‘By the Heart’s Vigorous Beat’

A History of Cardiac Output Monitoring from its Origins to the Present

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Introduction

Cardiac output measurement in its many guises is now ubiquitous in intensive care units. Over recent years, it has also found an increasing role in the anaesthetic management of high risk general surgical and orthopaedic patients. Techniques employed in these measurement systems are based on physiological principles developed over the last 150 years and refined with the advent of technology. Monitoring that was a research tool as recently as ten years ago is now entering widespread clinical use.

A monitor was once one who admonished others but has come to mean a reminder or warning device. The advent of electronic patient monitoring has made anaesthesia safer and has aided clinical precision in measuring physiological variables. However, these variables can only be interpreted in the context of understanding how these measurements are obtained. In turn, knowledge of the way in which these measurements were first determined gives greater insights still.

The first written evidence of human understanding of the heart as a moving organ is some 3500 years old. The Ebers papyrus, which was written around 1550 BC but is based on older documents, talks of finding the pulse impalpable in cases when ‘the heart does not speak.’

More than three millennia later, in 1628, William Harvey debunked Galen’s classical viewpoint by establishing the circulatory pattern of blood in the cardiovascular system.

‘For it is by the heart's vigorous beat that the blood is moved.’

By multiplying stroke volume and heart rate, Harvey’s mechanical approach to his proof represented the first attempt at assessing cardiac output in a scientific fashion. But it was here that the story lay, largely untouched, until it was re-awakened in 1870, at the start of the golden age of German science.
This essay will examine the history of the development of cardiac output measurement and its underpinning principles from the nineteenth century to the present.

**The Fick Principle**

With two brothers as professors, Adolf Fick was destined for and fulfilled an academic career. He is best remembered today for both his law on diffusion and his eponymous principle underpinning the measurement of cardiac output. This genius of physiology was born the youngest of nine children in Kassel, Germany in 1829. He attended the University of Marburg in 1847 where he began his studies in mathematics and physics. This clearly did not suit him as within a year his brother Heinrich had persuaded him to change course and read medicine, from which he duly qualified MD in 1851. Fick’s mathematical background contributed to his dissertation on visual errors due to astigmatism and would also prove useful in his future career in physiology. He worked initially in Zurich as an anatomy demonstrator where he was fortunate enough to begin an academic and social relationship with Ludwig which lasted for the remainder of their lives. Ludwig was one of the leading anatomists and physiologists of the time who, amongst other things, invented the Stromuhr: the first device that could reliably measure blood flow in a vessel.

In 1849 Fick moved to Berlin where he studied with Langenbeck, Romberg and Schönlein; names that still resonate through hospitals today. After another spell working in Zurich, Fick moved to the University of Würzburg in 1868 where he became professor of physiology. He remained there for the next thirty years. Throughout this time much of his work was in the design of instruments to measure physiological variables, including blood pressure. He also postulated a number of physiological concepts.

Harvey’s treatise had been published several centuries previously; but despite this, there had been little further work since then on the measurement of cardiac output. In fact Fick offered
no experimental data when he first postulated his theory (his excuse was that he did not possess the two required gas pumps) but had been interested in, and studying, cardiac output for years prior to this. He understood the relationship between gas exchange and blood flow in the lungs and this mathematical approach to physiology and application of logic independently proved its validity.5

It is worth quoting Fick in full as it gives such a clear explanation of the principle and also his undoubted clarity of thought. How else could he describe this principle that had eluded others as being so self-evident?

‘It is astonishing that no one has arrived at the following obvious method by which (the amount of blood ejected by the ventricle of the heart with each systole) may be determined directly, at least in animals. One measures how much oxygen an animal absorbs from the air any given time, and how much carbon dioxide it gives off. During the experiment one obtains a sample of arterial and venous blood; in both the oxygen and carbon dioxide content are measured. The difference in oxygen content tells how much oxygen each cubic centimetre of blood takes up in its passage through the lungs. As one knows the total quantity of oxygen absorbed in a given time one can calculate how many cubic centimetres of blood passed through the lungs in this time. Or if one divides by the number of heartbeats during this time one can calculate how many cubic centimetres of blood ejected with each beat of the heart.’

Fick’s principle is in some respects a way of applying the law of conservation of mass, since the oxygen taken up by the lungs must equal the oxygen used by the tissues.8 It can be restated in a simpler way as: cardiac output equals oxygen consumption divided by arterio-venous oxygen difference (Eqn. 1).
It is this succinct description that has been described as a turning point in the quantitative measurement of blood flow. The oxygen analysis method shown above is properly described as the direct Fick method. The variables that need to be measured in order to calculate cardiac output accurately via this method are oxygen uptake and arterial and mixed venous oxygen content. In the nineteenth century this presented insurmountable technical obstacles, particularly in obtaining mixed venous blood.

Fick retired at the age of seventy, as he believed younger men should teach, having devoted little more time to his idea over the course of his life. He died a year later of apoplexy but even in death the importance of the Fick principle was not recognised by his successor von Frey. In his eulogy, Fick’s pioneering idea was buried amongst his other papers and achievements. However, while his life’s major work in other areas of physiology has largely disappeared into obscurity; his brief comment on cardiac output measurement has resulted in immortality.

It is not true to say that Fick saw no attempt to provide experimental proof for his principle before his death. In 1898, some three years before he died, the first experiments were described in which the cardiac output of horses was measured. In a classic study, Zuntz and Hageman introduced a catheter into the right atria of horses in various states of rest and exertion. Equine right heart catheterisation was not a new technique, having been pioneered in 1711 by the Revd. Hales. The hypocoagulability of horses made them particularly suitable for experimentation. This also made central venous blood sampling possible and it has been argued that the contribution of these pioneering experimenters should be acknowledged instead of Fick.
The oxygen content of central venous blood from the right atrium and mixed venous blood from either the right ventricle or pulmonary artery differs, as superior and inferior vena caval blood have different compositions. At the time this was not known, so these early estimates were not wholly accurate. However, this was the only foray into the measurement of cardiac output until interest was re-kindled in the 1920s.

At around this time another German group were experimenting with the possibility of intra-cardiac injections in dogs by means of passing a central venous catheter. Bleichroder, who was one of these experimenters, decided to become a subject himself and had catheters passed via both his basilic and femoral veins. He experienced severe chest pain during one of these procedures suggesting intra-cardiac placement of the catheter but no X-ray or pressure evidence was offered to support this.¹³

For thirty years after his death, the direct Fick method remained a theoretical concept as there was no means to measure the components. However, an indirect Fick method was used in which the absorption of a foreign gas from the lungs was measured. The indirect method relied on two assumptions, first that expired air equilibrated with alveolar gas and secondly that the uptake of that gas depended on pulmonary blood flow. If the solubility of a particular gas in blood was known and its rate of absorption measured, pulmonary blood flow and hence cardiac output could be calculated. Early experiments with this approach used, amongst others, nitrogen, nitrous oxide and acetylene. They produced wildly variable results for cardiac output of between 4 and 8 l min⁻¹. The source of this error appears to have been in incorrectly overestimating the human circulation time to more than double the correct figure of 10 to 18 seconds.¹⁰ This would have resulted in a significant recirculation of gas containing blood before the first samples were taken.
Alongside these setbacks and erroneous assumptions the pieces required to use the direct Fick method in man were slowly appearing. In 1924, van Slyke and Neill had described a method for determining oxygen content accurately in arterial blood.\textsuperscript{14} Five years later, unaware of Bleichroder’s early foray into human cardiac catheterisation, another German, Forssman cannulated his right atrium.\textsuperscript{15} He used a ureteric catheter inserted via his left median cubital vein and proved his bravery with X-ray evidence. It is said that he incurred the wrath of his head of department for this and as a result he lost his clinical privileges.\textsuperscript{16}

However, due to the nature of the catheter used, sampling central venous blood from the right atrium was still not possible via Forssman’s approach. In 1930, Baumann and Grollmann made the first attempts at obtaining mixed venous blood from the human heart by employing the direct approach of a spinal needle introduced into the right ventricle. In employing Fick’s method they found that cardiac output increased by more than 1 l min\textsuperscript{-1} if arterial puncture preceded ventricular puncture. As a consequence they advised the ethically suspect approach of keeping the true nature of the experiment a secret from their subjects.

‘If one carries out the entire procedure involved in removing blood from the right heart during the period of a single circulation of the blood and the subject is unaware of the nature of the contemplated procedure the effect of psychic disturbance is avoided . . . Hence, the arterial puncture necessary in applying the direct Fick’s principle always followed the heart puncture.’\textsuperscript{8}

Later the same year Klein managed to aspirate central venous blood from a right heart catheter and went on to calculate the cardiac output of thirty patients. This combination of mixed venous blood sampling and accurate oxygen content analysis finally enabled verification of Fick’s principle in 1930, some sixty years after his statement. It is testament
to the man that Fick’s method remains the standard by which new technologies are measured against.

The next decades saw Andre Cournand, in particular, develop right heart catheterisation as a tool to measure haemodynamics and in the diagnosis of disease. He reported the safe right heart catheterisation of over 1200 patients in which cardiac output was measured using a direct Fick method. It was first reported in 1946 that true mixing of blood did not occur in the right atrium, but Cournand believed that his samples were mixed venous. Despite this, his results gave the now familiar figures of an oxygen consumption of 240 ml min\(^{-1}\) in a resting subject with a mean cardiac output of 5.3 l min\(^{-1}\). These achievements earned Forssman, Cournand and Dickinson Richards the Nobel Prize for medicine in 1956.

Although used in the cardiac catheterisation laboratory, the direct Fick method did not gain acceptance as a useful technique during anaesthesia in the decades that followed. Not only were the errors inherent in not sampling at steady state potentially greater; but also anaesthetic gases were found to complicate measurements. Much more practicable in the operating theatre were found to be methods involving indicator dilution.

**Indicator Dilution Techniques**

There are two theoretically possible ways of using an indicator to measure the output of the heart. The first of these is to inject a known amount of indicator at a constant rate into the venous circulation and measure its concentration downstream on the arterial side. If the indicator has mixed completely with the blood it is being carried in, then the dilution factor gives the ratio of the two flows in steady state. The second method involves the injection of a bolus of indicator which is then measured downstream with a concentration-time profile. If a known amount of indicator is injected as rapidly as possible and its concentration measured downstream then there will be a short time lag followed by a rise and then an exponential
decrease. In the graph below, a 12 mg bolus results in an average concentration of 4 mg l\(^{-1}\) for 30 s. This means that the 12 mg bolus has been diluted by 3 l of blood over 30 s which is equivalent to a cardiac output of 6 l min\(^{-1}\).

![Graph](image)

The pioneer of the first method to measure cardiac output was Stewart, whose contribution is remembered as one half of the famous Stewart-Hamilton equation. In fact, the use of injected indicators to investigate the cardiovascular system had been around for more than a century before Stewart published his seminal work in 1897. In 1761, Haller injected dye into the vena cava of a dead animal to measure transit times through inflated and collapsed lungs. Later, in the early part of the nineteenth century, Hering injected potassium ferrocyanide into one jugular vein of a horse then collected samples from the contralateral vein to assay blood for ferric ferrocyanide (Prussian blue) and hence calculate circulatory time.\(^{21}\)
Stewart was interested in cardiac output and the circulatory time, and for this he used the rather neat method of injecting hypertonic saline. Using arterially placed electrodes as one arm of a Wheatstone bridge, he was able to measure the electrical conductivity of blood which in turn reflected the concentration of saline. He was aware of, and used, dyes such as methylene blue; but found that measuring their concentration in blood was too difficult to be regularly practicable.22

Credit for the bolus injection technique is harder to attribute. For fifty years after Stewart’s initial publication, it was a select few who had the patience to use indicator dilution techniques. For the assays to be described as ‘tedious’ by a leading worker in the field, suggests that they were not experiments for the easily bored.21 In 1913, Henriques used a ‘sudden single injection’ technique of thiocyanate in his experiments.23 Seven years later Bock and Bucholtz used a constant injection of iodide technique. Both groups found their particular markers easier to measure.24 Whether Stewart appreciated the difference between the two methods described above has been the subject of some debate.

In a scathing criticism of Stewart’s understanding of the theory of indicator dilution, a review in 1956 asserted that the original description of the indicator dilution method demonstrated some ‘crippling misconceptions’. It claimed that Stewart believed that the constant rate injection would result in a square wave of indicator with no distortion in the downstream vasculature.24 But can it really be possible that the pioneer of these techniques could believe in something that is so self-evidently false? Another commentary from the same time believes not.21

Whilst Stewart did not distinguish between either a rapid or slow injection in his original paper, it is clear from his reported experiments that he did vary his injection speed from anything between 4 and 12 seconds (see fig 2). He described taking samples as the
concentration ‘tapered’ at the beginning and end of each sampling run. These all suggest that he was aware of the different concentration-time profiles with each technique.  

Whether it was Stewart or others who can claim credit for the bolus injection technique, it was a group from Louisville, Kentucky led by Hamilton who simplified the process to eventually allow for its use in clinical practice. Hamilton’s work from 1928 to 1932 addressed the problem of recirculation of indicator. It had been noted previously that the exponential decrease in indicator concentration is complicated by recirculation. Hamilton’s step forward was to extract this re-circulating indicator by semi-logarithmic re-plotting and extrapolation of the downslope of the degradation curve (Fig. 1). Simplifying this process, he is rightly rewarded with the other half of the Stewart-Hamilton equation (Eqn. 2). This equation shows that flow is inversely proportional to area under the concentration-time curve and can be calculated from that area if the amount of indicator injected is known.

\[ \dot{Q} = \frac{n}{\int_{T_1}^{T_2} c \, dt} \]

Eqn 2. The Stewart-Hamilton equation. \( n \) = amount of indicator, \( c \) = concentration.
It is at this point that the two halves of the story come together: the direct Fick method via right heart catheterisation and the indicator dilution technique. A joint publication from the Hamilton and Cournand groups in 1948 showed the results of their simultaneous Fick and indicator dilution methods in man. The close correlation of the indicator technique with the Fick standard meant it gained acceptance and the stage was set for the next step in clinical cardiac output measurement.

The problem that investigators had wrestled with since Stewart’s original experiments was in the choice of indicator. It had to be non-toxic, not diffusible out of the circulation and readily measurable. Numerous organic dyes were used, but unfortunately for these early investigators, no such indicator existed and the laborious nature of serial blood concentration assays made the indicator method unpopular. The most successful dye was indocyanine green which can be measured in blood by spectrophotometry. This however was not a clinically useful tool as, in the early days at least, the densitometer had to be calibrated with samples of the patient’s blood with known concentrations of the dye. In addition, the dye is expensive and repeated use has the unfortunate adverse effect of turning the patient green.

At the 19th International Congress of Physiology in 1954 Fegler made the first reports of thermodilution as a tool to measure cardiac output. There had been previous reports of using cooled Ringer’s lactate solution to measure time-temperature profiles in the pulmonary artery but Fegler was the first to place thermocouples in the right ventricle and aorta. He measured the time-temperature profile in both these places following the injection of a known volume of cold saline. By measuring the difference in temperature and heat capacity between the saline and blood, he was able to calculate the flow of blood which diluted the injection.

At last a potentially clinically useful tool had been described, but it was not greeted with widespread acceptance. At the conference, it was said that there was a reception of ‘polite
incredulity’ despite the good correlation between Fegler’s method and the direct Fick method. One eminent author found it hard to conceive of the dilution of a negative phenomenon like cold at all.  

The potential of thermodilution was not recognised immediately and as late as 1962 the organic dyes were declared the ‘most convenient and most satisfactory’ indicators available. However, efforts continued and thermodilution was refined over the next fourteen years. It was finally demonstrated in man by Branthwaite and Bradley working at St Thomas’s Hospital in 1968. This technique was subsequently refined by a group including Ganz and Swan and it is here, in the development of the pulmonary artery catheter (PAC) made famous by these two men, that the story of cardiac output measurement continues. Assisted by the introduction of Seldinger’s technique for cannulating vessels, the laboratory and tentative clinical work of the previous seventy years was about to enter widespread clinical practice.

**Pulmonary Artery Catheters**

The story goes that on a sunny afternoon in 1967 Swan was sitting on the beach in Santa Monica, California watching the yachts race past. He noticed that those boats with a spinnaker raised were moving faster than those without and struck upon the idea that a balloon tipped right heart catheter could ‘sail’ through the right side of the heart, across the pulmonary valve and into the pulmonary vasculature. Swan and his colleague Ganz have since been immortalised with their eponymous PAC, but the story of a flow directed right heart catheter to measure cardiac output has more than just these two players. The first part, the story of right heart catheterisation pioneered by Forssman and continued by Cournand, has been described above. It is the second part that now follows.
The use of right heart catheterisation to determine cardiac output through the application of the direct Fick method had been going on for years. These techniques had revealed a wealth of information on haemodynamic variables in health and disease. However, use was restricted by the difficulty presented not just by insertion and ongoing care of an indwelling catheter but also the difficulty using the catheter. It took over a minute to aspirate a 1 ml sample through the 0.5 mm bore of the early catheters. To be truly clinically useful, a device needed to be easy to insert at the bedside in critically ill patients, without the problems of fluoroscopic guidance and also straightforward to obtain mixed venous blood samples.

In 1964 Bradley had reported his experiences of right heart catheterisation in the critically ill. The previous decade had seen the description of the self-guiding PAC by Lategola and Rahn in 1953. They reported two years experience of a balloon tipped catheter that floated into the pulmonary vasculature ‘acting like a sail’ and wedged in a distal artery. It seems too much of a coincidence that Swan chose this analogy when describing the inspiration for his device.

Ten years later, Swan originally proposed that the device be used to measure right sided pressures and the pulmonary capillary wedge pressure. Although aspiration of mixed venous blood and hence estimation of cardiac output using the direct Fick method would have been possible with this, it was Ganz who suggested adding a thermistor proximal to the tip in order to make cardiac output measurements using thermodilution possible. Cold injectate could be added to the right atrium via a proximal lumen and a temperature-time curve plotted from downstream measurements. Application of the Stewart-Hamilton equation would yield the cardiac output.

The Swan-Ganz PAC (Edwards Lifescience, Irvine, California, US) was introduced in 1970 and rapidly gained widespread usage: first in patients who had suffered myocardial
infarction, secondly to the operating theatre and finally all critically ill adults. The quality of the catheter and balloon, relatively straightforward insertion and the ease of withdrawing mixed venous blood made Swan-Ganz catheters extremely popular. Some 2 million Swan-Ganz catheters per annum were sold worldwide in the mid to late 1980s. So popular were the PACs that, on intensive care ward rounds at least, ‘to Swan’ became a verb adopted into the English language.

Insertion of the Swan-Ganz catheter is an invasive procedure that is fraught with risk. Not only are there the attendant risks of central venous cannulation but the additional problems of valvular damage, arrhythmias and pulmonary artery trauma. The Swan-Ganz catheter was introduced and accepted on the perfectly reasonable premise (especially to an intensivist) that detection and correction of abnormal physiological variables would benefit the patient. No such evidence existed and in the mid 1980s concerns were first raised as to whether these unquantified benefits of knowing, amongst other things, the cardiac output outweighed the significant risks. Could it be that this quest for bedside cardiac output monitoring that had begun more than 100 years previously was not of benefit of patients?

Over the subsequent twenty years a wealth of evidence began to emerge that indeed the benefits were overstated. Interpretation of the data produced by the PAC was not consistent and furthermore, rather than improving outcomes, PACs were increasing the risk:benefit ratio in a wide range of patient groups. The decline and fall of the Swan-Ganz PAC has been ongoing since the mid 1990s and, even in cardiac operating theatres, its forty year story is drawing to a close. However, the quest for bedside haemodynamic data continues and it seems likely that one of the factors that contributed to the demise of the PAC is the arrival of novel, less invasive ways of measuring cardiac output.
Pulse Contour Analysis

Not long after Stewart’s seminal work, Erlanger and Hooker in 1904 suggested using pulse pressure analysis to measure cardiac output in humans. They made the prescient statement that:

‘upon the amount of blood that is thrown out by the heart during systole then, does the magnitude of the pulse-pressure in the aorta depend.’

Although this is true, it was recognised early that there are other factors, such as arterial distensibility, that are critical. As such, there may be statistical correlation between pulse pressure and stroke volume but it was not found to be close enough to predict one from the other.

The origins of pulse contour analysis lie with Windkessel theory which was first proposed by another great physiologist: Frank in 1930. This suggests that the central vasculature, including aorta and proximal large arteries, can be viewed as filling during systole and draining during systole and diastole. Initial investigation was directed towards trying to correlate pulse wave velocity changes with distensibility but this was found too difficult. So by simply relating stroke volume and pulse pressure it was found that 1 ml stroke index was approximately equivalent to 1 mmHg in pulse pressure.

The attraction of finding a technique that could estimate cardiac output from pulse contour was in finding a method that would work continuously. A newer warm thermodilution variation on the Swan-Ganz PAC uses a heating element to release thermal pulses every 30-60 s to provide virtually continuous cardiac output measurements. However, both the Fick and indicator dilution techniques, described above, work on an intermittent basis. Despite the efforts of a number of investigators, it was found that significant individual intervariation in elasticity of the proximal arterial tree meant that no reasonable technique using pulse contour
Peripheral resistance alone was found not to account for the shape of the arterial pressure wave.

In 1953 Hamilton suggested using a proven output method, such as an indicator dilution curve, as a means of calibrating the distensibility of a patient’s arteries but this did not gain widespread usage. A number of formulae were proposed, but a comparison published in 1972 found that although the correlation between pulse contour, Fick and indicator dilution was high; variability was also substantial. This led to a conclusion that pulse contour analysis could only be recommended as a ‘very approximate’ alternative to established methods.

In the early 1990s a number of attempts were made at refining the model using a three element system of impedance, resistance and capacitance to represent the arterial vasculature. The impedance and capacitance of the patient’s arterial system were estimated from patient sex, age and the pulse pressure waveform. Two of the commercially available systems that are commonly used today employ an algorithm based on this and a dilution technique, with the Stewart-Hamilton equation to further refine these values. In the case of PiCCO (Pulsion Medical Systems, Munich, Germany), a transpulmonary thermodilution technique is used to calibrate the area under the arterial waveform. LiDCO (LiDCO ltd, Cambridge, UK) uses a lithium dilution curve and then the pulse power is analysed using the PulseCO algorithm.

Another currently commercially available system is the FloTrac sensor (Edwards Lifescience, Irvine, California, US). With distant echoes of Ludwig’s Stromuhr, this utilises a blood flow sensor attached to an arterial cannula which then measures arterial pulsatility.

Both PiCCO and LiDCO require the insertion of a central venous and peripheral arterial catheter, but have the advantage of continuous cardiac output measurement without the need for a PA catheter. The quest for progressively less invasive methods has not stopped and it is with these techniques that the story continues.
Oesophageal Doppler & Bioimpedance Monitoring

The Doppler effect was enunciated nearly thirty years before Fick made his famous statement. In 1842 Doppler stated that the frequency emitted or reflected by a moving object was proportional to the velocity of the object. The effect was originally proposed to relate to light but was soon found also to apply to sound. The principle was revised by Hubble in 1929 and the resultant Doppler equation is stated below (Eqn. 3). It indicates that if the Doppler shift in frequency can be measured then flow velocity can be derived.

\[ V = \frac{c \cdot f_d}{2 \cdot f_T \cdot \cos \theta} \]

The basis for using this to measure flow is that flow in a vessel is equal to the product of the cross-sectional area of a vessel and the velocity of blood in that vessel. Measuring cardiac output using the Doppler effect first began in humans in the late 1960s. Initially transthoracic Doppler ultrasound probes were described which measured blood flow in the ascending aorta.\(^{49}\) In 1971, not long after the introduction of the Swan-Ganz catheter, the first description of a trans-oesophageal probe was made.\(^{50}\) In the case of pulsatile flow, as in the aorta, the velocity changes over time so can be calculated from the area under the velocity-time curve. By using this and making an assumption of the aortic area, stroke volume can be estimated.\(^{51}\) Singer refined this technique in the late 1980s and its use has since been validated in a range of clinical situations.\(^{52}\)

Bioimpedance monitoring describes a method by which a change of tissue volume in the body is measured based on its impedance to an electrical current. As such, it is more properly known as bioimpedance plethysmography. Plethysmography as a technique to measure cardiac output has been used since the 1930s but was only possible in experimental animals as it required enclosing the heart in a plethysmograph in order to measure change in
volume during systole.\textsuperscript{20} The bioimpedance method involves passing a current through the thorax via electrodes attached to the chest wall and measuring the resultant impedance. This is proportional to thoracic tissue volume which includes tissue fluid, pulmonary and aortic blood. Changes in cardiac output result in changes in aortic blood volume, which in turn mean changes in bioimpedance.\textsuperscript{53}

The first description of this method was in detecting blood flow in the arm in 1943.\textsuperscript{54} Measurement of blood volume and hence flow in the limbs at rest and exercise continued and the technique was refined over the next twenty years. Its use to measure thoracic fluid volume was described in 1966 by Kubicek. At this stage the differentiation between blood and tissue fluid could not be made so he foresaw its use being as a way of measuring absolute volumes and hence providing a means of diagnosing pulmonary oedema rather than dynamic changes like cardiac output measurement.\textsuperscript{55} The principle was refined by Kubicek and later Bernstein and there are now several commercially available systems of this least invasive method of measuring cardiac output on the market. Their accuracy has been demonstrated in steady state but is less reliable in acute hemodynamic instability.\textsuperscript{53}

**Conclusions**

The story of clinical cardiac output measurement is one of laboratory physiology translated into the operating theatre and intensive care unit. It began with a flash of genius from Fick and continued with the search for the means to make his direct method possible. The development of right heart catheterisation, the refinement of the indicator dilution technique and the introduction of thermodilution set the stage for the PAC. This device brought the widespread use of cardiac output measurement to the bedside. Novel methods, not involving PA catheterisation, have now largely superseded this. The future of cardiac output monitoring lies with the quest to find a truly non-invasive device that is accurate in both
health and disease. Whether that future lies with Doppler, bioimpedance monitoring or another technique remains to be seen. What is certain is that these devices will lie rooted in the physiology of Fick, Hamilton and the other great insights of the past.
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