From the Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine

Karolinska Institutet, Stockholm, Sweden

PERFORMANCE OF A REVISED CAPNODYNAMIC METHOD FOR CARDIAC OUTPUT MONITORING

Thorir Sigmundsson

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Til Huldu og strákanna

"It always seems impossible until it´s done"
Nelson Mandela

Institutionen för Fysiologi och Farmakologi
Sektionen för Anestesiologi och Intensivvård

Performance of a revised capnodynamic method for cardiac output monitoring

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av
Thorir Sigmundsson
MD

Huvudhandledare:
Dr. Håkan Björne
Karolinska Institutet
Institutionen för Fysiology och Farmakologi
Sektionen Anestesi och Intensivvård

Bihandledare:
Dr. Caroline Hällsjö Sander
Karolinska Institute
Institutionen för Fysiologi och Farmakologi
Sektionen Anestesi och Intensivvård

Prof. Anders Oldner
Karolinska Institute
Institutionen för Fysiologi och Farmakologi
Sektionen Anestesi och Intensivvård

Fakultetsopponent:
Prof. Thomas W.L. Scheeren
University of Groningen
Department of Anaesthesiology

Betygsnämnd:
Prof. Claes Frostell
Karolinska Institute
Institutionen för Kliniska Vetenskaper

Docent Miclos Lipcsey
Uppsala Universitet
Institutionen för Kirurgiska Vetenskaper
Enheten för Aestesiologi och Intensivvård

Docent Sigurbergur Kárason
University of Iceland
School of Health Sciences
Faculty of Medicine

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Summary in Icelandic

Markviss meðferð (*e. goal-directed therapy*) með vökva og samdráttarhvetjandi lyfjum getur fækkað fylgikvillum og aukið lífslíkur í kjölfar stórra skurðaðgerða með því að hjálpa líkamanum að mæta aukinni súrefnisþörf við slíkar aðstæður. Meðferðinni er yfirleitt stýrt með tækjum sem mæla hjartaútfall (*e.cardiac output*), sem er blóðmagnið sem hjartað dælir á hverri mínútu. Þýski lífeðlisfræðingurinn Adolf Fick lýsti fyrstur aðferð til mæla útfall hjartans árið 1870, en ekki var hægt að gera það hjá sjúklingum fyrr en árið 1940. Aðferðin þóaðist og á áttunda áratug nítjándu aldar var lungnaslagæðaleggurinn (*e. pulmonary artery catheter - PAC*) tekinn í notkun sem gat gefið nákvæmar upplýsingar um starfsemi hjartans og blóðrásarkerfisins. Ekki hefur verið sýnt fram á ávinning af notkun hans og hætta á alvarlegum fylgikvillum er mikil. Á síðustu árum hafa komið fram fjölmargar nýjar aðferðir sem eru einfaldari í notkun og áhættuminni en PAC, en hafa verið gagnrýndar fyrir að vera ónákvæmar við aðstæður þegar mest á reynir, kostnaðarsamar og takmörkunum háðar. Það er því mikil eftirspurn eftir nákvæmri og einfaldri aðferð til að stýra meðferð markvisst við erfiðar aðstæður, án allra aukahluta eða ífarandi inngripa svo að áhætta fyrir sjúkling verði sem minnst og fylgikvillar í kjölfar stórra aðgerða mögulega færri.

Árið 1980 komu Gedeon og félagar fram með byltingarkennda hugmynd um aðferð til að áætla hjartaútfall til lungna út frá mælingum á koltvísýrlingi í útöndunarlofti. Hjartaútfall til lungna sem samsvarar hjartaútfalli um meginslagæð líkamans þegar framhjá-flæði (*e. shunted flow*) er lítið.

Aðferðin, sem er án allra ífarandi inngripa, þróaðist með hléum en ekki tókst að gera hana nógu stöðuga til að mæla hjartaútfallið samfellt frá einum andardrætti til hins næsta fyrr en árið 2014. Kapnódýnamíska aðferðin (*e. capnodynamic method*), eins og hún kallast, krefst þess að sjúklingurinn sé sofandi og tengdur við öndunarvél sem stjórnar önduninni alfarið. Með því að lengja útöndunartímann í þremur af hverjum níu andardráttum er hægt að breyta styrk koltvísýrings í útöndunarlofti milli andardrátta og reikna blóðflæðið till lugnanna (*e. effective pulmonary blood flow - EPBF*). Það er gert með sjálfvirkri bestun á minnstu fervikum (*e. least square error optimization*) þegar níu stærðfræðijöfnum (ein fyrir hvern andardrátt) er raðað saman.

Markmið þessarar doktorsritgerðar var að bera saman kapnódýnamísku aðferðina við nákvæmar viðmiðunaraðferðir í krefjandi aðstæðum sem geta komið upp í skurðaðgerðum. Í fyrstu þremur rannsóknunum, sem allar eru tilraunir á stórum grísum, bárum við kapnódýnamísku aðferðina saman við flæðismæli sem umlykur lugnaslagæðina og mælir nákvæmlega hjartaútfall. Í þessum tilraunum var aðferðin prófuð við margbreytilegar aðstæður, til dæmis við skyndilega breytingu á blóðflæði til hjartans, inngjöf samdráttarhvetjandi lyfja, stóra blæðingu, endurflæði (*e. reperfusion*), öndunarbilun og margar mismunandi stillingar á öndunarvélinni. Í fjórðu og síðustu rannsókninni var kapnódýnamíska aðferðin notuð í fyrsta skipti á 35 sjúklingum sem gengust undir stórar kviðarholsaðgerðir og borin

saman við nákvæma viðmiðunaraðferð (*transpulmonary thermodilution*) sem krefst æðaleggja í stóra bláæð og slagæð.

Í þessum rannsóknum reyndist kapnódýnamíska aðferðin nákvæm og áreiðanleg við margbreytilegar aðstæður hjá grísum og mönnum og fylgdi vel breytingum (*e. trending*) á hjartaútfalli.

Við mikið endurflæði, sem oft á sér stað í stórum æðaskurðaðgerðum, varð tímabundin truflun á mælingum sem endurstilltist innan 5 mínútna. Við öndunarbilun eftir lungnaskaða minnkaði nákvæmnin, eins og við var að búast, en fylgnin við breytingar á hjartaútfalli hélst nokkurn veginn óbreytt miðað við hefðbundnar aðstæður í heilbrigðum lungum. Í klínísku rannsókninni var nákvæmnin góð og kapnódýnamíska aðferðin fylgdi vel breytingum á hjartaútfalli, t.d. þegar gefinn var vökvi í æð, samdráttarhvetjandi lyf notuð, eða öndunarþrýstingur aukinn.

Kapnódýnamíska gæti reynst öruggur og ódýr valkostur þegar stýra á flókinni meðferð við erfiðar aðstæður í umfangsmiklum skurðaðgerðum í framtíðinni. Áframhaldandi rannsóknir munu vonandi leiða í ljós hvort það leiði til ávinnings fyrir sjúklinga.

Abstract

Cardiac output (CO) monitoring is ideal for guiding fluid, vasopressor and inotropic therapy for sufficient oxygen delivery and may improve outcome in high risk surgery. In this context, many minimally-and non-invasive methods have emerged during recent years, however, they appear less reliable when compared to the thermodilution methods during rapid changes in vascular volume and resistance, a common feature during major surgery.

The capnodynamic method calculates non-shunted cardiac output, the effective pulmonary blood flow (CO_{EPBF}), on the basis of a capnodynamic equation describing the mole balance of CO_2 transported to and from the lungs. By prolonging three out of every nine breaths in mechanically ventilated patients, CO_{EPBF} is automatically and continuously calculated with each new breath.

In previous studies the capnodynamic method with inspiratory holds provided CO monitoring, however with unacceptable accuracy and precision during lung injury and elevated positive end-expiratory pressure (PEEP).

In this thesis we evaluated the revised capnodynamic method with expiratory holds in four separate studies. In a large animal model (study I-III), CO_{EPBF} was compared to a gold standard flowmeter placed around the pulmonary trunk during different hemodynamic, ventilatory, respiratory and metabolic challenges. Finally, CO_{EPBF} was compared to transpulmonary thermodilution in patients undergoing high risk abdominal cancer surgery.

The capnodynamic method showed overall acceptable agreement and good trending abilities in a variety of conditions familiar to a perioperative team. The agreement was temporarily disrupted after ischemia-reperfusion, however reestablished within five minutes. The accuracy was marginally affected during lung injury, both at high shunt fractions and after recruitment manoeuvre with PEEP adjustment. However, both precision and trending ability were maintained. In high risk patients, CO_{EPBF} showed good accuracy, acceptable precision and good trending ability in various conditions. The performance was especially robust after individualized lung recruitment and PEEP adjustment.

CO_{EPBF} may provide continuous CO monitoring with short response time, good trending abilities and acceptable agreement to guide hemodynamic treatment during surgery.

Keywords: cardiac output; carbon dioxide; capnography; hemodynamics; thermodilution; animal model; mechanical ventilation, reperfusion; lung injury; respiratory failure; surgery

List of scientific papers

The following papers compose the thesis presented here and will be referred to by their roman letters.

I. A modified breathing pattern improves the performance of a continuous capnodynamic method for estimation of effective pulmonary blood flow
Sander CH, Sigmundsson T, Hallbäck M, Sipmann FS, Wallin M, Oldner A, Björne H.
J Clin Monit Comput. 2017 Aug;31(4):717-725. doi: 10.1007/s10877-016-9891-z. Epub 2016 Jun 1.

II. Performance of a capnodynamic method estimating effective pulmonary blood flow during transient and sustained hypercapnia
Sigmundsson TS, Öhman T, Hallbäck M, Redondo E, Sipmann FS, Wallin M, Oldner A, Hällsjö Sander C, Björne H.
J Clin Monit Comput. 2018 Apr;32(2):311-319. doi: 10.1007/s10877-017-0021-3. Epub 2017 May 11.

III. The performance of a modified capnodynamic method in respiratory failure and after lung recruitment
Sigmundsson TS, Öhman T, Hallbäck M, Redondo E, Sipmann FS, Wallin M, Oldner A, Hällsjö Sander C, Björne H.

Manuscript

IV. The performance of the capnodynamic method for cardiac output monitoring during major abdominal surgery
Sigmundsson TS, Öhman T, Hallbäck M, Wallin M, Sipmann FS, Oldner A, Hällsjö Sander C, Björne H.

Manuscript

List of abbreviations

4Q	Four Quadrant
ASA	American Society of Anesthesiology
BL	Baseline
C_aCO_2	Content of Carbon dioxide in arterial blood
C_cCO_2	Content of Carbon dioxide in pulmonary end-capillary blood
C_vCO_2	Content of Carbon dioxide in mixed venous blood
CE	Coefficient of Error
C_aO_2	Content of Oxygen in arterial blood
C_cO_2	Content of Oxygen pulmonary end-capillary blood
CO	Cardiac Output
CO_2	Carbon dioxide
CO_{EPBF}	Effective pulmonary blood flow as assessed by the capnodynamic method with *expiratory* holds
$CO_{EPBFinsp}$	Effective pulmonary blood flow as assessed by the capnodynamic method with *inspiratory* holds
CO_{PAC}	Cardiac Output as assessed by the pulmonary artery catheter
CO_{TPT}	Cardiac Output as assessed by the Transpulmonary Thermodilution method (in animal studies)
CO_{TPTD}	Cardiac Output as assessed by the Transpulmonary Thermodilution method (in human studies)
CO_{TS}	Cardiac Output as assessed by the ultrasonic flow probe
CV	Coefficient of Variation
Δt^n	Duration of each breathing cycle
ELV	Effective Lung Volume
EELV	End-Expiratory Lung Volume
EPBF	Effective Pulmonary Blood Flow
F_ACO_2	Alveolar fraction of Carbon dioxide
F_iO_2	Fraction of inspired oxygen
Fr	French (as a measurement of catheter size)
FRC	Functional Residual Capacity
GDT	Goal-Directed hemodynamic Therapy
I:E ratio	Ratio between length of inspiration and expiration.
ICU	Intensive Care Unit
L_{gas}/L_{blood}	Liter gas per Liter blood
L/min	Liter per minute
LSC	Least Significant Change
LoA	Levels of Agreement
MAP	Mean Arterial Pressure
ME	Mean Error (same as percentage error)
n	Current breath (in the capnodynamic equation)
n-1	Previous breath (in the capnodynamic equation)
O_2	Oxygen
Q_s/Q_t	Shunted fraction
PAC	Pulmonary Artery Catheter
Pb	Barometric pressure
PE	Percentage Error
PEEP	Positive End Expiratory Pressure
P/F ratio	Partial pressure of oxygen in arterial blood divided by inspired fraction of oxygen
P_aO_2	Partial pressure of arterial oxygen
P_aCO_2	Partial pressure of Carbon dioxide in arterial blood
P_ACO_2	Partial pressure of Alveolar carbon dioxide
$PeCO_2$	Partial pressure of Carbon dioxide in mixed expired air
$P_{ET}CO_2$	Partial pressure of end-tidal Carbon dioxide
PP	Polar Plot
RM	Recruitment Manoeuvre
RQ	Respiratory Quotient
RR	Respiratory Rate
S_{CO2}	Solubility coefficient for Carbon dioxide in blood
SD	Standard Deviation
Sec	Seconds
SV	Stroke Volume
SVR	Systemic Vascular Resistance
VCO_2	Volume of carbon dioxide eliminated from the lungs
$VTCO_2^n$	Volume of Carbon dioxide exhaled by the ^{nth} tidal volume

Introduction

Since ether was first introduced in Boston 1846, anaesthesia providers have endeavored to keep patients safe during surgery. Swiping someone into his dreams carries great responsibilities as vital functions are left in the hands of the caring team. Meticulous delivery of all essential ingredients, keeping the perfect physiological balance resides deep in the profession and can make all the difference for the patient. In high risk surgery, where rapid changes in vital functions are common, this quest can be arduous. With technological advancements during the last two centuries; the sphygmomanometer measuring blood pressure, the electrocardiograph showing the mystical electronic waves of the heart, the blood gas analysis, the pulse oximeter and the evolution of mechanical ventilation from the iron lung in the polio epidemic to the modern ventilator, has moved our boundaries and improved care. However, an important physiological parameter like the cardiac output, representing the volume of blood pumped by the heart each minute, is still difficult to measure reliably, especially during surgery where situations rapidly change. For the last few decades, a plethora of new technology has emerged to provide useful information to the caring team, however, lapsing in critical situations.

A new capnodynamic method, integrated in a modern ventilator, utilizes carbon dioxide in exhaled air to continuously estimate the cardiac output. Based on old physiological principles, this method brings the heart closer to the lungs and could provide monitoring when needed the most. In this thesis we have vigorously tested the capnodynamic method to define its limits and reliability in various situations and ultimately its performance during high risk surgery.

Background

Goal-directed hemodynamic therapy (GDT) has been proposed to counteract the surgical stress response and oxygen demand by improving organ perfusion and oxygen delivery to the cells [1-4]. Cardiac output (CO) represents the flow to the body organs and is considered ideal to guide GDT [5,6]. Patients with reduced capacity to compensate for the increased oxygen demand in the perioperative period are more likely to acquire complications or even die within 30 days after surgery [7,8]. In fact, out of total 300 million surgical procedures performed each year, 10% are considered high risk accounting for the large majority of deaths and complications [9,10]. Even after moderate risk surgery, complications are relatively common [11,12] and may cause increased length of hospital stay, higher costs and importantly, decreased life expectancy *per se* [11,13].

A common pathway to postoperative complications is either hypoperfusion or edema, both affecting oxygen delivery to the cells [7,14]. The ultimate goal is therefore to accomplish a perfect physiological homeostasis for the individual patient with regards to both flow and pressure in a timely fashion to avoid organ dysfunction, complications and death.

Numerous meta-analyses have proposed beneficial effect of GDT on perioperative complications and mortality, especially in high risk surgery [3,8,15,16]. However, recent evidence has questioned its benefit [17-20]. The benefit or lack thereof seems to depend on many factors; the patient population and type of surgery [8,21,22], the hemodynamic goals [23], composition of interventions (fluids/vasopressors/inotropy) [24], timing of implementation [3,25] and the monitoring methods used [23,26].

Professors Michael R Pinsky and Didier Payen wrote [27]: *"No monitoring device, no matter how accurate or complete, would be expected to improve patient outcome, unless coupled to a treatment that itself improves outcome*". True as it can be, one might however turn the argument around and state: without hemodynamic monitoring, there is no GDT. If we are to react to and treat all the rapid physiological changes commonly encountered in the operation theatre we are nevertheless dependent on continuous monitoring and preferably of both pressure and flow. In this thesis we focus on CO, which is ideally used to guide flow in constantly changing hemodynamic situations, where heart rate and blood pressure sometimes fail to give reliable information on patient´s hemodynamic status [28]. The ideal CO monitor should be safe for the patient, easy to use and operator independent, produce continuous accurate and reproducible measurements with short response time and provide reliable trending when changes in CO emerge.

Cardiac output measurement

Historic review – the Fick method

In 1870 the German physiologist Dr. Adolf Fick (see figure 1) presented his famous equation to calculate CO, originally derived from the oxygen consumption and the difference in arteriovenous content of oxygen between the right and left ventricle of the heart [29].

$$CO = \frac{VO_2}{CaO_2 - CvO_2}$$

Equation 1. The Fick equation presented in 1870.

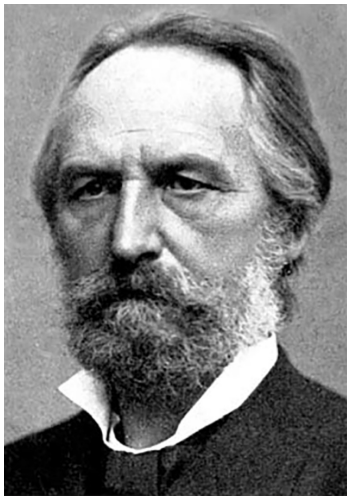

Figure 1. Adolf Fick, physiologist 1829 -1901. Reprinted with permission from Springer Science+Business media, Inc. Science and technology in medicine by Andras Gedeon © 2006

At the time, calculation of oxygen content in blood was impossible and expired air had to be equilibrated with alveolar gas to determine the content in mixed venous blood. In addition, the oxygen consumption could only be analyzed indirectly [30]. Provided with data from the laboratory in Ludwig and the assumption that humans and dogs have the same difference in arterio-venous content, Fick calculated the CO to be 5.4 L/min [31]. The equation describes a mass balance and can be used with other tracers or gases. Carbon dioxide (CO_2) was early identified as an alternative to oxygen, as it can be found in large stores in the body and both elimination and mixed venous/arterial CO_2 tension (P_vCO_2 and P_aCO_2) are more stable and easier to measure [32]. Gréhant and Quinquaud were the first to measure the pulmonary perfusion in dogs using elimination of CO_2 from the lungs in 1886 [31]. The first "non-invasive" measurements of CO in man, were made by Löwy and v. Schrötter in 1905, where they obtained oxygen gas samples through a catheter placed in a closed section of the lung (see figure 2) [31]. The Fick method did not become clinically available until right heart catheterization was introduced by Forssman in 1929. Cournand and Richards were the first to directly measure CO directly in humans. All three received the Nobel Prize in 1956 [33]. The direct Fick method was used clinically until the

Figure 2. One of the first non-invasive measurments of CO by Löwy and von Schrötter. Venous blood gas samples (O_2 in this case) were obtained through a catheter placed in a closed off section of the lung [31]. Reprinted by permission from Springer Science+Business media, Inc. Science and technology in medicine by Andras Gedeon © 2006

balloon flotation pulmonary artery catheter (PAC) was presented by Swan and Ganz in the 1970´s [34] and thermodilution became the clinical reference method to calculate CO [35].

Thermodilution methods

Soon after its arrival, the PAC was used for hemodynamic monitoring during surgery and intensive care. The PAC calculates CO via trans-cardiac thermodilution (triplicate cold saline boluses or thermofilament) and measures pressure (right atrial pressure, pulmonary artery pressure, pulmonary artery occlusion pressure) in the right sided circulation and enables gas sampling of mixed venous blood [36]. However, its use has greatly diminished in recent years as catheterization through the right heart is cumbersome, risks serious complications and the interpretation of the values provided is user dependent [36,37]. Besides complex cardiac surgery it is mainly used in patients in the intensive care unit (ICU) with right sided heart failure [38].

Transpulmonary thermodilution (TPTD) provides accurate measurement of CO, equivalent to the PAC [39]. TPTD utilizes three cold boluses of fluid injected in a central vein catheter (CVC) and sensed by a thermistor tipped arterial catheter creating a thermodilution curve allowing calculation of CO by the Stewart Hamilton equation. The arterial catheter is most commonly inserted in the femoral artery but the PiCCO system offers catheters also for the axillary and brachial artery [40].

Both the PAC and TPTD are considered invasive methods that requires special skills and equipment. Both techniques are considered time consuming and are rarely used in the non-cardiac perioperative settings [41,42].

Minimally and non-invasive methods

In recent years, many minimally and non-invasive CO monitors have emerged with different qualities and limitations [43]. These new monitors are commonly compared to the thermodilution methods to estimate their accuracy, precision and trending ability. However, they all have technology-specific and device-specific problems when used in routine clinical practice (see table 1 for overview) [44-47].

In summary

The thermodilution methods are too invasive and complex for routine use in non-cardiac surgery. Validation studies have found the new minimally- and non-invasive monitoring methods, each with its own advantages and limitations, to be less reliable than thermodilution based methods. This pertains especially to rapid changes in vascular volume and resistance which is a common feature during major surgery [45,48-51]. This underlines the need for a feasible minimally- or non-invasive CO monitor which is both fast, safe and reliable during hemodynamic changes providing continuous, accurate monitoring of trends during surgery in a safe manner [23,52].

Technology	Requirements	System	Peyton *et al*, 2010 42 studies, 1373			Joosten *et al*, 2017 37 studies, 1543 patients			Limitations	Advantages
			N/n	Bias LOA (L/min)	PE (%)	N/n	Bias LOA (L/min)	PE (%)		
Uncalibrated pulse contour analysis	Arterial catheter Extra monitor	FloTrac ProAQT LiDCO Rapid	24/714	-0,0 -1,2 to 1,2	41,3				Dependent on high quality arterial waveform signal Arrhythmias and aortic disease Reliant on mechanical ventilation for dynamic indices	Mini-invasive Can be used on awake patients Positive outcome studies (FloTrac) Newer versions with better performance
	Finger Cuff Volume clamp	Clearsight CNAP		N/A	N/A	9/334	-0,2 -2,3 to 2,0	42	Decreased accuracy during vasoconstriction and finger edema	Non-invasive Can be used on awake patients Continuous non-invasive blood pressure measurements
Pulse wave transit time	Basic hemodynamic variables	esCCO				5/532	0,31 -2,5 to 3,1	62	Low accuracy without calibration	Needs only basic monitoring Continuous monitoring
Doppler	Oesophageal probe Extra monitor	Cardio Q	2/57	-0,77 -1,8 to 0,3	42,1				Easily interrupted by electrical interference (diathermy) Dependent on correct placement and operator skills	Positive outcome studies
CO_2 rebreathing	Rebreathing loop Extra monitor	NICO	8/167	-0,05 -1,2 to 1,1	44,5	14/297	-0,2 -2,4 to 2,0	40	Mechanical ventilation High pulmonary shunt fraction Low $PaCO_2$	Independent of heart rhythm and vascular disease
Thoracic electrical -bioimpedance -bioreactance	Electrodes placed on the skin of the thorax	Aescolon NICOM	13/435	-0,1 -1,2 to 1,0	42,9	10/380	-0,2 -2,4 to 2,0	42	Easily interrupted by electrical interference and motion	Easy installation Continuous measurements

Table 1. Adapted from [45,46,53,54], showing pooled mean bias, precision and PE of different minimally invasive and non-invasive hemodynamic monitoring systems as well as requirements, advantages and disadvantages for each technology.

Carbon dioxide and cardiac output monitoring

A journey from the mitochondria to the lungs and back

Carbon dioxide is the end-product of energy metabolism; continuously produced in large amounts (200 ml/minute) in the mitochondria as the final catabolite of aerobic oxidative phosphorylation and in small amounts in conjunction with anaerobic glycolysis. Via concentration gradients, CO_2 diffuses through the cytoplasm and extracellular fluid into the nearest venous capillaries, promoting the release of oxygen from hemoglobin (Bohr effect). Carbon dioxide is transported via the bloodstream mainly as bicarbonate (80-90%) or bound to proteins (5-15%) including hemoglobin, as well as dissolved in plasma (5-10%). Via the right heart, blood full of CO_2 is pumped into the lungs (i.e., pulmonary blood flow) which approximates the total cardiac output. When it reaches the pulmonary capillary network, it is released again as CO_2, with the help of hemoglobin-bound carbonic anhydrase catalyst and the Haldane effect when hemoglobin binds to oxygen again. CO_2 then diffuses from the perfused alveoli, into the alveolar gas and lastly eliminated by alveolar ventilation to the atmosphere.

A note on pulmonary physiology

The pulmonary circulation is a low-pressure circuit accommodating to approximately the same flow as the systemic circulation, both during exercise and rest. The volume of blood in the pulmonary circuit at any given time in a normal adult is about 0.5-1.0 L and is mainly affected by body posture. The pulmonary blood flow is determined by the driving pressure, the difference between the mean intravascular pulmonary artery pressure (mPAP) and the pressure in the left atrium. Unlike the systemic circulation, arteries, capillaries and veins contribute equally to resistance and can adapt to large changes in flow by either passive dilatation and/or recruitment of more capillaries, producing only small changes in pulmonary artery pressure.

PVR as the product of the driving pressure divided by the pulmonary blood flow can be affected in many ways; Δlung volumes (↑ at both extremely high and low volumes); Δ alveolar pressure (↑ at high pressure compressing the capillaries); Δ autonomic system (small effect in human); hypoxia (↑ due to reflex contraction of smooth muscle cells, diverting blood flow to the more oxygenated areas); and drugs (mainly ↓ to counteract pulmonary arterial hypertension).

In healthy lungs the ventilation (V) and perfusion (Q) through the capillary network are closely matched and often presented in terms of a ratio (V/Q). Both V and Q are preferentially distributed to the dependent and central regions of the lungs, mainly because of gravity and branching of the bronchial- and vascular tree. Theoretically if V and Q were uniformly distributed the ratio for each alveolus would be 0.8. Pulmonary disease commonly causes mismatch in the V/Q ratio and sometimes mechanical ventilation is used to try to restore the balance. Regions with perfusion but no ventilation have a V/Q ratio approaching zero

and regions where there is ventilation but no perfusion the ratio approaches infinity. Severely injured, mechanically ventilated lungs can have ratios from zero to infinity.

Shunt

The degree of admixture of venous blood with end-capillary blood is commonly divided into anatomical and physiological shunt. In a healthy normal person, there is always some anatomical admixture of blood mainly via the bronchial- and Thebaesian veins and physiologically from regions of the lung with a V/Q ratio >0 and <1. Pathological states such as atelectasis, bronchial obstruction and congenital heart disease, with flow from right to left, will increase the shunt. Shunt is calculated as a fraction, however precise volume or anatomical pathway cannot be defined. When calculated during FiO_2 1.0, the physiological component from different V/Q regions is minimized and only anatomical and pathological shunt estimated. For more details, please read the method section.

Dead space

The portion of the tidal volume that is not involved in the gas exchange is called dead space and as with the shunt, it is divided into anatomical (VD_{aw}) and alveolar components (VD_{alv}). Together they comprise what´s called physiological dead space (VD_{phys}), commonly calculated with either Bohr or Enghoff formula. Enghoff dead space (P_aCO_2-$PeCO_2$/P_aCO_2) is measured with volumetric capnography (mixed expired partial pressure of CO_2 – $PeCO_2$) and arterial blood gas sample and represents the global V/Q mismatch (units A-C in figure 3) as it includes venous admixture from low to zero V/Q areas. Bohr dead space (P_ACO_2-$PeCO_2$/P_ACO_2) can be measured continuously, breath by breath with volumetric capnography and represents V/Q areas >1 to infinity (see figure 3).

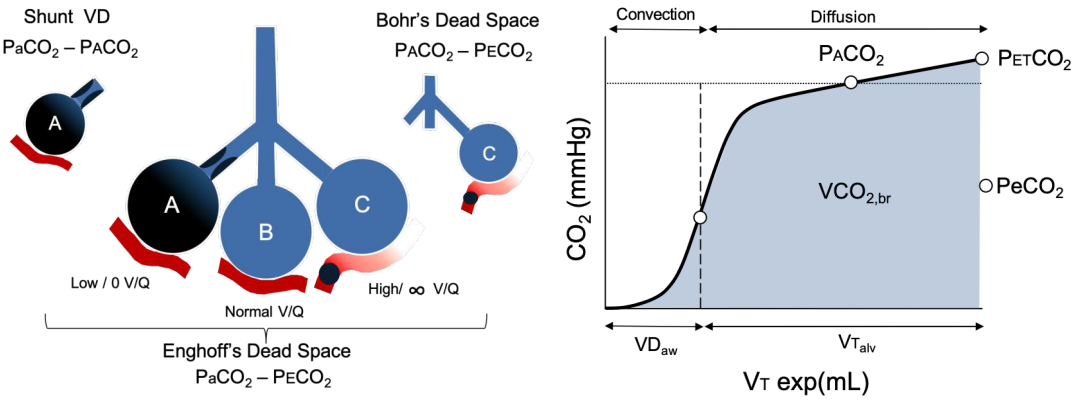

Figure 3. A simplified model of the lungs (*left*) showing A) shunt (V/Q = low to zero), B) an ideal unit, C) dead space and volumetric capnography (*right*) which describes the transport of CO_2 by convection (VDaw) and diffusion within alveoli (V_{Talv}). The area under the curve (*greyblue*) is VCO_2 for each breath and P_ACO_2, $P_{ET}CO_2$ and $PeCO_2$ are the mean alveolar, end-tidal and mixed expired partial pressures of CO_2. *Kindly provided by Fernando Suarez Sipmann.*

Differential Fick principle

In 1980, Gedeon *et al* described a new approach to circumvent invasive measurements of mixed venous CO_2 content (C_vCO_2) and called it the differential Fick's method [55]. The new method was dependent on a change in the alveolar CO_2 concentration; large enough to be measured accurately with capnography and small enough to keep C_vCO_2 stable (see equation 3).

The essential change in alveolar CO_2 can be accomplished by three means; (1) changes in the alveolar ventilation as originally described by Gedeon and applied by both the capnodynamic method, described in this thesis and the Capnotracking method (see below) [55], (2) changes in dead space by adding a rebreathing circuit as originally described by Capek *et al* [56] and used in the NICO system with different software versions (see below) [32,57] or (3) adding CO_2 to the inspiratory gas by different means [58].

Non-invasive calculations of EPBF, as described above, can be derived from the Fick method in the following way. Rewriting equation 1 with CO_2 instead of O_2 and where VCO_2 represents the elimination of CO_2 from the lungs, and C_vCO_2 and C_cCO_2 the content of CO_2 in mixed venous and pulmonary capillary blood, respectively (see figure 4 for visual explanation);

$$EPBF = \frac{VCO_2}{CvCO_2 - CcCO_2}$$

Equation. 2. The equation for effective pulmonary blood flow, based on the Fick principle. For simplicity we use *EPBF* when referring to the non-shunted CO. In Gedeon studies (and others) this entity has had different names.

By altering the CO_2 elimination between two time points (A and B) at steady state we can write;

$$EPBF = \frac{VCO_2^A - VCO_2^B}{(C_vCO_2^A - C_cCO_2^A) - (C_vCO_2^B - C_cCO_2^B)}$$

Equation 3. Two differential equations combined at two time points, A and B.

If we assume C_vCO_2 to be unchanged between the two time points A and B it can be shortened out and the EPBF can be expressed as;

$$EPBF = \frac{VCO_2^A - VCO_2^B}{C_cCO_2^B - C_cCO_2^A} = \frac{\Delta VCO_2}{\Delta C_cCO_2}$$

Equation 4. EPBF as a product of the change in CO_2 elimination (VCO_2) divided by the change in content of CO_2 in pulmonary capillary blood.

C_cCO_2 can be estimated non-invasively by measurement of alveolar or end-tidal CO_2 partial pressure (P_ACO_2 or $P_{ET}CO_2$) combined with the solubility coefficient of CO_2 in blood (S_{CO2}). The S_{CO2} is affected by the hemoglobin level and the oxygen saturation *per se* [56]. The final equation to describe the pulmonary flow using changes in alveolar partial pressure during steady state is therefore;

$$EPBF = \frac{\Delta VCO_2}{S_{CO_2} \times (P_ACO_2^B - P_ACO_2^A)}$$

Equation 5. EPBF as a product of the change in CO_2 elimination from the lungs divided by the change in alveolar (or end-tidal) partial pressure of CO_2 and the solubility coefficient for CO_2 in blood.

To accomplish the required changes in P_ACO_2 promptly, without affecting C_vCO_2 returning to the lungs (recirculation), mechanical ventilation is preferred.

Gedeon's original studies

In Gedeon´s original study from 1980 in anesthetized dogs, the alteration in P_ACO_2 was achieved by changes in the I:E ratio to have the least effect on the lung mechanics and dead space [55]. The results showed good agreement with thermodilution, however, the method required 15 minutes to achieve a new steady state for an additional measurement.

In 1985, Gedeon and colleagues applied calculations of EPBF in eight "seriously ill" patients with data from Wolff et al (1982) and 23 patients in "acute pulmonary failure" from Klose and Oswald (1981) to compare with oxygen delivery, static compliance and P_aO_2 at different PEEP levels. They observed that oxygen delivery was coincided with EPBF rather than the highest compliance or P_aO_2 and speculated that EPBF could be used to individually select the best PEEP for oxygen delivery.

With further refinement, Gedeon and his co-workers introduced two new features in 2002; a single breath hold (3 sec) for less interference in alveolar ventilation and effective lung volume (ELV) to account for the total amount of CO_2 stored in the lungs at time of change in P_ACO_2. After testing different equations they applied the most promising one to 18 patients following CABG operation and compared EPBF with thermodilution (Bias -0.18 L/min and standard deviation (SD) 0.62 L/min).

Capnotracking

In 2006, Peyton et al described the first breath-to-breath "capnodynamic" approach to calculate CO. Based on Gedeon's previous work, the tidal volumes where changed (±200ml) for every six breaths. The method was compared to an ultrasonic flow probe placed around the pulmonary trunk in sheep and showed relatively good agreement. However, there were difficulties achieving stable measurements. In 2012, Peyton *et al* presented a modified method he called "Capnotracking" which involves an automatic calibration manoeuvre where alveolar ventilation is changed by altering the respiratory rate and the I:E ratio to obtain a base-

line measurement of EPBF. Changes in EPBF are then "tracked" via measured elimination of VCO_2 and $P_{ET}CO_2$. The system includes a shunt correction obtained non-invasively and was recently upgraded with additional calibrations to increase precision [59,60]. Impressively, in patients undergoing cardiac surgery and liver transplantation with a wide range of CO and receiving vasopressor treatment, Capnotracking attained low bias (-0.3 L/min) and a precision of 38.3% when compared to thermodilution (PAC). Concordance rate when 15% change in CO was achieved was 81.4%. Interestingly, there was no correlation between lung function measured pre-operatively and the PE.

Partial carbon dioxide rebreathing

In 1988, Capek *et al* described another approach to estimate CO[56]. Based on Gedeon's studies, a rebreathing loop with automated opening valve near the Y-piece was added to the patient's breathing system to increase dead space and achieve the desired changes in VCO_2/C_aCO_2. The procedure included a 30 sec rebreathing time which kept C_vCO_2 stable during the 3.5 minutes each measurement lasted. Intuitively, hemoglobin was added to the equation as large changes could cause errors in the obtained value. Since then a few semi-continuous partial rebreathing instrument have been introduced commercially; NICO (Respironics, Murrysville, PA, USA) and the upgraded NM3 (Philips Respironics, Wallingford, CT, USA). Correction for shunt fraction is added non-invasively via pulse oximetry, FiO_2 inserted into Nunn´s iso-shunt fraction plots. In a recent meta-analysis the partial rebreathing CO_2 methods had the best agreement to a thermodilution method compared to the other non-invasive methods (bias -0.2 L/min, LoA -2.4 to 2.0 L/min and PE 40%). However, the partial CO_2 rebreathing methods are not suitable for use in the operation theatre, because of discontinuity and each measurement requires a steady state.

The capnodynamic equation

In 2013, Albu *et al* presented a new developed capnodynamic equation, allowing continuous measurements of EPBF, ELV and C_vCO_2. The capnodynamic equation can be explained in the following way.

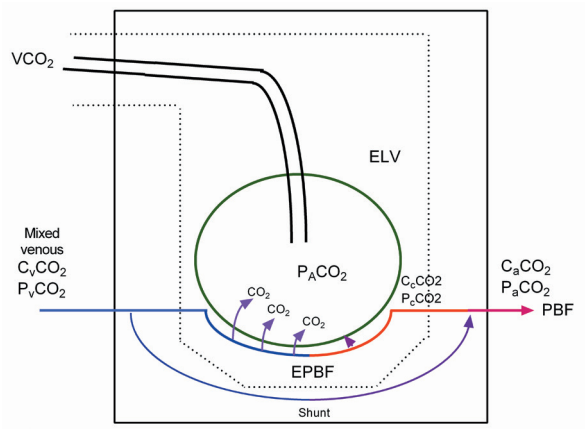

Figure 4. The flow of CO_2 through the lung. Mixed venous blood with certain partial pressure (P_vCO_2) and content (C_vCO_2) of CO_2 flows into the lung where part of the blood flow is shunted past the alveoli and admixtures arterial blood. Within the alveolar capillary unit (dotted lines) CO_2 diffuses into the alveoli (Haldane effect) and oxygen diffuses from the alveoli into the blood and binds hemoglobin. As CO_2 diffuses easily over the alveolar membrane, equilibrium with P_ACO_2 is quickly established, which then can act as a surrogate for the pulmonary capillary content of CO_2 (C_cCO_2).

The Fick principle, rewritten from equation 1 with CO_2, describes the blood flow outside of the *whole line* in figure 4 and can be rewritten as:

$$VCO_2 = PBF \times (C_vCO_2 - C_aCO_2)$$

Equation 6. VCO_2 is the elimination of CO_2 from the lungs, PBF is the total pulmonary blood flow and C_vCO_2 and C_aCO_2 represents the mixed venous and arterial content of CO_2 respectively.

In a steady state, where the amount of CO_2 in the lungs is constant the inflow of CO_2 is equal to the outflow and equation 6 can be expressed:

$$0 = PBF \times (C_vCO_2 - C_aCO_2) - VCO_2$$

Equation 7.

With the same argument, the balance within the *dotted lines* in figure 4 can be written as

$$0 = EPBF \times (C_vCO_2 - C_cCO_2) - VCO_2$$

Equation 8. EPBF is the non-shunted pulmonary blood flow and C_cCO_2 is the capillary content of CO_2.

By changing the alveolar P_ACO_2 between two different time points equation 8 can be further developed into:

$$\boldsymbol{ELV \times \left(F_ACO_2^n - F_ACO_2^{n-1}\right) = EPBF \times \Delta t^n \times (C_vCO_2 - C_cCO_2^n) - VTCO_2^n}$$

Equation 9. The capnodynamic equation. See explanation below.

ELV, effective lung volume (L) containing CO_2 at the end of expiration.
EPBF, effective pulmonary blood flow (L/min).
n, current breath.
n-1, previous breath.
$\boldsymbol{F_ACO_2}$, alveolar CO_2 fraction (of the total gas volume) estimated from the midpoint value (phase III) of the volumetric capnogram.
$\boldsymbol{C_VCO_2}$ mixed venous CO_2 content (L_{gas}/L_{blood}).
$\boldsymbol{C_cCO_2^n}$, lung capillary CO_2 content (calculated from F_ACO_2, the solubility of carbon dioxide in blood and hemoglobin concentration).
$\boldsymbol{V_TCO_2^n}$, volume (L) of CO_2 eliminated by the current, nth, breath.
$\boldsymbol{\Delta t^n}$, current breath cycle time (min).

The capnodynamic equation describes the mole balance between the flow of CO_2 delivered to the parts of the lungs participating in the gas exchange (EPBF), the volume taking part in the gas exchange (ELV) and the volume of CO_2 excreted from the lungs ($VTCO_2$). Normally there is no difference in CO_2 between the actual and the preceding breath as approximately the same amount of CO_2 is delivered to the lungs as is excreted. However, when short inspiratory or expiratory pauses are repeatedly introduced, small changes in F_ACO_2 concentration are

created between each breath (0.5 -1.0 kPa). In a loop of 9 to 10 breaths, equally many equations are formed and then stacked together. By optimizing the fit between a one compartment lung model and the measured data, the three unknown variables (ELV, EPBF and C_vCO_2) can be solved with a least square error optimization. The breathing pattern is automatically controlled by the ventilator which provides continuous calculations of EPBF where each value represents the average of the preceding 9 or 10 breaths. Each new breath creates a new equation which replaces the oldest in the equation system.

In the Albu *et al* study from 2013, the capnodynamic equation was used to calculate ELV and compare to end-expiratory lung volume (EELV) in anesthetized rabbits [61]. The essential changes in CO_2 were attained by automatic alterations in the I:E ratio in a predetermined breathing pattern including five consecutive normal breaths (I:E 1:2) with five breaths with inspiratory holds (I:E 1.5:1). EPBF was not reported in this study. For further information on ELV as an estimation of lung volumes, please read [62] and a recently published thesis [63].

The capnodynamic method with inspiratory holds

In 2014, Hällsjö Sander *et al* further evaluated the capnodynamic method with inspiratory holds to estimate CO ($CO_{EPBFinsp}$) in a large animal model in a series of induced hemodynamic changes [64]. When compared to an ultrasonic flow probe placed around the pulmonary trunk, accuracy, precision and trending were equivalent to the CO_{PAC} (PE 47 vs 49% and 4Q plot 97 vs 95-100%) [64]. In a following study [65], $CO_{EPBFinsp}$ was evaluated with the same reference method during changes in PEEP, both before and after lung injury (lung lavage surfactant depletion). As expected, lung injury created a large shunt fraction (up to 36%) affecting both accuracy and precision. As expected, with no shunt correction incorporated into the method, $CO_{EPBFinsp}$ underestimated CO after lavage. However, trending ability was largely unaffected. Unexpectedly, $CO_{EPBFinsp}$ overestimated CO at higher PEEP levels both before and after lung injury. There was no correlation between bias and dead space (Vd/Vt) calculated with the Bohr equation. The authors concluded that the phasic elevated airway pressure parallel to the inspiratory pause *per se,* may have disturbed the carbon dioxide signal, causing errors in the obtained $CO_{EPBFinsp}$ value [65].

The current revised capnodynamic method

After the studies conducted by Albu et al and Hällsjö Sander *et al*, the capnodynamic method was revised and modified. The difference in P_ACO_2, essential for the capnodynamic calculations, were now attained via extension of the expiratory part with six normal breaths in between, in total 9 breaths creating 9 equations as described before.

The revised capnodynamic method has recently been compared to a suprasternal Doppler in small children (6-23 months, 7.8-10.5 kg) during cleft lip surgery. CO_{EPBF} changed as expected to both increased PEEP (9 cmH_2O) and atropine, however, the agreement with the suprasternal Doppler was poor, which the authors prescribed to limitations of the ref-

erence method. An identical study protocol was repeated in piglets with an ultrasonic flow probe on the pulmonary trunk as reference. The agreement and trending ability reported was good [66]. The same small animals were (in another study protocol) subjected to hypoxia and inhaled nitric oxide (iNO), without affecting the performance of the method [67].

In summary, the current capnodynamic method has been in development for almost 35 years and is based on well-known physiological and mathematical principles. It provides non-invasive calculations of EPBF (CO minus shunt) and the ELV (proposedly the volume in the lungs that participates in the gas exchange).

How to validate a new cardiac output monitor?

As elegantly described by Saugel et al [68]: "CO is a hemodynamic variable that changes over time and is modified by a variety of factors closely related to oxygen supply and consumption, such as cardiac preload, cardiac afterload, and cardiac contractility. When performing validation studies for CO-monitoring technologies, it has therefore to be kept in mind that both the studied technology and the reference technology are aiming to hit a moving target".

Inherent precision

Describes the precision of the method during repeated measurments at steady state and is defined as two times the coefficient of variation (CV) where CV= SD/mean. Inherent precision is sometimes used to calculate the least significant change (LSC) which is the minimum change that can be detected as a "real" change by the method [69]. LSC is calculated as inherent precision × $\sqrt{2}$ and can be used to define exclusion zones (see trending ability below).

Accuracy and precision

The accuracy describes how close to the actual or real value the measurement is, whereas the precision describes how close together the measurements are [69]. A method consistently measuring CO 3 L/min when the "real" value is 5 L/min would be considered inaccurate but precise.

The Bland-Altman plot, introduced in the 1980s, provides visual assessment of the agreement between two methods by plotting the difference between the paired measurements against the average of the measurements [70]. The bias gives us estimation of accuracy (corresponding to the systematic error between both methods) and should preferably be as close to the X-axis as possible. The standard deviation of the bias (SD_{bias}) gives us the precision (corresponding to random error between the methods agreement) [69]. The level of agreement (LoA) is calculated as bias ± 1.96xSD_{Bias} and spans an interval that covers (with 95% certainty) the average differences between the two methods (see fig 5) [71].

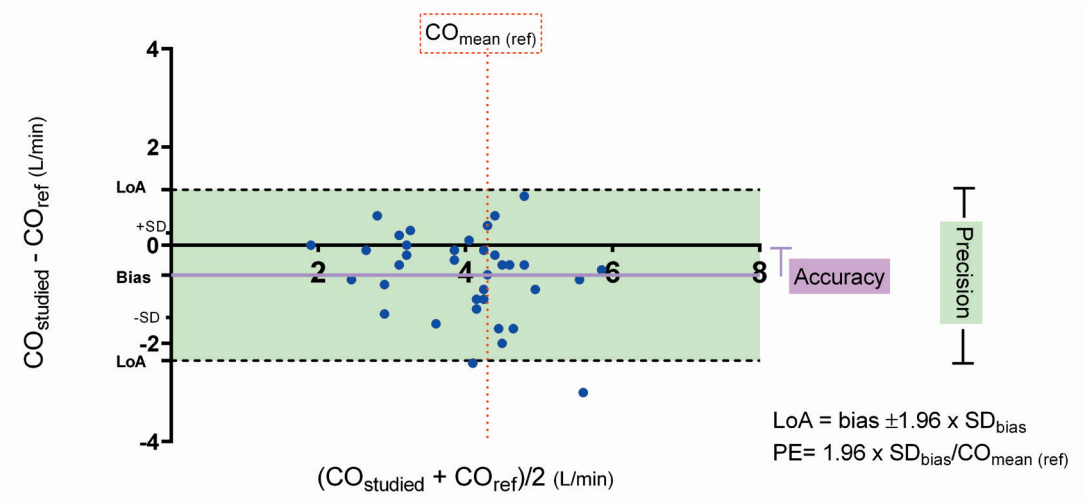

Figure 5. An example of Bland Altman plot. The whole pink line represents the mean bias and represents the accuracy. The precision is calculated from the mean bias and the standard deviation of the bias times 1.96 (or a factor adapted from a t-table, as in study II and III). The percentage error (PE) takes the mean cardiac output (CO) into account.

Percentage error

Level of agreement (LoA) is independent of the magnitude of the mean CO; for example, a LoA of 1 L/min would be considered excellent in a population with a high mean CO (hyperdynamic circulation) but not in a pediatric population where the mean CO is low. Critchley and Critchley proposed that percentage error (PE – sometimes referred to as mean error) should be used for more righteous comparison of the population studied and is calculated as $\frac{1.96 \times SD_{bias}}{CO_{mean\ (ref)}}$[72]. The Critchley brothers established a cut-off point for interchangeability between the compared methods at 28.3% (rounded up to 30%) which was entirely based on the inherent precision of the PAC itself* [72]. However, it should be noted that the calculations were mainly based on data from two studies measuring CO_{PAC} during stable hemodynamic situations and a simulation model [35,73]. Nevertheless, the Critchleys criteria for PE is commonly used as *a priori* in CO method comparison. To avoid erroneous conclusions, it is important that the *inherent precision* of the reference method itself is low (<20%), as the Bland-Altman analyses cannot take standpoint of which is better than the other.

**The calculated inherent precision of the PAC was around 20% in these studies. If the new method was to attain equal or better precision than the PAC, the desired precision of the new method would have to be 20% or lower. The cut-of was calculated as $\sqrt{(20^2+20^2)} = 28{,}3 \approx 30\%$.*

Percentage error in a clinical perspective

In their meta-analysis from 2010, Peyton and Wong challenged the Critchley and Critchley criteria stating that none of the non-invasive methods in the analysis achieved the 30% cut-off and suggested a PE 45% could be used when two methods are compared in clinical situations. The authors argued that even the PAC itself did not live up to the 30% criteria in clinical situ-

ations, i.e. during cardiac surgery when compared to ultrasonic flow probe around the aorta, as well as during hemodynamic changes in a porcine model [74,75]. In a recent follow up meta-analysis by Joosten *et al*, none of the new non-invasive methods came close to the 30% cut off when compared to thermodilution methods (see table 1). A major limitation of these studies is the clinical heterogeneity and selection bias, as the large majority is conducted in the cardio-thoracic suites or ICU, not reflecting the group of patients intended for their use. Recently, Pinsky and his group, somewhat provocatively stated there is no meaning in comparing new CO methods to the PAC, both due to safety reasons and the high "intrinsic error". Based on the observation/results that most of these methods show good accuracy (low bias), we should shift our focus to the ability of these methods to trend dynamic changes in CO [76].

Trending during changes in cardiac output

The trending ability of new methods is commonly assessed by calculating the concordance of the change, in both direction and magnitude, using either the four-quadrant (4Q) plot and/or polar plot [68,77]. The 4Q plot calculates the concordance rate (%) by dividing the number of data points that change in the same direction (that are within the two quadrants of agreement) with the total number of data points. When one device detects a larger change than the other, the paired value lies closer to the horizontal or vertical axis. If the detected change is the same in both devices, the paired value falls on a line at 45° [68].

The polar plot methodology, derived from the 4Q plot, is based on non-linear transformation to polar coordinates, where each paired value receives an angle and a radius. The angular bias is the mean of all polar angles and the radial limits of agreement is the sector that includes 95% of the data points [78]. An angular bias of ±5° and radial limits of ±30° indicates good trending ability. An exclusion zone of 10% is commonly applied to eliminate values with only small change (background noise), however in the polar plot, highly disconcordant values are also excluded, which is a limitation to the method. The concordance rate is calculated from number of points within the radial limits (±30°) divided all data points outside of the exclusion zone.

There is no clear consensus on which concordance rate is clinically acceptable, although equal or more than 90-92% are commonly used for both methodologies [68,77].

As with accuracy and precision, the performance of the minimally and non-invasive methods rarely reaches the desired concordance. However the development over the years has been positive, resulting in better agreement and trending ability [51].

Aims

The overall objective of this thesis was to evaluate the revised capnodynamic method (CO_{EPBF}), for estimation of CO and ability to track changes in a large animal model and in patients undergoing high risk abdominal surgery.

Specific aims:

In a large animal model compared to an experimental gold standard reference method:

1. To evaluate CO_{EPBF} at different CO, tidal volumes and PEEP for agreement and trending ability.
2. To evaluate CO_{EPBF} for agreement during transient and sustained changes in mixed venous CO_2 content after reperfusion and hypercapnia and trending ability during sustained high mixed venous content of CO_2.
3. To evaluate CO_{EPBF} during severe lung injury, both at high shunt fractions and after lung recruitment and the trending ability during both these conditions.

In high risk abdominal surgery:

4. To evaluate CO_{EPBF} for agreement and trending ability compared to a transpulmonary thermodilution during a variety of clinically relevant hemodynamic changes.

Material and methods

Detailed descriptions of the experimental methods can be found in the method section in respective paper.

Ethical consideration

Studies I-III were approved by Uppsala animal research ethical committee (nr. C 47/15) and performed at the Hedenstierna laboratory in Uppsala University, Sweden. Result are reported according to the ARRIVE guidelines [79].

In total 26 pigs of both sexes with a mean weight 35 kg (range 32 – 44 kg) were collected from the same breeding colony (Mångsbo Farm, Uppsala, Sweden). At the farm they had unlimited access to tap water and food on a standardized schedule and kept in a light and temperature controlled environment.

Study IV was approved by Stockholm regional ethics committee (Dnr. 2010/1296-31, 2012/1477-32, 2015/170-32, 2017/1096-32, 2017/2327-32) and registered at US National Institutes of Health via clinicaltrials.gov (Identifier: NCT03444545) and conducted in accordance with good clinical practice and the Helsinki declaration [80]. Results are reported according to the GRRAS guidelines [81].

Studies I-III

Anesthesia and preparation

After weighing, the animals were sedated with an intramuscular injection of 0.04 mg/kg atropine, 6 mg/kg tiletamine-zolazepam and 2.2 mg/kg xylazine chloride followed by insertion of an intravenous line in a peripheral vein in the ear. After a bolus dose of 5μg/kg fentanyl, an intravenous infusion of ketamine 30 mg/kg/h, midazolam 0.1mg/kg/h and fentanyl 4 μg/kg/h was administered for maintenance of anesthesia and rocuronium 2mg/kg/h for muscle relaxation. Anaesthetic level was evaluated prior to administration of muscle relaxant by applying pain stimuli to the fore hoof with forceps. If necessary, additional injections of fentanyl or midazolam were given. The animals were intubated via open tracheostomy and ventilation was started in a volume-controlled mode (Servo-i; Maquet, Solna, Sweden) with a tidal volume of 8 mL/kg and FiO2 0.4 except in paper III were F_iO_2 1.0 was used during lung injury. Positive end-expiratory pressure (PEEP) was set to 5 cmH_2O and the respiratory rate was adjusted to obtain a systemic arterial partial pressure of carbon dioxide (P_aCO_2) of approximately 40 mmHg during inherent precision and baseline measurement.

An intravenous infusion of Ringer's lactate was infused at the rate of 10 mL/kg/h throughout the experiment.

If hypovolemia was suspected, i.e. significant tachycardia and/or hypotension, additional-colloid solution was administered in boluses of 100-200 mL.

Pulmonary artery catheter (Edwards Lifesciences Corp., Irvine, CA, USA) was inserted in

the internal jugular vein for blood sampling, pressure and CO recordings. Via left sided thoracotomy, a flow probe was mounted on the pulmonary trunk (see figure 6). The chest was then closed and the animals repositioned in the supine position.

Via ultrasound guidance, a 10 French (Fr), 80 cm thrombectomy catheter (Dispomedica GmbH, Hamburg, Germany) was inserted into the inferior cava vein for controlled preload reduction.

A urinary catheter was placed via small surgical incision into the urinary bladder and the body temperature was maintained at 38-39°C with a warming mattress and blankets.

In study I, a 13.5 Fr arterial catheter was inserted in the femoral artery for controlled bleeding and an 8 cm, 4 Fr thermistor-tipped (Pulsiocath, Pulsion, Munich, Germany) in the contralateral femoral artery for pressure recordings and transpulmonary thermodilution. In study II and III the arterial catheter for pressure recordings was inserted in the carotid artery. In study II, a 12 Fr stent graft balloon catheter (Reliant®, Medtronic Inc. Minneapolis, MN, USA) was inserted into the femoral artery with ultrasound guidance and placed in the abdominal aorta just beneath the diaphragm, verified with fluoroscopy.

When the preparation was finished the animals were left to recover for 30 minutes before precision and baseline measurements were obtained. When all the study measurements were secured, the animals were euthanized in deep anesthesia by potassium chloride injection.

Study IV

Patients undergoing high risk abdominal surgery were scanned for eligibility from the surgical planning program (Orbit 5) on dates when at least two members of the research team were available. At these dates, patients older than 18 years without any known chronic lung emphysema or symptomatic coronary artery disease with an indication for invasive hemodynamic monitoring were offered to participate in the study. Patients received verbal and written information at the preoperative clinic or via telephone and email, at least five days before planned surgery. All patients planning to participate in the study were visited at the surgical department at admission for quick review of the study details and to obtain written consent.

Initially, 25 patients were planned to participate in the study. After the initial data analysis, the protocol was changed, and recruitment manoeuvre (RM) and PEEP adjustment were included in additional 10 patients.

Anesthesia and preparation

At the morning of surgery, patients arrived in the operation theatre where a designated research team including an anesthesiologist and a nurse assisted from start in addition to the existing anesthesia team (attending anesthesiologist and anesthesia nurse). After safe surgical checklist assessment, vital signs were measured and an epidural catheter inserted in a light sedation. Anesthesia was induced with a bolus of propofol, short acting opioid and neuromuscular blockade to facilitate intubation. Patients were mechanically ventilated in a

volume-controlled mode (Servo I, Maquet Critical Care AB, Solna, Sweden), with tidal volumes (V_T) 6-8 ml per predicted body weight (kg). A mainstream infrared sensor was used to measure concentration of expired CO_2 essential for the capnodynamic calculations (see details below).

A 7 Fr central vein catheter was inserted in the internal jugular vein and a 5 Fr thermistor tipped catheter (Pulsiocath, PV2015L20F or PV2014L08A; Pulsion Medical Systems SE, Feldkirchen, Germany) in either the femoral or axillary artery, determined by type of surgery and patient position. Both catheters were inserted with ultrasound guidance under strict sterile conditions. Maintenance of anesthesia was secured with propofol in a target-controlled infusion (TCI) and complemented with remifentanil infusion if indicated. All patients received maintenance fluid, either buffered 2.5% Glucose solution or Ringer Acetate 1 ml/kg/h. An esophageal Doppler probe (Cardio Q, EDM; Deltex Medical, Inc., Chichester, UK) was inserted as part of the standard method for fluid optimization during open abdominal surgery at Karolinska University Hospital and used by the anesthesia team to assess the need for any extra fluids during the operation. A final checklist was carried out before start of the research protocol. The epidural was activated as a separate step in the experimental protocol (see below) and infusion with ropivacaine 20-25 mg/h was continued until 30 minutes before end of surgery when the infusion was changed to a postoperative mixture of ropivacaine and sufentanil (2 mg/ml + 0.5 ug/ml), 6 to 8 ml/h. Core temperature was maintained at 36-37°C with a forced air warming system.

Cardiac output monitoring

Ultrasonic flow probe

The reference method for CO in study I-III was an ultrasonic flow probe with an Ultrafit liner, 18-20mm (AU series Confidence Flowprobe®) connected to an accompanying monitor (T 401; Transonic system Inc, Ithaca NY, USA) (CO_{TS}) [82]. Ultrasonic gel was applied between the vessel and the liner to secure best possible signal. The probe transmits ultrasound signals back and forth between two opposite transducers with an X-beam and custom made crystals to eliminate positional sensitivity [83]. It measures the wave time intersecting the flow between the transducers and is not dependent on cross sectional area as the Doppler technology. CO_{TS} and CO_{EPBF} were recorded simultaneously, where each reading was an average of approximately five to ten seconds.

The reported precision for the CO_{TS} is 6% and was 1% at baseline conditions in our preceding animal studies [64,82].

Pulmonary artery catheter

A balloon-tipped 7.5 Fr pulmonary artery catheter (PAC) (Edwards Lifesciences, Irvine, CA, USA) was inserted via the right jugular vein and floated through the right atrium and right

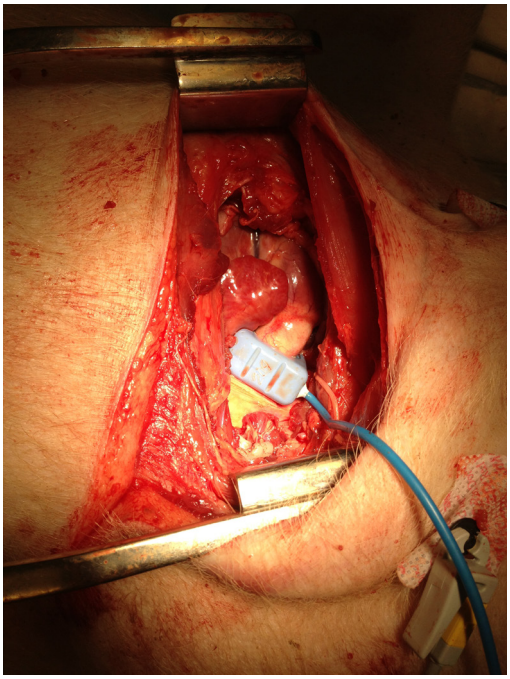

Figure 6. A flow probe attached to an Ultrafit liner mounted on the pulmonary trunc in one of the research animals. Used with permission (Caroline Hällsjö-Sander©).

ventricle into the pulmonary artery. The PAC was used for sampling of mixed venous blood for gas analyses and calculation of hemodynamic parameters.

The PAC was mainly used for CO measurements (CO_{PAC}) in study I. In addition values for CO_{PAC} were shown in one figure in study II for comparison during reperfusion. Calculation of CO was performed with three 10 mL boluses of ice cold saline, performed after the CO_{TS} and CO_{EPBF} readings as the injections caused instability in the CO_2 signal in the expired gas.

Transpulmonary thermodilution

Transpulmonary thermodilution (TPTD) was used as a reference for CO (CO_{TPTD}) and measures the change in temperature when cold saline traverses from a central vein catheter in the superior vena cava, through the right heart, pulmonary circulation, the left heart, aorta and finally acquired by a thermistor tipped centrally inserted arterial catheter (either the femoral or axillary artery). When three cold boluses are used, the method is considered accurate and precise when compared to the clinical gold standard (PAC) and highly reproducible in critically ill patients [84]. In this study we used the PiCCO2® monitor (Pulsion Medical Systems SE, Feldkirchen, Germany) where each CO_{TPTD} represents the average of triple thermodilutions with 10-, 15- or 20-ml ice cold Ringer Acetate. Measurements were considered accurate based on visual assessment of the thermodilution curve and if the difference between the three measurements was less than 15%. If these requirements were not fulfilled, one or two additional thermodilutions were performed and the deviating values were removed from the average. One designated member of the research team was responsible for performing all the thermodilutions in each case.

Capnodynamic method

The capnodynamic method estimates CO based on effective pulmonary blood flow calculated by the capnodynamic equation. The equation describes the mole balance of CO_2 transport in the lungs and the rate of change of the CO_2 content in the lungs achieved by the superimposed breathing pattern (see background section).

In the revised method, short automatic expiratory pauses (1-2 seconds in the pigs and 4-5 seconds in humans) are introduced in three out of every nine breaths resulting in small differences (0.5-1 kPa) in the alveolar concentration of CO_2 between each breath (see fig 7). Using a least square-error optimization of the fit between the left and right side of the equation, ELV, EPBF and C_vCO_2 can be calculated from a set of 9 equations (breaths). Each breath creates a new equation and replaces the last equation, providing continuous calculations that represent the average of the preceding 9 breaths.

A mainstream infrared sensor (Capnostat-3, Respironics Inc, Wallingford, CT, USA) was used for volumetric capnography. Gas flow was analyzed by the flow sensor incorporated in the ventilator (Servo I, Maquet Critical Care AB, Solna, Sweden) and transmitted to a connected computer where all the mathematical analysis was carried out with a software written in Matlab™ (The Mathworks Inc, Natick, MA, USA).

In *study I-III* CO_{EPBF} and CO_{TS} readings were obtained simultaneously and were based on an average of approximately 5-10 s. Thermodilution measurements were performed subsequently to not disturb the other measurements due to potential cold-induced bradycardia.

In *study IV*, CO_{EPBF} was photographed as the first thermodilution was initiated and again when value for the third thermodilution appeared on screen. The value for each measurement was therefore an average of three thermodilutions (CO_{TPTD}) and two CO_{EPBF} values.

Lung injury

Lung injury was induced with a combination of lavage and ventilator induced lung injury (VILI). Isotonic saline (30 ml/kg) at 37°C was used to lavage the lungs and deplete them from surfactant. For additional injury, subsequent 30 – 60 min of injurious mechanical ventilation combining zero PEEP with high inspiratory pressure (30 – 35 cmH_2O).

Calculation of shunt and dead space

Shunt fraction was calculated using Berggren's formula $\frac{Qs}{Qt} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$; where Qs/Qt = shunt fraction; CcO_2 = pulmonary capillary content of oxygen; CaO_2 = arterial content of oxygen and CvO_2 = mixed venous content of oxygen [85].

Oxygen content (ml/dl) was calculated = $(Hb \times 1.34 \times (\frac{S_xO_2}{100})) + (P_xO_2 \times 0.0031)$; where Hb = hemoglobin concentration (g/dl); 1.34 represents the amount of oxygen (ml) bound to hemoglobin (g/dl); S_xO_2 = oxygen saturation in respective blood sample (arterial/mixed venous) and P_xO_2 = oxygen tension in the respective blood sample (arterial/mixed venous) and 0.0031 represents the amount of CO_2 dissolved in blood.

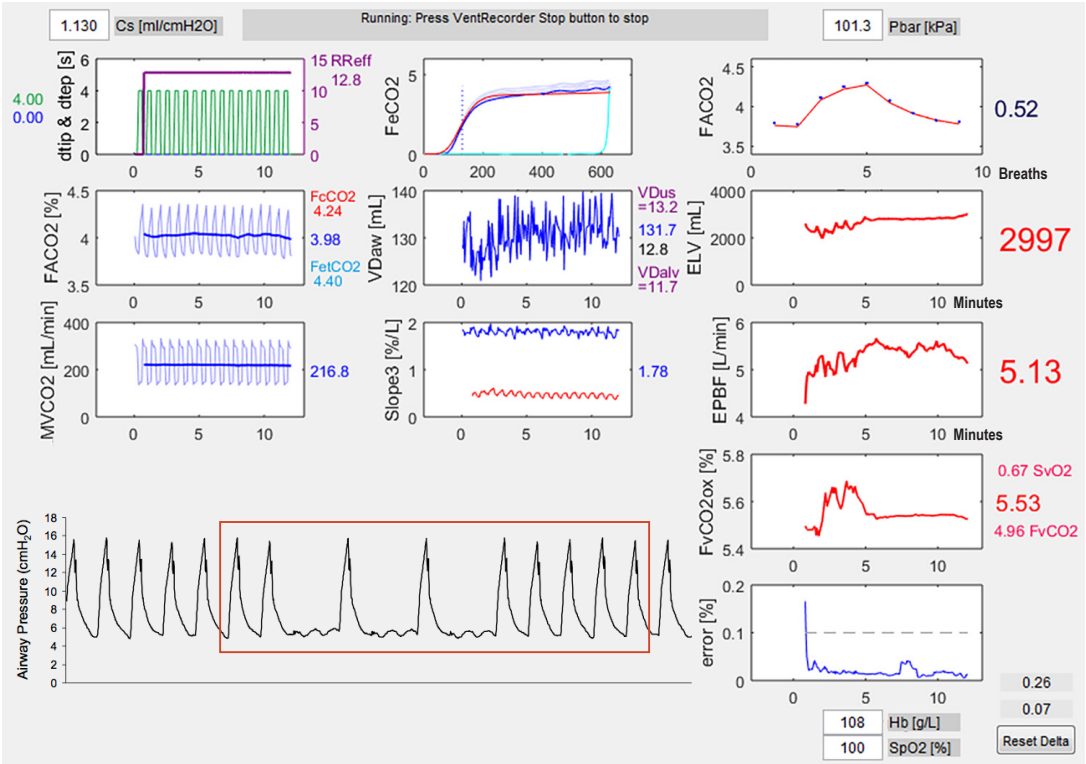

Figure 7. Adapted screenshot of the data output from the experimental program. A schematic overview of the superimposed breathing pattern has been added for explanation (lower left corner). The red box represents the 9 breaths being analyzed for that moment. With every new breath the box of nine breaths moves along and continuously producing changes in F_ACO_2 necessary for the capnodynamic calculations (see upper right corner). ELV and EPBF are continuously calculated below.

As the capillary content cannot be measured directly, it is estimated from an alveolar air equation.

$P_AO_2 = ((Pb-47) \times F_iO_2) - \frac{P_aCO_2}{RQ}$ where Pb is the barometric pressure (torr) and 47 = barometric pressure of water (torr). RQ = respiratory quotient estimated 0.8.

Physiological dead space (V_D/V_T), *ad modum* Enghoff, representing the global V/Q mismatch in the lungs was measured with P_aCO_2 (obtained via arterial blood gas) and volumetric capnography (NICO monitor, Respironics, Wallingford CT, USA) according to $\frac{V_D}{V_T} = \frac{P_aCO_2 - P_eCO_2}{P_aCO_2}$ where P_aCO_2 = systemic arterial pressure of carbon dioxide and P_eCO_2 = partial pressure of carbon dioxide in mixed expired air [86].

ABL-800FLEX (Radiometer Medical ApS, Brønshøj, Denmark) was used for blood gas analyses.

Data sampling and collection

In *study I-III* hemodynamic parameters were sampled into a data acquisition system (Acknowledge, version 3.2.7, Bio Pac Systems, Santa Barbara, CA, USA).

In *study IV*, each measurement was photographed in real-time and transferred to a secure

server at the end of each case. All data from the Servo-i ventilator was automatically saved on a computer containing the capnodynamic program. Continuous data from the PiCCO2 monitor was transferred to a secure server (available for 16 patients). Other data collected included preoperative patient characteristics, body mass index (BMI) and American Society of Anesthesiologists (ASA) class. Predictive body weight and body surface area were automatically calculated by the PiCCO2. Operative information recorded included fluid boluses, blood transfusion requirements, intraoperative fluid balances and duration of surgery. Fluid balances were calculated by subtracting total output (urine output, blood loss, loss from drains and vomitus) from total input (all intravenous fluid intervention or parental medications). Third space losses were not included, as they were considered negligible. Mortality at 30 days was recorded.

Experimental protocols

Study I

Baseline measurements of CO_{TS}, CO_{EPBF}, CO_{PAC} and CO_{TPT} were obtained at PEEP 5 cmH_2O and a V_T of 8 mL/kg. Hemodynamic and ventilatory parameters were then changed in the following order:

1) PEEP 0 cmH_2O and 12 cmH_2O.
2) Increased tidal volume from 8 to 12 mL/kg.
3) From BL conditions; preload reduction (50%) estimated by the CO_{TS} with controlled inflation of caval balloon.
4) Increase in PEEP from 5 to 12 cmH_2O.
5) At PEEP 12; preload reduction (50%) estimated by the CO_{TS} by a controlled inflation of caval balloon.
6) PEEP decrease from 12 to 5 cmH_2O.
7) From BL conditions; CO increase (150%) estimated by the CO_{TS} with dobutamine infusion.
8) Controlled bleeding titrated to a MAP target of 35 mmHg.

All measurements were performed at a steady state as estimated with the CO_{TS}. The animals were allowed to recover and stabilize between all interventions.

Study II

The protocol was twofold performed in separate group of animals. In the first part, eight animals, after routine precision and baseline (BL) measurements at F_iO_2 0.4, PEEP 5 cmH_2O and V_T of 8 mL/kg, an aortic balloon catheter was inflated, just beneath the diaphragm, until blood flow was attenuated in the contralateral femoral artery. At the end of the ischemia a new measurement was performed, and the balloon was released with a consequent reperfusion.

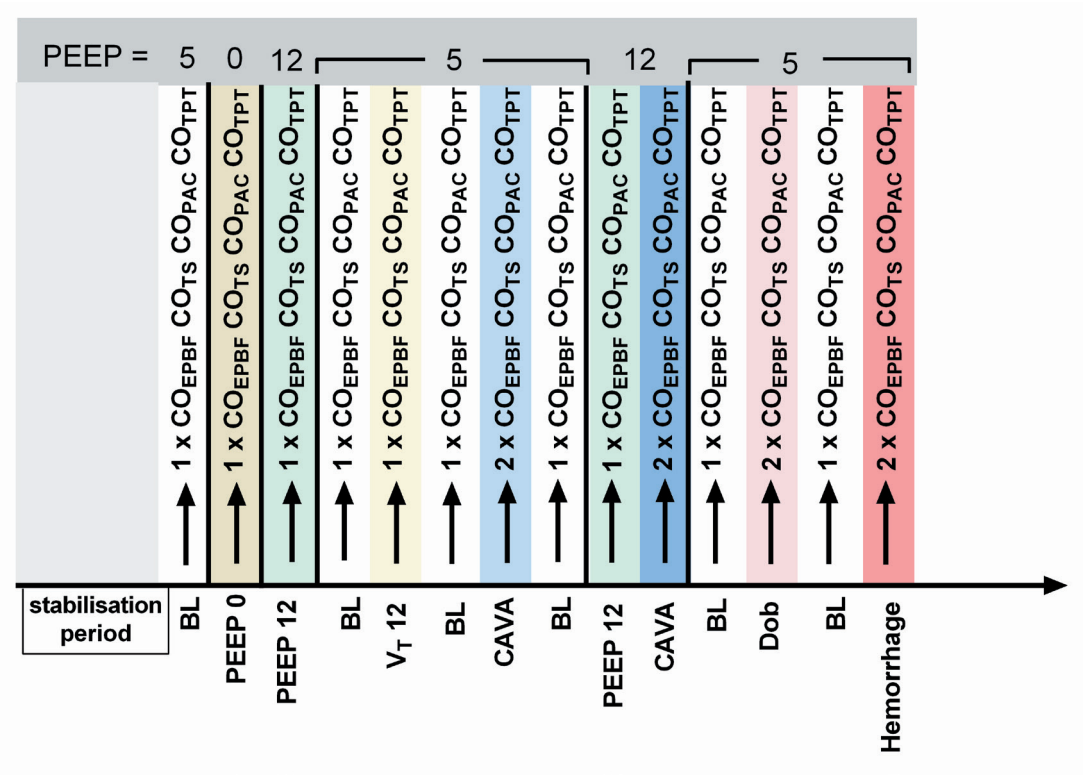

Figure 8. A schematic overview of the hemodynamic and ventilatory changes induced during study I. CO was calculated with the capnodynamic method (CO_{EPBF}), ultrasonic flow probe around the pulmonary trunk (CO_{TS}), pulmonary artery catheter (CO_{PAC}) and transpulmonary thermodilution (CO_{TPTD}). BL= Baseline, VT= Tidal Volume, PEEP= Positive End-Expiratory Pressure, CAVA= inflation of balloon in vena. CAVA, Dob= Dobutamine infusion.

Measurements with all three CO methods were performed at minute one, three and five and CO_{EPBF} and CO_{TS} additionally at minute two and four.

The second part of the protocol, performed in another eight animals, identical precision and baseline measurements were conducted as described before at F_iO_2 0.4, PEEP 5 cmH_2O and V_T 8ml/kg. At the airway opening, between the y-piece and carbon dioxide sensor, an external dead space was added, aiming for 50-60% increase in P_aCO_2. Although not part of this published study, hypercapnia was additionally induced by lowering respiratory rate (with CO changes) and tidal volumes separately. These results have been published in an abstract form and are included in the results section [87].

Study III

At the start of the day, baseline measurement with healthy lungs (HL) was obtained as previously described. After the ischemia/reperfusion, the animals had time to recover before initiation of lung injury. After completed lung injury at F_iO_2 1.0 and PEEP 5 cmH_2O, three baseline measurements were performed with CO changes (+/- 30%) in between (caval balloon inflation and dobutamine infusion). Thereafter, a RM was performed and the level of

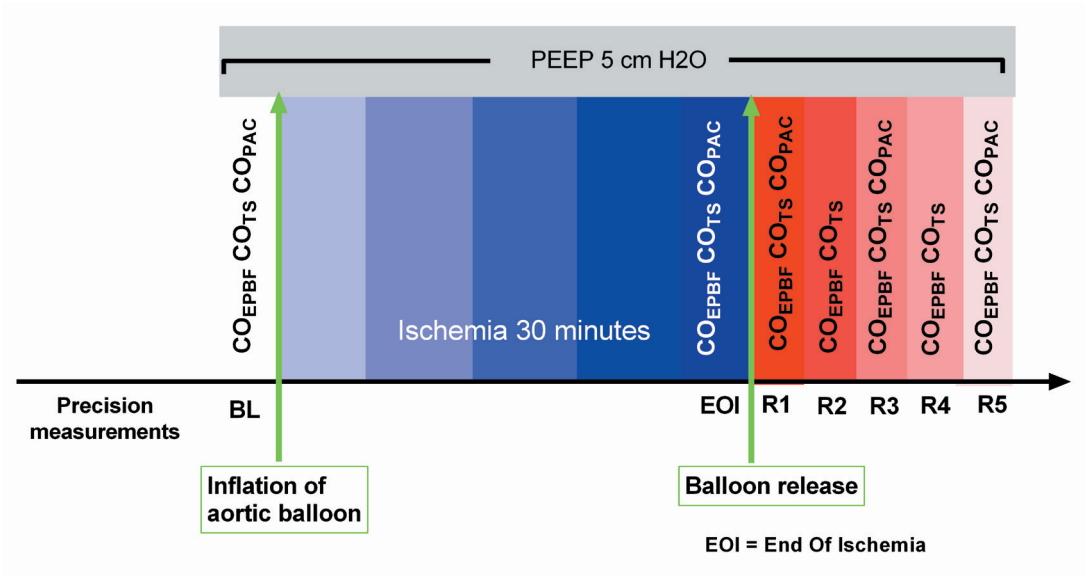

Figure 9. Schematic overview of the transient hypercapnia produced by inflating the aortic balloon catheter just beneath the diaphragm. BL= Baseline, R1-5= Reperfusion with measurements every minute for five minutes.

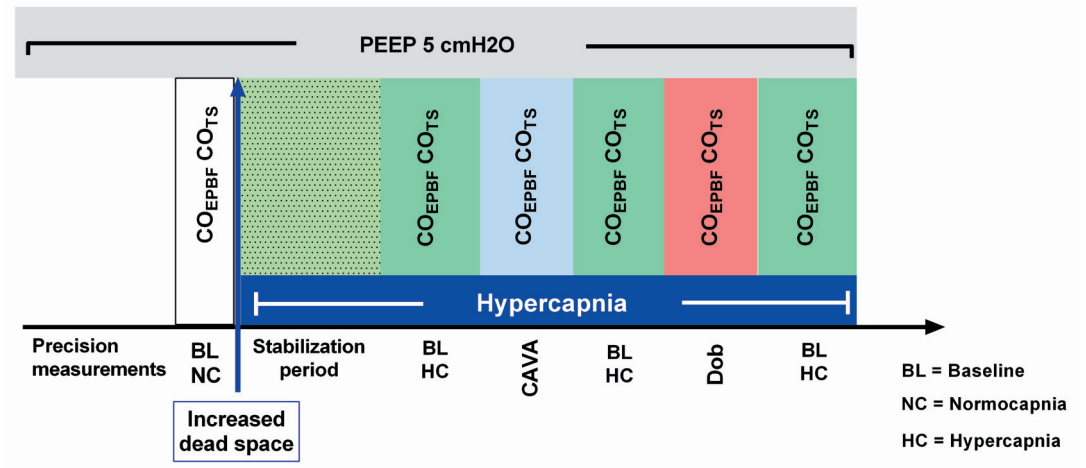

Figure 10. Schematic overview of the sustained hypercapnia induced with increased dead space at the y-piece. Measurements were obtained at baseline, after establishing a stable hypercapnia on average 44 (8) min later and at 7–12 min intervals between baseline and the interventions. Cardiac output manipulations with caval balloon inflation (CAVA) and dobutamine infusion (Dob) performed in between, aiming for ±30% change in CO.

PEEP resulting in maximum dynamic compliance was considered the closing pressure. PEEP was set at 2-3 cmH_2O higher than the closing pressure. The procedure lasted for 22 ±14 minutes and resulted in a PEEP range of 11-17 cmH_2O.

Study IV

In the first 25 patients (CON_{P5}) CO_{EPBF} and CO_{TPTD} measurements were performed (1) on three successive occasions at PEEP 5 cmH_2O (baseline – BL 1-3), (2) 1-2 minutes after change

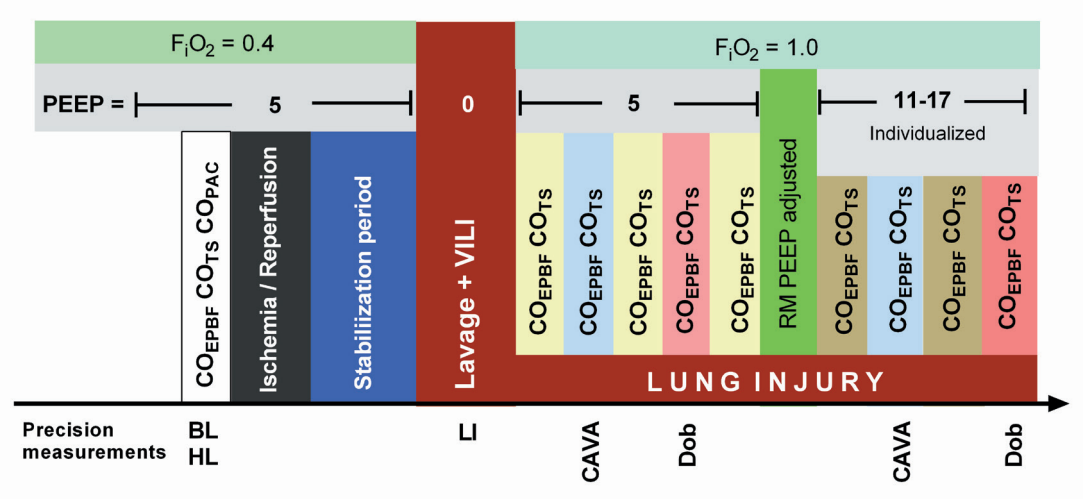

Figure 11. Schematic overview of study III. Lung injury commenced and simultaneous measurements with both the capnodynamic method (CO_{EPBF}) and the ultrasonic flow probe (CO_{TS}) performed before and after RM and PEEP adjustment and CO changes. BL= Baseline, HL= Healthy Lungs, LI= Lung injury, CAVA= inflation of caval balloon, Dob= Dobutamine infusion, PEEP= Positive End-Expiratory Pressure, RM= Recruitment Manoeuvre, F_iO_2= fraction of inspired oxygen

to PEEP 15 cmH_2O, (3) 1-2 minutes after return to PEEP 5 cmH_2O, (4) before epidural activation (pre-EDA) at PEEP 5 cmH_2O and (5) 10 to 15 minutes later after epidural activation (EDA). The protocol was interrupted in six patients in the CON_{P5} group at the discretion of the attending anesthesia team, either to give volume bolus or start dobutamine infusion. These patients were not included in the event line *per se*, however in the Bland-Altman analysis, and 4Q plot.

In the last ten included patients (CON_{Padj}), compliance based RM was performed before initiation of the study protocol. In pressure control mode, inspiratory pressure (P_{insp}) and PEEP were raised and reduced in a stepwise manner and the level of PEEP resulting in maximum dynamic compliance at the desired VT was considered the closing pressure. PEEP was then set at 1-2 cmH_2O higher than the closing pressure and the ventilatory mode was changed back to volume controlled. Measurements were then performed in the same order as described above in the CON_{P5} group with one exception; in the PEEP step, 10 cmH_2O was instantaneously added to the adjusted PEEP and then reduced again to the adjusted level.

During the surgical procedure, the attending anesthesiologist, routinely assessed if fluid optimization was indicated, based on an institutional algorithm for ODM (CardioQ), before and during surgery. If suitable, measurements were performed, as described above before and after fluid infusion. In case of hemorrhage or low cardiac output (CI < 2.5 L/min/m^2), if hemodynamically stable, measurements were performed before and after instillation of treatment. The attending anaesthesiologist chose the dose and type of local anaesthetic used (100-160 mg mepivacaine in all except two cases) for the epidural activation and could at any time change the order of the steps in the protocol if fluid optimization or dobutamine was indicated.

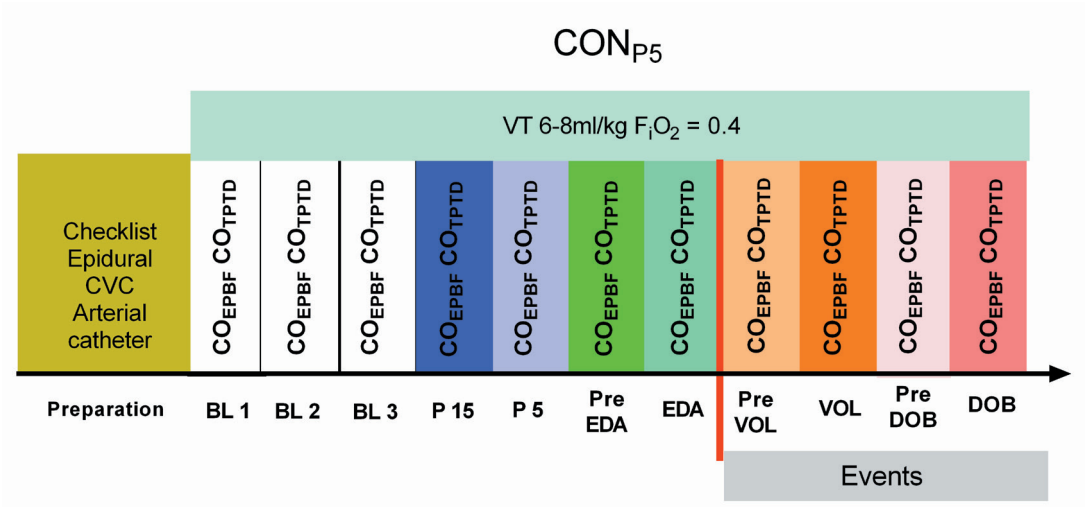

Figure 12. Schematic overview of the first 25 patients in study IV (CON_{P5}). Cardiac output was measured with the capnodynamic method (CO_{EPBF}) and transpulmonary thermodilution (CO_{TPTD}) at baseline 1 to 3 (BL 1-3), before and after changes in PEEP (P15 and back to P5) and epidural activation (pre EDA and EDA). During surgery events were captured (volume- and cardiac output optimization) with measurements before and after instillation of treatment (Pre VOL= before volume bolus, VOL = after volume bolus, Pre DOB= before dobutamine infusion, DOB= after dobutamine infusion. CVC= Central Vein Catheter.

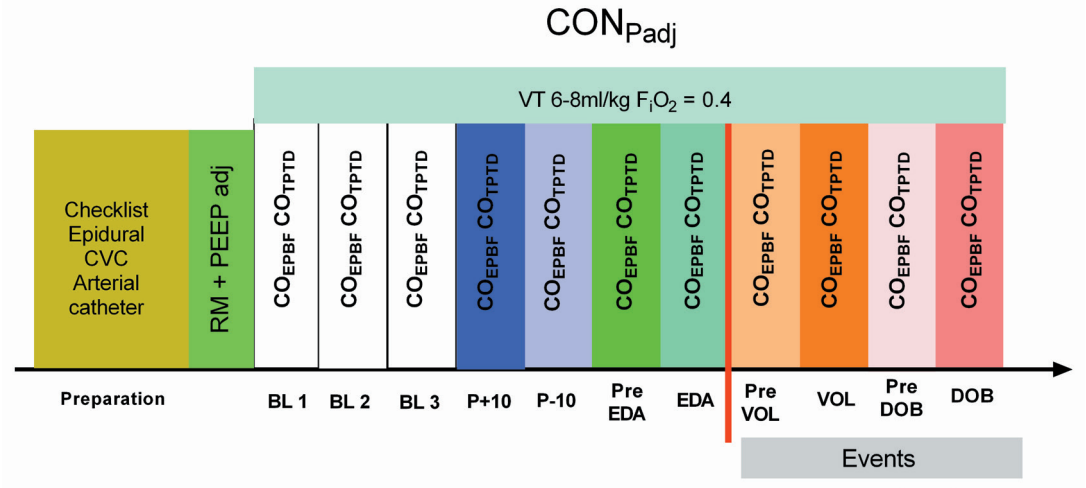

Figure 13. Schematic overview of the last 10 patients in study IV (CON_{Padj}). Recruitment manoeuvre was performed and PEEP individually adjusted before start of the protocol. Cardiac output was measured with the capnodynamic method (CO_{EPBF}) and transpulmonary thermodilution (CO_{TPTD}) at baseline 1 to 3 (BL 1-3), before and after changes in PEEP (P+10 and -10 cmH2O) and epidural activation (pre EDA and EDA). During surgery events were captured (volume- and cardiac output optimization) with measurements before and after instillation of treatment (Pre VOL= before volume bolus, VOL = after Volume bolus, Pre DOB= before dobutamine infusion, DOB= after dobutamine infusion.

Statistics

The statistical methods applied in this thesis are discussed in the background section and are described in each paper.

The reliability of a statistical test is dependent on the sample size. In animal studies there

is a compromise between ethical and economical reasoning to use as few animals as possible but also accomplish statistical reliability. Although sample size calculations would have been possible based on data from the original capnodynamic method with inspiratory holds, i.e. with regards to precision, it was considered insufficient since they were tested during different conditions. Our previous animal studies were performed in 8-10 animals provided realistic evaluation of the new method against a highly accurate and precise reference method.

In the human study, ten patients were added to the study after data analysis of the first 25 patients. Of logistical reasons, recruiting more patients to the study was impossible.

Normality and distribution of data was checked with D´Agostino and Pearson omnibus K2 test for all studies and presented as mean (SD) or median (range) as appropriate. Proportional bias, i.e. the spread at different CO values was checked with linear regression and visual assessment. Pearson´s correlation coefficients were used to examine the relationship between shunt and bias (study III). Unpaired t-test was used to compare mean of two groups (study IV) with adjustments (Mann-Whitney) when assumption of normality was violated. A p-value <0.05 was considered statistically significant.

Inherent precision

In the animal studies, inherent precision of CO_{EPBF} (study I-III) and CO_{TS} (study II and III) was calculated as twice the coefficient of variation (CV = SD/meanCO) from 10 repeated measurements obtained at 1 min intervals in each animal at baseline conditions. In study IV the precision of CO_{EPBF} was calculated from six baseline values as described above. For CO_{TPTD}, CV was calculated from total three triplicates (9 thermodilutions) as SD_{TPTD}/sqrt (3)/ mean CO_{TPTD}. The previously reported inherent precision for CO_{TS} was ±10% and for TPTD 6-12% [82,88].

Agreement

As described, Bland-Altman plots were used to calculate the mean bias between the CO_{EPBF} and the reference methods. Limits of agreement (LoA) were calculated differently between studies to adapt to current guidelines when validating new CO methods [89]. In study II and III, a t-table was introduced to account for the small sample size. In case of only few measurements as during certain conditions a t-value was used, corresponding to the degrees of freedom and a type I error (α) of 0.05. As an example, for eight measurements the t_{α} was 2.365 instead of 1.96 when calculating the LoA. Corresponding t-value was used to calculate percentage error and confidence intervals.

In study IV however, we used 1.96 for more righteous comparison to other CO methods as it appears to be exclusively used in clinical studies and meta-analysis.

A *priori* percentage error was set at equal or less than 30% to indicate if the two methods were interchangeable [72].

Trending ability

The ability to track changes in CO was calculated with 4Q and polar plots describing the proportion and magnitude of measurements that change in the same direction. In study I-III and IV, an exclusion zone of 10 and 15% was used, respectively, with regards to the inherent precision of the reference methods and the calculated LSC. In study IV the calculated inherent precision for the both methods was ~11%, and therefore the LSC~15%.

Results

Study I

Inherent precision of CO_{EPBF} was ±14. The different hemodynamic and ventilatory alterations produced large changes in CO. All animals survived the interventions.

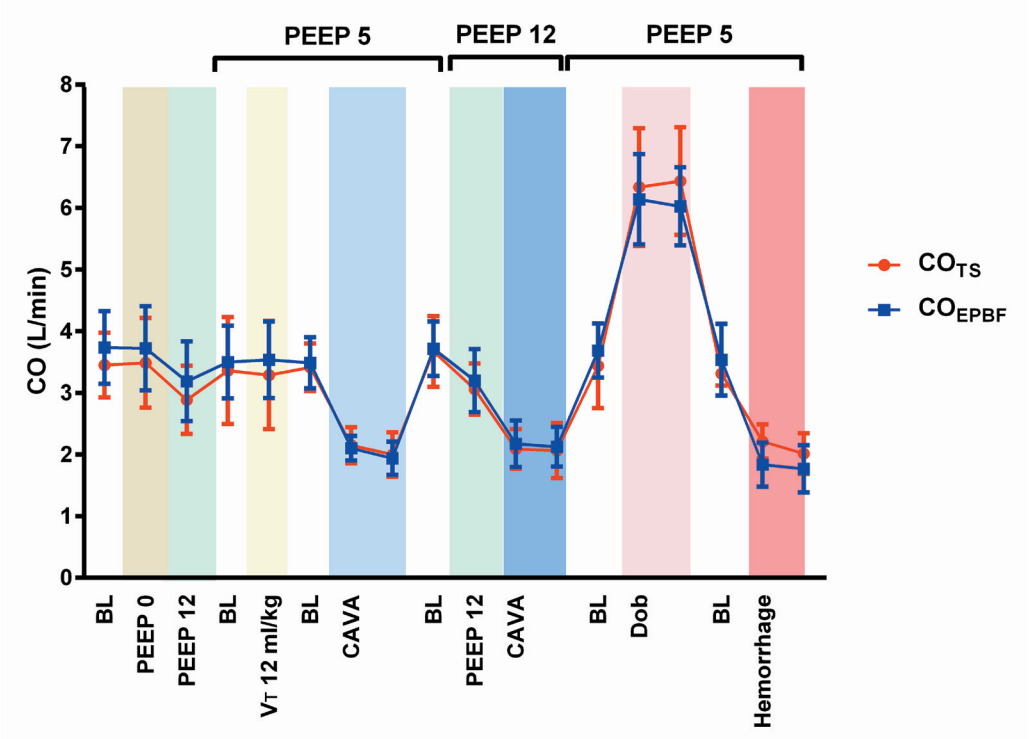

Figure 14. Changes in mean (SD) cardiac output (L/min – left y-axis) measured with the capnodynamic method (CO_{EPBF}, blue line) and the ultrasonic flow probe (CO_{TS}, red line) during different interventions (x-axis). BL= Baseline, VT= Tidal volume, PEEP= Positive end-expiratory pressure, CAVA= inflation of balloon in v. CAVA, Dob= Dobutamine infusion.

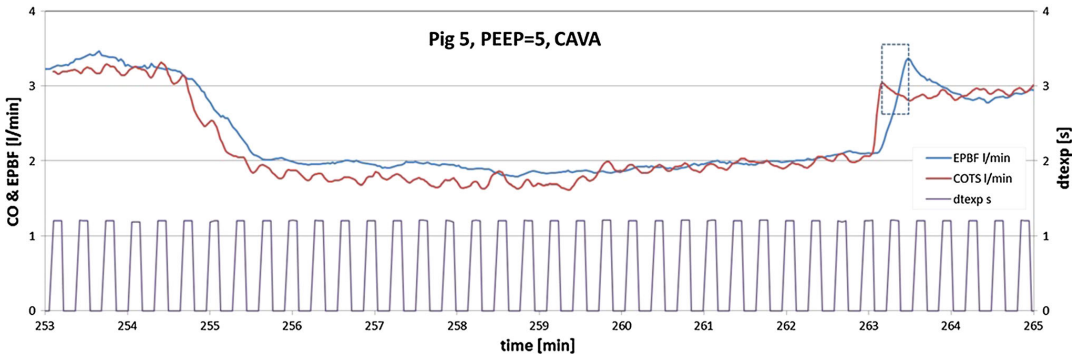

Figure 15. A trace from one animal representing the change and the response time after inflation and deflation of the caval balloon. Time to fully capture the change was approximately 19 seconds or 9 breaths (Respiratory Rate = 28 breaths/min).

The agreement and concordance of CO_{EPBF}, CO_{PAC} and CO_{TPT} compared to CO_{TS} is shown in table 2.

	CO_{EPBF} Bias (LoA) L/min PE n	CO_{PAC} Bias (LoA) PE n	CO_{TPT} Bias (LoA) PE n
Overall	0.05 (-1.1-1.2) 36% (n=141)	-0.2 (-1.6-1.2) 45% (n=97)	0.5 (-0.4-1.5) 29% (n=116)
PEEP 5	0.1 (-0.9-1.2) 32% (n=47)	-0.2 (-1.7-1.2) 38% (n=48)	0.5 (0.6-1.6) 29% (n=54)
PEEP 12	0.2 (-1.0-1.4) 41% (n=32)	0.1 (-1.3-0.1) 46% (n=21)	-0.5 (-0.3-1.2) 30% (n=24)
Dobutamine infusion	-0.3 (-2.0-1.4) 27% (n=16)	0.09 (-1.4-1.6) 24% (n=7)	-0.05 (-2.1-2.0) 31% (n=14)
Caval occlusion	-0.09 (-0.8-0.6) 33% (n=46)	-0.08 (-1.0-0.8) 45% (n=21)	0.43 (-0.2-1.1) 28% (n=24)
Concordance (4Q) **(10% exclusion zone)**	97%	96%	97%
Concordance (PP) **Mean polar angle** **(10% exclusion zone)**	94% 0.4°	92% -8.1°	95% 1.8°

Table 2. The results from Bland-Altman analyses for CO_{EPBF}, CO_{PAC}, CO_{TPT} when compared to the CO_{TS}, respectively. The results are divided into overall performance, different PEEP levels and high and low CO. *4Q = Four-Quadrant Plot; PP = Polar Plot; LoA= Level of Agreement; PE= Percentage Error*.

The overall performance was on level with the thermodilution methods, superior to theCO_{PAC} and inferior to CO_{TPT}.

Study II

The inherent precision at baseline conditions were 8, 4 and 10% for CO_{EPBF}, CO_{TS} and CO_{PAC}, respectively. After 30 minutes of caudal ischemia, the balloon was released followed by a significant reperfusion and transient hypercapnia, temporarily affecting the performance of CO_{EPBF} when compared to CO_{TS} (see figure 16).

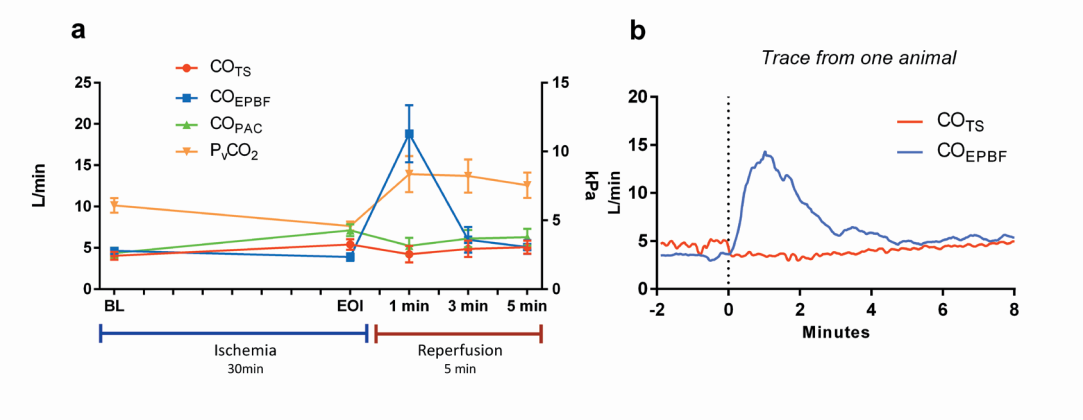

Figure 16. Timeline showing a mean (SD) values for CO_{EPBF}, CO_{TS} and CO_{PAC} from baseline (BL) to end of ischemia (EOI) approximately 30 min later and every minute for five minutes after reperfusion (CO_{PAC} only at 1, 3 and 5 min), and b continuous values from one animal for CO_{EPBF} and CO_{TS} (not possible with CO_{PAC}) starting 2 min before balloon release (*vertical broken line*) and up to 8 min after reperfusion.

During sustained hypercapnia, induced with different ventilatory changes, the overall agreement of CO_{EPBF} and CO_{TS} was similar to baseline performance, except in the low respiratory rate (RR) group where the bias was increased. Trending ability during both increased dead space ventilation and low RR was good in these eight animals (see table 3 and figure 17).

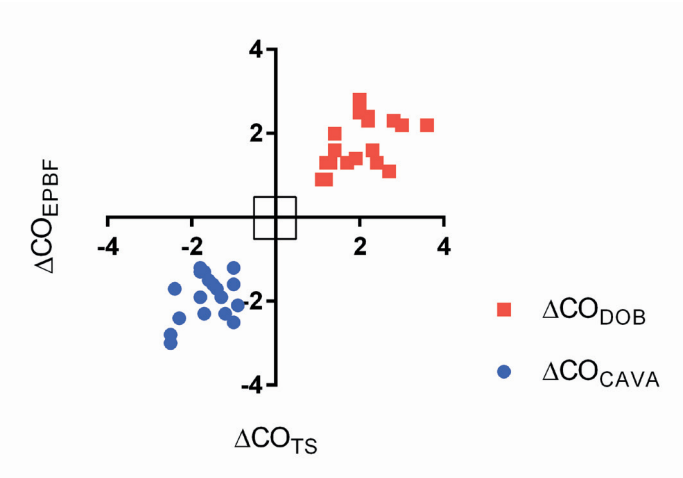

Figure 17. Four-quadrant plot for 32 paired values of ΔCO_{EPBF} and ΔCO_{TS} during caval balloon inflation (ΔCO_{CAVA}) and dobutamine infusion (ΔCO_{DOB}) at sustained hypercapnia (increased dead space and low respiratory rate). All values were outside of exclusion zone (10%).

Study III

Two animals were excluded from the data analysis. In one animal, measurements after lung injury were unattainable because of cardiorespiratory instability. A computer failure made CO_{EPBF} data retrieval impossible in another animal.

The calculated inherent precision of CO_{EPBF} and CO_{TS} was 9 and 6% at baseline conditions.

Induced lung injury caused respiratory failure including; elevated shunt, increased physiological dead space and lowered P_aO_2/F_iO_2 ratio, as expected. Hemodynamic manipulations

	Bias L/min	LoA L/min	ME %
NC	0.6 (0.1 – 1.0)	-0.8 – 1.9	42
HC low RR	1.4 (1.2 – 1.7)	0.1 – 2.8	33
-> CAVA	0.8 (0.5 – 1.0)	-0.1 – 1.6	37
-> DOB	1.6 (1.0 – 2.2)	-0.3 – 3.5	35
HC low TV	0.7 (0.0 – 1.4)	-1.2 – 2.7	38
HC DS	0.5 (0.3 - 0.7)	-0.5 - 1.4	21
-> CAVA	0.4 (0.0 - 0.7)	-0.7 – 1.4	38
-> DOB	0.0 (-1.0 - 0.9)	-2.8 - 2.7	38

Table 3. Bland Altman data for sustained hypercapnia. The bias was increased in the low RR group, without affecting precision. NC= Normocapnia, HC= Hypecapnia, RR= Respiratory Rate, CAVA= inflation of caval balloon, DOB= infusion of dobutamine, TV= Tidal Volume, DS= Dead Space, ME= Mean Error (same as percentage error), LoA= limits of Agreement.

at these different conditions resulted in large changes in CO. CO_{EPBF} consequently underestimated CO_{TS} at high shunt fractions (mean bias -0.6 L/min) and overestimated after RM and PEEP adjustment (mean bias 1.1 L/min) (see figure 18).

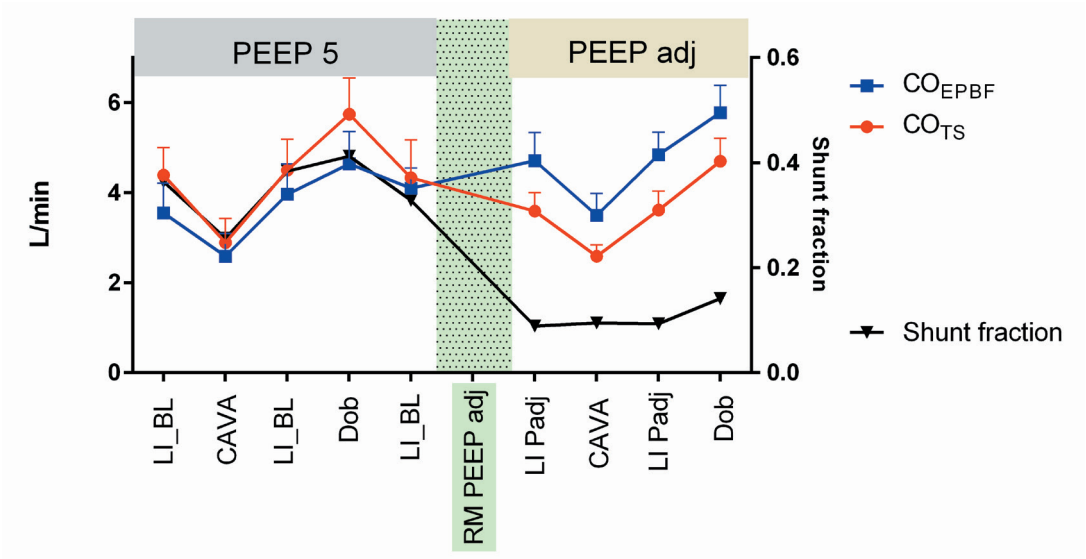

Figure 18. Time line showing mean values and standard deviation for CO_{EPBF}, CO_{TS} (*left y-axis*, L/min) and shunt fraction (*right y-axis*) during lung injury (LI), before and after recruitment manoeuvre (RM) and PEEP adjustment (adj). Cardiac output changes were induced with caval balloon inflation (*CAVA*) and dobutamine infusion (*Dob*) during both conditions.

Percentage error during LI, both before and after was the same (40%) and comparable to baseline levels. Trending ability was 87% during high shunt fractions and 100% after RM and PEEP adjustment according to the 4Q-plot. The polar plot showed a mean angle -14.8° and radial limits of -40.0° to -10.5° at high shunt fractions and 2.3° and -22.9 to 18.3 after RM and PEEP adjustment.

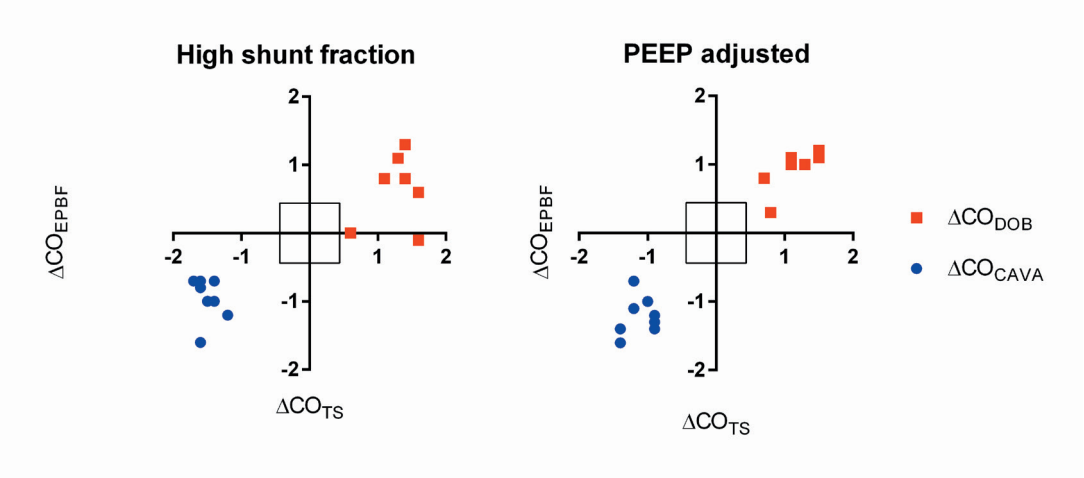

Figure 19. Four-quadrant plot showing 15 paired values of ΔCO_{EPBF} and ΔCO_{TS} during cava balloon inflation (ΔCO_{CAVA}) and dobutamine infusion (ΔCO_{DOB}) at both high shunt fraction and after recruitment manoeuvre and PEEP adjustment. All values were outside of the exclusion zone (10%).

Study IV

In total, 35 patients were included in the study and produced 329 paired values; thereof 234 in the first 25 patients (CON_{P5}) where all patients started equally at PEEP 5 cmH_2O and 95 in the last 10 patients (CON_{Padj}) where a lung RM and PEEP adjustment was performed before initiating the protocol.

Inherent precision calculated for CO_{EPBF} and CO_{TPTD} at baseline conditions was 10 and 11% in CON_{P5} and 11 and 9% in CON_{Padj}, respectively. There were no differences in demography or factors related to the operation between the groups. Mean CO_{EPBF} and CO_{TPTD} for all 35 patients was 4.7 and 4.8 L/min, respectively. There was no significant difference between CO_{EPBF} and CO_{TPTD} within each group 4.6 vs 4.8 L/min (p=0.06) in CON_{P5} and 4.9 vs 5.0 L/min (p=0.2) in CON_{Padj}). Changes in PEEP and activation of epidural analgesia all produced

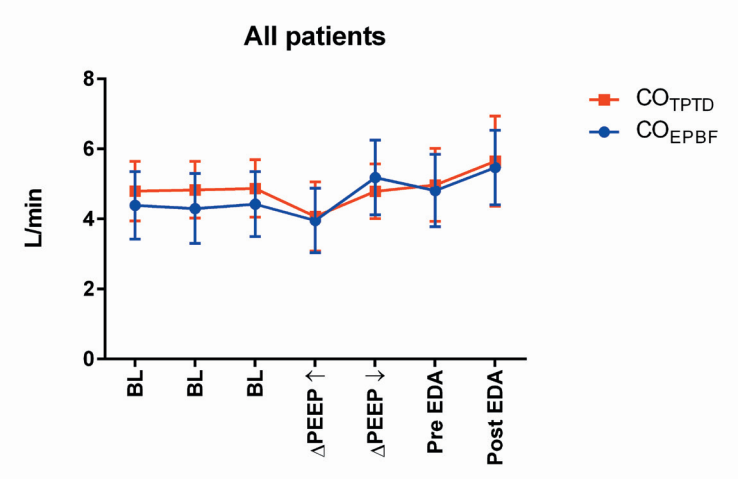

Figure 20. Event line displaying cardiac output measured with the capnodynamic method (CO_{EPBF}) and transpulmonary thermodilution (CO_{TPTD}) for total 30 patients from both groups (CON_{P5} and CON_{Padj}). Data for five patients was excluded from the graph (all from the CON_{P5} group) as the steps were performed in different order. BL= Baseline, ΔPEEP↑ (+ 10cmH_2O) and ΔPEEP ↓(-10cm-H_2O), Pre EDA= Before epidural activation, Post EDA= After epidural activation.

	CON_{P5}			CON_{2excl}			CON_{Padj}		
Condition (n)	Bias (L/min)	LoA (L/min)	PE %	Bias (L/min)	LoA (L/min)	PE %	Bias (L/min)	LoA (L/min)	PE %
BL_1-3 (75/69/30)	-0.4	-2.2 – 1.5	39	-0.3	-1.9 – 1.4	36	-0.24	-2.1 – 1.7	39
PEEP + 10 cmH_2O (25/23/10)	-0.1	-1.5 – 1.3	34	0.1	-1.0 – 1.1	27	-0.22	-1.33 – 0.9	26
PEEP -10 cmH_2O (25/23/10)	0.3	-1.7 – 2.3	41	0.5	-1.2 – 2.2	37	0.57	-0.8 – 1.9	27
Pre EDA (17/15/9)	-0.3	-2.4 – 1.7	41	-0.2	-1.3 – 1.0	26	0.2	-1.3 – 1.7	28
EDA (17/15/9)	-0.3	-2.2 – 1.7	36	-0.1	-1.6 – 1.5	29	0.0	-1.7 – 1.7	28
Event (30/28/13)	-0.4	-2.3 – 1.6	42	-0.1	-1.5 – 1.3	32	-0.3	-1.4 – 0.9	24
Post event (30/28/13)	-0.4	-2.5 – 1.8	41	-0.1	-1.4 – 1.2	26	-0.2	-1.3 – 0.8	20

Table 4. Comparison of Bland Altman values for the first 25 patients who all had PEEP 5 cmH2O from start (purple columns) and the last 10 patients where a recruitment manoeuvre and individualized PEEP adjustment was performed before measurements (pink columns). In the green columns (CON_{2Excl}), two clinical outliers (highest weight and large abdomens) are excluded from the CON_{P5} group. BL= Baseline, PEEP= Positive end-expiratory pressure, Pre EDA= Prior to epidural activation, EDA= After epidural activation (10-15 minutes).

significant changes in CO (see figure 20 for event line). The CON_{Padj} group, with individual compliance-based lung recruitment before protocol start had smaller bias, narrower LoA and lower PE compared to the CON_{P5} group who all had PEEP 5 cmH_2O from start. Two clinical outliers (118 and 98 kg with predominant abdominal fat) were identified in the CON_{P5} group with mean bias -2.1 (1.0) and -1.9 (0.7) L/min, respectively. When excluded from the CON_{P5} group, changes in bias, LoA and PE were observed for the remaining 23 patients (CON_{2excl}). See table 4 for comparison between the groups.

A few episodes of hemorrhage were captured with the continuous CO_{EPBF} monitoring and continuous pulse contour CO monitoring via the PiCCO2 monitor in individual patients during the course of surgery (see figure 22 for example).

One patient developed a small dissection in the axillary artery with acute arterial thrombosis partially occluding the peripheral flow, after removal of the thermistor tipped catheter. The patient had full recovery after conservative anticoagulation treatment.

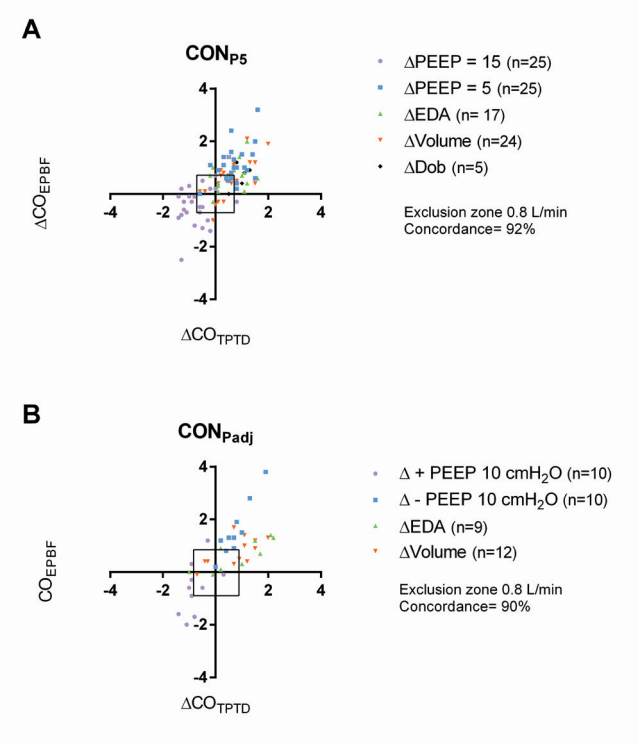

Figure 21. Four-quadrant plots for CON_{P5} (A) showing 96 paired delta values and CON_{Padj} (B) showing 41 paired delta values displayed by the capnodynamic method (CO_{EPBF}) and transpulmonary thermodilution (CO_{TPTD}) from all interventions. ΔPEEP 15 (purple dots) = increase in PEEP from 5 to 15 cmH_2O; ΔPEEP 5 (blue squares) = decrease in PEEP from 15 to 5 cm H_2O; ΔEDA (green triangle up) = before and after epidural activation with 10-15 minutes apart; ΔVolume (orange triangle down) = before and after volume bolus; ΔDob (black rhomboid) = before and after dobutamine infusion.

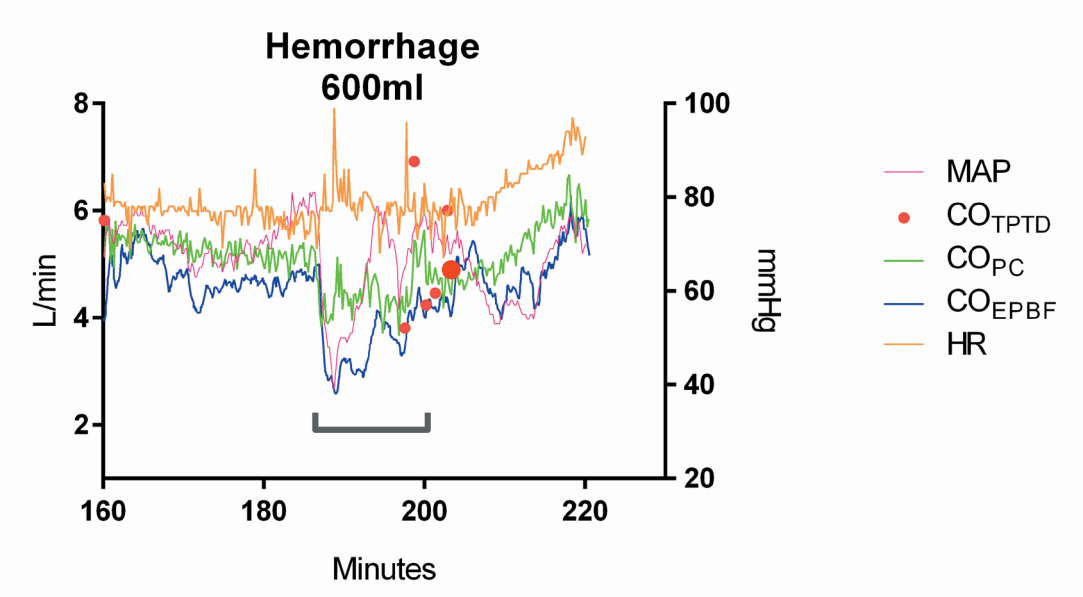

Figure 22. A continuous trace of various hemodynamic parameters from one patient with a sudden blood loss (600ml) from a large pelvic artery and an ongoing resuscitation with fluids (Ringer acetate and 20% Albumin) and increase in noradrenaline (0.06 to 0.12 µg/kg/min). Mean arterial pressure (MAP, pink line) was measured in the femoral artery from the thermistor-tipped catheter. *Red dots* indicate single transpulmonary thermodilution measurements (CO_{TPTD}) and the largest *red dot* is the average of three preceding measurements; *CO_{PC}* (green line) = CO derived from the PiCCO pulse contour analysis. *CO_{EPBF}* (blue line) CO estimated with the capnodynamic method. *HR* (orange line) = heart rate.

Discussion

In this thesis we have evaluated the revised capnodynamic method with expiratory holds for CO estimation. In a variety of clinically relevant and challenging situations both in a large animal model and patients undergoing high risk abdominal cancer surgery, the capnodynamic method was compared to the best available and acceptable reference methods. For this purpose, we used study designs and statistical methods that are considered current practice.

The principal findings are:

The capnodynamic method showed overall good performance, comparable to the thermodilution methods when altogether compared to the ultrasonic flow probe during various hemodynamic and ventilatory changes in a large animal model.

The performance remained good during sustained hypercapnia in a large animal model, but as expected, temporarily disrupted during the transient large change in mixed venous CO_2 content following reperfusion. Somewhat surprisingly, the method quickly adapted to a new steady state within five minutes.

During lung injury and respiratory failure, the capnodynamic method slightly underestimated CO at high shunt fractions and unexpectedly overestimated CO after recruitment and PEEP adjustment. Precision and trending ability were maintained despite these extreme conditions.

Evaluated for the first time in major abdominal cancer surgery, the capnodynamic method showed overall good performance, with further improvement after individualized RM and PEEP adjustment.

Aspects on the experimental model

During high risk surgery hemodynamic changes are to be expected and as clinicians we wish to respond in real time based on accurate continuous information. Animal studies provide us with great possibilities to induce physiological changes and compare one or more methods to a highly accurate reference method, which is unattainable and unethical in humans. For the evaluation of the capnodynamic method we chose large animals (porcine) 32-44 kg with comparable hemodynamic and respiratory physiology. However, possible differences in CO_2 metabolism between species i.e. due to higher baseline core temperature are unaccounted for as well as congenital heart and lung defects in the individual animal.

In the caudal ischemia model we wanted to simulate high risk aortic surgery with subsequent reperfusion. Severe hemodynamic and metabolic changes were observed that were partially attenuated with pharmacological support to keep the animals alive. Despite inter-individual differences, all animals had an instantaneous rise in P_vCO_2 and P_aCO_2 and significant hemodynamic changes as intended. Sustained hypercapnia (P_vCO_2 >10 kPa), occasionally seen clinically (i.e. laparoscopy), was induced by three different approaches without affecting

precision or trending ability. The positive bias seen at low RR was significantly different from the other two (increased dead space and low TV) which raised suspicion of recirculation, although this could not be confirmed with serial blood gases.

The lung injury model with lavage induced surfactant depletion is commonly employed in animal studies to replicate respiratory failure [90]. We added VILI to the model to limit the reversibility of the lavage-induced injury after lung recruitment and PEEP adjustment, for stronger clinical correlation. There were also inter-individual differences in this model and therefore both these models are relatively heterogeneous. However, the main objective was to challenge the capnodynamic method in situations where limitations are to be expected in a CO_2-based method, and not to produce a perfect model *per se*. It is important nonetheless to keep in mind that animal studies can only serve as a model for human physiology and results cannot be directly transferred to clinical practice.

Aspects on the clinical study

In total 35 patients, undergoing high risk open abdominal cancer surgery, motivating invasive transpulmonary thermodilution, were included in the study after informed consent. Standard clinical procedures, such as minor PEEP changes and epidural activation were formalized in a protocol. Other intraoperative events where hemodynamic changes were expected (i.e. volume bolus and dobutamine infusion when clinically indicated) were captured with measurements performed before and after installation of treatment. In 75% of the patients the change in CO was >15% in either method creating total 96 paired delta values with 90-92% concordance. In this heterogeneous surgical population, inter-individual differences were also noticed, particularly in the +PEEP step where we, frequently observed an initial rise in CO_{EPBF} when PEEP was increased, preceding the anticipated drop due to elevated intrathoracic pressure compromising venous return. This could possibly be explained by the initial alveolar recruitment and CO_2 being squeezed into the alveoli. No objective measurements of atelectasis, shunt or dead space were performed. Despite the fact that CO_{EPBF} calculates another physiological entity, the mean CO of the two methods was essentially the same for all measurements. The small negative total bias observed, was expected, as CO_{EPBF} does not account for the shunted blood flow.

Transpulmonary thermodilution as a reference method

The transpulmonary thermodilution was chosen as a reference due to good reported inherent precision and familiarity with its use. The measured inherent precision at baseline conditions was approximately 10%. However, in 10% of the triplicates performed, a >15% difference between individual thermodilutions was observed. A possible explanation could be that a steady state was not fully accomplished when the thermodilution process was started. In these cases we added one or two thermodilutions and excluded the diverted one to regain accuracy. CO_{EPBF} measurements were registered when the first thermodilution started and the last one

ended. This could be considered a strength to the study, i.e. that each paired measurement represents the measured period as accurately as possible. However, it also reinforces the argument discussed in the background that the thermodilution methods lose their inherent precision during hemodynamic changes and therefore challenges the validity of the 30% cut-off in percentage error commonly used as *a priori*.

Only high risk surgery patients scheduled for a central vein catheter were included in the study. Addition arterial catheter was added for invasive CO monitoring and more precise perioperative hemodynamic guidance. Temporary arterial occlusion is a rare complication after insertion of arterial catheter in the femoral or axillary artery (1.2-1.5%) [91]. However it was a reminder that all interventions convey risk and all the more reason to develop non-invasive alternatives that can perform well in the operation theatre.

The capnodynamic method in challenging situations

An important feature of a hemodynamic monitor is reliability and trending ability in critical situations. The objective of this thesis was therefore to expose the revised capnodynamic method to challenging situations to reveal both strengths and limitations. The capnodynamic method calculates non-shunted CO and thereby estimates CO based on the changes in alveolar CO_2. The calculations are based on physiological and mathematical principles; thus some assumptions are inevitable for the non-invasive function. One of these assumptions is that the content of mixed venous CO_2 must be in a steady state when measurements are performed. Historically this has been a major limitation to all CO_2 based methods. The capnodynamic method however, with its superimposed breathing pattern, automatically recalibrates itself and quickly re-establishes a new steady state, continuously correcting for sources of error. This is evident from our animal studies; the fast response time to hemodynamic changes and overall good agreement in different challenging hemodynamic and ventilatory situations, observed in study I [92]; the resilience after major reperfusion, restoring the function within five minutes and unaffected agreement during sustained hypercapnia, as observed in study II [93]; and maintained precision and trending ability during lung injury, as observed in study III.

Shunt correction or lung optimization?

It is obvious that conditions that increase the shunt flow will influence the accuracy of all CO_2-based methods. Both the semi continuous rebreathing method (NICO®) which is the only clinically available CO_2 based method up to now and the continuous Capnotracking method currently under clinical development by Peyton *et al* in Australia, have shunt corrections included [59,60]. Shunt correction could easily be incorporated into the capnodynamic equation, however, the capnodynamic method has qualities that might be utilized in diverse clinical situations as it estimates the non-shunted CO. Perhaps instead of correcting for shunt, we should focus on reducing shunt with individualized respiratory optimization. In modern

anesthesia management, lung recruitment and PEEP adjustment are commonly performed to counteract the effect of anesthesia on lung function, which *per se*, can cause atelectasis and further develop into postoperative pulmonary complications [94]. These effects are commonly magnified by other factors such as obesities, increased intraabdominal pressure (laparoscopy) and different body positions (i.e. Trendelenburg, prone), emphasizing the importance of personalized respiratory treatment [95-97].

The results from our clinical study (study IV) when compared to the other CO_2 based methods indicate that shunt correction may not be needed. In fact, the overall agreement in patients with VT 6-8ml/kg and PEEP 5 cmH_2O might be considered clinically acceptable considering the good trending ability. In the CON_{P5} group, we observed two clinical outliers who had by far the largest negative bias. They were both obese with predominant abdominal fat, where lung recruitment and PEEP adjustment would clinically been indicated. When they were excluded from the Bland-Altman analysis the PE decreased by 5% (41 to 34%). In light of these results and current anesthesia management we added 10 patients where we, with a simple lung recruitment and PEEP adjustment, tried to individualize the respiratory treatment. We had no objective measure of shunt or atelectasis before or after the procedure. Although not statistically significant, PE error was reduced from 41 to 31%, when RM and PEEP adjustment were performed before starting the study protocol.

In the animal study, severe respiratory failure was induced with lung injury causing high shunt fraction, hypoxemia and increased driving pressure. As expected, bias increased, however, precision and trending ability were mostly unaffected. After recruitment and PEEP adjustment, the shunt was reversed. CO_{EPBF} overestimated the CO by ca 30%, however there was no correlation between the PEEP level and bias *per se* in these animals, as previously observed at high PEEP levels in animals with healthy lungs (data not shown). This overestimation was not observed in the clinical study.

This could be valuable when the deteriorating patient arrives in the ICU and needs emergency airway and breathing management. With physiological understanding and clinical skills, the method, either solely or in combination with i.e. echocardiography, could possibly guide resuscitation and PEEP titration for optimal oxygen delivery instead of relying entirely on compliance and P_aO_2:F_iO_2 ratio.

Interpretation of performance

The term "agreement" encompasses both accuracy (bias) and precision (LoA and PE). Although interrelated, the tracking ability is a measure of a concordance after a change and reported separately. Forced to choose between agreement and trending ability, as an anesthesiologist, I would prefer to know if CO drops suddenly by 15% during surgery rather than if the CO is exactly 5.0 or 6.0 L/min in a steady state.

In study I-III, the capnodynamic method showed a small positive bias (overestimation) at baseline conditions, not observed in the clinical study. Accuracy was interrupted in situations

where one would expect, during transient change in mixed venous content of CO_2 and at high shunt fraction. The positive bias observed at high airway pressures after lung recruitment and PEEP adjustment in the animal study was not detected in healthy lungs after a related procedure in the clinical study.

The precision in the animal studies was in the range of 28-42%, aside from the reperfusion. In study II and III we used more stringent criteria for calculations of percentage error to account for the small sample size. In study IV, the group who received individualized respiratory treatment had PE from 20 to 39% (mean 31%) and patients who received PEEP 5 cmH_2O had PE from 34 to 42% (mean 41%).

The trending ability was >90% according to both 4Q- and polar plots during all CO changes except during at high shunt fraction in study III. However, the CO changes induced in the animal model are large >30% and one might expect good concordance in such experiments. In clinical situations (study IV), the change in CO was >15% in 3 out of 4 paired values and the concordance 92% for the whole group. For volume bolus the concordance was 100%, although there was a large difference in the variation of the change.

In this thesis, we use the word "acceptable" to describe agreement. This is based on an overall good accuracy, (except for the special conditions described above) and a PE above the *priori* (30%) but within 45%. Considering that some difference is expected as the methods represent different entities, we believe that "acceptable" is entitled. Trending ability was good (90%) throughout the studies (with one exception) and in some conditions excellent. All qualities accounted for, we considered the overall performance of the capnodynamic method as good.

Strengths and possibilities

The capnodynamic method has many qualities as a CO monitor, which would be desired by clinicians. It provides continuous relatively accurate and reproducible estimates of CO and reliably corresponds to changes thereof in real time. According to our current and previous studies and observations it is unaffected by changes in arterial resistance or heart rhythm. The method is non-invasive, in the sense that it requires controlled mechanical ventilation, which is common practice during high risk surgery. It is easy to use and runs automatically, providing breath by breath values within a couple of minutes. It could be turned on and off at the discretion of the anesthesia team and used in combination with other monitoring. As a unique physiological entity, it could theoretically be used for PEEP titration for optimal oxygen delivery as CO_{EPBF} will fall when the increased airway pressure constrains the venous return.

In addition, the capnodynamic method provides calculations of the ELV, closely related to the FRC, although considered to be a functional volume more than an anatomical one. There are ongoing studies describing ELV functionality in relation to end expiratory lung volume (EELV) and functional residual capacity (FRC).

Limitations

There are important limitations to the capnodynamic method that need to be addressed. The capnodynamic method is still only available as a research module and requires a mainstream volumetric capnometer. It requires a controlled mechanical ventilation, almost exclusively conducted under general anesthesia or intensive care. It has not been validated with inhaled anesthetic drugs and has only been studied with intravenous anesthesia. The method does not account for shunted blood flow and RM and PEEP adjustment are advised for better V/Q match and optimal performance, especially in overweight patients. The method has not been tested in patients with respiratory failure or BMI > 35 kg/m^2.

Future perspectives

The results from extensive animal studies and the clinical pilot study during high risk abdominal surgery are encouraging and with great potential. A precise continuous monitoring of the effective pulmonary blood flow, estimating CO, could be valuable for the individual patient, providing real time feedback to guide treatment (fluids, vasopressors, inotropy and PEEP).

However, no method will improve outcome unless coupled to a treatment strategy. One possibility would be to optimize CO_{EPBF} in a goal directed fashion with fluids (+/- inotropy) and PEEP combined with clear (personalized) blood pressure targets. An interesting feature would be to connect the breathing pattern to variations in pulse pressure and stroke volume.

With the emergence of artificial intelligence and machine learning one can be indulged by the thought of a futurized fully automated monitoring station. An algorithm combining flow (i.e. via CO_{EPBF}), continuous (non-invasive) blood pressure, dynamic parameters (such as variation in stroke volume and pulse pressure) and depth of anesthesia (i.e. MAC values or bispectral index) and perhaps an objective estimation of the microcirculation to navigate a patient through a demanding surgery, with a skilled anesthesia team ready to act in case of (predicted) crisis.

The next logical step for the capnodynamic method is to integrate the software into the modern anesthesia machine with a user-friendly interface. Further development to allow parallel use of halogenated anesthetic gases is a priority and would facilitate further feasibility- and validation studies in other surgical populations, i.e. emergency surgery, head and neck surgery, neurosurgery and complex spine surgery where access to the patient during surgery is often limited.

In the intensive care unit, it would be interesting to test CO_{EPBF} in patients with respiratory failure, in whom invasive hemodynamic monitoring is already applied. Perhaps PEEP titration based on CO_{EPBF} versus the standard compliance/P_aO_2:F_iO_2 based recruitment could be favourable in terms of oxygen delivery and right ventricular strain.

Parallel to this project, in collaboration with the Royal Institute of Technology, a development of a nano-CO_2 sensor is underway that could provide highly accurate volumetric assessment of CO_2 without any further equipment or cables. Integrated into the y-piece or endotracheal tube it could seamlessly transmit information wirelessly to the anesthesia machine.

The capnodynamic method has a unique potential. With over 300 million operations performed worldwide each year, including a large part in general anesthesia with mechanical ventilation, a flow based method like CO_{EPBF} integrated into the anesthesia machine at low cost with well-defined hemodynamic targets could have a large impact on outcome.

Conclusions

In summary, we have evaluated the revised capnodynamic method (CO_{EPBF}) with expiratory holds, for cardiac output estimation. CO_{EPBF} was compared to an ultrasonic flow probe mounted on the pulmonary trunc during various hemodynamic and respiratory challenges in a large animal model and to a transpulmonary thermodilution in patients undergoing high risk abdominal cancer surgery.

Overall, CO_{EPBF} showed acceptable agreement and precision during a range of hemodynamic and respiratory situations and good trending ability, in both large animal models and during high risk abdominal cancer surgery.

In a large animal model

1. CO_{EPBF} showed acceptable agreement and precision at different cardiac outputs, tidal volumes and PEEP in healthy lungs compared to an experimental gold standard reference method. After induced changes in cardiac output, the response time was fast and trending ability good.
2. CO_{EPBF} agreement was disrupted during transient large change in mixed venous CO_2 content, however restored within five minutes. The overall agreement and trending ability were maintained during sustained elevation of mixed venous CO_2 content.
3. CO_{EPBF} accuracy was marginally affected during severe lung injury, both at high shunt fractions and after compliance based lung recruitment. Precision was maintained during both conditions and trending ability was acceptable at high shunt fractions and excellent after lung recruitment.

In high risk abdominal surgery

4. CO_{EPBF} showed acceptable agreement and precision compared to a transpulmonary thermodilution measured cardiac output. Trending ability was good during a variety of clinically relevant hemodynamic changes.

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