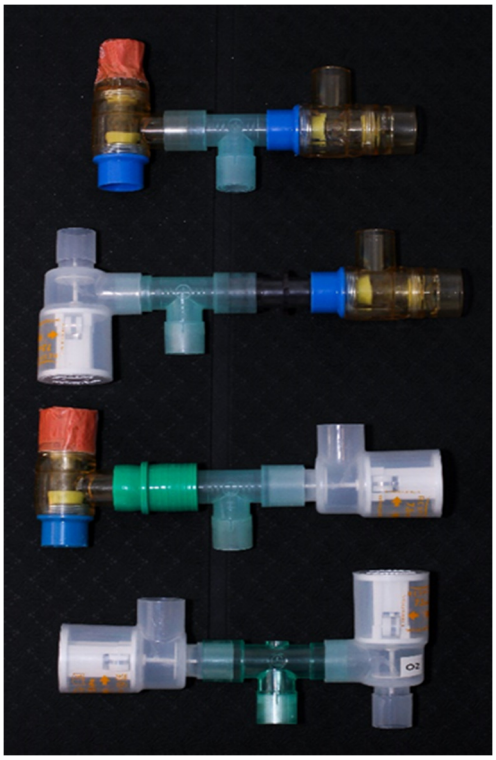

Figure 3-1. The four different resistors. From top to bottom, it is the device with 1) no resistance, 2) inspiratory resistance, 3) expiratory resistance and 4) combined in- and expiratory resistance

inspiratory resistance, only expiratory resistance and no resistance, we therefore switched the expiratory resistance, the inspiratory resistance or both resistances with an AMBU E2 valve (Ambu A/S, Denmark) to ensure that the airflow remained rectified.

Using this concept, we produced four different resistors that provided 1) combined in- and expiratory resistance, 2) inspiratory resistance 3) expiratory resistance and 4) no resistance (Figure 3-1).

To make sure that both the inspiratory and expiratory resistors had a threshold resistance of at least 7.5 cm H_2O when mounted with the T-piece connector, we performed a bench test before use. This test verified a 7.5 cm H_2O resistance through the expiratory resistor (as proclaimed by the manufacturer) and 8.5 cmH_2O through the inspiratory resistor, whereas the T-piece connector and Ambu E2 valve applied less than 1 cm H_2O. The slightly higher resistance during inspiration was considered acceptable as a consequence of the opposite airflow.

3.2. DEFINITIONS USED

Pulse pressure variation (PPV) was defined as $\frac{PP_{max} - PP_{min}}{(\frac{PP_{max} + PP_{min}}{2})}$ x 100, where PP_{max} and PP_{min} is the maximal and minimal difference between systolic and diastolic pressure during the respiratory cycle, respectively (F Michard et al., 1999).

Systolic pressure variation (SPV) was defined as $\frac{SP_{max} - SP_{min}}{(\frac{SP_{max} + SP_{min}}{2})}$ x 100, where SP_{max} and SP_{min} is the maximal and minimal systolic pressure during the respiratory cycle (F Michard et al., 1999).

Peak Height of pulse oximetry plethysmography waveform variations (ΔPH_{POP}) was defined as $\frac{PH_{max} - PH_{min}}{(\frac{PH_{max} + PH_{min}}{2})}$ x 100, where PH_{max} and PH_{min} is the maximal and minimal pulse oximetry plethysmography waveform amplitude during the respiratory cycle.

3.3. FIRST STUDY – THE ANIMAL STUDY

The national animal ethics committee approved the study according to the National Institutes of Health principles of laboratory care. The study was performed at the animal laboratory facility at Aarhus University Hospital, Skejby, Denmark. The study included eight Danish landrace pigs, weighing 25 to 30 kg.

3.3.1. ANESTHESIA

The animals were premedicated shortly after arrival to the laboratory facility. When the animals were calm and sleepy, an intravenous access was established in a superficial ear vein. Subsequently the animals were intravenously anesthetized (Box 3.3.1) and orally intubated to secure the airway prior to instrumentation. To minimize stress and potential discomfort due to the orotracheal tube when anesthesia was reduced to achieve spontaneous breathing, we performed a surgical tracheotomy, placing a Portex 9.0 ID tube (Smiths Medical, London, UK) with local infiltration of 20 ml lidocaine 10 mg/mL to reduce any wound pain.

Box 3.3.1: Anesthesia

Premedication:
Inj. Apazerone 80 mg i.m.
Inj. Midazolam 10 mg i.m.

Induction:
Inj. Remifentanile 1 µg/kg
Inj. Propofole 3 mg/kg.

During monitoring:
Inf. S-ketamine 10 mg/kg/hour
Inf. Remifentanil 0.5 µg/kg/hour
Inf. Propofol 10 mg/kg/hour

During spontaneous breathing:
Inf. S-ketamine 2.5-5 mg/kg/hour
Inf. Propofol 2.5-5 mg/kg/hour

A Servo 900 C ventilator (Siemens-Elema, Solna, Sweden) with volume control modus and a fixed tidal volume of 8 mL/kg was used. We applied a positive end-expiratory pressure of 5 cm H_2O to prevent atelectasis and to ensure sufficient oxygenation, the fraction of inspired oxygen (FiO_2) was set to 1.0.

To ensure a low breathing workload, the inspiratory raise time was 35% and the end-inspiratory pause time was 10%, corresponding to an I:E ratio of approximately 1:1 depending on the ventilatory rate. We adjusted the ventilation to achieve an arterial pH of around 7.4.

After monitoring the animal, we reduced the anesthesia to elicit spontaneous breathing. The remifentanil infusion was stopped, and s-ketamine and propofol infusions were halved and then adjusted to maintain adequate anesthesia, defined as no movement and no reaction to painful stimulation of the anterior toes.

3.3.2. MONITORING

We measured the airway pressure with an air-filled 6 French catheter inserted into the tracheal tube placed so that the end-aperture was 1 cm below the distal opening. The distal esophageal pressure, as a surrogate for the pleural pressure, was measured via a 100-mm latex balloon catheter with a diameter of 36 mm (Viasys Healthcare, Hochberg, Germany), as described by Ingimarsson et al. (2000). We transferred both

pressure signals via transducers (Edwards Lifesciences) to a monitor (S/5 Avance Carestation; GE Healthcare, Chalfont St. Giles, UK).

We placed five invasive catheters during deep general anesthesia: one catheter in the right carotid artery for monitoring intravascular pressure and blood sampling, one catheter (Pulsiocath, 4 Fr., 16 cm; Pulsion Medical Systems, Munich, Germany) in a femoral artery for obtaining the pulse contour CO (PiCCO Monitor, Pulsion Medical Systems, Munich, Germany), one catheter in the right internal jugular vein for blood sampling, and a pulmonary artery catheter (Swan-Ganz CCO mbo CCO/SvO2 7.5 Fr; Edwards Lifesciences, Irvine, CA, USA) through the right external jugular vein to monitor pulmonary artery and central venous pressures as well as to allow blood sampling. An ABL 710 (Radiometer, Copenhagen, Denmark) was used to analyze blood gas variables.

The pulse contour CO was calibrated in triplicate with the transpulmonary arterial thermodilution technique using cold saline injected (3 × 10 mL) immediately after catheter placement and again before each measurement sequence. Additional measurements obtained from the PiCCO device were the intrathoracic blood volume and pulse pressure variation calculated by the monitor (PPV_{PiCCO}).

Furthermore, we continuously monitored the electrocardiogram (ECG), HR and pulse oximetry (placed on the tail) of the animals, and a suprapubic urinary catheter was inserted for monitoring urine production as a parameter of sufficient organ perfusion.

To ensure sufficient perfusion during the instrumentation phase, we infused Ringer's acetate at 20 mL/kg.

3.3.3. EXPERIMENTAL PROTOCOL

After instrumentation, we placed the animal in the prone position for 20 minutes to achieve a hemodynamic steady state before we reduced the anesthesia to achieve spontaneous breathing. When spontaneous trigger breathing was sufficient, we reduced the ventilatory rate to one-half, and the triggering level of the ventilator was set at -1 cm H_2O. Parallel to the increasing spontaneous breathing activity, we successively reduced the pressure support to 2 cm H_2O above the positive end-expiratory pressure. All animals achieved spontaneous breathing while still sufficiently anesthetized.

To ensure sufficient oxygenation during the spontaneous breathing, an anesthesia balloon with a valve regulating the oxygen flow was attached proximal to the inspiratory valve, and the oxygen flow regulated manually, keeping the balloon slightly expanded but still flaccid.

Baseline data were obtained without any resistor applied. Subsequently, we performed the measurements with the animals breathing through the four resistors applied in the same order (randomized by computer between animals) at four levels: 30% hypovolemia, normovolemia, and 20% and 40% hypervolemia. The order of the volemic levels was identical for all animals (Figure 3-2).

Hypovolemia was achieved by venesection of approximately 30% of the estimated blood volume, and hence normovolemia was achieved by replacing the depleted blood with a starch solution (Voluven; Fesenius Kabi, Uppsala, Sweden), and 20% and 40% hypervolemia were achieved by infusion of corresponding volumes of the starch solution. The blood volume of the animal was estimated using the formula 179 × (body weight$^{0.73}$), which is about 8% of the body weight (van Englehardt, 1966), corresponding to venesection of approximately 550–650 mL. The blood removal and each fluid infusion were performed over 5 to 10 minutes. This was followed by a 5-minute stabilization period before a new measurement sequence was performed.

ECG findings, CO, systolic and diastolic arterial blood pressures, HR, PAWP, CVP, intrathoracic blood volume (ITBV), PPV_{PiCCO} and samples of arterial and venous blood gasses were registered 3 minutes after the resistor was changed. The arterial pressure tracing and the airway and esophagus pressure measurements were stored for subsequent determination of SPV and transpulmonary pressure.

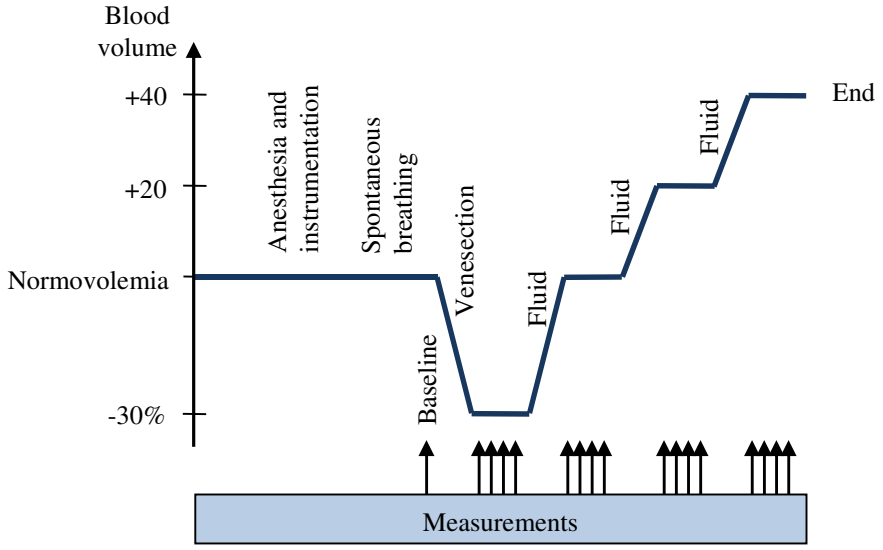

Figure 3-2. Simple overview of the animal study

We defined fluid responsiveness as an increase in the SV of at least 15% after fluid loading. Prior to the experimental study, we decided to manually calculate the SPV from the pressure tracings, because a significant variation in the PiCCO monitor's stated SPV values during controlled ventilation of pigs (Lambert et al., 2007).

The SPV was calculated over six respiratory cycles as described by Michard and colleagues (Michard et al., 2000). The SV was calculated as $\frac{\text{cardiac output}}{\text{heart rate}}$. Airway pressure variations were calculated as the mean values for six respiratory cycles of maximal airway pressure (expiration) minus minimum airway pressure (inspiration). The same calculations were carried out regarding the pleural (esophageal) pressure. The transpulmonary pressure was calculated as the airway pressure minus esophageal pressure at similar time points, and the variations were registered simultaneously with the airway pressure.

At the end of the experiment, the animal was sacrificed by an overdose of thiopental and potassium chloride intravenously.

We used the SigmaStat 3.5 program (Systat Inc., Point Richmond, CA, USA) for statistical analyses. Results are presented as the mean and standard deviation, if not otherwise indicated. $P < 0.05$ was considered statistical significant. Data were not normally distributed (Kolmogorov–Smirnov test).

The overall changes in CO, SV, CVP and ITBV between the different volemic levels for no resistor were analyzed by one-way analysis of variance (ANOVA) and the Tukey test. The changes in PPV and SPV between the different volemic levels with the different resistors in place were analyzed by two-way ANOVA and the Tukey test. The differences in hemodynamics and in respiratory pressures caused by the different resistors at 30% hypovolemia were analyzed by one-way ANOVA and the Tukey test. The relation between the SV and the SPV or PPV was analyzed by linear regression, and the sensitivity and specificity were calculated by standard formulas after inspection of the receiver operating characteristic (ROC) curves (SigmaPlot 11.0; Systat Inc.).

Hemodynamic data were analyzed using two-way ANOVA, with interaction for the different airway resistors. Estimation of central hypovolemia was analyzed using two-way ANOVA and ROC curves.

3.4. THE SECOND STUDY – HEALTHY VOLUNTEERS

This experimental setup focused on the ability to predict central hypovolemia in healthy volunteers breathing spontaneously, which was assessed first by invasive pressure variations (Paper II) and second by non-invasive pulse oximeter plethysmography waveform variations (Paper III).

The National Committee on Health Research Ethics approved the experimental setup (H-4-2010-110), and the study was conducted in accordance with the Helsinki II declaration. Furthermore, the Data Protection Agency approved the experimental setup.

Prior to inclusion, the volunteer was given a written trial description and scheduled a time for verbal information before oral and written informed consent was obtained. All the interviewed volunteers decided to participate and none withdrew their consent during the experiments.

3.4.1. ESTABLISHING A CENTRAL VOLUME DEFICIT

In the first study (Paper I), central hypovolemia was established by exsanguinating the pigs for 30% of their calculated total blood volume. However, this technique could obviously not be used in healthy volunteers. We wanted to use a reversible method to simulate central hypovolemia. Head-up tilt is an established method for simulating central hypovolemia suitable for healthy volunteers.

Therefore, in collaboration with Professor Niels H. Secher, these studies were performed in his research laboratory facility at Rigshospitalet, Copenhagen, Denmark – an international laboratory for human cardiovascular research where central hypovolemia can be simulated using head-up tilt.

According to the literature, head-up tilt causes the cardiac dimensions to be significantly reduced along with a reduction in thoracic electrical admittance and plasma atrial natriuretic peptide (ANP), supporting the notion that a depletion of the central blood volume to more peripheral capacitance vessels takes place, thereby simulating central hypovolemia (Jans et al., 2008). Furthermore, head-up tilt has previously been demonstrated to be able to simulate an acute blood loss above 1000 ml, with an increased heart rate of 30 min^{-1} and with both a sensitivity and specificity of 98%. The maximum heart rate increase after head-up tilt was seen after 1 minute. This indicates that head-up tilt aggravates the central hypovolemia and that the equilibration is brought to completion after approximately 1 minute (Knopp et al., 1980). At the same time, head-up tilt to 50 degrees produces central hypovolemia that results in pre-syncopal symptoms within 1 hour in almost 90% of healthy volunteers. (Madsen et al., 1998).

Thus head-up tilt provokes a reduction in the central blood volume, thereby simulating central hypovolemia (Jans et al., 2008; Madsen et al., 1998). Conversely, 20° head-down tilt was used to expand the central blood volume, thereby simulating mild hypervolemia (Brigden et al, 1950; Matzen et al., 1991).

Using this method, our subjects were exposed to some slight discomfort because the simulated central hypovolemia may result in pre-syncopal symptoms (nausea caused

by drop in blood pressure). If such symptoms developed, the attempt would be interrupted immediately by returning the table to a horizontal position. The symptoms then disappeared within seconds.

3.4.2. THE HEALTHY VOLUNTEERS

For a 1-beta (power) of 0.8 and an alpha (*P*) of 0.05 and assuming an increase in arterial pressure variations as well as pulse oximeter plethysmographic waveform variations of 10% and a SD of 5%, only a minimum of eight subjects was needed because they were their own control.

We recruited 13 healthy volunteers (four women), average age 25 years (range 18–36), through an internet-based site (www.forsøgsperson.dk). Exclusion criteria were pregnancy, breast-feeding or use of any medication.

3.4.3. MONITORING

HR and heart rhythm were monitored by a three-lead ECG and arterial oxygen saturation by pulse oximetry (SpO_2). A peripheral venous access was established and maintained by infusion of isotonic saline (3 mL/h). A 20 G arterial catheter was placed in the brachial artery of the non-dominant arm and connected to a transducer kept at heart level for continuous registration of arterial pressure and SVV (Vigileo-Flotrac™, version 1.07, Edwards Lifesciences, Nyon, Switzerland). Finally, a catheter was placed via a brachial vein and advanced to the subclavian vein. This was connected to a transducer kept at heart level to register CVP and central venous oxygen saturation ($ScvO_2$).

Blood was drawn from the arterial and central venous catheters for blood gas variables and electrolytes (ABL, Radiometer, Copenhagen, Denmark).

Capnography (Philips CO_2 Filterline, ViCare Medical, Denmark) measured the respiratory rate, and SpO_2 was measured by a Philips SpO_2 Sensor M1191BL (ViCare Medical, Denmark) placed on the right third finger of the dominant hand.

3.4.4. EXPERIMENTAL PROTOCOL

During monitoring, the volunteers were placed in the supine position on a tilt table supported by a bicycle saddle, but without support for the feet, and to further minimize venous return, the subjects were requested to abstain from any movement. A tight facemask were placed over nose and mouth (Intersurgical Ltd., Wokingham, Berkshire, UK) fitted with one of the four different resistors (Figure 3-1 and 3-3). Each resistor were applied for 2 minutes (Monnet et al., 2006), with variables obtained in the second minute. Then the table was tilted 45° head-up, accumulating

blood in the legs and providing a central volume deficit, and measurements were repeated with the four resistors. Finally, the table was tilted 20° head-down, simulating slight hypervolemia, and measurements were repeated with the four resistors

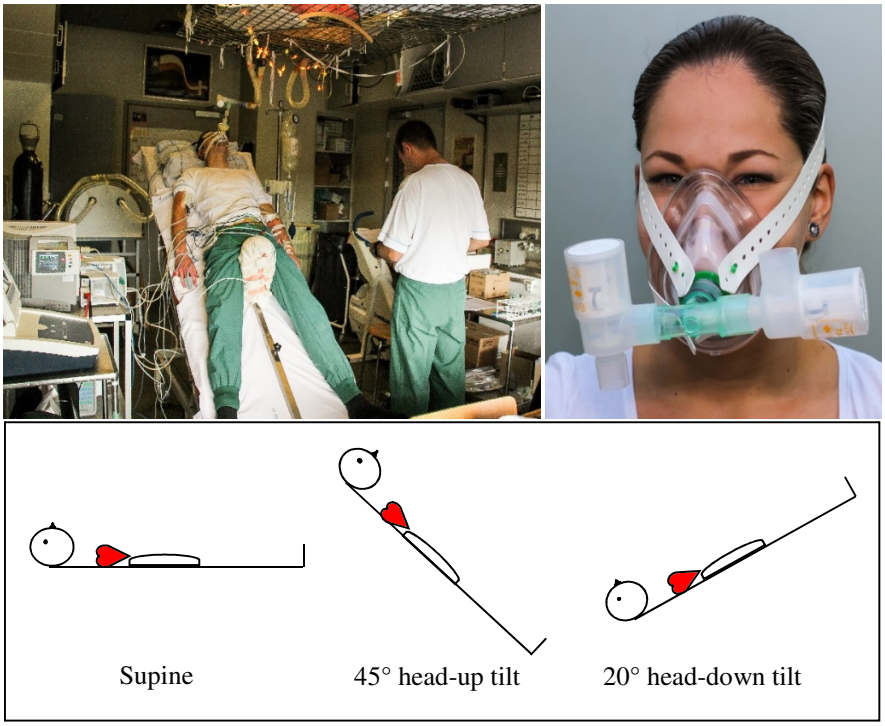

Figure 3-3. Upper left: Volunteer places head-up tilt supported by the bicycle saddle. Upper right: Facemask applied and fitted with the combined in- and expiratory resistors. Bottom: Simple overview of the healthy volunteer study.

For each volunteer, the order of the four resistors was randomized by envelope, whereas the tilt table position was in fixed order: supine, head-up tilt, and head-down tilt (Figure 3-3). We define simulated central hypovolemia as a decrease in CO of at least 10% when the central blood volume was manipulated by head-up tilt. (Feihl & Broccard, 2009a; Magder, 2006; Michard et al., 2000; Michard & Teboul, 2002).

The arterial and oximetry tracings were recorded from the monitor, and each recording was stored individually according to whether the subject was in supine, head-up tilt or head-down tilt position. The data were then extracted from the monitor

by screen dumping a suitable sequence from the recording using QuickTime (Apple Inc., Cupertino, CA, USA). A suitable sequence is a visible arterial pulse curve fluctuation simultaneous with a fluctuation in the capnography curve and, on the same screen dump, a fluctuation of the arterial pulse curve that did not take place during a capnography fluctuation. The file was imported to Adobe Illustrator CS5, where the picture, if needed, was horizontally aligned using one of the horizontal lines of the recording as a guideline. This would also serve as a reference line that could be used for data collection based on the distance from the reference line to a given point on the arterial pressure fluctuation. SP_{min} and SP_{max} were defined as the estimated peaks, whereas PP_{min} and PP_{max} were the estimated lowest points of each of two fluctuations.

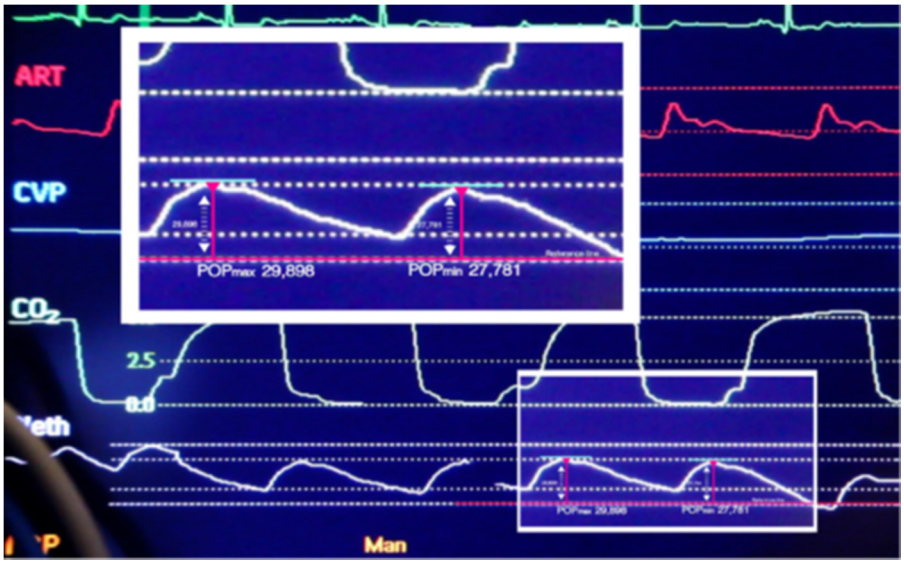

Figure 3-4. Screen dump illustrating measurements of PH_{max} and PH_{min}

A corresponding process was undertaken to calculate ΔPH_{POP} (Figure 3-4). The recorded values were imported to a template in Microsoft Excel for further processing.

For statistical analyses, we used Stata 11.2 (StataCorp LP 1985-2009, Texas, USA) in Studies II and III. Results are presented as the mean and standard deviation, if not otherwise indicated. $P < 0.05$ was considered significant. Due to the small number of subjects in the studies, data were assumed not to be normally distributed (QQ-plots).

The overall changes in CO, SV and CVP between the different volemic levels for no resistor were analyzed by one-way ANOVA and the *t*-test for repeated measurements. The overall changes in PPV, SPV, ΔPH_{POP} and PVI® between the different volemic levels with the different resistors in place were analyzed by two-way ANOVA and the *t*-test for repeated measurements. The differences in hemodynamics and in respiratory pressures caused by the different resistors at 30% hypovolemia were analyzed by one-way ANOVA of variance and the *t*-test for repeated measurements. The relation between the SV and the SPV, PPV, ΔPH_{POP} or PVI® was analyzed by linear regression, and the sensitivity and specificity were calculated by standard formulas after inspection of the ROC curves (SigmaPlot 11.0; Systat Inc.).

Hemodynamic data regarding the interaction between the different airway resistors were analyzed using two-way ANOVA. Estimation of central hypovolemia was analyzed using two-way ANOVA and ROC curves.

CHAPTER 4. RESULTS

4.1. FIRST STUDY – THE ANIMAL STUDY (PAPER I)

Draining 30% of the blood volume, corresponding to approximately 550–650 mL, is obviously a model for hypovolemia. When achieved, this condition showed significantly reduced CO, SV, CVP and ITBV compared to normovolemia when the animals were breathing without any resistor. Between normovolemia and hypervolemia, there were only minor or insignificant changes (Table 4-1).

Table 4-1. Hemodynamic and respiratory measurements at different volemic levels for the animals without any resistor applied.

	Hypovolemia	**Normovolemia**	**Hypervolemia**	
	-30%	**0%**	**+20%**	**+40%**
CO (L/min)	3.2 ± 0.7	7.5 ± 1.6*	7.9 ± 2.0	7.7 ± 2.2
SV (mL)	24 ± 5	65 ± 11*	63 ± 10	62 ± 10
CVP (mm Hg)	0 ± 2	6 ± 2*	7 ± 2*	8 ± 2*
ITBV (mL)	485 ± 88	814 ± 177*	849 ± 156	924 ± 213
SvO_2	0.89 ± 0.05	0.99 ± 0.04*	1 ± 0.02	0.98 ± 0.04
PaO_2 (kPa)	57.41 ± 5.25	66.36 ± 5.13*	55.02 ± 7.77*	62.69 ± 9.58
$PaCO_2$ (kPa)	7.23 ± 1.45	7.39 ± 1.37	7.37 ± 1.36	7.30 ± 1.38
Lactate (mmol/L)	1.2 ± 1.3	2.4 ± 1.8	1.9 ± 1.2	1.2 ± 0.8
BE (mmol/L)	4.1 ± 1.5	2.2 ± 1.7	2.2 ± 1.6	3.0 ± 1.9

*CO Cardiac output, SV stroke volume, CVP central venous pressure, ITBV intrathoracic blood volume, SvO_2 central venous oxygen saturation, PaO_2 arterial oxygen parietal pressure, $PaCO_2$ arterial carbon dioxide parietal pressure and BE base excess. Mean ± standard deviation. * $P < 0.05$ compared with the previous volemic level.*

SvO_2 decreased from normovolemia to 30% hypovolemia, whereas $PaCO_2$ as well as base excess and lactate were stable during the experiment, with no significant changes between the volemic levels. PaO_2 varied significantly between the volemic levels. Because of the very high oxygen tension, this variation was not clinically interesting.

Applying the different resistors, the airway and esophageal pressure oscillations were generally amplified (Table 4-2). Compared to the situation with no resistor applied, the transpulmonary pressure oscillations tended to be somewhat higher when the combined in- and expiratory resistors were applied.

At 30% hypovolemia, compared to the situation with no resistor applied, all the different resistors amplified SPV, whereas no changes were found during normovolemia or 20% and 40% hypervolemia.

Table 4-2. Animal respiratory pressures and hemodynamics at 30% hypovolemia with the different resistors.

	No resistor	Inspiratory	Expiratory	In- and Expiratory
Airway Pressure (AP)				
Inspiratory (cmH_2O)	-1 ± 4	-7 ± 2*	-3 ± 4	-5 ± 2*
Expiratory (cmH_2O)	3 ± 5	1 ± 2	5 ± 2	5 ± 2
ΔAP (cmH_2O)	4 ± 1	8 ± 1*	8 ± 2*	11 ± 4*
Esophageal Pressure (EP)				
Inspiratory (cmH_2O)	-4 ± 2	-9 ± 3*	-6 ± 3	-8 ± 2*
Expiratory (cmH_2O)	-2 ± 1	-3 ± 3	-1 ± 2	-2 ± 3
ΔEP (cmH_2O)	3 ± 1	6 ± 1*	5 ± 2*	6 ± 2*
Transpulmonary Pressure (TP)				
Inspiratory (cmH_2O)	3 ± 4	2 ± 4	4 ± 2	3 ± 4
Expiratory (cmH_2O)	5 ± 5	5 ± 4	6 ± 1	7 ± 3
ΔTP (cmH_2O)	1 ± 2	3 ± 1	2 ± 1	4 ± 3*
Heart rate (min^{-1})	130 ± 21	133 ± 12	138 ± 18	137 ± 23
Cardiac output (l/min)	3.2 ± 0.7	3.3 ± 0.4	3.3 ± 0.5	3.2 ± 0.5
Stoke volume (ml)	25 ± 5	25 ± 4	24 ± 4	24 ± 5
PAWP insp (mmHg)	-2 ± 5	-7 ± 4	-3 ± 4	-5 ± 3
PAWP exp (mmHg)	4 ± 3	6 ± 2	8 ± 2*	7 ± 2
MAP (mmHg)	55 ± 6	59 ± 5	60 ± 7	59 ± 5
CVP (mmHg)	0 ± 2	-1 ± 3	1 ± 3	1 ± 3

*PAWP exp pulmonary artery wedge pressure obtained during expiration, PAWP insp pulmonary artery wedge pressure obtained during inspiration, MAP mean arterial pressure, CVP central venous pressure. Mean ± standard deviation. * $P < 0.05$ compared to no resistor applied.*

Regardless of volemic level, the inspiratory and the in- and expiratory resistor amplified PPV (Table 4-3).

Applying these different resistors had no influence on CO, SV, MAP and HR rate regardless of volemic level, whereas the variations in PAWP were slightly related to the swings in airway pressure (r^2 0,12) (Table 4-2). SPV was similar at all volemic levels, whereas PPV was significantly higher at -30% hypovolemia (Table 4-3).

Table 4-3. SPV and PPV with the different resistor applied at different volemic levels for the animals.

	Hypovolemia	Normovolemia	Hypervolemia	
	-30%	**0%**	**+20%**	**+40%**
SPV – No resistor (%)	5 ± 2	3 ± 2	2 ± 1	2 ± 1
SPV – Inspiratory (%)	10 ± 5†	4 ± 2*	5 ± 2	4 ± 2
SPV – Expiratory (%)	11 ± 2†	4 ± 2*	4 ± 1	3 ± 2
SPV – In- and Expiratory (%)	13 ± 5†	5 ± 3*	5 ± 2	4 ± 2
PPV – No resistor (%)	17 ± 5	12 ± 2*	12 ± 4	12 ± 1
PPV – Inspiratory (%)	25 ± 6†	16 ± 4* †	16 ± 6 †	15 ± 5†
PPV – Expiratory (%)	25 ± 6	13 ± 6*	12 ± 3	11 ± 3
PPV – In- and Expiratory (%)	26 ± 7†	14 ± 6* †	14 ± 5†	13 ± 6†

*SPV systolic pressure variations and PPV pulse pressure variation are shown with the different resistors at the four volemic levels. Mean ± standard deviation. * P < 0.05 compared with previous volemic level. † P < 0.05 compared with 'no resistor' at the same volemic level.*

Table 4-4 shows the correlation between changes in SV and SPV or PPV using the different resistors. r^2 was generally higher when the expiratory resistor was applied with the highest r^2 (0.83) for SPV.

When fluid responsiveness was defined as an increase in SV of ≥ 15%, the sensitivity and specificity for SPV and PPV are as shown in Table 4-5. The highest sensitivity was found with the expiratory resistor applied. We found a sensitivity of 100% and specificity of 100% for a SPV cut-off value of 7% with the expiratory resistor applied, and 63% and 94%, respectively, for a cut-off value of 4% without any resistor. Corresponding values for PPV were 100% and 81%, respectively, and 88% and 69%, respectively, for PPV cutoff-values of 16% and 13%, respectively

Table 4-4. ***r***-squared for SPV and PPV versus change in SV.

	SPV	PPV
No resistor	0.37	0.37
Inspiratory resistor	0.45	0.36
Expiratory resistor	0.83	0.52
In- and expiratory resistor	0.50	0.31

r^2 obtained by linear regression for systolic pressure variation (SPV) or pulse pressure variation (PPV) versus increase in stroke volume by a subsequent fluid loading without any resistor and with the inspiratory, expiratory, and inspiratory and expiratory resistors.

The linear regression for systolic pressure variation and pulse pressure variation before fluid administration versus change in stroke volume following fluid loading without and with the expiratory resistor is shown in Figure 4-1. All measurement points are used in the regression analyses, and the regression lines are indicated. The horizontal lines depict the relevant change in stroke volume (15%), and the vertical lines depict the cut-off values used.

Table 4-5. Sensitivity, specificity, positive and negative predictive values for systolic pressure variation and pulse pressure variation with the different respiratory interventions

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
SPV –No resistor	63	94	83	83
SPV – Inspiratory	88	88	78	93
SPV – Expiratory	100	100	100	100
SPV – In- and expiratory	75	94	86	88
PPV – No resistor	88	69	58	92
PPV – Inspiratory	88	69	58	92
PPV – Expiratory	100	81	73	100
PPV –In- and expiratory	88	94	88	94

SPV systolic pressure variation, PPV pulse pressure variation.

Figure 4-1 also shows the receiver operating characteristic (ROC) curves for SPV (Panels A and B) and PPV (Panels C and D) for predicting a 15% increase in stroke volume by subsequent fluid loading using the different respiratory resistors

4.2. THE SECOND STUDY – HEALTHY VOLUNTEERS (PAPERS II AND III)

Thirteen healthy volunteers 25 yrs. (range 18–36) of age were included (four females). Their average weight was 73 (±13; mean ±SD) kg and height 178 (±10) cm, giving a body mass index of 23.0 (±3.2) kg/m^2 and a body surface area of 1.9 (±0.2) m^2.

The hemodynamic response when the volunteer test subjects changed position from supine to 45° head-up tilt showed a significant decrease in CO, SV, systolic blood pressure, diastolic blood pressure and $ScvO_2$. HR increased significantly ($P < 0.05$). Similarly, changing position from supine to 20° head-down tilt caused a significant decrease in CO, SV and systolic pressure but no changes in HR, diastolic pressure or $ScvO_2$ (Table 4-6).

For 10 of the volunteers, the decrease in CO from supine to head-up tilt was at least 10%.

There was no significant (P between 0.17 and 0.46) difference between those in whom decreased CO ≥ 10% and those in whom did not even though those in whom a decrease was not seen tended to be younger and smaller (three females versus one; aged 26 ±5 versus 21 ±0.6; height 178.7 ±9.5 versus 173.7 ±11.9; weight 75 ±12 versus 65 ±13; BMI 23.5 ±3.5 versus 21.4 ±1.6 and BSA 1.93 ±0.18 versus 1.78 ±0.24).

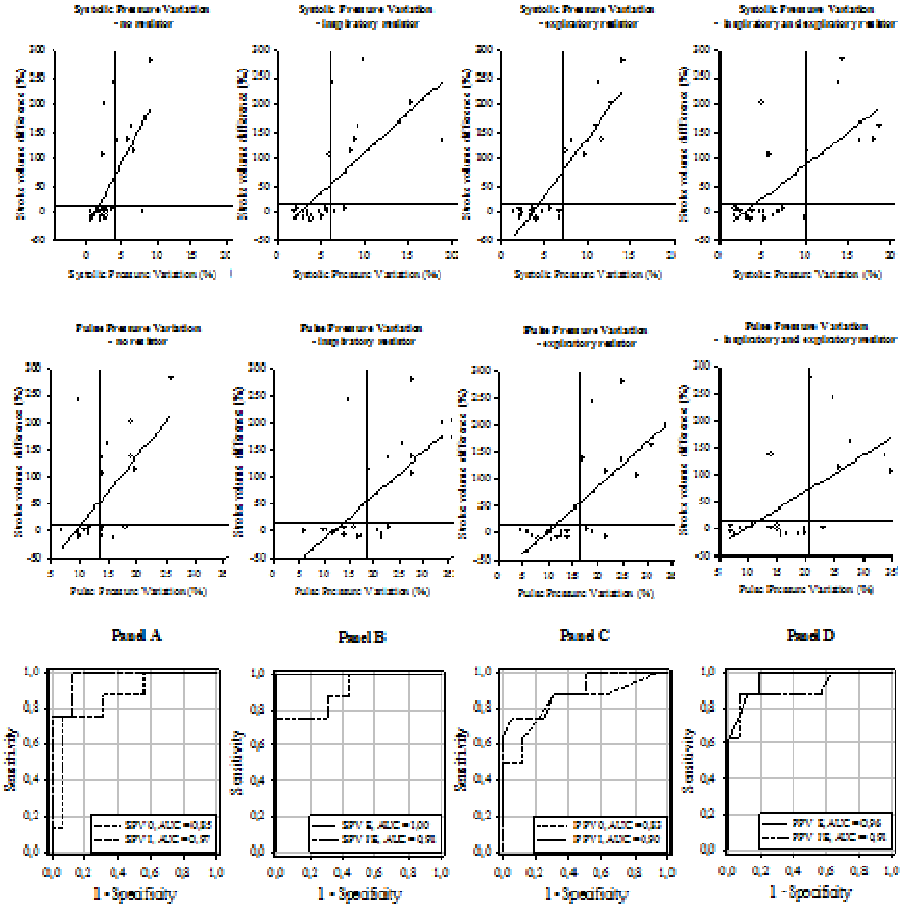

Figure 4-1. The linear regression for systolic pressure variation (SPV) and pulse pressure variation (PPV). See text for details. Panel A-D is the ROC curves for SPV and PPV. 0 is no resistor applied; I is inspiratory resistor applied; E is expiratory resistor applied and IE is combined in- and expiratory resistors applied.

There were no changes in respiratory rate or SpO_2 between the three body positions and only small changes in arterial blood gas variables. There were no significant interactions between position and respiratory resistor application.

Table 4-6. Hemodynamic and respiratory variables at the three volemic levels regardless of respiratory resistor(s) applied.

	Supine position	Head-Up Tilt	Head-Down Tilt
Cardiac output (L/min)	5.8 ± 2.9	4.0 ± 1.8*	5.1 ± 2.2*
Stroke Volume (mL)	91 ± 46	55 ± 24*	81 ± 36*
Systolic blood pressure (mm Hg)	127 ± 14	121 ± 13*	120 ± 11*
Diastolic blood pressure (mm Hg)	64 ± 7	69 ± 6*	65 ± 6
Heart rate (min^{-1})	65 ± 11	75 ± 13*	65 ± 11
$ScvO_2$	0.79 ± 0.07	0.68 ± 0.13*	0.79 ± 0.09
Respiratory rate (min^{-1})	10 ± 4	10 ± 4	10 ± 3
SpO_2 (%)	99 ± 2	99 ± 1	99 ± 2
Ph	7.43 ± 0.03	7.45 ± 0.04*	7.44 ± 0.04
PaO_2 (kPa)	14.1 ± 1.6	14.3 ± 1.0	14.7 ± 1.6*
$PaCO_2$ (kPa)	5.0 ± 0.6	4.6 ± 0.7*	4.8 ± 0.7*

$ScvO_2$ Central venous oxygen saturation obtained via a catheter placed in the pulmonary artery. SpO2 Peripheral oxygen saturation. PaO_2 Arterial oxygen partial pressure (kPa). $PaCO_2$ Arterial carbon dioxide partial pressure (kPa). Mean ± standard deviation.
** P < 0.05 compared to the supine position. There was no interaction between position and application of resistors.*

4.2.1. PAPER II

Regardless of tilt table position, the combined inspiratory and expiratory resistors increased SVV, SPV and PPV, while the inspiratory resistor increased SPV and PPV and the expiratory resistor only SPV (Table 4-7). Sensitivity, specificity, positive predictive value, negative predictive value, area under the curve (AUC), and optimal cut-off for these variables are shown in Table 4-8.

Table 4-7. Arterial pressure variations with different airway resistors during head-up tilt.

	No resistor (%)	Inspiratory resistor (%)	Expiratory resistor (%)	In- and expiratory resistor (%)
SPV	17 ± 11	26 ± 14*	26 ± 18*	28 ± 14*
SVV	15 ± 8	19 ± 8	23 ± 7*	29 ± 12*
PPV	7 ± 4	9 ± 6	8 ± 6	10 ± 6*

*SPV systolic pressure variation. SVV stroke volume variation. PPV pulse pressure variation Mean ± standard deviation. * P < 0.05 compared to no resistor.*

The best prediction of a central volume deficit (a 10% reduction in CO) was obtained with SPV when the combined resistors were applied. For that configuration, SPV tended to increase (from 17 (±11)% to 28 (±14)%) and revealed a sensitivity of 78% and specificity of 100%, with a positive predictive value of 100%, a negative predictive value of 60%, and an AUC of 0.96 (confidence interval 0.86-1.00) (Figure 4-2) when SPV was larger than 37%.

Table 4-8. Sensitivity, specificity, positive predictive value and negative predictive value using 10% difference in cardiac output between supine position to head-up tilt to define central hypovolemia

Arterial pressure variation and applied resistor	AUC	Optimal cut-off (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
SVV						
No resistor	0.73 (0.44;1.00)	13	60	100	100	43
Expiratory	0.82 (0.57-1.00)	28	70	100	100	50
Inspiratory	0.75 (0.43-1.00)	18	50	100	100	38
In- / exp.	0.58 (0.27-0.89)	31	40	100	100	33
SPV						
No resistor	0.43 (0.07-0.80)	19	20	100	100	27
Expiratory	0.70 (0.34-1.00)	33	70	67	88	40
Inspiratory	0.67 (0.18-1.00)	36	80	67	89	50
In- / exp.	0.96 (0.86-1.00)	37	78	100	100	60
PPV						
No resistor	0.83 (0.60-1.00)	7	80	100	100	60
Expiratory	0.73 (0.35-1.00)	4	70	67	88	40
Inspiratory	0.73 (0.39-1.00)	7	50	100	100	38
In- / exp	0.59 (0.22-0.96)	12	67	67	86	40

AUC Area Under the Curve with confidence interval. SVV stroke volume variations.SPV systolic pressure variations. PPV pulse pressure variations. In- / exp. Combined inspiratory and expiratory resistor.

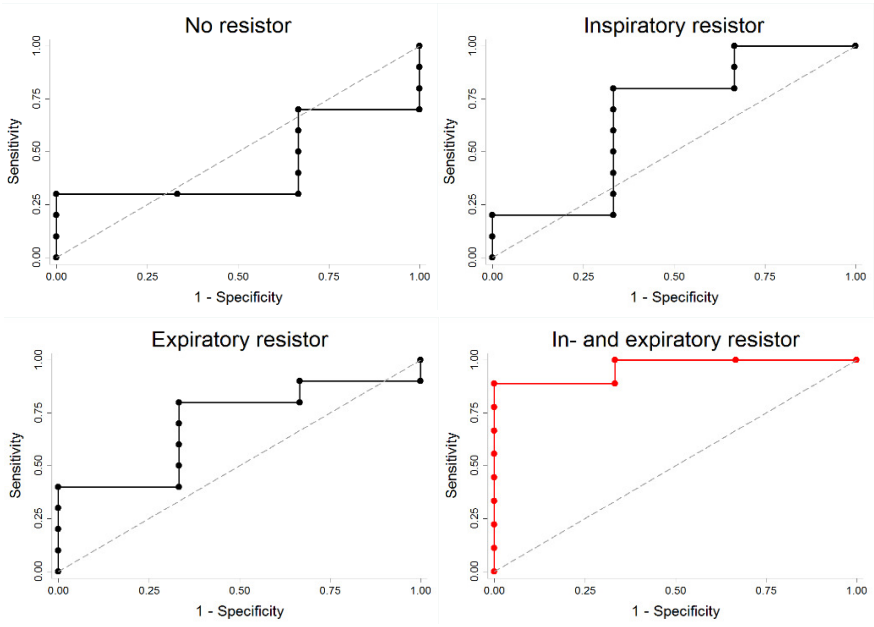

Figure 4-2. Receiver operating characteristic (ROC) curves during head-up tilt for systolic pressure variation (SPV) with the four different respiratory resistors.

4.2.2. PAPER III

The inspiratory resistor, expiratory resistor and the combination of both resistors tended to increased PVI® during head-up tilt, while there was no change between resistors during supine or head-down tilt. ΔPH_{POP} was not enhanced by any of the respiratory resistor (Table 4-9).

Sensitivity, specificity, positive predictive value, negative predictive value, AUC, and optimal cut-off for these variables are shown in Table 4-10. The best prediction of a 10% reduction in CO was obtained with ΔPH_{POP} with no resistor applied. For that configuration, ΔPH_{POP} revealed a sensitivity of 70% and specificity of 100%, with a positive predictive value of 100%, a negative predictive value of 40%, and an AUC of 0.80 (Figure 4-3) when ΔPH_{POP} was larger than 14%.

Furthermore, there was no correlation between ΔPH_{POP} or PVI® and PPV, SPV or SVV

Table 4-9. Airway resistor influence of PVI® and ΔPH_{POP}.

	No resistor (%)	**Inspiratory resistor (%)**	**Expiratory resistor (%)**	**Inspiratory/expiratory resistor (%)**
PVI®				
Supine position	28 ± 9	29 ± 9	30 ± 9	29 ± 7
Head-up tilt	24 ± 10	29 ± 9*	32 ± 8*	35 ± 7*
Head-down tilt	30 ± 13	31 ± 9	28 ± 10	30 ± 7
ΔPH_{POP}				
Supine position	12 ± 5	7 ± 6	11 ± 7	11 ± 4
Head-up tilt	10 ± 5	12 ± 6	10 ± 7	11 ± 7
Head-down tilt	11 ± 9	12 ± 6	10 ± 5	13 ± 8

*Mean ± standard deviation. * $P < 0.05$ compared to no resistor.*
PVI® Pleth variability index. ΔPH_{POP} Variation in Peak Height of Pulse oximeter plethysmographic waveform.

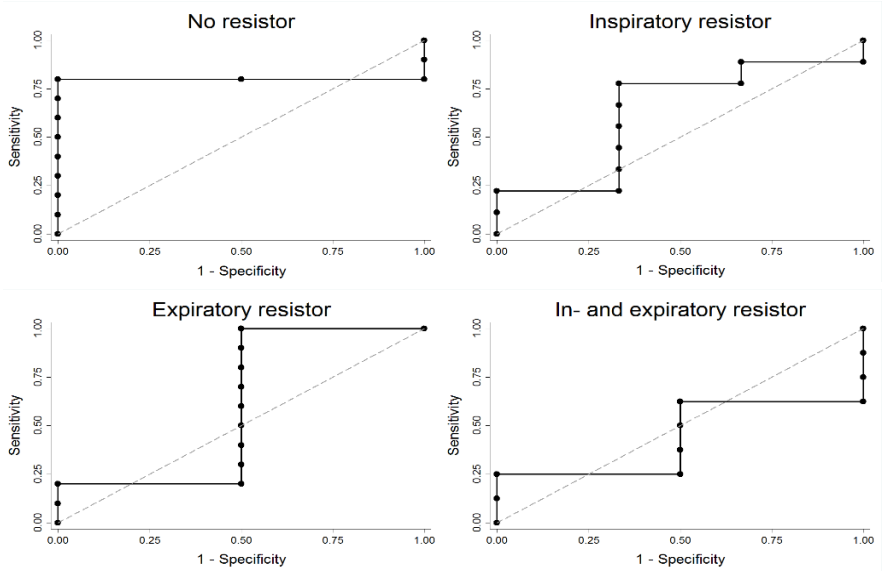

Figure 4-3. Receiver operating characteristic (ROC) curves for ΔPHPOP with the four respiratory resistors.

Table 4-10. Sensitivity, specificity, positive predictive value and negative predictive value using a 10% difference in cardiac output between supine position and head-up tilt defining central hypovolemia.

Applied resistor	AUC	Optimal cut-off (%)	Sensi-tivity (%)	Speci-ficity (%)	Positive predictive value (%)	Negative predictive value (%)
PVI®						
No resistance	0.65 (0.27-1.00)	28	70	67	88	40
Inspiratory	0.67 (0.11-1.00)	39	78	67	88	50
Expiratory	0.68 (0.15-1.00)	41	90	67	90	67
In- / exp.	0.43 (0.00-1.00)	22	90	33	82	50
ΔPH_{POP}						
No resistance	0.80 (0.54-1.00)	14	70	100	100	40
Inspiratory	0.63 (0.18-1.00)	9	78	67	88	50
Expiratory	0.60 (0.00-1.00)	32	100	50	91	100
In- / exp.	0.44 (0.00-0.91)	8	63	50	83	25

AUC = Area Under the Curve with confidence interval. PVI® Pleth variability index. ΔPH_{POP} Variation in Peak Height of Pulse oximeter plethysmographic waveform. In- / exp. combined inspiratory and expiratory resistor.

CHAPTER 5. DISCUSSION

My Ph.D. project evaluated the hypothesis that augmentation of the intrathoracic pressure oscillations by inspiratory/expiratory resistors would enhance arterial pressure variations and pulse oximetry plethysmographic variations during central hypovolemia during spontaneous breathing. We found that when test animals breathed spontaneously through the combined in- and expiratory resistor, the transpulmonary pressure oscillations were significantly amplified during simulated hypovolemia and that both SPV and PPV were enhanced when different resistor were applied (Paper I). Almost the same pattern was seen in the healthy volunteers (Paper II). In contrast, for the non-invasive parameters, we only found PVI® to be enhanced when the resistors were applied (Paper III). SPV and PPV predicted fluid responsiveness with good sensitivity and specificity (Paper I), and SPV also detected central hypovolemia with acceptable specificity and sensitivity (Paper II). The non-invasive variables ΔPH_{POP} and PVI® were not able to detect central hypovolemia at all (Paper III).

The important clinical background for my study was that central hypovolemia is very difficult to detect in spontaneously breathing patients both by clinical signs and by simple pressure measurements. However, it is essential to detect hypovolemia early in order to correct the circulatory impairment and the resultant inadequate oxygen transport to the tissues and organs. If this is not done urgently, the patient can develop a severe shock condition, which may be irreversible. Therefore, methods to detect hypovolemia are of outmost importance. Historically CVP has been the most common method used to detect hypovolemia. But it is not reliable and cannot be used with confidence (Berlin & Bakker, 2015). The only method that has been shown to reliably detect the volemic status of the patient is passive leg raising followed by assessment of pulse pressure variations or exhaled end-tidal CO_2 (X. Monnet et al., 2006; Xavier Monnet et al., 2013). This method is based on the hypothesis that a change in preload by centralization of volume by leg raising will increase SV/CO output if the patient is hypovolemic but not if the patient is normo- or hypervolemic according to the Frank–Starling law. Our idea was that manipulating the preload by increasing the intrathoracic pressure during expiration and decreasing the intrathoracic pressure during inspiration by the use of an inspiratory/expiratory resistor would move the OP_{CIRC} on the Frank Starling curve if the patient was hypovolemic. We are aware that this hypothesis has not been discussed or explore in association with spontaneous breathing. However, it is well known that the severe increase in intrathoracic pressure in patients with pneumothorax or cardiac tamponade will induce paradoxical pulses (Cohn et al., 1967; Pinsky, 2007), and in addition, that breathing through an inspiratory resistance will improve venous return in hypovolemic animals (Lurie et al., 2004).

In addition, the increased intrathoracic pressure caused by fully controlled mechanical ventilation during inspiration will induce arterial pressure variations that can be used to detect hypovolemia (Bendjelid & Romand, 2003; Michard, 2005; Perel, 1998). Here the ventilator-induced cyclic changes in intrathoracic pressure produce significant arterial pressure variations if the circulation is fluid responsive. However, this requires that the tidal volume is above 8 ml/kg lean body weight (De Backer et al., 2005; De Backer & Scolletta, 2011) (which is a higher level than recommended in critically ill, ventilated patients (Girard, 2007)) and that the patient has a normal right heart function without atrial fibrillation. Furthermore, there may not be any spontaneous breathing activity (Bendjelid & Romand, 2003; Michard, 2005; Perel, 1998). If the patient is breathing in a spontaneous ventilator mode, the arterial pressure variations will not give any information about fluid responsiveness (Heenen et al., 2006). This might be explained by the opposite and minor transpulmonary pressure oscillations. During spontaneous breathing, the intrathoracic pressure oscillations are simply too small. Therefore, we hypothesized that enhancing these intrathoracic pressure oscillations during spontaneous breathing might bring back the arterial pressure variation and hence the ability to predict fluid responsiveness and central hypovolemia.

Theoretically, an inspiratory resistor will increase the negative intrathoracic pressure and improve right heart filling by reducing the pressure difference between the vena cava and the right atrium, in other words, increase Q_{RV}. Thus, after a few heartbeats (coinciding with the expiration), left heart filling increases and hence stroke volume. An expiratory resistor will increase the intrathoracic pressure during expiration by opposing venous return to the right heart and reducing Q_{RV}. Thus, after a few heartbeats (coinciding with inspiration), this will decrease left heart filling and hence the stroke volume. A combination of these two resistors ought to be even more effective. As described in the section “3.1 The Resistors” (p. 25), we developed three simple resistors because we could not find any commercial devices for this purpose since no previously published studies have explored this approach. Without enhancing the intrathoracic pressure oscillations, Soubier et al. found in spontaneously breathing, hemodynamically unstable patients a sensitivity and specificity for predicting the effect of a subsequent fluid administration of 63% and 92%, respectively for PPV, and 47% and 92% for SPV (Soubrier et al., 2007). In the same study, they also investigated whether a forceful inspiration and expiration (without any resistance) would improve the ability of SPV and PPV to predict fluid responsiveness (Soubrier et al., 2007). However, sensitivity was even lower with this maneuver. Subsequently, in an editorial to the paper by Soubier et al., de Backer and Pinsky discussed whether manipulation of the intrathoracic pressure by a Valsalva maneuver, that is a forceful expiration against a resistance, could be used to generate arterial pressure variations that could predict fluid responsiveness (Soubrier et al., 2007). In fact, this has been shown in a study by Garcia et al. (Monge García et al., 2009). A Valsalva maneuver causes an immediate increase in cardiac output by squeezing blood from the pulmonary circulation to the left heart, but this is very

quickly followed by a marked reduction in cardiac output due to reduced right heart filling (Zema et al., 1980). This problem is that even though the Valsalva maneuver may induce a pronounced drop in blood pressure during hypovolemia, it may be difficult to be performed by a patient distressed by circulatory compromise or pain, and it may induce changes in heart rate. Moreover, it may generate quite different intrathoracic pressures depending on the patient's efforts.

On the other hand, we hypothesized that breathing against an expiratory resistance could give rise to a short, intermittently uniform Valsalva maneuvers. This would cyclically reduce right heart filling and induce variations in arterial blood pressure that theoretically would be more pronounced when the circulation is volume depleted.

In this study, we used an inspiratory/expiratory resistor with a pressure threshold of 7.5 cm water. The pressure level was chosen arbitrarily, i.e. the commercial resistors were set on this threshold pressure, and we anticipated that this pressure should be clinically tolerable for patients. Indeed, the volunteers did not complain about difficulties with breathing with this level of threshold pressure. Higher threshold pressures would probably give more pronounced intrathoracic pressure oscillations that could produce arterial pressure variations at a lower degree of central hypovolemia, but we believe that high pressures would not be tolerable in the clinical setting. In both the animals and the volunteers, the airway pressure oscillations of 15 cm water were adequate to detect central hypovolemia, defined as a decrease in cardiac output of 10%. However, in the animals, the highest sensitivity and specificity were obtained with only expiratory resistance. The increased expiratory pressure, as shown by Lambert et al., may in many circumstances be enough to detect an incipient hypovolemia (Lambert et al., 2007), but it is important to recognize that pigs have a prominent Hering-Breuer reflex (van Englehardt, 1966), decreasing the respiratory rate. Thus, at PEEP, the respiratory rate is lower, prolonging the expiratory phase and therefore the duration of reduced venous return to the heart.

We use the term central hypovolemia, because we induced hypovolemia in the pigs by bleeding and in the volunteers by the head-up position on a tilt table. In both of these settings, cardiac output was increased by correcting the hypovolemia, i.e. the subjects were fluid responsive. Since it is difficult to assess central functional hypovolemia in a clinical setting, fluid responsiveness has commonly replaced the term central hypovolemia. Fluid responsiveness indicates that a cardiac output increases by fluid administration. In the animals, we re-administered a fluid volume corresponding to the amount of blood removed, and thus we knew exactly the amount of fluid administered. However, in the volunteers we were only certain that the central hypovolemia had been corrected when we changed their body position, and we did not know the exact amount of blood that was centralized by this procedure. However, in previous studies in the same laboratory, it has been found that about 300–800 mL blood (Pawelczyk et al., 1994) will be removed from or added to the central

compartment by tilting the table. This corresponds to the amount of fluid administered when testing fluid responsiveness in patients (Michard et al., 2000; Soubrier et al., 2007).

In the animal study, we simply exsanguinated the pigs for 30% of their estimated total blood volume – corresponding to 550–650 mL in our animals (van Englehardt, 1966). That the pigs actually became hypovolemic was confirmed by a significant reduction in CO, SV, CVP, ITBV and SvO_2 (Table 4-1). All the animals tolerated this hypovolemia, except for one that became severely hypotensive after induction of anesthesia, but before the main experiment, and needed stabilization by a bolus of Ringer's acetate 10 ml/kg. This animal was not an outlier; however, it was the only non-responder.

During the healthy volunteer study, we used 45° head-up tilt to simulate central hypovolemia. Head-up tilt (Jans et al., 2008; Knopp et al., 1980; Matzen et al., 1991)like lower body negative pressure, especially when combined with heat stress, (Wilson et al., 2009) reduces the central blood volume and has the advantage compared to exsanguination that the intervention can be terminated immediately if the subject becomes ill.

We performed the head-up tilt using a tilt table on which the volunteers were supported by a bicycle saddle but without any support for the feet. Furthermore, they were requested to abstain from any movement. This was to minimize the venous return from the legs by muscle pumping. That central hypovolemia actually was established by head-up tilt was confirmed by a significant decrease in CO, SV, systolic and diastolic blood pressure and $ScvO_2$, while HR significantly increased. Jans Ø, et al. also found that the cardiac dimensions are reduced along with a reduction in thoracic electrical admittance and plasma atrial natriuretic peptide (ANP) during head-up tilt, supporting depletion of the central blood volume as the root cause (Jans et al., 2008).
All the healthy volunteers tolerated the head-up tilt-induced central hypovolemia very well.

We defined fluid responsiveness in the animal study as an increase in SV of at least 15%, and in the healthy volunteer study, we defined central hypovolemia as at least a 10% drop in CO (Feihl & Broccard, 2009a; Magder, 2006; Michard et al., 2000; Michard & Teboul, 2002). The reason for using SV and a higher threshold to define fluid responsiveness in the animals was that these young animals have a relative high heart rate (115 ±16 min^{-1} when normovolemic) compared to humans (van Englehardt, 1966). By these definitions, seven of eight pigs were responders and 10 of 13 volunteers were responders. However, draining a larger volume of blood from an animal and tilting the volunteers to a more vertical position might have altered our findings because of more severe hypovolemia. Even though a head-up tilt to 50 degrees produces central hypovolemia resulting in pre syncopal symptoms within 1

hour in almost 90% of healthy volunteers and the slope of the tilt probability curve seems almost linear (Madsen et al., 1998), we chose 45° head-up tilt, seeking a compromise between established hypovolemia and the comfort of the volunteers. Furthermore, venous pooling between 50° and 90° differs very little (Pawelczyk et al., 1994).

Likewise, using, for example, a 20% or 25% change in SV or CO to define responders might potentially enhance our findings in favor of the use of the respiratory resistors.

Especially for the head-up tilt, the degree of hypovolemia might have been dynamic and changed from the first measurements to the last because of further sequestration of blood in the capacitance vessels and fluid in the interstitial spaces.

We obtained the variables after a 10-minute equilibration period in each body position. A shorter period, e.g. 1 minute, is probably enough to complete venous sequestration in the capacitance vessels. Knopp R, et al. (1980) found that the maximum heart rate increase after head-up tilt was after 1 minute. This indicates that the equilibration is brought to completion after approximately 1 minute (Knopp et al., 1980).

Since this was a novel approach using a homemade device (constructed however of approved parts), we started the investigation with an animal study. We found that the inspiratory resistor significantly enhanced both the airway and esophageal pressure during inspiration, and a similar result was seen for the expiratory resistor during expiration. Since both the airway and esophageal (pleural) pressures were almost equally enhanced, there was only a minor enhancement of the transpulmonary pressure (Table 4-2). However, due to anatomy, the caval veins should be more affected by the pleural pressure (as estimated by the esophageal pressure) than by the airway or the transpulmonary pressures, and thus Q_{RV} should be primarily dependent on the difference between the venous pressure and the pleural pressure.

We found that SPV, PPV and SVV were more or less enhanced by the different resistors (Tables 4-4 and 4-7), and some combinations resulted in improved prediction of central volume deficit and fluid responsiveness (Tables 4-5 and 4-8). Moreover, agreeing with Soubier et al., we also found sensitivity and specificity for predicting central hypovolemia of 63% and 94%, respectively, for SPV, and 88% and 69% for PPV when no resistor were applied in the animal study (Paper I). Corresponding figures for the healthy volunteers were 80% and 100% for PPV, 20% and 100% for SPV, and 60% and 100% for SVV (Paper II). Thus, our studies confirm that arterial pressure variations during normal spontaneous breathing without resistors are not useful for prediction of fluid responsiveness, mainly because of low sensitivity.

Thus, the difference between the resistors could be explained by the Frank–Starling heart function curve. With an expiratory resistor, the filling becomes lower, causing the heart function to work on the steeper left part of the curve, whereas an inspiratory resistor improves filling, causing the heart function to work on the right less steep part of the curve. This would make the pressure variations with the expiratory resistor somewhat higher than with the inspiratory resistor, and the signal more pronounced. According to this reasoning, the inspiratory/expiratory resistor, making the heart work on a wider part of the Frank–Starling curve, would give the highest pressure variations.

The minor difference in performance between PPV and SPV in our studies is probably due to differences in obtaining these variables. PPV was obtained from the PiCCO device (Paper I) or the Vigileo Flowtrac device (Paper II), and SPV was obtained manually from the pressure tracings.

According to the practice in our hospital, and to minimize discomfort, we used an uncalibrated pulse contour technique to detect SV and CO in the healthy volunteer study. Using alternative commercial techniques, e.g. PiCCO, as we did during the animal study, might have altered the results (Monnet et al., 2010; Thiele et al., 2015). Furthermore, it would have been preferable to use the same technique in both studies.

Our studies have some strengths; they are based on a novel approach to predicting fluid responsiveness and central hypovolemia during spontaneous breathing and the method used is standardized, reproducible and strong because of use of paired data despite relatively few subjects. However, our studies also have several limitations and therefore caution should be taken before extrapolating the results to the clinical setting with regard to spontaneously breathing patients with hypovolemia. First, the studies involved only a small number of animals and volunteers. Secondly, both the animals and volunteers were healthy, with normal heart function and without any arrhythmias. Therefore, neither the healthy animals nor the healthy volunteers may reflect a hospitalized population. For example, in a study in ICU patients, only 50% increased CO ≥ 10% when treated with a fluid bolus (Magder, 2006) We found 87% (Paper I) and 77% (Papers II and III). Moreover, in the healthy volunteers we tested the "the reverse" of the animal study and clinical practice, i.e. we provoked central hypovolemia by tilting the subjects head-up and evaluated the change in CO and arterial pressure variations, and did not study whether these changes would be corrected by fluid administration or by immediately adopting the Trendelenburg's position. Thirdly, because we did not *a priori* know the effect on the arterial pressure variations of the hypovolemia and volume challenges in the animals, both the hypovolemic level and the volume challenges were substantial, and furthermore, two different volume challenges were used. Fourthly, the results depend not only on the resistance of the resistors, but also on the respiratory effort of the subjects. The level of expiratory resistance used might not be optimal in patients. However, we chose these resistors because 5–10 cmH_2O is commonly used as expiratory impedance

clinically, e.g. for PEEP or continuous positive airway pressure, and this level is accepted by most patients. Sixthly, the non-invasively measurement typically evaluated is ΔPOP, which is the amplitude variation in the plethysmographic waveform. We chose to evaluate the peak height variation because of the similarity with SPV.

Fluid therapy is an important part of the management of the circulation in emergency and critical care medicine as well as during anesthesia, during which optimization of CO may reduce postoperative complications (Hamilton et at., 2011). However, during spontaneous breathing, it is not established how hypovolemia should be determined or how to improve a patient's cardiovascular function (Rooke et al., 1995). We believe that using a combination of in- and expiratory resistor SPV could provide information on volume status and fluid responsiveness in conscious patients during spontaneous ventilation; however, clinical studies are needed. If confirmed, this method is expected to have clinical impact in acute medicine, including use in traumatized patients, patients with uncontrollable bleeding and in those with sepsis, and even in a pre-hospital setting It is also expected that the method can be used in the perioperative period to detect and titrate fluid therapy

CHAPTER 6. CONCLUSION

- Central hypovolemia, defined as a decrease in cardiac output ≥ 10%, can be predicted during spontaneous breathing by amplification of intrathoracic pressure oscillations using inspiratory and expiratory resistance.

- Arterial pressure variations are amplified by in- and expiratory resistors during hypo-, normo- and hypervolemia.

- Arterial pressure variations can predict the hemodynamic effect of subsequent fluid loading.

- Systolic pressure variation is the most sensitive variable for the detection of a significant reduction of the central blood volume.

- ΔPH_{POP} and PVI® cannot detect a significant reduction in the central blood volume

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APPENDICES

Appendix A. Paper I

Dahl MK, Vistisen ST, Koefoed-Nielsen J, Larsson A:
Using an expiratory resistor, arterial pulse pressure variations predict fluid responsiveness during spontaneous breathing: an experimental porcine study.
Crit Care 2009, **13**:R39

Available online http://ccforum.com/content/13/2/R39

Research

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Using an expiratory resistor, arterial pulse pressure variations predict fluid responsiveness during spontaneous breathing: an experimental porcine study

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Received: 23 Oct 2008 Revisions requested: 14 Jan 2009 Revisions received: 11 Feb 2009 Accepted: 20 Mar 2009 Published: 20 Mar 2009

Critical Care 2009, **13**:R39 (doi:10.1186/cc7760)
This article is online at: http://ccforum.com/content/13/2/R39

Abstract

Introduction Fluid responsiveness prediction is difficult in spontaneously breathing patients. Because the swings in intrathoracic pressure are minor during spontaneous breathing, dynamic parameters like pulse pressure variation (PPV) and systolic pressure variation (SPV) are usually small. We hypothesized that dunng spontaneous breathing, inspiratory and/or expiratory resistors could induce high arterial pressure variations at hypovolemia and low variations at normovolemia and hypervolemia. Furthermore, we hypothesized that SPV and PPV could predict fluid responsiveness under these conditions.

Methods Eight prone, anesthetized and spontaneously breathing pigs (20 to 25 kg) were subjected to a sequence of 30% hypovolemia, normovolemia, and 20% and 40% hypervolemia. At each volemic level, the pigs breathed in a randomized order either through an inspiratory and/or an expiratory threshold resistor (7.5 cmH_2O) or only through the tracheal tube without any resistor. Hemodynamic and respiratory variables were measured during the breathing modes. Fluid responsiveness was defined as a 15% increase in stroke volume (ΔSV) following fluid loading.

Results Stroke volume was significantly lower at hypovolemia compared with normovolemia, but no differences were found between normovolemia and 20% or 40% hypervolemia. Compared with breathing through no resistor, SPV was magnified by all resistors at hypovolemia whereas there were no changes at normovolemia and hypervolemia. PPV was magnified by the inspiratory resistor and the combined inspiratory and expiratory resistor. Regression analysis of SPV or PPV versus ΔSV showed the highest R^2 (0.83 for SPV and 0.52 for PPV) when the expiratory resistor was applied. The corresponding sensitivity and specificity for prediction of fluid responsiveness were 100% and 100%, respectively, for SPV and 100% and 81%, respectively, for PPV.

Conclusions Inspiratory and/or expiratory threshold resistors magnified SPV and PPV in spontaneously breathing pigs during hypovolemia. Using the expiratory resistor SPV and PPV predicted fluid responsiveness with good sensitivity and specificity.

Introduction

It may be difficult to assess whether a spontaneously breathing patient would hemodynamically benefit from intravenous fluid administration [1,2]. The oldest and most common procedure is observing whether blood pressure will drop by an upright tilt test – and the reverse to this procedure, leg raising, has recently been shown to accurately predict fluid responsiveness [3-5]. This procedure should be performed passively, however, and it is therefore not possible to perform with all beds or stretchers [4,5]. Static measures such as the central venous pressure or the pulmonary artery wedge pressure, if not extremely low, are not useful for assessment of fluid responsiveness [6-8]. A fluid challenge may tip patients with borderline cardiac insufficiency into an overt pulmonary edema, necessitating ventilatory support.

During controlled mechanical ventilation using relatively large tidal volumes with the patient deeply sedated and muscle-relaxed, dynamic measures such as pulse pressure variation (PPV) and systolic pressure variation (SPV) predict fluid

PPV: pulse pressure variation; SPV: systolic pressure variation; SV: stroke volume.

responsiveness well [8-10]. These variations are caused by tidal changes in the intrathoracic pressure induced by positive pressure ventilation. During spontaneous breathing the changes in intrathoracic pressures are minimal and often the normal increase in arterial pressure during expiration is difficult to discern [11]. In pathological situations where the left heart filling is hampered during inspiration, such as cardiac tamponade, or when the right heart filling is reduced during expiration by high intrathoracic pressure, for example at acute exacerbation of chronic obstructive lung disease or asthma, however, the normal respiratory variations in arterial pressure may be enhanced, creating pulsus paradoxus [11,12]. In addition, pulsus paradoxus has been reported as a sign of severe hemorrhagic shock [12].

We hypothesized that a low level of expiratory resistance – reducing right heart filling and, some beats later (during the inspiratory phase), reducing the left ventricular stroke volume (SV) – or an inspiratory resistance – enhancing the right heart filling and, some beats after, enhancing the left ventricular SV – could induce high arterial pressure variations at hypovolemia and low arterial pressure variations at normovolemia and hypervolemia. The SPV or PPV might therefore predict fluid responsiveness during spontaneous breathing when expiratory and/or inspiratory resistances are used. In addition, we hypothesized – because an expiratory resistance would theoretically give similar changes as repeated short Valsalva maneuvers (that is, initial augmentation of the arterial pressure followed by a depression) – that tidal changes in arterial pressure caused by an expiratory resistor might give similar or better information about fluid responsiveness than an inspiratory resistor or an inspiratory/expiratory resistor.

The aim of this study was to test in a porcine experimental model whether the SPV and the PPV would be magnified by an expiratory resistor, an inspiratory resistor or a combined inspiratory/expiratory resistor during hypovolemia, normovolemia and hypervolemia, and to test whether the SPV or PPV when using an expiratory resistor would predict the hemodynamic effect of subsequent fluid loading.

Materials and methods

The study was approved by the national animal ethics committee, and the National Institutes of Health principles of laboratory care were followed. Eight pigs, weighing 25 to 30 kg, were premedicated with apazerone 80 mg intramuscularly and midazolam 10 mg intramuscularly. Anesthesia was induced by remifentanil 1 μg/kg intravenously and propofol 3 mg/kg intravenously. A tracheotomy was performed and the trachea was intubated with a Portex 9.0 ID tube (Smiths Medical, London, UK). The lungs were ventilated by a Servo 900 C ventilator (Siemens-Elema, Solna, Sweden) with volume control, tidal volume of 8 ml/kg, positive end-expiratory pressure of 5 cmH_2O and a fraction of inspired oxygen of 1.0. The inspiratory time was 35%, the end-inspiratory pause time was 10% and the ventilatory rate was adjusted to achieve an arterial pH of approximately 7.4. Anesthesia was maintained with ketamine 10 mg/kg/hour, remifentanil 0.5 μg/kg/hour and propofol 10 mg/kg/hour. Ringer's acetate 20 ml/kg was infused during the instrumentation phase. In one animal, a bolus of Ringer's acetate 10 ml/kg was administered to stabilize circulation before the main experiment. Monitoring with electrocardiography and pulse oximetry (placed on the tail) was initiated.

Catheters were placed in the right carotid artery, in a femoral artery, and in the right internal jugular vein for sampling of blood gases, monitoring of intravascular pressures and obtaining the pulse contour cardiac output. A pulmonary artery catheter (Swan-Ganz CCO mbo CCO/SvO_2 7.5 Fr; Edwards Lifescience, Irvine, CA, USA) was placed via the right external jugular vein to monitor the pulmonary artery and central venous pressures. A suprapubic urinary catheter was inserted for monitoring diuresis.

An air-filled 6 Fr catheter was inserted in the tracheal tube with the end-hole 1 cm below the distal opening of the tracheal tube for airway pressure monitoring. The distal esophageal pressure was measured via a latex balloon catheter (Viasys Healthcare, Hochberg, Germany) and an adequate position was ensured as previously described [13]. The tracheal and esophageal catheters were connected to transducers (Edwards Lifesciences) and the signals were transferred to a monitor (S/5 Avance Carestation; GE Healthcare, Chalfont St Giles, UK).

The pulse contour cardiac output was obtained through the catheter (Pulsiocath, 4 Fr, 16 cm; Pulsion Medical Systems, Munich, Germany) placed in a femoral artery connected to the PiCCO monitor (Pulsion Medical Systems). The pulse contour cardiac output measurement was calibrated in triple with the transpulmonary arterial thermodilution technique using cold saline injectate (3 × 10 ml) immediately after induction of anesthesia and before each measurement sequence. In addition, the intrathoracic blood volume and PPV were obtained from the PiCCO device.

During the entire study period, electrocardiography, the cardiac output, blood pressures, the heart rate, and the airway and esophageal pressures were recorded continuously for later analyses. Blood gases were sampled from the right carotid and the pulmonary artery and were analyzed by an ABL 710 (Radiometer, Copenhagen, Denmark).

Experimental protocol

The outline of the experiment is shown in Figure 1. After instrumentation, the animal was placed prone and an interval of 20 minutes was allowed before spontaneous breathing was attempted; the ventilatory rate was reduced to one-half, the triggering level of the ventilator was set at -1 cmH_2O, the remifentanil infusion was stopped, and the ketamine and pro-

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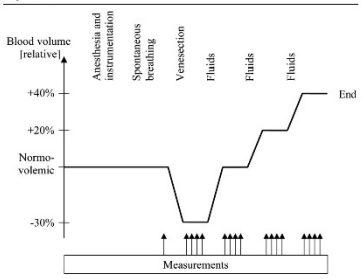
Figure 1



Outline of the experiment. The experimental procedure. Venesection, venesection of 30% of the estimated blood volume. Fluids, intravenous infusion of a starch solution of first 30% and then 20% of the estimated blood volume. Measurements, measurements of hemodynamic and respiratory variables. Tests were performed with the different resistors in a randomized order (see text). End, end of the experiment.

pofol infusions were halved and then adjusted to maintain adequate anesthesia (no movement and no reaction to painful stimulation of the anterior toes). When spontaneous breathing attempts began (the animal started to initiate breaths by triggering the ventilator), the ventilator was set to low-level pressure support (2 cmH_2O above the positive end-expiratory pressure). After about 2 minutes, the animal was connected to a spontaneous breathing device consisting of a Y-piece with inspiratory and expiratory valves and an anesthesia balloon with a valve regulating the oxygen flow from a flowmeter connected to a central pressurized oxygen source. The balloon was attached proximal to the inspiratory valve and the oxygen flow was regulated manually, keeping the balloon slightly expanded but still flaccid. In a bench test, the valves and the Y-piece generated <1 cmH_2O resistance to inspiratory and expiratory flow.

In the main experiment, when testing the effect of an expiratory resistance, the expiratory valve was replaced with a 7.5 cmH_2O threshold resistor (CPAP; Philips Respironics, Herrshing, Germany); when the effect of an inspiratory resistance was tested, the inspiratory valve was replaced with a 7.5 cmH_2O threshold resistor (CPAP; Philips Respironics); and when the effect of both expiratory and inspiratory resistances was tested, both resistors were connected as described above. In a bench test before the experiment, with the connectors used, the inspiratory resistor gave a resistance of 8.5 cmH_2O and the expiratory resistor gave a resistance of 7.5 cmH_2O.

Baseline data were obtained during spontaneous breathing without a resistor. Thereafter, the main experiment was initiated. Measurements were performed when the animals breathed without a resistor, with the expiratory resistor, with the inspiratory resistor and with the inspiratory/expiratory resistor at four volemic levels: 30% hypovolemia, normovolemia, and 20% and 40% hypervolemia. The order of breathing modes was randomized by computer randomization. Hypovolemia was achieved by venesection of 30% of the estimated blood volume, normovolemia was achieved by replacing the depleted blood with a starch solution (Voluven; Fresenius Kabi, Uppsala, Sweden), and 20% and 40% hypervolemia were achieved by infusion of corresponding volumes of the starch solution.

The blood volume was estimated as 179 × body weight$^{(0.73)}$, which is about 8% of the body weight [14]. The sequence of intravascular volume levels was always hypovolemia, normovolemia, and 20% and 40% hypervolemia. Each infusion or blood removal was performed over 5 to 10 minutes. During these procedures the animal breathed with pressure support using the settings as described above. This was followed by a 5-minute stabilization period with spontaneous breathing before a new measurement sequence was performed. Electrocardiography, the cardiac output, systolic arterial blood pressures, the heart rate, the pulmonary artery wedge pressure, the central venous pressure, the intrathoracic blood volume, and the SPV and PPV were registered 3 minutes after the resistor change. Blood gases were sampled, and the airway and esophageal pressures were obtained for calculation of the transpulmonary pressure and respiratory intrathoracic pressure variations.

After the experiment, the animal was killed by an overdose of thiopental and potassium chloride intravenously.

Calculations

Fluid responsiveness was defined as an increase in the SV of 15% after fluid loading.

Before the study, we decided to manually calculate the PPV and the SPV from the pressure tracings, because we have previously found a significant variation in the PiCCO monitor's stated SPV and PPV values during controlled ventilation of pigs [15]. We had problems with measuring the PPV correctly, however, and therefore the PPV was obtained automatically from the PiCCO device. The SPV was calculated over six respiratory cycles as previously described by Michard and colleagues [16].

The SV was obtained as the ratio of cardiac output/heart rate.

Airway pressure variations were calculated as the mean values for six respiratory cycles of maximal airway pressure (expiration) minus minimum airway pressure (inspiration). The same

calculations were carried out regarding the pleural (esophageal) pressure. The transpulmonary pressure was obtained as the airway pressure minus esophageal pressure at similar time points, and the variations were registered simultaneously with the airway pressure.

Statistical analysis

The statistical analyses were performed using the SigmaStat 3.5 program (Systat Inc., Point Richmond, CA, USA). Results are presented as the mean and standard deviation, if not otherwise indicated. $P < 0.05$ was considered significant. Normal distribution of the data was checked with the Kolmogorov–Smirnov test.

The overall changes in cardiac output, SV, central venous pressure and intrathoracic blood volume between the different volemic levels for no resistor were analyzed by one-way analysis of variance and the Tukey test. The overall changes in PPV and SPV between the different volemic levels with the different resistors in place were analyzed by two-way analysis of variance and the Tukey test. The differences in hemodynamics and in respiratory pressures caused by the different resistors at 30% hypovolemia were analyzed by one-way analysis of variance and the Tukey test. The relation between the SV and the SPV or PPV was analyzed by linear regression, and the sensitivity and specificity were calculated by standard formulas after inspection of the receiver operating characteristic curves (SigmaPlot 11.0; Systat Inc.).

Results

Hemodynamics without a resistor

The cardiac output, the SV, the central venous pressure and the intrathoracic blood volume were significantly lower during hypovolemia than during normovolemia, whereas there were minor or insignificant changes between the other volemic steps (Table 1). The SPV was similar at all volemic levels, whereas the PPV was significantly higher at -30% hypovolemia (Table 1).

Effects of resistors on airway and esophageal pressures

The airway and esophageal pressure swings were generally higher with resistors than without a resistor (Table 2). The transpulmonary pressure swings were somewhat higher with the inspiratory/expiratory resistor compared with no resistor, indicating larger tidal volumes.

Table 1

Central hemodynamics and arterial pressure variations at the four volemic levels

	-30% hypovolemia	0% normovolemia	+20% hypervolemia	+40% hypervolemia
No resistor				
Cardiac output (l/min)	3.2 ± 0.7	7.5 ± 1.6*	7.9 ± 2.0	7.7 ± 2.2
Stroke volume (ml)	24 ± 5	65 ± 11*	63 ± 10	62 ± 10
Central venous pressure (mmHg)	0 ± 2	6 ± 2*	7 ± 2*	8 ± 2*
Intrathoracic blood volume (ml)	485 ± 88	814 ± 177*	849 ± 156	924 ± 213
Central venous oxygen saturation	0.89 ± 0.05	0.99 ± 0.04*	1 ± 0.02	0.98 ± 0.04
Lactate (mmol/l)	1.2 ± 1.3	2.4 ± 1.8	1.9 ± 1.2	1.2 ± 0.8
Base excess (mmol/l)	4.1 ± 1.5	2.2 ± 1.7	2.2 ± 1.6	3.0 ± 1.9
Systolic pressure variation				
No resistor (%)	5 ± 2	3 ± 2	2 ± 1	2 ± 1
Inspiratory resistor (%)	10 ± 5†	4 ± 2*	5 ± 2	4 ± 2
Expiratory resistor (%)	11 ± 2†	4 ± 2*	4 ± 1	3 ± 2
Inspiratory/expiratory resistor (%)	13 ± 5†	5 ± 3*	5 ± 2	4 ± 2
Pulse pressure variation				
No resistor (%)	17 ± 5	12 ± 2*	12 ± 4	12 ± 1
Inspiratory resistor (%)	25 ± 6†	16 ± 4*†	16 ± 6†	15 ± 5†
Expiratory resistor (%)	25 ± 6	13 ± 6*	12 ± 3	11 ± 3
Inspiratory/expiratory resistor (%)	26 ± 7†	14 ± 6*†	14 ± 5†	13 ± 6†

Data presented as the mean ± standard deviation. *$P < 0.05$ compared with the previous volemic level. †$P < 0.05$ compared with no resistor at the same volemic level.

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Table 2

Respiratory pressures and hemodynamics at 30% hypovolemia

	No resistor	Inspiratory resistor	Expiratory resistor	Inspiratory/expiratory resistor
Airway pressure (AP)				
Inspiratory (cmH_2O)	-1 ± 4	-7 ± 2*	-3 ± 4	-5 ± 2*
Expiratory (cmH_2O)	3 ± 5	1 ± 2	5 ± 2	5 ± 2
ΔAP (cmH_2O)	4 ± 1	8 ± 1*	8 ± 2*	11 ± 4*
Esophageal pressure (EP)				
Inspiratory (cmH_2O)	-4 ± 2	-9 ± 3*	-6 ± 3	-8 ± 2*
Expiratory (cmH_2O)	-2 ± 1	-3 ± 3	-1 ± 2	-2 ± 3
ΔEP (cmH_2O)	3 ± 1	6 ± 1*	5 ± 2*	6 ± 2*
Transpulmonary pressure (TP)				
Inspiratory (cmH_2O)	3 ± 4	2 ± 4	4 ± 2	3 ± 4
Expiratory (cmH_2O)	5 ± 5	5 ± 4	6 ± 1	7 ± 3
ΔTP (cmH_2O)	1 ± 2	3 ± 1	2 ± 1	4 ± 3*
Heart rate (/min)	130 ± 21	133 ± 12	138 ± 18	137 ± 23
Cardiac output (l/min)	3.2 ± 0.7	3.3 ± 0.4	3.3 ± 0.5	3.2 ± 0.5
Stroke volume (ml)	25 ± 5	25 ± 4	24 ± 4	24 ± 5
PAWP during inspiration (mmHg)	-2 ± 5	-7 ± 4	-3 ± 4	-5 ± 3
PAWP during expiration (mmHg)	4 ± 3	6 ± 2	8 ± 2*	7 ± 2
Mean arterial pressure (mmHg)	55 ± 6	59 ± 5	60 ± 7	59 ± 5
Central venous pressure (mmHg)	0 ± 2	-1 ± 3	1 ± 3	1 ± 3

Data presented as the mean ± standard deviation. *$P < 0.05$ compared with no resistor. PAWP, pulmonary artery wedge pressure.

Hemodynamic consequences at each volemic level of applying the resistors

At each volemic level, the cardiac output, the SV, the mean arterial pressure and the heart rate did not change when applying the resistors, whereas the swings in pulmonary artery wedge pressure were slightly related to the swings in airway pressure ($R^2 = 0.12$) (Table 2).

At 30% hypovolemia, as compared with no resistor, the SPV was magnified by all resistors, whereas no changes were found at normovolemia and at 20% and 40% hypervolemia. The PPV was magnified by the inspiratory resistor and the inspiratory/expiratory resistor (Table 1).

Correlations between changes in stroke volume and systolic or pulse pressure variation using the different resistors

The regression analyses between the change in SV and the SPV or PPV using the different resistors are presented in Table 3. The R^2 value was generally higher when the expiratory resistor was applied with the highest correlation ($R^2 = 0.83$) for the SPV.

Table 3

Correlation of systolic pressure variation and pulse pressure variation versus the change in stroke volume

	Systolic pressure variation	Pulse pressure variation
No resistor	0.37	0.37
Inspiratory resistor	0.45	0.36
Expiratory resistor	0.83	0.52
Inspiratory/expiratory resistor	0.50	0.31

Data presented as R^2 values obtained by linear regression for systolic pressure variation or pulse pressure variation versus the increase in stroke volume by a subsequent fluid loading with no resistor and with the inspiratory, expiratory, and inspiratory/expiratory resistors.

Performances of systolic pressure and pulse pressure variations for each resistor

Using a 15% increase in SV as the definition of fluid responsiveness, the sensitivity and specificity for SPV and PPV were as shown in Table 4. The highest sensitivity was found for the expiratory resistor. The SPV gave sensitivity and specificity of 100% for a SPV cutoff value of 7% with the expiratory resistor, and sensitivity and specificity of 63% and 94%, respectively, for a cutoff value of 4% without a resistor (Figures 2 and 3). Corresponding values for the PPV were sensitivity and specificity of 100% and 81%, respectively, and sensitivity and specificity of 88% and 69%, respectively, for PPV cutoff values of 16% and 13%, respectively (Figures 2 and 3).

Central venous oxygen saturation, lactate and blood gases

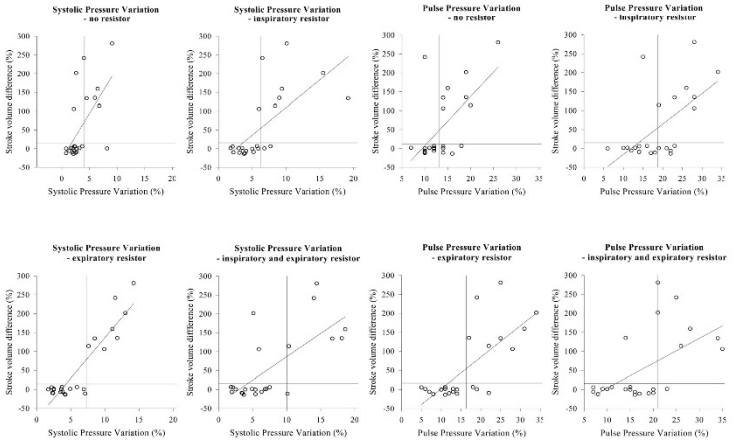
The central venous oxygen saturation increased from normovolemia, whereas the partial arterial tension of oxygen and the partial arterial tension of carbon dioxide (data not shown) as well as the base excess and lactate were stable during the experiment, with no significant changes between the volemic levels or respiratory modes.

Discussion

We have shown in this exploratory study in spontaneously breathing pigs that inspiratory and/or expiratory threshold resistors magnified arterial pressure variations markedly during hypovolemia, whereas changes in arterial pressure variations were minor during normovolemia and hypervolemia; that the expiratory resistor gave a better relation between the SPV or PPV and the change in SV by subsequent fluid loading than the inspiratory resistor or the inspiratory/expiratory resistor; and that the SPV and PPV using the expiratory resistor predicted fluid responsiveness with good sensitivity and specificity.

We manipulated the intrathoracic pressure to magnify the normal swings in arterial pressure. This concept has long been used clinically during controlled mechanical ventilation [8-10]. The ventilator-induced cyclic changes in intrathoracic pressure produce significant arterial pressure variations if the circulation is fluid responsive. The tidal volume, however, has to be above 8 ml/kg predicted body weight [17], which is higher than recommended in critically ill, ventilated patients [18]. Furthermore, the patient should have normal right heart function, no atrial fibrillation, and no spontaneous breathing activity [8-

Figure 2



Linear regression for systolic pressure variation and pulse pressure variation. Systolic pressure variation and pulse pressure variation before fluid administration versus the change in stroke volume following fluid loading without and with the expiratory resistor. Regression lines are indicated. All measurement points are used in the regression analyses. Horizontal lines, relevant change in stroke volume (15%); vertical lines, cutoff values used.

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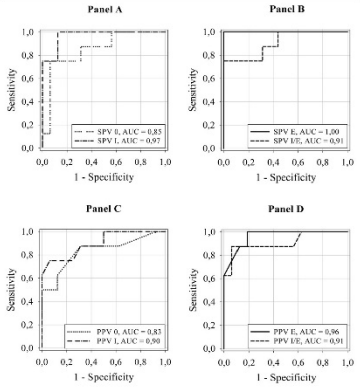
Figure 3



Receiver operating characteristic curves for systolic pressure variation and pulse pressure variation. Receiver operating characteristic curves for **(a)**, **(b)** systolic pressure variation and **(c)**, **(d)** pulse pressure variation, with the four different respiratory interventions, for predicting a 15% increase in stroke volume by subsequent fluid loading. SPV 0, systolic pressure variation with no resistor; SPV I, systolic pressure variation with the inspiratory resistor; SPV E, systolic pressure variation with the expiratory resistor; SPV I/E, systolic pressure variation with the combined inspiratory and expiratory resistor; PPV 0, pulse pressure variation with no resistor; PPV I, pulse pressure variation with the inspiratory resistor; PPV E, pulse pressure variation with the expiratory resistor; PPV I/E, pulse pressure variation with the combined inspiratory and expiratory resistor; AUC, area under the curve.

10]. Indeed, if the patient is breathing in a spontaneous ventilator mode, the arterial pressure variations will not give any information about fluid responsiveness [19].

In spontaneously breathing, hemodynamically unstable patients, Soubrier and colleagues found a sensitivity and specificity for predicting the effect of a subsequent fluid administration of 63% and 92%, respectively, for the PPV, and a sensitivity and specificity of 47% and 92%, respectively, for the SPV – as discussed in the accompanying editorial [20] – agreeing well with our results without resistors. Our study therefore confirms that arterial pressure variations during normal spontaneous breathing are not useful for fluid responsiveness prediction, mainly because of low sensitivity. Soubrier and colleagues also investigated whether a forceful inspiration and expiration (with no resistance) would improve the ability of the SPV and the PPV to predict fluid responsiveness [21]. The sensitivity was even lower, however, with this maneuver [21]. Indeed, we found a somewhat lower sensitivity with the expiratory/inspiratory resistor for SPV than with the other resistors.

In the editorial to the paper by Soubrier and colleagues, de Backer and Pinsky discussed whether manipulation of the intrathoracic pressure by a Valsalva maneuver – that is, a forceful expiration against a resistance – could be used to generate arterial pressure variations that could predict fluid responsiveness [20]. In fact, this has now been shown in a very recent study by Garcia and colleagues [22]. A Valsalva maneuver causes an immediate increase in cardiac output by squeezing blood from the pulmonary circulation to the left heart, but this is very quickly followed by a marked reduction in cardiac output due to reduced right heart filling [23]. As the Valsalva maneuver may induce a pronounced drop in blood pressure during hypovolemia, it may be difficult to perform in a patient distressed by circulatory compromise or pain – and the maneuver may induce changes in the heart rate. Moreover, the Valsalva maneuver may generate quite different intrathoracic pressures dependent on the patient's effort.

On the other hand, breathing against an expiratory resistance could be considered to give short, intermittent Valsalva maneuvers. This will cyclically reduce right heart filling and induce variations in arterial blood pressure that theoretically would be more pronounced when the circulation is fluid responsive. Indeed, in our study when using the expiratory resistor, the SPV was markedly enhanced during hypovolemia and became normalized during normovolemia; in addition, the SPV and the PPV could be used to predict fluid responsiveness. The minor difference in performance between the PPV and the SPV in our study is probably due to differences in obtaining these variables. The PPV was obtained from the PiCCO device and the SPV was obtained manually from the pressure tracings (see Calculations).

The inspiratory resistor and the inspiratory/expiratory resistor did also magnify the arterial pressure variations. Both of these resistors, however, gave inferior precision for fluid responsiveness prediction compared with the expiratory resistor. An explanation could be the different changes in intrathoracic pressures induced by the resistors; the expiratory resistor mainly increases the intrathoracic pressure during expiration, whereas the inspiratory resistor decreases the intrathoracic pressure during inspiration (Table 2). This decrease in the inspiratory intrathoracic pressure decreases left heart filling by reducing the pressure difference between the pulmonary vessels and the left atrium (as reflected in the markedly negative inspiratory pulmonary artery wedge pressure; Table 2), but simultaneously it improves right heart filling and thus, some beats afterwards, improves the left heart filling and the SV. Because of anatomical reasons the caval veins should be more affected by the pleural pressure than by the airway or the transpulmonary pressures, and thus the right heart filling should be dependent on the difference between the vein pres-

Table 4

Sensitivity, specificity, positive and negative predictive values for the pressure variations with different respiratory interventions

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Systolic pressure variation				
No resistor	63	94	83	83
Inspiratory resistor	88	88	78	93
Expiratory resistor	100	100	100	100
Inspiratory/expiratory resistor	75	94	86	88
Pulse pressure variation				
No resistor	88	69	58	92
Inspiratory resistor	88	69	58	92
Expiratory resistor	100	81	73	100
Inspiratory/expiratory resistor	88	94	88	94

sure and the pleural (esophageal) pressure. In fact, the inspiratory resistor reduced the inspiratory esophageal pressure and theoretically improved the right heart filling, whereas the expiratory device increased the expiratory esophageal pressure and theoretically reduced the right heart filling. The inspiratory/expiratory device had a combined effect.

The difference between the inspiratory and inspiratory/expiratory resistors could therefore be explained by the Frank–Starling heart function curve. With an expiratory resistor the filling becomes lower, causing the heart function to work on the steeper left part of the curve; whereas an inspiratory resistor improves filling, causing the heart function to work on the right less steep part of the curve. This would make the pressure variations with the expiratory resistor somewhat higher than with the inspiratory resistor, and the signal would be more pronounced. According to this reasoning, the inspiratory/expiratory resistor – making the heart work on a wider part of the Frank–Starling curve – would give highest pressure variations, agreeing with our result.

Inspiratory resistors have been found to improve cardiac output in experimental settings of hypovolemia [24,25]. We could not confirm this finding. The resistance level used in our study, however, was less than in the studies investigating the effect on cardiac output by inspiratory threshold resistors [24,25].

The use of an expiratory resistor connected to a nose–mouth mask is feasible in the clinic. It is used commonly for breathing physiotherapy in patients in the intensive care unit and in patients before and after surgery [26].

Our study has several limitations and caution should therefore be taken when translating the results to patients. First, we studied a limited number of young healthy animals with normal heart function and with no arrhythmias. Second, because we did not *a priori* know the effect on the arterial pressure variations by hypovolemia and volume challenges, both the hypovolemic level and the volume challenges were substantial and, furthermore, two different volume challenges were used. Third, the level of expiratory resistance used might not be optimal in patients. We chose these resistors because 5 to 10 cmH_2O is commonly used as expiratory impedance clinically (for example, for positive end-expiratory pressure or continuous positive airway pressure) and are accepted by most patients. Fourth, some values used in the receiver operating characteristic and linear regression analyses were dependent, making these analyses less strong.

Conclusions

The present exploratory animal study shows that arterial pressure variations predict fluid responsiveness during spontaneous breathing with an expiratory resistor.

Key messages

- Using an expiratory resistor, fluid responsiveness can be predicted by assessment of arterial pressure variations during spontaneous breathing.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MKD and AL participated in the design, laboratory work, data analyses and writing of the manuscript. STV, JK-N participated in the design, the laboratory work and in the finalizing of the manuscript.

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Appendix B. Paper II

Dahl M, Hayes CF, Rasmussen BS, Larsson A, Secher NH.
Can a central blood volume deficit be detected by systolic pressure variation during spontaneous breathing?
Submitted

Can a central blood volume deficit be detected by systolic pressure variation during spontaneous breathing?

Michael Dahl[1], Chris Hayes[1], Bodil Steen Rasmussen[1], Anders Larsson[2] and Niels H. Secher[3].

Short title: Hypovolemia assessed by systolic pressure variation

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KEY MESSAGES

In spontaneous breathing healthy volunteers combined inspiratory and expiratory resistors enhances systolic pressure variation and allows identifying a central volume deficit with a sensitivity and specificity of 78% and 100%, respectively. Combined inspiratory and expiratory resistors might help detecting a fluid deficit in spontaneously breathing patients.

ABSTRACT

Introduction: Whether during spontaneous breathing systolic pressure variations (SPV) can detect a central volume deficit is not established. We hypothesized that amplification of intra-thoracic pressure swings by breathing through inspiratory and expiratory resistors would enhance SPV to an extent that allows identification of a reduced cardiac output (CO). The aim of this study was to test that hypothesis in healthy volunteers exposed to central hypovolemia by head-up tilt.

Methods: Thirteen healthy volunteers were exposed to central hypovolemia by 45° head-up tilt while breathing through a facemask with 7.5 cmH_2O inspiratory and expiratory resistors. A brachial arterial catheter was used to measure blood pressure and thus SPV. Pulse contour analysis determined stroke volume (SV) and CO and we evaluated whether SPV could detect a 10% decrease in CO.

Results: From the supine position to head-up tilt SV decreased form 91 (±46) to 55 (±24) mL (mean ±SD) and CO form 5.8 (±2.9) to 4.0 L/min (±1.8) ($p < 0.05$), while heart rate increased (65 (±11) to 75 (±13) bpm; $P < 0.05$). Systolic pressure decreased from 127 (±14) to 121 (±13) mmHg during head-up tilt, while SPV tended to increase (from 21 (±15)% to 30 (±13)%). Yet during head-up tilt, a SPV ≥ 37% predicted a decrease in CO ≥ 10% with a sensitivity and specificity of 78% and 100%, respectively.

Conclusion: In spontaneously breathing healthy volunteers combined inspiratory and expiratory resistors enhances SPV during head-up tilted induced central hypovolemia and allows to identify a 10% reduction in CO. Breathing through inspiratory and expiratory resistors might be applied to identify a fluid deficit in spontaneously breathing patients.

Trial registration: ClinicalTrials.gov NCT02549482

Keywords: fluid responsiveness; spontaneous breathing; head-up tilt; pulse pressure variation; stroke volume variation; systolic pressure variation.

INTRODUCTION

Fluid therapy is an integrated part of emergency and critical care medicine as for anesthesia. However, there are few measures that assess hypovolemia and therefore whether, or to what extent a patient is in need for fluid, i.e. respond with improved cardiovascular function after volume administration (is "fluid responsive") [1]. Unfortunately, clinical judgment or, e.g. recording of central venous pressure [2–7] do not provide adequate information for whether a patient is in need of added volume. In mechanically ventilated patients without cardiac arrhythmia exposed to a tidal volume larger than 8 mL/kg lean body weight, arterial pressure variation predicts volume responsiveness defined as an increase in stroke volume (SV) or cardiac output (CO) when the patient is exposed to a volume load [8–13]. In spontaneously breathing patients however arterial pressure variation are not large enough to guide volume therapy [14] and volume therapy may be guided by recording of the SV and/or CO response or change in end-tidal CO_2 concentration, e.g. when the patient is exposed to passive raising the legs [15–17] or placing the patient in Trendelenburg's position [18].

Yet, arterial pressure variation can detect fluid responsiveness as demonstrated in swine breathing through an inspiratory and expiratory resistor that augments pulse pressure variations [19]. Similarly, we considered that if the intrathoracic pressure variations are amplified by inspiratory (increasing the negative intrathoracic pressure) and expiratory resistors (increasing the expiratory intrathoracic pressure) that would allow for detection a volume deficit in humans. In this study, we tested that hypothesis in healthy humans exposed to a reduction in central blood volume by head-up tilt. Separate evaluation was made by providing the subjects to an inspiratory resistance, to an expiratory resistance, or to both with no application of resistors serving as control. We aimed to identify which expression of blood pressure variation is most sensitive to a significant reduction of the central blood volume taken as resulting in a 10% reduction in CO.

METHODS

Thirteen healthy volunteers (four women) 25 yrs. (range 18–36) of age (Table 1) were recruited through www.forsøgsperson.dk. Exclusion criteria were pregnancy, breast-feeding or use of any medication. The protocol was approved by the ethics committee for human research (H-4-2010-110) in accordance with the Helsinki II declaration and oral and written informed consent was obtained.

The volunteers were placed supine on a tilt table with heart rate monitored by a three-lead ECG and arterial oxygen saturation by pulse oximetry (SpO_2) (Philips SpO2 Sensor M1191BL ViCare Medical, Denmark) on right third finger of the dominant hand. A peripheral venous access was established and a 20 G arterial catheter was placed in the brachial artery of the non-dominant arm and both were maintained by infusion of isotonic saline (3 mL/h). The arterial catheter was connected to a transducer kept at heart level for registration of arterial pressure and stroke volume variation (SVV) (Vigileo-Flotrac™, version 1.07, Edwards Lifesciences, Nyon, Switzerland) as well as blood gas variables and electrolytes (ABL, Radiometer, Copenhagen). CO and the arterial pressure curve were stored for subsequent determination of arterial pulse pressure (PPV) and systolic pressure variation (SPV). Finally, a catheter was placed via a brachial vein and advanced to the subclavian vein to register central venous oxygen saturation ($ScvO_2$) (ABL, Radiometer, Copenhagen).

The subjects were breathing spontaneously with respiratory rate determined by capnography (Philips CO_2 Filterline, ViCare Medical, Denmark) and provided with a facemask (Intersurgical Ltd., Wokingham, Berkshire, UK) (Fig. 1) randomly fitted with an inspiratory resistor, an expiratory resistor, a combination of the two resistors, or with no resistors. Each resistor provided a 7.5 cmH_2O threshold resistance (CPAP; Philips Respironics, Herrshing, Germany) and were applied for two minutes [15] with variables obtained in the second minute.

First, variables were recorded with each resistor configuration while the subjects were supine (normovolemia). Secondly, the table was tilted 45° head-up to reduce the central blood volume hence simulating hypovolemia [20] (Fig. 2) and variables obtained after 10 min. Finally, 20° head-

down tilt was used to expand the central blood volume and hence simulating mild hypervolemia [20, 21] and variables were obtained after 10 min.

PPV was $((PP_{max} - PP_{min}) / ((PP_{max} + PP_{min})/2)) \times 100$, where PP_{max} and PP_{min} are the maximal and minimal difference between systolic and diastolic pressure during the respiratory cycle, respectively [11] and SPV was calculated by an analogous formula. PPV and SPV were calculated from the stored recordings, while other variables were noted on-line.

Statistics

For a 1-beta (power) of 0.8 and an alpha (*P*) of 0.05 and assuming an increase in arterial pressure variations by 10% with a SD of 5% by the intervention a minimum of 8 subjects were needed. Statistics was performed with Stata 11.2 (StataCorp LP 1985-2009, Texas, USA) and QQ-plots identified that the data were normally distributed. Hemodynamic data were analyzed using two-way ANOVA with interaction for the different airway resistors. Estimation of fluid responsiveness was analyzed using two-way ANOVA and Receiver Operating Characteristic (ROC) and a *P* value < 0.05 was considered statistically significant.

RESULTS

Hemodynamic responses and blood gas variables

From the supine position to head-up tilt CO decreased from 5.8 (±2.9) to 4.0 (±1.8) L/min (mean ±SD), SV from 91 (±46) to 55 (±24) ml, systolic pressure from 127 (±14) to 121 (±13) mmHg and $ScvO_2$ from 0.79 (±0.07)% to 0.68 (±0.13)%, while diastolic pressure (64 (±7) to 69 (±6) mmHg) and heart rate (65 (±11) to 75 (±13) bpm) increased ($P < 0.05$). Similarly, from the supine position to head-down tilt there was a decrease in CO, SV and systolic pressure but no changes in heart rate, diastolic pressure or $ScvO_2$ (Table 2). There were no changes in respiratory rate or SpO_2 between the three body positions and only small changes in arterial blood gas variables and no significant interactions between position and respiratory resistor application.

Detecting central hypovolemia

Ten volunteers showed a ≥ 10% decrease in CO between the supine position and head-up tilt positions. Regardless of tilt table position the combined inspiratory and expiratory resistors increased SVV, SPV and PPV, while the inspiratory resistor increased SPV and PPV and the expiratory resistor only SPV (Table 3). Sensitivity, specificity, positive predictive value, negative predictive value, area under the curve (AUC), and optimal cut-off for these variables are showed in Table 4. The best prediction of a central volume deficit (a 10% reduction in CO) was obtained with SPV when the combined resistors were applied. For that configuration SPV tended to increase (from 21 (±15)% to 30 (±13)%) and reviled a sensitivity of 78% and specificity of 100% with a positive predictive value of 100%, a negative predictive value of 60%, and an AUC of 0.96 (0.86;1.00) (confidence interval) (Fig. 3) when SPV was larger than 37%.

DISCUSSION

In spontaneously breathing healthy volunteers a 7.5 cmH_2O threshold resistance on both the inspiratory and expiratory side of a facemask during head-up tilt induced central hypovolemia enough variation in arterial pressure during the respiratory cycle to detect a 10% reduction in CO. The highest sensitivity (78%) and specificity (100%) was for systolic pressure variation with a threshold of 37%.

Head-up tilt [20, 22] as, e.g. lower body negative pressure, eventually combined with heat stress [23] reduces the central blood volume and has the advantage compared to a blood loss that the intervention can be terminated immediately if the subject becomes ill. That central hypovolemia was provoked by head-up tilt was confirmed by a decrease in $ScvO_2$ and an increase in heart rate [24]. We found CO and SV to decrease during head-down tilt, however the reduction was so small that it did not affect $ScvO_2$ significantly and neither Harms et al. [24] nor Bundgaard-Nielsen et al. [25] found a decrease in CO during head-down tilt and only a decrease in SV when the subjects were tilted 90° head-down. Similarly, moderate head-down tilt did not affect heart rate significantly [24, 25]. Variables were obtained after a ten minute equilibration period in each body position with randomized application of the resistors. A shorter observation period, e.g. one minute, is probably

enough to register pulse changes during tilt tests [22].

The study has several limitations: First, we studied healthy volunteers who may not be representative for a hospitalized population. For example, in a ICU population only 50% of patients increase CO ≥ 10% when challenged with a fluid bolus [26]. Secondly, our test was "the reverse" of the clinical practice; i.e. we provoked central hypovolemia by tilting the subjects head-up and evaluated the change in CO and arterial pressure variations, and did not study whether these changes would be corrected by fluid administration. The CO decreased by more than 10% in 10 of 13 subjects when exposed to 45° head-up tilt and a larger tilt angle would likely result in a more significant reduction of CO. Thirdly, we used an uncalibrated pulse contour technic to detect SV and CO [27]. Fourthly, the results depend not only on the resistance of the resistors, but also on the respiratory effort by the subjects. The threshold resistance was set at 7.5 cmH_2O and chosen because that level is in accordance with an animal study using SPV to indicate hypovolemia [19]. An airway threshold resistor between 5 and 10 cmH_2O is used for positive end-expiratory pressure or continuous positive airway pressure and is accepted by most patients.

Conclusion

Applying inspiratory and expiratory resistors to spontaneously breathing healthy volunteers allows for identifying significant central hypovolemia by recording of systolic pressure variations.
The clinical implication of the results is that systolic pressure variations might be used to detect a volume deficit in spontaneously breathing patients.

List of abbreviations

CO = Cardiac Output

CVP = Central Venous Pressure

PP_{max} = Maximal Pulse Pressure

PP_{min} = Minimal Pulse Pressure

PPV = Pulse Pressure Variation

SV = Stroke Volume

$ScvO_2$ = Central Venous Oxygen Saturation

SPV = Systolic Pressure Variation

SVV = Stroke Volume Variation

Competing interests

The authors declare no conflict of interest.

Authors' contribution

MD and NHS participated in the design, laboratory work, data analysis and writing the manuscript. AL, CH and BSR participated in the design, data analysis and in finalizing the manuscript.

Acknowledgements

Anders Larsson is supported by grants from the Swedish Heart and Lung foundation and from the Swedish Research Council (K2015-99X-22731-01-4). We thank the Laerdal Foundation for Acute Medicine for financial support, María Rodrigo, MSc, statistician, Aalborg University Hospital for help, and Tina Hellevik, LPN, Aalborg University Hospital for Figure 1.

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FIGURE LEGENDS

Figure 1. Left: four respiratory resistors: no resistance, expiratory resistance, inspiratory resistance, and both inspiratory and expiratory resistances. Right: facemask applied with combined inspiratory and expiratory resistors.

Figure 2. Three postures representing normovolemia (supine) and central hypovolemia (head-up tilt), and central hypervolemia (head-down tilt).

Figure 3. Receiver operating characteristic (ROC) curves during head-up tilt for systolic pressure variation (SPV) with the four different respiratory resistors. Area under the ROC curve 0.43 (0.07;0.80) (confidence interval) for no resistor, 0.67 (0.18;1.00) for the inspiratory resistor, 0.70 (0.34;1.00) for the expiratory resistor, and 0.96 (0.86;1.00) for the combined inspiratory and expiratory resistor.

TABLES

Table 1. Characteristics of the subjects (n = 13).

Gender (F/M)	4/9
Age (years)	25 ± 5
Height (cm)	178 ± 10
Weight (kg)	73 ± 13
BMI (kg/m^2)	23.0 ± 3.2
BSA (m^2)	1.9 ± 0.2

Values are mean ± standard deviation.
BMI body mass index; BSA body surface area

Table 2. Hemodynamic and respiratory variables at three postures whatever respiratory resistor(s) applied

	Supine position	Head-Up Tilt	Head-Down Tilt
Cardiac output (L/min)	5.8 ±2.9	4.0 ±1.8*	5.1 ±2.2*
Stroke Volume (mL)	91 ±46	55 ±24*	81 ±36*
Systolic blood pressure (mmHg)	127 ±14	121 ±13*	120 ±11*
Diastolic blood pressure (mmHg)	64 ±7	69 ±6*	65 ±6
Heart rate (min^{-1})	65 ±11	75 ±13*	65 ±11
Respiratory rate (min^{-1})	10 ±4	10 ±4	10 ±3
Ph	7.43 ±0.03	7.45 ±0.04*	7.44 ±0.04
Oxygen partial pressure (kPa)	14.1 ±1.6	14.3 ±1.0	14.7 ±1.6*
Carbondioxid partial pressure (kPa)	5.0 ±0.6	4.6 ±0.7*	4.8 ±0.7*

Values are mean ± standard deviation. * $P < 0.05$ compared to the supine position.
There was no interaction between position and application of resistors.

Table 3. Arterial pressure variations with different airway resistors during head-up tilt.

	No resistor (%)	Inspiratory resistor (%)	Expiratory resistor (%)	Inspiratory/expiratory resistor (%)
Systolic pressure variation	17 ±11	26 ±14*	26 ±18*	28 ±14*
Stroke volume variation	15 ±8	19 ±8	23 ±7*	29 ±12*
Pulse pressure variation	7 ±4	9 ±6	8 ±6	10 ±6*

Values are mean ± standard deviation. * $P < 0.05$ compared to no resistor.

Table 4. Sensitivity, specificity, positive predictive value and negative predictive value using 10% difference in cardiac output between supine position to head-up tilt to define central hypovolemia

	AUC	Optimal cut-off (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Stroke volume variation						
No resistor	0.73 (0.44;1.00)	13	60	100	100	43
Expiratory resistor	0.82 (0.57;1.00)	28	70	100	100	50
Inspiratory resistor	0.75 (0.43;1.00)	18	50	100	100	38
Inspiratory/expiratory resistor	0.58 (0.27;0.89)	31	40	100	100	33
Systolic pressure variation						
No resistor	0.43 (0.07;0.80)	19	20	100	100	27
Expiratory resistor	0.70 (0.34;1.00)	33	70	67	88	40
Inspiratory resistor	0.67 (0.18;1.00)	36	80	67	89	50
Inspiratory/expiratory resistor	0.96 (0.86;1.00)	37	78	100	100	60
Pulse pressure variation						
No resistor	0.83 (0.60;1.00)	7	80	100	100	60
Expiratory resistor	0.73 (0.35;1.00)	4	70	67	88	40
Inspiratory resistor	0.73 (0.39;1.00)	7	50	100	100	38
Inspiratory/expiratory resistor	0.59 (0.22;0.96)	12	67	67	86	40

AUC Area Under the Curve with confidence interval.

Figure 1. Dahl et al.

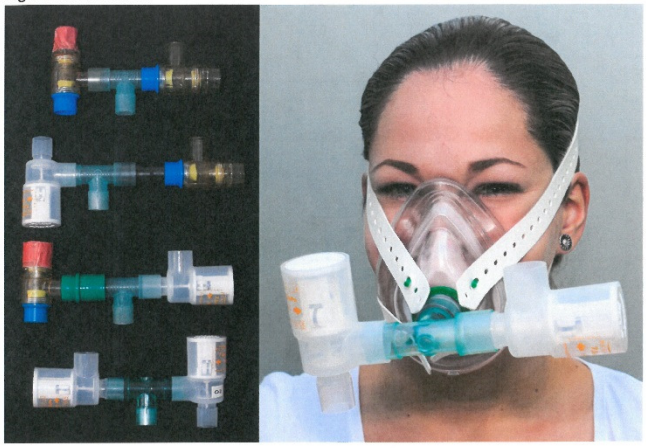


Figure 2. Dahl et al.

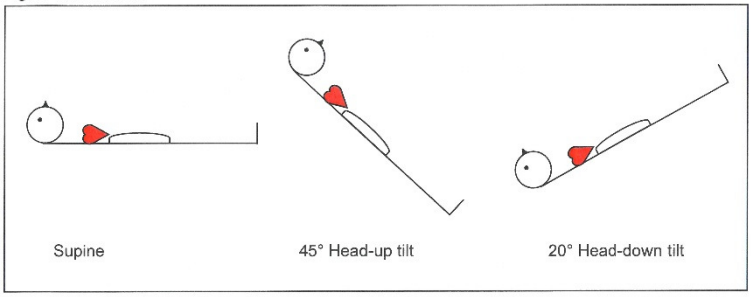
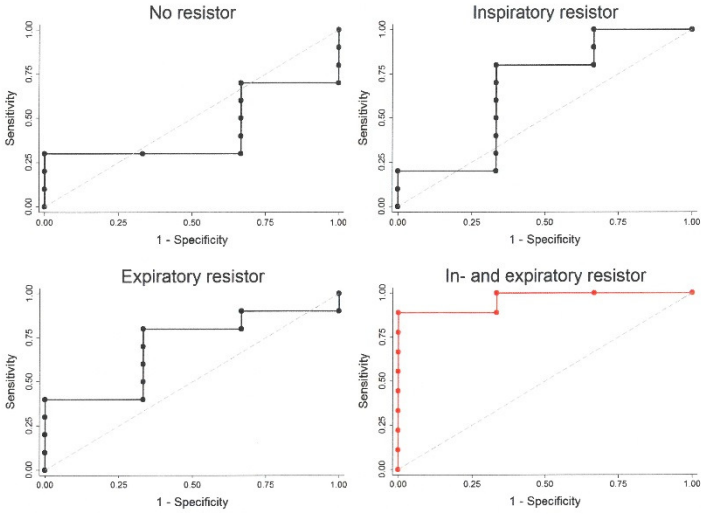


Figure 3. Dahl et at.



Appendix C. Paper III

Dahl M, Hayes CF, Rasmussen BS, Larsson A, Secher NH.
Ventilatory variation in pulse oximetry plethysmography peak height does not detect central hypovolemia during spontaneous breathing.
Draft

Ventilatory variation in pulse oximetry plethysmography peak height does not detect central hypovolemia during spontaneous breathing

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Short title: Plethysmography for detection of hypovolemia

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KEY MESSAGES

Ventilatory variation in pulse oximetry plethysmography peak height is not enhanced by breathing through inspiratory or expiratory resistors and does not detect head-up tilt induced central hypovolemia.

ABSTRACT

Introduction: Variations in peak height of the pulse oximetry plethysmography waveform (ΔPH_{POP}), and the continuous estimate PVI® (Pleth Variability Index; Masimo Comp. CA, USA) can detect functional hypovolemia during mechanical ventilation, but its reliability during spontaneous breathing is not established. We hypothesized that amplification of intra-thoracic pressure swings by breathing through inspiratory and expiratory resistors would enhance ΔPH_{POP} and PVI® and allow detection of central hypovolemia.

Methods: Thirteen healthy volunteers were exposed to central hypovolemia by 45° head-up tilt while breathing through a facemask fitted with 7.5 cm H_2O inspiratory and expiratory resistors. A brachial arterial catheter was placed for blood pressure measurement and pulse contour analysis determined stroke volume and cardiac output (CO). A 10% reduction in CO by head-up tilt was considered to indicate significant central hypovolemia.

Results: During head-up tilt CO decreased from 5.8 ± 2.9 (mean ± SD) to 4.0 ± 1.8 L/min ($P < 0.05$). ΔPH_{POP} was not enhanced significantly by any respiratory resistor. During head-up tilt PVI® was 24 ± 10 with no resistor applied and tended to increase (to 29 ± 9, 32 ± 8 and 35 ± 7, respectively) with an inspiratory resistor, an expiratory resistor, and with combined resistors. Also, no significant correlation was found between ΔPH_{POP} or PVI® and variation in pulse pressure, systolic pressure or stroke volume. Based on AUC between 0.43 and 0.68, neither ΔPH_{POP} nor PVI® detected central hypovolemia.

Conclusion: Variation in peak height of the pulse oximetry plethysmography waveform is not enhanced by breathing through inspiratory or expiratory resistors and does not detect head-up tilt induced central hypovolemia.

Keywords: pulse oximeter plethysmography waveform; peak height variation; Pleth Variability Index; fluid responsiveness; head-up tilt; spontaneous breathing.

INTRODUCTION

We have previously shown in both an experimental model and in healthy volunteers that central hypovolemia can be detected by increased arterial variations during spontaneous breathing if the subject is breathing through combined in- and expiratory resistors. In this study we wanted to explore whether the methodology could be fully noninvasive by using the variations in pulse oximetry plethysmography tracings instead of invasively obtained arterial pressure variations.

The necessity to monitor whether ventilation is adequate became realized during the polio epidemic in Denmark 1952-1953 and was established by monitoring blood gas variables [1]. Non-invasive monitoring of arterial oxygen saturation became available when the Japanese engineer Takuo Aoyagi developed pulse oximetry by spectrophotometric methodology [2]. This technique illuminates the tissue by two wavelengths (660 nm; red light and 940 nm; infrared light) and measures the absorption of oxygenated and de-oxygenated blood. Assuming that only arterial blood pulsates each absorption is divided into a pulsatile component (alternating current (AC)) and a non-pulsatile component (direct current (DC)). While AC represents the absorption of the pulsating arterial blood, the DC represents the absorption of the skin, other tissues and non-pulsatile venous blood. The ratio (R) is based on calculation of AC/DC for each wavelength; $R = (AC_{660}/DC_{660})/(AC_{940}/DC_{940})$. The pulse oximeter software calibrates R to display arterial oxygen saturation.

To assists clinicians interpreting eventually artifacts of the pulse oximetry, most commercial pulse oximeters display the plethysmographic waveform representing AC, which closely resembles the arterial blood pressure curve [3, 4], hence reflecting the arterial blood pulsation at the measured site.

In mechanically ventilated patients without cardiac arrhythmia and provided with a tidal volume >8 mL/kg lean body mass, arterial pressure variations as variation in pulse pressure (PPV), systolic pressure (SPV) and stroke volume (SVV) predict volume responsiveness, defined as an increase in stroke volume (SV) or cardiac output (CO) [5–10]. The peak height of the pulse oximetry plethysmographic waveform (ΔPH_{POP}) depends on the arterial pulsatility and is related to PPV [11–13]. Thus, ΔPH_{POP} and a continuous estimate of the plethysmographic waveform

variations, PVI® (Pleth Variability Index, Masimo Comp., CA, USA) predict hypovolemia and fluid responsiveness under similar circumstances [14–17].

The ventilatory induced variations in SV are too small to predict fluid responsiveness during spontaneous breathing but we considered that intra-thoracic pressure variations can be amplified by breathing through an inspiratory or an expiratory resistor thus augmenting the respiratory variations in SV and hence ΔPH_{POP} and PVI®. We tested the hypothesis that ΔPH_{POP} and PVI® can be augmented in healthy humans exposed to an inspiratory resistance, to an expiratory resistance or to both, with no application of in- or expiratory resistances serving as control. We aimed to identify whether ΔPH_{POP} and PVI® can detect a significant reduction in the central blood volume taken as a 10% reduction in CO by exposing subjects to head-up tilt.

METHODS

After protocol approval by the local ethics committee for human research (H-4-2010-110) in accordance with the Helsinki II declaration, thirteen healthy volunteers were recruited through an internet based portal (www.forsøgsperson.dk). Pregnant and breast-feeding subjects and subjects who used medication were excluded. Oral and written informed consent was obtained.

The volunteers were monitored for heart rate by a three-lead ECG. A 20 G arterial catheter was placed in the brachial artery of the non-dominant arm and connected to a transducer kept at heart level for continuous registration of arterial pressure and SVV (Vigileo-Flotrac™, version 1.07, Edwards Lifesciences, Nyon, Switzerland). A peripheral venous access was established and maintained by infusion of isotonic saline (3 mL/h). Finally, a catheter was placed via a brachial vein and advanced to the subclavian vein to register central venous oxygenation ($ScVO_2$). Blood was sampled from both the arterial and central venous catheters for analysis of blood gas variables and electrolytes (ABL, Radiometer, Copenhagen).

Arterial oxygen saturation was continually measured by pulse oximetry (SpO_2) (Philips SpO2 Sensor M1191BL ViCare Medical, Denmark) placed on the third finger of the dominant hand. The pulse oximetry plethysmographic waveform was stored for subsequent determination of ΔPH_{POP}. Concomitantly, PVI® (Rainbow DCI-dc12 Sensor, Radical-7, software version 7.5.0.3, Masimo

Comp., Irving, CA, USA) was registered on the second finger on the dominant hand. Both sensors were wrapped to minimize interference with ambient light. The respiratory rate was measured by capnography (Philips CO_2 Filterline, ViCare Medical, Denmark).

The volunteer was provided with a facemask (Intersurgical Ltd., Wokingham, Berkshire, UK) randomly fitted with either an inspiratory resistor, an expiratory resistor, a combination of the two resistors, or with no resistors. Each resistor provided a 7.5 cm H_2O threshold resistance (CPAP; Philips Respironics, Herrshing, Germany) and was applied for two minutes [18] with variables obtained in the second minute.

First, the variables were recorded with each resistor configuration while the subjects were supine ("normovolemia"). Secondly, the table was tilted 45° head-up to reduce the central blood volume and hence simulating hypovolemia (Fig. 1) [19]. Finally, 20° head-down tilt was used to expand the central blood volume hence simulating mild hypervolemia [19, 20]. For each subject the four respiratory configurations were randomized, whereas the tilt table position was in fixed order: supine, head-up tilt, and head-down tilt. After each change in position the subject was resting for 10 min. before the facemask was re-applied.

ΔPH_{POP} was defined as $((PH_{max} - PH_{min}) / ((PH_{max} + PH_{min})/2)) \times 100$, where PH_{max} and PH_{min} are the maximal and minimal peak height during the respiratory cycle [12]. ΔPH_{POP} was calculated from the stored recordings (Fig. 2), while PVI® and other variables were noted on-line.

Statistics

For a 1-beta (power) of 0.8 and an alpha (*P*) of 0.05 and assuming an increase in ΔPH_{POP} and PVI® by 10% with a SD of 5% by the intervention a minimum of 8 subjects were needed. Statistics was performed with Stata 11.2 (StataCorp LP 1985-2009, Texas, USA) and Quantile-Quantile plots identified that the data were normally distributed. Hemodynamic data were analyzed using two-way ANOVA with interaction for the different airway resistors and values expressed as mean ± SD. Estimation of fluid responsiveness was analyzed using two-way ANOVA and Receiver Operating Characteristic (ROC) and a *P* value < 0.05 was considered statistically significant.

Results

Thirteen healthy volunteers 25 yrs. (range 18–36) of age were included (four females). Weight 73 (± 13; mean ± SD) kg and height 178 (± 10) cm. giving body mass index of 23.0 (± 3.2) kg/m^2 and a body surface area of 1.9 (± 0.2) m^2.

The inspiratory resistor, expiratory resistor and the combination of both resistors increased PVI® during head-up tilt, while there was no changes between resistors during supine or head-down tilt. ΔPH_{POP} was not enhanced by any respiratory resistor (Table 1).

For 10 subjects CO decreased ≥ 10% from the supine to the head-up tilt position. Sensitivity, specificity, positive predictive value, negative predictive value, area under the curve (AUC), and optimal cut-off for these variables are shown in Table 2. The best prediction of a 10% reduction in CO was obtained with ΔPH_{POP} with no resistor applied. For that configuration ΔPH_{POP} revealed a sensitivity of 70% and specificity of 100% with a positive predictive value of 100%, a negative predictive value of 40%, and an AUC of 0.80 (Fig. 3) when ΔPH_{POP} was larger than 14%. Furthermore there was no correlation between ΔPH_{POP} or PVI® and PPV, SPV or SVV.

Hemodynamic variables supporting central hypovolemia during head-up tilt are shown in Table 3 along with respiratory variables.

Discussion

This study indicates that central hypovolemia, i.e. at least 10% decrease in CO, cannot be detected during spontaneous breathing by variations in pulse oximetry tracings, using an inspiratory and/or expiratory resistor.

Fluid therapy supports the circulation in emergency and critical care medicine as during anesthesia and optimization of CO reduces postoperative complications [21]. However, during spontaneous breathing it is not established how hypovolemia or fluid responsiveness should be determined [22]. In spontaneously breathing swine arterial pressure variation can detect fluid responsiveness if they are breathing through combined inspiratory and expiratory resistors that

augments PPV [23] and in healthy volunteers arterial pressure variations can be augmented by such resistors and be used to detect a central volume deficit [Dahl et. al In press].

After enhancing the intrathoracic pressure swings we evaluated ΔPH_{POP} and PVI® as non-invasively variables to detect a 10% reduction in CO provoked by 45° head-up tilt. In contrast to our expectation we were not able to demonstrate any significant effect in spontaneously breathing subjects when the subjects were breathing through various resistances. The inspiratory resistor, the expiratory resistor and the combination of these resistors tend to enhance PVI® during head-up tilt while there was no effect on ΔPH_{POP}.

We considered head-up tilt to be a suitable model for central hypovolemia. The cardiac dimensions are reduced along with a reduction in thoracic electrical admittance and plasma atrial natriuretic peptide (ANP) supporting depletion of the central blood volume [24]. The maximum heart rate increase after head-up tilt was after one minute. This indicates that head-up tilt induces or aggravates central hypovolemia and that the equilibration is brought to completion after approximately one minute [25]. At the same time, head-up tilt to 50 degrees produces central hypovolemia resulting in pre-syncopal symptoms within one hour in almost 90% of healthy volunteers. The sloop of the tilt probability curve seems almost linear [26].

Our study has several limitations: First, we defined central hypovolemia as at least a 10% drop in CO [7, 9, 27, 28]. However, using, e.g. 15%, 20% or 25% might change the findings. Secondly, our subjects were healthy volunteers and they may therefore not be representative for a hospitalized population. Thirdly, even though we used head-up tilt to provoke central hypovolemia and a decrease in CO by more than 10% in 10 of 13 subjects when exposed to 45° head-up tilt, a larger tilt angle might result in a more significant drop in CO. Fourthly, according to practice in our hospital, we used an uncalibrated pulse contour technic to detect SV and CO. Using alternative commercial techniques, e.g. PiCCO® might alter the results [29]. Fifthly, we used a 7.5 cm H_2O threshold resistance that in our animal study gave clear indications of hypovolemia on SPV [23]. Whether higher resistance would have given other results is unclear from this study. Nevertheless, the used threshold resistance is used for positive end-expiratory pressure and continuous positive airway pressure and is tolerated by most patients.

CONCLUSION

Ventilation induced variations in the noninvasive variable PVI® tend to be enhanced by breathing spontaneously through inspiratory or expiratory resistors while the variable ΔPH_{POP} is not. Neither PVI® nor ΔPH_{POP} were able to detect central hypovolemia induced by a 10% CO reduction after 45° head-up tilt.

List of abbreviations

ANP = Atrial Natriuretic Peptide

CO = Cardiac Output

CVP = Central Venous Pressure

PH_{max} = Maximal Peak Height of the Pulse Oximetry Plethysmographic waveform

PH_{min} = Minimal Peak Height of the Pulse Oximetry Plethysmographic waveform

PVI© = Pleth Variability Index

SV = Stroke Volume

ΔPH_{POP} = peak height of the pulse oximetry plethysmography waveform variations

PPV = Pulse Pressure Variations

SPV = Systolic Pressure Variation

SVV = Stroke Volume Variation

Competing interests

The authors declare no conflict of interest.

Authors' contribution

MD and NHS participated in the design, laboratory work, data analysis and writing the manuscript. AL, CH and BSR participated in the design, data analysis and in finalizing the manuscript.

Acknowledgements

Anders Larsson is supported by grants from the Swedish Heart and Lung foundation and from the Swedish Research Council (K2015-99X-22731-01-4). We thank the Laerdal Foundation for Acute Medicine for financial support, Maria Rodrigo, MSc, statistician, Aalborg University Hospital for help.

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FIGURE LEGENDS

Figure 1. Healthy volunteer placed head-up with combined inspiratory and expiratory resistor applied.

Figure 2. Screen dump illustrating measurements of PH_{max} and PH_{min}.

Figure 3. Receiver operating characteristic (ROC) curves for ΔPH_{POP} with the four respiratory resistors. Area under the ROC curve is 0.80 (0.54;1.00) (confidence interval) for no resistor, 0.63 (0.18;1.00) for the inspiratory resistor, 0.60 (0.00;1.00) for the expiratory resistor, and 0.44 (0.00;0.91) for the combined in- an expiratory resistor.

TABLES

Table 1. Airway resistor influence of PVI® and ΔPH_{POP}.

	No resistor (%)	Inspiratory resistor (%)	Expiratory resistor (%)	Inspiratory/expiratory resistor (%)
PVI®				
Supine position	28 ± 9	29 ± 9	30 ± 9	29 ± 7
Head-up tilt	24 ± 10	29 ± 9*	32 ± 8*	35 ± 7*
Head-down tilt	30 ± 13	31 ± 9	28 ± 10	30 ± 7
ΔPH_{POP}				
Supine position	12 ± 5	7 ± 6	11 ± 7	11 ± 4
Head-up tilt	10 ± 5	12 ± 6	10 ± 7	11 ± 7
Head-down tilt	11 ± 9	12 ± 6	10 ± 5	13 ± 8

Values are mean ± standard deviation. * $P < 0.05$ compared to no resistor.
PVI® Pleth variability index. ΔPH_{POP} Variation in Peak Height of Pulse oximeter plethysmographic waveform.

Table 2. Sensitivity, specificity, positive predictive value and negative predictive value using a 10% difference in cardiac output between supine position and head-up tilt defining central hypovolemia.

	AUC	Optimal cut-off (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
PVI®						
No resistor	0.65 (0.27;1.00)	28	70	67	88	40
Inspiratory resistor	0.67 (0.11;1.00)	39	78	67	88	50
Expiratory resistor	0.68 (0.15;1.00)	41	90	67	90	67
Inspiratory/expiratory resistor	0.43 (0.00;1.00)	22	90	33	82	50
ΔPH_{POP}						
No resistor	0.80 (0.54;1.00)	14	70	100	100	40
Inspiratory resistor	0.63 (0.18;1.00)	9	78	67	88	50
Expiratory resistor	0.60 (0.00;1.00)	32	100	50	91	100
Inspiratory/expiratory resistor	0.44 (0.00;0.91)	8	63	50	83	25

AUC = Area Under the Curve with confidence interval.
PVI® Pleth variability index. ΔPH_{POP} Variation in Peak Height of Pulse oximeter plethysmographic waveform.

Table 3. Hemodynamic and respiratory variables in three positions regardless of respiratory resistors applied

	Supine position	Head-Up Tilt	Head-Down Tilt
Cardiac output (L/min)	5.8 ± 2.9	4.0 ± 1.8*	5.1 ± 2.2*
Stroke Volume (mL)	91 ± 46	55 ± 25*	81 ± 36*
Systolic blood pressure (mm Hg)	127 ± 14	121 ± 13*	120 ± 11*
Diastolic blood pressure (mm Hg)	64 ± 7	69 ± 6*	65 ± 6
Heart rate (min^{-1})	65 ± 11	75 ± 13*	65 ± 11
Respiratory rate (min^{-1})	10 ± 4	10 ± 4	10 ± 3
Ph	7.43 ± 0.03	7.45 ± 0.04*	7.44 ± 0.04
Peripheral oxygen saturation (%)	99 ± 1	99 ± 1	99 ± 2
Oxygen partial pressure (kPa)	14.1 ± 1.6	14.3 ± 1.0	14.7 ± 1.6*
Carbondioxid partial pressure (kPa)	5.0 ± 0.6	4.6 ± 0.7*	4.8 ± 0.7*

Values are mean ± standard deviation. * $P < 0.05$ compared with the supine position.
There was no interaction between position and application of resistors.

Fig. 1. Dahl et. al. Paper_III

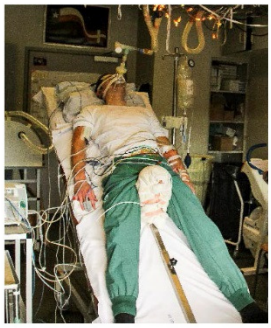


Fig. 2. Dahl et. al. Paper_III

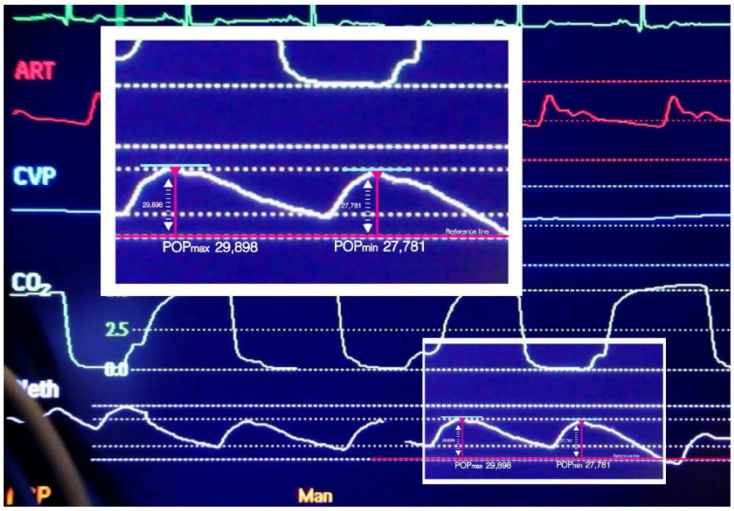
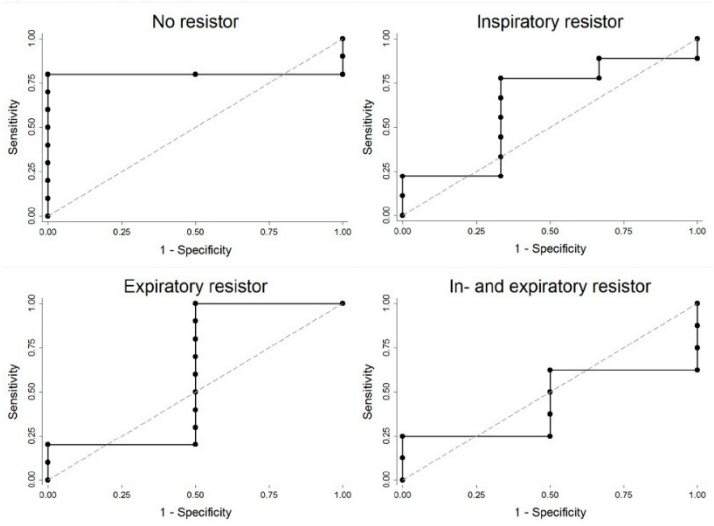


Figure 3. [ΔPH_{PCP}_10_HUT_paperIII] Dahl et at.



ISSN (online): 2246-1302
ISBN (online): 978-87-7112-450-7

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