Review Article
Cardiac output monitoring: basic science and clinical application

S. Jhanji,1 J. Dawson2 and R. M. Pearse1

1 Barts and The London School of Medicine and Dentistry, London
2 Intensive Care Unit, Royal London Hospital, London, UK

Summary
Derangements in the circulation are a common feature of sepsis, trauma, major surgery and other critical illnesses. Detailed evaluation of the circulation is therefore an essential aspect of the clinical management of such patients. The use of cardiac output monitoring technology is an increasingly important aspect of evaluating patients in the operating theatre, critical care unit and elsewhere. There are now a number of different technologies available for this purpose, which use a diverse range of physiological principles. A detailed understanding of the physiological principles applied by such technology is essential for safe and effective use in clinical practice. The aim of this article is to describe the physiological principles used to measure cardiac output and their application in various monitors in common clinical use.

One of the earliest attempts to take physiological measurements of the circulation was made in 1733 by the Reverend Stephen Hales who measured arterial pressure by attaching a manometer to the carotid artery of a horse. However, the measurement of blood flow has proved to be much less straightforward than the measurement of blood pressure. As a consequence, an undue emphasis has been placed on the value of arterial pressure measurements, which often give a poor indication of tissue blood flow [1, 2]. It was not until the early 1970s that the introduction of the balloon-tipped pulmonary artery catheter finally allowed the routine measurement of cardiac output at the bedside [3, 4]. As use of the pulmonary artery catheter became more widespread, a number of commentators voiced concerns that this technique was associated with an increase in mortality [5–7]. Although this belief has now been refuted by three large multicentre trials [8–10], there has, in the meantime, been a shift towards the use of less invasive technology. A number of different cardiac output monitoring devices are now commercially available. The use of such technology to guide fluid and inotropic therapy may lead to improved outcomes [11, 12]. However, a detailed understanding of the physiological principles used by such technology is essential for safe and effective use in clinical practice. The aim of this article is to describe the physiological principles used to measure cardiac output and their application in various monitors in common use.

Methods
A search of PubMed, incorporating Medline, was performed to identify articles published between January 1966 and October 2006 using predefined search terms. The Medical Subject Heading (MeSH) search term ‘Cardiac Output’ was used with the following search terms: ‘dye dilution’, ‘Fick principle’, ‘thermodilution’, ‘pulmonary artery catheter’, ‘lithium dilution’, ‘pulse power analysis’, ‘pulse contour analysis’, ‘trans-pulmonary thermodilution’, ‘oesophageal Doppler’, ‘trans-oesophageal Doppler’, ‘Doppler echocardiography’, ‘carbon dioxide re-breathing’, ‘inert gas re-breathing’, ‘foreign gas re-breathing’, ‘electrical velocimetry’, ‘bioimpedance’, ‘electrical impedance’. References were screened by title and then by abstract before the full text was acquired. The bibliographies of original papers and

Correspondence to: R. M. Pearse
E-mail: rupert.pearse@bartsandthelondon.nhs.uk
Accepted: 25 August 2007
review articles were also searched. In addition, a search was performed using the Google online search tool to identify any outstanding articles and relevant manufacturers’ product information. Where necessary, companies were contacted for further information. The search was restricted to reports in English.

**Physiological concepts of cardiac output measurement**

**Fick principle**

In 1870, Adolf Fick suggested that blood flow through an individual organ might be calculated by measuring the arteriovenous concentration gradient of an indicator, a known mass of which having previously been added to the arterial circulation [13]. Fick originally suggested the calculation of pulmonary blood flow and therefore total cardiac output by taking measurements of oxygen consumption and carbon dioxide production along with the pulmonary arterial and venous concentrations of these gases (eqn 1 and Fig. 1). Fick’s principle was subsequently used to measure cardiac output in animals [14, 15], but it was not until 1929, when Werner Forssman devised a method of sampling mixed venous blood, that the application of the Fick principle became possible in man. Forssman passed a ureteric catheter through his own cephalic vein and into his right ventricle, before walking to the X-ray department to confirm its position, an experiment that led both to his dismissal and the award of the Nobel prize [16]. The following year, Otto Klein became the first person to draw mixed venous blood and calculate cardiac output using the Fick principle [17]. This technique was then perfected by Courmand and colleagues during the 1940s [18, 19]. Although now rarely used in clinical practice, the Fick technique is still regarded by many as the most accurate method of cardiac output measurement currently available (eqn 1).

\[
Q = \frac{\text{VO}_2}{\text{CaO}_2 - \text{CvO}_2}.
\]  

Blood flow (Q), or in this example cardiac output, is equal to oxygen uptake (\( \text{VO}_2 \)) divided by the arteriovenous oxygen difference. The arteriovenous oxygen difference is calculated by subtracting the mixed venous oxygen content (\( \text{CvO}_2 \)) from the arterial oxygen content (\( \text{CaO}_2 \)). This equation can be adapted to look at blood flow across individual organs.

**Indicator dilution technique**

The use of exogenous indicators to determine circulation time was first reported as early as 1761, when Haller described the measurement of pulmonary circulation time in an animal model using coloured dye [20]. During the 1890s, George Stewart further developed the concept of indicator dilution in a series of papers on circulation time [21–23]. By using a hypertonic saline indicator, Stewart was able to detect a signal in circulating blood by measuring changes in electrical conductance. William Hamilton then developed Stewart’s work to allow the measurement of cardiac output using an indicator dilution technique [24]. Hamilton used phenolphthalein as an indicator and, with the help of an automated system of blood sampling, was able to plot the systemic arterial concentration of dye against time. This now familiar curve was characterised by a brief delay following injection during which dye transits the pulmonary circulation followed by a rapid rise to a peak value before an exponential decline with a second much smaller peak due to indicator recirculation (Fig. 2). Cardiac output was shown to be inversely proportional to the area under the curve as described by the Stewart-Hamilton equation (eqn 2).

![Figure 1](image1.png)

**Figure 1** Blood flow (Q) across the tissue bed is equal to the arteriovenous oxygen difference (arterial oxygen content [\( \text{CaO}_2 \)] minus the venous oxygen content [\( \text{CvO}_2 \)]).

![Figure 2](image2.png)

**Figure 2** Indicator-dilution curve. Changing dye concentration with respect to time demonstrating initial peak followed by exponential decline and 2nd peak due to recirculation.
\[ M = Q \int C(t) \, dt \]  

Eqn 2 **Stewart-Hamilton equation.** If an indicator is injected rapidly into the right atrium, it will appear downstream in the pulmonary artery in a concentration that varies with time, \( C(t) \). As all the injected indicator \( (M) \) must leave the system, \( M \) is equal to the sum of the concentrations at each interval \( (t) \) multiplied by flow \( (Q) \), which is assumed to be constant.

Various dyes have been used for indicator dilution measurements, most commonly Indocyanine green. However, few indicators conform closely to the ideal indicator, which is stable, non-toxic, easily measured, uniformly distributed within the fluid compartment of interest, not lost from the circulation during the first transit and yet rapidly dissipated to avoid recirculation. The most common difficulties with indicator dilution techniques have been lack of indicator stability, inaccurate concentration measurement and indicator accumulation. The use of thermal indicators (thermodilution) may help to avoid some of these difficulties, an approach which was first described by Fegler in 1954 [25]. However, temperature equilibration may still result in significant indicator loss during transit.

In 1967, Branthwaite and Bradley [3] described the measurement of cardiac output using thermal indicator dilution using a thermistor-tipped pulmonary artery catheter. Indicator loss was minimised because of the short path between indicator injection in the right atrium and measurement in the pulmonary artery. Trans-pulmonary indicator dilution techniques in which indicator is injected into the superior vena cava and measured in a systemic artery are also well described [26, 27]. This approach is less invasive and may provide additional physiological data describing the pulmonary circulation [26, 27].

**Arterial waveform analysis**

Otto Frank first suggested calculating cardiac output by analysis of the arterial pressure waveform in 1899 [28]. Frank realised that total peripheral resistance may be calculated from the time constant of diastolic aortic pressure decay and arterial compliance, estimated by measuring aortic pulse wave velocity. Cardiac output may then be calculated from total peripheral resistance and mean arterial pressure (eqn 3).

\[ CO = \frac{MAP}{TPR} \]  

Eqn 3 **Relationship between cardiac output \((CO)\), mean arterial pressure \((MAP)\) and total peripheral resistance \((TPR)\).**

In 1904, Erlanger and Hooker suggested that the principal determinant of aortic pulse pressure was the volume of blood ejected during each cardiac cycle. Measurement of pulse pressure should therefore allow the calculation of stroke volume and hence cardiac output [29]. In 1970, Kochoukos et al. described a more accurate method of stroke volume estimation involving measurement of the area under the systolic portion of the arterial pressure waveform (Fig. 3) [30].

This work was developed by Wesseling and colleagues, who devised an algorithm for the calculation of stroke volume from arterial impedance and the change in arterial pressure during systole (eqn 4) [31, 32]. However, calculation of stroke volume and cardiac output through analysis of the arterial pressure waveform is far from straightforward. This complex waveform comprises both an incident pressure wave, which is proportional to stroke volume, and a reflected pressure wave created as the incident wave reflects back from the periphery. Changes in arterial compliance affect both the velocity and amplitude of the pressure waves and will in turn be affected by changes in arterial wall tension. As a consequence, the arterial waveform may vary considerably with physiological circumstances and anatomical location. Although the method of pulse contour analysis suggested by Wesseling may provide a reliable estimate of changes in cardiac output [33–35], accuracy may be influenced by changes in total peripheral resistance [36]. Perhaps the most important difficulty with arterial waveform analysis is that aortic impedance is dependent both on cardiac output and aortic compliance. Consequently, it is only possible reliably to estimate changes in stroke volume rather than absolute values. Such systems must therefore be calibrated before use.

\[ SV = \frac{\int \frac{dP}{dt}}{Z} \]  

Eqn 4 **Calculation of stroke volume using pulse contour analysis.** Stroke volume \((SV)\) is estimated from the integral of the change in pressure \((P)\) from end diastole to end systole \((\ell)\),
i.e. the systolic portion of the curve until aortic valve closure. This estimate of stroke volume is also dependent on the impedance of the aorta ($Z$).

An alternative method of arterial waveform analysis is to apply the physical principle of conservation of mass to calculate changes in pulse power. The net power change in the aorta is determined by the difference between the input and removal of mass. The change in power during a single cardiac cycle should therefore be determined by stroke volume (input of mass) and the distribution of blood from the aorta into the peripheral circulation (removal of mass). Ejection of blood into the aorta during systole causes fluctuations in blood pressure around a mean value. Using a mathematical technique termed autocorrelation, analysis of these fluctuations allows determination of changes in stroke volume with each cardiac cycle [37]. This algorithm is not morphology based and takes account of changes in the arterial waveform throughout the cardiac cycle rather than systole alone. This approach may be more accurate because the effects of the reflected arterial pressure wave are taken into consideration. Once again, calibration is required to correct for arterial wall compliance damping and interindividual variability.

**Aortic velocimetry**

Cardiac output may be calculated from measurements of aortic blood velocity and cross-sectional area. Such techniques include the measurement of Doppler frequency shift of ultrasound waves and electromagnetic methods. The simplicity of these methods of velocity measurement is a major advantage. However, in most situations, the diameter of the aorta cannot be measured directly, introducing a possible source of error. If velocity measurements are made on blood flowing through the descending aorta, a correction factor must also be applied to account for distribution of part of the total cardiac output to the upper body, introducing another potential source of error.

**Cardiac output measurement in clinical practice**

**Pulmonary artery catheter**

Although catheterisation of the right heart in man was first performed in 1929 [16], it was not until 1967 that the thermistor-tipped pulmonary artery catheter was used to measure cardiac output by thermal indicator dilution [3]. Swan and Ganz made a further adaptation in 1970 [4], adding a small inflatable balloon to the catheter tip. Flow-directed placement of the catheter without fluoroscopic imaging allowed the routine clinical use of the pulmonary artery catheter. Temporary occlusion of the pulmonary artery during balloon inflation also allowed measurement of pulmonary artery occlusion pressure, an index of left ventricular preload.

Traditionally, five successive measurements were made at end-expiration following manual injection of a cold saline bolus. An average was then taken of the three most closely related values. However, many centres now use an automated system; a filament incorporated into the body of the catheter intermittently warms aliquots of blood passing through the right ventricle, the output signal being an increase in temperature rather than a decrease. Measurements are repeated automatically every few seconds and averaged over 10 readings. This method is as accurate as manual measurement but more convenient [38, 39]. Measurements of cardiac output by pulmonary artery catheter thermodilution correlate well with alternative methods including dye dilution and the Fick technique [3, 40–43]. Important sources of error include indicator loss [3, 44, 45], and structural cardiac abnormalities [46]. Cardiac output measurement is affected by positive pressure ventilation, particularly in hypovolaemic patients [47, 48]. However, provided intermittent measurements are taken at the same point in the respiratory cycle, this physiological effect will not result in measurement error.

Perhaps the greatest limitation of the pulmonary artery catheter is the risk of damage to cardiac valves with prolonged use. Ideally, use should be limited to 48 h and a maximum of 72 h. Other complications include catheter knotting, pulmonary artery rupture and pulmonary embolism [49]. It is important to note, however, that several multicentre trials have shown that pulmonary artery catheter use is not associated with excess mortality [8–10]. Use of this device is now declining in favour of less invasive technology, although the technique will continue to have a niche role in management of pulmonary hypertension, in patients receiving intra-aortic balloon counterpulsation and in the estimation of pulmonary shunt.

**Trans-pulmonary lithium indicator dilution and arterial waveform analysis**

This monitor utilises the lithium indicator dilution technique to calibrate software which performs continuous arterial waveform analysis by a pulse power method to provide updated cardiac output data each cardiac cycle. Lithium indicator dilution is a novel concept that was first described in 1993 [26]. Lithium satisfies many of the criteria for the ideal indicator; whilst there is minimal indicator loss during the first circulation, and rapid redistribution allows repeated measurements [50, 51]. In the doses used for calibration, lithium chloride is considered safe, even in a 40-kg patient with non-functioning kidneys [52]. Following intravenous injection, lithium is detected by an external lithium ion sensitive electrode attached to a standard arterial catheter. Cardiac output is
calculated using a modified Stewart–Hamilton equation (eqn 5). A correction is applied for plasma sodium concentration which, in the absence of lithium, is the chief determinant of potential difference across the electrode. As lithium is only distributed in plasma, a correction for haematocrit is also required [53].

\[
CO = \frac{Li \times 60}{AUC \times (1 - PCV)}
\]  

Eqn 5 Modified Stewart-Hamilton equation for the measurement of cardiac output by lithium indicator dilution. CO, cardiac output; Li, lithium dose; AUC, area under lithium concentration/time curve; PCV, packed cell volume.

Lithium indicator dilution measurements are generally performed every 8 h but may be required more frequently where there is evidence of significant changes in arterial compliance or damping of the arterial waveform [54]. In an animal study, lithium indicator dilution compared well with measurements taken using an electromagnetic aortic flow probe [55]. Studies in humans suggest a good correlation between lithium indicator dilution and other methods [26, 56, 57]. Similarly, comparisons of pulse power analysis to intermittent determinations of cardiac output by thermodilution and lithium dilution suggest this method of continuous cardiac output measurement is reliable [54, 58, 59].

This combined technology has a number of advantages when compared to pulmonary artery catheter thermodilution. The method is less invasive, allowing use for longer periods of time in a wider range of patients. The technique may be employed in both conscious and unconscious patients without the need for insertion of specific arterial or venous catheters. There are also some limitations to this combined technology. The use of non-depolarising muscle relaxants may interfere with the lithium ion sensitive electrode, resulting in difficulties with calibration due to baseline drift. Irregular cardiac rhythms may occasionally result in an irregular data output from the pulse power analysis software and, as with all arterial waveform analysis techniques, damping of the arterial waveform will result in measurement error.

Trans-pulmonary thermodilution and arterial waveform analysis

This technology has a number of similarities to trans-pulmonary lithium indicator dilution and arterial waveform analysis. Both techniques involve the use of intermittent trans-pulmonary indicator dilution to calibrate continuous arterial waveform analysis software. In the case of trans-pulmonary thermodilution, a cold saline indicator is injected via a central venous catheter and measurement of the temperature of arterial blood is performed using a thermistor-tipped catheter sited in the femoral or brachial artery. Cardiac output is then calculated using a modified Stewart–Hamilton equation allowing calibration of continuous arterial waveform analysis software which provides continuous cardiac output data by a pulse contour analysis method.

This technology may be safely used in both conscious and unconscious patients for prolonged periods. The combined technology correlates well with measurements made by pulmonary artery catheter thermodilution [60, 61], and the direct Fick technique [62, 63]. The trans-pulmonary technique also provides an estimate of extravascular lung water volume, which may prove of clinical value. An important limitation is the requirement for a specific thermistor-tipped arterial catheter sited in either the femoral or brachial artery to allow thermodilution measurements. In most cases this necessitates the insertion of a new arterial catheter to facilitate cardiac output measurement by this technique. Changes in compliance of the arterial tree or damping of the arterial pressure transducer system may cause measurement error, necessitating repeated calibration.

Arterial waveform analysis without calibration

A recently developed cardiac output monitoring technology involves arterial waveform analysis utilising a proprietary algorithm applied to the digitalised arterial pressure wave to calculate cardiac output without calibration. At present, limited information is available about this technology, although published data suggest that further development is necessary before the device can be recommended for clinical use [64–66].

Non-invasive arterial pressure analysis

Non-invasive measurements of arterial pressure may be performed using the volume-clamp method with a small pressure cuff placed on the finger [67]. An aortic flow waveform is constructed by simulating a non-linear three-element model of the aortic input impedance as described by Wesseling et al. [68]. Integration of the computed aortic flow waveform allows the calculation of stroke volume and thus cardiac output. This method does not appear to correlate well with bolus thermodilution using the pulmonary artery catheter [69, 70]. However, the method does have a useful role in research and outpatient medical practice.

Oesophageal Doppler

The change in the observed frequency of a sound wave when the source of the signal is moving in relation to the observer is known as Doppler shift. The measurement of the Doppler shift of transmitted ultrasound waves has been used to calculate aortic blood velocity and estimate cardiac output. The oesophageal Doppler technique involves the measurement of blood velocity in the
descending thoracic aorta using an ultrasound probe placed in the lower oesophagus. The probe emits an ultrasound beam at a 45° angle to its long axis which is aimed towards the aorta by the operator. A continuous visual velocity vs time display helps to ensure correct probe placement (Fig. 4). Measurement of the Doppler frequency shift of the reflected ultrasound waves allows calculation of blood velocity. Cardiac output may then be calculated by one of two methods. The first involves measurement of the aortic cross-sectional area, measured using M mode ultrasound visualisation of the aorta and then multiplying this value by blood velocity to calculate flow. A correction factor is then applied to take account of distribution of part of the total cardiac output to the upper body and assumes that this ratio is constant. A simpler, and seemingly equally reliable, method is simply to derive a value of total cardiac output from a nomogram using aortic blood velocity, height, weight and age [71].

A systematic review of 11 studies in which the nomogram-based oesophageal Doppler technique was compared to pulmonary artery catheter thermodilution suggested minimal bias and good limits of agreement between the two techniques [72]. The principal advantage of this technique is speed and ease of use and the method has proved ideal for intra-operative use. The major limitation of this technique is that the probe is not well tolerated by conscious patients and use is generally confined to anaesthetised or sedated patients. The most important contra-indication to use is severe oesophageal pathology, in particular varices or recent surgery.

Trans-oesophageal echocardiography

The use of trans-oesophageal echocardiography allows real time imaging of the left ventricular outflow tract. Stroke volume may be calculated by measurement of the blood velocity profile using the Doppler technique and then measuring aortic valve area. Studies suggest measurements taken using this technique are similar to those taken using pulmonary artery catheter thermodilution [77–80]. This approach allows a detailed evaluation of cardiac function as well as the measurement of cardiac output. However, accuracy is highly dependent on both the quality of echocardiographic views and operator skill.

Supra-sternal Doppler

Using a non-invasive ultrasound probe positioned in the jugular notch (Fig. 5), it is possible to measure blood velocity in the ascending aorta. This is essentially a non-invasive alternative to the oesophageal Doppler technique. Stroke volume and cardiac output are calculated using a measurement of cross-sectional area of the aortic outflow tract. Because these measurements are taken from the aortic root, the technique is not affected by changes in distribution of cardiac output between the upper and lower body. Cardiac output measurements taken using the supra-sternal Doppler method were similar to those taken with an electromagnetic aortic flow probe in an animal study [73], and with pulmonary artery catheter thermodilution in clinical studies [74–76]. The portable and non-invasive nature of this technology is a major advantage, allowing use in any clinical setting. However, it may be very difficult to identify the aortic root in some subjects. Although the supra-sternal probe should allow ultrasound waves to be orientated at 0° to the direction of blood flow, in practice this alignment is affected by operator skill as well as the anatomy and position of the subject. Consequently, this technique may have greater interobserver variability than other methods. Where identification of the aortic root proves difficult, the pulmonary valve may be used instead. Because measurements are taken in the supine position, they may be poorly tolerated by breathless patients.
This technique is contra-indicated in patients with significant oesophageal pathology. The probe is much larger than the oesophageal Doppler probe and is only appropriate for intermittent assessments.

**Pulmonary gas clearance**
The carbon dioxide re-breathing technique allows estimation of cardiac output through the measurement of changes in expired carbon dioxide concentration, estimation of end-capillary carbon dioxide content and therefore pulmonary blood flow. This measurement does not include pulmonary shunt but, by deriving this value using Nunn’s iso-shunt plots, total arterial carbon dioxide content and hence total cardiac output can be calculated. Whilst the technique is easy to use, it can only be performed in intubated patients. The technique is contra-indicated in patients who are susceptible to harm as a result of hypercapnia, for example in the case of traumatic brain injury. Comparisons of the partial carbon dioxide re-breathing technique with other forms of cardiac output monitoring suggest good agreement in some situations [81, 82], although accuracy may be affected by increased carbon dioxide production [83], spontaneous ventilation [84], and high cardiac output states [85, 86].

Another pulmonary gas clearance technique which has been used successfully in the clinical setting is the combined sulphur hexafluoride and nitrous oxide method, which involves the use of an insoluble gas (nitrous oxide) to determine lung volume together with measurement of pulmonary clearance of minute quantities of a soluble gas (sulphur hexafluoride) to allow calculation of pulmonary blood flow. In common with the carbon dioxide re-breathing technique, the relationship between pulmonary blood flow and cardiac output will depend on the pulmonary shunt fraction. Pulmonary acetylene clearance may also be used to measure pulmonary blood flow, but the technique involves the use of mass spectrometry, limiting use mainly to the research setting.

**Electrical impedance**
Bioimpedance is a non-invasive technique which involves the application of a small alternating current across the chest via topical electrodes. This current is thought to distribute primarily to blood because of its high electrical conductivity compared with muscle, fat and air. Pulsatile changes in thoracic blood volume result in changes in electrical impedance. The rate of change of impedance during systole is measured allowing a value of cardiac output to be derived. A number of studies have compared bioimpedance to alternative methods of cardiac output measurement, although the findings have proved inconsistent [87, 88]. The mathematical method of cardiac output derivation from thoracic impedance has been revised on several occasions [89], presumably reflecting concern over the accuracy of this technique. Despite these changes, it seems likely that bioimpedance systems will only provide accurate data describing changes in cardiac output.

**Electrical velocimetry**
Electrical velocimetry also utilises body surface electrodes in a similar approach to the bioimpedance technique. At present, this technology is available only as an integrated feature of a bedside cardiovascular monitor. Electrical velocimetry is based on the theory that the change in the alignment of red blood cells from an arbitrary orientation during diastole to a parallel alignment during systole causes an increase in the electrical conductivity of blood. Stroke volume and cardiac output are calculated from the rate of change of conductance. The algorithm used is thought to be unaffected by changes in low conductivity compartments such as lung and in theory should be more accurate than bioimpedance. The technique has compared well to trans-oesophageal echocardiography [90], and bolus thermodilution with the pulmonary artery catheter [91].

**Conclusions**
Derangements in the circulation are a common feature of sepsis, trauma, major surgery and other critical illnesses. The use of cardiac output monitoring is an increasingly important aspect of the evaluation and treatment of such patients. A range of devices are available for this purpose. There is no single ‘gold standard’ of cardiac output monitoring. The choice of technology will depend on the clinical application as well as local expertise. However, a detailed understanding of the physiological principles applied by any given technology remains essential for safe and effective use.

**Acknowledgements**
Dr Pearse has received unrestricted educational grants from LiDCO and USCOM Ltd for research purposes.

**References**
21 Stewart GN. Researches on the circulation time in organs and on the influences which affect it. *Journal of Physiology* 1893; 15: 1–89.
22 Stewart GN. Researches on the circulation time and on the influences which affect it. IV. The output of the heart. *Journal of Physiology* 1897; 22: 159–83.
23 Stewart GN. The measurement of the output of the heart. *Science* 1897; 5: 137.
24 Hamilton W, Moore J, Kinsman J, Spurling R. Simultaneous determination of the greater and lesser circulation time, of the mean velocity of blood flow through the heart and lungs, of the cardiac output and an approximation of the amount of blood actively circulating in the heart and lungs. *American Journal of Physiology* 1928; 85: 377–8.


66 Mayer J, Boldt J, Scholthorn T, Rohn KD, Mengitsu AM, Suttner S. Semi-invasive monitoring of cardiac output by a new device using arterial pressure waveform analysis: a


79 Perrino AC Jr, Harris SN, Luther MA. Intraoperative determination of cardiac output using multiplane transeosophageal echocardiography: a comparison to thermodilution. *Anesthesiology* 1998; **89**: 350–7.


84 Tachibana K, Imanaka H, Takeuchi M, Takauchi Y, Miyano H, Nishimura M. Noninvasive cardiac output measurement using partial carbon dioxide rebreathing is less accurate at settings of reduced minute ventilation and when spontaneous breathing is present. *Anesthesiology* 2003; **98**: 830–7.


