Measuring Cardiac Output in the Critically Ill

Cornelis Slagt

Measuring Cardiac Output in the Critically Ill

Cornelis Slagt

Measuring Cardiac Output in the Critically Ill.
Cornelis Slagt, Dissertation, Erasmus University Rotterdam, The Netherlands

ISBN 978-94-6228-323-7

Financial support for the printing of this thesis has kindly been provided by:
Fonds Gerbrand de Jong, B. Braun Medical BV, AbbVie BV, Itémedical, Pfizer BV, Fresenius Medical Care Nederland BV, ChipSoft BV, Merck Sharp & Dohme BV, Mundipharma Pharmaceuticals BV.

Layout and cover design: Alice Zondervan
Artwork: Body Paint Ref. A18 by Betty Mbitjana from Utopia, Central Australia.
This dissertiation was printed by van Wijk, Oostzaan, The Netherlands.

Meten van het hartminuutvolume tijdens ernstige ziekte

Measuring Cardiac Output in the Critically Ill

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 5 februari 2014 om 13:30 uur

door

Cornelis Slagt

geboren te Broek in Waterland

Promotiecommissie:

Promotor: Prof.dr. A.B.J. Groeneveld

Overige leden: Prof.dr. J. Bakker
Prof.dr. G.J. Scheffer
Prof.dr. R. J. Stolker

Copromotor: Dr. I. Malagon

Steeds weer een afslag
Een kruising, een bocht
De reis is pas over
Aan het eind van de tocht

Huub van der Lubbe

Aan Alice, Sydney en Tobin

Table of Contents

List of abbreviations

ABG	arterial blood gas analysis
APACHE	acute physiology and Chronic health evaluation
AS/ AI	aortic stenosis/insufficiency
BSA	body surface area
CABG	coronary artery bypass grafting
CCO	continuous cardiac output
CI	cardiac index
CO	cardiac output
COap	arterial pressure derived cardiac output
COfv	FloTrac/Vigileo™ cardiac output
COtd	intermittent thermodilution cardiac output
CPB	cardiopulmonary bypass
CPCSNB	combined psoas compartment–sciatic nerve block
CVP	central venous pressure
DBP	diastolic blood pressure
DO_2I	oxygen delivery index;
Dop	dopamine
Eno	enoximone
EVLI	extra vasculair long water
FNSNB	femoral nerve–sciatic nerve blocks
GEE	generalised estimating equations
GEDV	global end-diastolic volme
GEF	global ejection fraction
HR	heart rate
ICU	intensive care unit
IP	impedance plethysmography
ITBV	intra thoracic blood volume
LiDCO	lithium dilution cardiac output
MAP	mean arterial pressure
Nit	nitroglycerine
Nor	norepinephrine
OD	oesophageal doppler
OR	operating room
PAC	pulmonary artery catheter
PAOP	pulmonary artery occlusion pressure
COpc	pulse contour cardiac output

PPV	pulse pressure variation
PVPI	pulmonary vascular permeability index
ScvO2	central venous oxygen saturation
ScO2	mixed venous oxygen saturation
S_pO_2	pulse oxymetry oxygen saturation
SPV	systolic pressure variation
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
SVV	stroke volume variation
TPTD	transpulmonary thermodilution
UO	urine output

1

General introduction

Introduction and outline of the thesis

Haemodynamic monitoring plays an essential part on the care of the critically ill patient. Monitoring has two goals; the first goal is a signalling function if the patients clinical condition improves or deteriorates adequate measures can be taken. Maintaining the adequacy of the circulation reduces the chance of inadequate oxygen transport to the tissues preventing organ ischemia. The second goal is using the monitoring as a decision making tool.[1] Historically, arterial pressures were measured because they were easier to measure than bloodflow. But the introduction of the pulmonary artery catheter (PAC) in 1970[2] allowed the regular measurement of cardiac output (CO) at the beside. Beside CO a new array of variables could be monitored. Measuring more variables did not automatically relate to better outcomes.[3 4]

Over the last 40 years a number of alternative devices to measure CO have been introduced in the market.[1] Depending on the severity of illness and the clinical condition of our patients more invasive techniques can and should be used, taken into account the limitations and risk of these devices.[5 6] Most devices perform well during steady state haemodynamic conditions, which is in contrast with the setting in which we want to use them: haemodynamic instability, sepsis and septic shock, acute respiratory distress syndrome where oxygen demand and delivery is most critical. These clinical conditions are also challenging with respect to haemodynamic measurement. The gold standard to measure CO at the bedside does not exist and should be most ideally be reliable, continuous, non-invasive, operator-independent and cost-effective and should have a fast response time.[7]

This thesis will focus on one of the newest CO measuring devices, the FloTrac/Vigileo™ system which uses the arterial waveform to calculate stroke volume (SV). This system mimics some of the features of the ideal CO monitoring system as it is less-invasive, continues, operator-independent, and has a fast response time of 20 seconds. Its plug and play set up has the potential for use outside the intensive care unit.

Validation of new haemodynamic measurement devices

New haemodynamic measurement devices have to be validated against a gold standard. For many years comparing two methods of measuring clinical parameters was done using the incorrect statistical tools. Results obtained using correlation and regression coefficients did not provide an accurate and meaningful answer to the question: is method A as accurate and reproducible as method B. A first attempt to objectively assess new clinical monitoring devices was made by Bland and Altman.[8] Critchley and Critchley[9] went further and based on the Bland Altman plot, suggested guidelines to accept or reject the performance of new CO measurement devices in 1999. When reporting the results of validation studies, they recommended quoting the mean CO, the bias, the precision, the limits of agreement and the percentage error (1.96 * precision / mean CO). The acceptance of a new method should be judged against the accuracy of the reference method. A percentage of error of up to ±30% should lead to acceptance of the new method. Only recently extra criteria were proposed by Cecconi and colleagues[10] and Critchley[11] to new haemodynamic measurement devices. In a recent meta-analysis by Peyton et al[12] evaluating the performance of clinically used less invasive CO measuring devices using the arterial waveform to calculate CO showed that none of the devices fulfilled the Critchley criteria; all having a percentage of error around the 40%. The debate around the clinical usefulness of less invasive CO devices based on their performance (accuracy and precision) has not ended.

Haemodynamic targets or there surrogates

In a seminal study Shoemaker showed that a strict treatment protocol improved patient outcome targeting haemodynamic "supraphysiological" values.[13] A recent meta-analysis by Hamilton in 2011 showed that mortality could be significantly reduced if a PAC was used, fluid and inotropes were given during the optimization of the high risk surgical patients and cardiac index (CI) or oxygen delivery (DO_2) were targeted to reach supranormal values.[14] A reduction in complications was achieved when variables such as CI, DO_2 and SV where used to target (supra)normal values. When dynamic haemodynamic parameters were optimised during the perioperative setting morbidity was also reduced.[15-17] Unfortunately, these positive findings could not be reproduced in patients admitted to intensive care.[18] [19] Targeting supranormal values in this cohort of patients has been shown to increased mortality.[20] What appears to be a beneficial treatment to one cohort of patients might be detrimental to other. Measuring haemodynamic variables on its own will not change patient's outcome.[21] [22]

In recent years, more emphasis has been given to the fluid management of intensive care and surgical patients. Fluid overload has been associated with increased morbidity.[23] [24] The balance between intravascular filling and systemic fluid overload is a delicate balance which will differ per patient and per surgical procedure. It seems that goal directed fluid therapy results in better outcome compared to a liberal regime.[24] [25] Restrictive fluid management improves patient's outcome when compared to liberal fluid management.[26] Identifying parameters that will help the clinician to guide fluid management at the bedside is essential in patient care. Volumetric parameters like central venous pressure (CVP), global end diastolic volume (GEDV) or pulmonary artery occlusion pressure have poor predictive value[27-30] to identify fluid responders. Dynamic parameters like pulse pressure variation (PPV), systolic pressure variation (SPV), stroke volume variation (SVV) on the other hand are better in predicting fluid responders as long as their limitations are taken into consideration.[31-38]

Arterial waveform analysis

Haemodynamic monitoring devices that use the arterial waveform to calculate SV use the assumption that aortic pulse pressure is proportional to SV.[39] [40] The higher the pressure in a vessel, the greater the SV. As pressure increases, more blood must be accommodated in the arterial tree and as a consequence pulse pressure will increase. With each systole the left ventricle pumps blood into the aorta. Due to the resistance met by the blood, most of the SV is stored in the aortic wall (arterial compliance) and released during diastole (Windkessel function). Mathematically, SV can be calculated if arterial blood pressure, arterial compliance and systemic vascular resistance (SVR) are known (Ohm's law). At the bedside often only blood pressure in known so these devices use external calibration to overcome the problem of unknown arterial compliance and SVR in order to establish the relation between blood pressure and SV.

FloTrac/Vigileo system™ [31]

The system consists of a specialised blood pressure sensor and monitoring device that collects and analysis output variables generating CO, CI, SV, stroke volume index (SVI) and if CVP is available also SVR and systemic vascular resistance index (SVRI). Next to the CO module, there is a central venous saturation ($S_{CV}O_2$) module available that uses a specific central venous line (PreSep® catheter). After calibration (in vivo or vitro) the $S_{CV}O_2$ is displayed and updated every 2 seconds. Within one monitor we get information regarding oxygen delivery and oxygen consumption. Targeting $S_{CV}O_2$ has been shown to reduce mortality in septic shock.[41]

Since its introduction in 2005 the software that calculates SV has been updated four times. Software versions subsequently released include first generation (1.01, 1.03), second generation (1.07, 1.10, 1.14) and the most recent third generation version 3.02 and 3.06. In the 1.03 software version the "vascular" calibration window was 10 min. In the 1.07 software version the window was changed to 1 minute. In the 1.10 version, the algorithm was improved to better account for hypertension, tachycardia, and volume loading. The 1.14 version was only an update of the display. The third generation version includes 2 models for arterial tone, dynamic tone technology: (1) a model that was developed predominantly from patients in normo- and hypodynamic conditions (as in the previous version 1.10) and (2) a model that was developed predominantly from patients in hyperdynamic conditions.[42] Alternating between the two models is based on an algorithm that uses 14 parameters of the arterial pressure waveform to detect the occurrence of hyperdynamic conditions.

Stroke volume variation is calculated as follows: $SVV_{FloTrac}$ (%) = 100 x (SV_{max} – SV_{min}) / SV_{mean}. Software calculating SVV_{xtra} has been updated in version 3.02. Detection of abnormal beats, rejection of these beats and interpolation of the remaining beats and restoration of missing beats allows calculation of SVV. SVV_{xtra} can predict fluid responsiveness despite 20-25 extra systoles per minute.[43]

The FloTrac/Vigileo™ system is the only system using the arterial waveform that does not require external calibration but uses internal calibration based on waveform analysis instead. The algorithm uses the assumption that all pulsatile flow is transformed into a continuous flow at the distal arteries due to pressure difference, vascular compliance and the peripheral resistance. The arteries provide resistance and compliance and with it are also responsible for the shape of arterial waveform. Vascular tone is a primary determinant of the relation between SV and arterial pressure so vascular tonus is estimated within the analysis. The system calculates CO by using the standard deviation of the arterial pulse pressure and analyses arterial compliance and resistance.[31] The following formula applies: CO = HR x σsAP x χ(chi), where HR is heart rate and σsAP, is the standard deviation of arterial pressure, sampled at 100 Hz over a period of 20 seconds. Subsequently σsAP is matched with empirical data correlating σsAP with SV (database). σsAP in not directly correlated to MAP to calculate SV, and therefore SV could increase or decrease without changes in MAP.

The function that analysis vascular tone is χ(chi)(it is a moving window of 1 minute). It takes into account natural changes and intervention effects on vascular compliance

and resistance. Chi is a proprietary polynomial equation that relates the impact of vascular tone on pulse pressure. χ = M (HR, σsAP, C(P), BSA, MAP, μ3ap, μ4ap), where M is multivariate approximating function, C(P) is a function of arterial compliance, μ3ap is the skewness (lack of symmetry of the waveform) of arterial pressure data, μ4ap is the kurtosis (how peaked or flat a sample distribution is from normal) of arterial pressure data and BSA is body surface area. A polynomial multivariate fitting function is used to calculate χ as a measure of vascular tone. As aortic compliance inversely affects pulse pressure it is important to compensate for differences between patients. C(P) is derived from Langewouters, using sex and age and modified by adding weight, height and BSA.[44]

Aim of this thesis

With this thesis we have sought to improve our knowledge base around CO measurement using waveform analysis without external calibration: the FloTrac/Vigileo™ system. In particular its use, accuracy and reproducibility in different clinical circumstances. We have evaluated FloTrac™ derived haemodynamic parameters in intensive care patients (mostly sepsis) in consecutive software versions with pulmonary artery catheter and transpulmonary thermodilution as reference. We examined the difference between calibrated and uncalibrated waveform analysis for haemodynamic monitoring in patients suffering from septic shock. We investigated as well changes in CO in patients undergoing hemisympathectomy in elective orthopaedic surgery and we performed a meta analysis of available FloTrac/Vigileo™ literature.

Chapter 2 provides an overview to aid the choice: which haemodynamic monitor can be used best in a individual patient in a particular clinical setting.

In **chapter 3** we studied the effect of two consecutive software versions (software version 1.07 and 1.10) on the accuracy of the FloTrac/Vigileo™. We hypothesized that the newer software version was more accurate than its predecessor. A comparison with pulmonary artery catheter-derived thermodilution measurements in patients with septic shock was the objective.

In **chapter 4** we describe our results of the haemodynamic changes measured with the FloTrac/Vigileo™ monitor during combined psoas compartment–sciatic nerve block (CPCSNB) for elective orthopaedic surgery. Our research question was: CPCSNB does not cause clinical significant haemodynamic effects in patients undergoing elective orthopaedic surgery. The CPCSNB was performed using 10 mL of

bupivacaine 0.3% administered to the sciatic nerve and 40 mL of bupivacaine 0.3% which was injected into the psoas compartment. Epinephrine 1:200.000 (5μg ml^{-1}) was added to the local anaesthetic solution.

In **chapter 5** we studied the 3.02 (third generation) software version of the FloTrac/Vigileo™ system. We compared FloTrac/Vigileo™ CO measurements with pulmonary artery catheter thermodilution-derived CO. The goal of this study was to evaluate the accuracy of the FloTrac/Vigileo™ derived CO using the latest 3.02 software version compared with intermittent thermodilution-derived CO in the course of treatment of patients with septic shock.

In **chapter 6** we studied the CO measured by the FloTrac/Vigileo™ monitor using the third generation software and compared it with transpulmonary thermodilution CO, derived from the recently introduced VolumeView/EV1000™ system, Edwards Lifesciences, Irvine CA, USA, measurements in critical ill patients. Since both monitoring devices the VolumeView/EV1000™ system and FloTrac/Vigileo™ use waveform analysis to calculate continues CO a comparison between the two would be of interest. The aim of this prospective observational single centre study was to compare calibrated waveform analysis (COap) and uncalibrated waveform analysis (COfv) with COtptd (VolumeView/EV 1000**™**, Edwards Lifesciences, Irvine, CA, USA) in critically ill patients in the course of treatment for severe sepsis in the intensive care unit (ICU). We hypothesized that calibrated outperforms uncalibrated less invasive CO in this conditions.

In **chapter 7** we present a systematic review which summarises the results of studies using FloTrac/Vigileo™ monitor.. A literature search on the FloTrac/Vigileo™ system using the headings FloTrac™ and uncalibrated waveform analysis was performed on the use of the system until May 1 2013. One hundred and fifteen manuscripts were used in this review. The aim of this review was to define the current role of FloTrac/Vigileo™ in clinical practice with regards to: a) CO validation according to underlying conditions in patients and subsequently released software versions. b) SVV measurements by the system. And finally, studies on the use of FloTrac/Vigileo™ -derived variables guiding treatment in the critically ill patient.

In **chapter 8** we report our main conclusions, general discussion on the clinical applicability of the FloTrac/Vigileo™ monitor and suggestions for future research.

References

1. Vincent JL, Rhodes A, Perel A, et al. Clinical review: Update on hemodynamic monitoring - a consensus of 16. *Crit Care* 2011;15:229.
2. Swan HJ, Ganz W, Forrester J, et al. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med* 1970;283:447-51.
3. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients. Meta-analysis of randomized clinical trials. *JAMA* 2005;294:1664-1670.
4. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA* 1996;276:889-897.
5. Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. *Crit Care* 2011;15:214.
6. Slagt C, Breukers RBGE, Groeneveld ABJ. Choosing patient-tailored hemodynamic monitoring. *Crit Care* 2010; 14:208.
7. de Waal EE, Wappler F, Buhre WF. Cardiac output monitoring. *Curr Opin Anaesthesiol* 2009;22:71-7.
8. J.M. Bland, D.G. Altman. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–310.
9. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85-91.
10. Cecconi M, Rhodes A, Polaniecki J, et al.. Bench –to bedside review: The importance of the precision of the reference technique in method comparison studies – with specific reference to the measurements of cardiac output. *Crit Care* 2009;13:201.
11. Critchley LA, Yang XX, Lee A. Assessment of trending ability of cardiac output monitors by polar plot methodology. *J Cardiothorac Vasc Anesth* 2011;25:536-46.
12. Peyton PJ. Continuous minimally invasive peri-operative monitoring of cardiac output by pulmonary capnotracking: comparison with thermodilution and transesophageal echocardiography. *J Clin Monit Comput* 2012;26:121-32.
13. Shoemaker W C, Appel P L, Kram H B, et al.. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;94:1176-1186.
14. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011;112:1392-402.
15. Lopes MR, Oliveira MA, Pereira VO, et al.. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. *Crit Care* 2007,11:R100.
16. Mayer J, Boldt J, Mengistu A, et al. Goal-directed intraoperative therapy based on arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized controlled trial. *Crit Care* 2010;14: R18.
17. Zhang J, Qiao H, He Z, et al. Intraoperative fluid management in open gastrointestinal surgery: goal-directed versus restrictive. *Clinics (Sao Paulo)* 2012;67:1149-55.
18. Heyland DK, Cook DJ, King D, et al. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. *Crit Care Med* 1996;24:517-24.
19. Ospina-Tascón GA, Cordioli RL, Vincent JL.What type of monitoring has been shown to improve outcomes in acutely ill patients? *Intensive Care Med* 2008;34:800-20.
20. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994;330:1717-22.
21. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005;366:472-477.
22. Takala J, Ruokonen E, Tenhunen J, et al. Early noninvasive cardiac output monitoring in hemodynamically unstable intensive care patients: a multi-center randomidzed controlled trial. *Crit Care* 2011;15:R148.
23. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med* 2006;34:332-344.
24. Bundgaard-Nielsen M, Holte K, Secher NH, et al. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol Scand* 2007;51:331–40.

25. Corcoran T, Rhodes JE, Clarke S, et al. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 2012;114:640-51.
26. Lobo SM, Ronchi LS, Oliveira NE, et al. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high-risk surgery. *Crit Care* 2011;15:R226.
27. Hofer CK, Senn A, Weibel L, et al. Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTracTM and PiCCOplusTM system. *Crit Care* 2008;12:R82.
28. Cannesson M, Musard H, Desebbe O, et al. The ability of stroke volume variations obtained with Vigileo/FloTrac system to monitor fluid responsiveness in mechanically ventilated patients. *Anesth Analg* 2009;108:513-517.
29. Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007;35:64–68.
30. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med.* 2004;32:691-9.
31. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-411.
32. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; 103:419-28
33. Daudel F, Tüller D, Krähenbühl S, et al. Pulse pressure variation and volume responsiveness during acutely increased pulmonary artery pressure: an experimental study. *Crit Care* 2010,14:R122.
34. Wyler von Ballmoos M, Takala J, Roeck M, et al. Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care* 2010,14:R111.
35. Magder S: Further cautions for the use of ventilatory-induced changes in arterial pressures to predict volume responsiveness. *Crit Care* 2010,14:R197.
36. De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005;31:517-523.
37. Kim HK, Pinsky MR. Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. *Crit Care Med* 2008,36:2858-2862.
38. De Backer D, Taccone FS, Holsten R, et al. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009;110:1092-7.
39. van Lieshout JJ, Wesseling KH. Continuous cardiac output by pulse contour analysis? *Br J Anaesth* 2001;86: 467-9.
40. Erlanger J, Hooker DR. An experimental study of blood pressure and of pulse-pressure in man. *John Hopkins Hosp Rep* 1904;12:145-378.
41. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
42. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J Appl Physio* 2011; 111:853-60.
43. Canneson M, Tran NP, Cho M, et al. Predicting fluid responsiveness with stroke volume variation despite multiple extrasystoles. *Crit Care Med* 2012;40:193-8.
44. Langewouters G, Wesseling K, Goedhard W. The pressure dependent dynamic elasticity of 35 thoracic and 16 abdominal human aortas in vitro described by a five component model. *J Biomech* 1985;18:613-620.

2

Choosing patient-tailored haemodynamic monitoring

Slagt C, Breukers RM, Groeneveld AB.

In: Yearbook for intensive care and Critical Care medicine 2010 Vincent JL. Section II Hemodynamic monitoring: Choosing patient-tailored hemodynamic monitoring, p 64-71.

Crit Care 2010;14:208.

Introduction

Currently, the number and (worldwide) availability of techniques for haemodynamic monitoring in the critically ill patient is overwhelming, as nicely summarised elsewhere.[1–11] Techniques vary from completely invasive to non-invasive, from intermittent to continuous, and differ in basic principles, methods, parameters, and costs, among others. The older a device, the more literature is available, but the latter may not always help in choosing haemodynamic monitoring tools for departments or for individual patients, i.e. patient-tailored monitoring.

This chapter is not intended to compare one technique to another, which has been done abundantly in the literature, but to provide a conceptual framework to guide therapy of individual patients in various hospital settings by defining the elements that may help to choose among the available techniques, in the absence of a clear evidence-based survival benefit of any haemodynamic monitoring tool.[12–16] First, a brief discussion of what is available and of underlying basic principles seems warranted, since knowledge of possibilities, limitations and pitfalls is required before responsible choices can be made. We will not address tools to monitor the microcirculation.

What do we have and what can they do?

A physical examination remains the cornerstone of assessing patients with haemodynamic compromise, even though signs and symptoms often poorly predict measured haemodynamic variables.[13 17] Nevertheless, clinical signs and symptoms help to clearly define the clinical problem and its differential diagnosis. As an adjunct, some type of haemodynamic monitoring is often decided upon, depending on the clinical severity of disease and the (department of) presentation of the patient, among other factors. Table 1 briefly summarises the currently available equipment for advanced haemodynamic monitoring, beyond that of mean arterial pressure (MAP) and heart rate/rhythm. As indicated, a wide variety of haemodynamic parameters can be monitored by the different techniques, in addition to cardiac output (CO). The parameters pertain to cardiac filling and function and its adequacy related to tissue needs. In addition, pulmonary variables pertaining to edema and gas exchange can be assessed with some devices.

There is a large amount of literature concerning the comparability of techniques and derived parameters, such as (absolute values and changes in) CO and preload indicators.[4-7 18 19] However, the manner in which the comparability (or

Table 1. What do we have and what can they do?

Equipment
Central venous catheter (many companies)
Pulmonary artery catheter
and modifications (some companies)
PiCCO^{II} (Pulsion)
LiDCO^{plus} (LiDCO)
NICO (Novametrix)
Modelflow pulse contour analysis (BMI-TNO)
Nexfin (Bmeye)
FloTrac/Vigileo^{TM}(Edwards Life Sciences)
Pulse-dye densitometry PDD (Nihon Kohden)
Bioimpedance cardiography (Aesculon, Osypka Medical)
Haemosonic (Arrow)
CardioQ (Deltex Medical)
Ultrasonic cardiac output monitors (Uscom)
Echocardiographs (some companies)
Parameters
Cardiac pressures and volumes
Cardiac output, flow, velocity/time
Dynamic indices
Cardiac anatomy and regional function
Oxygen-related variables
Carbon dioxide- related variables
Vascular diameters

Manufacturers within parentheses

clinically important absence thereof) is judged varies greatly among studies. Uniformly accepted criteria to assess the clinical relevance of comparability of monitoring techniques and parameters are lacking. For instance, comparability of techniques for tracking changes and trends in CO may be more relevant in clinical practice than the degree of agreement of absolute values, provided that `low' and `high' values can be separated.[19] Moreover, literature on the practical utility of many of these devices and parameters is scarce, so that negativism regarding their practical value may predominate.[16 20] There is, however, some literature to suggest that insertion of a pulmonary artery catheter (PAC) and measuring haemodynamic variables may influence the clinical appraisal of haemodynamics at the bedside and may help or prompt the treating physician to change treatment.

Since its introduction in the 1970s, the PAC has indeed become the reference standard for haemodynamic monitoring and measurement of CO.[13-15] A substantial knowledge database has been built up since then, in a variety of institutions, patient populations, and circumstances.[16] However, in the absence of any rigidly proven survival benefit, the catheter has become discredited in critical care medicine.[12-16] The

lack of apparent benefit may relate, in part, to adverse effects of insertion, improper use, poor interpretation of haemodynamic data, and inadequate treatment decisions based on the collected variables, or combinations of these factors.[20] Conversely, the value of pulmonary artery pressures, pulmonary artery occlusion pressure (PAOP), mixed venous oxygen saturation (SvO2), and right heart volumes, some of the variables that can be uniquely assessed at the bedside of the critically ill patient with help of the PAC and right-sided thermodilution, remains hotly debated.[13-15 20] The patient population or circumstance that is most likely to benefit from pulmonary artery catheterisation is, therefore, still being actively looked for.[13-15 21 22] A second generation haemodynamic monitoring principle includes the less invasive transpulmonary (dye) thermodilution technique, e.g. PiCCO. This technique offers the unique possibility of estimating cardiac preload volumes, measurements of which are not confounded by mechanical ventilation in contrast to pressure and dynamic indices of preload and fluid responsiveness, and of extravascular lung water as a direct measure of pulmonary edema and permeability. Dilutional methods to measure CO include the transpulmonary lithium and indocyanine green (pulse dye) techniques, allowing peripheral injections and peripheral and, for pulse dye, non-invasive detection.

Pulse-contour or pulse-power methods, needing relatively frequent recalibration for optimal performance in tracking changes in CO, are often incorporated in dilutional CO measurement devices needing arterial access.[5 18] Some of these methods are truly non-invasive, however. The algorithms used differ from one method to the other, some perform better than others, and the need for recalibration upon changes in time or in vascular tone upon treatment continue to limit their independent applicability.[5 18] Calibration can also be performed by ultrasonically obtained aortic diameter for the otherwise well performing Model flow method.[23] The algorithm used in the latter method computes the aortic flow waveform from pulsating arterial blood pressure by simulating a nonlinear, self-adaptive (three-element Windkessel) model of the aortic input impedance. Characteristic impedance and compliance of the aorta non-linearly depend on arterial pressure, and peripheral resistance adapts to changes in blood flow. The degree of non-linearity depends on the subjects sex, age, height, and weight.

An arterial waveform analysis without external calibration, the FloTrac/Vigileo™ system, is supposed to be relatively independent of vascular tone.[9] Each arterial waveform detected via an arterial catheter is analysed with a frequency of 100 Hz. The arterial waveform is analysed for 8 different characteristics, including the upstroke and down slope of the curve. Each curve is analysed separately and additional curves are

analysed and compared with former and subsequent curves. From this analysis, which takes 20 seconds, the average curve is given, by means of the standard deviation of the given characteristics of the curves. From the given stroke volume and heart rate, the CO is determined, which is updated every 20 seconds. A filter is embedded in the computer to adjust for excesses in systolic blood pressures and heart rates. The accuracy of this method has increased with consecutive software versions.

Doppler ultrasound methods estimate CO by measuring aortic blood flow velocity[10 11 24 25] and multiplying it by the cross-sectional area of the aorta at the insonation point. The probe is introduced orally or nasally and placed at the level of the descending aorta. Some systems measure the descending aortic diameter; others use a monogram to estimate it. Limitations of the technique include operator-dependency in finding the optimal angle of insonation, turbulent flow, and changes in relative perfusion of upper and lower body parts via the aorta. Obviously, echocardiography yields clinically useful information on cardiac anatomy and (regional) function that is hard to obtain otherwise, in addition to non-unique parameters, such as cardiac filling and output.[26 27] The technique is highly dependent on available expertise and commitment.

Factors affecting choices

Tables 2-4 describe the issues that may be relevant for decision making, including theoretical considerations, the hardware involved, and patient-bound factors. Indeed, demands put on technologies may vary according to need in different hospital environments and patient populations. We will highlight just some of the considerations mentioned in the Tables. Table 2 essentially notes theoretical considerations, suggesting that the ideal haemodynamic monitoring tool should be simple, safe, relatively versatile, uniformly applicable and beneficial for survival in each patient subjected to that tool, at low or at least affordable costs. Obviously, no method yet fits this `ideal' list, and perhaps never will, so some compromise on these issues remains necessary.

Some haemodynamic optimisation strategies, such as fluid management guided by prediction of fluid responses, early goal-directed therapy, and perioperative haemodynamic optimisation or fluid restriction, may help to improve patient outcomes, in terms of reducing complications, lengths of stay, and prevention of overhydration, for example, even irrespective of vital status.[1 6 25 28-33] Devices and parameters to assess fluid responsiveness include transpulmonary dilution-derived cardiac volumes, esophageal Doppler flow and echocardiographic indices, and dynamic indices provided by pulse-contour methods.[10 11 24 25 33 34] In contrast, central

Table 2. Theoretical considerations for choosing among haemodynamic monitoring tools

- Safety and side effects
- Versatility, number, relevance and utility of parameters
- Can be utilised by nurses and physicians: ease of use, user-friendliness, education, learning curve
- Possibilities for assessing fluid responsiveness, goal-directed therapy and other resuscitation strategies of proven outcome benefit even if not decreasing mortality
- Demonstrated treatment alterations
- Acceptable cost-effectiveness

Table 3. Hardware considerations for choosing among haemodynamic monitoring tools

- Availability
- Expertise; personal, colleagues, and in the literature
- Ease of use and interpretation; operator-dependency
- Level of integration in monitors
- Uniformity of applicability
- Continuous vs. intermittent
- Invasive vs. non-invasive
- Accuracy/reproducibility of parameters
- Response time to interventions and accurate trending

venous pressure (CVP) monitoring may suffice in successful fluid restriction policies.[32] The well-known outcome (survival) benefit of early goal directed therapy in septic shock, with treatment guided by CVP, central venous oxygen saturation (ScvO2) and MAP, has been confirmed by others, since the landmark paper by Rivers et al.[35] and this approach is included in current guidelines on the management of septic shock[1 31] even though CVP may poorly predict fluid responses.[36] Hence, monitoring tools could be judged on their ability to provide parameters that help physicians to implement the strategies mentioned, even if these are slightly different from those originally used in demonstrating benefit but apply similar physiologic and clinical concepts.[1 15 30 37-39] For example, the benefit of responses.[36] Hence, monitoring tools

Table 4. Patient-bound considerations for tailoring haemodynamic monitoring

- Cardiac rhythm, function and valvular disease
- Mechanical ventilation: tidal volume, frequency, positive end-expiratory pressure
- Type, severity and stage of (anticipated) disease warranting haemodynamic monitoring, such as shock and acute lung injury
- Type of circulatory support and change herein contemplated: fluids, drugs, devices for circulatory support
- Vascular access and other anatomic factors (contraindications)
- Tolerance

could be judged on their ability to provide parameters that help physicians to implement the strategies mentioned, even if these are slightly different from those

originally used in demonstrating benefit but apply similar physiologic and clinical concepts.[1 15 30 37–39] For example, the benefit of perioperative haemodynamic optimisation with help of the PAC,[28] transpulmonary/lithium dilution,[29 30] esophageal Doppler,[10 11 24 25] or dynamic indices[38] could translate into a benefit of optimisation of central/mixed venous oxygen saturation since all are intended to optimise tissue oxygenation.[37] Nevertheless, not all devices and parameters have been successfully evaluated yet in haemodynamic optimisation strategies and these issues continue to be subject to ongoing research and debate.[1 15 37 39 40] Thus, we may need to formulate and test haemodynamic monitoring strategies, rather than to evaluate performance and efficacy of single devices and parameters. The rationale of these strategies may be enforced if led by physiological and clinical considerations as well as by epidemiological and economic issues. Finally, effectiveness could be defined in terms of the clinical utility of devices and parameters that may go beyond their formally reported efficacy.

Hardware considerations (Table 3) include the environment where the haemodynamic monitoring is used. Different departments may have different facilities, patient populations and staffing, and pressures on time by emergencies may drive choices for less invasive techniques that can be applied immediately by most of the available staff. Non-invasive haemodynamic monitoring devices may also be of help in departments without facilities for invasive techniques, such as step-down units, long-term facilities, and stroke units. By virtue of definition, any device that is able to accurately detect rapid changes in CO upon fluid challenge would suffice in evaluating fluid responsiveness and some methods may be too slow to fulfill this criterion.

General considerations regarding patient-bound factors (Table 4) include the notion that the sicker the patient the greater the need for accurate haemodynamic parameters to be collected to supplement clinical judgment and the greater likelihood that invasive, rather than less invasive, techniques will meet these needs. In the patient with severe septic shock admitted to the intensive care unit (ICU) for instance, non-invasive arterial waveform analysis-derived CO measurements are less useful as they are affected by vascular tone and require repeated recalibration, at least in the initial resuscitation phase. In patients with or at great risk of pulmonary edema, haemodynamic monitoring by transpulmonary dilution and measurements of extravascular lung water could be chosen to help to prevent harmful overhydration and prolonged mechanical ventilation, unless the patient will anyway need to be intubated and mechanically ventilated. Catheters in the femoral artery are relatively contraindicated during/after aortic-bifemoral reconstruction, and transesophageal

echocardiography is not feasible during/after esophageal resection. Esophageal disease may be a contraindication for the use of esophageal Doppler probes, which are also poorly tolerated in awake, non-intubated patients.[10 20 25] The presence of cardiac disease and mechanical ventilation may also affect choices. It is likely that a PAC and measurement of PAOP is more helpful in guiding (fluid) management in the presence of systolic/diastolic cardiac dysfunction than during hypovolemic shock, for example.[21 34] In severe left-sided valvular disease, right-sided measurements of CO are probably preferable to transpulmonary ones, even though the debate on the confounding effect of even minimal tricuspid regurgitation on these measurements has not yet ended. In the presence of endocarditis, intracardiac catheters may be relatively contraindicated. In contrast, a suspected ventricular septal defect may require monitoring with help of a PAC, echocardiography, or both. In mechanically ventilated patients, filling pressures that are confounded by airway pressures may be less useful in predicting and guiding fluid responses than volumetric preload measurements.[34 36] whereas the currently proposed superiority of dynamic indices[33] can be questioned, as they are affected by ventilatory frequency and tidal volume. Finally, pulse-contour methods are sensitive to arrhythmias, aortic valve regurgitation, intra-aortic balloon pumping and peripheral vascular disease.

Conclusions and perspective

This chapter attempts to provide a conceptual framework for choosing patient-tailored haemodynamic monitoring from available techniques, in an era dominated by lack of proven survival benefits for any haemodynamic monitoring device. Decisions for implementing different haemodynamic monitoring devices may improve when systematically considering the relevant issues, according to a predefined checklist, for example. This approach may help to end debates on the use of haemodynamic monitoring equipment from single perspectives only, but obviously choices may differ from one hospital, unit, patient and physician to another, given the variability in facilities, clinical presentations, and expertise. One tool may supplement another, so that it is advisable to gain expertise in more than one method, particularly in training environments. Health technology assessment institutions and agencies can be of help in advising on these complex issues and emergency and intensive care medicine organisations could benefit from their expertise.[1 12 13 25 41] The underlying idea, of course, is that helping physicians to direct therapy using numbers rather than signs and symptoms, and helping the medical community by providing clear clinical guidelines on haemodynamic monitoring strategies will effectively result in health care improvements. Perhaps, we also need a new research agenda on these issues.

References

1. Gunn SR, Fink MP, Wallace B. Equipment review: the success of early goal-directed therapy for septic shock prompts evaluation of current approaches for monitoring the adequacy of resuscitation. *Crit Care* 2005;9:349-359.
2. Hofer CK, Ganter MT, Zollinger A. What technique should I use to measure cardiac output ? *Curr Opin Crit Care* 2007;13:308-317.
3. Jhanji S, Dawson J, Pearse RM. Cardiac output monitoring: basic science and clinical application. *Anaesthesia* 2008;63:172-181.
4. Mathews L, Singh KRK. Cardiac output monitoring. *Ann Card Anaesth* 2008;11:56-68.
5. Maus TM, Lee DE. Arterial pressure-based cardiac output assessment. *J Cardiothorac Vasc Anesth* 2008;22:468-473.
6. Morgan P, Al-Subaie N, Rhodes A. Minimally invasive cardiac output monitoring. *Curr Opin Crit Care* 2008;14:322-326.
7. De Waal EEC, Wappler F, Buhre WF. Cardiac output monitoring. *Curr Opin Anaesthesiol* 2009;22:71-77.
8. Funk DJ, Moretti EW, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. *Anesth Analg* 2009;108:887-897.
9. Mayer J, Boldt J, Poland R, et al. Continuous arterial pressure wave form-based cardiac output using the FloTrac/Vigileo: a review and meta-analysis. *J Cardiothor Vasc Anesth* 2009;23:401-406.
10. Schober P, Loer SA, Schwarte LA. Perioperative hemodynamic monitoring with transesophageal Doppler technology. *Anesth Analg* 2009;109:340-353.
11. Singer M. Oesophageal Doppler. *Curr Opin Crit Care* 2009;15:244-248.
12. Scales DC, Sibbald WJ. Medical technology in the intensive care unit. *Curr Opin Crit Care* 2004;10: 238-245.
13. Harvey S, Stevens K, Harrison D, et al. An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial. *Health Technol Assess* 2006;10:1-152.
14. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients. Meta-analysis of randomised clinnical trials. *JAMA* 2005;294:1664-1670.
15. Antonelli M, Levy M, Andrews PJ, et al. Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27-28 April 2006. *Intensive Care Med* 2007;33:575-590.
16. Ospina-Tascón GA, Cordioli RL, Vincent J-L. What type of monitoring has been shown to improve outcomes in acutely ill patients ? *Intensive Care Med* 2008;34:800-820.
17. Sevransky J. Clinical assessment of hemodynamically unstable patients. *Curr Opin Crit Care* 2009;15:234-238.
18. De Wilde RB, Schreuder JJ, van den Berg PC, et al. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 2007;62:760-768.
19. Squara P, Cecconi M, Rhodes A, et al. Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices. *Intensive Care Med* 2009;35:1801-8.
20. Vincent J-L, Pinsky MR, Sprung CL, et al.. The pulmonary artery catheter: in medio virtus. *Crit Care Med* 2008;36:3093-3096.
21. Ranucci M. Which cardiac surgical patients can benefit from placement of a pulmonary artery catheter ? *Crit Care* 2006;10:S6
22. Harvey SE, Welch CA, Harrison DA, et al. Post hoc insights from PAC-Man-The UK pulmonary artery catheter trial. *Crit Care Med* 2008;36:1714-1721.
23. de Waal JB, de Wilde RB, van den Berg PC, et al. Less invasive determination of cardiac output from the arterial pressure by aortic diameter-calibrated pulse contour. *Br J Anaesth* 2005;95:326-331.
24. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitoring for fluid replacement in major abdominal surgery. *Anaesthesia* 2008;63:44-51.
25. Mowatt G, Houston G, Hernndez R, et al. Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients. *Health Technol Assess* 2009;13:1-120.
26. Slama M, Maizel J. Echocardiographic measurement of ventricular function. *Curr Opin Crit Care* 2006;12:241-248.
27. Salem R, Vallee F, Rusca M, et al. Hemodynamic monitoring by echocardiography in the ICU: the role of the new echo techniques. *Curr Opin Crit Care* 2008;14:561-568.
28. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 2002; 30:1686-1692.

29. Pearse R, Dawson D, Fawcett J, et al. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care* 2005;9:R687-693.
30. Goepfert MSG, Reuter DA, Akyol D, et al. Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. *Intensive Care Med* 2007;33:96-103.
31. Rivers EP, Coba V, Whitmill M. Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. *Curr Opin Anesthesiol* 2008;21:128-140.
32. Stewart RM, Park PK, Hunt JP, et al. Less is more: improved outcomes in surgical patients with conservative fluid administration and central venous catheter monitoring. *J Am Coll Surg* 2009 208:725-737.
33. Marik PE, Cavalazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009;37:2642-2647.
34. Breukers RM, Trof RJ, de Wilde RB, et al. Relative value of pressures and volumes in assessing fluid responsiveness after valvular and coronary artery surgery. *Eur J Cardiothorac Surg* 2009;35:62-68.
35. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness ? A systematic review of the literature and the tale of seven mares. *Chest* 2008;134:172-178.
36. Collaborative Study Group on Perioperative $S_{cv}O_2$ Monitoring. Multicentre study on peri- and postoperative central venous oxygen saturation in high-risk surgical patients. *Crit Care* 2006;10:R158.
37. Lopes MR, Oliveira MA, Pereira VOC, et al. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomised controlled trial. *Crit Care* 2007;11:R100.
38. Buettner M, Schummer W, Hiettemann E, et al. Influence of systolic-pressure variation guided intraoperative fluid management on organ function and oxygen transport. *Br J Anaesth* 2008;101:194-199.
39. Uchino S, Bellomo R, Morimatsu H, et al. Pulmonary artery catheter versus pulse contour analysis: a prospective epidemiological study. *Crit Care* 2006;10:R174.
40. Oortwijn WJ, Hanney SR, Ligtvoet A, et al. Assessing the impact of health technology assessment in the Netherlands. *Int J Technol Assess Health Care* 2008;24:259-269.

3

Cardiac output derived from arterial pressure waveform analysis without calibration vs. thermodilution in septic shock: evolving accuracy of software versions

Slagt C, Beute J, Hoeksema M, Malagon I, Mulder JW, Groeneveld JA.

Eur J Anaesthesiol 2010; 27:550-4.

Abstract

Background and objective

We studied the evolution of software in the accuracy of the FloTrac/Vigileo™ system to measure cardiac output less invasively from arterial pressure waveform analysis without calibration, in comparison with pulmonary artery catheter-derived thermodilution measurements, in patients with septic shock and presumed alterations in vascular tone.

Methods

Nine patients who received a pulmonary artery catheter and were on mechanical ventilation and in sinus rhythm were monitored by the FloTrac/Vigileo™. Paired cardiac output measurements by both techniques were analysed for 86 measurements in four patients using the 1.07 software version and 73 measurements in five subsequent patients using the later 1.10 version.

Results

For the 1.07 version, bias was -1.6 L min^{-1}, precision 1.6 L min^{-1}, limits of agreement -4.8 to 1.5 L min^{-1} and error 48%. Measurements correlated at partial r equal to 0.32 ($P=0.003$). For the 1.10 version, bias was -1.2 L min^{-1}, precision 1.1 L min^{-1}, limits of agreement -3.5 to 1.0 L $min^{-1}$and error 32%. Measurements correlated at partial r equal to 0.90 ($P<0.001$ vs. version 1.07). Differences were inversely related to mean cardiac output ($P<0.001$, generalised estimating equations), particularly for software version 1.07 vs. 1.10 ($P=0.017$, generalised estimating equation). Changes in thermodilution cardiac output over the course of time were also better tracked by the FloTrac/Vigileo™ when applying the latest software ($P<0.001$, generalised estimating equation).

Conclusions

Evolving software versions are thus better able to account for the effect of vascular tone on cardiac output measurements by less invasive waveform analyses without calibration FloTrac/Vigileo™), so that the latter may become useful in the haemodynamic monitoring of septic shock.

Introduction

Cardiac output (CO) is traditionally measured by bolus thermodilution using a pulmonary artery catheter (PAC). In view of potential complications and low evidence for improving outcome, alternatives to the PAC for haemodynamic monitoring are continuously explored. Many less invasive techniques employing contour analysis of arterial pressure to derive stroke volume and CO necessitate relatively frequent calibration by independent techniques, reducing their clinical value. The fairly recently introduced FloTrac/Vigileo™ (Edwards Lifesciences, Irvine, California, USA) system, however, is claimed to yield relatively accurate continuous CO readings, without calibration, at least after cardiac surgery.[1-5] Indeed, evolving software for this system improved the accuracy of CO measurements, as compared with those by bolus thermodilution, after cardiac surgery, suggesting decreasing dependency on vascular tone, a common problem of pulse-contour methods underlying the need for frequent (re)calibration.[6] In the single study on septic shock, characterised by a vasodilated state, however, the FloTrac/Vigileo™ system proved inaccurate, using relatively old software.[7] The new software that has been introduced and is claimed to further improve the method in noncardiac surgery patients, though with varying results,[8 9] has not yet been evaluated in septic shock only. Therefore, the aim of the current study was to evaluate the accuracy of less invasive FloTrac/Vigileo™ CO compared with bolus thermodilution-derived measurements over the course of septic shock and as a function of software versions 1.07 and 1.10 (latest).

Patients and methods

In this clinical observational study, nine patients, above 18 and below 80 years of age, were included after approval by the Medical Ethics Review Committee. Informed consent was waived because of the less invasive characteristics of the system. Consecutive patients with septic shock, as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference, and with arterial catheter and PAC in place were included for this study. Further inclusion criteria were the presence of mechanical ventilation, sinus rhythm and vasoactive therapy consisting of dopamine more than 15 mg $kg^{-1}min^{-1}$ or any dose of norepinephrine. Preterminal illness was an exclusion criterion.

Patients received standard care by intensive care physicians according to local guidelines, including appropriate antibiotics, after taking specimens for microbial cultures. A PAC was placed in the jugular vein (CritiCath, SP5507H TD Catheter, Becton Dickinson Infusion Therapy Systems Inc., Sandy, Utah, USA) to aid haemodynamic management when considered clinically necessary, at 7±3 and 6±4 hours after admission for version 1.07 and 1.10, respectively. The weight and height of the patient were measured.

Protocol

A FloTrac™ sensor was connected to the existing radial artery catheter (Arterial Cannula with FloSwitch 20 G/1.10mm*45mm) and connected to the Vigileo monitor. The system was zeroed and CO measurement initiated. The PAC measurement was performed using intermittent bolus CO by averaging three bolus measurements using 10 ml of iced isotonic saline. Injections were not synchronised to the respiratory cycle. The mean value was recorded and regarded as the thermodilution CO (COtd). At the start of each bolus CO measurement, the FloTrac/Vigileo™ CO (COfv) was measured. The mean value of the three measurements was recorded. Measurements were performed after major therapeutic changes, including administration of fluid boluses and start of vasoactive drugs considered necessary on clinical grounds by treating physicians, for up to 72 hours after inclusion. The FloTrac/Vigileo™ system calculates CO by using the SD of the pulse pressure incorporating actual vascular tone based on waveform analysis and patient characteristics[10].The continuous analysis of the arterial waveform to detect changes in the vascular tone makes external calibration unnecessary and operator error is minimised. The arterial pressure waveform analysis method that may not need calibration, irrespective of vascular tone, works as follows. Each arterial waveform is analysed with a frequency of 100 Hz, over 20 s. The arterial waveform is analysed for eight different characteristics, such as the upstroke and down slope of the curve. Each curve is analysed separately and additional curves are

analysed and compared with former and subsequent curves. From this analysis, which also takes 20 s, the average curve is given, by means of the SD of the given characteristics of the curves. From the given stroke volume and heart rate, the CO is determined, which is updated every 20 s. In the Vigileo computer, a filter is embedded to filter out excesses in high systolic blood pressures and high frequency atrial fibrillation. The following formulas apply as incorporated in the Vigileo algorithm:
HR x σsAP x χ, where HR is heart rate and σAP, as a measure of stroke volume, is the standard deviation of arterial pressure. χ=M (HR, σap, C(P), BSA, MAP, μ_{3ap}, μ_{4ap}), where M is multivariate approximating function M, MAP is mean arterial pressure, C(P) is a function of arterial compliance, μ_{3ap} is the skewness of arterial pressure data, μ_{4ap} is the kurtosis of arterial pressure data and BSA is body surface area calculated from weight and height. A polynomial multivariate fitting function is used to calculate χ as a measure of vascular tone. C(P) is derived from Langewouters, using sex and age and modified using weight, height and BSA. Results are in the algorithm incorporated in the Vigileo™ computer software. In the 1.10 version, the algorithm was improved to better account for hypertension, tachycardia, and volume loading.

Statistical analysis

Data are presented as mean ± SD, because they were distributed normally (Kolmogorov-Smirnov test). Systemic vascular resistance (SVR) was calculated according to standard formulae using COtd. Bland–Altman plots of differences vs. means of techniques were constructed to illustrate tracking of COtd by FloTrac/Vigileo™ using two different types of software, for pooled data without separating between-subject and within-subject variability. Limits of agreement were calculated as bias ±1.96*SD of the bias. Linear regression was used to calculate partial Pearson correlation coefficients taking repeated measures in the same patients into account. Correlation coefficients were compared after z transformation. Generalised estimating equations (GEEs) were used to test for differences in software versions in assessing (differences and changes in) COfv vs. COtd, taking repeated measurements in the same patients into account. Standardised regression coefficients and their 95% confidence intervals (CIs) were calculated. The method was also used to evaluate the effect of versions on the relation between differences in CO and MAP and for measurements over the course of time. Exact P values less than 0.05 and more than 0.001 are given for statistical significance.

Results

Nine patients were included (Table 1), four haemodynamically monitored by the FloTrac/Vigileo™ and software version 1.07 and five with version 1.10, for 58±10 and 47±26 hours after inclusion, respectively. The mortality rate in the ICU was 25 and 40% in the series with version 1and 2, respectively. Haemodynamic parameters at study entrance are shown in Table 2. Over the course of time, the MAP was 7mmHg higher during measurements with the help of software version 1.07 than those with 1.10 (P=0.048, GEE), but HR, COtd, COfv, SVR and dopamine doses did not differ.

Table 1. Patient characteristics on admission to ICU

Age, year	65±6
Sex, m/f	3/6
Origin of sepsis	
Pneumonia	6
Peritonitis	2
Meningitis	1
Bacteremia	
Gram-negative	3
Gram-positive	3
Mycoplasma/Legionella spp.	2
APACHE II score	25±7
Mortality in the ICU	3 (33)

APACHE = acute physiology and chronic health evaluation. Mean ± SD or number of patients (percentage), where appropriate.

Bias, precision and partial correlation

Eighty-six paired measurements were obtained in patients using the 1.07 software version. COtd ranged from 3.6 to 10.4 L min^{-1} and COfv from 3.6 to 7.1 L min^{-1}, so that mean bias was -1.6 L min^{-1}, precision 1.6 L min^{-1}, limits of agreement -4.8 to 1.5 L min^{-1} and error 48%. For pooled data, measurements correlated at partial r equal to 0.32 and P value equal to 0.003. Seventy-three paired measurements were obtained in patients using the 1.10 software version. COtd ranged from 2.9 to 12.6 and COfv from 3.3 to 10.8 L min^{-1}, so that mean bias was -1.2 L min^{-1}, precision 1.1 L min^{-1} and limits of agreement -3.5 to 1.0 L min^{-1} with an error of 32%. Measurements correlated at partial r equal to 0.90 and P value less than 0.001 ($P<0.001$ vs. version 1.07).

Table 2. Haemodynamic characteristics and Vigileo/FloTrac™ software version at study entrance

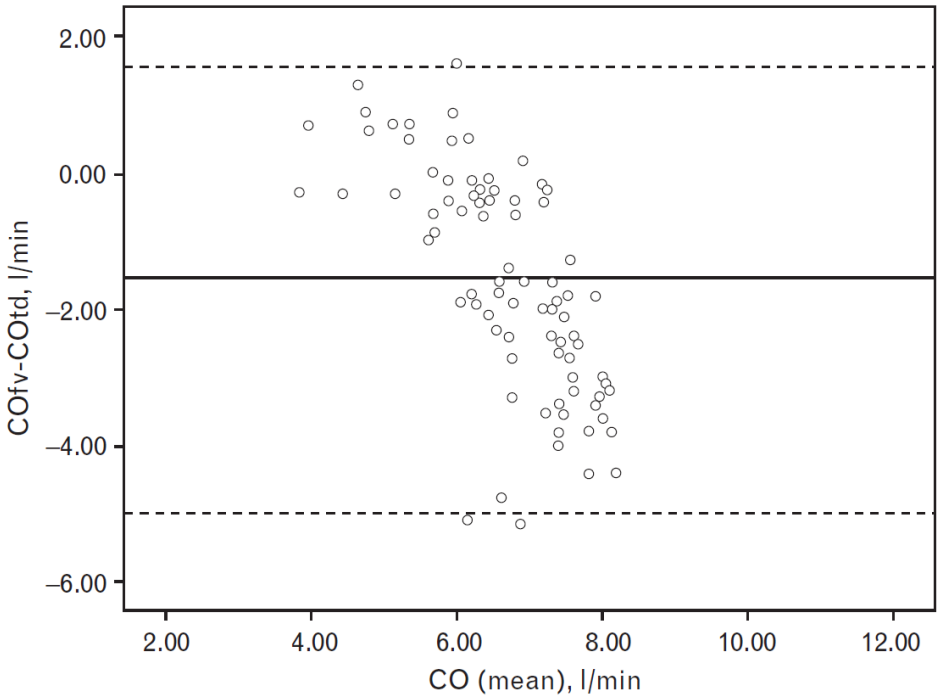
Patient	Version	HR	MAP	PAOP	Drugs	No of simultaneous measurements
1	1.07	87	69	21	Dop, Nor, Nit	17
2	1.07	118	80	20	Dop, Nor, Eno	21
3	1.07	106	79	35	Dop, Nit, Eno	21
4	1.07	125	64	21	Dop, Nor, Eno, Nit	26
5	1.10	110	58	19	Dop, Eno, Nit	6
6	1.10	137	74	23	Dop, Eno, Nit	16
7	1.10	77	80	32	Dop, Eno	19
8	1.10	120	42	15	Dop, Nor, Eno	20
9	1.10	100	80	25	Dop, Nor, Eno	12

Abbrevations: HR = heart rate (beat .min^{-1}); MAP = mean arterial pressure (mmHg); Dop = dopamine; Nor = norepinephrine; Nit = nitroglycerine; Eno = Enoximone; PAOP, pulmonary artery occlusion pressure (mmHg)

Comparison of software versions

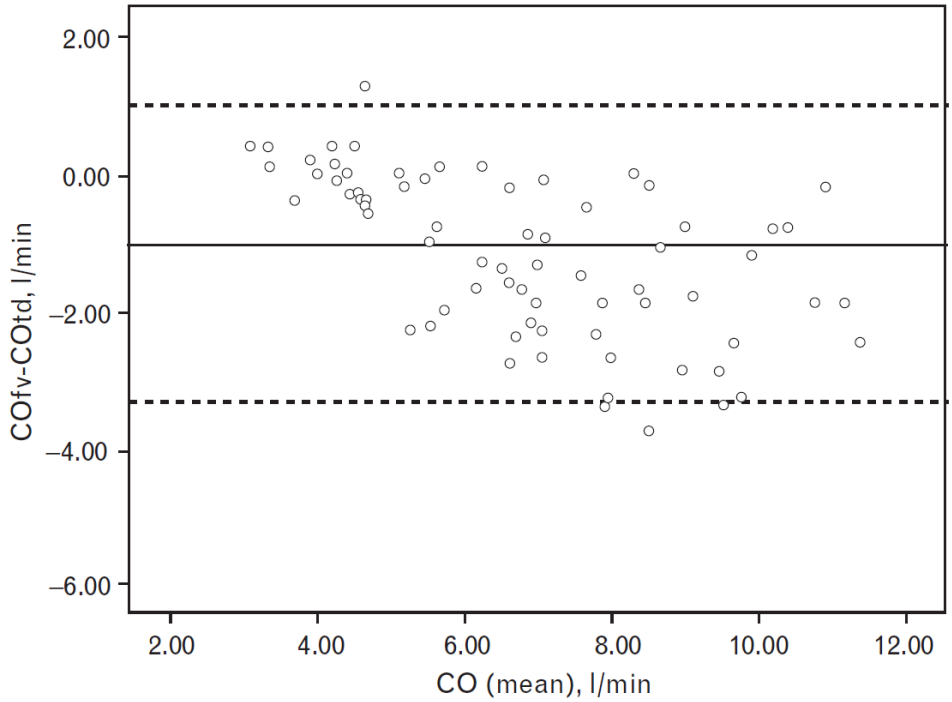
Bland–Altman plots (Figs 1 and 2) show the negative bias for COfv compared with COtd for both software versions, which increases with CO ($P<0.001$, GEE), but less so for the latest software [$P=0.017$ for interaction between mean CO and version, GEE; standardised regression coefficient (95%CI) for version 1.07 is -0.34 (-0.49 to -0.19) and for version 1.10, -0.49 (-0.59 to -0.39); partial r for version 1.07 is -0.56, $P<0.001$, and for version 1.10, -0.38, $P=0.001$]. Differences in CO between techniques were also inversely related to MAP ($P<0.001$, GEE), more so for version 1.07 than for 1.10 ($P=0.012$ for version and $P=0.001$ for interaction between MAP and version, GEE). For pooled changes from one time point to the other (Fig. 3), the COtd and COfv changed in the same direction in 61 and 75% in versions 1.07 (partial $r=0.31$, $P=0.004$) and 1.10 (partial $r=0.77$, $P<0.001$), respectively, so that changes in COtd were better predicted by changes in COfv with the latest software [$P<0.001$ vs. version 1.07, GEE; standardised regression coefficient (95%CI) for version 1.07 is 0.31 (-0.10-0.72) and for version 1.10, 0.78 (0.65–0.91)].

Figure 1. Bland-Altman analysis software version 1.07



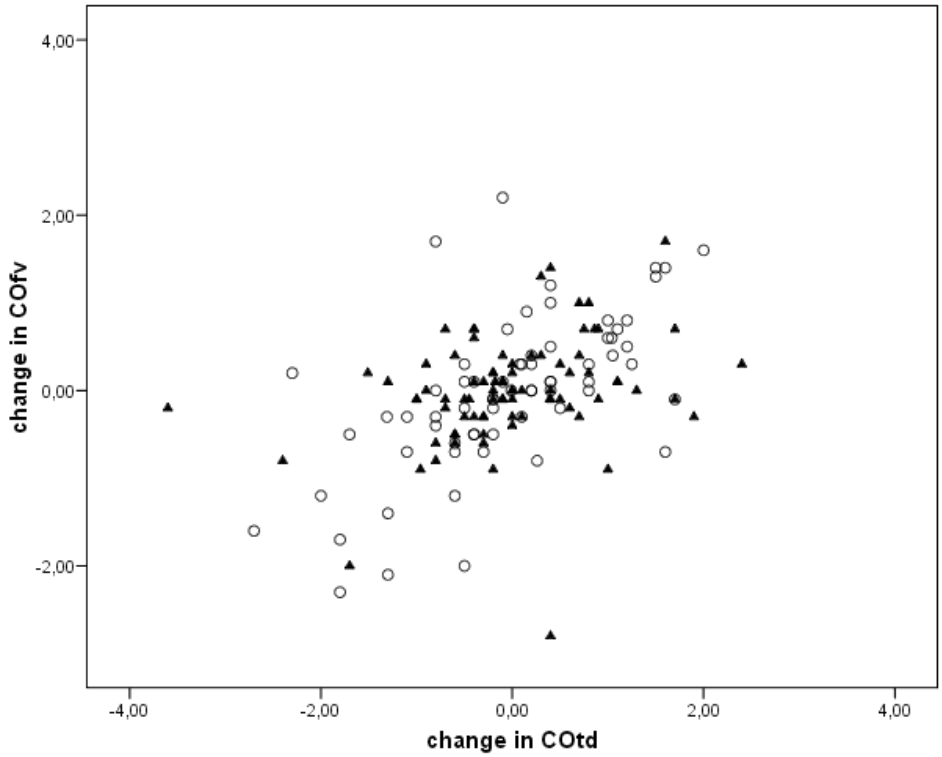
Bland-Altman analysis of differences of FloTrac/Vigileo™ cardiac output (COfv) and thermodilution cardiac output (COtd), COfv-COtd, versus their means. The uninterrupted line indicates the (negative) bias and the interrupted lines the 95% limits of agreement, according to software version 1.07.

Figure 2. Bland-Altman analysis software version 1.10



Bland-Altman analysis of differences of FloTrac/Vigileo™ cardiac output (COfv) and thermodilution cardiac output (COtd), COfv-COtd, versus their means. The uninterrupted line indicates the (negative) bias and the interrupted lines the 95% limits of agreement, software version 1.10.

Figure 3. Concordance of changes in cardiac output



Concordance of changes in FloTrac/Vigileo™ cardiac output (COfv), to changes in thermodilution cardiac output (COtd) in L/min, according to 2 software versions (closed triangles version 1.07 and open circles version 1.10).

Discussion

In this study, we compared CO measurements by the FloTrac/Vigileo™ system with those by the bolus thermodilution technique in patients with septic shock. Results indicate that software improvements can lead to increasing accuracy of the less invasive measurements of CO and changes therein upon treatment in the course of disease. Indeed, the Critchley criterion[11] of less than 30% error for a clinically applicable alternative to COtd was almost met with the latest software. Nevertheless, the FloTrac/Vigileo™ systematically underestimated high COs, even when using the software 1.10 version, which remained sensitive to vascular tone.

Our study, thus, has the advantage of being the first to report on evaluation of software versions in the course of septic shock and expected wide variations in vascular tone, rather than in postcardiac surgery patients as done previously.[12] A comparison of our results with the literature is, thus, limited because most comparison studies have been performed in haemodynamically stable cardiac surgery patients, in whom the

FloTrac/Vigileo™ performed relatively well, with the help of software version 1.07, even though CO underestimations at low vascular tones have been recognised before[2-4]. Indeed, the first software version (1.03) proved insufficient for clinical purposes in mixed populations, but results improved with later versions.[2 5 9 12] Comparisons of software versions in the same patient population (cardiac surgery) are relatively rare. [5 6] In the latter study, the updated software seemed to perform better than older versions. Sakka et al.[7] were the first to compare the FloTrac/Vigileo™ (version 1.07) with transpulmonary COtd measurements in sepsis and shock, and they found that FloTrac/Vigileo™ underestimated CO changes in response to therapeutic interventions. Biancofiore et al.[8] stated that the 1.10 version resulted in relatively inaccurate CO measurements in 29 cirrhotic patients with a hyperdynamic circulation undergoing liver surgery, thereby precluding clinical applicability, even though the concordance of changes (68%) was only slightly lower than that in our study. Compton et al.[9] described insufficient performance of the 1.10 version in a mixed patient population, but measurements were compared with the pulse-contour technique after calibration by transpulmonary COtd only.

In our study, hypotension was associated with greater underestimation of CO by the FloTrac/Vigileo™ system, particularly when using software version 1.07, indicating that the accuracy of the system critically depends on the degree to which changes in vascular tone are taken into account by the software. Moreover, the SVR varied by 30 and 47% during monitoring with versions 1.07 and 1.10, respectively (data not shown). From a higher MAP, similar SVR and lower variability of SVR for measurements with version 1.07 than 1.10, we may, thus, infer that the vascular tone-dependent inaccuracy of the 1.07 version is not overestimated. This observation may overcome the lack of paired observations in the same patient. Further limitations include the relatively low number of patients studied on repeated occasions. Nevertheless, the data were gathered in a clinically relevant manner and differences between software versions were independent of repeated measurements in the same patients.

In conclusion, evoluting software versions are increasingly able to account for the effect of vascular tone on CO measurements by less invasive waveform analyses without calibration (FloTrac/Vigileo™), so that the latter may become useful in the haemodynamic monitoring of septic shock. As the 1.10 version is still affected by vascular tone, further software improvements, which are underway, are eagerly awaited.

Acknowledgements

CS is a Lecturer of the Edwards Essence Educational Program for Anaesthetists and has received lecture fees from Edwards Lifesciences.

None of the other authors have any conflict of interest to declare.

References

1 McGee W, Horswell J, Calderon J et al. Validation of a continuous, arterial pressure-based cardiac output measurement: a multicenter, prospective clinical trial. *Crit Care* 2007;11:R105.

2. Button D, Weibel L, Reuthebuch O et al. Clinical evaluation of the FloTrac/Vigileo system and two established continuous cardiac output monitoring devices in patients undergoing cardiac surgery. *Br J Anaesth* 2007; 99: 337-42.

3. Breukers RMBGE, Sepehrkhouy S, Spiegelenberg SR et al. Cardiac output measured by a new arterial pressure waveform analysis method without calibration compared with thermodilution after cardiac surgery. *J Cardiothorac Vasc Anesth* 2007;21:632-5.

4. Lorsomradee S, Lorsomradee S, Cromheecke S et al. Uncalibrated pulse contour versus continuous thermodilution techniques: effects of alterations in arterial waveform. *J Cardiothorac Vasc Anesth* 2007;21:636-43.

5. Mayer J, Boldt J, Poland R, et al. Continuous arterial pressure waveform-based cardiac output using the FloTrac/Vigileo: a review and meta-analysis. *J Cardiothor Vasc Anesth* 2009;23:401-406.

6. Mayer J, Boldt J, Wolf MW et al. Cardiac output derived from arterial pressure waveform analysis in patients undergoing cardiac surgery: validity of a second generation device. *Anesth Analg* 2008;106:867-872.

7. Sakka SG, Kozieras J, Thuemer O et al. Measurement of cardiac output: a comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007;99:337-42.

8. Biancofiore G, Critchley LA, Lee A et al. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. *Br J Anaesth* 2009;102:47-54.

9. Compton FD, Zukunft B, Hoffman C et al. Performance of a minimally invasive uncalibrated cardiac output monitoring system (Flotrac/Vigileo) in haemodynamically unstable patients. *Br J Anaesth* 2008;100:451-6.

10. Pratt B, Roteliuk L, Hatib F et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-411.

11. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85-91.

12. Prasser C, Bele S, Keyl C et al. Evaluation of a new arterial pressure-based cardiac output device requiring no external calibration. *BMC Anesthesiol* 2007;7:9.

4

Haemodynamic changes during a combined psoas compartment – sciatic nerve block for elective orthopaedic surgery

de Leeuw MA, Slagt C, Hoeksema M, Zuurmond WW, Perez RS.

In revised form published in Anesth Analg 2011;112:719-24.

Abstract

Background and objective

Haemodynamic parameters can theoretically be influenced by a combined psoas compartment–sciatic nerve block (CPCSNB) owing to a relative high systemic absorption of local anaesthetics and extended vasodilatation in the anaesthetised limb (hemisympatectomy). In this study we assessed and documented haemodynamic changes during CPCSNB for elective orthopaedic surgery.

Methods

Twenty consecutive patients scheduled for a total hip arthroplasty revision surgery were subjected to a CPCSNB with 150 mg bupivacaine (with epinephrine 1:200.000) 90 minutes before surgery (2 separate single-injection blocks: 30 mg bupivacaine for the sciatic nerve block and 120 mg bupivacaine for the psoas compartment block). Cardiac index, invasive blood pressure and heart rate were measured at baseline and 60 minutes after puncture using a minimally invasive cardiac output monitoring device (FloTrac/Vigileo™ system (Edwards Lifesciences, Irvine, CA)).

Results

Cardiac index did not change after a CPCSNB (pre block cardiac index 2.98 ± 0.54 L min^{-1} m^{-2} versus post block cardiac index 2.99 ± 0.60 L min^{-1} m^{-2}). There was a significant reduction in mean arterial blood pressure (108 ± 16 mmHg vs. 99 ± 16 mmHg ($p<0.001$)) and diastolic blood pressure (75 ± 9 mmHg vs. 68 ± 10 mmHg ($p=0.001$)). Heart rate increased significantly (68 ± 9 beats min^{-1} vs. 73 ± 10 beats min^{-1} ($p=0.001$)).

Conclusions

CPCSNB did not affect cardiac index. Changes in arterial blood pressure and heart rate, although statistically significant, remained within acceptable clinical range (<10% variation). CPCSNB does not appear to induce clinically significant haemodynamic changes in this group of patients.

Introduction

A posterior lumbar plexus block (psoas compartment block) is often combined with a sciatic nerve block[1] to provide adequate anaesthesia for surgery of the lower limb. To achieve extended anaesthesia or prolonged postoperative analgesia, a combined psoas compartment–sciatic nerve block (CPCSNB), requires large doses of potentially cardiotoxic, long acting local anaesthetic. Animal and human studies alike have shown that (intravascular) administration of high doses of local anaesthetic produce a dose dependent negative inotrope effect.[2-6] The lumbar plexus is anatomically located predominantly within muscle tissue[7] and a CPCSNB may be vulnerable to a relative high systemic absorption of the administered local anaesthetics.[8] CPCSNB also induces a hemisympathectomy with vasodilatation in the anaesthetised limb. A reduction in arterial blood pressure after this hemisympathectomy could influence cardiac index.

There is limited information about changes in arterial blood pressure during CPCSNB[9-11] and no information relating to changes in cardiac output (CO). Two studies described CO measurements after femoral nerve-sciatic nerve blocks (FNSNB)[12 13] with conflicting results. Whereas Martin et al.[12] described a positive inotrope effect with increase of CO, Fanelli et al.[13] found no changes at all in CO. The aim of the present study was to document the effect of CPCSNB on CO in patients undergoing orthopaedic hip surgery using a bupivacaine solution.

Methods

After approval by the local medical ethics committee and written informed consent, 20 patients were included in this prospective clinical observational study. Inclusion criteria were patients scheduled for total hip arthroplasty revision surgery, with ASA physical status I-III, age older than 18 years with a sinus rhythm documented on the electrocardiogram (atrial arrhythmias render the FloTrac/Vigileo™ device unreliable). Exclusion criteria were patient refusal, disorders of the coagulation system, infections at the puncture site, known allergy to local anaesthetics, pre-existing neurological disorders, or unable to comprehend the Dutch language.

Patients did not receive any premedication before surgery. Patients were brought to the holding area of the operating complex, where the CPCSNB was performed. Monitoring standards for hip revision/replacement surgery in our institution include; five lead electrocardiogram, pulse oximetry, and invasive blood pressure measurement. An IV catheter was inserted and to compensate for pre-operative fluid deficit (nill per os minimum 6 hours), we started Ringer's lactate infusion at 7 $mL.kg^{-1}hr^{-1}$. The patients did not receive any further IV preload. After infiltrating the area with local anaesthetic, a radial artery was cannulated (20 G/1.10 mm*45 mm, BD Critical Care Systems Pte Ltd, Singapore). The arterial catheter was connected to a FloTrac™ sensor and a Vigileo™ monitor (with software version V 1.10; Edwards Lifesciences, Irvine, CA).[14 15] The FloTrac/Vigileo™ system is a minimally invasive CO measuring device that calculates CO by using the standard deviation of the pulse pressure incorporating actual vascular tone based on waveform analysis and patient characteristics. The continuous analysis of the arterial waveform to detect changes of the vascular tone makes external calibration unnecessary and operator error is minimised. Each arterial wave form is analysed with a frequency of 100 Hz, over 20 seconds. The arterial waveform is analysed for 8 different waveform characteristics, such as the upstroke and down slope of the curve. To determine the stroke volume, one calculates the average and standard deviation for the given waveform characteristics of 8 consecutive curves. Subsequently, CO is determined from heart rate and calculated stroke volume, which is updated every 20 seconds.

Fifteen minutes before the CPCSNB, baseline haemodynamic values were recorded (during a period of 15 minutes) with the patient in a supine position in a stress free environment (patients included in the study were cared for by a dedicated nurse and kept in a separate area to prevent distraction from other patients). The following data were obtained: heart rate, invasive blood pressure, CO/cardiac index, stroke volume/stroke volume index. When stable baseline values were obtained, the patient

was turned to the lateral decubitis position, with the limb to be operated nondependent. All the patients had the skin where the needle was to be inserted previously infiltrated with lidocaine. The sciatic nerve block was performed first using landmarks described by Labat[16] followed by the psoas compartment block using landmarks described by Chayen.[17] Nerve blocks were all performed by the same person (MdL) with the aid of a nerve stimulator (Stimuplex®, HNS 11, Braun Medical, Melsungen, Germany) and stimulating needles (Stimuplex® - A Needle, 150 mm/20G, Braun Medical, Melsungen, Germany). Stimulating frequency was initially set at 2 Hz, and stimulating current was set at 1 mA. Pulse duration was 0.1 ms. After appropriate muscle contractions were found between 0.3 mA and 0.5 mA and after negative aspiration for blood and cerebrospinal fluid, 10 mL of bupivacaine 0.3% were administered to the sciatic nerve and 40 mL of bupivacaine 0.3% were injected into the psoas compartment. Epinephrine 1:200.000 (5μg ml^{-1}) was added to the local anaesthetic solution. Gentle aspiration of the syringe after injection of every 5 mL of local anaesthetic solution was part of the safety procedures. The velocity of injection was approximately 0.5 $mL.sec^{-1}$. The time between the blocks was recorded and the time at which all of the local anaesthetic solution had been injected was taken as time zero (T_0). No sedation was given during the procedure, which is the standard of care in our hospital. At the end of CPCSNB the patient was turned to the supine position. Recording of baseline haemodynamic data was limited to the first 15 minutes (T_{-30} –T_{-16}) before positioning the patient. Recording started again for 60 minutes after finishing the injection of local anaesthetic and the patient was returned to the supine position (T_0–T_{60}). Haemodynamic data were downloaded in real time on a laptop computer connected to the monitor, as well as handwritten at regular intervals by the same person who performed the blocks (MdL). Patients were observed separately from other patients and a dedicated nurse kept the patient in a stress-free environment. After the 60-minute period, the CPCSNB was tested (motor block tested by the patients' ability to flex the hip / knee and dorsiflex the foot, sensory block was tested by cold–warm differentiation at the leg dermatomes, using a very cold flannel). To evaluate for a possible epidural spread of the local anaesthetic, we performed motor and sensory block tests in the contralateral limb as well. After these tests, the patient was transferred to the operation theatre and prepared for surgery. As part of the standard clinical practice in our institution, CPCSNB was combined with general anaesthesia.

With Cardiac Index (CI) (mean 3.25 L min^{-1} m^{-2}, SD 0.76 assumed[18]) as the primary outcome measurement, standard power calculation for the paired samples *t*-test revealed 17 patients to be necessary to find a difference of 20% in comparison with

baseline with a power of 90% and an α of 0.05. Data were collected in an Excel spreadsheet, and analysed using SPSS for Windows version 15.0. Preblock values for measurement period T_{-30} to T_{-16}, puncture period T_{-15} to T_{-1}, and post block values T_0 to T_{60} were averaged and presented as mean ± SD. Paired samples *t*-tests were used to analyse differences between pre- and post block values. To identify possible linear or non-linear (i.e. cubic, quadratic) trends over the course of the intervention, we used a general linear model analysis using a 1-sample repeated measures design on the basis of individual time points from T_{-30} to T_{60}. For all assessments, a $P<0.05$ (2 sided) was considered statistically significant.

Results

Twenty patients were included in the study. One patient was excluded post hoc from the data analysis. The patient developed sepsis intraoperatively, rendering the haemodynamic data unreliable. Missing data due to clinical reasons (i.e., need to proceed with the operation before the end of the allocated data collection time) occurred in <5% of all CO data acquisitions. Patient characteristics are presented in Table 1.

Table 1. Patient characteristics

Age (year)	68 ± 11
Sex (male/female)	10 / 9
ASA I / II / III	5 / 11 / 3
Height (cm)	170 ± 12
Weight (kg)	78 ± 16
Body surface area (m^2)	1.89 ± 0.2
Body mass index (kg m^{-2})	26.9 ± 4.0

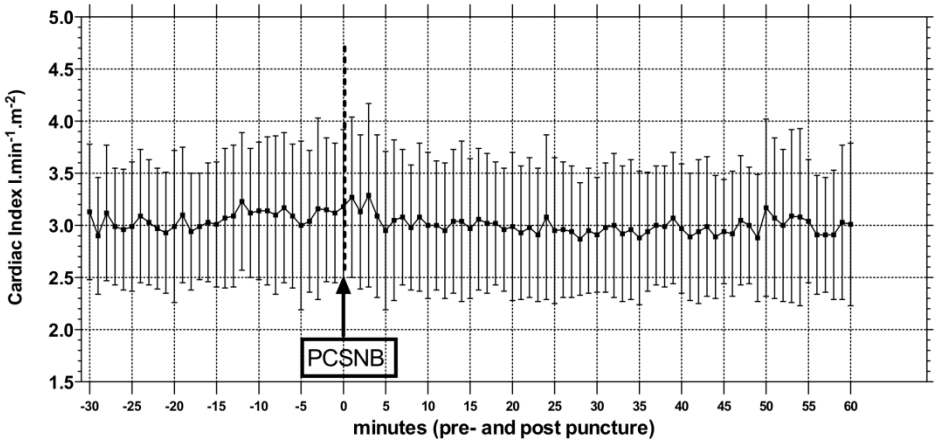
Data are presented as mean ± SD or number of patients, where appropriate.

Sciatic nerve blocks and psoas compartment blocks were all technically successful (muscle contractions between 0.3 and 0.5 mA). The average time between sciatic nerve block and psoas compartment block was 6.8 ± 3.1 minutes. Sixty minutes after the CPCSNB, all patients had a complete motor and sensory block of the limb scheduled to be operated, suggesting a clinically successful block. None of the patients showed any signs of an epidural spread of the local anaesthetic.

There were no significant differences between postblock CI data and preblock baseline values (2.98 ± 0.54 L min^{-1} m^{-2} vs. 2.99 ± 0.60 L min^{-1} m^{-2})(Fig. 1). A significant cubic trend ($P=0.048$) was found, indicating an increase towards the block performance period, followed by a decrease and subsequent increase of cardiac index towards preblock values.

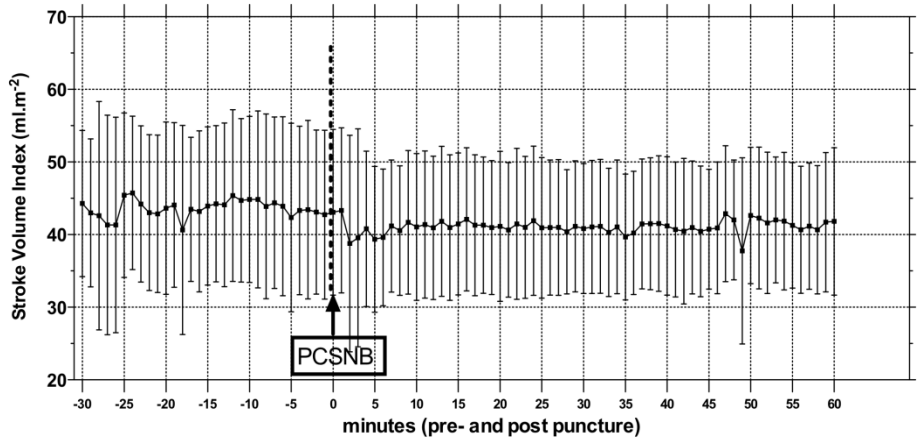
Postblock stroke volume index values were significantly decreased in comparison with baseline values (43.4 ± 10.6 ml m^{-2} vs. 40.9 ± 9.0 ml m^{-2}; $P = 0.034$) (Fig. 2).

Figure 1. Cardiac index (L min^{-1} m^{-2}) pre- and post puncture



Values are mean ± SD. PCSNB psoas compartment–sciatic nerve block.

Figure 2. Stroke volume index (ml.m^{-2}) pre- and post puncture

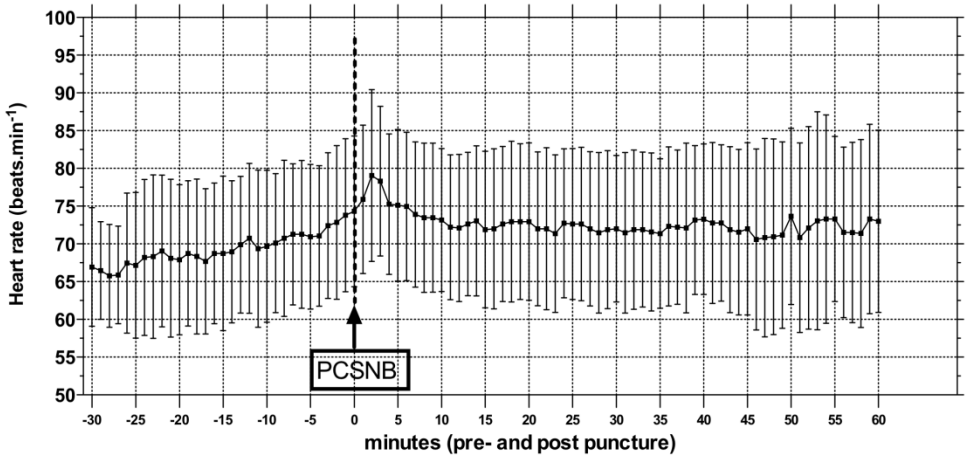


Values are mean ± SD. PCSNB psoas compartment–sciatic nerve block.

There was a significant ($P<0.001$) increase of the heart rate during the nerve block procedures (71± 9 beats min^{-1} vs. 68 ± 9 beats min^{-1}) in comparison with baseline values. Postblock heart rate was significantly increased in comparison with base line (68 ± 9 beats min^{-1} vs. 73 ± 10 beats min^{-1}; $P=0.001$) (Fig.3). Trend analysis showed a

significant quadratic trend (*P*=0.002), indicating a statistically significant increase in heart rate (i.e., during nerve block procedures and the first period post block), followed by a decrease towards the end of postblock period.

Figure 3. Heart rate (beats min^{-1}) pre- and post puncture



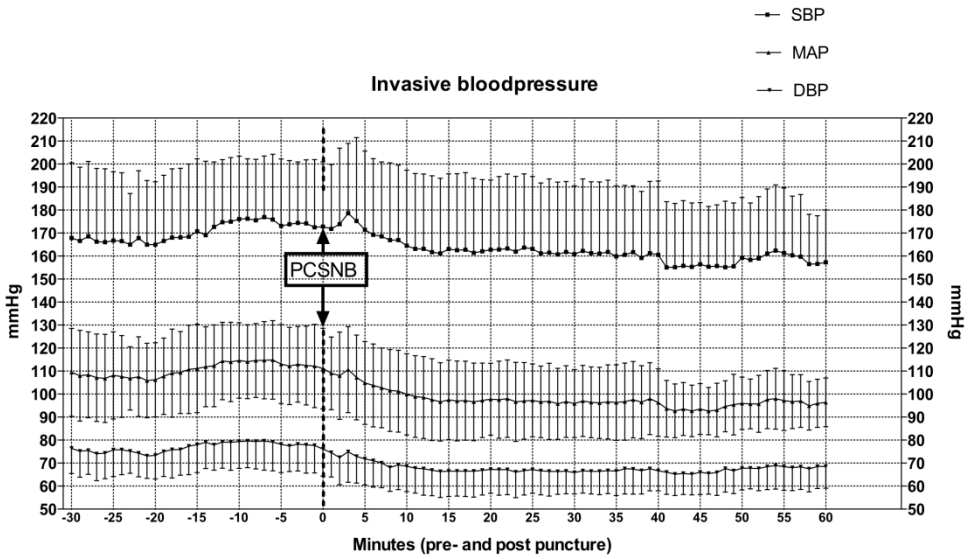
Values are mean ± SD. PCSNB psoas compartment–sciatic nerve block

No significant change in mean arterial blood pressure and diastolic blood pressure during the peripheral nerve block procedure was observed. Postblock invasive blood pressures decreased in comparison with preblock baseline values (*P*<0.001 mean arterial pressure, *P*=0.001 diastolic blood pressure) (Fig. 4). Pre- and postblock systolic blood pressure were not significantly different. Mean arterial blood pressure was significantly decreased from 108 ± 16 mmHg to 99 ± 16 mmHg (pre- vs. post block, *P*<0.001). Trend analysis showed significant linear (*P*=0.008), quadratic (*P*=0.036) and cubic (*P*=0.008) trends for mean arterial blood pressure, indicating a significant increase during nerve block procedures, followed by a decrease and subsequent increase during the postblock period, without returning to baseline values.

Diastolic blood pressure was significantly decreased from 75 ± 9 mmHg to 68 ± 10 mmHg (pre- vs. post block, *P*=0.001). Trend analysis showed significant linear (*P*=0.048) and cubic (P=0.033) trends for diastolic blood pressure, indicating a significant increase during nerve block procedures, followed by a decrease and subsequent increase during the post block period, without returning to baseline values.

Post block total systemic vascular resistance decreased compared to pre block values (1643 vs. 1477 dyne·s·cm^{-5}; P= 0.001).

Figure 4. Invasive arterial blood pressure pre- and post puncture



Values are mean ± SD. SBP systolic blood pressure; MAP mean arterial blood pressure; DBP diastolic blood pressure; PCSNB psoas compartment–sciatic nerve block

Discussion

This prospective clinical observational study documented haemodynamic changes after a CPCSNB during elective orthopaedic surgery. Two previous studies in the literature measured CO after a femoral nerve – sciatic nerve block, with contradicting results.[12] [13] Large methodological differences (used local anaesthetics, peripheral nerve block techniques, CO measurement devices and patient characteristics) between these studies and our present investigation make further comparison impossible.

Our present study has shown no overall changes in cardiac index in patients undergoing a CPCSNB. Trend analysis showed a small, but significant increase of cardiac index when compared directly before and after the CPCSNB procedure. This may be due to stress factors, although any influences of the added epinephrine could not be excluded. The clinical relevance of these small changes must be questioned.
There is a small, but significant, reduction of the stroke volume index after the CPCSNB, which started within a few minutes after the CPCSNB. A possible explanation is a negative inotrope effect due to the systemic absorption of the administered bupivacaine. Experimental data shows that peak plasma concentration of local anaesthetics appears within a different postblock time frame and it is not present within a few minutes post puncture.[8] [19] [20] However, we did not measure bupivacaine

plasma concentrations and therefore individual variations of plasma concentrations (i.e., incidental high levels of bupivacaine plasma concentrations) cannot be excluded. It is more likely that this post puncture reduction of stroke volume was the result of a reduction of preload and afterload due to vasodilatation in the anaesthetised limb (hemisympathectomy).

Changes in arterial blood pressure although statistically significant remained within an acceptable clinical range (<10%). A reduction in blood pressure after a CPCSNB has been described in other studies.[9-11] De Visme et al.[9] described a decrease of 27% in mean arterial blood pressures after a CPCSNB. Differences in age of their study patients, local anaesthetics used, approach of the lumbar plexus block (Winnie) and the preblock administration of opioids could be the reason for the more pronounced hypotension in comparison with our study. Epidural spread, as a most frequent complication of a CPCSNB, could also result in lower blood pressure. The incidence of epidural diffusion of local anaesthetics varies from <1% to 27% and often depends on the approach of the lumbar plexus.[1] Epidural diffusion was more frequent when the position of the inserted needle was too medial.[21] The Chayen approach[17] to the lumbar plexus used in our investigation has a lateral needle insertion point that theoretically should reduce the incidence of epidural diffusion. Although none of our patients showed any signs of epidural spread of local anaesthetics, epidural diffusion of local anaesthetics cannot be completely excluded. This phenomenon often occurs without clinical manifestation. In addition, Dalens et al.[22] described a relatively large incidence of epidural diffusion using the Chayen approach in posterior lumbar plexus blocks in children.

Heart rate increased significantly after the CPCSNB. This may be due to a baroreceptor-mediated reflex, induced by a decline in arterial blood pressure. CO could theoretically be influenced by a CPCSNB if the patient does not have this intact compensatory mechanism (using beta blockers or diabetic autonomic dysfunction for instance). The increase in heart rate is accompanied by a reduction in arterial blood pressure. The added epinephrine in the local anaesthetic solution could explain the former but not the latter.

Cardiac Output was measured using an arterial pressure waveform analysis device (FloTrac/Vigileo™, software version V 1.10, Edwards Lifesciences, Irvine, CA). Cardiac output derived from this software version has shown to be interchangeable with a pulmonary artery catheter-derived CO in the cardiac index range measured in our study.[23-28] Cardiac output changes of approximately 10–15% may go undetected

using either method. The stroke volume reduction of 10% found in our study could be explained by the error of our CO measurement device or the CPCSNB. Further randomised controlled studies or case-control studies are needed to evaluate the role of both factors.

The clinical relevance of the cardiovascular changes found in our study after a CPCSNB might be questioned. The small haemodynamic changes should not affect normal organ function, and probably would have been prevented by IV preloading. Further studies are needed to investigate the influence of such IV preloading on the cardiovascular changes after a CPCSNB.

We acknowledge the following limitations in our study. First, it is an observational study. Data collection was in some cases stopped due to clinical and logistical constrains. Blood concentrations of local anaesthetic were not measured. Epidural spread of local anaesthetic could not totally be excluded. Finally, changes in CO and stroke volume fall within the margins of error of the monitoring device.

In conclusion, a CPCSNB induces changes in arterial blood pressure. Although statistically significant, these changes remain within clinically acceptable limits. Further studies to establish its safety features in patients with a compromised cardiovascular system (low CO state, cardiac valve pathology) are warranted.

Acknowledgment:
We are very grateful to Dr. I Malagon for assistance with the preparation of this manuscript.

References

1. Touray ST, de Leeuw MA, Zuurmond WWA, et al.. Psoas compartment block for lower extremity surgery: a meta-analysis. *Br J Anaesth* 2008;101:750-60.
2. Lynch C 3rd. Depression of myocardial contractility in vitro by bupivacaine, etidocaine and lidocaine. *Anesth Analg* 1986;65:551-9.
3. Bruelle P, Lefrant JY, de la Coussaye JE, et al. Comparative Electrophysiologic and Hemodynamic Effects of Several Amide Local Anesthetic Drugsin Anesthetised Dogs. *Anesth Analg* 1996;82:648-56.
4. Lefrant JY, de La Coussaye JE, Ripart J, et al. The Comparitive Electrophysiologic and Hemodynamic Effects of a Large Dose of Ropivacaine and Bupivacaine in Anesthetised and Ventilated Piglets. *Anesth Analg* 2001;93:1598-1605.
5. Bardsley H, Gristwood R, Baker H, et al. A comparison of the cardiovascular effects of levobupivacaine and *rac*-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* 1998;46:245-9.
6. Knudsen K, Beckman Suurküla M, et al. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;78:507-14.
7. Kirchmair L, Lirk P, Colvin J, et al. Lumbar Plexus and psoas Major Muscle: Not always as Expected. *Reg Anesth Pain Med* 2008;33:109-14.
8. Kaloul I, Guay J, Côté C, et al. Ropivacaine plasma concentrations are similar during continuous lumbar plexus blockade using the anterior three-in-one and the posterior psoas compartment techniques. *Can J of Anaesth* 2004;51:52-6.
9. De Visme V, Picart F, Le Jouan R, et al. Combined Lumbar and Sacral Plexus Block Compared With Plain Bupivacaine Spinal Anesthesia for Hip Fractures in the Elderly. *Reg Anesth Pain Med* 2000;25:158-62.
10. Ho AMH, Karmakar MK. Combined paravertebral lumbar plexus and parasacral sciatic nerve block for reduction of hip fracture in a patient with severe aortic stenosis. *Can J Anaesth* 2002;49:946-50.
11. Stevens RD, Van Gessel E, Flory N, et al. Lumbar Plexus Block Reduces Pain and Blood Loss Associated with Total Hip Arthroplasty. *Anesthesiology* 2000;93:115-21.
12. Martin WE, Everett G, Kennedy jr. WF, et al. A Comparison Between Cardiovascular Effects of Sciatic-Femoral Block With Bupivacaine and With Lidocaine. *Anesth Analg* 1973;52:454-61.
13. Fanelli G, Casati A, Aldegheri G, et al. Cardiovascular effects of two different regional anesthetic techniques for unilateral leg surgery. *Acta Anaesthesiol Scand* 1998;42:80-4.
14. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-11.
15. Button D, Weibel l, Reuthebuch O, et al. Clinical evaluation of the FloTrac/Vigileo system and two established continuous cardiac output monitoring devices in patients undergoing cardiac surgery. *Br J Anaesth* 2007;99:337-42.
16. Labat G: Regional Anesthesia. Its Technique and Clinical Application. Philadelphia, PA: Saunders; 1922.
17. Chayen D, Nathan H, Chayen M. The psoas compartment block. *Anesthesiology* 1976;45;95-9.
18. Guyton AC, Hall JE Textbook of medical Physiology. Tenth edition. W.B. Saunders Company. Philadelphia, USA. Chapter 20, page 210.
19. Vanterpool S, Steele SM, Nielsen KC, et al. Combined Lumbar-Plexus and Sciatic-Nerve Blocks: An Analysis of Plasma Ropivacaine Concentrations. *Reg Anesth Pain Med* 2006;31:417-21.
20. de Leeuw MA, Bet PM, Wilhelm AJ, et al. Total plasma concentrations of bupivacaine, levobupivacaine and ropivacaine after combined psoas compartment – sciatic nerve Block. *Eur J Anaesth* 2009;26:1083-5.
21. Capdevila X, Coimbra C, Choquet O. Approaches to the lumbar plexus: success, risks, and outcome. *Reg Anesth Pain Med* 2005;30:150-62.
22. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children: A comparison of two procedures in 50 patients. *Anesth Analg* 1988;67:750-8.
23. Breukers RMBGE, Sepehrkhouy S, Spiegelenberg SR, et al. Cardiac output measured by a new arterial pressure waveform analysis method without calibration compared with thermodilution after cardiac surgery. *J Cardiothorac Vasc Anesth* 2007;21:632-5.
24. Mayer J, Boldt J, Wolf MW, et al. Cardiac output derived from arterial pressure waveform analysis in patients undergoing cardiac surgery: validity of a second generation device. *Anesth Analg* 2008;106:867-72.

25. Prasser C, Trabolt B, Schwab A, et al. Evaluation of an improved algorithm for arterial pressure-based cardiac output assessment without external calibration. *Intensive Care Med* 2007;33:2223-5.
26. Senn A, Button D, Zollinger A, et al. Assessment of cardiac output changes using a modified FlowTrac/Vigileo™ algorithm in cardiac surgery patients. *Crit Care* 2009;13:R32.
27. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare measurement techniques. *J Clin Monit Comput* 1999;15:85-91.
28. Mayer J, Boldt J, Poland R, et al. Continuous Arterial Pressure Waveform–Based Cardiac Output Using the FloTrac/Vigileo: A Review and Meta-analysis. *J Cardiothorac Vasc Anesth* 2009;23:401-406.

5

Cardiac output measured by uncalibrated arterial pressure waveform analysis by recently released software version 3.02 versus thermodilution in septic shock

Slagt C, de Leeuw MA, Beute J, Rijnsburger E, Hoeksema M, Mulder JW, Malagon I, Groeneveld ABJ.

J Clin Monit Comput 2013;27:171-7.

Abstract

Background and objective

To evaluate the 3.02 software version of the FloTrac/Vigileo™ system for estimation of cardiac output by uncalibrated arterial pressure waveform analysis, in septic shock.

Methods

Nineteen consecutive patients in septic shock were studied. FloTrac/Vigileo™ measurements (COfv) were compared with pulmonary artery catheter thermodilution-derived cardiac output (COtd).

Results

The mean cardiac output was 7.7 L min^{-1} and measurements correlated at r=0.53 (P<0.001, n=314). In Bland Altman plot for repeated measurements, the bias was 1.7 L min^{-1} and 95% limits of agreement (LA) were -3.0 to 6.5 L min^{-1}, with a %error of 53%. The bias of COfv inversely related to systemic vascular resistance (SVR) (r=-0.54, P<0.001). Above a SVR of 700 dyne·s·cm^{-5} (n=74), bias was 0.3 L min^{-1} and 95% LA were -1.6 to 2.2 L min^{-1} (%error 32%). Changes between consecutive measurements (n=295) correlated at 0.67 (P<0.001), with a bias of 0.1% (95% limits of agreement -17.5 to17.0%). All changes >10% in both COtd and COfv (n=46) were in the same direction.. Eighty-five percent of the measurements were within the 30^{o}–330^{o} of the polar axis.

Conclusions

COfv with the latest software still underestimates COtd at low SVR in septic shock. The tracking capacities of the 3.02 software are moderate-good when clinically relevant changes are considered.

Introduction

In the haemodynamic management of septic shock, monitoring of cardiac output (CO) may play a role. Classically, CO is measured by intermittent thermodilution using a pulmonary artery catheter. In the last decade alternative and less invasive measurement devices have become available. The FloTrac/Vigileo™ system (Edwards Lifesciences, CA, USA) has been introduced in 2005. Since its introduction and driven by validation studies, software updates have been provided to improve the accuracy of measurements. Under low-flow conditions, FloTrac/Vigileo™-derived CO (COfv) may be almost interchangeable with pulmonary or femoral artery thermodilution-derived CO (COtd).[1 2] Under hyperdynamic conditions like liver disease/surgery or septic shock, however, COfv generally underestimates reference values particularly when vascular tone is severely diminished and CO is high, although increasing accuracy has been reported with software updates.[3-10] The recently introduced 3.02 software version was especially developed to increase accuracy during hyperdynamic conditions like septic shock.[11 12]

The goal of this study was to evaluate the accuracy of the COfv using the latest 3.02 software version compared with intermittent thermodilution-derived COtd in the course of treatment of patients with septic shock.

Materials and methods

After Medical Ethics Review Committee approval (Ethics Committee, Noord-Holland, Alkmaar, The Netherlands No. M09-035; 13 July 2009) and written informed consent from the next of kin, nineteen consecutive patients were included in this clinical observational study. Patients had to suffer from septic shock, as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference. Patients requiring advanced haemodynamic monitoring, in addition to arterial pressure monitoring via a radial or femoral artery catheter, with help of a pulmonary artery catheter as judged by the medical team, were eligible for this study. The catheter was placed in the internal jugular vein (CritiCath, SP5507H TD Catheter, Becton Dickinson Infusion Therapy Systems Inc., Sandy, Utah, USA). Additional inclusion criteria were the presence of mechanical ventilation, sinus rhythm, and need for vasoactive therapy by either dopamine or norepinephrine. Exclusion criteria where age <18 years, no sinus rhythm, severe tricuspid regurgitation and aortic valve regurgitation. Patients received standard care by attending intensive care physicians according to local guidelines, including early antibiotics and drainage, where applicable.

Protocol

Patient characteristics were recorded. Paired CO measurements were performed until removal of the pulmonary artery catheter, at least once every shift and prior to and after starting or changing therapy with fluids or vasoactive agents, in the course of haemodynamic management. A FloTrac™ sensor was connected to the existing radial (or femoral) artery catheter (Arterial Cannula with FloSwitch 20 G/1.10mm*45mm) and connected to the Vigileo™ monitor. Before each measurement the system was zeroed. The intermittent thermodilution CO measurement was performed by averaging measurements with help of 3 consecutive central venous injections via the pulmonary artery catheter of 10 ml of iced isotonic saline. Values were averaged, regardless of outliers, provided that thermodilution curves were adequate and not distorted. Injections were not synchronised to the respiratory cycle. The mean value was recorded and regarded as the COtd. At the start of each bolus CO measurement, the COfv was measured. The mean value of the three measurements was recorded. The mean arterial pressure (MAP) was monitored with help of radial (n=17) or femoral (n=2) artery catheter and the central venous pressure (CVP) with help of the pulmonary artery catheter, after calibration and zeroing to atmospheric pressure with patients in the supine position (Spacelabs^{R}, Spacelabs, Med, WA, USA). The radial or femoral artery delivers CO's by FloTrac/Vigileo™ that are not greatly dissimilar.[2 5 11 13] The electrocardiogram was monitored throughout and the heart rate (HR) was taken from the monitor. The systemic vascular resistance (SVR) was calculated from (MAP-CVP)*80/COtd, dyne·s·cm^{-5}.

The FloTrac/Vigileo™ system calculates CO by using the SD of the pulse pressure incorporating actual vascular tone based on waveform analysis and patient characteristics.[14] The continuous analysis of the arterial waveform to detect changes in the vascular tone makes external calibration unnecessary and operator error is minimised. Each arterial waveform is analysed with a frequency of 100 Hz, over 20 s. The following formulas apply as incorporated in the Vigileo™ algorithm: CO = HR x σsAP x χ, where HR is heart rate and σsAP, as a measure of stroke volume, is the standard deviation of arterial pressure. χ = M (HR, σsAP, C(P), BSA, MAP, μ_{3ap}, μ_{4ap}), where M is multivariate approximating function M, C(P) is a function of arterial compliance, μ_{3ap} is the skewness of arterial pressure data, μ_{4ap} is the kurtosis of arterial pressure data and BSA is body surface area calculated from weight and height. A polynomial multivariate fitting function is used to calculate χ as a measure of vascular tone. C(P) is derived from Langewouters, using sex and age and modified using weight, height and BSA. The third generation version includes 2 separate models for the arterial tone factor: (1) an arterial tone model that was developed predominantly from patients who were not in hyperdynamic

conditions (this is the same model used in the previous version 1.10) and (2) an arterial tone model that was developed predominantly from patients who were in hyperdynamic conditions. The need for using 2 separate models is because the cardiovascular physiology relating peripheral arterial pressure to flow during hyperdynamic conditions is different from the physiology during non-hyperdynamic conditions. The switching between the 2 models is based on an algorithm that uses 14 parameters of the arterial pressure waveform to detect the occurrence of hyperdynamic conditions.

Statistical analysis

Based our pilot study where we found a mean difference of 0.80 L min^{-1} and a standard deviation of 1.30 L min^{-1} between the two methods, a sample size of 300 measurements to detect a 0.5 L min^{-1} difference with an alpha =0.05 and a power of 80% was calculated to be needed. Data are presented as mean ± standard deviation, because they were distributed normally (Kolmogorov-Smirnov test, P>0.05). Linear regression was used to calculate partial correlation coefficients taking repeated measurements in the same patients into account, with a dummy variable as covariate. CO by techniques were compared using Bland Altman (BA) plots for differences versus means, corrected for repeated measurements, yielding bias and 95% limits of agreement (bias ± 1.96* standard deviation) (Medcalc® software, Belgium). The 1.96* standard deviation/mean CO yields the %error. We evaluated the effect of MAP and SVR on the differences in CO between techniques with help of generalised estimating equations (GEE), taking repeated measurement in patients into account. To further evaluate agreement between techniques as a function of low SVR and individual patients, we also made BA plots for values at SVR without a systematic difference and for values in each patient, respectively. The latter yielded %error per patient. Changes of CO between consecutive measurements were analysed for concordance of measurements and polar plot analyses.[15] The $\varkappa$ statistic was calculated and a receiver operating characteristic (ROC) curve constructed. Exact P values <0.05 and >0.001 are given, with the former considered to indicate statistical significance.

Results

Patient's characteristics

Nineteen patients were included in this study (Table 1). Initial and overall haemodynamic data are summarised in Tables 2 and 3. A total of 314 paired measurements were obtained during the haemodynamic management of these patients, as summarised in Table 4. Hence, the number of paired measurements per patient ranged from 6 to 31.

Table 1. Patient characteristics on admission in the ICU.

Age (year)	62 ± 15
Sex (male/female)	6/13
Weight (kg)	79 ± 14
Height (cm)	171 ± 0
Origin of sepsis	
Pneumonia	11
Peritonitis	3
Urogenital	2
Other	3
Microorganism	
Gram-negative bacteria in blood	5
Gram-positive bacteria in blood	8
Legionella spp.	1
Viral	1
Other	4
APACHE II score	30 ± 10
Length of ICU stay (days)	19 ± 7
Mortality in the ICU	7 (37)
Hospital mortality	11 (58)

Mean ± SD or number of patients (percentage), wherever appropriate. ICU = intensive care unit; APACHE = Acute Physiology And Chronic Health Evaluation.

Comparison of COfv with COtd

COtd ranged from 3.8-17.3 and COfv from 4.0-13.7 L min^{-1}, at a mean of 7.7 L min^{-1}. The correlation plot is shown in Figure 1. The BA plot corrected for repeated measurements showed that the differences related to the means of measurements indicating a systematic underestimation of COtd by COfv. Nevertheless, agreement statistics were calculated showing a bias of 1.7 L min^{-1} and 95% limits of agreement ranging from -3.0 to 6.5 L min^{-1}. At a standard deviation of 2.4 L min^{-1}, the %error was 53% (Figure 2). The SVR ranged from 229-1067 dyne·s·cm^{-5} and the difference between COtd and COfv inversely related to the SVR ($r=-0.54$, $P<0.001$, Figure 3). Indeed, the differences were inversely associated with MAP and SVR ($P=0.044$) or lower, GEE). Above a SVR of 700 dyn·s·cm^{-5} ($n=74$), differences did not relate to the mean, the bias in a BA plot for repeated measurements was only 0.3 L min^{-1} and 95% limits of agreement were -1.6 to 2.2 L min^{-1}, so that %error was 32%. Table 4 shows that this is in the range of individual %errors. Norepinephrine was continuously infused during 269 and dopamine during 233 of the 314 measurements.

Table 2. Haemodynamic data at study inclusion

N	HR, min^{-1}	MAP, mm Hg	COtd, L min^{-1}	COfv, L min^{-1}	Drugs used in treatment
1	95	81	6.3	6.0	nor, dopa, eno
2	116	66	9.9	6.8	nor, eno
3	118	78	10.4	13.7	nor, eno
4	62	54	5.8	4.2	nor, dopa, eno
5	125	68	6.4	5.6	nor, dopa, eno
6	113	67	5.9	6.9	nor ,dopa, eno
7	96	50	8.2	6.9	nor, eno
8	95	62	5.9	5.7	nor, dopa, eno
9	138	89	7.5	5.3	nor, dopa, eno
10	127	57	11.6	6.6	nor, dopa, eno
11	95	80	9.8	8.2	nor, eno
12	110	74	7.2	5.1	nor, dopa
13	121	75	13.7	9.4	nor, dopa, eno
14	125	71	5.1	5.3	nor, dopa, eno
15	96	97	7.4	5.3	nor, dopa, eno
16	101	100	11.4	8.3	nor, dopa, no
17	105	70	6.4	6.8	nor, eno
18	91	67	4.5	5.1	nor, dopa, eno
19	103	78	9.2	6.4	nor, dopa, eno

HR = heart rate; MAP = mean arterial pressure; COtd = intermittent thermodilution cardiac output; COfv = FloTrac/Vigileo™ cardiac output; nor = norepinephrine; dopa = dopamine; eno = enoximone.

Table 3. Haemodynamic data using all measurements.

Heart rate (min^{-1})	101 ± 14
Mean arterial pressure (mmHg)	71 ± 12
COtd (L min^{-1})	8.6 ± 2.7
COfv (L min^{-1})	6.8 ± 2.0
Systemic vascular resistance (dyne·s·cm^{-5})	586 ± 169

Numbers are expressed in mean ± SD, COtd = intermittent thermodilution cardiac output; COfv = FloTrac/Vigileo™ cardiac output.

Table 4. Individual haemodynamic data in the course of disease

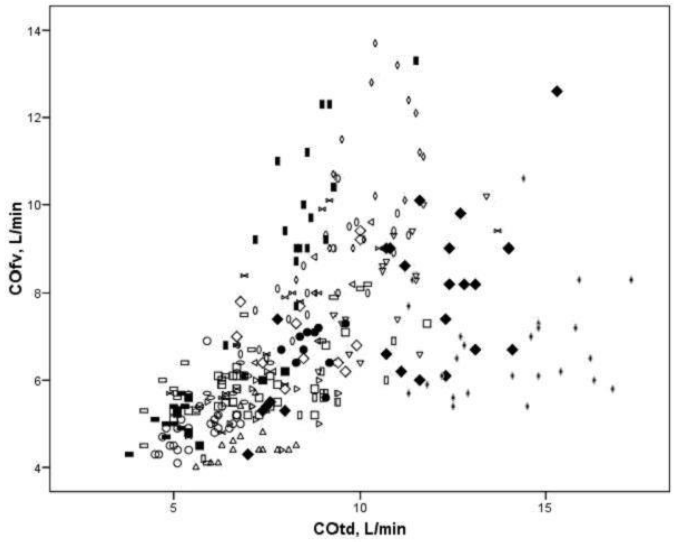
N	No of measurem ents	Range COtd	Range COfv	Mean CO	SVR	CO difference	% error
1	31	5.0-11.8	5.1–7.1	6.4 ± 0.9	667 ± 14	1.3 ± 1.2	36
2	15	6.7-10.0	5.8–9.4	7.9 ±1.0	500 ± 97	1.4 ± 1.4	35
3	12	8.3-11.7	8.3-13.7	10.7 ± 1.2	549 ±105	-0.6 ± 1.4	26
4	10	5.8-10.9	4.2–6.9	7.3 ± 1.0	431 ± 83	3.4 ± 0.8	22
5	16	4.2-10.2	4.1-8.2	6.4 ± 1.6	677 ± 109	0.3 ±0 .2	38
6	25	4.5-6.8	4.1–6.9	5.3 ± 0.6	627 ± 156	0.7 ± 0.7	25
7	21	6.8-11.3	6.6–10.6	8.7 ± 1.2	540 ± 60	0.7 ± 0.9	20
8	12	5.4-7.6	5.3–6.4	6.1 ± 0.5	694 ± 77	0.5 ± 0.5	17
9	17	5.6-8.3	4.0–5.7	5.8 ± 0.5	687 ± 132	2.3 ± 0.8	28
10	17	8.9-13.4	6.2–10.2	9.4 ± 1.1	529 ± 89	2.7 ± 0.9	19
11	9	6.7-10.3	6.2-9.6	8.1 ± 1.1	681 ± 144	1.1 ± 0.8	21
12	15	5.9-9.4	4.4–6.2	6.5 ± 0.6	577 ± 123	2.0 ± 1.1	33
13	19	4.9-13.7	4.7–10.1	7.4 ± 1.8	740 ± 178	0.6 ± 1.3	35
14	6	5.1-8.0	4.5–6.2	5.8 ± 0.9	579 ± 140	0.8 ± 0.8	29
15	25	7.0-15.3	4.3–12.6	9.4 ± 2.0	484 ± 69	3.7 ± 0.8	38
16	26	11.3-17.3	5.4–10.6	10.3 ± 1.2	385 ± 97	7.2 ± 2.0	39
17	18	6.4-11.5	6.1–13.3	9.1 ± 1.4	493 ± 116	-1.2 ± 1 .2	27
18	10	3.8-5.3	4.3–5.7	5.0 ± 0.4	921 ± 116	-0.2 ± 0.3	12
19	10	7.9-9.6	5.6–7.2	7.7 ± 0.4	544 ± 182	2.0 ± 0.7	18

Data are expressed as mean ± SD; COtd = intermittent thermodilution cardiac output, L min^{-1}; COfv =FloTrac/ Vigileo™ cardiac output, L min^{-1}; SVR=systemic vascular resistance, dyne·s·cm^{-5}; CO difference = COtd-COfv, L min^{-1}

Concordance

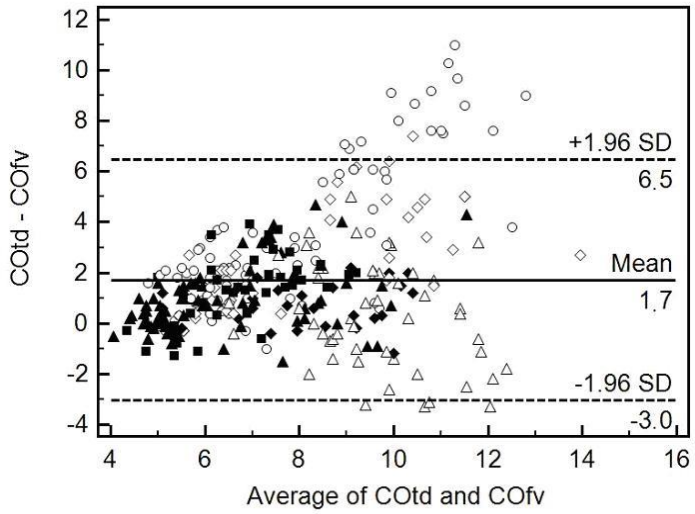
Changes in consecutive measurements correlated as shown in Figure 4, r=0.67, P<0.001 (n=295). Changes in MAP (GEE, P=0.001 and 0.006 for first order interaction) contributed to changes in COfv (P<0.001) to predict changes in COtd. For changes (increases/decreases) in CO >10%, considered as clinically relevant, the $\varkappa$ statistic was 0.34 (P<0.001) and the area under the ROC curve for COfv changes to predict >10% changes in COtd was 0.72 (P<0.001). Both COtd and COfv changed by >10% in the same direction in all of 46 paired measurements. Changes >10% in either COtd or COfv were in the same direction in 100 of 115 (87%) measurements. Figure 5 depicts the polar plot for changes in CO (L min^{-1}) for both techniques. After exclusion of measurements with minimal, i.e. <0.5 L min^{-1}, CO changes, 163 paired measurements remained. Eighty-five percent of the measurements were within the 30^{o}–330^{o} of the polar axis.

Figure 1.



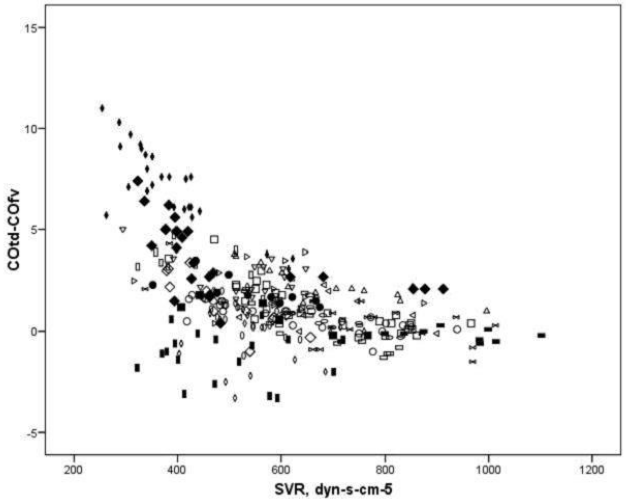
FloTrac/Vigileo™ cardiac output (COfv, L min^{-1}) versus intermittent thermodilution cardiac output (COtd, L min^{-1}); each symbol represents a patient: r=0.53, P<0.001.

Figure 2.



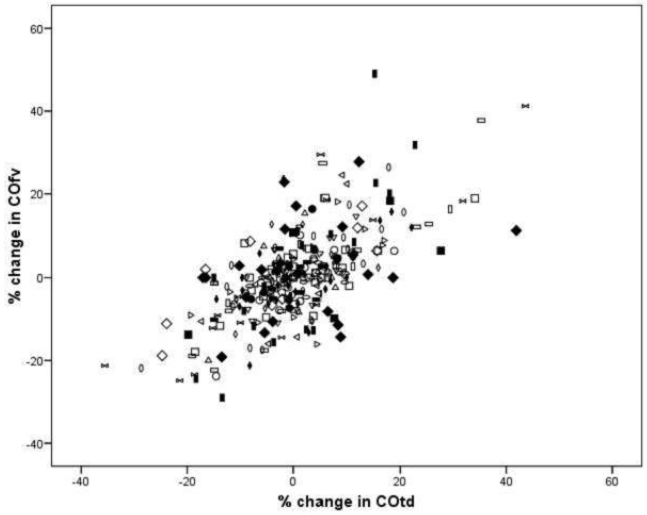
Bland-Altman plot corrected for repeated measurements of intermittent thermodilution cardiac output (COtd, L min^{-1}) and FloTrac/Vigileo™ cardiac output (COfv, L min^{-1}). Bias and 95% limits of agreement. The difference related to the mean (r=0.32, P<0.001). Each symbol represents a patient.

Figure 3.



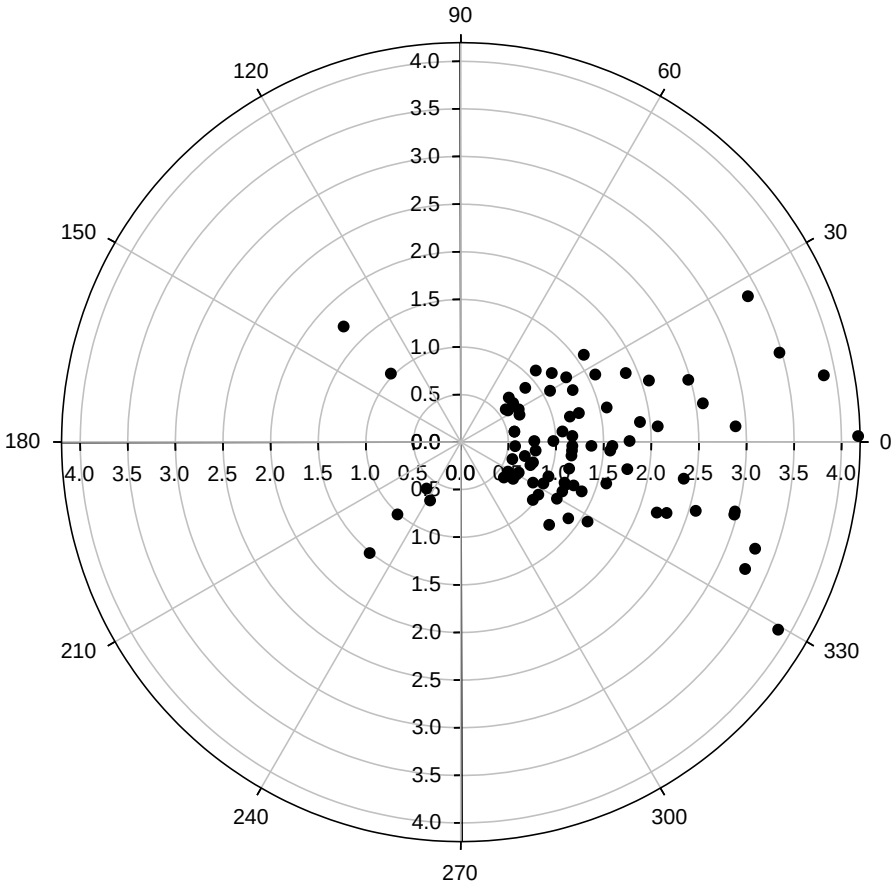
The differences between FloTrac/Vigileo™ cardiac output (COfv, L min^{-1}) and intermittent thermodilution cardiac output (COtd, L min^{-1}) in relation to systemic vascular resistance (SVR): r=-0.54, P<0.001. Each symbol represents a patient.

Figure 4.



Concordance of changes between consecutive measurements in FloTrac/Vigileo™ cardiac output (COfv, L min^{-1}) with changes in thermodilution cardiac output (COtd, L min^{-1}) in %. Each symbol represents a patient; r=0.67, P<0.001.

Figure 5. Polar plot changes in intermittent thermodilution cardiac output (horizontal axis, COtd, L min^{-1}) and FloTrac/Vigileo™ cardiac output (vertical axis, COfv, L min^{-1}).



Discussion

In this study, we compared the COfv with COtd via a pulmonary artery catheter in patients with septic shock. Our results suggest that the COfv with the latest software version 3.02 still considerably underestimates COtd, unless the SVR exceeds 700 dyne·s·cm^{-5}. The tracking ability of the FloTrac/Vigileo™ is fair, for clinically relevant changes in CO.

The relatively high bias and %error when using old versions of the software of the FloTrac/Vigileo™ under hyperdynamic haemodynamic conditions have been noted before.[3 4 6-9] The discrepancies appeared greatest when vascular tone was moderately to severely diminished.[4 6 7] In a previous study[10] we compared COfv with software versions 1.10 and 1.07 to COtd in septic shock patients, and concluded that the former software version was associated with less bias and %error. We cannot fully judge nor compare agreement statistics, however, when differences in measurements with the reference standard relate to the means, suggesting a systematic rather than random error. Indeed, this evaluation is not commonly done even when BA plots strongly suggest greater systematic than random error[2 4-8 11 12] in contrast to our current and previous[6] studies. Nevertheless, in the range where COfv did not systematically underestimate COtd in the current study, the %error was still slightly above the clinically acceptable criterion of 30% proposed by Critchley et al.[16] Our current data thus suggest that the 3.02 software version is not a major improvement over previous versions and should not be the final one, particularly since the error of intermittent thermodilution as the reference technique may be lower than 20%. In any case, the overall higher %error of pooled than of individual data or data at relatively high SVR indicates that the systematic error at low SVR particularly occurred in some patients with the most severe fall in vascular tone. The concordance of measurements have been described in previous studies and software versions, being relatively low during hyperdynamic conditions, including sepsis.[3-5 9 10] Eighty-five percent of our measurements were within the 30^{o}-330^{o} to the polar axis, reflecting moderate-good trending ability.[17] The FloTrac/Vigileo™ version 3.02, in contrast to previous ones, is suitable for tracking clinically relevant CO changes in septic shock, even more so than for estimating absolute numbers of CO.

De Backer et al. recently published data on the 3.02 compared with the 1.10 software versions applied in 58 patients with septic shock in various institutions involving 401 paired measurements.[11] Their data suggesting improvement in accuracy with the latest software version and only minimum dependency of bias on vascular tone are not fully confirmed by our study in a comparable number of data sets. The analyses reported in their study were obtained offline, while ours were obtained at the bedside. The severity of

illness was not reported in the De Backer study. In our study an APACHE II score with a mean of 30±10 indicates severe illness and organ failure. Our patients were probably more vasoplegic and hyperdynamic, thereby explaining greater dependence of COfv on SVR than in the De Backer study. Biancofiore et al. published the performance of the latest FloTrac/Vigileo™ software during liver surgery.[12] Comparing these data with previous results obtained with the 1.10 software version[7] they concluded that performance had improved but still seemed insufficient to allow for routine use in liver transplant surgery. We cannot exclude that the patients in the other studies on the 3.02 software[11 12] had a less severe decline in vascular tone with less effect on bias than in our study.

Conclusion

The latest 3.02 software COfv still underestimates COtd in patients suffering from septic shock when SVR decreases below 700 dyne·s·cm^{-5}. However, the tracking ability is fair when clinically relevant CO changes are considered.

Acknowledgments

We are very grateful to Drs M. Helmi, research fellow at Erasmus Medical Centre for constructing the polar plots.

References

1. Breukers RM, Sepehrkhouy S, Spiegelenberg SR, et al. Cardiac output measured by a new arterial pressure waveform analysis method without calibration compared with thermodilution after cardiac surgery. *J Cardiothorac Vasc Anesth* 2007;21:632-635.
2. Hofer CK, Button D, Weibel L, et al. Uncalibrated radial and femoral arterial pressure waveform analysis for continuous cardiac output measurement:an evaluation in cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2010;24:257-264.
3. Sakka SG, Kozieras J, Thuemer O, et al. Measurement of cardiac output:a comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007;99:337-342.
4. Biais M, Nouette-Gaulain K, Cottenceau V, et al. Cardiac output measurement in patients undergoing liver transplantation:pulmonary artery catheter versus uncalibrated arterial pressure waveform analysis. *Anesth Analg* 2008;106:1480-1486.
5. Compton FD, Zukunft B, Hoffmann C, et al. Performance of a minimally invasive uncalibrated cardiac output monitoring system (Flotrac/Vigileo) in haemodynamically unstable patients. *Br J Anaesth* 2008;100:451-456.
6. Della Rocca G, Costa MG, Chiarandini P, et.al. Arterial pulse cardiac output agreement with thermodilution in patients in hyperdynamic conditions. J Cardiothorac *Vasc Anesth* 2008;22:681-687.
7. Biancofiore G, Critchley LA, Lee A et al. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. *Br J Anaesth* 2009;102:47-54.
8. Krejci V, Vannucci A, Abbas A, et al. Comparison of calibrated and uncalibrated arterial pressure-based cardiac output monitors during orthotopic liver transplantation. *Liver Transpl* 2010;16:773-782.
9. Monnet X, Anguel N, Naudin B, et al. Arterial pressure based cardiac output in septic patients:different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010;14:R109.
10. Slagt C, Beute J, Hoeksema M, et al. Cardiac output derived from arterial pressure waveform analysis without calibration versus thermodilution in septic shock:evolving accuracy of software versions. *Eur J Anaesthesiol* 2010;27:550-554.
11. De Backer D, Marx G, Tan A et al. Arterial pressure-based cardiac output monitoring:a multicenter validation of the third-generation software in septic patients. *Intensive Care Med* 2011;37:233-40.
12. Biancofiore G, Critchley LA, Lee A et al. Evaluation of a new software version of the FloTrac/Vigileo (Version 3.02) and a comparison with previous data in cirrhotic patients undergoing liver transplant surgery. *Anesth Analg* 2011;113:515-22.
13. Schramm S, Albrecht E, Frascarolo P, et al. Validity of an arterial pressure waveform analysis device:does the puncture site play a role in the agreement with intermittent pulmonary catheter thermodilution measurements*? J Cardiothorac Vasc Anesth* 2010;24:250-256.
14. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-411.
15. Critchley LA, Yang XX, Lee A. Assessment of trending ability of cardiac output monitors by polar plot methodology. *J Cardiothorac Vasc Anesth* 2011;25:536-546.
16. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85-91.
17. Critchley LAH. Validation of the most care pulse contour cardiac output monitor:beyond the bland and altman plot. *Anesth Analg* 2011;113:1292-1294.

6

Calibrated arterial pressure waveform analysis is superior to the uncalibrated technique as compared to transpulmonary thermodilution in monitoring cardiac output in severe sepsis or septic shock

Slagt C, Helmi M, Malagon I, Groeneveld ABJ.

Submitted for publication.

Abstract

Background and objective

To compare calibrated arterial pressure waveform analysis-derived cardiac output (COap, Volume View/EV1000™) and the uncalibrated form (COfv, FloTrac/Vigileo™) with transpulmonary thermodilution cardiac output (COtptd) in septic shock.

Methods

Twenty consecutive severe sepsis or septic shock patients, requiring advanced hemodynamic monitoring while on mechanical ventilation, were included in this prospective observation study on an intensive care unit of a teaching hospital. Cardiac output measurements were compared during the clinical course.

Results

Two hundred and sixty seven paired measurements were available for comparison of COap with COtptd: they related at r^2=0.74 (P<0.001). Bland Altman analysis corrected for repeated measurements showed a bias of -0.02 L min^{-1} and limits of agreement of -2.52 to 2.49 L min^{-1}, with %error of 31%. The %error between COtptd and COap remained <30% until 8 hours after calibration. Three hundred and one paired measurements were available for the comparison of COfv with COtptd: they related at r^2 =0.52 with a %error of 48%. The bias of COap and COfv showed an inverse relation to systemic vascular resistance (r=-0.13, P=0.029 and r=-0.42 P<0.001, respectively). Clinically significant changes in cardiac output (excluding <1.2 L min^{-1}) correlated with COtptd at r^2=0.27 (P<0.001) and r^2=0.41 (P<0.001) for COap and COfv, respectively.

Conclusions

The recently introduced calibrated arterial pressure waveform analysis-derived cardiac output is more accurate and less dependent on vascular tone than the uncalibrated technique in monitoring cardiac output in patients with severe sepsis or septic shock, up to 8 hours after calibration. However, the tracking capacity of COap is moderate and somewhat better for COfv, as compared to COtptd.

Introduction

A new transpulmonary thermodilution (tptd) platform has recently been introduced to monitor cardiac output (COtptd) in patients (VolumeView/EV1000™, Edwards Lifesciences, Irvine, CA, USA). It is equipped with a continuous cardiac output (CO) measurement derived from arterial pressure waveform analysis (COap), similar to the technique of the FloTrac/Vigileo™ monitor yielding COfv, except for calibration of the former each time a thermodilution measurement is performed.[1] There is one prior validation study in haemodynamically relatively stable patients, suggesting that COap is as accurate as its tptd reference and better than pulse contour-derived continuous CO ($PiCCO_2$, Pulsion Medical Systems, Munich, Germany).[1] We have suggested before,[2] that even with the most recent third generation FloTrac/Vigileo™ software, the calculated (uncalibrated) CO is still inaccurate in vasodilated and septic patients to allow for clinically meaningful CO monitoring and therapeutic decision making.

The aim of the current prospective observational single centre study was therefore to compare calibrated COap and uncalibrated COfv with COtptd in critically ill patients in the course of treatment for severe sepsis or septic shock in the intensive care unit (ICU). We hypothesized that calibrated outperforms uncalibrated less invasive CO in this condition.

Materials and methods

After Medical Ethics Review Committee approval (Ethics Committee, Noord-Holland, Alkmaar, The Netherlands No. M011-019; 26 April 2011) and written informed consent, 20 consecutive patients were included in this clinical observational study. All patients requiring advanced haemodynamic CO monitoring, because of severe sepsis or septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference, needing vasoactive therapy, in addition to arterial pressure monitoring via a radial artery catheter, as judged by the medical team, were eligible for this study. Additional inclusion criteria were the presence of mechanical ventilation, organ failure and norepinephrine use. The study was performed in the ICU of a teaching hospital from June 2011 to April 2013. Exclusion criteria were age <18 years, contraindications for a femoral artery catheter and known severe tricuspid or aortic valve regurgitation. This study did not alter the standard of care provided by medical staff, which adhered to international guidelines, and included antibiotics guided by likely (or proven) sources and associated microorganism and their sensitivity, as well as fluids and vasoactive drugs, when indicated on clinical grounds.

Protocol

Patient characteristics were recorded, including disease severity scores. Paired CO measurements were performed until it was no longer deemed necessary by the medical team, at least once every shift and prior to and after starting or changing therapy with fluids or vasoactive agents, in the course of haemodynamic management. A FloTrac™ sensor was connected to the radial artery catheter (Arterial Cannula with FloSwitch 20 G/1.10 mm 9 45 mm) already in situ and connected to the Vigileo™ monitor. After placement of the femoral TPTD catheter (VolumeView/EV1000™ system, Edwards Lifesciences, Irvine CA, USA) all time clocks from the Space lab monitor (Spacelabs Medical Inc, Issaquah, Washington, USA), VolumeView/EV1000™ and FloTrac/Vigileo™ monitor were synchronised. The mean arterial pressure (MAP, mm Hg) was monitored with help of the femoral artery catheter, and the central venous pressure (CVP, mm Hg) with help of a central venous catheter, prior inserted for clinical reasons. The electrocardiogram was monitored throughout and the heart rate (HR) was taken from the monitor. The systemic vascular resistance (SVRtptd) was calculated from (MAP-CVP) x80/COtptd, dyne·sec·cm^{-5}. The tptd measurement was performed in sets of 3-5 central venous injections of 20 mL of iced isotonic saline, irrespective of the ventilator cycle. All individual bolus measurements had to be manually validated before averaged. The mean value was recorded and regarded as the COtptd. At the start of each tptd bolus CO measurement, the COfv was measured and the mean value was recorded. All haemodynamic data stored in the EV1000™ computer and FloTrac/Vigileo™ monitor were downloaded for analysis. All paired COap and COtptd measurements were analysed in relation to the time since the last calibration to establish the calibration-free period in which COap remains clinically acceptable with a %error <30%.[3]

Description of techniques

The tptd measurement using the VolumeView/EV1000™ system uses bolus injection through a central venous line above the diaphragm and the thermodilution curve is measured by an arterial catheter with a specific thermistor tip. This method provides CO measurements as well as global end-diastolic volume (GEDV), intra-thoracic blood volume (ITBV), extra vascular lung water (EVLW), global ejection fraction (GEF) and pulmonary vascular permeability index (PVPI).[4] The VolumeView/EV1000™ monitor combines the area under the systolic part of the arterial pressure waveform and waveform analysis as used in the FloTrac/Vigileo™ system to calculate continuous CO. After each intermittent bolus tptd measurement, the COap is recalibrated.[1]

The FloTrac/Vigileo™ system estimates CO by using the standard deviation of the pulse pressure incorporating actual vascular tone based on waveform analysis and patient characteristics. [5] Each arterial waveform is analysed with a frequency of 100 Hz, over 20 sec. The third generation software version (3.02) includes 2 separate models for the arterial tone factor: (1) an arterial tone model that was developed predominantly from patients who were not in hyperdynamic conditions (this is the same model used in the previous version 1.10) and (2) an arterial tone model that was developed predominantly from patients who were in hyperdynamic conditions. The need for using 2 separate models is because the cardiovascular physiology relating peripheral arterial pressure to flow during hyperdynamic conditions is different from the physiology during non-hyperdynamic conditions.[6] The switching between the 2 models is based on an algorithm that uses 14 parameters of the arterial pressure waveform to detect the occurrence of hyperdynamic conditions.

Statistical analysis

After confirming normally distributed data by Kolmogorov-Smirnov test ($P>0.05$), continuous variables were summarised as mean and standard deviation (SD) and parametric tests were performed. Linear regression was used to calculate Pearson correlation coefficient (for negative relations) and the coefficient of determination (r^2), in order to express how well a CO measurement method confirmed another. All analysis was conducted using SPSS version 21 (SPSS Inc, Chicago, Ill, USA). A Bland-Altman analysis[3] was performed, for the mean versus differences between each method (and their changes), adjusted for repeated measurements (Medcalc software version 12.2.1.0, Mariakerke, Belgium). Bias was defined as the mean difference between COs derived from two methods. Limits of agreement were calculated from ±1.96 SD of the bias. The precision of the reference COtptd was calculated using the method proposed by Cecconi et al.[7], to calculate the precision of the test methods. The %error (1.96 SD/mean CO) was calculated.[8] Polar plots (SigmaPlot software version 11, San Jose, CA) were also used to analyse the agreement in CO trend monitoring between methods.[9] In the polar plot, the changes of CO data are converted to a radial vector where degree of agreement between 2 devices becomes the angle between radial vector and horizontal axis (i.e., polar axis). If agreement is perfect, the radial vector lies along the polar axis and the angle is zero. The distance from the center of the plot (vector) represents the mean changes in CO. As COap is recalibrated with COtptd, we analysed the effect of time on the difference between the two methods. A P value less than 0.05 was considered statistically significant and exact values are given when >0.001.

Results

The characteristics of the 20 patients included in the study are listed in Table 1. The haemodynamic data at inclusion are given in Table 2. A total of 301 paired measurements were obtained, and the number of paired measurements per patient ranged from 5 to 24. The mean (SD) COap, COfv and COtptd were 8.2 (2.5), 7.3 (3.6) and 8.2 (2.3) L min^{-1}, respectively. Mean SVRtptd was 636 (246) dyne·s·cm^{-5}. Eighty-five percent of the intermittent measurements were performed during norepinephrine infusion at a mean dose of 0.34 (0.71) $\mu g.kg^{-1}.min^{-1}$.

Table 1. Patient characteristics at intensive care unit admission.

Age (yrs)		63 (11)
Sex (male/female)		16/4
Weight (kg)		89 (22)
Height(cm)		178 (7)
Cause of sepsis	Pneumonia	9
	Abdominal	8
	Urogenital	1
	Others	2
APACHE II score		31 (8)
SAPS II		58 (17)
Length of ICU stay (days)		19 (14)
Mortality at 28 days		4/20

Mean (SD) or number of patients; ICU, intensive care unit, APACHE= acute physiology and chronic health evaluation; SAPS = simplified acute physiology score.

For comparison of COap with COtptd 267 paired measurements were available. COap ranged from 2.7 to 15.1 L min^{-1} and COtptd ranged from 2.6 to 15.9 L min^{-1}. The measurements related at r^2=0.74 (P<0.001). Bland Altman analysis corrected for repeated measurements showed a bias of -0.02 L min^{-1} and limits of agreement of -2.52 to 2.49 L min^{-1}, with %error of 31% (Figure 1 and Table 3). The precision of the COtptd was 6.7% so that the precision of the COap was 30%. The pooled bias of COtptd - COap related to SVRtptd (r= -0.13, P=0.029, Figure 2). The pooled data per time period (2 hours) since last calibration is shown in Table 4. It shows that COap remains within the clinically acceptable range up to 8 hours after the last calibration. Changes between clinically significant CO measurements (excluding changes <1.2 L min^{-1} [10]) correlated at r^2=0.27. After exclusion 68 measurements remained. From these measurements 46 (68%) were within the 30-330 and 150-210º polar axis (Figure 3).

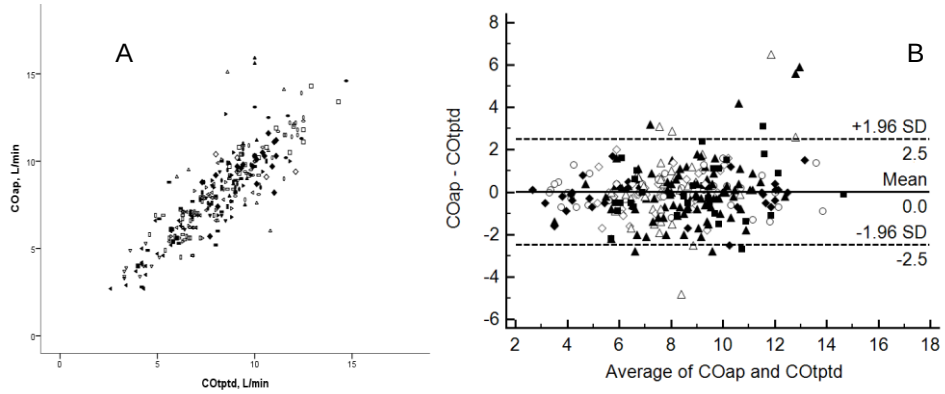
Table 2. Haemodynamic data at study entrance and drugs used during the studied period

N	COtptd	COfv	SVR	GEDI	ITBI	ELWI	HR	MAP	CVP	Drugs
1	12.6	9.4	196	805	1011	17.4	143	35	5	nor, eno
2	5.2	6.3	107	561	692	6.0	99	82	12	nor
3	9.0	4.4	415	920	1159	11.9	80	53	6	nor ,eno
4	9.6	5.2	483	832	1053	7.8	81	69	11	nor, dop, eno
5	11.1	7.0	438	1162	1488	16.4	116	75	14	nor, eno
6	7.7	7.3	636	557	692	7.1	90	71	10	nor, eno, ket
7	9.7	11.9	452	694	875	10.0	91	67	12	nor, eno
8	9.4	5.8	638	768	958	8.8	95	94	19	nor, eno
9	5.1	3.3	1070	978	1240	12.1	116	82	14	nor,eno, ket
10	7.7	4.5	1133	633	785	8.5	106	120	11	nor, eno
11	9.5	9.5	4.6	656	825	9.7	104	62	14	nor, eno
12	10.0	11.3	618	483	598	11.5	105	95	18	nor
13	6.8	6.2	760	1027	1315	18.6	101	91	27	nor, eno, ket
14	5.0	5.2	1124	771	962	18.7	75	90	21	nor, eno
15	7.3	4.9	825	954	1155	11.5	90	87	12	nor, eno, ket, ter
16	8.9	8.7	749	538	658	6.8	109	98	14	nor, eno
17	8.3	9.6	554	834	1057	13.3	109	68	10	nor, dop, eno, ket, ter
18	7.9	6.7	864	1110	1421	18.1	123	99	17	nor, eno
19	9.4	13.1	888	681	850	6.2	100	119	16	nor, eno, ket
20	4.2	5.6	490	494	600	8.8	99	46	20	nor, dop, eno

COtptd = cardiac output transpulmonary thermodilution (L min^{-1}); COfv = cardiac output FloTrac/Vigileo™ system (L min^{-1}); SVRtptd = systemic vascular resistance by transpulmonary thermodilution (dyne•s•cm^{-5}); GEDI = global end diastolic index (mL m^{-2}); ITBI = intra-thoracic blood volume index (ml m^{-2}); ELWI= extra vascular lung water index (mL m^{-2}); HR = heart rate (min^{-1}); MAP = mean arterial pressure (mmHg); CVP = central venous pressure (mmHg); nor = norepinephrine; eno = enoximone; dop = dopamine; ket = ketanserin; ter = terlipressin

For the comparison COfv with COtptd, 301 paired measurements were available (Figure 4 and Table 3). With a precision of 6.7% for COtptd, COfv precision was 47.5%. The SVRtptd inversely correlated to the bias of COtptd-COfv: r= -0.42, P <0.001 (Figure 2). Polar plots of changes in cardiac output by techniques after exclusion of changes of <1.2 L min^{-1} are shown in Figure 3. Sixty-two (77%) of remaining 81 measurement results were within the 30-330º and 150-210º polar axis. Both the correlation and polar plots for CO changes reflect moderate to good trending capabilities during severe sepsis and septic shock.

Figure 1. Calibrated arterial pressure cardiac output vs. transpulmonary thermodilution.



COap = arterial pressure cardiac output (VolumeView/EV1000™); COtptd = cardiac output transpulmonary thermodilution (VolumeView/EV1000™) L min^{-1} ; Panel A: The correlation of cardiac output measurements between COap and COtptd (r=0.86, P<0.001); Panel B: Bland Altman plot bias 0.0, precision 1.3, limits of agreement -2.5 to 2.5 L min^{-1}, %error 31%. Each symbol represents a patient.

Table 3. Overall results of comparisons between COap and COfv with COtptd.

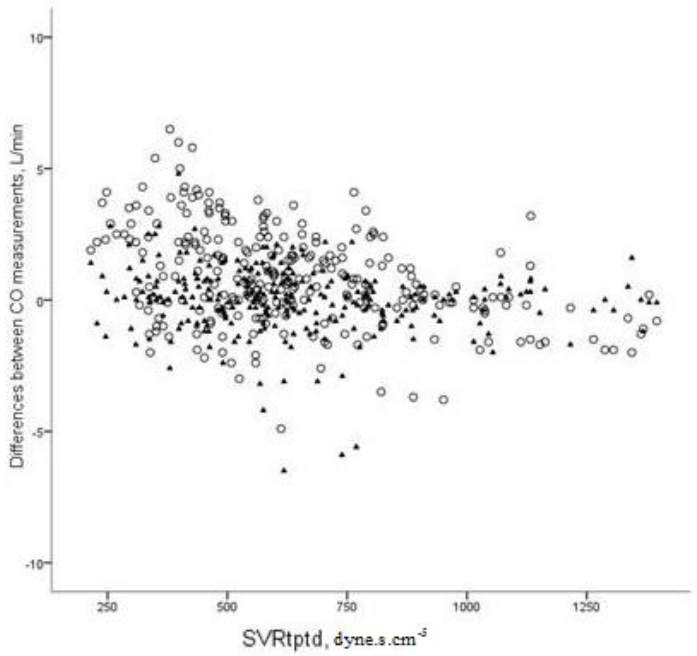
	COap vs. COtptd	**COfv vs. COtptd**
Bias (precision)	-0.0 (1.3)	-0.9 (1.8)
LOA	-2.5 to 2.5	-4.5 to 2.8
%error	31	48
r^2	0.74	0.52
r^2 for changes in cardiac output	0.27	0.41

COap = arterial pressure cardiac output (VolumeView/EV1000™); COfv = cardiac output FloTrac/Vigileo™ system; COtptd = cardiac output transpulmonary thermodilution (VolumeView/EV1000™); Bias = the average of all the differences; precision = standard deviation of the bias; %error = 1.96x standard deviation/mean cardiac output; Bias, precision and limits of agreement (LOA) expressed in L min^{-1}; r^2 = coefficient of determination; r^2 = coefficient of determination of the changes between CO measurements after exclusion of clinically insignificant cardiac output changes (<1.2 L min^{-1} or <15% mean cardiac output).

Discussion

To our knowledge this is the first study on the Volume View/EV1000™ monitor platform in severe sepsis or septic shock patients. Our results show that calibrated arterial pressure wave analysis COap derived from this monitor platform is more accurate than uncalibrated pressure waveform analysis when compared to COtptd. COap remains within the clinically acceptable range (%error <30%)[8] up until 8 hours after calibration. However, the trending capacity of uncalibrated is greater than of calibrated, less invasive CO measurements.

Figure 2. Correlation between differences between cardiac output measurements and systemic vascular resistance.



COtptd = cardiac output transpulmonary thermodilution (VolumeView/EV1000TM); COfv = cardiac output FloTrac/VigileoTM system; COap = arterial pressure cardiac output (VolumeView/EV1000TM); SVRtptd= systemic vascular resistance measured by transpulmonary thermodilution (VolumeView/EV1000TM); open-circle symbols, COtptd-COfv (r=-0.42, P<0.001); closed-triangle symbols, COtptd – COpc (r=-0.13, P=0.029).

Table 4. Time interval since last calibration in relation to bias, precision and %error for both COap and COfv.

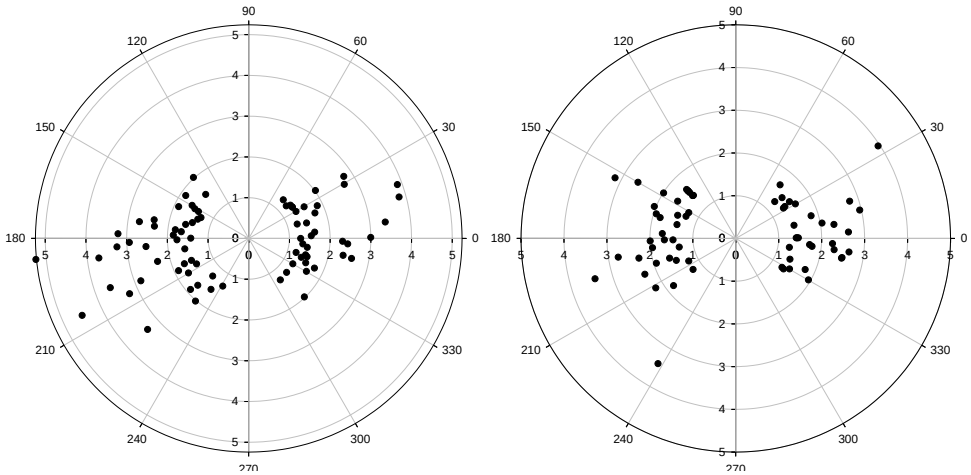
Time interval since last calibration	COap vs COtptd (n=267)					COfv vs COtptd (n=281)				
in hours	n	r^2	P	Bias (SD)	%error	n	r^2	P	Bias (SD)	%error
0-2	40	0.70	<0.001	0.0 (0.9)	21	41	0.46	<0.001	-0.9 (1.9)	45
2-4	107	0.80	<0.001	0.0 (1.12)	27	113	0.59	<0.001	-0.9 (1.8)	47
4-6	76	0.77	<0.001	0.0 (1.2)	29	81	0.49	<0.001	-0.8 (1.8)	46
6-8	20	0.81	<0.001	-0.3 (0.9)	25	20	0.38	<0.004	-0.5 (1.8)	52
8-10	9	0.34	0.098	-0.5 (1.8)	45	10	0.24	0.15	-1.7 (2.1)	56
>10	15	0.49	0.1	0.4 (2.1)	50	16	0.58	0.01	-0.4 (1.8)	44

COap = arterial pressure cardiac output (VolumeView/EV1000TM) (L min^{-1}); COtptd = cardiac output transpulmonary thermodilution (L min^{-1}); COfv = cardiac output FloTrac/Vigileo system (L min^{-1}); n= number of patients; r^2 = coefficient of determination; Bias = the average of all the differences; %error = 1.96x standard deviation (SD)/mean CO.

The Volume View/EV1000TM system has been investigated and validated in an animal model.[11] When this method was compared to tptd using the $PiCCO_2$TM (Pulsion Medical Systems, Munich, Germany) to measure CO in a number of haemodynamic conditions, overall bias was 0.2, precision 0.3 L min^{-1} and %error 7%. Kiefer and

colleagues[4] reproduced the previous validation study in critically ill patients (n=72) comparing tptd CO. Bias was 0.2 L min^{-1}, limits of agreement were 0.45 to 0.82 L min^{-1} and %error was 9.7%. Both studies confirm interchange ability between the two tptd measuring devices.

Figure 3. Polar plot representing the changes in cardiac output after exclusion clinically insignificant changes.



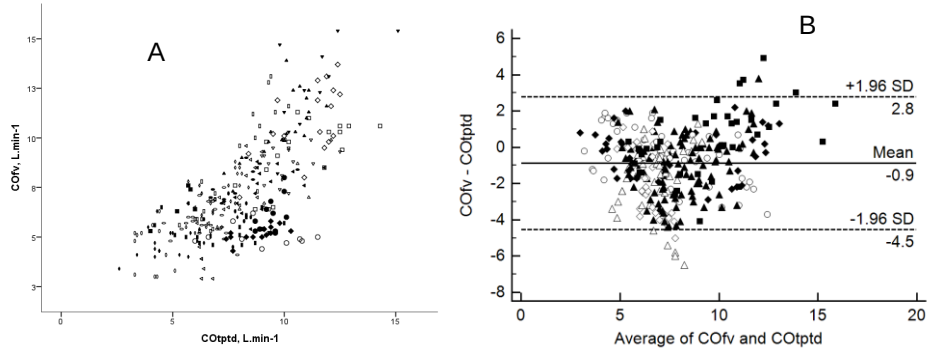
Panel A, COtptd and COfv

Panel B, COtptd and COap.

Cardiac measurements derived by COtptd, COfv and COap. COtptd = cardiac output transpulmonary thermodilution (VolumeView/EV1000™); COfv = cardiac output FloTrac/Vigileo™ system; COap = arterial pressure cardiac output (VolumeView/EV1000™). After exclusion of clinically insignificant cardiac output changes (<1.2 L min^{-1} or 15% of mean cardiac output). The distance from the center of the plot (vector) represents the mean change in cardiac output. The angle with horizontal (0° radial) axis represents disagreement.

Comparing calibrated COap with COtptd in severe sepsis and septic shock reveals a %error of 31% almost reaching the Critchley and Critchley criteria for interchange ability of 30%.[8] As we focused on the time since the last recalibration, our data suggest that COap this criterion up until the first 8 hours after calibration. Our results are comparable to those obtained by Bendjelid and colleagues[1] who compared the pressure waveform analysis CO measured by the EV1000™ with the pulse contour CO by PiCCO$_2$™ in 72 critically ill patients. Both methods used tptd to calibrate the COap and were used as gold standard for comparative purposes. The Volume View/EV1000™ arterial pressure waveform analysis compared to COtptd showed a bias of -0.1, limits of agreement of 2 L min^{-1} and %error of 29%. However, the clinical conditions were very heterogeneous: less than 10% of patients were septic.[1] More than 50% underwent cardiac surgery and measurements of CO were performed under all modes of ventilator support.

Figure 4. Uncalibrated arterial pressure cardiac output vs. transpulmonary thermodilution.



COfv = cardiac output FloTrac/Vigileo™ system (L min^{-1}); COtptd = cardiac output transpulmonary thermodilution (VolumeView/EV1000™) L min^{-1} ; Panel A: The correlation of cardiac output measurements between COfv and COtptd (r=0.72, P<0.001); Panel B: Bland Altman plot bias -0.9, precision 1.8, limits of agreement -4.5 to 2.8 L min^{-1}, %error 48%. Each symbol represents a patient.

Critchley and Critchley have shown that the %error between two CO measurement methods consists of the precision of both the reference and the new method. [7] [8] Knowing the precision of the reference method thus gives the precision of new CO monitoring device. The coefficient of variation (precision) of the tptd was low (6.7%) as reported in the literature.[12] [13] The precision of the COap and COfv were thus relatively high, at 31 and 47.5%, respectively. Recently the Critchley criteria have been challenged as more non-invasive CO measuring devices clinically used do not meet the 30 %error, commonly regarded as acceptable.[14]

Indeed, the FloTrac/Vigileo™ has proven accuracy in stable haemodynamic conditions[15-18], but not in severe sepsis or septic shock[2] [10] [19-21] and liver surgery.[22-27] Our results are in line with the data in the literature. Large limits of agreement and a high precision and %error of the COfv, also in time, do not render the technique interchangeable with COtptd in patients suffering from sepsis and septic shock. As discussed previously[2], the SVR is an important factor influencing bias and precision and the COfv falls short at low SVR.

Changes in CO induced by intensive care therapy are suggested indeed to be of more clinical importance than absolute values[9], even though the definition of clinically significant changes is controversial.[3] [9] [10] The VolumeView/EV1000™ monitor platform combines tptd and pressure waveform analysis into COap and this gives a more robust CO measurement as shown in our study, even though this combination

seems to have a negative effect on the trending capabilities of the system compared to the uncalibrated version. This can be explained by greater changes in COfv than in COap upon changes in vascular tone associated with CO changes.[28] A concordance of measurements of 90% supposedly indicating clinically adequate tracking capability[9] was not reached for both measuring devices, however, in agreement with the literature.[2 10 19]

Hence, most less invasive methods attempting to integrate vascular tonus and arterial compliance to calculate CO[5 29 30] fall short, when uncalibrated, in septic patients with large changes in vascular properties.[2 19 22-24] Indeed, our results are in line with those obtained by Jellema and colleagues[30] who compared the Modelflow™ method for arterial pressure-derived CO estimation with bolus thermodilution in sepsis patients. They found that uncalibrated measurements were less accurate (%error 55%) compared to calibrated measurements (%error 18%) and concluded that initial calibration of the Modelflow™ method was needed especially during hyperdynamic haemodynamics. A single calibration of the model appeared sufficient to monitor continuous CO up until 48 hour, however. Gödje and co-workers[31] compared the reliability of the old PiCCO algorithm with the recent algorithm and concluded that the reliability of the pulse contour was good even up to 44 hours after calibration, however if the Critchley criteria were met is unclear as no %error was reported.

Hamzaoui et al.[12] investigated the accuracy of $PiCCO_2$ pulse contour method (Pulsion Medical Systems, Munich, Germany) during the course of critically ill patients, most of them suffering from sepsis or septic shock. One hour after calibration the %error increased above 30% and therefore early recalibration was recommended. Jellema et al. [30] and Godje and colleagues[31] conclude that continues CO remains reliable up to 44 hours after initial calibration even during sepsis conditions. Hamzaoui[12] and our data suggest a shorter time period, which corresponds more with clinical practise

Limitations of our study include its single centre and observational nature. However, all the data were prospectively collected during the clinical course of our patients suffering from sepsis or septic shock with organ failure. Hence, extrapolation of results to other conditions is unrealistic. The issue of repeated measurements has been taken into account as much as possible.

Conclusion

The recently introduced calibrated arterial pressure waveform analysis-derived COap is more accurate and less dependent on vascular tone compared to the uncalibrated COfv in monitoring CO in patients with severe sepsis and septic shock, up to 8 hours after calibration. The tracking capacity of COap is moderate and less than of COfv, however.

References

1. Bendjelid K, Marx G, Kiefer N, et al. Performance of a new pulse contour method for continuous cardiac output monitoring: validation in critically ill patients. *Br J Anaesth* 2013; published before print.
2. Slagt C, de Leeuw MA, Beute J, et al. Cardiac output measured by uncalibrated arterial pressure waveform analysis by recently released software version 3.02 versus thermodilution in septic shock. *J Clin Monit Comput* 2013;27:171-177.
3. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10.
4 Kiefer N, Hofer CK, Marx G, et al. Clinical validation of a new thermodilution system for the assessment of cardiac output and volumetric parameters. *Crit Care* 2012;16:R98.
5. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403–411.
6. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J Appl Physiol* 2011;111:853-60.
7. Cecconi M, Rhodes A, Poloniecki J, et al. Bench-to-bedside review: The importance of the precision of the reference technique in method comparison studies - with specific reference to the measurement of cardiac output. *Crit Care* 2009;13:201.
8. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15: 85-91.
9. Critchley LA, Yang XX, Lee A; Assessment of trending ability of cardiac output monitors by polar plot methodology. *J Cardiothorac Vasc Anesth* 2011; 25:536-546.
10. Monnet X, Anguel N, Naudin B, et al. Arterial pressure based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010;14:R109.
11. Bendjelid K, Giraud R, Sigenthaler N, et al. Validation of a new transpulmonary thermodilution system to assess global end-diastolic volume and extravascular lung water. *Crit Care* 2010;14:R209.
12. Hamzaoui O, Monnet X, Richard C, et al. Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. *Crit Care Med* 2008;36:434-40.
13. Holm C, Mayr M, Hörbrand F, et al. Reproducibility of transpulmonary thermodilution measurements in patients with burn shock and hypothermia. *J Burn Care Rehabil* 2005;26:260-5.
14. Peyton PJ, Chong SW. Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. *Anesthesiology* 2010;113:1220-35.
15. Mutoh T, Ishikawa T, Kobayashi S, et al. Performance of third-generation FloTrac/Vigileo system during hyperdynamic therapy for delayed cerebral ischemia after subarachnoid hemorrhage. *Surg Neurol Int* 2012;3:99.
16. Jo YY, Song JW, Yoo YC, et al. The uncalibrated pulse contour cardiac output during off-pump coronary bypass surgery: performance in patients with a low cardiac output status and a reduced left ventricular function. *Kor J Anesthesiol* 2011;60:237-243.
17. Vasdev S, Chauhan S, Choudhury M, et al. Arterial pressure waveform derived cardiac output FloTrac/Vigileo system (third generation software: comparison of two monitoring sites with the thermodilution cardiac output. *J Clin Monit Comput* 2012;26:115-120.
18. Broch O, Renner J, Gruenewald M, et al. A comparison of third-generation semi-invasive arterial waveform analysis with thermodilution in patients undergoing coronary surgery. *Scientific World Journal 2012;2012:45108*119.
19. Monnet X, Anguel N, Jozwiak M, et al. Third-generation FloTrac/Vigileo does not reliably track changes in cardiac output induced by norepinephrine in critically ill patients. *Br J Anaesth* 2012;108:615-622.
20. Sakka SG, Kozieras J, Thuemer O, et al. Measurement of cardiac output: a .comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007;99:337-342.
21. Slagt C, Beute J, Hoeksema M, et al. Cardiac output derived from arterial pressure waveform analysis without calibration versus thermodilution in septic shock: evolving accuracy of software versions. *Eur J Anaesthesiol* 2010;27:550-554.

22. Biais M, Nouette-Gaulain K, Cottenceau V, et al. Cardiac output measurement in patients undergoing liver transplantation: pulmonary artery catheter versus uncalibrated arterial pressure waveform analysis. *Anesth Analg* 2008;106:1480-1486.
23. Della Rocca G, Costa MG, Chiarandini P, et al. Arterial pulse cardiac output agreement with thermodilution in patients in hyperdynamic conditions. *J Cardiothorac Vasc Anesth* 2008;22:681-687.
24. Krejci V, Vannucci A, Abbas A, et al. Comparison of calibrated and uncalibrated arterial pressure-based cardiac output monitors during orthotopic liver transplantation. *Liver Transpl* 2010;16:773-782.
25. Akiyoshi K, Kandabashi T, Kaji J, et al. Accuracy of arterial pressure waveform analysis for cardiac output measurement in comparison with thermodilution methods in patients undergoing living donor liver transplantation. *J Anesth* 2011;25:178-183.
26. Biancofiore G, Critchley LA, Lee A, et al. Evaluation of a new software version of the FloTrac/Vigileo (version 3.02) and a comparison with previous data in cirrhotic patients undergoing liver transplant surgery. *Anesth Analg* 2011;113:515-522.
27. Su BC, Tsai YF, Chen CY, et al. Cardiac output derived from arterial pressure waveform analysis in patients undergoing liver transplantation: validity of a third-generation device. *Transplant Proc* 2012;4:424-428.
28 Lorsomradee S, Lorsomradee SR, Cromheecke S, et al. Continuous cardiac output measurement: arterial pressure analysis versus thermodilution technique during cardiac surgery with cardiopulmonary bypass. *Anaesthesia* 2007;62:979-983.
29. Wesseling KH, Jansen JR, Settels JJ, et al. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993;74:2566-73.
30. Jellema WT, Wesseling KH, Groeneveld AB, et al. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* 1999;90:1317-28.
31. Gödje O, Höke K, Goetz AE, et al. Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. *Crit Care Med* 2002;30:52-8

7

A systematic review of uncalibrated arterial pressure waveform analysis to determine cardiac output and stroke volume variation

Slagt C, Malagon I, Groeneveld ABJ.

Accepted for publication by Br J Anesth.

Abstract

Background and objective

The FloTrac/Vigileo™, introduced in 2005, uses arterial pressure waveform analysis to calculate cardiac output and stroke volume variation (SVV) without external calibration. The aim of this systematic review is to evaluate the performance of the system.

Methods

Sixty-five full manuscripts on validation of cardiac output measurements in humans, published in English until, were retrieved, including 2,234 patients and 44,592 observations. Results have been analysed according to underlying patient conditions, i.e. general critical illness and surgery as normodynamic conditions, cardiac and (post) cardiac surgery as hypodynamic conditions and liver surgery and sepsis as hyperdynamic conditions, and subsequently released software versions. Eight studies compared SVV to other dynamic indices (n=291 patients, n=935 data).

Results

Cardiac output, bias, precision, %error, correlation and concordance differed among underlying conditions, subsequent software versions and their interactions, suggesting increasing accuracy and precision, particularly in hypo- and normodynamic conditions. The bias and the trending capacity remain dependent on (changes in) vascular tone with most recent software. The SVV only moderately agreed with other dynamic indices, although it was helpful in predicting fluid responsiveness in 85% of studies addressing this.

Conclusions

Since its introduction, the performance of uncalibrated FloTrac/Vigileo™ has improved particularly in hypo– and normodynamic conditions. A %error at or below 30% with most recent software allows sufficiently accurate and precise cardiac output measurements and trending for routine clinical use in normo- and hypodynamic conditions, in the absence of large changes in vascular tone. The SVV may usefully supplement these measurements.

Introduction

The use of the peripheral arterial waveform to calculate stroke volume (SV) stems from 1904.[1] Although pulse pressure (PP) directly relates to SV, arterial compliance and tone shape the arterial waveform and thus affect the SVcalculation from PP. The majority of cardiac output (CO) measurement devices utilising the arterial pressure waveform need external calibration to establish the relation between PP and SV by taking arterial compliance and tone into account in individual patients and (stages of) diseases. In 2005 the FloTrac/Vigileo™ system (Edwards LifeSciences, Irvine, CA, USA) has been introduced.[2,3] This technique allegedly does not require external calibration and uses the arterial pressure signal obtained by a standard peripheral arterial catheter to calculate SV (and thus SV variations, SVV) and thereby CO. The mean, standard deviation, skewness and kurtosis of arterial pressure, and arterial compliance derived from Langewouters using sex, age, weight and height,[4] are used for that purpose with help of an undisclosed algorithm. The use of the arterial waveform to calculate SV (variations) places high demands on the quality of the signal.[5] The presence of sinus rhythm and the absence of rhythm disturbances reduces the chances of error in the measurements.[3 6-10] Moreover, the relation between PP and SV becomes less fixed in pathophysiological conditions like liver disease, liver surgery or septic shock associated with hyperdynamic and vasodilated states. Normally PP increases down the arterial tree, but in the latter conditions the PP decreases down the arterial tree leading to an underestimation of SV. This may thus affect FloTrac/Vigileo™ readings.

Software versions subsequently released in order to allegedly, yet unproven, improve performance and applicability include first generation (1.01, 1.03), second generation (1.07, 1.10, 1.14) and the most recent third generation version 3.02 . In the 1.03 software version the internal calibration window was 10 min. In the 1.07 software version the window was changed to 1 minute. In the 1.10 version, the algorithm was improved to better account for hypertension, tachycardia and volume loading. The 1.14 version was only an update of the display. The third generation version includes 2 models for arterial tone: (1) a model that was developed predominantly from patients in normo- and hypodynamic conditions (as in the previous version 1.10) and (2) a model that was developed predominantly from patients in hyperdynamic conditions.[11] The switching between the 2 models is based on an algorithm that uses 14 parameters of the arterial pressure waveform to detect the occurrence of hyperdynamic conditions.

We hypothesised that the performance of the FloTrac/Vigileo™ to measure CO depends on underlying condition and haemodynamic profile, and on the software version applied. This systematic review summarises data from clinical studies, analysed to define

the current performance of the system in clinical practice and to explore future areas for improvement, as attempted before using 16 early studies.[12] We will systematically review the performance according to commonly used criteria for CO and SVV measurements but will only summarise the findings on use of the system in therapeutic settings in a narrative way.

Methods

A PubMed literature search on the FloTrac/Vigileo™ system using the headings FloTrac and uncalibrated waveform analysis was performed on the use of the system until May 1 2013. In total 139 full manuscripts were found. We excluded animal experimental studies (n=20), non English publications (n=16), non original manuscripts (n=8) and the papers from the German group which have been retracted (n=3). All references of these articles were searched for additional FloTrac™ articles which yielded an extra 23 manuscripts. One hundred and fifteen manuscripts were included in this review. In 65 papers CO was compared to a reference standard. The following values were documented: type of patients, underlying clinical condition, software version involved, the mean CO, bias, precision (standard deviation of the bias), percentage (%) error (95% limits of agreement or 2x standard deviation, divided by the mean, according to Bland-Altman plots), correlation and concordance with the reference technique if available. The latter is defined by the similarity of direction (in %) or correlation of changes in FloTrac/Vigileo™ and reference method-derived CO. The correlation coefficients are given as coefficients of determination r^2. The CO was calculated using a body surface area of 1.73 m^2 when only cardiac index was given. Bias and precision are expressed in L min^{-1} in order to facilitate comparison among studies. We have also recalculated other variables, when appropriate and possible from the available data, to standardise the format of reporting. In many studies, horizontal lines in Bland-Altman plots were drawn for reporting bias, precision and %error (or 95% limits of agreement) and we extrapolated numbers from these plots if unavailable in the text. Bias was always expressed (or converted if necessary) as the difference between the FloTrac/Vigileo™ and the reference method, so that a negative number indicates underestimation. A 30% error is generally considered acceptable, depending on the error of the reference technique, taken from its reproducibility if solely available.[13] The age and number of patients and paired data were recorded. We did a similar analysis for SVV as far as data were available (n=8 studies). The quality of the validation studies were rated according to Cecconi and colleagues[14] using the following criteria: the reference technique should be as accurate and precise as possible for instance by pulmonary or transpulmonary thermodilution; the precision of the reference technique should be measured within the study; the desired precision of the Flotrac/Vigileo™ technique should be described a

priori or thoroughly analysed in the discussion; the bias and limits of agreement between the two techniques should be quoted, and the precision of the new tested technique should be calculated. We evaluated comparisons of radial and other artery pressure-derived CO and evaluated therapeutic studies utilising the system.

Statistical analysis

We evaluated the factors that may affect system performance of measuring CO. The range of observations and lumping of haemodynamic conditions may confound bias, precision and %error.[12] [15-18] We therefore evaluated conditions separately and divided patients into three groups accordingly: a group of general critically ill patients including general critically ill or (post)surgical patients with presumably normodynamic conditions, a group of cardiac and (post) cardiac surgery patients with presumably hypodynamic conditions and a group on patients with liver disease (surgery) or sepsis with hyperdynamic conditions in order to evaluate differences among patient categories and associated haemodynamic states. If data had been obtained in general critically ill patients and the number of patients with sepsis exceeded 50%, we included the respective study in the sepsis category. We constructed tables with relevant variables from the studies and summarised key variables, weighted for patients or data number, by mean and 95% confidence intervals for the 3 software generations involved. For concordance only r^2 was summarised and evaluated. The Kolmogorov-Smirnov test showed that variables were normally distributed ($P>0.05$). Generalised estimating equations (GEE)[19] were used to estimate the effect of underlying condition and software version and their first order interaction on study variables taking repeated measurements into account and adjusted for patient and data numbers. A $P<0.05$ was considered statistically significant and exact numbers are given if >0.001.

Results

A total of 65 CO validation studies involved 2,234 patients and 44,592 data points. Results are shown in Tables 1-3. For hypo- and normodynamic conditions, only few data for concordance with third generation software is available. Adjusted for repeated measurements, patient and data number, the CO, bias, precision, %error, correlation and concordance with the reference standard differed among underlying conditions, software versions and their interactions, except for %error which did not differ among underlying conditions (Table 4). CO was thus low in cardiac (surgery) patients, intermediate in general critically ill and surgical patients and relatively high in patients with sepsis or liver disease as expected. The system performed better, considering bias, precision, %error, correlation and concordance in hypo- and normodynamic than in hyperdynamic

Table 1. Validation studies for FloTrac/Vigileo™ cardiac output performed in general critically ill and (post)surgical patients (n=16), grouped according to year of publication and name of first author.

Author	Year	Version	Patient type	Age, years	Ref. method	Mean CO, L min^{-1}	CO range L min^{-1}	Bias, L min^{-1}	Precision, L min^{-1}	%error	r^2	Concordance, r^2 or %	Patients	Data	CS
McGee§ [15]	2007	1.03	ICU	24-84	ITD	5.4 (1.7)	1.7-9.2	0.20	1.28	43	na	59	84	561	4
Prasser§ [16]	2007	1.03	ICU	55 (19)	ITD	5.9 (1.2)	2.8-10.8	-0.02	1.46	49	0.34	0.21	20	164	2
Compton§ [8]	2008	1.10	ICU	29-83	TPTD/PC	5.7		-1.18	1.68	59	na	na	25	324	2
					TPTD	5.8		-1.31	1.51	52	na	na	25	90	2
Biais** [17]	2009	1.14	ICU, 2 interventions	53 (9)	Echo	6.2		-0.04	0.73	24	na	0.67	30	120	1
Chatti**§ [18]	2009	1.03	OR/ICU	19-92	OD	6.6		-0.08	3.00	103	0.01	0.08	29	207	1
		1.07	OR/ICU		OD	6.6		-0.32	1.70	58	0.23	0.19	31	240	1
Concha [30]	2009	1.07	OR, 7 time points	59 (12)	Echo	4.8 (1.1)	2.9-8.5	-1.17	1.60	40	na	na	10	88	1
Mutoh* [31]	2009	1.14	OR/ICU,	65 (10)	TPTD	5.0 (1.4)	2.2-8.7	-0.99	0.77	25	0.67	na	16	179	5
			7 time points		PC	5.0 (1.4)		-0.93	0.80	27	0.63	na	16	179	5
Cecconi§ [32]	2010	1.03	ICU, 7 time points	61 (15)	ITD	6.7	3.0-14.6	-1.10	1.85	55	0.61	na	29	203	5
Junttila§ [28]	2011	1.10/1.14	ICU	54 (13)	ITD	6.0 (1.7		-1.50	1.95	58	na	na	16	407	2
Kotake [27]	2011	1.10	OR, 5 time points	76 (6)	Echo	4.6		0.35	1.42	69	na	na	20	100	0
Metzelder [25]	2011	1.10	ICU, 7 time points	24-57	TPTD	7.9 (1.7)	4.1-13.7	-0.87	1.14	30	0.52	0.07	10	68	5
		3.02	ICU, 7 time points		TPTD	7.4 (1.8)		-0.95	1.04	28	0.58	0.07	14	90	5
Saraceni [33]	2011	1.07	ICU	59 (16)	ITD	6.5 (1.4)		0.19	2.50	77	0.40	na	15	96	2
		1.10	ICU		ITD	6.5 (1.4)		0.97	1.83	56	0.32	na	6	45	2
Kusaka [34]	2012	3.02	OR, 8 time points	71 (8)	Echo	4.3 (0.8)		-0.12	0.89	41	0.31	na	20	160	1
Murthi§ [35]	2012	na	ICU	61 (20)	Echo	5.8 (1.9)		-0.22	1.09	39	0.40	na	78	78	1
Mutoh [36]	2012	3.02	ICU	67 (10)	TPTD	5.9 (0.9)		-0.57	0.45	15	0.77	na	20	95	2
Grensemann [29]	2013	1.07	ICU	51 (14)	TPTD	5.4 (1.2)		-0.52	1.38	48	na	73	16	32	3
Total													530	3526	

Author	Year	Version	Patient type	Age, years	Ref. method	Mean CO, L min^{-1}	CO range L min^{-1}	Bias, L min^{-1}	Precision, L min^{-1}	%error	r^2	Concordance, r^2 or %	Patients	Data CS
Weighted average for first generation software														
Patients						5.9		-0.11	1.71	57	0.32	0.13		3.4
95% confidence interval						(5.8-6.0)		(-0.18- -0.04)	(1.61-1.81)	(53-60)	(0.26-0.38)	(0.11-0.15)		(3.2-3.6)
Data						5.9		-0.12	1.72	57	0.32	0.14		3.3
95% confidence interval						(5.9-6.0)		(-0.14- -0.09)	(1.68-1.76)	(56-58)	(0.29-0.34)	(0.13-0.14)		(3.3-3.4)
Weighted average for second generation														
Patients						5.8		-0.60	1.43	48	0.44	0.38		2.1
95% confidence interval						(5.7-5.9)		(-0.68- -0.52)	(1.37-1.49)	(46-50)	(0.40-0.47)	(0.32-0.44)		(1.9-2.3)
Data						5.8		-0.82	1.51	50	0.47	0.30		2.3
95% confidence interval						(5.8-5.8)		(-0.85- -0.79)	(1.49-1.53)	(49-50)	(0.45-0.48)	(0.28-0.33)		(2.3-2.4)
Weighted average for third generation														
Patients						5.7		-0.50	0.77	28	0.55	0.07 (n=1)		2.4
95% confidence interval						(5.4-6.0)		(-0.59--0.41)	(0.70-0.83)	(25-31)	(0.50-0.60)			(2.0-2.8)
Data						5.6		-0.46	0.81	30	0.51	0.07 (n=1)		2.3
95% confidence interval						(5.4-5.7)		(-0.50- -0.42)	(0.78-0.83)	(29-32)	(0.49-0.53)			(2.1-2.5)

Abbreviations: A body surface area of 1.73 m^2 was used to convert data from cardiac index to CO (*), if appropriate; **CO calculated from reported stroke volume; §Financial industry sponsorship; Age expressed as mean (standard deviation) in years or range, where appropriate; Ref = reference; CO = cardiac output, mean values (standard deviation) for FloTrac/Vigileo™ if available, otherwise for combination with reference method; CO range = measured by FloTrac/Vigileo™ or reference standard; r^2 = coefficient of determination; CS = Cecconi score (see text); OR = operating room; ICU = intensive care unit; ITD = intermittent thermodilution; CCO = continuous cardiac output; OD = oesophageal Doppler; TPTD = transpulmonary thermodilution; PC = pulse contour; na = not available.

Table 2. Validation studies for FloTrac/Vigileo™ cardiac output performed in cardiac and (post)cardiac surgery patients (n=30), grouped according to year of publication and name of first author.

Author	Year	Version	Patient type	Age, years	Ref. method	Mean CO, L min^{-1}	CO range, L min^{-1}	Bias, L min^{-1}	Precision, L min^{-1}	%error	r^2	Concordance, r^2 or %	Patients	Data	CS
Opdam* [38]	2006	1.03	ICU	64 (11)	ITD	5.5		0.01	1.04	38	0.27	na	6	218	2
					CCO	4.6		-0.42	0.84	37	0.06	na	6	218	2
Sander [20]	2006	1.03	OR/ICU, 4 time points	67 (8)	ITD	4.9 (1.2)		-0.60	1.40	54	0.28	0.30	30	108	2
Breukers [6]	2007	1.07	ICU, 3 time points	72 (9)	ITD	5.5 (1.2)	2.8-8.8	-0.14	1.00	36	0.55	0.52	20	56	4
Button §[44]	2007	1.07	OR/ICU, 6 time points	46-85	ITD	5.2 (1.0)	2.4-7.5	0.25	1.13	4	na	na	31	186	2
Cannesson [45]	2007	1.07	OR/ICU, 21 time points	69 (7)	ITD	4.7 (0.9)	1.9-8.2	0.26	0.87	37	0.44	0.41	11	166	2
Chakravarthy* [46]	2007	na	OR/ICU	na	ITD	3.0	1.0-6.9	0.15	0.33	22	0.24	86	15	438	2
de Waal [39]	2007	1.07	OR/ICU, 9 time points	66 (8)	TPTD	5.2 (0.9)		0	0.87	33	0.56	na	22	184	3
					TPTD/PC			0.01	1.08	40	0.36	na	22	184	3
Lorsomradee [5]	2007	1.01	OR	47-82	CCO	5.1		-0.12	1.68	66	na	na	36	900	2
Lorsomradee [37]	2007	1.07	OR, CABG, 4 time points	67 (10)	CCO	4.9 (0.8)		-0.09	1.29	53	0.07	na	20	550	2
			AS after CPB	70 (10)	CCO	5.0 (0.9)		0.05	0.72	29	na	na	10	315	2
			AI after CPB	65 (14)	CCO	5.2 (0.9)		-0.10	0.86	33	na	na	10	305	2
Manecke [47]	2007	1.03	ICU, 2 measurement sites	61 (14)	ITD	5.1	2.-9.6	0.55	0.98	38	na	na	50	295	2
					CCO	5.1		0.06	1.06	42	na	na	50	295	2
Mehta [43]	2008	1.07	OR, 8 time points	58 (8)	ITD	4.7 (0.8)		-0.26	0.66	29	na	na	12	96	3
Staier [21]	2008	1.07	OR, 4 time points	45-81	ITD	4.6 (0.9)		0.02	1.01	44	na	na	30	120	4
Zimmerman [48]	2008	1.01	OR/ICU, 7 time points	51-80	ITD	6.0	2.1-10.6	-0.13	1.53	51	0.31	na	30	192	3
Chakravarthy* [49]	2009	na	OR/ICU	59 (5)	CCO	4.3	2.8-6.2	0.03	0.71	33	na	na	20	140	2
					IP	4.3		0.31	0.88	41	na	na	20	140	2
de Wilde [23]	2009	1.07	ICU, 4 interventions	55-82	ITD	5.3		0.33	0.90	34	na	81	13	104	2

Author	Year	Version	Patient type	Age, years	Ref. method	Mean CO, L min^{-1}	CO range, L min^{-1}	Bias, L min^{-1}	Precision, L min^{-1}	%error	r^2	Concordance, r^2 or %	Patients	Data	CS
Eleftheriadis§ [50]	2009	1.14	OR, 7 time points	62 (10)	ITD	5.0		0.40	0.85	34	0.26	na	16	112	2
Marqué§ [40]	2009	1.01	ICU	63 (10)	CCO	5.0 (1.1)	2.1-12.8	-0.01	0.81	32	0.48	na	29	12,099	2
Østergaard [22]	2009	1.03	OR	44-76	ITD	4.4	2.9-6	0.51	0.93	48	na	na	25	25	5
Senn§ [9]	2009	1.03	ICU, 4 time points and 2 interventions	65 (11)	ITD	5.5 (0.9)		-0.06	1.01	37	na	100	25	100	2
		1.07	ICU	67 (8)	ITD	5.2 (1.3)		-0.30	0.55	22	na	100	25	100	2
Hadian [51]	2010	na	ICU	73 (9)	ITD	6.9 (1.5)		0.43	1.68	59	na	0.08	10	36	2
					CCO	4.8 (1.7)		0.05	1.30	42	na	na	7	19	2
					TPTD/PC	6.1 (1.9)		0.67	1.72	61	na	0.11	15	55	2
					LiDCO/PC	6.1 (1.9)		0.63	1.49	53	na	0.23	15	55	2
Hamm [52]	2010	1.07	OR/ICU	69 (9)	ITD	4.4 (0.6)		-0.09	1.18	48	0.14	na	9	6,492	3
					CCO	4.4 (0.6)		-0.10	1.13	46	0.14	na	9	6,492	3
Hofer§ [53]	2010	1.07	OR/ICU, 6 time points and 2 measurement sites	67 (10)	ITD	5.3 (1.5)	2.4-9.1	0.20	1.00	38	na	na	26	156	2
					TPTD/PC	5.3 (1.5)		0.20	1.13	42	na	na	26	156	2
Jeong [54]	2010	1.10	OR, 9 time points	61 (8)	CCO	4.1 (1.1)	1.2-7.4	0.23	1.14	57	0.08	na	28	234	2
Schramm [55]	2010	1.07	OR, 4 time points, 2 measurement sites	64 (14)	ITD	4.9		-0.12	1.84	72	na	na	20	78	2
Vetrugno [41]	2010	1.10	OR/ICU, 8 time points	70 (9)	ITD	4.9 (0.8)	2.8-7.2	0.50	0.86	37	na	0.49	15	360	2
					CCO	5.0 (0.8)	2.8-8.2	0.06	0.92	8	na	0.53	15	360	2
Haenggi [56]	2011	1.07	ICU, 2 time points	68 (12)	CCO	6.1 (2.6)		-0.50	0.66	29	na	53	8	55	2
Jo [42]	2011	1.07	OR 5 time points	47-77	CCO	4.5 (0.7)		-0.12	0.58	7	na	na	50	250	2
Teng [24]	2011	na	ICU	0.75-16	ITD	7.2		0.70	3.48	131	na	na	31	136	2
Broch [57]	2012	3.02	OR, pre CBP	63 (5)	TPTD	4.5 (1.0)		0.01	0.62	28	0.67	0.60	50	468	2
Vasdev [58]	2012	3.02	OR 9 time points 2 measurement sites	58 (9)	ITD	5.1		-0.05	0.53	21	na	na	38	342	5
Total													956	33,408	

Continued

Author	Year	Version	Patient type	Ref. method	Mean CO, L min^{-1}	CO range L min^{-1}	Bias, L min^{-1}	Precision, L min^{-1}	%error	r^2	Concordance, r^2 or %	Patients	Data	CS
Weighted average for first generation software														
Patients					5.1		0.04	1.16	45	0.33	0.30 (n=1)			2.4
95% confidence interval					(5.1-5.2)		(0.00-0.08)	(1.13-1.20)	(44-47)	(0.31-0.35)				(2.3-2.5)
Data					5.0		-0.01	0.89	35	0.47	0.30 (n=1)			2.0
95% confidence interval					(5.0-5.0)		(-0.02--0.01)	(0.89-0.90)	(35-35)	(0.46-0.47)				(2.0-2.0)
Weighted average for second generation														
Patients					4.9		0.04	0.96	39	0.29	0.50			2.4
95% confidence interval					(4.9-5.0)		(0.02-0.06)	(0.94-0.99)	(38-40)	(0.26-0.33)	(0.48-0.51)			(2.3-2.5)
Data					4.5		-0.05	1.11	45	0.15	0.49			2.8
95% confidence interval					(4.5-4.5)		(-0.06--0.05)	(1.10-1.11)	(45-45)	(0.15-0.15)	(0.49-0.50)			(2.8-2.8)
Weighted average for third generation														
Patients					4.7		-0.02	0.58	25	0.67 (n=1)	0.60 (n=1)			3.3
95% confidence interval					(4.6-4.8)		(-0.02--0.01)	(0.57-0.59)	(24-26)					(3.0-3.6)
Data					4.7		-0.01	0.58	25	0.67 (n=1)	0.60 (n=1)			3.2
95% confidence interval					(4.7-4.7)		(-0.01--0.01)	(0.58-0.59)	(25-25)					(3.1-3.3)

Abbreviations: A body surface area of 1.73 was used to convert data from cardiac index to CO (*), if appropriate; Financial industry sponsorship§; Age expressed as mean (standard deviation) in years or range, where appropriate; Ref. method = reference method; CO = cardiac output; mean values (standard deviation) for FloTrac/Vigileo™ if available otherwise for combination with reference method; CO range = measured by FloTrac/Vigileo™ or reference method; r^2 = coefficient of determination; CS = Cecconi score (see text); ITD = intermittent thermodilution; CCO = continuous cardiac output; TPTD = transpulmonary thermodilution cardiac output; IP = impedance plethysmography; PC = pulse contour cardiac output; LiDCO = lithium dilution cardiac output; ICU = intensive care unit; OR = operating room; CABG = coronary artery bypass grafting; AS/ AI = aortic stenosis/insufficiency; CPB = cardiopulmonary bypass; na = not available.

conditions, even though performance increased with software updates. However, the latest software version most improved performance in hypo- and normodynamic conditions and decreased the %error to 30% or lower. Some studies reported the coefficient of variation for the reference method, ranging between 5-18% for intermittent thermodilution,[6 15 20-24] and 2.4-6.8% for transpulmonary thermodilution.[7 25 26] The Cecconi score[14] increased with increasing software version. For comparison of SVV comparison with other dynamic indices, 8 studies (n=291 patients and n=935 data) were available (Table 5) but evaluation of effect of patient and software types was not considered meaningful because of paucity of data. The Table shows moderate agreement of FloTrac/Vigileo™ SVV with other dynamic indices.

Discussion

The last eight years have witnessed an exponential increase of clinical research on the application of the FloTrac/Vigileo™ system and this systematic review was intended to identify areas for routine clinical use and for future development. Our analysis is useful, even though older software will not be used anymore, by displaying the capability to improve the performance of this less invasive CO measurement technique. Indeed, the accuracy and precision of the FloTrac/Vigileo™ system can be regarded as sufficient for routine clinical use in hypo- or normodynamic conditions in the absence of large changes in vascular tone. Performance of the system in hyperdynamic conditions, even with the latest software version, is still inadequate as our systemic review suggests. Even though SVV may not perfectly agree with that obtained by other means, it is useful in predicting fluid responsiveness.

We will now illustrate that our systematic review is limited by the heterogeneity of the included studies, so that conclusions should be drawn cautiously. An unconventional reference method was used in one study of general critically ill and surgical patients (Table 1),[18] since SV derived from the FloTrac/Vigileo™ was compared to SV determined with help of two oesophageal Doppler probes, a technique that is operator-dependent. In comparing FloTrac/Vigileo™ with transthoracic Doppler during induction of anaesthesia and intubation in patients undergoing abdominal aortic reconstruction,[27] increases in arterial blood pressure led to an overestimation of CO by FloTrac/Vigileo™. On the other hand, second and even third generation software resulted in underestimation of CO during vasodilation in patients with intracranial haemorrhage.[25 28] The second generation software may not suffice to monitor prone positioning of patients with acute respiratory distress syndrome.[29] In cardiac (surgical) patients (Table 2), the accuracy of FloTrac/Vigileo™-derived CO was limited by arrhythmias, alterations in the arterial pressure waveform in aortic stenosis and

Table 3. Validation studies for FloTrac/Vigileo™ cardiac output in liver disease/surgery or sepsis (n=19), grouped according to year of publication and name of first author.

Author	Year	Version	Patient type	Age, years	Ref. method	Mean CO, L min^{-1}	CO range L min^{-1}	Bias, L min^{-1}	Precision, L min^{-1}	% error	r^2	Concordance, r^2 or%	Patients	Data	CS
Sakka [7]	2007	1.07	Sepsis, 3 time points	58 (12)	TPTD	6.2 (2.4)	3-17.6	-0.50	2.30	74	0.26	0.14	24	72	3
Biais [69]	2008	1.07	Liver surgery, fluid loading	51 (11)	CCO	6.2	5.3-7.3	-0.65	1.05	33	na	0.77	35	70	2
					Echo	6.2		-0.50	1.00	33	na	0.74	35	70	2
Biais [60]	2008	1.07	Liver surgery, 20 time points	51 (9)	CCO	5.5 (1.3)	2.1-9.5	-0.80	1.35	43	na	na	20	400	3
Della Rocca [65]	2008	1.10	Liver surgery, 7 time points	50 (8)	ITD	7.2	3.1-11.5	-0.95	1.41	26	0.46	na	18	126	2
					CCO	7.2		-1.29	1.28	29	0.50	na	18	864	2
Biancofiore* [70]	2009	1.10	Liver surgery, 10 time points	47 (12)	ITD	6.7 (1.6)	3.6-12.0	-2.25	2.42	54	0.15	0.06	29	290	2
Krejci* [59]	2010	1.10	Liver surgery, 6 time points	56 (9)	ITD	5.5 (1.1)		-3.08	1.71	69	na	0.20	16	96	2
Monnet* [26]	2010	1.10	Sepsis, 2 interventions and 2 measurement sites	53-72	TPTD	5.1		-0.20	2.34	61	na	0.05	80	160	2
Slagt [66]	2010	1.07	Sepsis	65 (6)	ITD	5.3	3.6-7.1	-1.60	1.60	48	0.10	0.09	4	86	3
		1.10	Sepsis		ITD	7.0	3.3-10.8	-1.20	1.10	32	0.81	0.59	5	73	3
Akiyoshi§ [64]	2011	1.10	Liver surgery, 6 time points	54 (9)	ITD	5.9		-1.73	1.09	30	na	na	20	138	3
		3.02			ITD	6.3		-0.89	1.35	38	na	na	20	138	3
Biancofiore* [63]	2011	3.02	Liver surgery, 10 time points	51 (8)	ITD	7.4 (1.7)	3.5-13.5	-0.66	1.99	52	0.45	0.45	21	210	3
De Backer§ [68]	2011	1.10	Sepsis	62 (14)	ITD	6.5 (1.5)	2.5-14.4	-0.80	0.94	29	na	75	58	401	4
		3.02	Sepsis, 2 measurement sites		ITD	7.3 (2.1)	2.5-17.0	0.0	1.09	30	na	78	58	401	4
Machare** [71]	2011	1.07	Mostly sepsis, fluid loading	61 (13)	Echo	4.2		-0.28	1.11	46	na	0.10	25	50	1
McLean [10]	2011	1.10	Mostly septic	67 (15)	Echo	5.6 (2.0)		0.35	1.35	49	0.53	0.74	53	53	1
Mahjoub [72]	2012	3.02	Sepsis	40-69	Echo	5.9		1.70	2.25	81	0.03	0.17	20	90	1
Monnet [73]	2012	3.02	Sepsis, 2 interventions	64 (15)	TPTD	5.6 (1.7)		0.45	1.63	54	na	0.19	60	60	2
Su [62]	2012	3.02	Liver surgery	55 (10)	CCO	6.4		-0.80	2.4	75	na	na	28	3234	3

Tsai [74]	2012	3.02	Liver surgery		ITD	5.9 (1.8)		-0.22	1.67	55	na	na	20	200	3
Udy [75]	2012	1.10	Sepsis/Trauma	44 (18)	Echo	8.2 (2.7)		1.36	2.51	65	0.29	0.14	62	62	1
Slagt [67]	2013	3.02	Sepsis	62 (15)	ITD	6.8 (2.0)	4.0-13.7	-1.7	2.4	53	0.28	0.45	19	314	3
Total													748	7658	
Weighted average for second generation															
Patients						6.2		-0.47	1.65	48	0.37	0.32			2.1
95% confidence interval						(6.1-6.3)		(-0.56- -0.38)	(1.60-1.71)	(46-49)	(0.35-0.39)	(0.29-0.35)			(2.0-2.2)
Data						6.4		-1.11	1.46	39	0.41	0.24			2.5
95% confidence interval						(6.4-6.5)		(-1.14- -1.09)	(1.44-1.48)	(39-40)	(0.40-0.42)	(0.23-0.26)			(2.4-2.5)
Weighted average for third generation															
Patients						6.4		-0.12	1.71	51	0.25	0.27			2.9
95% confidence interval						(6.3-6.5)		(-0.22-0.02)	(1.65-1.77)	(49-53)	(0.21-0.30)	(0.25-0.29)			(2.8-3.1)
Data						6.5		-0.70	2.19	66	0.30	0.39			3.7
95% confidence interval						(6.5-6.5)		(-0.71- -0.68)	(2.18-2.21)	(66-67)	(0.29-0.31)	(0.38-0.40)			(3.7-3.8)

Abbreviations: A body surface area of 1.73 was used to convert data from cardiac index to CO (*), if appropriate ; **CO calculated from stroke volume; Financial industry sponsorship §; Age expressed as mean (standard deviation) in years or range where available; Ref. method = reference method; CO=cardiac output mean values (standard deviation) for FloTrac/Vigileo™ if available otherwise for combination with reference method; CO range = measured by FloTrac/Vigileo™ or reference standard, where available; r^2 = coefficient of determination; CS = Cecconi score (see text); TPTD = transpulmonary thermodilution cardiac output; PC = pulse contour cardiac output; CCO = continuous cardiac output; ITD = intermittent thermodilution; na = not available.

Table 4. Statistical analysis of performance characteristics.

	P for	Type of patient condition	Software version	Interaction
Cardiac, L min^{-1}		<0.001	<0.001	<0.001
Bias, L min^{-1}		<0.001	<0.001	<0.001
Precision, L min^{-1}		0.001	<0.001	<0.001
Error, percentage		0.16	<0.001	<0.001
Correlation, r^2		0.017	0.017	<0.001
Concordance, r^2		0.005	0.038	<0.001
Cecconi score		0.73	0.034	0.058

P values adjusted for patient and data number.

insufficiency and during intra-aortic balloon pumping.[38] However, a good correlation between FloTrac/Vigileo™ and thermodilution CO was documented during atrial pacing.[20 22 38 39] Marqué and co-workers[40] studied 12,099 paired data obtained with the first generation FloTrac/Vigileo™ software and continuous thermodilution CO, yielding acceptable performance with small bias and %error, short response time, accurate amplitude response and ability to detect significant directional changes. In comparing 1.03 and 1.07 versions of the software with intermittent thermodilution CO, the latter version proved better.[7] For measurement around cardiac surgery, utilising the second generation software patients with moderately abnormal left ventricular function, good agreement with intermittent thermodilution CO was noted, except in the presence of large changes in vascular tone.[41 42] Mehta and colleagues[43] used the 1.07 version in 12 patients and compared CO at 8 different intervals during cardiac surgery. The %error was 29%, rendering Flotrac/Vigileo™-derived CO almost identical to intermittent thermodilution CO. Sampling 136 data points in 30 small children post cardiac transplantation revealed poor agreement between intermittent thermodilution and FloTrac/Vigileo™-derived CO, reflecting the limitations of the Langewouters-derived vascular compliance at young age.[24] In comparing calibrated and uncalibrated (FloTrac/Vigileo™ version 1.10) arterial pressure-based CO during liver transplantation (Table 3),[59] both methods show increased error with decreasing resistance as compared to intermittent thermodilution CO. Other authors also noted that the mean difference between FloTrac/Vigileo™, using the 1.07 or 1.14 versions, and thermodilution CO increases below a systemic vascular resistance of about 800 dyne.s.cm^{-5}.[60-62] The latest software version 3.02 may not fully prevent this phenomenon.[60,62-64] In comparing two FloTrac/Vigileo™ software versions (1.10 and 3.02) with right-sided thermodilution during liver surgery, the 3.02 version performed even worse.[64] An increased bias was observed with 31% error compared to intermittent thermodilution CO and of 38% compared to continuous CO when exceeding 8 L min^{-1}, while bias was lower and %error stayed below 30% at lower CO.[65] During septic shock, another condition with a well

Table 5. Flotrac/Vigileo™ -derived stroke volume variation compared with other dynamic indices (provided by indicated manufacturers) , grouped according to year of publication and name of first author.

Author	Year Data	Version	Patient type	Age	Ref. method years	Mean SVV	Bias, %	Precision, %	%error	r^2	Concordance, r^2 or %	Patients	Data
Hofer§ [79]	2008	1.07	CABG	67 (9)	SVV_{PiCCO}	na	2.0	2.4	na	0.75		40	80
Biais [80]	2009	1.07	Liver surgery	53 (9)	$SVV_{Doppler}$	11.4	-0.7	2.5	44	na		30	130
Cannesson [83]	2009	1.10	CABG	na	$PPV_{Intellivue}$	na	1.3	2.8	na	na		25	50
Derichard [84]	2009	1.10	Abdominal surgery	48-75	$PPV_{Intellivue}$	na	na	na	na	0.71		11	77
Monge Garcia [87]	2009	1.10	ICU	55	$Doppler_{\Delta VPeak,Vivid\ 3}$	na	na	na	na	0.47	0.26	38	76
					PPV_{Datex}	na	na	na	na	0.59	0.39	38	76
Wilde de [82]	2009	1.07	CABG	66	SVV_{Lidco}	10.2	1.5	2.5	49	na		15	136
Qiai [89]	2010	3.02	Neuro surgery	43 (12)	SPV_{Datex}	na	2.31	1.8	na	0.80		26	138
					PPV_{Datex}	na	0.7	2.0	na	0.77		26	138
Khwannimit [94]	2012	3.02	Sepsis	54 (20)	$PPV_{Intellivue}$	na	na	na	na	0.92		42	34
Total												291	935
Weighted average for Patients						11	1.2	2.2	46	0.71	0.32		
95% confidence interval						(11-11)	(1.0-1.3)	(2.1-2.3)	(45-46)	(0.69-0.73)	(0.31-0.34)		
Data						11	1.1	2.0	47	0.71	0.33		
95% confidence interval						(11-11)	(1.0-1.2)	(2.0-2.1)	(46-47)	(0.71-0.73)	(0.31-0.34)		

Abbreviations: Ref = reference; CABG = coronary artery bypass grafting; ICU=intensive care unit; Age expressed as mean (standard deviation) in years or range if unavailable; SVV= stroke volume variation, mean values for FloTrac/Vigileo™ if available, otherwise for combination with reference method (in subscript); SPV= systolic pressure variation; PPV = pulse pressure variation; Financial industry sponsorship §; na = not available.

Table 6. Therapeutic studies utilizing guidance by FloTrac/Vigileo™ (n=7) vs standard monitoring in randomized clinical trials grouped according to type, year of publication and name of first author.

Author	Year	Version	Patient type	Treatment guided by FloTrac/Vigileo™-derived variables Number of patients	Control guided by routine variables or other values Number of patients	Outcomes
Kapoor[104]	2008	na	Cardiac surgery	CI, SVI, SVV, $S_{cv}O_2$, DO_2I, SVRI 13	MAP, CVP, UO, ABG, S_pO_2 14	More fluid volume and frequency of changes of inotropics in the treatment arm. No differences in duration of ventilator support, duration of inotropic drug use, length of ICU and hospital stay.
Benes[105]	2010	1.10	High risk surgery	CI, SVV, CVP 60	MAP, CVP, HR, UO 60	Improved intraoperative haemodynamic stability, decreased serum lactate at the end of surgery and less postoperative complications in treatment arm. No differences in mortality, ICU and hospital lengths of stay.
Mayer[106]	2010	1.14	High risk surgery	CI, SVI, SVV, MAP 30	MAP, CVP, UO 30	Reduced length of hospital stay by 4 days in treatment arm. Less postoperative complications in treatment arm. No differences in ICU length of stay and mortality.
Cecconi[107]	2011	1.07	Hip surgery	SVI, DO_2I 20	MAP 20	The treatment group received more intraoperative fluids, dobutamine and blood transfusion. Less postoperative complications in treatment arm.
Takala[108]	2011	1.07	Intensive care	CI, MAP 201	MAP 187	Early, non-invasive continuous cardiac output monitoring did not shorten the time to reach hemodynamic stability, produce any outcome benefit, or reduce the amount of resources used during the ICU stay as compared to standard treatment (with echo or pulmonary artery catheter).
Wang[109]	2012	1.07	Liver surgery	SVV 25	CVP 25	Greater diuretic use in the control group, but no differences in blood loss, acute kidney injury and survival.
Wang[110]	2012	na	Gastrointestinal	SVV 5-7% 20	SVV11-13% 20	With high SVV guidance less fluids and urinary output; enhanced gastrointestinal recovery and surgery reduced length of hospital stay.

Abbreviations: NA, not applicable; CI = cardiac index; SVI = stroke volume index; SVV = stroke volume variation; $S_{cv}O_2$ = central venous oxygen saturation ; DO_2I = oxygen delivery index; SVRI = systemic vascular resistance index; MAP = mean arterial pressure; CVP = central venous pressure; UO = urine output; ABG = arterial blood gas analysis; S_pO_2 = pulse oxymetry oxygen saturation; ICU=intensive care unit; HR = heart rate.

known decrease in vascular tone, a similar underestimation of FloTrac/Vigileo™ compared to thermodilution CO has been observed.[26] During a comparison of FloTrac/Vigileo™ with transpulmonary thermodilution CO during norepinephrine treatment of patients suffering from septic shock,[9] arrhythmias were accepted and the average systemic vascular resistance was below 800 dyne.s.cm^{-5}. The latter was associated with large bias, limits of agreement and %error as in other studies.[10 59 62] We[66 67] compared software versions1.07, 1.10 and 3.02 with intermittent thermodilution CO in septic shock and showed improved accuracy and precision with the subsequent versions although a bias dependent on systemic vascular resistance persisted with the most recent one. A French group compared calibrated and uncalibrated FloTrac/Vigileo™ measurement of CO (version 1.10) during the treatment of patients with septic shock and favoured the former.[26] Recently, the latest software (3.02) was studied in multiple centres and 58 patients with sepsis were included.[68] Simultaneous data were obtained for CO derived from intermittent and continuous thermodilution and the FloTrac/Vigileo™ 1.10 and 3.02 software versions. The bias (and its dependence on vascular tone) improved with the latest software version (3.02) but the %error remained unchanged at 30%. However, most measurements where performed at a systemic vascular resistance of >500 dyne.s.cm^{-5} and data analyses were performed offline.

Changes in CO rather than absolute values may be of greater clinical use if highly predictive of those in a reference standard, for instance in evaluating fluid responsiveness and other responses to therapeutic interventions. However, only few studies evaluated the concordance of CO changes with a reference standard and they suggest improving performance with evolving software versions, even though highly variable indicators of concordance and acceptability for clinical use have been described.[15-18 34] In hypovolaemic patients with spontaneous breathing SV, as measured by FloTrac/Vigileo™, increased within 2 min following passive leg raising and adequately predicted fluid responsiveness assessed by echocardiography.[17] Changes in PP with aortic clamping and declamping may alter Flotrac/Vigileo™ CO but not that measured by echocardiography.[34] Changes in Flotrac/Vigileo™ CO during large alterations in vascular tone may less well correlate to those measured by a reference technique than during fluid loading or passive leg raising, particularly in hyperdynamic conditions and in spite of most recent software.[17 26 45 69] Indeed, concordance of measurements with the reference standard seemed high during and after cardiac surgery[23 41 45 57] but moderate (60-75% or r^2 <0.50) in patients with an impaired left ventricular function[41 56] or with hyperdynamic conditions, including sepsis.[8 20 26 60 63 71 73] The latter has been denied by other studies.[63 66-68] Changing doses of inotropes, vasopressors or vasodilators, which is commonly done in clinical practice, can thus transiently change FloTrac/Vigileo™ compared to thermodilution CO but a slow

response of the latter to detect rapid changes in CO cannot always be excluded.[5 7 8 25-28 32 33 37 40 41 50 62 68 76 77] An early study[15] reported a concordance of 59% with intermittent thermodilution-derived CO for changes less than 15% in a mixed patient population. These changes may be too small to be clinically relevant. However, the FloTrac/Vigileo™ failed to detect an increase in transpulmonary thermodilution CO of 15% or greater after fluid challenges and use of norepinephrine in septic patients.[26] With use of the most recent software, the same group reported slightly improved performance, but with better concordance with transpulmonary thermodilution for CO changes during fluid loading than norepinephrine administration in septic patients.[73] We[66 67] compared software versions 1.07, 1.10 and 3.02 with intermittent thermodilution CO in the treatment of septic shock and showed good tracking ability during the course of treatment of the syndrome. Dobutamine treatment of subarachnoid haemorrhage patients with delayed cerebral ischemia resulted in an error of only 15% when comparing FloTrac/Vigileo™ with transpulmonary thermodilution CO, at an unaltered vascular tone.[36] Otherwise, we did not individually assess the interventions for reporting concordance.

The pressure (wave form) differs at different measuring sites within the same patient.[8 31 40 47 55 61 78] Ascending aorta and radial artery pressure have been used to calculate CO by FloTrac/Vigileo™ during cardiac surgery and indicate that results may vary according to site.[78] Studies compared radial and femoral arterial pressure-derived CO, showing considerable differences.[17 20 30 78] However, studies using more recent software versions have contradicted these findings.[25 26 47 51 53 57 58 61 68] In contrast to CO measurements, the sampling site may not affect stroke volume variations (SVV).[31]

There were 8 comparative studies of SVV measurements (Table 5). The FloTrac/Vigileo™ –derived SVV moderately agreed with the SVV obtained with other devices and analyses of the arterial pressure waveform,[79-81] but not in all studies.[82] FloTrac/Vigileo™-derived SVV was able to predict fluid responsiveness in 85% of studies addressing this in mechanically ventilated patients. Arterial pressure, prone position or various ventilation modes did not affect these results.[31 45 69 79-81 83-97] First to third generation software has been suggested to yield successfully discriminating SVV's, performing equally well as PP variation or pleth variability index.[45 69 79 81 83 84 87-89 90 92 94] Others observed that the FloTrac/Vigileo™-derived SVV was a better predictor and monitor of fluid responsiveness than static parameters.[31 45 79 85 95-98] In mechanically ventilated cardiac surgery patients,[86] the increase of SVV with removal of blood and the decrease with replacement by colloids were predictive of the course of CO and echocardiography-determined left ventricular end-diastolic volume. The SVV derived

from FloTrac/Vigileo™ predicted, as well as PP variation, a decrease in SV (thermodilution and FloTrac/Vigileo™) induced by positive end-expiratory pressure.[99] After oesophageal surgery,[85 100] FloTrac/Vigileo™-derived SVV may be a useful parameter to predict hypovolaemia and fluid responsiveness. Only few studies failed to validate usefulness of FloTrac/Vigileo™-derived SVV to predict fluid responsiveness.[71 101-103] Echocardiography-derived variations in vena cava inferior diameter predicted fluid responsiveness in fully mechanically ventilated, mostly septic, critically ill patients, but the FloTrac/Vigileo™-derived SVV did not.[71] In patients undergoing liver surgery or pneumoperitoneum for laparoscopic surgery, FloTrac/Vigileo™-derived SVV appeared less useful,[101 103] whereas oesophageal Doppler-derived SV was used as a reference standard, even though its reproducibility is operator-dependent.[80 83 84] Obviously, the validity of SVV as a predictor of fluid responsiveness is subject to some conditions, including a regular cardiac rhythm, absence of right ventricular overloading and others.

Recommendations for comparison of haemodynamic monitoring devices[14] have rarely been fully followed. Ignoring to account for repeated measurements and for the error of the reference technique may have contributed to the varying results in the tables. Nevertheless, many studies reported separate agreement statistics for the multiple time points of measurements. Only few studies compared the reference standard for FloTrac/Vigileo™ with another reference technique, sometimes showing less error in comparing reference standards than in FloTrac/Vigileo™-derived CO with either reference standard.[9 23 26 32 41 43 44 47 51 59 68 78] A relatively low measurement error of the thermodilution reference method may increase the error of the FloTrac/Vigileo™-derived CO to unacceptably high levels, for a %error of 30% which is generally regarded as acceptable.[13 14 23 25 26 32] Otherwise, the dependency of bias on vascular resistance implies a systematic error which results in (and can be inferred from) a significant relation between differences and means with the reference technique. Even when clear from the Bland-Altman plots provided, this has rarely been objectively evaluated or accounted for.[41 66] Conversely, the % (random) error may be overestimated when data are pooled on repeated measurements of patients with differences in vascular tone and thus in systematic error. Finally, none of the studies directly compared software versions in the same patients; in some studies the version was not reported. Our study does not provide an answer to the question whether this technology should be used or not; it merely demonstrates that system performance has positively evolved over the years, allowing its routine use in specific conditions. Table 6 finally summarises results of the 7 heterogeneous intervention studies published so far utilising the Flotrac/Vigileo™ in randomised clinical trials. They show that utilisation of FloTrac/Vigileo™-derived parameters have not decreased patient mortality.[104-110] Other studies successfully used the

system to monitor patients perioperatively, during interventions[35 76 77 85 86 93 95 100 102 103 110 111-123] or when receiving vasoactive drugs.[115 117] During one-lung ventilation and recruitment, CO changes were adequately monitored by the FloTrac/Vigileo™ system.[111 112] Others[76 113] used the FloTrac/Vigileo™ to successfully monitor haemodynamic changes during induction of anaesthesia in patients with left ventricular dysfunction and during fluid challenges and vasopressor administration around caesarean sections.

Conclusion

The performance of uncalibrated FloTrac/Vigileo™ has improved since its introduction, particularly in hypo– and normodynamic conditions. Since the average %error is below 30%, the CO measured with help of most recent software may be sufficiently accurate for routine clinical use in these conditions, even though trending capacity remains affected by changes in vascular tone. The SVV may usefully supplement these measurements, particularly in future outcome studies.

Competing interests

CS and ABJG have received lecture fees from Edwards Lifesciences. IM has no competing interests.

Authors' contributions

CS, IM and ABJG have made substantial contributions to conception and design, literature search, analysis and interpretation of data. All have been involved in drafting the manuscript. All authors have read and approved of the final manuscript.

References

1. Erlanger J, Hooker DR. An experimental study of blood pressure and of pulse-pressure in man. *John Hopkins Hosp Rep* 1904;12:145–378.
2. Manecke GR. Edwards FloTrac sensor and Vigileo monitor: easy, accurate, reliable cardiac output assessment using the arterial pulse wave. *Expert Rev Med Devices* 2005;2:523-527.
3. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-411.
4. Langewouters G, Wesseling K, Goedhard W. The pressure dependent dynamic elasticity of 35 thoracic and 16 abdominal human aortas in vitro described by a five component model. *J Biomech* 1985;18:613-620.
5. Lorsomradee S, Lorsomradee SR, Cromheecke S, et al. Continuous cardiac output measurement: arterial pressure analysis versus thermodilution technique during cardiac surgery with cardiopulmonary bypass. *Anaesthesia* 2007;62:979-983.
7. Sakka SG, Kozieras J, Thuemer O, et al. Measurement of cardiac output: a comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007;99:337-342.
8. Compton FD, Zukunft B, Hoffmann C, et al. Performance of a minimally invasive uncalibrated cardiac output monitoring system (FloTrac/Vigileo) in haemodynamically unstable patients. *Br J Anaesth* 2008;100:451-456.
9. Senn A, Button D, Zollinger A, et al. Assessment of cardiac output changes using a modified FloTrac/Vigileo algorithm in cardiac surgery patients. *Crit Care* 2009;13:R32.
10. McLean AS, Huang SJ, Kot M, et al. Comparison of cardiac output measurements in critically ill patients: FloTrac/Vigileo vs transthoracic Doppler echocardiography. *Anaesth Intensive Care* 2011;39:590-598.
11. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J Appl Physiol* 2011;111:853-60.
12. Mayer J, Boldt J, Poland R, et al. Continuous arterial pressure waveform-based cardiac output using the FloTrac/Vigileo: a review and meta-analysis. *J Cardiothor Vasc Anesth* 2009;23:401-406.
13. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85-91.
14. Cecconi M, Rhodes A, Polaniecki J, et al. Bench - to bedside review: The importance of the precision of the reference technique in method comparison studies - with specific reference to the measurements of cardiac output. *Crit Care* 2009;13:201.
15. McGee WT, Horswell JL, Calderon J, et al. Validation of a continuous, arterial pressure-based cardiac output measurement: a multicenter, prospective clinical trial. *Crit Care* 2007;11:R105.
16. Prasser C, Bele S, Keyl C, et al. Evaluation of a new arterial pressure-based cardiac output device requiring no external calibration. *BMC Anesthesiology* 2007;7:9.
17. Biais M, Vidil L, Sarrbay P, et al. Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo™/FloTrac™ device. *Crit Care* 2009;13:R195.
18. Chatti R, de Rudniki S, Marqué S, et al. Comparison of two versions of the Vigileo-FloTrac system (1.03 and 1.07) for stroke volume estimation: a multicentre, blinded comparison with oesophageal Doppler measurements. *Br J Anaesth* 2009;102:463-469.
19. Hanley JA, Negassa A, Edwardes MD, et al. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003;157:364-375.
20. Sander M, Spies CD, Grubitzsch H, et al. Comparison of uncalibrated arterial waveform analysis in cardiac surgery patients with thermodilution cardiac output measurements. *Crit Care* 2006;10:R164.
21. Staier K, Wiesenack C, Günkel L, et al. Cardiac output determination by thermodilution and arterial pulse waveform analysis in patients undergoing aortic valve replacement. *Can J Anesth* 2008;55:22-28.
22. Østergaard M, Nielsen J, Nygaard E. Pulse contour cardiac output: an evaluation of the FloTrac method. *Eur J Anaesthesiol* 2009;26:484-489.
23. de Wilde RB, Geerts BF, Cui J, et al. Performance of three minimally invasive cardiac output monitoring systems. *Anaesthesia* 2009;64:762-769.
24. Teng S, Kaufman J, Pan Z, et al. Continuous arterial pressure waveform monitoring in pediatric cardiac transplant, cardiomyopathy and pulmonary hypertension patients. *Intensive Care Med* 2011;37:1297-1301.
27. Kotake Y, Yamada T, Nagata H, et al. Transient hemodynamic change and accuracy of arterial blood pressure-based cardiac output. *Anesth Analg* 2011;113:272-4.

28. Junttila EK, Koskenkari JK, Ohtonen PP, et al. Uncalibrated arterial pressure waveform intracranial hemorrhage. *Br J Anaesth* 2011:107:581-6.
29. Grensemann J, Bruecke U, Treszl A, et al. The influence of prone positioning on the accuracy of calibrated and uncalibrated pulse contour-derived cardiac index measurements. *Anesth Analg* 2013;116:820-826.
30. Concha MR, Mertz VF, Cortínez LI, et al. Pulse contour analysis and transesophageal echocardiography: a comparison of measurements of cardiac output during laparoscopic colon surgery. *Anesth Analg* 2009;109:114-118.
31. Mutoh T, Ishikawa T, Nishino K, et al. Evaluation of the FloTrac uncalibrated continuous cardiac output system for perioperative hemodynamic monitoring after subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 2009;21:218-225.
32. Cecconi M, Dawson R, Casaretti R, et al. A prospective study of the accuracy and precision of continuous cardiac output monitoring devices as compared to intermittent thermodilution. *Minerva Anesthesiol* 2010;76:1-8.
33. Saraceni E, Rossi S, Persona P, et al. Comparison of two methods for cardiac output measurement in critically ill patients. *Br J Anaesth* 2011;106:690-4.
34. Kusaka Y, Yoshitani K, Irie T, et al. Clinical comparison of an echocardiograph-derived versus pulse counter-derived cardiac output measurement in abdominal aortic aneurysm surgery. *J Cardiothorac Vasc Anesth* 2012;26:223-226.
35. Murthi SB, Hess JR, Hess A, et al. Focused rapid echocardiographic evaluation versus vascular catheter-based assessment of cardiac output and function in critically ill trauma patients. *J Trauma Acute Care Surg* 2012;72:1158-1164.
36. Mutoh T, Ishikawa T, Kobayashi S, et al. Performance of third-generation FloTrac/Vigileo system during hyperdynamic therapy for delayed cerebral ischemia after subarachnoid hemorrhage. *Surg Neurol Int* 2012;3:99.
37. Lorsomradee S, Loromradee S, Cromheecke S, et al. Uncalibrated arterial pulse contour analysis versus continuous thermodilution technique: effects of alterations in arterial waveform. *J Cardiothor Vasc Anesth* 2007;21:636-643.
38. Opdam HI, Wan L, Bellomo R. A pilot assessment of the FloTrac cardiac output monitoring system. *Intensive Care Med* 2007;33:344-349.
39. de Waal EC, Kalkman CJ, Rex S, et al. Validation of a new arterial pulse contour-based cardiac output device. *Crit Care Med* 2007;35:1904-1909.
40. Marqué S, Cariou A, Chiche J-D, et al. Comparison between Flotrac-Vigileo and Bioreactance, a totally noninvasive method for cardiac output monitoring. *Crit Care* 2009;13:R73.
41. Vetrugno L, Costa MG, Spagnesi L, et al. Uncalibrated arterial pulse cardiac output measurements in patients with moderately abnormal left ventricular function. *J Cardiothor Vasc Anesth* 2011;25:53-58.
42. Jo YY, Song JW, Yoo YC, Park JY, et al. The uncalibrated pulse contour cardiac output during off-pump coronary bypass surgery: performance in patients with a low cardiac output status and a reduced left ventricular function. *Kor J Anesthesiol* 2011;60:237-243.
43. Mehta Y, Chand RK, Sawhney R, et al. Cardiac output monitoring: comparison of a new arterial pressure waveform analysis to the bolus thermodilution technique in patients undergoing off-pump coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2008;22:394-399.
44. Button D, Weibel L, Reuthebuch O, et al. Clinical evaluation of the FloTrac/Vigileo™ system and two established continuous cardiac output monitoring devices in patients undergoing cardiac surgery. *Br J Anaesth* 2009;99:329-336.
45. Cannesson M, Attof Y, Rosamel P, et al. Comparison of FloTrac™ cardiac output monitoring system in patients undergoing coronary artery bypass grafting with pulmonary artery cardiac output measurements. *Eur J Anaesthesiol* 2007;24:832-839.
46. Chakravarthy M, Patil TA, Jayaprakash K, et al. Comparison of simultaneous estimation of cardiac output by four techniques in patients undergoing off-pump coronary artery bypass surgery-a prospective observational study. *Ann Card Anaesth* 2007;10:121-126.
47. Manecke GR, Auger WR. Cardiac output determination from the arterial pressure wave: clinical testing of a novel algorithm that does not require calibration. *J Cardiothor Vasc Anesth* 2007;21:3-7.
48. Zimmermann A, Kufner C, Hofbauer S, et al. The accuracy of the Vigileo/FloTrac continuous cardiac output monitor. *J Cardiothorac Vasc Anesth* 2008;22:388-393.
49. Chakravarthy M, Rajeev S, Jawali V. Cardiac index value measurement by invasive, semi-invasive and non invasive techniques: a prospective study in postoperative off pump coronary artery bypass surgery patients. *J Clin Monit Comput* 2009;23:175-180.

50. Eleftheriadis S, Galatoudis Z, Didilis V, et al. Variations in arterial blood pressure are associated with parallel changes in FloTrac/Vigileo-derived cardiac output measurements: a prospective comparison study. *Crit Care* 2009;13:R179.
51. Hadian M, Kim HK, Severyn DA, et al. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. *Crit Care* 2010;14:R212.
52. Hamm J-B, Nguyen B-V, Kiss G, et al. Assessment of a cardiac output device using arterial pulse waveform analysis, Vigileo, in cardiac surgery compared to pulmonary arterial thermodilution. *Anaesth Intensive Care* 2010;38:295-301.
53. Hofer CK, Button D, Weibel L, et al. Uncalibrated radial and femoral arterial pressure waveform analysis for continuous cardiac output measurement: an evaluation in cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2010;24:257-264.
54. Jeong YB, Kim TH, Roh YJ, et al. Comparison of uncalibrated arterial pressure waveform analysis with continuous thermodilution cardiac output measurements in patients undergoing elective off-pump coronary artery bypass surgery. *J Cardiothor Vasc Anesth* 2010;24:767-771.
55. Schramm S, Albrecht E, Frascarolo P, et al. Validity of an arterial pressure waveform analysis device: does the puncture site play a role in the agreement with intermittent pulmonary catheter thermodilution measurements? *J Cardiothorac Vasc Anesth* 2010;24:250-256.
57. Broch O, Renner J, Gruenewald M, et al. A comparison of third-generation semi-invasive arterial waveform analysis with thermodilution in patients undergoing coronary surgery. *ScientificWorldJournal 2012;2012:451081.*
58. Vasdev S, Chauhan S, Choudhury M, et al. Arterial pressure waveform derived cardiac output FloTrac/Vigileo system (third generation software): comparison of two monitoring sites with the thermodilution cardiac output. *J Clin Monit Comput* 2012;26:115-120.
59. Krejci V, Vannucci A, Abbas A, et al. Comparison of calibrated and uncalibrated arterial pressure-based cardiac output monitors during orthotopic liver transplantation. *Liver Transpl* 2010;16:773-782.
60. Biais M, Nouette-Gaulain K, Cottenceau V, et al. Cardiac output measurement in patients undergoing liver transplantation: pulmonary artery catheter versus uncalibrated arterial pressure waveform analysis. *Anesth Analg* 2008;106:1480-1486.
61. Kim YK, Shin WJ, Song JG, et al. Comparison of stroke volume variations derived from radial and femoral arterial pressure waveforms during liver transplantation. *Transpl Proc* 2009;41:4220-4228.
62. Su BC, Tsai YF, Chen CY, et al. Cardiac output derived from arterial pressure waveform analysis in patients undergoing liver transplantation: validity of a third-generation device. *Transplant Proc* 2012;4:424-428.
64. Akiyoshi K, Kandabashi T, Kaji J, et al. Accuracy of arterial pressure waveform analysis for cardiac output measurement in comparison with thermodilution methods in patients undergoing living donor liver transplantation. *J Anesth* 2011;25:178-183.
65. Della Rocca G, Costa MG, Chiarandini P, et al. Arterial pulse cardiac output agreement with thermodilution in patients in hyperdynamic conditions. *J Cardiothorac Vasc Anesth* 2008;22:681-687.
66. Slagt C, Beute J, Hoeksema M, et al. Cardiac output derived from arterial pressure waveform analysis without calibration versus thermodilution in septic shock: evolving accuracy of software versions. *Eur J Anaesthesiol* 2010;27:550-554.
67. Slagt C, de Leeuw MA, Beute J, et al. Cardiac output measured by uncalibrated arterial pressure waveform analysis by recently released software version 3.02 versus thermodilution in septic shock. *J Clin Monit Comput* 2013;27:171-177.
68. De Backer D, Marx G, Tan A, et al. Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. *Intensive Care Med* 2011;37:233–240.
69. Biais M, Nouette-Gaulain K, Cottenceau V, et al. Uncalibrated pulse contour-derived stroke volume variation predicts fluid responsiveness in mechanically ventilated patients undergoing liver transplantation. *Br J Anaesth* 2008;101:761-768.
70. Biancofiore G, Critchley LA, Lee A, et al. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. *Br J Anaesth* 2009;102:47-54.
71. Machare-Delgado E, Decaro M, Marik PE. Inferior vena cava variation compared to pulse contour analysis as predictors of fluid responsiveness: a prospective cohort study. *J Intensive Care Med* 2011;26:116-124.
72. Mahjoub Y, Lakhdari M, Lorne E, et al. Assessment of an uncalibrated pressure waveform device's ability to track cardiac output changes due to norepinephrine dose adjustments in patients with septic shock: a comparison with Doppler echocardiography. *Ann Fr Anesth Reanim* 2012;31:677-681.

73. Monnet X, Anguel N, Jozwiak M, et al. Third-generation FloTrac/Vigileo does not reliably track changes in cardiac output induced by norepinephrine in critically ill patients. *Br J Anaesth* 2012;108:615-622.
74. Tsai YF, Su BC, Lin CC, et al. Cardiac output derived from arterial pressure waveform analysis: validation of the third-generation software in patients undergoing orthotopic liver transplantation. *Transplant Proc* 2012;44:433-437.
75. Udy AA, Altukroni M, Jarrett P, et al. A comparison of pulse contour wave analysis and ultrasonic cardiac output monitoring in the critically ill. *Anaesth Intensive Care* 2012;40:631-637.
76. Auler J, Torres MLA, Cardoso MM, et al. Clinical evaluation of the Flotrac/Vigileo™ system for continuous cardiac output monitoring in patients undergoing regional anesthesia for elective cesarean section: a pilot study. *Clinics (Sao Paulo)* 2010;65:793-798.
77. Nakasuji M, Suh SH, Nomura M, et al. Hypotension from spinal anesthesia in patients aged greater than 80 years is due to a decrease in systemic vascular resistance. *J Clin Anesth* 2012;24:201-206.
78. Sander M, Soies CD, Foer A, et al. Cardiac output measurement by arterial waveform analysis in cardiac surgery - a comparison of measurements derived from waveforms of the radial artery versus the ascending aorta. *J Int Med Res* 2008;36:414-419.
79. Hofer CK, Senn A, Weibel L, et al. Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTrac™ and PiCCOplus™ system. *Crit Care* 2008;12:R82.
80. Biais M, Nouette-Gaulain K, Roullet S, et al. A comparison of stroke volume variation measured by Vigileo™/FloTrac™ system and aortic Doppler echocardiography. *Anesth Analg* 2009;109:466-469.
81. Zimmermann M, Feibicke T, Keyl C, et al. Accuracy of stroke volume variation compared with pleth variability index to predict fluid responsiveness in mechanically ventilated patients undergoing major surgery. *Eur J Anaesthesiol* 2010;27:555-561.
82. de Wilde RB, Geerts BF, van den Berg PC, et al. A comparison of stroke volume variation measured by the LiDCOplus and FloTrac-Vigileo system. *Anaesthesia* 2009;64:1004-1009.
83. Cannesson M, Musard H, Desebbe O, et al. The ability of stroke volume variations obtained with Vigileo/FloTrac system to monitor fluid responsiveness in mechanically ventilated patients. *Anesth Analg* 2009;108:513-517.
84. Derichard A, Robin E, Tavernier B, et al. Automated pulse pressure and stroke volume variations from radial artery: evaluation during major abdominal surgery. *Br J Anaesth* 2009;103:678-684.
85. Kobayashi M, Koh M, Irinoda T, et al. Stroke volume variation as a predictor of intravascular volume depression and possible hypotension during the early postoperative period after esophagectomy. *Ann Surg Oncol* 2009;16:1371-1377.
86. Kungys G, Rose DD, Fleming NW. Stroke volume variation during acute normovolemic hemodilution. *Anesth Analg* 2009;109:1823-1830.
87. Monge García MI, Gil Cano A, Díaz Monrové JC. Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients. *Crit Care* 2009;13:R142.
88. Biais M, Bernard O, Ha JC, et al. Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery. *Br J Anaesth* 2010;104:407-413.
89. Qiao H, Zhang J, Liang WM. Validity of pulse pressure and systolic blood pressure variation data obtained from a Datex Ohmeda S/5 monitor for predicting fluid responsiveness during surgery. *J Neurosurg Anesthesiol* 2010;22:316-322.
90. Suehiro K, Okutani R. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing one-lung ventilation. *J Cardiothorac Vasc Anesth* 2010;24:772-775.
91. Monge García MI, Gil Cano A, Romero MG. Dynamic arterial elastance to predict arterial pressure response to volume loading in preload-dependent patients. *Crit Care* 2011;15:R15.
92. Suehiro K, Okutani R. Influence of tidal volume for stroke volume variation to predict fluid responsiveness in patients undergoing one-lung ventilation. *J Anesth* 2011;25:777-780.
93. Takeyama M, Matsunaga A, Kakihana Y, et al. Impact of skin incision on the pleth variability index. *J Clin Monit Comput* 2011;25:215-221.
94. Khwannimit B, Bhurayanontachai R. Prediction of fluid responsiveness in septic shock patients: comparing stroke volume variation by FloTrac/Vigileo and automated pulse pressure variation. *Eur J Anaesthesiol* 2012;29:64-69.
95. Li J, Ji FH, Yang JP. Evaluation of stroke volume variation obtained by the FloTrac™/Vigileo™ system to guide preoperative fluid therapy in patients undergoing brain surgery. *J Int Med Res.* 2012;40:1175-1181.

96. Suehiro K, Rinka H, Ishikawa J, et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing airway pressure release ventilation. *Anaesth Intensive Care* 2012;40:767-772.
97. Li C, Lin FQ, Fu SK, et al. Stroke volume variation for prediction of fluid responsiveness in patients undergoing gastrointestinal surgery. *Int J Med Sci* 2013;10:148-155.
98. Su BC, Tsai YF, Cheng CW, et al. Stroke volume variation derived by arterial pulse contour analysis is a good indicator for preload estimation during liver transplantation. *Transpl Proc* 2012;44:429-432
99. Biais M, Nouette-Gaulain K, Quinart A, et al. Uncalibrated stroke volume variations are able to predict the hemodynamic effects of positive end-expiratory pressure in patients with acute lung injury or acute respiratory distress syndrome after liver transplantation. *Anesthesiology* 2009;111:855-862.
100. Kobayashi M, Ko M, Kimura T, et al. Perioperative monitoring of fluid responsiveness after esophageal surgery using stroke volume variation. *Expert Rev Med Devices* 2008;5:311-316.
101. Lahner D, Kabon B, Marschalek C, et al. Evaluation of stroke volume variation obtained by arterial pulse contour analysis to predict fluid responsiveness intraoperatively. *Br J Anaesth* 2009;103:346-351.
102. Futier E, Christophe S, Robin E, et al. Use of near-infrared spectroscopy during a vascular occlusion test to assess the microcirculatory response during fluid challenge. *Crit Care* 2011;15:R214.
103. Høiseth LØ, Hoff IE, Myre K, et al. Dynamic variables of fluid responsiveness during pneumoperitoneum and laparoscopic surgery. *Acta Anaesthesiol Scand* 2012;56:777-786.
104. Kapoor PM, Kakani M, Chowdhury U, et al. Early goal-directed therapy in moderate to high-risk cardiac surgery patients. *Ann Card Anaesth* 2008;11:27-34.
105. Benes J, Chytra I, Altman P, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of a prospective randomized study. *Crit Care* 2010;14:R118.
106. Mayer J, Boldt J, Mengistu A, et al. Goal-directed intraoperative therapy based on arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized controlled trial. *Crit Care* 2010;14:R18.
107. Cecconi M, Fasano N, Langiano N, et al. Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. *Crit Care* 2011;15:R132.
109 Wang S-C, Teng W-N, Chang K-Y, et al. Fluid management guided by stroke volume variation faired to decrease the incidence of acute kidney injury, 30-day mortality, and 1-year survival in living donor liver transplant recipients. *J Chin Med Ass* 2012;75:654-659.
110. Wang P, Wang HW, Zhong TD. Effect of stroke volume variability- guided intraoperative fluid restriction on gastrointestinal functional recovery. *Hepato-Gastroenterology* 2012;59:2457-2460.
111. Garutti I, Martinez G, Cruz P, et al. The impact of lung recruitment on hemodynamics during one-lung ventilation. *J Cardiothor Vasc Anesth* 2009;23:506-508.
112. Ishikawa S, Shirasawa M, Fujisawa M, et al. Compressing the non-dependent lung during one-lung ventilation improves arterial oxygenation, but impairs systemic oxygen delivery by decreasing cardiac output. *J Anesth* 2010;24:17-23.
113 Singh R, Choudhury M, Kapoor PM, et al. A randomized trial of anesthetic induction agents in patients with coronary artery disease and left ventricular dysfunction. *Ann Cardiac Anaesth* 2010;13:217-223.
114. Wajima Z, Shiga T, Imanaga K, et al. Assessment of the effect of rapid crystalloid infusion on stroke volume variation and pleth variability index after a preoperative fast. *J Clin Monit Comput* 2010; 24:385-9.
115. Agrawal A, Gupta A, Consul S, et al. Comparative study of dopamine and norepinephrine in the management of septic shock. *Saudi J Anaesth* 2011;5:162-6.
116. Biais M, Stecken L, Ottolenghi L, et al. The ability of pulse pressure variations obtained with CNAP™ device to predict fluid responsiveness in the operating room. *Anesth Analg* 2011;113:523-8.
117. Davies SJ, Yates D, Wilson JT. Dopexamine has no additional benefit in high-risk patients receiving goal-directed fluid therapy undergoing abdominal surgery. *Anesth Analg* 2011;112:130-138.
118. de Leeuw MA, Slagt C, Hoeksema M, et al. Hemodynamic changes during a combined psoas compartment-sciatic nerve block for elective orthopedic surgery. *Anesth Analg* 2011;112:719-724.
119. Bickel A, Eitan A, Melnik D, et al. The use of pneumoperitoneum during laparoscopic surgery as a model to study pathophysiologic phenomena: the correlation of cardiac functionality with computerized acoustic indices--preliminary data. *J Laparoendosc Adv Surg Tech A* 2012;22:349-54.
120. Darlong V, Kunhabdulla NP, Pandey R, et al. Hemodynamic changes during robotic radical prostatectomy. *Saudi J Anaesth* 2012;6:213-218.

121. Isosu T, Obara S, Ohashi S, et al. Examination of the usefulness of non-invasive stroke volume variation monitoring for adjusting fluid supplementation during laparoscopic adrenalectomy in patients with pheochromocytoma. *Fukushima J Med Sci* 2012;58:78-81.
122. Yoshida, Suzuki T, Kashiwai A, et al. Correlation between cardiac output and reversibility of rocuronium-induced moderate neuromuscular block with sugammadex. *Acta Anaesthesiol Scand* 2012;56:83-7.
123. Lin FQ, Li C, Zhang LJ, et al. Effect of rapid plasma volume expansion during anesthesia induction on haemodynamics and oxygen balance in patients undergoing gastrointestinal surgery. *Int J Med Sci* 2013;10:355-361.

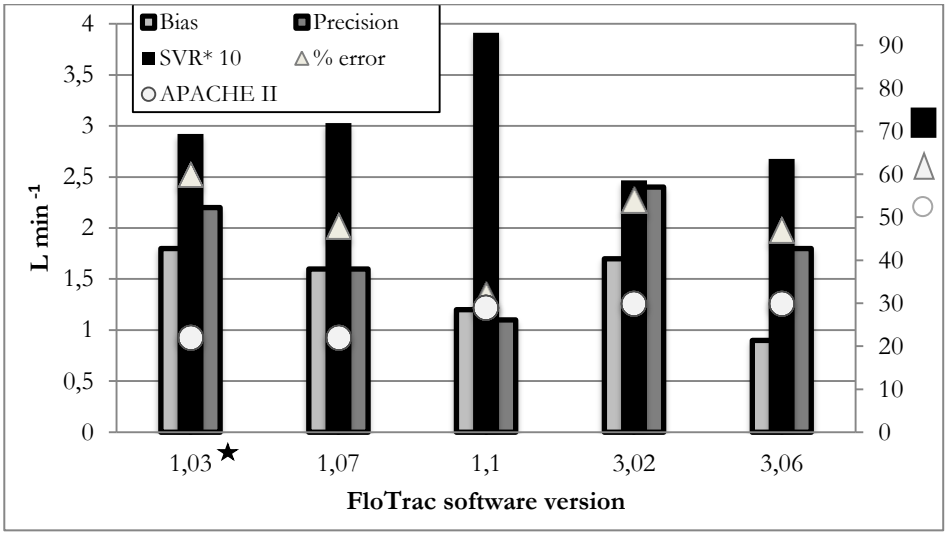
8

Summary and general discussion

Summary

In this thesis we have sought to improve our knowledge of the haemodynamic monitoring device that uses waveform analysis without external calibration, the FloTrac/Vigileo™ system. In particular its use, accuracy and reproducibility in different clinical circumstances. We have evaluated FloTrac/Vigileo™ derived haemodynamic parameters in intensive care patients (mostly sepsis) in consecutive software versions (version 1.03, 1.07, 1.10, 3.02 and 3.06) with pulmonary artery catheter (PAC) and transpulmonary thermodilution (COtptd) as reference (**chapter 3,4,6,7**). Overall results are summarised in Table 1.

Table 1. Results from validation studies using FloTrac/Vigileo ™ performed at Zaans Medical Centre



Bias = mean difference between reference method and COfv. Precision = standard deviation of the bias. SVR = systemic vascular resistance (dyne•s•cm^{-5}); APACHE II score = Acute Physiology and Chronic Health Evaluation score; % error = percentage of error (1.96 x standard deviation/mean CO). ★ = parts were published as abstracts[1 2]

We investigated as well changes in cardiac output in patients undergoing hemisympathectomy in elective orthopaedic surgery (**chapter 5**). We evaluated the difference between calibrated (COap) and uncalibrated (COfv) arterial pressure waveform analysis with COtptd (EV 1000™, Edwards Lifesciences, Irvine, CA, USA) in critically ill patients in the course of treatment for severe sepsis in the intensive care unit (ICU; **chapter 6**). Finally we reviewed the available literature regarding FloTrac/Vigileo™ in relation to different software versions, and its use in a number of clinical conditions (**chapter 7**).

Chapter 1 provides a general introduction of this thesis including its specific aims.

C**hapter 2** presents an overview of the available choices for haemodynamic monitoring in specific clinical settings, in an era dominated by lack of proven survival benefits for any haemodynamic monitoring device. The content is divided in four areas of interest; these include equipment properties (including parameters and limitations), theoretical background, hardware and patient bound considerations. Decision making for using different haemodynamic monitoring devices may improve when those four areas explored systematically and predefined checklist are used. This approach may help to end debates on the use of haemodynamic monitoring equipment from a single perspective only. The sole purpose for haemodynamic measurement devices is providing the physician with adequate knowledge that contributes to the patient's recovery and prevents complications.

C**hapter 3** describes the results of a comparison between PAC -derived thermodilution cardiac output (COtd) with FloTrac/Vigileo™ derived cardiac output (COfv) in patients with septic shock. We compared cardiac output (CO) measurements in two consecutive FloTrac™ software versions (1.07 and 1.10) and found that COfv underestimates COtd in patients suffering from septic shock. The difference however is less in the FloTrac/Vigileo™ 1.10 software version compared to the 1.07 version. The bias increases at higher CO values and inversely relates to mean arterial pressure (MAP), indicating that the accuracy of the system critically depends on the degree to which changes in vascular tone are taken into account by the software. Changes in COtd were better predicted by changes in COfv in the 1.10 software version.

C**hapter 4** describes the haemodynamic effects, measured by the FloTrac/Vigileo™ system, of the combined psoas compartment – sciatic nerve block (CPCSNB), which induces a hemisympathectomy with vasodilatation in the anesthetized limb. Post-CPCSNB haemodynamic values were compared to pre-CPCSNB values. Cardiac index did not change. Small but statistically significant changes were seen in stroke volume (decrease), heart rate (increase), mean and diastolic blood pressure (decrease) and total systemic vascular resistance (decreases). All changes were within a clinical acceptable range (less than 10% from baseline values). Hemisympathectomy induced by a CPCSNB does not change CO significantly from a clinical point of view when measured by FloTrac/Vigileo™ system.

In **chapter 5** we compared COfv measurements with COtd, using the 3.02 software version. We found that COfv underestimates COtd in patients suffering from sepsis or septic shock. The bias between paired measurements is inversely related to vascular tone. Our results appear to be in contrast with the original multicentre validation

study. However patients were probably more seriously ill compared to the original validation group. Our results reflect the performance of the FloTrac/Vigileo™ system at a lower range of systemic vascular resistance (SVR). Sub analysis shows that at an SVR above 700 dyne·s·cm^{-5}, our results are in agreement with the original validation study. The FloTrac/Vigileo™ version 3.02, in contrast to previous ones, is suitable for tracking clinically relevant CO changes in septic shock, even more so than for estimating absolute numbers of CO.

In **chapter 6** we presented the results of the validation study between intermittent TPTD CO (COtptd) with calibrated arterial pressure waveform analysis cardiac output (COap), both measured by the VolumeView/EV 1000**™** monitoring platform, and with CO measured by uncalibrated arterial pressure waveform analysis by the FloTrac/ Vigileo**™** monitor (COfv) in critical ill patients diagnosed and treated for severe sepsis or septic shock during their admission to the intensive care unit. Intermittent COtptd and COap have a %error of 31%. The difference between COtptd and COap remains clinically acceptable (% error < 30%) up until 8 hours after calibration and recalibration is required hereafter. Comparing COtptd vs. COfv revealed a bias (precision) 0.9 (1.8) L min^{-1} and a percentage error of 48%. COfv underscores compared COtptd and is inversely influenced by vascular tone. The recently introduced COap is superior to COfv for monitoring CO in patients with severe sepsis or septic shock compared to COtptd. The CO tracking capacity, of clinical significant CO changes, in patients with severe sepsis and septic shock for both measuring devices, COap and COfv is moderate to good compared to the changes in COtptd.

Chapter 7 is a meta analysis of the clinical studies where the FloTrac/Vigileo™ monitor was compared to other methods of measuring CO. One hundred and fifteen manuscripts were included in this review. In 65 papers CO was compared to a reference standard. The system performed better, considering bias, precision, percentage error, correlation and concordance in hypo- and normodynamic than in hyperdynamic (liver surgery and sepsis) conditions, even though performance increased with software updates. The latest software version (third generation) showed the best performance in hypo- and normodynamic conditions and decreased the percentage error to 30% or lower, which makes it (according to Critchley and Critchley criteria) interchangeable with their reference CO. FloTrac/Vigileo™-derived SVV is a better predictor and monitor of fluid responsiveness than static parameters. Recommendations for comparison of haemodynamic monitoring devices have rarely been fully followed, but quality of the reported data increases with newer software versions. Interventional studies published so far using the FloTrac/Vigileo™ monitor

in randomised clinical trials, have failed to reduce or improve either morbidity or mortality in this cohort of critically ill patients.

General discussion and future implications

Haemodynamic monitoring remains a cornerstone of critical care medicine,[3] and as mentioned in the introduction haemodynamic monitoring has two goals: 1) signalling function and 2) using the monitoring as a decision making tool.[4] This last goal is of increasing importance as it can help clinicians to make the right decision. Understandably haemodynamic goals are not limited to critical care medicine setting. With the introduction of the pulmonary artery catheter (PAC) clinicians were able to measure flow at the bedside. Many alternative cardiac output (CO) measuring devices have been introduce since (**chapter 2**). In recent years, the fluid management in general has attracted attention since studies have shown a relationship with complications. A parameter to help discriminate fluid responders from non responders was needed[5] in an effort to prevent the negative effects from fluid therapy. One of the early "dynamic" parameters pulse pressure variation (PPV) and stroke volume variation (SVV) were of interest more than 20 years ago.[6 7] It was much more sensitive to predict fluid responders than the "old" static parameters like central venous pressure and pulmonary artery occlusion pressure.[8 9] However in the intensive care, dynamic haemodynamic parameters have limited use because tidal volumes are relative low so heart lung interaction is reduced. Recently more limitations like, right ventricular dysfunction / failure and a wide PPV [10-15] have come to light. So clinical signs still remain an important trigger for fluid administration.[16 17] The FloTrac/Vigileo™ system derived SVV has been targeted with positive outcome in and outside the intensive care,[18 19 20] (**chapter 7**).

In a recent publication, Hamilton and colleagues showed in a meta analysis that haemodynamic optimisation reduces mortality and morbidity[21 22] and therefore will become the gold standard in perioperative medicine. High risk surgical patients benefit from haemodynamic optimisation using the FloTrac/Vigileo™ system too.[18 19] Identifying the patient who will most benefit from haemodynamic optimization has been done using risk stratifications or physical tests.[23-26] Combining the identification of high risk patients with pre-emptive haemodynamic interventions in the elective and the acute clinical setting will be a challenge for the years to come as our patients will become older, have more co-morbidities and stretch even further the ever increasing health costs. Cecconi et al[27] used the FloTrac/Vigileo™ to optimise twenty patients undergoing elective hip surgery under regional anaesthesia to reach supranormal haemodynamic values and compared them to 20 controls. They only found significant reductions of minor complications, in particular hypotension in the treatment group. Elective hip surgery by itself is characterised by a low complications rate. Establishing a direct relationship between improvement in morbidity and mortality, and the use of the FloTrac/Vigileo™ will require more than 20 patients. Using less invasive

monitoring devices and targeting SV or SVV will not reduce mortality as shown by Hamilton et al.[21] However future research addressing the high risk surgical patient group is still needed.[28]

In the past, groups of high risk surgical patients were identified and subjected to goals which everyone had to meet. Perhaps individual goals are more suitable. Which goal is preferable for each specific procedure in each particular patient remains the key question to be solved. Maybe the individual goals should be determined depending on the individual co-morbidities and organ dysfunction. Patients with active coronary ischemia could benefit from rate control while in the absents of significant coronary artery disease, increase of the oxygen delivery capacity could be beneficial.[28] Should we measure renal blood flow to prevent acute renal failure in patients who suffer from chronic renal failure during intensive care or surgical procedures? And what are the goals to target. Acute kidney injury has multiple causes. Hypovolaemia causes hypoperfusion of the kidney and secondary ischaemic kidney damage. Correcting hypovolaemia does prevent kidney injury as long as extra fluids are infused to increase the CO; unfortunately this strategy does not always succeed.[29] Should we integrate bio markers to construct individual goals, independent of the macro circulation with all its limitations?[30-35] It is possible to monitor the microcirculation at the bedside too, unfortunately the clinical significance of the measurements remain unclear.[36 37] Hopefully future research can change this. In the end we are left with the macro circulation and all its limitations, leaving a possible role for the FloTrac/Vigileo™ system which, within this background, has not been fully explored yet.[20]

Monitoring of the circulation in a "less invasive" way may have benefits. For instance using the arterial waveform can be done by using an existing arterial cannulae and hereby not inflicting additional complications compared to more invasive techniques. The FloTrac/Vigileo™ system uses such an existing arterial cannulae and a specialised blood pressure sensor. Unfortunately there are also disadvantages associated with the use of arterial waveform derived haemodynamics especially in patients suffering from sepsis and organ failure.[38-41] Jellema and colleagues[42] compared the Modelflow method and compared it with bolus thermodilution in sepsis patients. They found that uncalibrated measurements where less reliable compared to calibrated measurements and concluded that initial calibration of the Modelflow method was needed during sepsis. The FloTrac/Vigileo™ does not use external calibration to overcome the problem of unknown systemic vascular resistance and arterial compliance but uses an internal calibration to estimate arterial compliance.[43] At the introduction in 2005 the period in which the vascular tonus was (re)calculated was set on 10 minutes. The results of the early validation studies were disappointing. Software updates were

developed which led to an improvement in FloTrac™ performance (**chapter 3,7**). In general critically ill patients or (post)surgical patients (**chapter 4**) with presumably normodynamic conditions and in (post) cardiac surgery patients with presumably hypodynamic conditions, FloTrac/Vigileo™ can be used for routine haemodynamic monitoring using the latest (third generation) software version (**chapter 7**). For patients with liver disease (surgery) or sepsis with hyperdynamic haemodynamic conditions this does not apply. Our data show that COfv underestimates COtd and COtptd in patients with sepsis and septic shock (**chapter 3,5,6,7**). In line with Jellema and colleques[42] we found that calibrated arterial pressure waveform analysis performs better than uncalibrated arterial pressure waveform analysis in patients suffering from septic shock. The explicit loss of vascular tone which is present in these syndromes is responsible for underestimation of COfv especially when peripheral arteries are used to calculate SV[38] (**chapter 5,6**).

A CO measuring device that warns the clinician when less invasive uncalibrated devices lack accuracy would improve patient care. During the course of the patients critical illness, periods of low SVR can occur. A very low SVR has an adverse affect on the FloTrac/Vigileo™ accuracy as FloTrac/Vigileo™ system CO measurements do not reflect reference techniques (**chapter 3,5,6,7**). Using the waveform analysis to detect and report decoupling[38] would be of great added value for patient care. As the displayed haemodynamic values become unreliable, the option to introduce advanced haemodynamic monitoring or calibrate the uncalibrated version may be considered. At this moment the FloTrac/Vigileo™ can not be calibrated externally as yet. Maybe future developments can make this possible using the same catheter. At this moment we need another haemodynamic measuring system when we want to use calibrated waveform analysis.

Our data show that when the arterial waveform analysis (VolumeView/EV1000) is calibrated by COtptd, it maintains its clinical accuracy up until 8 hours, hereafter recalibration is needed (**chapter 6**). The calibrated waveform analysis outperforms the PiCCO pulse contour method by Pulsion Medical Systems, Munich, Germany. Hamzaoui[39] and co-workers showed that during the course of critically ill patients, most of them suffering from sepsis or septic shock recalibration was needed after one hour, as the %error increased above 30%. However we should keep in mind that all less invasive haemodynamic measuring devices do not fulfill the Critchley and Critchley criteria.[44] Software updates have led to an improved performance compared with COtptd and PAC derived COtd (**chapter 3,7**) but when the SVR drops below 700 dyne·s·cm^{-5} uncalibrated FloTrac/Vigileo™ performance is inaccurate for clinical use (**chapter 5,6,7**). The percentage of error is following Critchley and Critchley

proposal,[45] too high (**chapter 5,6,7** and Table 1). The bias between COfv and COtd or COtptd is inversely related to loss of vascular tonus at the lower range of SVR (**chapter 5,6,7**). Its use under these extreme clinical circumstances is not advised at this moment. Incorporating the correct vascular tonus / arterial compliance into less invasive CO models/algorithms requires external calibration when the patient suffers from a vasoplegic haemodynamic state (**chapter 6**).[39 42]

Because of its plug and play principle this system has the potential to be used outside the operation rooms and intensive care. Although our healthcare system is not comparable with the one in the USA, there is a potential for its use in the emergency room (ER). As Rivers et al.[46] used central venous saturation in the early goal directed therapy of sepsis this monitor also offers the possibility to integrate CO into patient monitoring and treatment. The FloTrac/Vigileo™ monitor gives us the option to use $ScvO_2$ and with it oxygen delivery and consumption can be monitored. The haemodynamic profile of patients in acute or chronic heart failure fits, the FloTrac/Vigileo™ system (low CO high SVR) perfectly (**chapter 7**). So the coronary care unit is another area in which the FloTrac/Vigileo™ could be of benefit. Future research should focus on acute or chronic heart failure as there are no published articles at this moment investigating its use in this patient population.

Despite the enormous increase of clinical research on the application of the FloTrac/Vigileo™ system, its use has not proven a consistent and reproducible improvement in mortality (**chapter 7**). In our view, the next definitive study should be multi-centre, focus on an early intervention,[46 47] before the development of multi-organ failure [48-50] and the therapy should be guided by a protocol since the lack of a protocol has not led to better outcomes.[47 50 51] The study which addresses all aforementioned points would be of great value.

There are also limitations within this thesis. All validation studies were performed in patients suffering from the sepsis or septic shock syndrome. A complex syndrome with multiple confounding factors. All studies were prospective observational and performed in one same hospital. Despite this our results are in line with results from other validation studies performed in septic patients.[52-56] In some studies the patient groups are relatively small (**chapter 3**). In all the validation studies repeated measurements are performed in the same patient. Although this factor was corrected, it could have influenced our results.

This thesis describes the clinical use of one of the newest haemodynamic monitoring devices introduced in 2005. We have improved our knowledge of the haemodynamic

monitoring device that uses waveform analysis without external calibration, the FloTrac/Vigileo™ system. The amount of publications on haemodynamic monitoring is profuse and does not seem to abate. New developments within this field of intensive care and anaesthesiology are numerous making it almost impossible to keep abreast. The principle goal of haemodynamic monitoring is to improve patient outcome. Ideally it is the patient's clinical presentation combined with the limitations and possibilities of each haemodynamic monitoring system that should determine which monitor is the best choice for that patient at that moment (**chapter 2**). If the clinical condition changes the haemodynamic monitoring should (could) change too. The introduction of a new haemodynamic monitoring system is a challenge that requires financial investment and training in new skills. When applied correctly patients benefit and costs are saved by reducing morbidity and morbidity.[28]

Conclusion

The FloTrac/Vigileo™ system performance has improved with new software versions. It can be clinically used in patients with hypo- or normodynamic haemodynamics like general ICU and postcardiac surgery patients. In patients suffering from severe sepsis, septic shock or liver surgery representing a hyperdynamic circulation, the vasoplegic state does not permit clinical use as yet. Advanced, more invasive haemodynamic monitoring is advised, using for instance calibrated waveform analysis. The calibrated waveform analysis (VolumeView/EV1000) performs better compared to the uncalibrated version FloTrac/Vigileo™ in patients with severe sepsis and septic shock. The calibrated waveform analysis remains clinical acceptable up until 8 hours after calibration. The SVV derived from the FloTrac/Vigileo™ can be used for fluid management. Clinical significant changes in CO have moderate to good correlation with changes in reference CO in patients with severe sepsis and septic shock. Future research should focus on high risk surgical patients, patients suffering from acute and chronic cardiac failure, combining individual haemodynamic monitoring devices, individual haemodynamic goals in relation with patient benefits.

References

1. Slagt C, Malagon I, Beute J, et al. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). Dutch Society Intensive Care 2008. Book of abstracts P10:p14
2. Slagt C, Malagon I, Beute J, et al. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists, Faculty of Pain Medicine and the Joint Faculty of Intensive Care 2008, Sydney. Book of abstracts P61
3. Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. *Crit Care* 2011; 15:214.
4. Vincent JL, Rhodes A, Perel A, et al. Clinical review: Update on haemodynamic monitoring - a consensus of 16. *Crit Care* 2011;15:229.
5. Hofer CK, Cannesson M. Monitoring fluid responsiveness. *Acta Anaesthesiol Taiwan* 2011;49:59-65.
6. Michard F. Changes in Arterial Pressure during Mechanical. *Anesthesiology* 2005;103:419-28.
7. Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000;4:282-289.
8. Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984;12:107-12.
9. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004;32:691-9.
10. Daudel F, Tüller D, Krähenbühl S, et al. Pulse pressure variation and volume responsiveness during acutely increased pulmonary artery pressure: an experimental study. *Crit Care* 2010;14:R122.
11. Wyler von Ballmoos M, Takala J, Roeck M, et al. Pulse-pressure variation and haemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care* 2010;14:R111.
12. Magder S. Further cautions for the use of ventilatory-induced changes in arterial pressures to predict volume responsiveness. *Crit Care* 2010;14:R197.
13. De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005;31:517-523.
14. Kim HK, Pinsky MR: Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. *Crit Care Med* 2008;36:2858-2862.
15. De Backer D, Taccone FS, Holsten R, et al. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009;110:1092-7.
16. Monge García MI, Gil Cano A, Díaz Monrové JC. Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients. *Crit Care* 2009;13:R142.
17. Takala J, Ruokonen E, Tenhunen J, et al. Early noninvasive cardiac output monitoring in haemodynamically unstable intensive care patients: a multi-center randomized controlled trial. *Crit Care* 2011;15:R148
18. Benes J, Chytra I, Altman P, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of a prospective randomized study. *Crit Care* 2010;14:R118.
19. Mayer J, Boldt J, Mengistu A, et al. Goal-directed intraoperative therapy based on arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized controlled trial. *Crit Care* 2010;14:R18.
20. Scheeren TW, Wiesenack C, Gerlach H, et al. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: a prospective randomized multicentre study. *J Clin Monit Comput* 2013;27:225-33.
21. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive haemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011,112:1392-1402.
22. Gurgel ST, do Nascimento P Jr. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. *Anesth Analg* 2011;112:1384-1391.
23. Shoemaker W C, Appel P L, Kram H B, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;94:1176-1186.
24. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991;78:355-60.
25. Older P, Hall A, Hader R: Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 1999;116:355-362.

26. Liebman B, Strating RP, van Wieringen W, et al. Risk modelling of outcome after general and trauma surgery (the IRIS score). *Br J Surg* 2010;97:128-33.
27. Cecconi M, Fasano N, Langiano N, et al. Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. *Crit Care* 2011;15:R132.
28. Lobo SM, de Oliveira NE. Clinical review: What are the best haemodynamic targets for noncardiac surgical patients? *Crit Care* 2013;19:17:210.
29. Brienza N, Giglio MT, Marucci M, et al. Does perioperative haemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009;37:2079-2090.
30. Ye J, Chen Z, Wang T, et al. Role of tissue disorder markers in the evaluation of disease progress and outcome prediction: a prospective cohort study in non-cardiac critically ill patients.*J Clin Lab Anal* 2010;24:376-84.
31. Chaykovska L, Tsuprykov O, Hocher B. Biomarkers for the prediction of mortality and morbidity in patients with renal replacement therapy. *Clin Lab* 2011;57:455-67.
32. Sun T, Wang X, Liu Z, et al. Plasma concentrations of pro- and anti-inflammatory cytokines and outcome prediction in elderly hip fracture patients. *Injury* 2011;42:707-13.
33. Kolditz M, Ewig S, Höffken G. Management-based risk prediction in community-acquired pneumonia by scores and biomarkers. *Eur Respir J* 2013;41:974-84.
34. Palazzuoli A, Masson S, Ronco C, et al. Clinical relevance of biomarkers in heart failure and cardiorenal syndrome: the role of natriuretic peptides and troponin. *Heart Fail Rev* 2013 Apr 7. In press.
35. McLean AS, Huang SJ, Salter M. Bench-to-bedside review: the value of cardiac biomarkers in the intensive care patient. *Crit Care* 2008;12:215.
36. De Backer D, Ospina-Tascon G, Salgado D, et al. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med* 2010;36:1813–1825.
37. Spronk PE, Zandstra DF, Ince C. Bench-to-bedside review: sepsis is a disease of the microcirculation. *Crit Care* 2004;8:462-8.
38. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J appl physio* 2011; 111:853-60.
39. Hamzaoui O, Monnet X, Richard C, et al. Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. *Crit Care Med* 2008;36:434-40.
40. Krejci V, Vannucci A, Abbas A, et al. Comparison of calibrated and uncalibrated arterial pressure-based cardiac output monitors during orthotopic liver transplantation. *Liver Transpl* 2010;16:773-82.
41. Yamashita K, Nishiyama T, Yokoyama T, et al. Effects of vasodilation on cardiac output measured by PulseCO. *J Clin Monit Comput* 2007;21:335-9.
42. Jellema WT, Wesseling KH, Groeneveld AB, et al. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* 1999;90:1317-28.
43. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-411.
44. Peyton PJ, Chong SW.Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. *Anesthesiology* 2010;113:1220-35.
45. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85-91.
46. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
47. Takala J, Ruokonen E, Tenhunen JJ, et al. Early non-invasive cardiac output monitoring in haemodynamically unstable intensive care patients: a multi-center randomized controlled trial. *Crit Care* 2011;15:R148.
48. Kern JW, Shoemaker WC. Meta-analysis of haemodynamic optimization in high-risk patients. *Crit Care Med* 2002;30:1686-1692.
49. Hayes MA, Timmins AC, Yau EH, et al. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med* 1997;25:926-936.
50. Rhodes A, Cusack RJ, Newman PJ, et al. A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. *Intensive Care Med* 2002;28:256-264.
51. Harvey SE, Welch CA, Harrison DA, et al. Post hoc insights from PACMan-the U.K. pulmonary artery catheter trial. *Crit Care Med* 2008;36:1714-1721.

52. Sakka SG, Kozieras J, Thuemer O, et al. Measurement of cardiac output: a comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007;99:337-342.
53. Monnet X, Anguel N, Naudin B, et al. Arterial pressure based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010;14:R109.
54. De Backer D, Marx G, Tan A, et al. Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. *Intensive Care Med* 2011;37:233-240.
55. Monnet X, Anguel N, Jozwiak M, et al. Third-generation FloTrac/Vigileo does not reliably track changes in cardiac output induced by norepinephrine in critically ill patients. *Br J Anaesth* 2012;108:615-622.
56. Marqué S, Gros A, Chimot L, et al. Cardiac output monitoring in septic shock: evaluation of the third-generation Flotrac-Vigileo. *J Clin Monit Comput* 2013;27:273-9

.

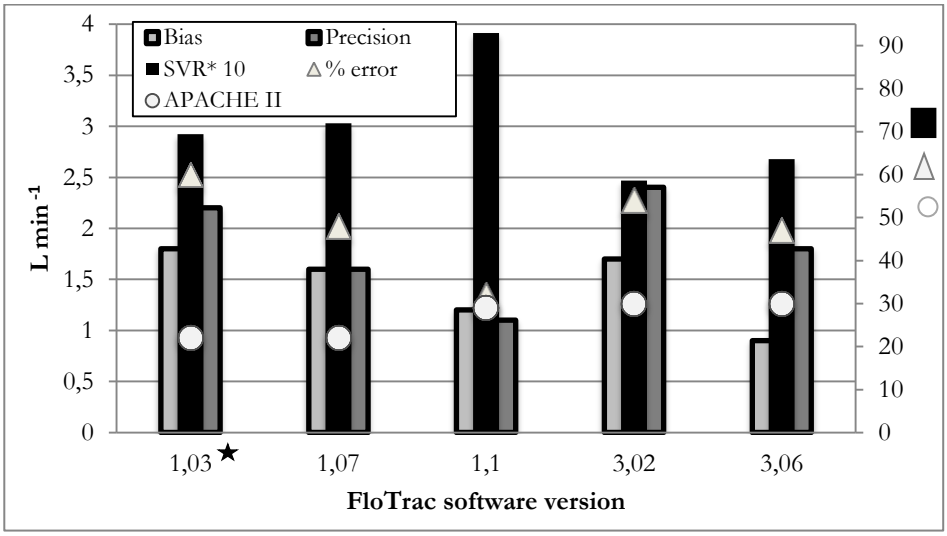
9

Nederlandse samenvatting en discussie

Samenvatting

In dit proefschrift hebben we geprobeerd om onze kennis met betrekking tot de hemodynamische bewakingsmonitor, de FloTrac/Vigileo™ monitor te verbeteren. De FloTrac/Vigileo™ past arteriële drukgolf analyse toe zonder externe kalibratie. Hierbij is de nadruk gelegd op het gebruik, de nauwkeurigheid en de reproduceerbaarheid van hartminuutvolume (HMV) meting onder verschillende klinische omstandigheden. Het HMV gemeten met de FloTrac/Vigileo™ monitor (COfv) is, met name bij intensive care patiënten met meestal sepsis, bepaald. In dit proefschrift zijn opeenvolgende softwareversies (versie 1.03, 1.07, 1.10, 3.02 en 3.06) vergeleken met de pulmonalis katheter (PAC) en trans pulmonale thermodilutie (TPTD) (**hoofdstuk 3,4,6,7**). Een overzicht van de resultaten is te vinden in tabel 1.

Tabel 1. Resultaten van de FloTrac/Vigileo™ validatiestudies welke plaatsvonden in het Zaans Medisch Centrum.



Bias = gemiddeld verschil tussen de referentiemethode en COfv. Precisie = standaarddeviatie rondom het gemiddelde verschil. SVR = systemische vaatweerstand (dyne•s•cm^{-5}); APACHE II score = Acute Physiology and Chronic Health Evaluation score; %error = foutpercentage (1,96 x standaardafwijking / gemiddelde CO). ★ = resultaten werden gepubliceerd als abstracts[1 2].

Naast patiënten met sepsis hebben we ook gekeken naar veranderingen in het HMV bij geplande orthopedische revisie chirurgie (**hoofdstuk 5**). In **hoofdstuk 6** hebben we gekeken naar het verschil tussen het HMV gemeten met gekalibreerde (COap) en niet gekalibreerde (COfv) arteriële drukgolf analyse ten opzichte van het HMV gemeten met trans pulmonale thermodilutie (COtptd; EV 1000 ™, Edwards Lifesciences, Irvine, CA, USA). Deze patiënten waren opgenomen op de intensive care voor behandeling van ernstige sepsis en septische shock. Tot slot hebben we de beschikbare literatuur van de FloTrac/Vigileo™ monitor, in relatie tot verschillende

softwareversies en het gebruik tijdens een aantal klinische aandoeningen, beoordeeld (**hoofdstuk 7**).

Hoofdstuk 1 bestaat uit een algemene inleiding met het doel van dit proefschrift.

In **hoofdstuk 2** beschrijven we in een overzichtsartikel keuze gebieden die kunnen helpen bij het kiezen van een bepaalde hemodynamische monitor, in een tijdperk gedomineerd door het gebrek aan bewezen overlevingsvoordelen voor welk type hemodynamisch bewakingsapparaat dan ook. Het artikel is opgebouwd uit vier keuze gebieden: materiaal eigenschappen (inclusief parameters en beperkingen), theoretische achtergrond, hardware en patiënt gebonden overwegingen. Het maken van de keuze, welke hemodynamische monitor bij welke patiënt, kan verbeteren wanneer elk van de vier gebieden systematisch en/of met behulp van een vooraf opgestelde checklist kan worden doorlopen. Hopelijk kan dit bijdragen om de voortdurende discussie over welke hemodynamische bewakingsapparatuur bij welke patiënt te beëindigen. Het enige doel van hemodynamische bewaking is het leveren van adequate hemodynamische gegevens aan de arts welke tevens bijdraagt tot het herstel van de patiënt en het voorkomen van complicaties.

Hoofdstuk 3 beschrijft de resultaten van de vergelijking tussen het met de PAC-thermodilutie gemeten HMV (COtd) en het HMV gemeten met de FloTrac/Vigileo™ (COfv) bij patiënten met septische shock. We vergeleken de HMV meting in twee op elkaar volgende FloTrac™ softwareversies (1.07 en 1.10) en vonden dat COfv de COtd meting onderschat bij patiënten gedurende de behandeling van septische shock. Het verschil tussen COfv en COtd is echter kleiner in de FloTrac/Vigileo™ software versie 1.10 ten opzicht van de 1.07 versie. Het gemiddelde verschil tussen COfv en COtd neemt toe bij hogere HMV waarden en heeft een negatieve relatie met de gemiddelde bloeddruk, wat aangeeft dat de nauwkeurigheid van het systeem afhankelijk is van de mate waarin de veranderingen in de vaatwand spanning worden meegenomen door de softwareversie. Veranderingen in COtd werden beter voorspeld door veranderingen in COfv in de software versie 1.10.

Hoofdstuk 4 beschrijft de hemodynamische effecten, gemeten met de FloTrac/Vigileo™ monitor, van het gecombineerde psoas compartiment-nervus zenuwblokkade (CPCSNB), welke klinisch een hemi sympathectomie induceert door vaatverwijding in het verdoofde ledemaat. Post-CPCSNB hemodynamische waarden werden vergeleken met pre-CPCSNB hemodynamische waarden. De cardiale index veranderde niet. Kleine maar statistisch significante veranderingen werden gezien in slagvolume (afname), hartslag (toename), gemiddelde en diastolische bloeddruk

(afname) en de totale systemische vaatweerstand (afname). Alle veranderingen vallen binnen de klinisch acceptabele grenzen (minder dan 10% van de uitgangswaarden). Een hemi sympathectomie geïnduceerd door een CPCSNB leidt niet tot een klinisch relevante hartminuutvolume verandering gemeten door FloTrac/Vigileo™ systeem.

In **hoofdstuk 5** vergeleken we COfv metingen met COtd metingen met behulp van de FloTrac/Vigileo™ softwareversie 3.02. We vonden dat COfv metingen de COtd metingen onderschatten bij patiënten met sepsis of septische shock. Het verschil tussen de twee metingen is omgekeerd evenredig aan de vaatwand spanning. Onze resultaten lijken niet overeen te komen met de oorspronkelijke multicenter validatiestudie. Echter onze patiënten waren waarschijnlijk zieker dan patiënten in de validatiestudie. Onze resultaten weerspiegelen de prestaties van het FloTrac/Vigileo™ systeem bij een gemiddeld lagere systemische vasculaire weerstand (SVR). Uit sub analyse blijkt dat wanneer de SVR boven 700 dyne·s·cm^{-5} komt, onze resultaten in overeenstemming zijn met de oorspronkelijke validatiestudie. De FloTrac™ software versie 3.02 is in tegenstelling tot de voorgaande versies beter geschikt voor het bijhouden van klinisch relevante HMV veranderingen bij septische shock, meer nog dan voor het inschatten van de absolute waarde van het HMV.

In **hoofdstuk 6** worden de resultaten gepresenteerd van de validatiestudie tussen TPTD gemeten HMV (COtptd) en het HMV bepaald door de gekalibreerde (COap) en de niet gekalibreerde (COfv) arteriële drukgolf analyse bij ernstig zieke patiënten behandeld voor ernstige sepsis of septische shock. COtptd en COap worden beide gemeten door de VolumeView/EV1000 **™** monitor. COfv wordt gemeten door de FloTrac/Vigileo**™** monitor. De metingen tussen COtptd en COap hebben een fout percentage van 31 %. Het verschil tussen beide metingen blijft gedurende 8 uur klinisch aanvaardbaar (fout percentage< 30 %). Na 8 uur is her kalibratie vereist. Het verschil tussen de COtptd en COfv metingen was gemiddeld (standaard deviatie) 0,9 (1,8) L min^{-1} met een foutpercentage van 48 %. Het verschil tussen COfv en COtptd is omgekeerd evenredig aan de vaatwand tonus. De onlangs geïntroduceerde COap is superieur ten opzichte van de COfv bij hemodynamische bewaking van het HMV bij patiënten met ernstige sepsis en septische shock vergeleken met COtptd als referentie. De mogelijkheid om klinisch relevante veranderingen van het HMV te vervolgen in de tijd bij patiënten met ernstige sepsis en septische shock is voor zowel COap als COfv redelijk tot goed in vergelijking met de veranderingen in COtptd.

Hoofdstuk 7 is een meta-analyse van klinische studies waarbij de FloTrac/Vigileo™ monitor is gebruikt. Honderd en vijftien manuscripten werden opgenomen in deze analyse. In 65 publicaties werd het HMV gemeten met de FloTrac/Vigileo™ monitor

vergeleken met een referentie methode. Het systeem presteerde beter bij patiënten met een hypo-en normo dynamische circulatie (met betrekking tot nauwkeurigheid, reproduceerbaarheid, fout percentage, correlatie en concordantie) dan bij patiënten met een hyper dynamische (leverchirurgie en sepsis) circulatie. De prestaties in de laatste groep verbeterden met software-updates. De nieuwste softwareversie (derde generatie) toonde de beste prestaties in hypo-en normo dynamische omstandigheden. Het fout percentage daalde tot 30% of lager waardoor het (volgens Critchley en Critchley maatstaven) uitwisselbaar wordt met de referentie meetmethode. FloTrac/Vigileo™-afgeleide SVV is een betere voorspeller en monitor van vloeistof responsiviteit dan statische parameters. Aanbevelingen over de kwaliteit van de validatie studies met betrekking tot hemodynamische monitoring worden zelden volledig opgevolgd. De kwaliteit van de gepubliceerde artikelen neemt toe bij de nieuwere softwareversies. De tot nu toe gepubliceerde gerandomiseerde klinische studies met betrekking tot de FloTrac/Vigileo™ monitor hebben nog geen mortaliteit reductie kunnen aantonen bij ernstig zieke patiënten.

Algemene discussie en toekomstige implicaties

Hemodynamische monitoring blijft een belangrijk onderdeel van de intensive care geneeskunde.[3] Zoals reeds vermeld in de inleiding heeft hemodynamische monitoring twee doelen: 1) een signaalfunctie en 2) gebruik van hemodynamische monitoring in de besluitvorming van de behandeling.[4] Dit laatste doel is van toenemend belang aangezien het artsen kan helpen om de juiste beslissing te nemen. Ten overvloede; bovengenoemde hemodynamische doelen beperken zich niet alleen tot de intensive care geneeskunde. Met de introductie van de pulmonalis katheter (PAC) konden artsen het HMV van patiënten aan het bed meten. Nadien zijn er nog veel andere hemodynamische meetmethodes en monitoren geïntroduceerd (**hoofdstuk 2**). In de laatste jaren heeft het vochtbeleid meer aandacht gekregen omdat het geassocieerd werd met het optreden van complicaties. Een parameter die patiënten kon identificeren die goed zouden reageren op extra vocht toediening (responders) was nodig.[5] Tegelijkertijd was het nodig om patiënten die niet goed op extra vocht toediening zouden reageren (non-responders) te identificeren, dit om de negatieve aspecten van te veel vloeistof therapie te voorkomen. Van de "dynamische" parameters zijn de polsdruk variatie (PPV) en het slagvolume variatie (SVV) al meer dan 20 jaar bekend.[6 7] Beide zijn veel gevoeliger om vocht responders te voorspellen dan de "oude" statische parameters zoals centrale veneuze druk en de wiggedruk.[8 9] Echter op de intensive care hebben de dynamische hemodynamische parameters een beperkt gebruik. Vanwege de relatieve lage teugvolumes wordt de hart-long interactie verminderd. Recentelijk zijn er meer beperkingen van het gebruik van de dynamische parameters gepubliceerd zoals rechter ventrikel dysfunctie/falen en een breed PPV.[10-15] Dus klinische symptomen vormen nog steeds een belangrijke trigger voor vloeistof toediening.[16 17] De FloTrac/Vigileo™ monitor afgeleide SVV, als hemodynamisch doel, is met positief resultaat gebruikt in en buiten de intensive care (**hoofdstuk 7**).[18 19 20]

In een recente meta-analyse toonde Hamilton en collega's aan dat pre operatieve hemodynamische optimalisatie van hoog risico patiënten de mortaliteit en morbiditeit aanzienlijk vermindert.[21 22] Hoog risico chirurgische patiënten profiteren ook van hemodynamische optimalisatie met behulp van het FloTrac/Vigileo™ systeem.[18 19] Het identificeren van de patiënt die zal profiteren van hemodynamische optimalisatie wordt gedaan met behulp van risico stratificaties en/of lichamelijke tests.[23-26] Het combineren van hoog risico patiënten identificatie met preoperatieve hemodynamische optimalisatie tijdens zowel electieve en acute chirurgische ingrepen zal de uitdaging zijn voor de komende jaren. Onze patiënten worden ouder, hebben meer co-morbiditeit en hierdoor steeds meer invloed op het steeds verder stijgen van

de kosten voor de gezondheidszorg. Daarom zal hemodynamische optimalisatie in de toekomst een prominentere rol krijgen in de perioperatieve geneeskunde.

Cecconi en collega's[27] gebruikten de FloTrac/Vigileo™ monitor om twintig patiënten, die een electieve heupoperatie onder regionale anesthesie ondergingen te, optimaliseren tot supernormale hemodynamische waarden en vergeleken ze met 20 controle patiënten. Zij vonden slechts verminderingen van kleine complicaties zoals minder lage bloeddruk in de behandelgroep. Een electieve heupoperatie wordt gekenmerkt door weinig complicaties. Het verbeteren van de morbiditeit en mortaliteit bij electieve heup chirurgie zal een grotere onderzoeksgroep vereisen dan 20 patiënten. Het gebruik van minder invasieve hemodynamische monitoring en streven naar een optimaal slagvolume (SV) of SVV zal overeenkomstig met Hamilton en collega's[21] niet leiden tot mortaliteit reductie. Toekomstig onderzoek met de focus op hoog risico (chirurgisch) patiënten is nog steeds nodig.[28]

In het verleden werden chirurgisch hoog risico patiënten geïdentificeerd en als groep onderworpen aan hemodynamische doelen die iedereen moest zien te halen. Misschien zijn individuele doelen wel meer geschikt. Welk hemodynamisch eindpunt heeft de voorkeur bij deze specifieke chirurgische procedure in deze specifieke patiënt is één van centrale vragen die wij de komende periode moeten proberen op te lossen. Misschien moeten individuele hemodynamische eindpunten worden bepaald afhankelijk van de individuele co-morbiditeit en/of orgaan falen. Hartpatiënten met bewezen coronaire ischemie zouden kunnen profiteren van bèta blokkade terwijl patiënten zonder coronaire ischemie juist baat zouden kunnen hebben bij een verhoging van de hartslag en hiermee toegenomen zuurstof transport.[28] Moeten we de nier doorbloeding gaan meten om acute nierinsufficiëntie te voorkomen bij patiënten met chronisch nierfalen op de intensive care of tijdens chirurgische procedures? En wat zijn dan de einddoelen die we moeten zien te behalen. Acute nier insufficiëntie heeft vele verschillende oorzaken. Intravasculaire onder vulling veroorzaakt hypoperfusie van de nier en secundair hieraan ontstaat ischemische nier schade. Correctie van intravasculair onder vulling kan nier schade voorkomen zolang het extra vocht dat wordt toegediend zich vertaalt in een toegenomen HMV. Helaas is deze strategie niet altijd succesvol.[29] Moeten we bio markers integreren binnen de individuele hemodynamische doelen?[30-35] Het is mogelijk om de microcirculatie aan het bed in beeld te krijgen. Helaas is de klinische betekenis van deze metingen en de onderlinge samenhang nog onduidelijk.[36 37] Hopelijk gaat toekomstig onderzoek dit veranderen. Vooralsnog blijven we afhankelijk van de macro-circulatie en al zijn beperkingen. Een eventuele toekomstige rol voor de FloTrac/Vigileo™ monitor binnen boven geschetste klinische dilemma is nog niet volledig onderzocht.[20]

De FloTrac/Vigileo™ monitor maakt gebruik van een gespecialiseerde bloeddruk sensor die op iedere bestaande arterielijn kan worden aangesloten. Hierdoor worden geen extra risico's toegevoegd zoals kan gebeuren bij meer invasieve technieken, bijvoorbeeld inbrengen nieuwe arterielijn. Helaas zijn er ook nadelen verbonden aan het gebruik van de arteriële drukgolf verkregen hemodynamische waarden, speciaal bij patiënten met sepsis en orgaan falen.[38-41] Jellema en colleagues[42] vergeleken het HMV berekend middels de Modelflow methode met het HMV gemeten middels bolus thermodilutie bij patiënten met sepsis. Zij vonden dat de niet-gekalibreerde Modelflow metingen minder betrouwbaar waren ten opzichte van de gekalibreerde metingen en concludeerde dat initiële kalibratie van de Modelflow methode nodig was bij patiënten met sepsis. De FloTrac/Vigileo™ monitor maakt geen gebruik van externe kalibratie om het probleem van de onbekende SVR en arteriële compliantie te berekenen, maar gebruikt een interne kalibratie voor de schatting van de arteriële compliance.[43] Bij de introductie in 2005 werd iedere 10 minuten de vasculaire tonus (her)berekend. De resultaten van de vroege validatiestudies waren teleurstellend. Software-updates zijn ontwikkeld en die hebben geleid tot een verbetering van FloTrac™ prestaties (**hoofdstuk 3,7**). Intensive care en (post) operatieve patiënten (**hoofdstuk 4**) met vermoedelijk "normale" hemodynamiek en (post) operatieve cardio chirurgische patiënten met vermoedelijk hypo dynamische hemodynamiek kunnen met de derde generatie software van de FloTrac/Vigileo™ monitor bewaakt worden (**hoofdstuk 7**). Voor patiënten die lijden aan een ernstige sepsis of leverziekte, gekenmerkt door een hyper dynamische circulatie, geldt dit niet. Onze gegevens laten zien dat COfv de waardes van COtd en COtptd bij patiënten met sepsis en septische shock onderschat (**hoofdstuk 3,5,6,7**). Net als Jellema en collega's[42] vonden wij dat gekalibreerde arteriële drukgolf analyse beter presteert dan de niet gekalibreerde versie bij patiënten met ernstige sepsis of septische shock. Het expliciete verlies van vaatwand spanning, aanwezig bij deze syndromen, is verantwoordelijk voor de onderschatting van COfv vooral wanneer perifere slagaders worden gebruikt als meetlocatie van het SV[38] (**hoofdstuk 5,6**).

Tijdens een opname van ernstig zieke patiënten kunnen perioden van lage SVR voorkomen. Een zeer lage SVR heeft een negatieve invloed op de nauwkeurigheid van de FloTrac/Vigileo™ meting. De FloTrac/Vigileo™ meting onderschat dan het HMV ten opzichte van de referentietechniek (**hoofdstuk 3,5,6,7**). Met behulp van de arteriële drukgolf analyse zou het detecteren en rapporteren van het proces genaamd "decoupling"[38] van grote waarde zijn. Als dit proces ontstaat (sepsis) zijn de weergegeven hemodynamische waarden onbetrouwbaar geworden. De arts kan dan kiezen om geavanceerde hemodynamische bewaking te introduceren of, indien al in

gebruik, een re-kalibratie uit te voeren. Op dit moment kan de FloTrac/Vigileo™ niet extern gekalibreerd worden door het ontbreken van een temperatuur sensor op de katheter. Er moet een specifieke arterielijn ingebracht worden als we gebruik willen maken van gekalibreerde arteriële drukgolf analyse. Misschien dat toekomstige ontwikkelingen dit wel mogelijk kunnen maken. Er hoeft dan geen nieuwe arterielijn geplaatst te worden wat weer goed is voor patiëntveiligheid.

Onze resultaten laten zien dat wanneer de arteriële drukgolf analyse (VolumeView/EV1000) wordt gekalibreerd met behulp van COtptd, de HMV waardes tot 8 uur nauwkeurig blijven. Na 8 uur is her kalibratie nodig (**hoofdstuk 6**). Deze gekalibreerde arteriële drukgolf analyse presteert beter dan de PiCCO puls contour methode (Pulsion Medical Systems, München, Duitsland). Hamzaoui[39] en medewerkers lieten zien dat tijdens de behandeling van ernstig zieke ICU patiënten, waarvan de meeste leden aan sepsis of septische shock, her kalibratie nodig was na een uur, omdat dan het foutpercentage boven de 30% steeg. Echter, we moeten niet vergeten dat veel minder invasieve hemodynamische monitoren niet voldoen aan de Critchley en Critchley criteria.[44] FloTrac/Vigileo™ software-updates hebben geleid tot een verbeterde nauwkeurigheid van de HMV meting, vergeleken met de COtptd en COtd HMV meting (**hoofdstuk 3,7**). Als de SVR daalt onder de 700 dyne·s·cm^{-5} dan zijn de prestaties van FloTrac/Vigileo™ monitor te onnauwkeurig voor klinisch gebruik (**hoofdstuk 5,6,7**). Het fout percentage wordt volgens Critchley en Critchley maatstaven te hoog (**hoofdstuk 5,6,7** en tabel 1).[45] Het gemiddelde verschil tussen COfv en COtd of COtptd is omgekeerd evenredig aan het verlies van vaatwand spanning in het lagere bereik van de SVR (**hoofdstuk 5,6,7**). Het correct integreren van de juiste vasculaire tonus of arteriële compliantie in minder invasieve HMV modellen of algoritmes vereist externe kalibratie wanneer de patiënt lijdt aan ernstige vasodilatatie (**hoofdstuk 6**).[39 42]

Vanwege het "plug and play" principe van dit apparaat heeft het ook potentie om buiten de intensive care of operatiekamers gebruikt te kunnen worden. Hoewel onze gezondheidszorg niet vergelijkbaar is met die van in de Verenigde Staten, zou het prima op de spoedafdeling (SEH) gebruikt kunnen worden. Rivers en collega's[46] gebruikten de centraal veneuze saturatie ($ScvO_2$) als hemodynamisch doel in hun studie van vroeg en doelgerichte behandeling van sepsis. De FloTrac/Vigileo™ monitor heeft de mogelijkheid om $ScvO_2$ en het HMV samen weer te geven. Hiermee kan zuurstof aanbod en verbruik worden gemonitord. Het hemodynamische profiel van patiënten met acute of chronisch hartfalen past prima bij de FloTrac/Vigileo™ monitor (laag HMV hoog SVR) (**hoofdstuk 3,5,6,7**). Het gebruik van de FloTrac/Vigileo™ monitor bij acuut of chronisch hartfalen is iets voor toekomstig

onderzoek, daar er tot op heden geen publicaties over deze patiëntengroepen bekend zijn.

Ondanks de enorme toename van het klinisch onderzoek naar de toepassing van de FloTrac/Vigileo™ heeft het nog niet geleid tot een consistente en reproduceerbare verlaging van de mortaliteit (**hoofdstuk 7**). Naar onze mening zou dat kunnen worden onderzocht in een multicenter studie, gericht op een vroege interventie,[46 47] bij patiënten voordat er orgaan falen is opgetreden. [48-50] In de behandelgroep dient de therapie geprotocolleerd te worden aangezien er bij het ontbreken van een behandelprotocol geen betere uitkomst is gevonden.[47 50 51] Een studie richt zich op alle deze punten is van grote klinische waarde.

Er zijn ook beperkingen binnen dit proefschrift. Alle validatiestudies werden uitgevoerd tijdens de behandeling van patiënten die lijden aan sepsis of septische shock. Dit is een complex syndroom met vele verstorende factoren. Alle studies waren prospectief observationeel en uitgevoerd op dezelfde intensive care afdeling van hetzelfde ziekenhuis. Ondanks dit komen onze resultaten overeen met de resultaten van andere validatiestudies uitgevoerd bij septische patiënten.[52-56] In sommige studies zijn de patiëntengroepen klein (**hoofdstuk 3**). In alle validatiestudies zijn meerdere metingen verricht bij dezelfde patiënt. Hoewel hiervoor gecorrigeerd is kan het onze resultaten hebben beïnvloed.

Dit proefschrift beschrijft het klinisch gebruik van één van de nieuwste hemodynamische bewaking apparaten geïntroduceerd in 2005. We hebben onze kennis van dit apparaat, dat gebruik maakt van arteriële drukgolf analyse zonder externe kalibratie, de FloTrac/Vigileo™ monitor, vergroot. De hoeveelheid publicaties over hemodynamische bewaking is overvloedig en lijkt niet te verminderen. Nieuwe ontwikkelingen binnen dit gebied van de intensive care en anesthesie zijn talrijk waardoor het bijna onmogelijk is om volledig op de hoogte te blijven. Het voornaamste doel van hemodynamische bewaking is het verbeteren van de patiëntenzorg. Het is het klinische beeld van de patiënt in combinatie met de beperkingen en mogelijkheden van elk hemodynamische monitoring systeem, wat bepaalt welke hemodynamische monitor gebruikt zou moeten worden (**hoofdstuk 2**). Indien de klinische toestand van de patiënt verandert dan zou ook de hemodynamische monitoring moeten (kunnen) veranderen. De introductie van een nieuw hemodynamische monitoring systeem is een uitdaging die naast financiële investeringen ook opleiding vereist. Indien correct toegepast zouden patiënten ervan moeten profiteren en zouden de gezondheidskosten verlaagd worden door het verminderen van morbiditeit en mortaliteit.[28]

Samenvattend kunnen we concluderen dat met de nieuwere softwareversies het FloTrac/Vigileo™ systeem zijn prestaties (nauwkeurigheid en reproduceerbaarheid) heeft verbeterd. De laatste versie kan klinisch gebruikt worden bij patiënten met een hypo-of normo dynamische circulatie zoals algemene ICU en (post) cardio chirurgische patiënten. In tegenstelling tot patiënten die lijden aan ernstige sepsis, septische shock of leveroperatie daar en tegen gekenmerkt door een hyper dynamische circulatie. De uitgebreide vasodilatatie die gepaard gaat met deze ziektebeelden staat het op dit moment nog niet toe de FloTrac/Vigileo™ monitor klinisch te gebruiken. Geavanceerde, meer invasieve hemodynamische monitoring wordt geadviseerd, bijvoorbeeld met behulp van gekalibreerde arteriële drukgolf analyse. De gekalibreerde arteriële drukgolf analyse (VolumeView/EV1000) presteert beter in vergelijking met de niet-gekalibreerde versie (FloTrac/Vigileo™) bij patiënten die lijden aan ernstige sepsis en septische shock. De gekalibreerde arteriële pols golf analyse behoudt klinisch aanvaardbare foutpercentages tot 8 uur na de kalibratie. De FloTrac/Vigileo™ monitor afgeleide SVV kan gebruikt worden voor vloeistof therapie. Klinisch significante veranderingen in HMV hebben een voldoende tot goede correlatie met de veranderingen in het HMV ten opzichte van het referentie HMV bij patiënten met ernstige sepsis en septische shock. Toekomstig onderzoek moet zich richten op chirurgische hoog risico patiënten, patiënten die lijden aan acute en chronische hartfalen, acuut en chronisch hartfalen, waarbij individuele hemodynamische monitoring wordt gecombineerd met individuele hemodynamische doelen, alles gericht op positieve patiënt uitkomsten.

Referenties

1. Slagt C, Malagon I, Beute J, et al. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). Dutch Society Intensive Care 2008. Book of abstracts P10:p14
2. Slagt C, Malagon I, Beute J, et al. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists, Faculty of Pain Medicine and the Joint Faculty of Intensive Care 2008, Sydney. Book of abstracts P61
3. Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. *Crit Care* 2011; 15:214.
4. Vincent JL, Rhodes A, Perel A, et al. Clinical review: Update on haemodynamic monitoring - a consensus of 16. *Crit Care* 2011;15:229.
5. Hofer CK, Cannesson M. Monitoring fluid responsiveness. *Acta Anaesthesiol Taiwan* 2011;49:59-65.
6. Michard F. Changes in Arterial Pressure during Mechanical. *Anesthesiology* 2005;103:419-28.
7. Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000;4:282-289.
8. Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984;12:107-12.
9. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004;32:691-9.
10. Daudel F, Tüller D, Krähenbühl S, et al. Pulse pressure variation and volume responsiveness during acutely increased pulmonary artery pressure: an experimental study. *Crit Care* 2010;14:R122.
11. Wyler von Ballmoos M, Takala J, Roeck M, et al. Pulse-pressure variation and haemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care* 2010;14:R111.
12. Magder S. Further cautions for the use of ventilatory-induced changes in arterial pressures to predict volume responsiveness. *Crit Care* 2010;14:R197.
13. De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005;31:517-523.
14. Kim HK, Pinsky MR: Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. *Crit Care Med* 2008;36:2858-2862.
15. De Backer D, Taccone FS, Holsten R, et al. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009;110:1092-7.
16. Monge García MI, Gil Cano A, Díaz Monrové JC. Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients. *Crit Care* 2009;13:R142.
17. Takala J, Ruokonen E, Tenhunen J, et al. Early noninvasive cardiac output monitoring in haemodynamically unstable intensive care patients: a multi-center randomized controlled trial. *Crit Care* 2011;15:R148
18. Benes J, Chytra I, Altman P, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of a prospective randomized study. *Crit Care* 2010;14:R118.
19. Mayer J, Boldt J, Mengistu A, et al. Goal-directed intraoperative therapy based on arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized controlled trial. *Crit Care* 2010;14:R18.
20. Scheeren TW, Wiesenack C, Gerlach H, et al. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: a prospective randomized multicentre study. *J Clin Monit Comput* 2013;27:225-33.
21. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive haemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011,112:1392-1402.
22. Gurgel ST, do Nascimento P Jr. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. *Anesth Analg* 2011;112:1384-1391.
23. Shoemaker W C, Appel P L, Kram H B, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;94:1176-1186.
24. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991;78:355-60.
25. Older P, Hall A, Hader R: Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 1999;116:355-362.

26. Liebman B, Strating RP, van Wieringen W, et al. Risk modelling of outcome after general and trauma surgery (the IRIS score). *Br J Surg* 2010;97:128-33.
27. Cecconi M, Fasano N, Langiano N, et al. Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. *Crit Care* 2011;15:R132.
28. Lobo SM, de Oliveira NE. Clinical review: What are the best haemodynamic targets for noncardiac surgical patients? *Crit Care* 2013;19:17:210.
29. Brienza N, Giglio MT, Marucci M, et al. Does perioperative haemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009;37:2079-2090.
30. Ye J, Chen Z, Wang T, et al. Role of tissue disorder markers in the evaluation of disease progress and outcome prediction: a prospective cohort study in non-cardiac critically ill patients.*J Clin Lab Anal* 2010;24:376-84.
31. Chaykovska L, Tsuprykov O, Hocher B. Biomarkers for the prediction of mortality and morbidity in patients with renal replacement therapy. *Clin Lab* 2011;57:455-67.
32. Sun T, Wang X, Liu Z, et al. Plasma concentrations of pro- and anti-inflammatory cytokines and outcome prediction in elderly hip fracture patients. *Injury* 2011;42:707-13.
33. Kolditz M, Ewig S, Höffken G. Management-based risk prediction in community-acquired pneumonia by scores and biomarkers. *Eur Respir J* 2013;41:974-84.
34. Palazzuoli A, Masson S, Ronco C, et al. Clinical relevance of biomarkers in heart failure and cardiorenal syndrome: the role of natriuretic peptides and troponin. *Heart Fail Rev* 2013 Apr 7. In press.
35. McLean AS, Huang SJ, Salter M. Bench-to-bedside review: the value of cardiac biomarkers in the intensive care patient. *Crit Care* 2008;12:215.
36. De Backer D, Ospina-Tascon G, Salgado D, et al. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med* 2010;36:1813–1825.
37. Spronk PE, Zandstra DF, Ince C. Bench-to-bedside review: sepsis is a disease of the microcirculation. *Crit Care* 2004;8:462-8.
38. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J appl physio* 2011; 111:853-60.
39. Hamzaoui O, Monnet X, Richard C, et al. Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. *Crit Care Med* 2008;36:434-40.
40. Krejci V, Vannucci A, Abbas A, et al. Comparison of calibrated and uncalibrated arterial pressure-based cardiac output monitors during orthotopic liver transplantation. *Liver Transpl* 2010;16:773-82.
41. Yamashita K, Nishiyama T, Yokoyama T, et al. Effects of vasodilation on cardiac output measured by PulseCO. *J Clin Monit Comput* 2007;21:335-9.
42. Jellema WT, Wesseling KH, Groeneveld AB, et al. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* 1999;90:1317-28.
43. Pratt B, Roteliuk L, Hatib F, et al. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. *Biomed Instrum Technol* 2007;41:403-411.
44. Peyton PJ, Chong SW.Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. *Anesthesiology* 2010;113:1220-35.
45. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85-91.
46. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
47. Takala J, Ruokonen E, Tenhunen JJ, et al. Early non-invasive cardiac output monitoring in haemodynamically unstable intensive care patients: a multi-center randomized controlled trial. *Crit Care* 2011;15:R148.
48. Kern JW, Shoemaker WC. Meta-analysis of haemodynamic optimization in high-risk patients. *Crit Care Med* 2002;30:1686-1692.
49. Hayes MA, Timmins AC, Yau EH, et al. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med* 1997;25:926-936.
50. Rhodes A, Cusack RJ, Newman PJ, et al. A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. *Intensive Care Med* 2002;28:256-264.
51. Harvey SE, Welch CA, Harrison DA, et al. Post hoc insights from PACMan-the U.K. pulmonary artery catheter trial. *Crit Care Med* 2008;36:1714-1721.

52. Sakka SG, Kozieras J, Thuemer O, et al. Measurement of cardiac output: a comparison between transpulmonary thermodilution and uncalibrated pulse contour analysis. *Br J Anaesth* 2007;99:337-342.
53. Monnet X, Anguel N, Naudin B, et al. Arterial pressure based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010;14:R109.
54. De Backer D, Marx G, Tan A, et al. Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. *Intensive Care Med* 2011;37:233-240.
55. Monnet X, Anguel N, Jozwiak M, et al. Third-generation FloTrac/Vigileo does not reliably track changes in cardiac output induced by norepinephrine in critically ill patients. *Br J Anaesth* 2012;108:615-622.
56. Marqué S, Gros A, Chimot L, Gacouin A, Lavoué S, Camus C, Le Tulzo Y. Cardiac output monitoring in septic shock: evaluation of the third-generation Flotrac-Vigileo. J Clin Monit Comput 2013;27:273-9.

List of publications

Abstracts

Slagt C, Vranken JH, Boon C, de Lange JJ. Total intravenous anaesthesia with remifentanil or alfentanil for endoscopic procedures of the larynx and pharynx. 12th World-Congress of Anaesthesiologists, Montreal 2000, Book of abstracts, 153.

Slagt C, Vranken JH, Boon C, Thone D, de Lange JJ. Vergelijking van Remifentanil met Alfentanil tijdens Panendoscopy. Ned. Tijdschrift voor Anesthesiologie. Vol. 13, September 2000, Abstractenboek, 20; P13.

Vranken JH, ter Riet SF, Giezeman MJMM, **Slagt C**, Zuurmond WWA. Treatment of Coccygodynia in a Pain relief unit. ESRA Baltic Meeting, Riga Latvia 28-29 April 2000, Book of abstracts.

Vranken JH, **Slagt C**, Giezeman MJMM, Sassen AM, Zuurmond WWA. The efficacy of Oral Ketamine in Patients with central pain. 3e Europese federatie congres IASP. Nice 2000, book of abstracts.

Slagt C, Zondervan A, Rijnsburger E, Patka P, de Lange J.J. A retrospective analysis of the intubations performed during five years of Helicopter Emergency Medical Service (HEMS) in Amsterdam, The Netherlands. The 8th World Congress of Intensive and Critical Care Medicine 2001 Sydney Australia. Book of abstracts P474.

de Leeuw MA, Berenschot J, **Slagt C**, Bierens JJLM, Patka P, de Lange JJ. Water related accidents and Helicopter Mobile Medical Team (HMMT) operations in Amsterdam, The Netherlands, during the period May 1995 until October 2001. World Congress of Drowning 2002 Amsterdam.

Slagt C, Innes R, Bihari D, Lawrence J, Shehabi Y. A Novel method for insertion of post pyloric feeding tubes at the bedside without endoscopic or fluoroscopic assistance. A prospective study. Annual meeting Dutch Society Intensive Care 2003. Book of Abstracts.

de Leeuw MA, Berenschot J, **Slagt C**, Bierens JJLM, Patka P, de Lange JJ. Water related accidents and Helicopter Mobile Medical Team (HMMT) operations in Amsterdam, The

Netherlands, during the period may 1995 until October 2001. Ned. Vereniging voor Anesthesiologie; Anesthesiologen dagen 25 en 26 september 2003. *Ned T Anesth* 2003;16(suppl 28):P41.

Slagt C, van Lier AA. Acuut Respiratoir falen als gevolg van een bijzonder vreemd lichaam in de luchtweg bij een volwassen man. Ned. Vereniging voor Anesthesiologie; 2005. Book of Abstracts; P1:26.

Slagt C, van Bennekom S, Beute J, Mulder JWR, Blankendaal- Janboers MH, Spoelder EM. Arterial Pressure based Cardiac Output is there a place in the Critical ill patient. Annual congress Dutch Society Intensive Care 2006. *Neth J Crit Care* (9) no 6 December 2005.

Slagt C, van Bennekom S, Beute J, Mulder JWR, Hoeksema M, Turk T, Perez RSGM. Arterial Pressure based Cardiac Output in the septic patient; a comparison with the pulmonary artery catheter. 26th International Symposium on Intensive Care and Emergency Medicine 21-24 March 2006. *Crit Care* 2006;10(suppl.1):P329.

Slagt C, Vink HBE, Bannink IMJ, de Stoppelaar EI, Schippers HC, Ephraim E, Bruynder LS, Beute J, Spoelder EM. Arterial Pressure based Cardiac Output in the Critical Ill patients without significant valvular dysfunction. Annual congress Dutch Society of Anaesthesiology 2006. Book of Abstracts; P49:86.

Slagt C, Beute J, Mulder JWR, Hoeksema M, Ramawadhdoebe S. Cardiac Output measurement using the FloTrac™ in the hemodynamic instable patients. *Intensive Care Med* 2006; 32(suppl. 1):P0117.

Slagt C, Bird-Lake E, Hoeksema M, Beute J, de Leeuw MA, Zondervan A, Spoelder EM. Cardiac output measurement by pulse-contour method without calibration compared to cardiac output measured with the pulmonary artery catheter in patients with severe left ventricle dysfunction. Annual congress Dutch Society of Anaesthesiology 2007. Book of abstracts; O19:24.

Slagt C, Malagon I, Beute J, Hoeksema M, de Leeuw MA. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). Annual congress Dutch Society Intensive Care 2008. Book of abstracts P10:14.

Slagt C, Malagon I, Beute J, Hoeksema M, de Leeuw MA. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists, Faculty of Pain Medicine and the Joint Faculty of Intensive Care 2008, Sydney. Book of abstracts P61.

Slagt C, Malagon I, Beute J, Hoeksema M, de Leeuw MA. Comparing two methods of cardiac output measurement during severe sepsis and septic shock; Pulmonary Artery Catheter (PAC) vs. FloTrac™ (three consecutive software versions). European Society Anesthesiology Copenhagen May 2008. Book of abstracts.

Liebman B, Beute J, **Slagt C**, Engel AF. Effects of organizational change in the intensive care unit on high risk surgical patients: a comparison of 'open' and 'closed' formats. 29th International Symposium on Intensive Care and Emergency Medicine 21-24 March 2009. *Crit Care* 2009;13(suppl 1):P483.

Liebman B, Beute J, **Slagt C**, Engel AF. Open versus closed format: the effect of a clear line of command on patient safety in the intensive care unit. ESICM 2009 Berlin. Book of Abstracts.

Slagt C, Hoeksema M, Malagon I. Cardiac output measured by arterial pressure waveform analysis without manual external calibration compared with thermodilution in critical ill patients. Third generation FloTrac software versus intermitted bolus thermodilution cardiac output measurement. European Society Anaesthesiology Helsinki 2010. Book of abstracts.

Slagt C, Hoeksema M, Malagon I. Cardiac output measured by arterial pressure waveform analysis without manual external calibration compared with thermodilution in critical ill patients. Third generation FloTrac software versus intermitted bolus thermodilution cardiac output measurement. Annual meeting Dutch Society Anaesthesiology 2010. Book of abstracts.

de Leeuw MA, **Slagt C**, Hoeksema M, Zuurmond WWA, Perez RSGM. Influence of psoas compartment – sciatic nerve blockade on cardiovascular performance. 29th annual ESRA, Portugal 8-11 September 2010. Book of abstracts.

van de Sluis FJ, **Slagt C**, Beute J, Mulder JWR, Engel AF. Mortaliteit en morbiditeit onder hoog risico chirurgische patiënten; de impact van organisatorische verandering naar een gesloten geformatteerde Intensive Care Unit. Annual meeting Dutch Surgical Society 2010, Veldhoven, The Netherlands. Book of Abstracts.

Slagt C, Platvoet-Sijtsma S, Beute J, Hoeksema M, Malagon I. Arterial pressure waveform derived cardiac output in patients suffering from septic shock. Third generation FloTrac software versus intermittent bolus thermodilution cardiac output. Annual meeting Dutch Society of Anesthesiology Maastricht. Book of Abstracts 2011: O18;19.

Slagt C, de Jongh E, Rijnsburger ER, Hoeksema M, Beute J, Malagon I. Arterial pressure waveform derived cardiac output in patients suffering from septic shock. Third generation FloTrac software versus intermittent bolus thermodilution cardiac output. 24th ESICM Berlin, Germany 2011. Book of abstracts S227;0888.

de Boer M, Bethlem-Schaap C, van der Hem KG, **Slagt C**. Diagnosis of Strongyloides stercoralis via bronchoalveolar lavage in an immunocompromised patient. Annual meeting Dutch internal medicine Society 2012, Book of Abstracts.

Articles

Slagt C, de Lange JJ, Patka P. Lifeliner one aloft in Amsterdam. *Air Med J* 2001;20:15-17.

Slagt C, Innes R, Bihari D, Lawrence J, Shehabi Y. A novel method for insertion of post-pyloric feeding tubes at the bedside without endoscopic or fluoroscopic assistance: a prospective study. *Intensive Care Med* 2004;30:103-107.

Slagt C, Zondervan A, Patka P, de Lange JJ. A retrospective analysis of the intubations performed during five years of helicopter emergency medical service (HEMS) in Amsterdam. *Air Med J* 2004;23:36-37.

Slagt C, Vranken JH, Hoedemaker C, Perez RSGM, Thöne D, de Lange JJ. Comparison of remifentanil-propofol and alfentanil-propofol based total intravenous anesthesia in patients undergoing panendoscopy. *Nederlands Tijdschrift voor Anesthesiologie* 2006;19: 39-43.

de Graaf P, **Slagt C**, de Graaf JL, Loffeld RJ. Fatal aspiration of polyethylene glycol solution. *Neth J Med* 2006;64:196-8.

Slagt C, Bakker SD, Strack van Schijndel RJM. Respiratory failure and septic shock after a secondarily infected retroperitoneal haematoma: A late life-threatening complication of Extracorporeal Shock Wave Lithotripsy. *Neth J Crit Care* 2009;13:145-147.

Slagt C, Beute J, Hoeksema M, Mulder JWR, Malagon I, Groeneveld ABJ. Cardiac output derived from arterial pressure waveform analysis without calibration versus thermodilution in septic shock: evolving accuracy of software versions. *Eur J Anaesthesiol* 2010;27:550-4.

Slagt C, Breukers RM, Groeneveld AB. Choosing patient-tailored hemodynamic monitoring. *Crit Care* 2010;14:208.

Slagt C, Sentjens REJH, Veen G, Spijkstra JJ, Vonk Noordegraaf A. Sildenafil getting it down. *Neth J Crit Care* 2010;14:210-212.

de Leeuw MA, **Slagt C**, Hoeksema M, Zuurmond WWA., Perez RSGM. Hemodynamic Changes During a Combined Psoas Compartment–Sciatic Nerve Block for Elective Orthopedic Surgery. *Anesth Analg* 2011;112:719-24.

van der Sluis FJ, **Slagt C**, Liebman B, Beute J, Mulder JWR, Engel AF. The impact of ICU format change on the outcome of high risk surgical patients: a cohort analysis: Effects of organizational change on high risk surgical patients. *BMC Surg* 2011;23:11:18.

Slagt C, de Leeuw MA, Beute J, Rijnsburger E, Hoeksema M, Mulder JWR, Malagon I, Groeneveld ABJ. Cardiac output measured by uncalibrated arterial pressure waveform analysis by recently released software version 3.02 versus thermodilution in septic shock: Third generation FloTrac/VigileoTM versus thermodilution cardiac output. *J Clin Monit Comput* 2013;27:171-7.

de Boer MP, Bethlem-Schaap C, de Jager S, Wesselink E, Ambrose I, **Slagt C**. Fatal strongyloidiasis in an immunocompromised HTLV-1 infected patient. *Intensive Care Med* 2013;39:339-40.

Slagt C, Malagon I, Groeneveld ABJ . A systematic review of uncalibrated arterial pressure waveform analysis to determine cardiac output and stroke volume variation. *Br J Anesth* 2013; *Accepted for publication.*

Books

PAOG-cursus cyclus Urgentiegeneeskunde 2002 . Vitale functies onder rampenomstandigheden. Hoofdstuk: De nacht van Volendam door **Slagt C,** blz. 49-52. VU uitgeverij, Amsterdam.

AMPA Handbook: *Principles and Direction of Air Medical Transport*: Air medical transport in the Netherlands. Huitink J, Burggraaf JP, Rennings H, **Slagt C**. 2006: Chapter 79: 651-656.

Yearbook for intensive care and Critical Care medicine 2010 Vincent JL. Section II Hemodynamic monitoring: Choosing patient-tailored hemodynamic monitoring. **Slagt C,** Breukers RM, Groeneveld ABJ, pages 64-71.

Dankwoord

Het boekje is af! Wat aanvankelijk begon als grappig initiatief in 2006, op zoek naar een nieuwe hemodynamische monitor, groeide uit tot een project waar geen einde aan leek te komen. Na mijn fellowtijd in het VUmc in 2009 werd het serieus. Als promovendus werk je nooit alleen aan je project, velen helpen. De combinatie van promoveren, samen met een full time baan als medisch specialist, papa, echtgenoot, ATLS instructeur, plaatsvervangend opleider en de laatste jaren unit voorzitter van de RvE-OK in het ZMC, waren bij tijd en wijlen iets te veel van het goede. Kortom ik ben niet de enige die blij is met dit behaalde resultaat. Iedereen bedanken dat kan niet, maar een aantal mensen wil ik speciaal noemen zonder anderen te kort te doen.

Allereerst wil ik de patiënten en hun familieleden danken voor de toestemming om te participeren in de onderzoeken welke beschreven zijn in dit proefschrift. Zonder uw toestemming had het nooit zover gekomen. Hartelijk dank daarvoor.

Mijn promotor, prof.dr. A.B.J. Groeneveld, beste Johan. Het begon tijdens mijn fellow tijd in 2008-2009 in de VU, toen wij aan de praat raakten over de resultaten van mijn onderzoek. Jouw ogen fonkelden, jij geloofde in mij. Daarna hebben we veel werk verricht. Eerst op de VU, later samen op je nieuwe kamer in het EMC. Wat was ik blij met email, niet altijd terecht overigens. Face to face gaf vaak de juiste accenten in veel kortere tijd. Hulde aan jouw vermogen tot het formuleren van de kernboodschap in een enkele zin. Lang leve onze Babylonische email verwarringen rondom de review (ik ga ze missen). In het zicht van de haven werd jij geconfronteerd met vreselijk nieuws. Nu zit je midden in de behandeling en blijft de toekomst onzeker. Ik wens je heel veel sterkte en hoop dat we in de toekomst wederom gezamenlijke projecten kunnen hebben.

Copromotor, beste Ignacio, in 2009 kwam je naar Zaandam op zoek naar perifere werkplek. Wij hadden elkaar nog nooit eerder ontmoet, maar het klikte. Jij zit nu in Manchester en hebt je droombaan gevonden. Plannen om langs te komen zijn in de maak. Tobin en ik komen binnenkort naar Manchester United kijken! Dank voor je steun vooral als een artikel niet geaccepteerd werd en ik er een beetje tabak van kreeg. Volhouden was het sleutelwoord. Super bedankt voor je steun in de afgelopen periode.

Graag bedank ik alle overige leden van de promotiecommissie, de hooggeleerde heren Professor J. Bakker, Professor R.J. Stolker, Professor G.J. Scheffer, Professor E. de Jonge, Professor W.F. Buhre, Professor T.W.L. Scheeren, Professor A.J.J.C. Bogers en Professor D. van Dijk voor het beoordelen van mijn proefschrift en de bereidheid te opponeren.

Ik wil graag de Erasmus Universiteit te Rotterdam bedanken voor de mogelijkheid om als "extern" medisch specialist te kunnen promoveren bij uw organisatie.

Johan, paranimf, broer, door ons beide drukke leven zien we elkaar niet veel, dat moet veranderen. Was wel even schrikken toen je in 2012 van de berg af viel. Gelukkig gaat het nu weer goed. Volgend jaar Dam tot Dam? Het doet me goed dat je deze speciale dag op deze manier met mij deelt.

Collega anesthesiologen, er is veel gebeurd de afgelopen jaren, hartelijk dank voor jullie steun. Het komende jaar zijn jullie waarschijnlijk verlost van nieuwe projecten. Wat hierna gebeurt is nog onduidelijk. Marcel: twee jaar geleden stond jij op deze plek. Bedankt voor je hulp rondom mijn project. Dagelijks op de fiets over de Zaanse Schans is een fantastische manier om de dag te beginnen. Martijn, vriend, jouw nuancering en "poldervermogen" vult mijn, soms iets te kort door de bocht, fantastisch aan. Dank voor de bespiegelingen in de afgelopen jaren. Uiteindelijk kregen we toch gelijk. Emmy, met enige trots: koningin van onze afdeling, ik ben blij dat ook jij ook de stap naar Zaandam hebt gewaagd. Hopelijk kunnen we onze plannen in het Zaanse verwezenlijken. Laten we in ieder geval zorgen dat het gezellig blijft. Houkje, bedankt voor je wijsheid, ik probeer er aan te denken, lukt helaas niet altijd. Erica, Erik, Ilse, Margret, Christel, Michel, Annemarie bedankt voor de tijd en jullie geduld. Annick jij bent de volgende, volhouden. Rien, Marriëlle en Jans, jullie zijn nog maar kort in het ZMC, maar zo voelt het niet.

Annemieke, Roos, Kelly, Chiel, Eline, Nicole, Martin, Annelies, Ton, Dik, Paula, Jenny, Pita, Brigitte, Marion, Marieke, Claudia, Wendy, Ruud, Daniëlle, Hans, Sandra en Sandra, Anja, Jose, Kirsten, Ria, Marjanne, Lianne, Evelien, Maaike, Simone, Claudia, Yesim, Carry, Wim, Ria, Joke, Carla, Ada, Claudia, Leonie en Ellen, collega's op de intensive care, mijn dank is groot. Jullie hebben allemaal veel werkvreugde mogen beleven aan mijn onderzoeken. Speciaal dank ik jullie voor jullie geduld en flexibiliteit, het verrichten van de hemodynamische profielen bij nacht en ontij, het keer op keer aanhoren van mijn hemodynamische ideeën, en vooral jullie flexibiliteit en bereidheid om steeds weer actief mee te denken.

Alle medewerkers op de OK wil ik bedanken voor hun interesse, steun en hulp gedurende de afgelopen periode. Hemodynamische monitoring op OK gaat door, onder andere met het "Optimal Track" project.

Beste Shanti en collega cardiologen, Erik en collega CCU verpleegkundigen bedankt dat jullie met mij de eerste stappen wilde zetten om de hemodynamiek van patiënten met acuut en chronisch hartfalen beter te bekijken. Al hoewel het nog in de kinderschoenen staat, hoop ik op een verdere voortzetting.

Fabian, Alexander, Ricco, Jan Willem, collega chirurgen en arts assistenen, bedankt voor de samenwerking met de afdeling heelkunde. Ons gezamenlijke project gericht op hoog risico patiënten gaat door hopende op een grote spin-off.

Jeannette, mijn steun en toeverlaat onder andere als het gaat over de financiën van onze afdelingen, die tezamen de RvE-OK vormen. De afgelopen jaren is het mooi geworden, dit is grotendeels jouw verdienste. Het viel niet altijd mee de spagaat tussen opleiden, promoveren, management en werken binnen het ziekenhuis. Bedankt voor je geduld en ondersteuning.

Neill bedankt voor je blijheid iedere dag weer. Uiteindelijk ben jij de enige die echt naar mij luistert. Samen uitwaaien door weer en wind, op z'n tijd was het therapeutisch voor mij.

Lieve Alice, ook voor jou komt er een einde van een periode van heel veel niet thuis eten, weer geen tijd ect. Dank je wel voor je steun door dik en dun, je liefde, het kritisch lezen van het document, de lay-out, het verbeteren van mijn schrijffouten, mij oppeppen als het even niet mee zat. Mede dankzij jouw aanmoedigingen is het nu zover gekomen. Met jou naast mij als paranimf krijgt deze dag nog iets mooiers. De komende tijd gaan we met z'n vieren weer leuke dingen doen.

Sydney en Tobin, mijn mannen, het boekje is af! Papa heeft weer tijd om papa te zijn. Tobin, we gaan naar Manchester. Sydney, voor jou was de laatste tijd niet makkelijk, ondanks alles heb je super je best gedaan. Papa Cor is ongelofelijk trots op jullie beiden.

Curriculum Vitae

Cornelis Slagt was born in Broek in Waterland on February 12, 1969. He started the secondary school in Monnickendam (MAVO) in 1981 hereafter he attended Damstede (HAVO and VWO) in Amsterdam, in the period 1985–1988. In 1988 he started the study Medicine at the VU University Medical Centre in Amsterdam. In 1995 he received his medical degree cum laude.

Hereafter he started as a surgical resident at the Boven-Y hospital in Amsterdam. One year later he started his anaesthetic training at the VU University Medical Centre in Amsterdam under supervision of Prof. JJ de Lange. During his residency he became interested in the intensive and acute care. He joined the Helicopter Emergency Medical Service of the Traumacentrum Noord-West-Nederland situated at the VU medical campus.

At the end of his anaesthesiology residency he and his wife moved to Australia to full fill his last intensive care training. He worked as a fellow at the intensive care at the Prince of Wales Hospital in Sydney during the year 2001.

After the return to the Netherlands he completed his training and started to work in the Zaans Medical Centre (ZMC) in Zaandam as a staff member anaesthesiology dividing his time between intensive care and operating theatres. He soon became active in the management of the anaesthetic department where he held various positions within the Executive Board of the anaesthetic discipline. Simultaneously he devoted himself to organize the peripheral year of anaesthesia training to start in het ZMC which was made possible in 2006 and he became deputy trainer. In 2006 he re-joined the Helicopter Emergency Medical Service of the Traumacentrum Noord-West-Nederland at the VU medical centre for one year. The last years he is responsible as chairman for the "unit OK" of the Zaans Medical Centre.

In 2008 he started his official intensive care training at the intensive care of the VU University Medical Centre in Amsterdam. He successfully completed the written and oral European Intensive Care exam at the end of 2009.

Cor is married to Alice Zondervan. They have two sons, Sydney (2001) and Tobin (2003).