

# Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine

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## Editor's key points

- The authors review the burgeoning array of non-invasive cardiac output monitors.
- They note the varied limitations of the devices and note the need for appropriate description of device performance.
- The need for uniformity in defining clinically acceptable performance is highlighted.

**Summary.** The determination of blood flow, i.e. cardiac output, is an integral part of haemodynamic monitoring. This is a review on noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. We present the underlying principles and validation data of the following technologies: thoracic electrical bioimpedance, thoracic bioreactance, vascular unloading technique, pulse wave transit time, and radial artery applanation tonometry. According to clinical studies, these technologies are capable of providing cardiac output readings noninvasively and continuously. They, therefore, might prove to be innovative tools for the assessment of advanced haemodynamic variables at the bedside. However, for most technologies there are conflicting data regarding the measurement performance in comparison with reference methods for cardiac output assessment. In addition, each of the reviewed technology has its own limitations regarding applicability in the clinical setting. In validation studies comparing cardiac output measurements using these noninvasive technologies in comparison with a criterion standard method, it is crucial to correctly apply statistical methods for the assessment of a technology's accuracy, precision, and trending capability. Uniform definitions for 'clinically acceptable agreement' between innovative noninvasive cardiac output monitoring systems and criterion standard methods are currently missing. Further research must aim to further develop the different technologies for noninvasive continuous cardiac output determination with regard to signal recording, signal processing, and clinical applicability.

**Keywords:** cardiac output; intensive care unit; monitoring, intraoperative

Determination of blood flow, i.e. cardiac output, is an integral part of advanced haemodynamic monitoring in perioperative and intensive care medicine. Besides the pulmonary artery thermodilution technique using the pulmonary artery catheter (PAC) and transpulmonary thermodilution, less invasive technologies for both intermittent and continuous cardiac output determination have been developed including calibrated and un-calibrated (i.e. calibrated according to algorithms based on biometric data) pulse contour analysis and oesophageal doppler.

In addition, completely noninvasive technologies such as thoracic electrical bioimpedance, thoracic bioreactance, vascular unloading technique, pulse wave transit time, and radial artery applanation tonometry are now available for cardiac output monitoring.

In this review, we focus on noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. We discuss how novel technologies should be appropriately evaluated with special regard to the statistical methods applied in comparison studies. Finally, we present the

underlying principles and validation data of currently available technologies for noninvasive continuous cardiac output determination.

## Clinical relevance of cardiac output determination and optimization

### The importance of cardiac output – pathophysiologic basics

The outstanding importance of cardiac output becomes clear when considering that the total amount of oxygen delivered by the cardiovascular system can be quantified by calculating oxygen delivery ( $DO_2$ ):

$$DO_2[\text{ml min}^{-1}] = \text{cardiac output} [\text{litre min}^{-1}] \\ \times \text{arterial oxygen content} [\text{ml dl}^{-1}] \times 10$$

(with cardiac output [ $\text{litre min}^{-1}$ ] = stroke volume [litre]  $\times$  heart rate [ $1 \text{ min}^{-1}$ ])

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Knowing a patient's  $\text{DO}_2$  and global oxygen consumption ( $\text{VO}_2$ ) the oxygen extraction ratio can be assessed. Critical illness or major surgery induces a systemic inflammatory response syndrome resulting in a marked increase in oxygen demand. To meet this increased oxygen demand in these clinical conditions, compensation mechanisms resulting in an increase in  $\text{DO}_2$  are needed. These mechanisms include an increase in cardiac output and oxygen extraction ratio. The inability to increase cardiac output can result in tissue hypoxia and ultimately organ dysfunction. Therefore, to avoid inadequate  $\text{DO}_2$  in these patients, therapeutic interventions such as administration of fluids and inotropic agents aim at optimization of cardiac output.

### Perioperative medicine

In surgical patients, protocol-based optimization of haemodynamic variables reduces postoperative mortality and morbidity in high-risk surgical patients according to large meta-analyses.<sup>1-3</sup> A recent Cochrane Systematic Review including more than 5000 patients from 31 studies provides evidence that goal-directed therapy aiming to increase global blood flow reduces postoperative complications and hospital length of stay.<sup>4</sup> In addition, improved patient outcome in terms of a reduction in postoperative complications and hospital length of stay by goal-directed haemodynamic therapy was revealed in a recent meta-analysis, also in cardiac surgery patients.<sup>5</sup>

Although this approach is still not widely adopted in routine clinical care, there is considerable evidence to show that goal-directed haemodynamic strategies aiming at an optimization of cardiac output/cardiac index and  $\text{DO}_2$  in selected high-risk surgical patients can contribute to a reduction of postoperative morbidity and mortality.<sup>6</sup>

### Critical illness

In critically ill patients treated in the intensive care unit (ICU), monitoring of blood flow and tissue oxygenation is an integral part of the management of these patients. The assessment of cardiac output plays a pivotal role in the differential diagnosis of shock states.<sup>7 8</sup>

In addition, cardiac output monitoring is crucial in the identification of patients who are fluid responsive, i.e. patients who are able to increase their stroke volume and cardiac output after a fluid challenge test or a passive leg raising test.<sup>9 10</sup>

Especially in patients with severe sepsis, relative intravascular hypovolemia due to a mediator-induced increased capillary permeability and septic myocardial dysfunction make close monitoring of cardiac preload and cardiac output inevitable.<sup>11</sup>

## How should we adequately evaluate innovative noninvasive cardiac output monitoring technologies?

### Criterion standard methods

One key problem related to validation studies for novel cardiac output monitoring technologies is that there is no generally accepted consensus on which established monitoring technology should be used as the criterion standard. While pulmonary

artery thermodilution measurements using a PAC are generally accepted as the clinical criterion standard method,<sup>12</sup> among other techniques, transpulmonary thermodilution, pulse contour analysis, and echocardiography have also been used in previous validation studies. The question still remains unanswered whether invasive criterion standard technologies such as thermodilution using a PAC or transpulmonary thermodilution are the appropriate comparators when testing innovative non-invasive devices.<sup>13</sup>

### Statistical analyses in method comparison studies evaluating innovative cardiac output monitoring technologies

Appropriate statistical analyses are the prerequisite for a sound interpretation of method comparison studies describing the measurement performance of novel cardiac output monitoring technologies.<sup>13</sup> Different statistical methods for the assessment of a system's accuracy, precision, and trending ability in comparison with a criterion standard technology have been described.

First, it should be noted that correlation analysis, although frequently used in method comparison studies evaluating agreement, does not measure *agreement* between two methods, but rather their *relationship*.<sup>14</sup> Therefore, correlation analysis should not be used as the single statistical method in clinical studies comparing new technologies for cardiac output measurement with an established reference technique.

To illustrate the statistical tests discussed in the following, we present two worked examples describing cardiac output measurements obtained with a reference technology in comparison with a studied technology in 20 individual patients at three different time points (Table 1). The two studied methods were chosen to represent good (example 1) and poorer (example 2) measurement performance with regard to absolute accuracy and precision as well as trending of cardiac output values compared with the reference technology.

Bland-Altman analysis including computation of a Bland-Altman plot has become the accepted standard statistical approach for the evaluation of the agreement, i.e. accuracy and precision, of a new cardiac output monitoring system in comparison with criterion standard cardiac output measurements.<sup>14 15</sup> Further development of the initially presented Bland-Altman analysis allows taking multiple and unequal numbers of measurements per individual into account.<sup>14</sup> When applying Bland-Altman analysis to evaluate the agreement of an innovative cardiac output measurement technology in comparison with a criterion standard method for cardiac output assessment, the mean difference (i.e. bias) and the limits of agreement (i.e.  $1.96 \times$  standard deviation of the mean difference) reflect the new technology's accuracy and precision, respectively (Fig. 1A and B).

In addition, the **percentage error** as proposed by Critchley and Critchley can be calculated as **2 times the standard deviation of the mean difference divided by the mean of measurements** (Fig. 1A and B).<sup>16</sup>

Besides high accuracy and precision, the ability to accurately follow changes in cardiac output is of crucial importance for

**Table 1** Worked examples. Two worked examples describing cardiac output measurements obtained with a reference technology in comparison with a studied technology. Measurements were performed in 20 individual patients at three different time points, i.e. measurement number 1, 2, and 3. At each time point, the cardiac output value assessed with the reference technology (i.e. pulmonary artery thermodilution using a pulmonary artery catheter) was obtained by averaging three consecutively recorded thermodilution curves

Patient ID	Measurement No.	Example 1		Example 2	
		Reference technology	Studied technology 1	Reference technology	Studied technology 2
1	1	6.9	7.5	6.9	2.6
1	2	6.2	6.9	6.2	2.6
1	3	7.5	7.8	7.5	2.8
2	1	6.4	5.8	6.4	4.0
2	2	6.9	7.0	6.3	3.6
2	3	5.0	4.8	5.5	3.7
3	1	3.9	4.3	3.9	6.2
3	2	3.5	3.7	3.5	5.5
3	3	4.3	4.6	4.3	6.1
4	1	8.5	9.9	8.5	5.3
4	2	8.9	10.8	8.9	3.2
4	3	8.3	10.0	8.3	3.3
5	1	4.9	5.6	4.9	2.0
5	2	5.0	5.7	4.8	2.7
5	3	6.0	6.7	6.0	2.2
6	1	11.8	11.7	11.8	7.2
6	2	12.4	12.0	12.4	5.0
6	3	11.0	11.2	11.0	7.0
7	1	11.0	9.9	10.2	14.0
7	2	9.9	9.0	9.9	12.2
7	3	10.0	9.3	10.9	12.0
8	1	7.3	7.5	9.3	6.3
8	2	7.0	7.0	11.3	6.3
8	3	7.1	7.1	10.0	6.7
9	1	13.9	13.4	14.9	9.9
9	2	13.5	13.0	13.5	9.9
9	3	12.9	12.4	12.9	14.0
10	1	5.6	6.0	5.6	6.5
10	2	4.6	4.5	5.0	6.6
10	3	3.2	3.0	4.0	6.5
11	1	12.2	11.4	12.2	13.4
11	2	12.4	11.9	12.9	13.9
11	3	12.2	11.7	13.1	12.3
12	1	9.3	10.2	9.3	10.0
12	2	9.1	9.9	9.1	10.1
12	3	9.0	9.5	9.0	7.8
13	1	6.9	6.0	6.4	4.3
13	2	7.0	6.1	6.9	5.2
13	3	5.0	4.0	5.0	8.1
14	1	12.8	12.7	11.8	12.5
14	2	10.4	10.2	11.4	12.4
14	3	11.4	11.6	11.5	12.9
15	1	4.3	4.0	4.3	6.0
15	2	3.1	3.0	4.8	6.1
15	3	4.6	4.9	4.6	5.9
16	1	7.5	7.0	7.5	7.0
16	2	7.3	6.9	7.3	6.7
16	3	6.8	6.5	6.8	6.7

Continued

**Table 1** Continued

Patient ID	Measurement No.	Example 1		Example 2	
		Reference technology	Studied technology 1	Reference technology	Studied technology 2
17	1	8.8	7.9	8.8	11.0
17	2	9.4	8.1	8.9	11.0
17	3	9.5	8.2	9.5	6.0
18	1	11.3	10.5	11.3	10.6
18	2	12.0	11.0	12.0	10.5
18	3	13.0	12.2	13.0	10.7
19	1	3.3	3.1	3.3	4.0
19	2	4.0	3.8	3.7	4.1
19	3	3.0	3.1	3.0	4.1
20	1	7.1	6.0	7.1	3.2
20	2	8.0	7.1	8.0	3.3
20	3	7.9	7.0	7.4	3.1

cardiac output monitoring devices. Adequate trending of increases and decreases in cardiac output can be assessed by concordance analysis giving the proportion of measurements that change in the same direction and all measurements. To illustrate the cardiac output monitoring technology’s ability to follow cardiac output changes, a 4-quadrant plot (Fig. 2A and B) or polar plot analysis (Fig. 3A and B) can be used.<sup>17 18</sup>

**Difficulties regarding the definition of ‘clinically acceptable agreement’ and ‘interchangeability’**

There is still a controversy about the definitions of ‘clinically acceptable agreement’ or ‘interchangeability’.<sup>13</sup> This basically holds true for all available statistical methods for the assessment of agreement and trending.

Regarding absolute accuracy and precision assessed by Bland-Altman analysis, so far no generally accepted cut-off values for the acceptable mean difference between two cardiac output measurement methods and the corresponding standard deviation (and therefore limits of agreement) exist. When using the percentage error by Critchley and Critchley, a cut-off value of 28.3% (rounded to 30%) is usually applied to define acceptable agreement.<sup>16</sup> However, the prerequisites for the use of this threshold of 30% described in the original publication of Critchley and Critchley<sup>16</sup> are frequently not fulfilled in clinical studies evaluating innovative cardiac output monitoring technologies.<sup>13 19</sup> The percentage error cut-off value of 30% can only be applied when both the criterion standard method and the method to be tested have a precision of ±20%.<sup>13 20</sup> In clinical cardiac output validation studies, it is of outstanding complexity to separately determine and report the precision of each technology.<sup>21 22</sup> In line with these theoretical considerations, the applicability of the 30% threshold has been questioned based on a meta-analysis evaluating studies testing minimally invasive cardiac output measurement methods in comparison with bolus thermodilution cardiac output measurements.<sup>19</sup>

With regard to the assessment of trending by 4-quadrant plot and polar plot analysis, definitions of good, acceptable, and poor agreement have been suggested<sup>17 18</sup> but still need to be confirmed. Of note, the suggested thresholds for the definition of good or poor trending abilities based on concordance rates (4-quadrant plot) or angular bias and radial limits of agreement (polar plot) are also dependent on the precision of the methods compared.<sup>18</sup> In addition, it is still a matter of debate whether all available cardiac output data should be included in the trending analysis. Very small as well as very large changes in cardiac output do not sufficiently contribute to the discriminative power of trending analysis.<sup>17</sup> While small changes of cardiac output are usually excluded from the 4-quadrant plot and polar plot analysis by the use of an exclusion zone (of for example 10% or 0.5 litre min<sup>-1</sup>), the optimal approach to very high cardiac output changes is still not defined.<sup>17</sup>

**Technologies for noninvasive cardiac output measurement**

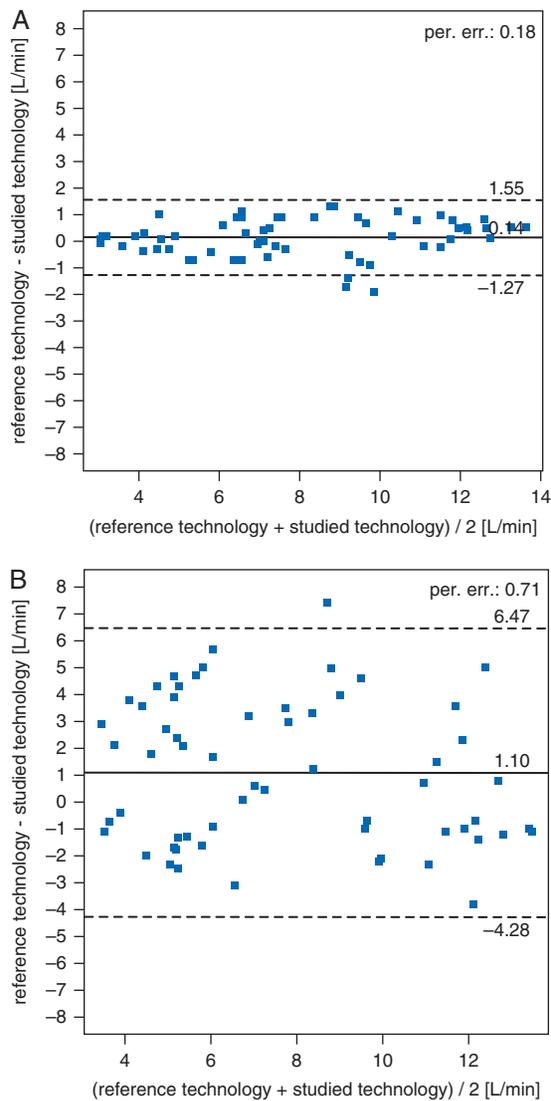
In the following, we will describe the underlying principles and validation data of several technologies that are nowadays commercially available for noninvasive continuous cardiac output measurement.

**Electrical bioimpedance**

**Technology description**

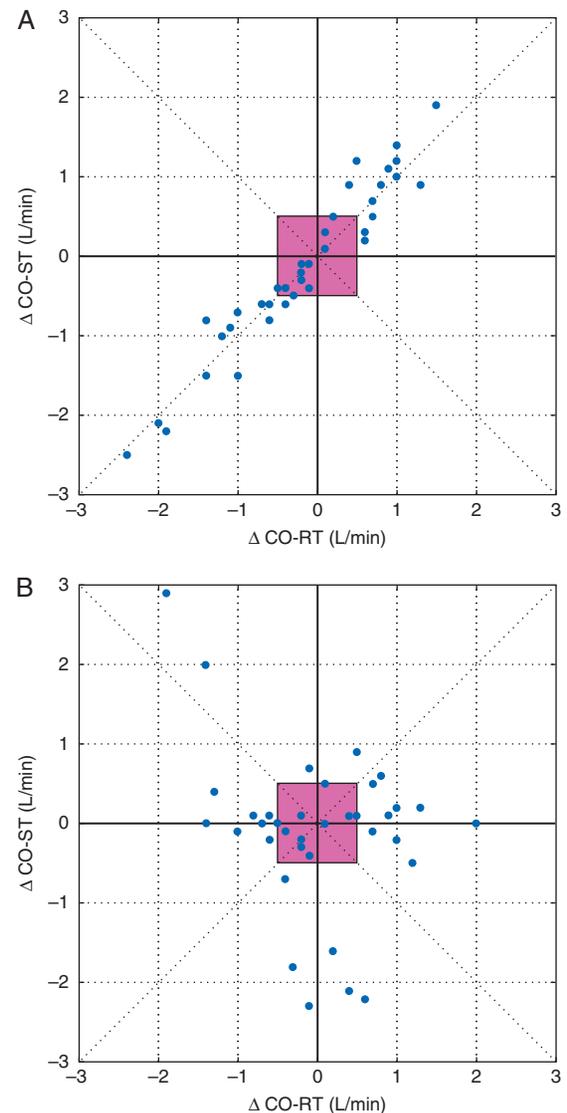
Different systems for cardiac output determination based on electrical bioimpedance are available.

The electrical bioimpedance technology relies on the fact that the impedance of the thorax (i.e. the resistance to electrical current) is dependent on the amount of fluid in the thoracic compartment. Based on the assumption that the varying amount of blood volume in the aorta during the cardiac cycle is related to the observed changes in impedance, the latter is assessed by applying a high-frequency current with a given



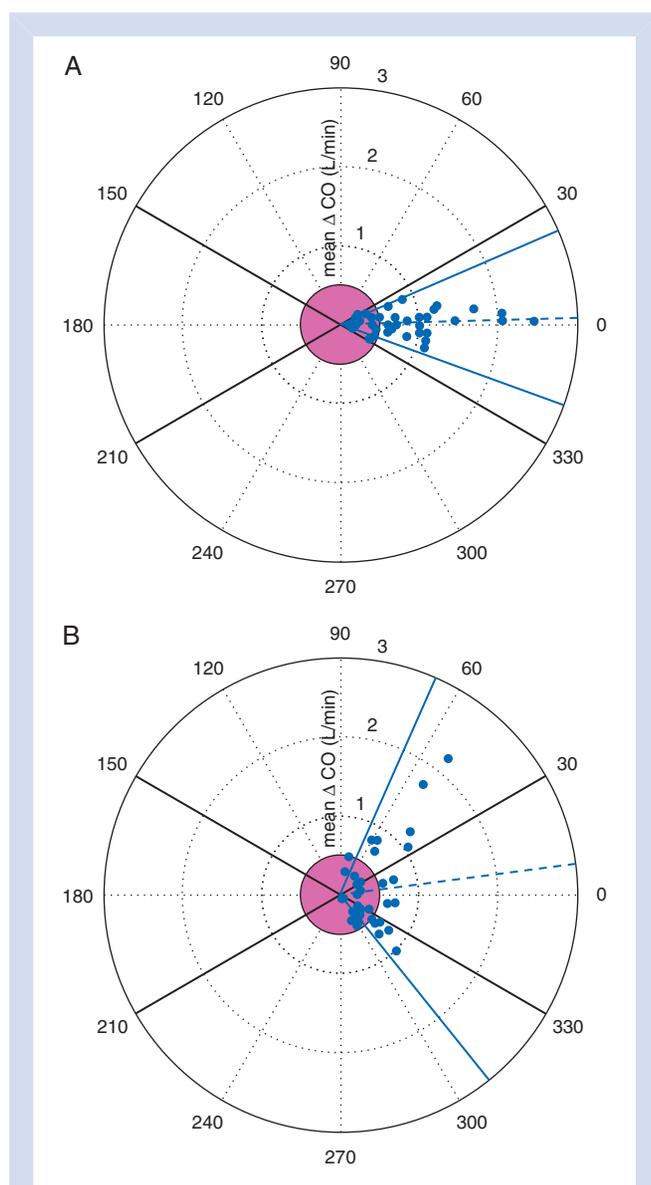
**Fig 1** Bland-Altman plots for repeated measurements in one individual. Bland-Altman analyses accounting for repeated measurements in one individual are presented for example 1 (A) and example 2 (B) described in Table 1.<sup>14, 15</sup> This statistical method plots the difference between cardiac output values assessed with the reference technology and the studied technology in dependence on the mean cardiac output values assessed with the two methods. The Bland-Altman plot allows reading off the mean difference, i.e. bias, between the reference technology and the studied technology (continuous line) and the 95% limits of agreement, i.e. mean difference  $\pm 1.96 \times$  standard deviation (dashed lines). While the mean difference represents the accuracy of the studied technology in comparison with the reference technology, the 95% limits of agreement represent its precision. The percentage error (per. err.) as proposed by Critchley and Critchley<sup>16</sup> (2 times the standard deviation of the mean difference divided by the mean of measurements) is shown in the upper right corner of the plots.

amplitude and frequency to the thorax and measuring the changes in voltage, i.e. the difference between the applied voltage and the detected voltage. Cardiac output is computed



**Fig 2** 4-quadrant plots. 4-quadrant plots are presented for example 1 (A) and example 2 (B) described in Table 1. This statistical method plots differences between consecutive cardiac output values assessed with the reference technology ( $\Delta\text{CO-RT}$ ; x-axis) and the studied technology ( $\Delta\text{CO-ST}$ ; y-axis) in a scatter plot. When both the reference technology and the studied technology indicate a concordant direction of cardiac output change the resulting data points appear in the upper right quadrant (increase in cardiac output) or lower left quadrant (decrease in cardiac output) of the 4-quadrant plot. The 4-quadrant plot allows reading off the direction and magnitude of change in cardiac output as assessed by the reference technology and the studied technology and the calculation of the concordance rate, i.e. the ratio of data points in the upper right quadrant (concordant increase in cardiac output) or lower left quadrant (concordant decrease in cardiac output) to all data points. As discussed in the text, a central exclusion zone (pink square) might be applied.

based on mathematical equations under the assumption that thoracic impedance changes over time are proportional to the stroke volume.



**Fig 3** Polar plot. Half circle polar plots as proposed by Critchley<sup>17 18</sup> are presented for example 1 (A) and example 2 (B) described in Table 1. This statistical method illustrates direction and magnitude of change analysis in polar coordinates, i.e. each data point is described by an angle and a radius. The polar plot allows reading off the angular bias (blue dashed line) and the radial limits of agreement (blue continuous lines), i.e. lines with angles of  $+30^\circ$  and  $-30^\circ$  to the horizontal axis.<sup>18</sup> For example 1 and example 2, the angular bias (radial limits of agreement) is  $1.8^\circ$  ( $\pm 21.5^\circ$ ) and  $7.5^\circ$  ( $\pm 58.7^\circ$ ), respectively. As discussed in the text, a central exclusion zone (pink circle) was applied.

The principles of electrical bioimpedance were described for the use in a clinical setting in 1966 by Kubicek and co-workers<sup>23</sup> and in 1986 by Bernstein.<sup>24</sup> Nowadays, several devices used for thoracic electrical bioimpedance with electrodes placed on the patient's skin are available.<sup>17</sup>

Further developments and modifications of the thoracic bioimpedance technology were described including 'electrical

velocimetry', a technology using a modified equation based on the maximum rate of change of impedance to assess aortic blood flow and thereby cardiac output.<sup>25</sup>

Further, a modification of the previously described thoracic electrical bioimpedance method with electrodes attached to a specially designed endotracheal tube (ECOM; ConMed Corp, Utica, NY, USA) is available. Thoracic electrical bioimpedance based on signal recording using electrodes attached to an endotracheal tube was first described in an animal model (swine) in 2000.<sup>26</sup> From a theoretical point of view, the placement of the electrodes in the trachea in close proximity to the aorta might help to improve signal recording by reducing the signal-to-noise ratio.

### Validation data

Early data on thoracic bioimpedance cardiac output determination demonstrated inconsistent results when compared with cardiac output measurements by pulmonary artery thermodilution.<sup>27–29</sup> Altogether, a large number of validation studies in different patient populations have been carried out to explore the measurement performance of thoracic electrical bioimpedance in a variety of different patient collectives including surgical patients and critically ill patients treated in the ICU.<sup>30</sup> In summary, the results of these older studies suggested that the overall agreement of thoracic electrical bioimpedance with established reference methods was poor. Despite these mainly disappointing results, the technology has been re-evaluated using upgraded computer technology and improved equations for the mathematical derivation of cardiac output in a number of validation studies during the last years. However, these validation studies still provide contradicting and inconsistent results with regard to the agreement with reference techniques and the ability to trend cardiac output changes. On the one hand, in post-cardiac surgery patients, several studies revealed promising results when comparing thoracic electrical bioimpedance with pulmonary artery thermodilution.<sup>31–34</sup> On the other hand, there are also data showing high bias and wide limits of agreement when comparing thoracic electrical bioimpedance with pulmonary artery thermodilution in cardiac surgery patients<sup>35</sup> and with pulmonary artery thermodilution in mixed ICU patients.<sup>36</sup> In a meta-analysis published in 2010,<sup>19</sup> more than 400 patients from 13 thoracic electrical bioimpedance validation studies were analysed. Compared with thermodilution cardiac output measurements, the authors reported a pooled bias of  $-0.10$  litre  $\text{min}^{-1}$  with a pooled weighted precision (one standard deviation) of agreement of  $1.14$  litre  $\text{min}^{-1}$  resulting in an overall percentage error of 42.9% for thoracic electrical bioimpedance measurements.

Electrical velocimetry – a modification of the bioimpedance technology – was also shown to have low accuracy and precision when compared with pulmonary artery thermodilution in cardiac surgery patients<sup>37</sup> and with transpulmonary thermodilution in patients with sepsis or systemic inflammatory response syndrome.<sup>25</sup>

Clinical studies on electrical bioimpedance with electrodes attached to an endotracheal tube demonstrated that the technology provides cardiac output with low precision and high

percentage error in cardiac surgery patients when compared with pulmonary artery thermodilution<sup>38–41</sup> and with transpulmonary thermodilution.<sup>42</sup>

### Limitations of the technology

Several limitations of thoracic electrical bioimpedance must be considered. In clinical practice, the applicability of all thoracic electrical bioimpedance devices is highly dependent on electrode positioning and is limited by electrical interference (e.g. from electrocautery), fluid in the thoracic compartment (pleural effusions, pericardial tamponade, pulmonary oedema),<sup>43</sup> changes in peripheral vascular resistance,<sup>44</sup> the patient's biometric data,<sup>45</sup> cardiac arrhythmias, and motion artefacts.<sup>46</sup> Regarding thoracic electrical bioimpedance using endotracheal electrodes (ECOM system) it has to be mentioned that both a specially designed endotracheal tube with electrodes and an arterial catheter for recording of the arterial pressure waveform are prerequisites for cardiac output determination. Considering the need for the presence of an arterial catheter, the ECOM system does therefore not represent a completely noninvasive technology for cardiac output assessment.

### Thoracic bioreactance

#### Technology description

In order to improve the processing of the bioimpedance signal, i.e. in order to improve the signal-to-noise ratio, a modification of the thoracic electrical bioimpedance technology, the so-called 'thoracic bioreactance' technology has been developed. 'Bioreactance' represents the phase shift in voltage across the thorax.<sup>47</sup> It is supposed that the phase shift almost exclusively depends on pulsatile flow, and that the bioreactance signal – in comparison with the bioimpedance signal – is therefore more closely related to aortic blood flow and less dependent on intra- and extravascular lung water.<sup>47</sup> The only commercially available system at present (NICOM, Cheetah Medical, Portland, OR, USA) uses 4 electrode patches each consisting of 2 electrodes and calculates cardiac output separately for the right and left side of the body with the final cardiac output being the average of these two values.<sup>47</sup>

#### Validation data

First described in 2007,<sup>48</sup> cardiac output measurement with the NICOM bioreactance system was subsequently validated in 110 ICU patients after cardiac surgery with a bias (standard deviation) of  $+0.06 \text{ litre min}^{-1}$  ( $0.71 \text{ litre min}^{-1}$ ).<sup>49</sup> In a multi-centre study evaluating the NICOM bioreactance method in 111 patients (mixed population of patients in cardiac care units, ICUs, and cardiac catheterization laboratories) in comparison with PAC-derived cardiac output (either continuous cardiac output measurements or intermittent bolus pulmonary artery thermodilution measurements), the authors observed a low bias of  $-0.09 \text{ litre min}^{-1}$  and wide 95% limits of agreement of  $-2.5 \text{ litre min}^{-1}$  to  $+2.3 \text{ litre min}^{-1}$  for ICU patients.<sup>50</sup> Comparable results were obtained in studies in post cardiac surgery patients when using cardiac output measurements obtained with transpulmonary thermodilution and

calibrated pulse contour analysis<sup>51</sup> or with pulmonary artery thermodilution as the criterion standard.<sup>52</sup> A study in surgical patients treated for ovarian cancer showed that **thoracic bioreactance does not sufficiently provide cardiac index** when compared with **transpulmonary thermodilution**.<sup>53</sup>

### Limitations of the technology

The bioreactance technology still has **several limitations**. As with bioimpedance, electrical interference can disturb bioreactance measurements. In addition, the system provides **cardiac output readings averaged over 60 s** and is therefore not able to indicate **very rapid changes** in cardiac output. The advantage of this 60-second average approach, however, is that the system might be **able** to provide cardiac output data in the presence of mild cardiac **arrhythmias**.<sup>47</sup>

### Vascular unloading technique (volume clamp method, Peñáz principle)

#### Technology description

Another technology capable of providing cardiac output measurements based on the analysis of the pulse contour of a continuously and noninvasively recorded arterial pressure waveform is the vascular unloading technique. This method is also called **volume clamp method** or the Peñáz principle, who was the first describing it in 1973.<sup>54</sup> The method was further developed over the last decades.<sup>55 56</sup> The vascular unloading technique uses a **finger cuff** which applies pressure to the finger. Further, the **finger artery's diameter** is assessed by sending **infrared light** through the finger and measuring the absorption of the light by the blood using a light detector integrated in the finger cuff. This photo-plethysmographic signal **controls** the finger cuff **pressure** in such way that the **blood volume** in the finger artery – and therefore the artery's **diameter** – is kept at a **constant level** during the **cardiac cycle**. When the artery's diameter is **constant**, the cuff **pressure** must be **equal** to the **intra-arterial pressure**. Thus, from the pressure needed to keep the volume in the finger artery constant throughout the cardiac cycle the **arterial pressure waveform** can indirectly be derived. As cuff pressure and intra-arterial pressure are **equal**, the resulting **transmural pressure** is **zero** and therefore there is **no wall tension** in the finger arterial wall, i.e. the artery is **'unloaded'**. Vasomotor changes influence the optimal 'unloading volume' of the finger artery and the device has to react on these vasomotor activities. Depending on the system used, the optimal 'unloading volume' of the finger artery is assessed differently and the raw arterial pressure waveform is further processed in different ways: when using the CNAP technology (CNSystems Medizin-technik AG, Graz, Austria), the optimal 'unloading volume' is assessed using 'interlocking control loops'<sup>56</sup> including a beat-to-beat vasomotor elimination mechanism called VERIFI.<sup>57</sup> The continuous arterial pressure signal obtained at the level of the finger is amplified and shifted to match systolic and diastolic arterial pressure values obtained by oscillometric arterial pressure using a proprietary transfer function. Subsequently, the mean arterial pressure is adjusted accordingly. When

using the other commercially available monitoring system based on the vascular unloading technology, the ClearSight system (Edwards Lifesciences, Irvine, CA, USA; formerly known as Nexfin system, BMEye, Amsterdam, The Netherlands), the 'unloading volume' is assessed by the 'Physiocal' principle, i.e. an algorithm analyzing the plethysmogram with regard to waveform characteristics to assess the optimal cuff pressure.<sup>55 58</sup> The brachial arterial pressure is mathematically reconstructed based on the arterial pressure assessed with the finger cuff.<sup>55 59 60</sup>

While the algorithm for cardiac output determination with the CNAP system has just recently been released, there are several clinical validation studies for cardiac output measurement with the Nexfin system. The latter computes stroke volume and thus cardiac output in a continuous manner from the analysis of the arterial pressure waveform with special regard to the systolic part of the arterial pressure curve and the impedance of the aorta that is determined from a '3-element Windkessel model'.<sup>55 61 62</sup>

### Validation data

Validation studies evaluating the Nexfin device for cardiac output determination revealed inconsistent results. Cardiac output determination with the Nexfin system proved to provide cardiac output with a low bias and narrow limits of agreement compared with transpulmonary thermodilution during cardiac surgery.<sup>63</sup>

In contrast, other studies in post-cardiac surgery patients demonstrated a high accuracy but low precision when comparing Nexfin cardiac index/cardiac output with cardiac index/cardiac output assessed by transpulmonary thermodilution or pulmonary artery thermodilution.<sup>64–67</sup>

In addition, in a study in medical ICU patients, a bias between cardiac index measured with Nexfin and transpulmonary thermodilution of  $+0.2 \text{ litre min}^{-1} \text{ m}^{-2}$  with 95% limits of agreement of  $-1.8 \text{ litre min}^{-1} \text{ m}^{-2}$  to  $2.2 \text{ litre min}^{-1} \text{ m}^{-2}$  (percentage error 57%)<sup>68</sup> demonstrated clinically unacceptable agreement of Nexfin cardiac index with the reference method.<sup>68</sup> A comparison of the Nexfin system with cardiac output obtained by transpulmonary thermodilution and pulse contour analysis in 45 mixed ICU patients resulted in a bias (95% limits of agreement, percentage error) of  $+0.4 \text{ litre min}^{-1}$  ( $\pm 2.32 \text{ litre min}^{-1}$ , 36%) and  $0.2$  ( $\pm 2.32 \text{ litre min}^{-1}$ , 37%), respectively, and (according to the authors' conclusion) acceptable cardiac output trending capabilities.<sup>69</sup>

### Limitations of the technology

Because the vascular unloading technology analyses the pulse contour of the arterial pressure waveform for cardiac output monitoring, it depends on a high quality arterial pressure signal assessed using the finger cuff. In patients with finger oedema, the arterial pressure signal can be markedly disturbed. Especially in critically ill patients, authors reported a relatively high proportion of patients in whom no arterial pressure signal could be derived with the vascular unloading technique probably to peripheral hypoperfusion.<sup>68 69</sup> In addition, concerns have been raised that cardiac output measurements

with the vascular unloading technique might be unreliable in patients with low cardiac output and high systemic vascular resistance, e.g. patients with cardiogenic or hypovolemic shock.<sup>64 69</sup>

## Pulse wave transit time

### Technology description

When used for noninvasive cardiac output assessment, pulse wave transit time is defined as the time between the R-wave in the electrocardiogram and the pulse wave rise-point assessed by pulse oximetry. The esCCO technology (Nihon Kohden, Tokyo, Japan) provides noninvasive continuous cardiac output readings assessed by analysis of the electrocardiogram, the pulse oximeter-derived waveform, and arterial pressure. The underlying assumption for cardiac output assessment using this technology is an inverse correlation between the pulse wave transit time and stroke volume.

### Validation data

Few validation studies exist for this innovative technology. After a first description of the technology (calibrated to a reference cardiac output value at the beginning of measurements) in a clinical setting in 2004,<sup>70</sup> Yamada and co-workers<sup>71</sup> evaluated the esCCO system in a multicentre study in 213 surgical and ICU patients in comparison with continuous pulmonary artery thermodilution and revealed a bias of  $0.13 \text{ litre min}^{-1}$  with 95% limits of agreement of  $-2.13 \text{ litre min}^{-1}$  to  $+2.39 \text{ litre min}^{-1}$  and a percentage error of 54%. Of note, in this study the esCCO system was also calibrated to the reference cardiac output value at the beginning of the study cardiac output measurements. In another study in 35 cardiac surgery patients, a bias of  $0.80 \text{ litre min}^{-1}$  (95% limits of agreement of  $-2.00 \text{ litre min}^{-1}$  to  $+3.61 \text{ litre min}^{-1}$ ; percentage error 53%) was observed.<sup>72</sup>

### Limitations of the technology

A major limitation of the esCCO system was that a reference cardiac output value was required at the start of the measurement for calibration.<sup>73</sup> Although a calibration approach based on patient demographic data and cardiovascular variables including heart rate, pulse pressure, and pulse wave transit time was described, this approach is not well investigated and probably needs further improvement.<sup>73 74</sup>

## Radial artery applanation tonometry

### Technology description

Radial artery applanation tonometry allows continuous (beat-by-beat) noninvasive recording of the arterial pressure waveform.<sup>75–81</sup> The basic principle of radial artery applanation tonometry was described for the first time in 1963.<sup>82 83</sup> While some devices needed arterial pressure values obtained with upper-arm cuff oscillometry for calibration,<sup>84–88</sup> the nowadays commercially available system, the T-Line system (Tensys Medical Inc., San Diego, CA, USA), uses a proprietary algorithm for continuous recording of the arterial pressure waveform.<sup>77</sup>

A sensor is placed over the radial artery and positioning of the sensor is refined by an electromechanical system. From the raw arterial pressure signal that is obtained in the optimal 'applanation' position, i.e. in the position in which the artery's transmural pressure is zero, mean arterial pressure can be determined. Subsequently, the arterial pressure waveform is scaled according to a proprietary algorithm based on biometrical data and thus systolic and diastolic arterial pressure can be derived.

### Validation data

Recently, an autocalibrating algorithm for noninvasive continuous cardiac output assessment based on the analysis of the radial artery applanation tonometry-derived arterial pressure waveform has been described and evaluated for the first time in a pilot study.<sup>89</sup> Radial artery applanation tonometry-based determination of cardiac output using this algorithm is possible by analysing the arterial pressure waveform with a non-linear mathematical model using physiological and biometrical input source data vectors of the patient.<sup>89</sup> In this proof of concept analysis, cardiac output measurements were simultaneously recorded using radial artery applanation tonometry and pulse contour analysis just calibrated by transpulmonary thermodilution.<sup>89</sup> A cardiac output bias of  $+0.1 \text{ litre min}^{-1}$  ( $0.8 \text{ litre min}^{-1}$ ) and 95% limits of agreement of  $-1.5 \text{ litre min}^{-1}$  to  $+1.7 \text{ litre min}^{-1}$  and a percentage error of 23% indicated good accuracy and precision in this selected patient collective.

### Limitations of the technology

Regarding the applicability of radial artery applanation tonometry for cardiac output determination in clinical routine care, it has to be stressed that this technology depends on the quality of the recorded arterial pressure waveform because the analysis of the latter is the basis for the assessment of cardiac output. In this context, the major prerequisite for arterial pressure recording is optimal positioning of the sensor over the radial artery. Rapid movement of the patient's arm to which the radial sensor is attached by the patient or by medical staff can disturb the accurate recording of the arterial pressure waveform and thus cardiac output determination.

## Heterogeneity of validation data and interpretation of study results

The available **validation studies** evaluating different noninvasive continuous cardiac output monitoring technologies are **heterogeneous** in terms of the criterion standard method used, the study setting and patient population, the observed results, and the conclusions presented by the authors based on the study findings. To illustrate this problem we exemplarily present the results on measurement accuracy and precision and the authors' conclusions of several validation studies in Table 2. Furthermore, the table illustrates that there is no generally accepted and uniform way to report the conclusions drawn from the observed measurement performance of

noninvasive cardiac output monitoring technologies in comparison with the criterion standard.

It is evident from Table 2 that some studies report raw data of cardiac output, while others report normalized cardiac index (i.e. cardiac output indexed to body surface area). With regard to the comparability of different studies evaluating cardiac output monitoring technologies, the uniform use of cardiac output would be preferable. On the other hand, cardiac index might be the more important variable for clinical decision making because it reflects individual biometric characteristics of different patients. Similarly, some studies evaluating innovative monitoring technologies alternatively report stroke volume or stroke volume index (i.e. stroke volume indexed to body surface area). In this context it is important to emphasize that **stroke volume is the primary variable these technologies measure**. In addition, **one could argue that a specific intervention (e.g. fluid challenge) increases stroke volume but decreases heart rate**, so that the **net effect on cardiac output is negligible**. Therefore, when comparing beat-to-beat haemodynamic monitoring technologies, stroke volume or stroke volume index could also be used to compare the measurement performance of different devices instead of cardiac output or cardiac index.

## Concept of completely noninvasive cardiac output monitoring – conclusion

In conclusion, determination of blood flow, i.e. cardiac output, plays a crucial role in patient care in anaesthesiology and intensive care medicine.

Several completely noninvasive technologies are available that allow for continuous cardiac output measurement. These technologies might –in theory– fulfil many properties of an 'ideal haemodynamic monitoring system' as described in a recent consensus statement.<sup>90</sup> They provide measurement of a relevant haemodynamic variable (cardiac output) that allows guidance of haemodynamic therapy. They are supposed to be easy to use, readily available, operator-independent, and (due to the complete noninvasiveness) causing no harm.

These technologies might therefore prove as innovative useful tools to noninvasively assess heart lung interaction and to look at the haemodynamic (patho)physiology at the bedside. Noninvasive cardiac output monitoring technologies might be incorporated in 'step-up' and 'step-down' approaches applying invasive, less invasive, and completely noninvasive technologies based on the individual patient's needs in different phases of disease states. These technologies might allow the application of haemodynamic optimization strategies in low- or intermediate-risk surgical patients, patients in the emergency department, or patients undergoing diagnostic or therapeutic procedures such as endoscopy or interventional radiology procedures. In addition, these technologies might facilitate noninvasive continuous monitoring of therapeutic interventions such as a passive leg raising test or a fluid challenge manoeuvre.

**Table 2** Heterogeneity of results and conclusions presented in validation studies of different noninvasive continuous cardiac output monitoring technologies. In this table, we present the results on accuracy and precision and the authors' conclusions of validation studies on different noninvasive continuous cardiac output monitoring technologies

Technology	Study/Reference	Studied device	Setting (patient population)	No. of patients	Criterion standard technology	Cardiac output (CO) or Cardiac index (CI)	Bias (standard deviation) (criterion standard - studied technology)	'Conclusion'
<i>Thoracic electrical bioimpedance</i>								
	Sageman and colleagues <sup>32</sup>	BioZ	intensive care unit (postoperative cardiac surgery patients)	20	pulmonary artery thermodilution	CI	-0.07 (0.20) litre min <sup>-1</sup> m <sup>-2</sup>	'Thoracic electrical bioimpedance <b>is equivalent</b> to pulmonary artery thermodilution-derived cardiac index [...]'
	Spieß and colleagues <sup>31</sup>	BioZ	operating theatre (cardiac surgery patients)	47	pulmonary artery thermodilution	CI	0.28 (0.67) litre min <sup>-1</sup> m <sup>-2</sup>	'Thoracic electrical bioimpedance reporting of cardiac index during coronary artery surgery <b>generally agreed</b> with pulmonary artery catheter thermodilution cardiac index [...]'
	Engoren and colleagues <sup>36</sup>	BioZ	intensive care unit (mixed population of critically ill patients)	46	pulmonary artery thermodilution	CO	1.0 (1.3) litre min <sup>-1</sup>	'Bioimpedance [and] thermodilution [...] determinations of cardiac outputs are <b>not interchangeable</b> in a heterogeneous population of critically ill patients.'
<i>Thoracic bioreactance</i>								
	Squara and colleagues <sup>49</sup>	NICOM	intensive care unit (postoperative cardiac surgery patients)	110	pulmonary artery thermodilution	CO	-0.06 (0.71) litre min <sup>-1</sup>	'Cardiac output measured by NICOM had <b>most often acceptable accuracy [and] precision</b> [...] in a wide range of circulatory situations.'
	Raval and colleagues <sup>50</sup>	NICOM	cardiac care units, intensive care units, cardiac catheterization laboratories (mixed population)	111	pulmonary artery thermodilution	CO	intensive care units: -0.09 (1.22) litre min <sup>-1</sup> catheterization laboratories: -0.17 (1.04) litre min <sup>-1</sup>	'On average, compared to thermodilution, bioreactance-based NICOM has <b>acceptable accuracy</b> in challenging clinical environments.'
	Kober and colleagues <sup>53</sup>	NICOM	operating theatre (surgical patients with ovarian cancer)	15	transpulmonary thermodilution	CI	-0.26 (0.85) litre min <sup>-1</sup> m <sup>-2</sup>	'Cardiac index assessment by bioreactance showed <b>acceptable accuracy</b> [...]. However, its <b>precision was poor</b> .'
<i>Vascular unloading technique</i>								
	Broch and colleagues <sup>63</sup>	Nexfin	operating theatre (cardiac surgery patients)	40	transpulmonary thermodilution	CI	pre-cardiopulmonary bypass 0.06 (0.27) litre min <sup>-1</sup> m <sup>-2</sup> post-cardiopulmonary bypass 0.09 (0.37) litre min <sup>-1</sup> m <sup>-2</sup>	'We conclude that the Nexfin is a <b>reliable method</b> of measuring cardiac output during and after cardiac surgery.'

Continued

Table 2 Continued

Technology	Study/Reference	Studied device	Setting (patient population)	No. of patients	Criterion standard technology	Cardiac output (CO) or Cardiac index (CI)	Bias (standard deviation) (criterion standard - studied technology)	'Conclusion'
Pulse wave transit time	Bubenek-Turconi and colleagues <sup>67</sup>	Nexfin	intensive care unit (postoperative cardiac surgery patients)	28	pulmonary artery thermodilution	CO	0.00 (1.0) litre min <sup>-1</sup>	'[...] the Nexfin has <b>limited accuracy</b> when compared with the pulmonary artery catheter [...].'
	Monnet and colleagues <sup>68</sup>	Nexfin	intensive care unit (mixed critically ill patients)	38	transpulmonary thermodilution	CI	0.20 (1.02) litre min <sup>-1</sup> m <sup>-2</sup>	'The estimation of cardiac index by the Nexfin device in critically ill patients is <b>not reliable</b> [...].'
	Yamada and colleagues <sup>71</sup>	esCCO (BSM-9101)	intensive care unit and operating theatre (mixed patient population)	213	pulmonary artery thermodilution	CO	-0.13 (1.15) litre min <sup>-1</sup>	'[...] datasets comparing esCCO and intermittent bolus thermodilution cardiac output showed [...] <b>small bias and precision</b> [...].'
	Ball and colleagues <sup>72</sup>	esCCO (BSM-9101K)	operating theatre (cardiac surgery patients)	28	pulmonary artery thermodilution	CO	0.80 (1.43) litre min <sup>-1</sup>	'esCCO is easy to use and provides continuous cardiac output measurements, but has <b>wide limits of agreement [...] with a consistently positive bias</b> in comparison to thermodilution.'
Radial artery applanation tonometry	Saugel and colleagues <sup>89</sup>	T-Line	intensive care unit (selected mixed critically ill patients)	22	pulse contour analysis calibrated by transpulmonary thermodilution	CO	0.10 (0.80) litre min <sup>-1</sup>	'In the selected patients included in this pilot analysis, a percentage error of 23% indicates <b>clinically acceptable agreement</b> between radial artery applanation tonometry cardiac output and pulse contour cardiac output.'

In validation studies comparing cardiac output measurements using noninvasive technologies in comparison with a clinically accepted criterion standard method, the ‘*conditio sine qua non*’ is the appropriate use of statistical methods for the assessment of a technology’s **accuracy, precision, and trending capability**. Uniform definitions for ‘clinically acceptable agreement’ and ‘interchangeability’ also considering the technology used as the criterion standard are eagerly longed for.

In addition, we should closely look at the limitations and problems of different technologies for noninvasive continuous cardiac output determination with regard to their use in clinical practice. On the one hand, several technologies have been shown to be capable of providing cardiac output measurements accurately and precisely under study conditions. On the other hand, for **most technologies there are conflicting data regarding the measurement performance**. Therefore, it is crucial to identify potential for improvement of the different technologies with regard to signal recording and processing (e.g. improvement of algorithms used for cardiac output computation based on the raw data signal). In addition, every technology has its own limitations regarding applicability in the clinical setting. Although the systems are theoretically easy to apply, for all available noninvasive cardiac output monitoring devices there are certain clinical settings in which measurement of cardiac output is made difficult or even impossible. These settings need to be clearly defined for each technology to be able to apply innovative devices prudently in both research and clinical practice. Further research and development is needed to improve the measurement performance and clinical applicability of technologies for noninvasive continuous cardiac output monitoring.

## Authors’ contributions

B.S.: conception of the review, literature search, writing of the manuscript. M.C.: conception of the review, writing of the manuscript. J.Y.W.: literature search, writing of the manuscript. D.A.R.: conception of the review, revision of the manuscript for important intellectual content.

## Declaration of interest

B.S. received unrestricted research grants from Tensys Medical, Inc. (San Diego, CA, USA) and refunds of travel expenses from CNSystems Medizintechnik AG (Graz, Austria). B.S. collaborates with Pulsion Medical Systems SE (Feldkirchen, Germany) as member of the Medical Advisory Board.

M.C. received advisory board fees, consultant fees, and research support from Edwards Lifesciences (Irvine, CA, USA), LiDCO (London, UK), and Masimo (Irvine, CA, USA).

JYW received refunds of travel expenses from CNSystems Medizintechnik AG (Graz, Austria).

D.A.R. provided consulting services and/or received speaker honoraria from Pulsion Medical Systems SE (Feldkirchen, Germany) as member of the Medical Advisory Board, Edwards Lifesciences (Irvine, CA, USA), and Masimo (Irvine, CA, USA).

DAR received an unrestricted research grant from Pulsion Medical Systems SE (Feldkirchen, Germany).

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