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REVIEW

A Perspective on Non-invasive Continuous Cardiac Output in the Critically Ill

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Abstract. The thermodilution technique is the accepted clinical method of estimating cardiac output (CO), but it is discontinuous and requires the presence of a pulmonary artery catheter for as long as CO monitoring is needed. Continuous monitoring of CO allows for the detection of rapid effects on systemic flow and conductance that may otherwise remain unnoticed in a recording of arterial pressure or heart rate. We consider such information on the circulation beyond what is detected by arterial pressure, to be of relevance both in clinical medicine and in human cardiovascular research. Continuous information on systemic flow may be obtained from the arterial pressure wave. In this review, a perspective on non-invasive continuous CO is presented with a focus on the information about arterial flow that can be obtained from the non-invasive arterial pulse wave.

Introduction

The primary evaluation of the haemodynamic condition of critically ill patients is made by reporting heart rate (HR) and mean blood pressure (BP) as a surrogate of tissue perfusing pressure. It was largely due to Harvey Cushing (1903) [1] that Riva Rocci's mercury sphygmomanometer [2] was introduced into medicine and then to the monitoring of BP in patients during anaesthesia. For continuous measurement of blood pressure, cannulation of an artery was necessary up to the early 1980s when the "Finapres", based on the volume-clamp method was introduced by the Czech physiologist Jan Peñáz [3] and developed by Wesseling et al. [4]. In this way continuous non-invasive measurement of arterial pressure in humans was introduced both for research purposes and for clinical medicine [5,6].

Values for BP and HR are easily to obtain and continue to serve as monitors for volume treatment in hypotension and shock. This approach seems physiological when considering that BP is the principal cardiovascular variable monitored by the body by the baroreceptors [7]. Cardiac stroke volume (SV) and output (CO) still play a subservient role although it is flow, not pressure which the tissues are in need of [8]. For instance, in patients with septic shock, artificially increasing BP beyond ~65 mmHg does not improve established parameters of tissue perfusion [9]. Nevertheless, a value for mean BP rather than flow continues to be the major target of treatment with fluids and inotropic agents.

HR, SV and BP change rapidly and a single measurement conveys very little, making continuous measurement desirable [10]. Even so BP and HR, by the nature of their regulation and depending on age and pre-existing cardiovascular morbidity, do not respond to even substantial blood loss, whereas mean BP is regularly maintained until blood loss exceeds one litre [11-15].

In consequence, the usual clinical and haemodynamic parameters are not reliable indices of preload to the heart [26-19] and an 'optimal' volume is neither defined nor is it an easily measurable entity. A functional definition of normovolaemia may be the filling of the heart that ensures adequate CO and tissue oxygen delivery [14,20]. Accordingly, a reduced preload to the heart is characteristic of hypovolaemia with SV and CO becoming dependent on the central blood volume. When CO increases with volume loading this is interpreted to imply that a patient is preload-responsive [18,19]. When both ventricles are 'preload dependent', mechanical ventilation results in greater cyclic changes in left ventricular SV [21]. These variations in flow being transferred to arterial pressure may provide for actual information on fluid responsiveness [21-24].

In order to avoid perioperative hypovolaemia or fluid overload, goal-directed therapy with individual maximization of flow-related haemodynamic parameters was introduced [25-27]. Goal-directed volume treatment makes use of flow-related techniques [27] and instrumentation to measure BP and flow on a continuous basis has been under development for over a century. Of the two, unfortunately, the measurement of CO has proved difficult to perform in a safe and continuous way whereas CO determination with indicator dilution is discontinuous [25,28].

In this review, we present a perspective on non-invasive continuous CO with a focus on the information about arterial flow that can be obtained from the non-invasive arterial pulse wave.

Invasive cardiac output

The standard techniques available are direct Fick, thermodilution, indirect Fick employing CO_2 and non-invasive foreign gas rebreathing [29,30]. In 1870, Adolph Fick set out an equation for the measurement of CO in steady states considering that the volume of O_2 consumed per unit time is proportional to the difference in O_2 content between arterial and venous blood [31]. Here CO is expressed as the ratio between oxygen consumption and arteriovenous difference in O_2. This is also valid for CO_2. Like thermodilution it requires cardiac catheterization and arterial cannulation and it was not until 1940 that this technique was used in humans [32,33].

With the "indirect Fick" procedure, mixed venous gas pressures are estimated and blood-gas contents are derived from knowledge of the chemical combination of blood with the gas at various partial pressures. The uptake or output of the gas is measured, and from

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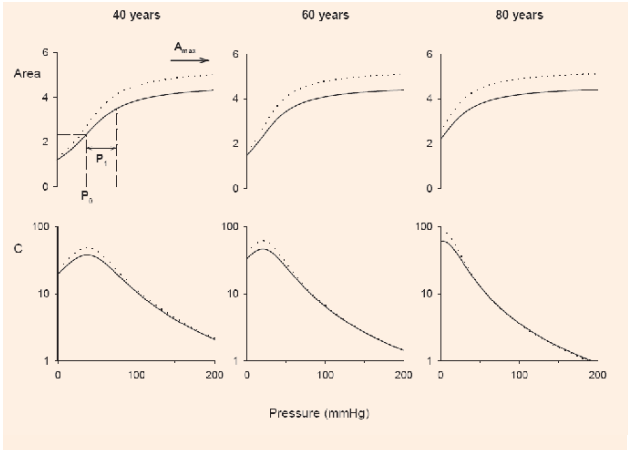

Figure 1. Upper panel: Pressure-area curves for human thoracic aortas with moderate atherosclerosis, solid line, and severe atherosclerosis, dotted line, at the ages of 40, 60 and 80 years respectively. Area, aortic cross-sectional area, in cm^2; Pressure, aortic pressure, in mmHg; A_{max}, maximal cross-sectional area at very high pressure; P_0, position of the inflection point on the pressure axis; P_1, steepness of the curve.
Lower panel: The matching compliance curves on a semi-logarithmic scale, in $10^{-3}.cm^2.mmHg^{-1}$. Compliance decreases when pressure rises because an aorta can expand elastically only until the collagen fibres in its wall are fully stretched.
Modified from data in Langewouters et al (Reproduced with permission, from Jellema WT, Wesseling KH, Groeneveld AB, Stoutenbeek CP, Thijs LG, Van Lieshout JJ. Anesthesiology 1999;90:1317-1328).

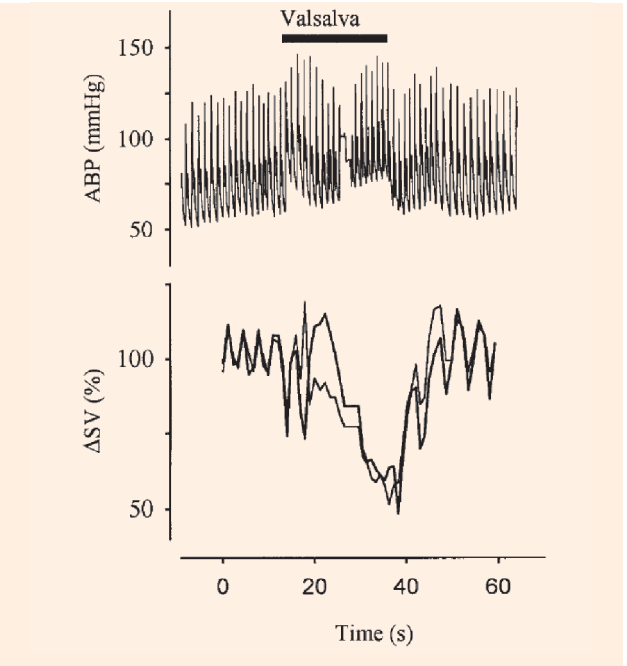

Figure 2. Beat-by-beat stroke volume (SV) during a Valsalva manoeuvre determined by model flow (thin line) from continuous Finapres arterial blood pressure (ABP) and transthoracic Doppler ultrasound (bold line). Interruptions in pressure tracings (top) represent determination of Finapres volume clamp set point (Reproduced with permission from (87).

this information a version of the Fick equation is used to calculate effective pulmonary blood flow (Q_{EP}). If no intrapulmonary shunt exists then Q_{EP} equals CO. Foreign gas rebreathing measures Q_{EP} non-invasively; it has the advantage that the mixed venous concentration of the test gas is zero before recirculation [34-36]. In contrast to CO_2, gases that do not depend on haemoglobin for transport equilibrate rapidly with blood and plasma in the alveoli, with the alveolar component of the expirate representing the mean end-capillary blood value [33].

Several techniques have become available to provide for a continuous CO measurement. The LiDCO ® system is a bolus indicator dilution method of measuring CO making use of lithium chloride and its subsequent detection in arterial blood through a lithium-sensitive electrode, which produces a lithium concentration-time curve. The CO estimate produced is used to calibrate a conventional pulse contour-derived SV. Compared to thermodilution an advantage of this technique is that pulmonary artery catheterization is not needed [37]. The PiCCO ® system makes use of aortic transpulmonary thermodilution and continuous CO monitoring by pulse contour analysis of intra-arterial BP [38]. The FloTrac/Vigileo^{TM} system is designated as a 'semi-invasive' device. It uses an intra-arterial pressure waveform based pulse contour analysis with a reported bias of 0.47 $l.min^{-1}.m^{-2}$ and precision of 1.15 $l.min^{-1}.m^{-2}$ in comparison to an ordinary bolus thermodilution [39-41].

Non-invasive continuous cardiac output

Non-invasive and continuous tracking of changes in SV can be delivered by thoracic electrical impedance [42,43], ultrasound [44,45] and by arterial pulse wave analysis [46-50]. Electrical impedance cardiography estimates CO by using electrodes attached to the neck and the thorax. A high frequency signal is transmitted from the neck electrodes to the thorax. The measured changes in resistance reflect dynamic aspects of the blood velocity and volume in the aorta [51,52]. Pitfalls of this method include electrode placement, motion artifacts and the validity of the equations [53,54].

Doppler ultrasound measurement of aortic blood velocity combined with echocardiographic determination of the aortic root cross-sectional area yields CO. The application of ultrasound is somewhat limited in that either a semi-invasive trans-oesophageal approach has to be applied or a probe has to be held over the root of the aorta requiring a skilled operator and constancy of Doppler device angle to minimize bias [45]. Of the monitors that may be applied for goal-directed therapy, only the oesophageal Doppler has been adequately tested [27,28].

So-called pulse contour methods attempt to determine cardiac SV from characteristics of the arterial pressure pulse. With the first publication in 1904 from Erlanger and Hooker [55], pulse contour preceded Korotkoff's auscultation paper [56] by one year. Pulse contour methods are based on solid physical principles, less solid physiological models, and involve substantial computations [57]. Conventional pulse contour methods compute changes in left ventricular SV from the pulsatile systolic area. SV is computed as: $SV = A_{sys} / Z_{ao}$, where SV is the pulse contour SV of the heart, A_{sys} the area under the systolic portion of the pressure wave and Z_{ao} the characteristic impedance of the aorta [46,58]. However, the characteristic properties of the aorta are pressure dependent and vary with age [59]. In addition, the pulse wave velocity increases with age causing peripheral reflections to return to the heart during systolic ejection, potentially disturbing the model.

Modelling flow from pressure

The major determinants of systolic inflow are the aortic characteristic impedance and the arterial compliance. Both depend on the elastic properties of the aorta [57, 60-62]. If it was known to what extent the human aorta complies with a 1 mmHg pressure increment by increasing its volume, then the SV ejected into the aorta

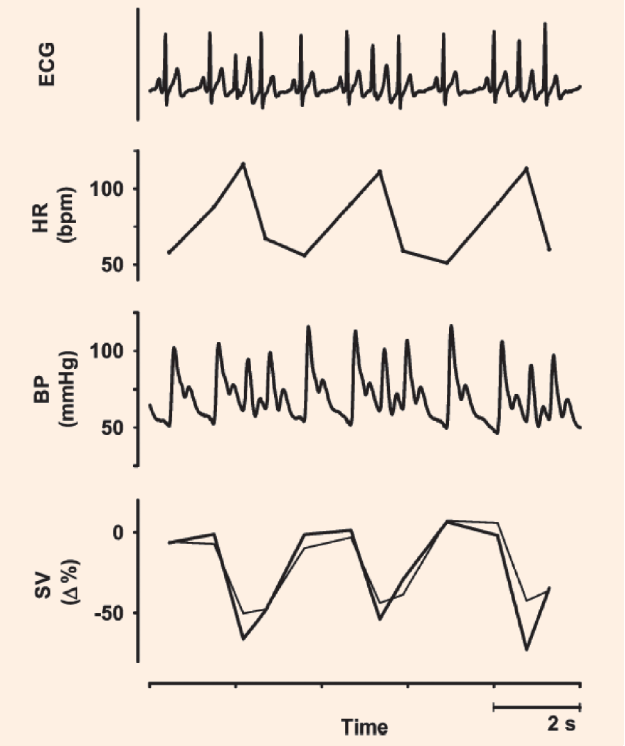

Figure 3. Instantaneous fluctuations in stroke volume (SV) during arrhythmia. Ultrasound SV, bold line; Modelflow SV, thin line. Premature atrial complexes recorded in a 56-year-old subject. Two-fold beat-to-beat changes in SV indicated with both non-invasive methods in near-identical manner (Reproduced with permission from (45)).

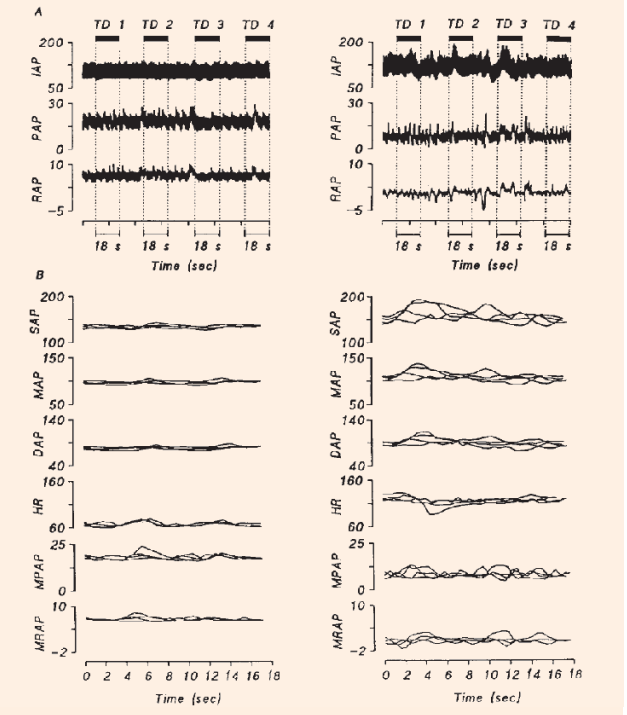

Figure 4. Stable vs. unstable haemodynamic conditions during thermodilution cardiac output estimation. Stable (left panels) and unstable (right panels) haemodynamic states. (A) Intra-arterial pressure (IAP), pulmonary artery pressure (PAP) and right atrial pressure (RAP). Rectangles indicate the duration of one thermodilution (TD) series. (B) Detail of (A), showing the plotted signals of systolic (SAP), mean (MAP), diastolic (DAP) and mean pulmonary (MPAP) arterial pressures, mean right atrial pressure (MRAP), and heart rate (HR) during TD1–TD4. One TD measurement takes 18 s. Note the difference in the variability of the signals between a stable and an unstable haemodynamic state (Reproduced with permission from (70) © the Biochemical Society).

could be derived from the associated pressure rise. The aorta's compliance, defined as $\Delta V/\Delta P$, is substantial at low distending pressure but at higher pressures, compliance progressively decreases thus resisting overstretching of the aortic wall. Such nonlinear behaviour hampers a simple approach to pulse contour estimates of SV [57]..

Typically, for a 50-year-old patient, the aorta compliance could be 3 ml·mmHg^{-1} at 50 mmHg distending pressure, 1.1 at 100 mmHg and 0.5 at 150 mmHg. Thus the same 40 mmHg pulse pressure equates to 120, 44 and 20 ml SV depending on prevailing pressure. Moreover, the values change with the patient's age and nonlinearity is more pronounced in the elderly [62,63]. The importance of aortic nonlinearity for pulse contour precision was recognized as early as 1928 [64] and for age dependency in 1954 [65], but both factors were measured with great precision only in 1984 [59] and implemented into the Modelflow method [62].

BP and CO, or pulsatile pressure and flow in the aorta, are related via an impedance and define the haemodynamic state in humans [8]. The response of the human aorta in opposing the ejection of blood by the left ventricle is described by a model of the aortic input impedance [66-69], also known as the three-element Windkessel [61]. The mechanical properties of the aorta dominate the impedance to outflow that is presented to the left ventricle in systole. The impedance to flow depends on the transmural pressure, the difference between the intra-arterial pressure and the tissue pressure exerted on the outside of the aortic and the arterial wall [70].

Peripheral vascular resistance, as the third element of the model, is not a major determinant of systolic inflow [62] and is time-varying, expressed for each heart beat as the quotient of mean BP and the modelled flow. An aortic flow waveform is computed from either intra-arterial or finger pressure by simulating a nonlinear model of the aortic input impedance. Integrating the computed aortic flow waveform per beat provides left ventricular SV, and CO by including HR.

Effects of atherosclerosis and vasoactive agents on thoracic aorta pressure-area relation

The relation of cross-sectional area to arterial pressure is described by an arctangent equation with age and gender dependent parameters based on data derived from human aortas [59]. The cross-sectional area of the aorta included in the model increases with aortic pressure in a nonlinear manner: at lower pressures the area increases quickly, at higher pressures the increase is slower. A_{max} during ejection is the parameter included in the model that does not regress with age [71-73]. The shape of the cross-sectional pressure-area curve of the human aorta changes with subject's age, gender, and degree of atherosclerosis [74]. Therefore the model needs actual age, length, weight and gender as additional input. From an in-built database the proper model parameters are then derived for each pressure level [75]. The arctangent pressure-area model has been verified in-vivo by simultaneous measurements of BP and aortic diameter [76].

If precise absolute values are required, calibration against an improved thermodilution method as introduced by Jansen [77-79] is needed, including respiratory phase-controlled quadruple automated injections of iced glucose [62,70,75,80].

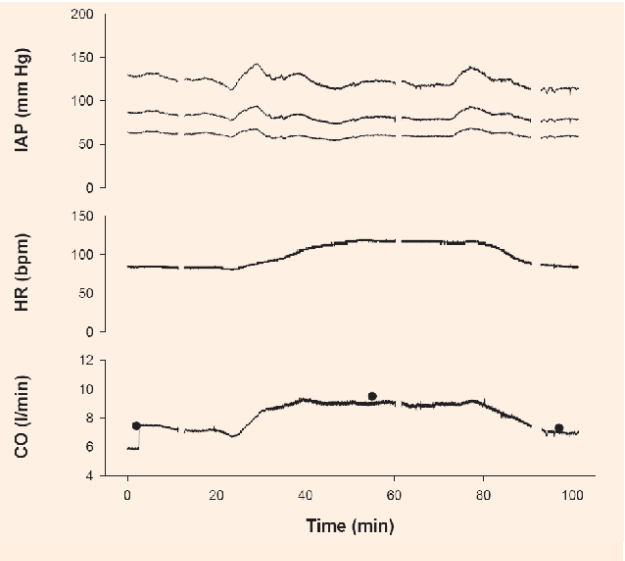

Figure 5. Continuous cardiac output by modelling flow from pressure during varying dosages of norepinephrine and dopamine. Thermodilution cardiac output (TDCO) estimates are indicated by dots. The first TDCO estimate is used to calibrate Modelflow CO in steady state (norepinephrine dose: 0.23 μg.kg^{-1}.min^{-1}, dopamine dose: 2.3 μg.kg^{-1}.min^{-1}). The second TDCO estimate was obtained following changing norepinephrine (to 0.06 μg.kg^{-1}.min^{-1}) and dopamine dosages (to 11.5 μg.kg^{-1}.min^{-1}), and the third TDCO following restoring the initial inotropic regime. IAP; systolic, mean and diastolic arterial pressure, mmHg; HR, heart rate, beats.min^{-1}; CO, cardiac output, in l.min^{-1} (Reproduced with permission, from Jellema WT, Wesseling KH, Groeneveld AB, Stoutenbeek CP, Thijs LG, Van Lieshout JJ. Anesthesiology 1999;90:1317-1328).

Changes in smooth muscle tone in the aortic wall with sympathetic outflow may modify aortic properties although the amount of smooth muscle in the aorta is small and major effects have not been found. With increasing age, the steep part of the pressure-area curve moves to the left along the pressure axis (Fig. 1) [75]. Changes in temperature and vasoconstriction or vasodilatation, modify vascular impedance. Conventional pulse contour methods are linear and do not compensate for changes in arterial pressure pulse behaviour under circumstances that affect vascular impedance. Modelflow does specifically account for these non-linear characteristics. Human atherosclerotic thoracic aortas have an increased A_{max} and an increased stiffness. The net effect of both increments is that they compensate each other for the effect on compliance: the compliant behaviour of a severely atherosclerotic aorta is almost identical to that of a moderately atherosclerotic aorta over the physiological pressure range. This conforms to that the model simulates aortic input impedance satisfactory in septic shock over a 2-day monitoring period [75], during cardiac surgery [75,80] and with both reflex sympathetic or pharmacological vasoconstriction and vasodilatation [62,70,75,81].

Application

Modelling arterial flow from pressure was developed for continuous monitoring of CO in operating theatres and in intensive care units. This method accepts invasively as well as non-invasively determined finger arterial pressure as input. CO is tracked during cardiac surgery, and in critically ill septic patients with inotropic support subjected to hyperinflation, and in a human model of endotoxaemia [62,75,80-84].

Combining non-invasive continuous finger pressure and CO enables non-invasive monitoring of drug treatment in malignant hypertension [85] and analysis of cerebrovascular autoregulatory control in healthy subjects [86-88] and in patients with acute ischaemic stroke [89].This approach has advanced the study of reflex cardiovascular adaptation in a human model of hypovolaemic shock [45,70,90,91] and during static [30] and dynamic exercise [92-96]. . Likewise the effects of positive intra-thoracic pressure (Fig. 2) and arrhythmia were quantified [83,87,97] (Fig. 3).

Aortic aneurysms modify aortic properties in unpredictable ways and the aortic input impedance model assumes a normal human aorta. Backflow in aortic regurgitation is not modelled and a normally functioning aortic valve is required. In addition the model uses the premise that the transmural aortic pressure is not affected, for example by extreme pulmonary hyperinflation or increased intra-abdominal pressure. Determination of arterial flow from intra-arterial pressure requires avoidance of damping, minimizing offset and verification of the catheter-manometer system resonance frequency [98-100].. Non-invasive arterial pressure as input involves dedicated application of the finger cuff, continuous maintenance of the finger position at heart level, and avoidance of sudden motion [6,45].

Comparing standard and continuous cardiac output - methodological considerations

Validation of beat-to-beat tracking of SV is generally based on conventional measurements of CO such as thermodilution-based estimates which are obtained as averages of several determinations each taken over at least some 18 heart beats [70,78,101]. Such comparisons are valid only under conditions of constancy of central venous and arterial pressures. Even then there is no way to appreciate the beat-to-beat fluctuations in SV, which may be considerable [102] (Figs. 2 and 3).

It has been proposed that pulse wave contour techniques have suffered from wave reflection phenomena [103]. However, the relationship between pressure and flow, if modelled properly, accounts for the reduction in stroke volume by reflection [8,104,105]. This is supported by data obtained under conditions with pharmacological arterial vasodilatation and constriction [62,75,80]. Accordingly, the amplification of reflex vasoconstriction during one hour of postural stress does not influence the offset of intra-beat determined SV (70). Also the finding that a single calibration of the model appears sufficient to monitor continuous CO in critically ill patients over a 2-day period with a bias of -0.1 ± 0.8 l·min^{-1} [75] refutes that CO delivered by intrabeat techniques is too inaccurate for clinical use [106].

Negligence of methodological principles biases the results of studies designed to compare continuous with discontinuous CO methodologies. For instance, when comparing PiCCO with thermodilution, the automatic recalibration of the system delivers a value of CO used in the comparisons as an average of the real CO value taken before the femoral artery thermodilution measurement, and the corrected CO value taken immediately following the thermodilution measurement [38]. In consequence, the new thermodilution-derived calibration factor attenuates the variation of the pulse contour CO determination during inconstant haemodynamic conditions. This introduces an error into the conclusions about the agreement and precision with thermodilution CO [107]. Another example is the recommendation not to employ bioimpedance for CO monitoring, which is based largely on a misinterpretation of methodologies used [108].

In spite of a lasting controversy about the application and risks of the pulmonary artery catheter in the monitoring and treatment of critically ill patients [109-115], no new gold standard has emerged. This leaves thermodilution CO as a reference method in the IC. A word of caution seems appropriate regarding the general shortcomings with respect to future validation of beat-to-beat tracking of SV.

First, the thermodilution method is based on the law of conservation of energy i.e. that there is no loss of coldness between the site of injection and detection, that mixing of the indicator and blood is complete and that the induced temperature change can be discriminated accurately from the fluctuations in baseline temperature. Application of the Stewart-Hamilton equation in the thermodilution technique also requires constancy of flow [116]. In patients in whom ventilation is mechanically controlled, flow modulations may result in large errors in the estimation of mean CO. To meet these assumptions more closely, the use of an automatic injector in combination with a closed injectate delivery system improves consistency in injected volume and linearity of injection rate. Restriction of the influence of oscillations by ventilation in CO seems logical given the variability in thermodilution estimates of CO [116]. By distributing four injections randomly through the respiratory cycle, the accuracy of the series average CO improves with the square root of the number of observations [77]. This approach inherently produces considerable differences between subsequent CO determinations, which reflect the physiological variation to be entered into the calculation rather than rejected. The scatter is reduced also by excluding series obtained under conditions where pressures and heart rate deviate more than 10% from their averages, violating the assumed constancy of blood flow [70] (Fig. 4).

Secondly, when comparing continuous and thermodilution determinations of CO, differences are generally attributed exclusively to the continuous method under investigation. Nevertheless, individual thermodilution CO estimates scatter substantially even under stable haemodynamic and ventilatory conditions [117] and also four quickly repeated thermodilution estimates of CO may differ more than 1 $l \cdot min^{-1}$ [80]. The general assumption to be made when comparing a beat-to-beat methodology with a discontinuous method is that where in a sequence discontinuous values generated by the methods are similar, the values in-between these époques would have been similar as well (Fig. 5).

Thermodilution-based estimates or inert gas rebreathing data, are obtained as averages over at least 20 heartbeats [70]. With thermodilution-based determinations of CO, an average of four injections is required to be 95% confident that the result is within 5% of the 'true' CO. The averages of two determinations need to differ by at least 7% before it is accepted that a change in CO has taken place [118]. For instance, when CO increases 20% in response to a fluid challenge, the increase is 1000 ml vs. 1600 ml for resting CO values of respectively 5 vs. 8 $l \cdot min^{-1}$. The 600 ml difference likely remains within the scatter of a thermodilution estimate [80,116,117] further supporting the idea that changes in flow rather than absolute values, are of clinical relevance. In future studies the methodology of discontinuous CO that is applied as a standard should satisfy rigorous criteria before any comparison can be made.

Conclusion

Continuous and non-invasive monitoring of cardiac output allows for the detection of rapid effects on systemic flow and conductance that would otherwise remain unnoticed in a recording of arterial pressure or heart rate. A disadvantage is that the true value remains difficult to obtain. We consider continuous information on the circulation beyond what is detected by arterial pressure, of relevance both in clinical medicine and in human cardiovascular research.

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