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Arterial waveform analysis

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The bedside measurement of continuous arterial pressure values from waveform analysis has been routinely available via indwelling arterial catheterization for >50 years. Invasive blood pressure monitoring has been utilized in critically ill patients, in both the operating room and critical care units, to facilitate rapid diagnoses of cardiovascular insufficiency and monitor response to treatments aimed at correcting abnormalities before the consequences of either hypo- or hypertension are seen. Minimally invasive techniques to estimate cardiac output (CO) have gained increased appeal. This has led to the increased interest in arterial waveform analysis to provide this important information, as it is measured continuously in many operating rooms and intensive care units. Arterial waveform analysis also allows for the calculation of many so-called derived parameters intrinsically created by this pulse pressure profile. These include estimates of left ventricular stroke volume (SV), CO, vascular resistance, and during positive-pressure breathing, SV variation, and pulse pressure variation. This article focuses on the principles of arterial waveform analysis and their determinants, components of the arterial system, and arterial pulse contour. It will also address the advantage of measuring real-time CO by the arterial waveform and the benefits to measuring SV variation. Arterial waveform analysis has gained a large interest in the overall assessment and management of the critically ill and those at a risk of hemodynamic deterioration.

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Introduction

The bedside measurement of continuous arterial pressure values from waveform analysis has been routinely available via indwelling arterial catheterization for >50 years. Invasive blood pressure monitoring has been utilized in critically ill patients, in both the operating room and critical care units, to facilitate rapid diagnoses of cardiovascular insufficiency and monitor response to treatments aimed at correcting abnormalities before the consequences of either hypo- or hypertension are seen.

Arterial blood pressure was first directly measured by Stephen Hales in 1733, when he used a 9′-long glass tube with a flexible connector (the trachea of a goose) and measured the pressures at the femoral and carotid arteries [1]. Other scientists and physicians improved on this method, including Daniel Bernoulli [2] and Jean-Louis Poiseuille who, in 1828, used a mercury-filled U-tube to determine the pressure at multiple points along the aorta [3]. The first clinically relevant placement of an arterial catheter was accomplished in 1949 by Peterson and colleagues who described the following methodology: "A small plastic catheter, inserted into an artery through a needle, is left in the artery when the needle is withdrawn. Attached to a capacitance manometer, this technique permits recording for long periods of time without discomfort and allows relatively free mobility of the subject." [4] Since that time, multiple techniques have been elucidated by Peirce [5] and Seldinger [6]. Seldinger described the "catheter-over-wire" technique commonly used today. As of 1990, >8 million invasive arterial catheters had been placed. One added advantage of an invasive arterial catheter is the ability to easily draw blood samples to measure levels of various including hemoglobin and electrolytes, allowing greater ease at diagnosis and managing disease. As medical technology improved, noninvasive technology was developed to provide continuous arterial waveform monitoring using plethysmographic principles with devices placed on a finger or wrist, that is, a continuous noninvasive arterial pressure (CNAP) monitor [7] and NexFin [8] (BMEYE, Amsterdam, the Netherlands) devices. Some noninvasive devices require calibration and others do not.

Hemodynamic monitoring in the operating room and the intensive care unit has evolved over time by the use of both arterial pressure monitoring and pulmonary artery catheter (PAC)-derived measures. PAC-derived measures include pulmonary artery pressure, pulmonary artery occlusion pressure, mixed venous oxygen saturation, and cardiac output (CO) by the thermodilution technique. Although it would seem that these invasive monitoring techniques to estimate CO would be useful in patient management, studies do not show improved outcomes when compared to their lack of use. There have been multiple randomized controlled trials that have reported no evidence of benefit or harm from the use of the PAC [9], and some literature has indicated that there may be an increase in complications secondary to the use of pulmonary artery catheterization [10–12]. There may be a few reasons why there has been a failure to show the benefit of PAC: some of the studies may not have used treatments requiring CO values to drive resuscitation, the treatments in the studies may not have been proven to improve outcome, and the groups studied are too heterogeneous to document a benefit [13].

Because of this overall lack of interest in the continued widespread use of the PAC, minimally invasive techniques to estimate CO have gained increased appeal. This has led to increased interest in arterial waveform analysis to provide this important information. The arterial waveform is measured continuously in many operating rooms and intensive care units, and obtaining the arterial pressure waveform can be accomplished by simple catheterization and even noninvasively. The benefit is the continuous measurement of arterial pressure with decreased risk to the patient. The cost that exists is the purchase of a device that allows for numerical computation but does not require further specialty staff. Arterial waveform analysis also allows for the calculation of many so-called derived parameters intrinsically created by this pulse pressure profile. These include estimates of left ventricular stroke volume (SV), CO, vascular resistance, and during positive-pressure breathing, SV variation, and pulse pressure variation (PPV). This article focuses on the principles of arterial waveform analysis and their determinants, components of the arterial system, and arterial pulse contour. It also addresses the advantage of measuring real-time CO by the arterial waveform and the benefits to measuring stroke volume variation (SVV). Thus, arterial waveform analysis has gained a large interest in the overall assessment and management of the critically ill and those at a risk of hemodynamic deterioration.

Technical aspects of pressure monitoring

Invasive monitoring requires the insertion of a catheter into a vessel, with all the associated potential complications of bleeding, thrombosis, and infection. The decision to insert an arterial catheter needs to be made with an understanding that it always carries a defined risk. Once the decision has been made to insert an arterial catheter and the arterial cannula is in place, it needs to be connected to a pressure transduction system so that accurate and continuous measures of arterial pressure can be made (Fig. 1). The catheter and its connecting tubing need to be made of stiff materials so as not to absorb the pressure waves which would potentially decrease pressure transfer from the catheter tip to the pressure transducer system. Currently, normal catheter transduction systems include a parallel saline or heparinized saline slow infusion system, which is pressurized (usually >200 mmHg) to allow for slow (2–4 ml/h) continuous flush of the catheter tip into the blood stream. This slow infusion rate does not affect pressure readings but tends to minimize thrombus formation on the catheter tip.

The pressure within the tubing of the column of saline varies with arterial pressure pulsation. As the pressure varies, so does the deformity of the pressure transducer dome diaphragm. The transducer diaphragm distortion causes a proportional change in resistance across a Wheatstone bridge-type electrical circuit, such that the change in transducer current is directly proportional to changes in pressure (Fig. 2) [14].

The arterial wave is a rather complex waveform and it can be expressed as a summation of harmonic waves based upon Fourier theorem calculations. To report these pressure changes, the monitoring system must have a frequency response that exceeds the natural frequency of the arterial pulse (1–2.5 Hz). While most commercially available transducers have a frequency of several hundred hertz, the addition of the tubing, micro-air bubbles in the tubing, thrombus on the catheter tip, and partially closed stopcocks will decrease the overall frequency response of the monitoring system. A monitoring system with too low a frequency response (over-dampened and a depressed waveform) or a high frequency response (under-dampened and a rather vibrant waveform) will result in underestimation or overestimation, respectively, of the arterial pulse pressure without altering the accuracy of reporting the mean arterial pressure (MAP). Further, hyperresonance, an artifact secondary to the pressure wave reverberation within the system, should be counterbalanced by an appropriate damping coefficient to allow for accurate pressure profile analysis [15,16].

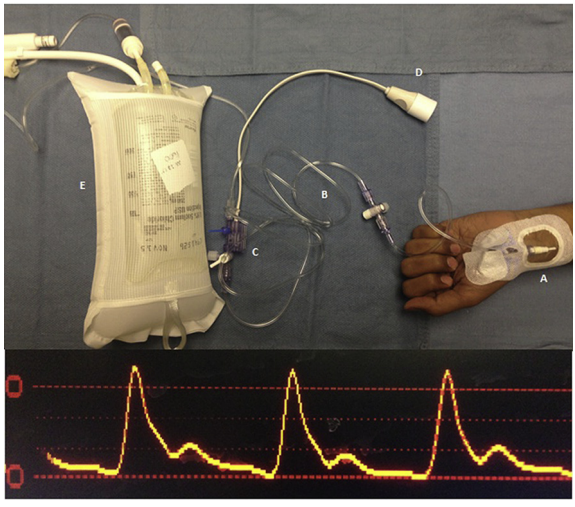

Fig. 1. 1a: (Top) Transduction system and arterial waveform. A: Arterial catheter in the radial artery. B: Stiff, low-compliance pressure tubing. C: Transducer, which converts mechanical energy into the electrical signal. D: Electrical cable that connects to the monitor. E: 250-mL bag of normal saline in a pressure bag inflated to nearly 300 mmHg. Fig. 1b: (Below) Arterial waveform signal on the monitor.

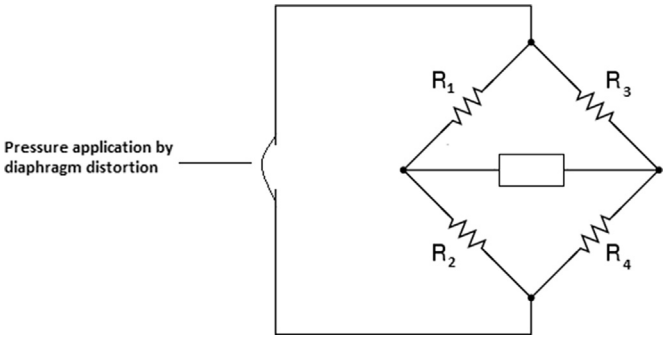

Fig. 2. Wheatstone Bridge. Pressure is applied to the diaphragm and distortion occurs. R1 and R3 increase, and R2 and R4 decrease proportionally.

Once the indwelling arterial catheter is connected through its fluid-filled stiff connecting tubing to the pressure transducer, the system must be calibrated and have its zero reference value defined. Zero pressure is defined as the isobestic point approximately equal to the hydrostatic pressure at the left of the left atrium. If the pressure transducer's zero reference stopcock is opened to air and transducer when the stopcock is at the isobestic point, then that value reported will be defined as zero for all subsequent pressure recordings. If the zero reference point for the catheter measuring intrathoracic pressures different than left atrial pressure once zeroing of the system has occurred, then the monitoring system needs to be re-zeroed or a systemic pressure error will occur to all measured pressures. If the patient sits up without a change in transducer height relative to the floor, then an artifactual low arterial pressure will be reported. As the patient moves, the transducer must always follow and stay at the level of the left atrium. Similarly, if the system is zeroed with the patient sitting up and the patient then reclines, the measured arterial pressure will increase equal to the decrease in the hydrostatic water column created by the position change. Finally, once zeroed, a reference electrical signal is placed through the pressure transducer circuit known to be directly correlated with the change in electrical output created by a known amount of increased pressure, usually 100 mmHg. The “gain” of the system is thus modified so that zero reads zero and the calibration 100 mmHg reports 100 mmHg. Once these processes are complete, the system can be used to monitor and use the arterial waveform for clinical decision making.

The physiologic basis of the arterial pressure waveform [17,18]

The systemic arterial pressure waveform is the result of systolic expulsion of blood from the left ventricle, which is subsequently followed by diastolic arterial dissipation of the SV (Fig. 3). The electrocardiograph (EKG) signal and the arterial waveform signal are inextricably tied together, one representing the electrical contraction of the heart and the other representing its mechanical contraction. The systolic upstroke of the arterial waveform in a peripheral artery may not appear for 120–200 ms after the R-wave on the EKG, reflecting a time interval from electrical initiation through the expulsion of blood by the ventricle, until it reaches the catheter and transducer.

The systolic components, as labeled in Fig. 4, include a very steep rise or upstroke of the arterial pressure from its nadir to a peak (systolic ejection with the opening of the aortic valve), as well as the decline, as the heart goes into the end of systole and then the start of relaxation. The dicrotic notch, or *incisura*, which interrupts the arterial downslope, represents the closure of the aortic valve, which occurs just moments after the start of diastole. At the end of diastole, the waveform reaches its nadir. Each component of the arterial waveform, diastolic pressure, peak pressure, ejection time, rate of rise of arterial pressure during systole, and MAP are created based on several interrelated ventriculo-arterial processes. There is a great deal of information that can be gleaned from examining the arterial waveform.

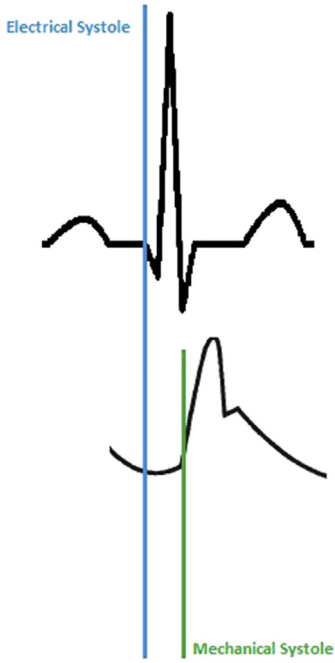

Fig. 3. Electrocardiogram and arterial waveform diagram.

Arterial pressure

MAP is the mean pressure averaged over time in the arterial tree at a defined locus (i.e., aortic arch, abdominal aorta, and radial artery). An algorithm measuring the pressure area under a single beat can also be used to calculate MAP [19]. As MAP is the pressure signal integrated over one cardiac cycle (effectively the area under the curve) and as systole is usually shorter than diastole, the MAP is less than the arterial pressure value halfway between systolic and diastolic arterial pressures. Mathematically, it can be estimated as the sum of the diastolic arterial pressure plus one-third of the difference between the diastolic and systolic arterial pressure.

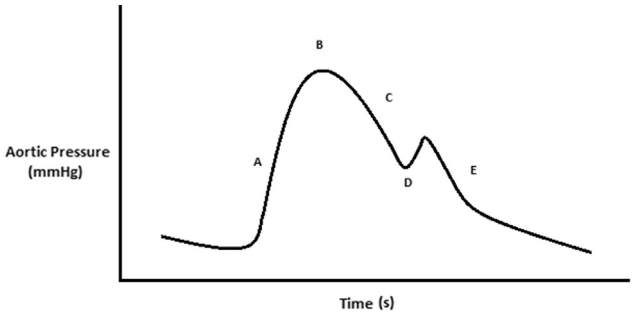

Fig. 4. An Arterial waveform. A: Upstroke of systole. B: Peak systole. C: Decreasing pressure during systole. D: Incisura. E: Diastole.

Distal arterial tree pressure amplification [20–24]

The arterial pulse pressure profile is not similar across the arterial tree but increases its systolic pressure and decreases its diastolic pressure slightly as one moves the sampling loci further away from the thoracic aortic root into the medium-sized arteries. Thus, the arterial pulse pressure increases as one moves the sampling site distal from the aortic root to the most peripheral pulse along the arterial tree (the radial artery in the upper extremity or the dorsalis pedis in the lower extremity). Different physical characteristics of the vascular tree and ejection velocity will result in different morphologies at each site. Owing to changes in impedance and harmonic resonance, the arterial upstroke becomes steeper and its slope increases. The systolic peak is higher and the dicrotic notch appears later in the cycle; the end-diastolic runoff is lower. There is an increase in systolic pressure and a decrease in diastolic pressure when peripheral measurements are compared to central measurements. Similarly, the further one measures the arterial pressure from the aortic values in the periphery, the wider the pulse pressure becomes. Some of the phase differences are due to pulse wave velocity, as there is a 60-ms delay between the aortic upstroke and its peripheral counterpart. However, despite these morphological changes, the MAP is remarkably similar across the arterial tree, decreasing only slightly in the distal periphery [25] (Fig. 5).

Contractility

The arterial waveform reflects the change in pressure over time, or dP/dt, and thus the slope of the upstroke reflects this. Generally speaking, the steeper the slope, the quicker the rise, the greater the dP/dt, and the stronger the contractile forces appear. The shallower the slope or the slower the rise in dP/dt, the weaker the contractile forces appear. This information has been used in the titration of inotropes. It is appropriate to mention that the relationship between dP/dt from the arterial waveform and left ventricular contractility is controversial and may be rather complex [26]. Some studies seem to support that the radial arterial waveform can be predictive of left ventricular function [27–29]. Other studies indicate that the radial waveform is not a reliable marker of left ventricular systolic function [30] and that dP/dt is not only affected by contractility but also by aortic diastolic pressure, ventricular end-diastolic pressure, the manner in which the ventricle is activated, and intrinsic adjustments of contractility [31]. One study suggested that the femoral measurement underestimated left ventricular dP/dt but changes in the femoral measurement accurately reflected changes during left ventricular treatment changes [32].

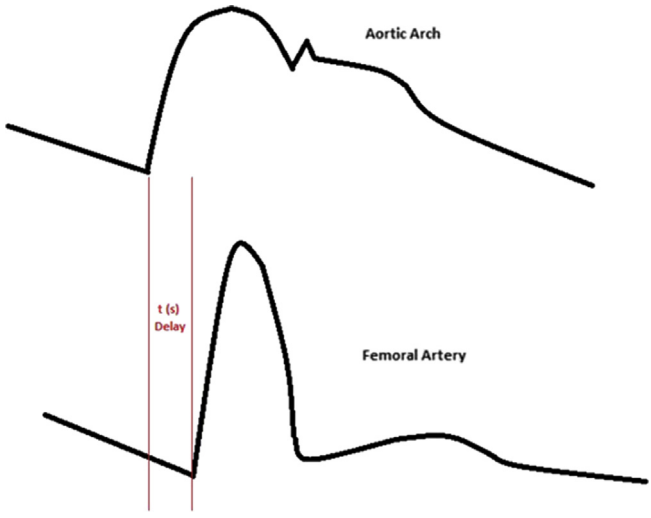

Fig. 5. Distal amplification of the arterial pulse, which includes the time delay.

Central arterial compliance

The arterial pulse pressure is a function of the left ventricular SV, contractility, and central arterial compliance. If the central arteries are stiffer, as often occurs with peripheral vascular atherosclerosis, then the pulse pressure will be greater than if it were normal. Similarly, neonates with highly complaint central arteries have a low pulse pressure. Finally, as the peripheral vasomotor tone changes, for the same SV, arterial pulse pressure will covary, increasing with increased arterial tone and decreasing with decreased arterial tone. Accordingly, arterial pulse pressure is an extremely revealing parameter within the arterial pressure profile.

Peripheral vascular resistance

The downstroke of the arterial waveform, or diastolic runoff, indicates how much resistance exists throughout the vascular tree to sustain pressure once left ventricular ejection into the arterial tree has stopped. When SV is stable and/or fixed, changes in vascular resistance will manifest as changes in the downslope of the arterial waveform. If the arterial waveform downstroke sharply decreases, as often is the case with vasodilator therapy or sepsis, there is little resistance to blood flow. If the downstroke of the arterial waveform is rather shallow, as is often in the case of severe heart failure, then this indicates a higher resistance. However, this feature has not been utilized clinically as it requires a priori knowledge of SV. Attempts to quantify SV and SVR purely from the shape of the arterial waveform have proven to be difficult.

Hypovolemia

As venous return to the heart varies with positive-pressure ventilation, the arterial pulse pressure may also vary. Thus, changes in pulse pressure across the ventilatory cycle, referred to as pulse pressure variation (PPV), can be used as a surrogate for volume responsiveness. Increasing PPV can be used to identify functional hypovolemia [33–35]. Hypovolemia will cause a large increase in the variation of both systolic pressure and pulse pressure compared to normovolemic states. Large systolic pressure or PPVs are correlated with lower amounts of intrathoracic blood volume and ventricular filling pressures [36]. Indeed, these functional hemodynamic parameters are more specific at defining volume responsiveness than are static measures of ventricular preload [33].

Practice points:

- Distal amplification results in an increase in systolic pressure readings and a decrease in diastolic pressure readings. However, throughout the arterial tree, the MAP is the same.
- The arterial waveform not only measures arterial pressure but can also be used to measure SVV, hypovolemia, contractility, and the magnitude of peripheral vascular resistance. This can help direct therapy in terms of the need for fluid, inotropy, or vasopressors

Means to measure CO using arterial waveforms [37]

There are multiple ways of measuring the CO. While the Fick principle and an electromagnetic flowmeter can be used to accurately predict CO, the most commonly used approach is using the indicator dilution technique to measure CO either periodically or continuously. Indicator dilution techniques can use any indicator that than be sensed downstream including thermodilution of a cold or hot thermal bolus, lithium, and indocyanine green. Following a venous bolus injection of the indicator, it is mixed by passage across the right ventricle and if sampled over time in the pulmonary artery, and the arterial tree will display a rapid indicator level increase followed by a logarithmic decay. The slope of

the decay portion of the curve is inversely related to blood flow. These approaches are based on the Stewart–Hamilton formula [38].

The PAC uses this principle by measuring the thermal signal in the pulmonary artery when a thermal signal is given into the upstream central venous site. The strength of this approach is that it requires only one catheter to measure CO. The weakness is that the pulmonary artery flow, which is what is measured, varies widely over the ventilatory cycle. Thus, measures of CO using the PAC will show a wide range of variability due to these non-artifactual effects. Accordingly, many measurements (usually four to five) need to be carried out and their values averaged to derive a relatively accurate CO estimation.

Indicator dilution can also be transpulmonary using two invasive devices, a central venous catheter, where the indicator is injected, and an arterial indicator sensor [39–41]. Different arterial sites can be used for indicator sampling, including the radial, brachial, axillary, and femoral arteries [42]. Studies have further verified transpulmonary thermodilution reliability [43] and precision [44] against the pulmonary artery thermodilution technique. Transpulmonary thermodilution has multiple advantages apart from providing CO. First, cold saline is cheap and readily available. Second, the variation in CO estimates due to respiratory changes in flow is less due to the buffering of blood within the pulmonary circulation. Third, it can provide other parameters that might be useful in bedside management, such as extravascular lung water [45]; pulmonary vascular permeability; the cardiac function index, which is a marker of the cardiac systolic function [46]; and the global end-diastolic volume, which is a marker of cardiac preload [43]. Lithium, as an indicator for estimating CO, has the same stability advantage as thermodilution but has an increased sensitivity, as no lithium is usually present in the blood stream. Thus, lithium indicator dilution has a greater signal to noise ratio than thermodilution. However, it requires injection of lithium and the need for a lithium sensor, which usually is extracorporeal requiring a small blood sampling technique. Any device using this type of indicator dilution is considered “less invasive” rather than “minimally invasive,” [47] because it does not require a PAC.

The Fick principle can also be applied to measure CO. The Fick principle states that the amount of oxygen consumed must equal the difference in oxygen quantity between the arterial and venous circulation [32]. Oxygen consumption and content are required for the actual measurement and, again, the use of an invasive monitor, the PAC, is necessary to obtain certain measurements because one needs to measure mixed venous and arterial blood oxygen levels.

The most accurate way to measure CO is using an electromagnetic or ultrasonic flow meter. An ultrasound can be applied to the aorta to obtain instantaneous pulsatile flow and produces a cardiac cycle flow curve, which when combined with the aortic diameter at the site of the velocity measure defined flow. The integral of this curve is the SV, and SV multiplied by the heart rate is the CO. Continuous measures of flow using these devices require an invasive procedure, either a sternotomy or a thoracotomy, making this an impractical universal solution. However, during cardiac surgery and with the insertion of left ventricular assist devices, such measures can be used to calibrate these ventricular support devices. A more practical way of measuring the CO with a less invasive approach, relative to surgical exposure, is by the use of transesophageal EKG and the Doppler method. This involves measuring the cross-sectional area of the left ventricular outflow tract as well as the instantaneous velocity through the left ventricular outflow tract and aortic valve at the point of the measurement. Then, integrating the velocity as a function of time, one can achieve SV measurements. This approach is operator dependent in getting a proper visualization window and can give CO estimates only when applied, not continually. Still, it is accurate in an experienced echocardiographer's hands and regrettably underutilized. A less invasive, simpler form of this approach is to use the ultrasonic cardiac output monitoring (USCOM) device that measures the aortic flow velocity at the aorta. As it does not usually measure aortic diameter, it can only estimate flow, but has as its main advantage ease of use, noninvasiveness, and reproducibility.

CO is a major part of the hemodynamic profile. CO is routinely used to categorize physiologic and pathologic cardiovascular states and to monitor response to therapy. Measurements of beat-to-beat SV and arterial pulse pressure have become important in analyzing the cardiovascular state. The percentage of variation of SV over time during positive-pressure breathing, known as the SVV, like PPV, defines preload reserve [48]. While multiple studies have revealed that PPV and SVV variations are not exactly the same [49,50], SVV has been just as reliable as PPV to predict fluid responsiveness [51–68].

Unfortunately, using the SVV to predict fluid responsiveness is still subject to the same limitations as using PPV. These limitations include a lack of spontaneous ventilatory efforts, large-enough tidal volumes to induce a venous return change (e.g., ~8 ml/kg tidal breath), decreased lung compliance (restrictive disease), open chest conditions, and cardiac arrhythmias [69,70]. Arterial pressure waveform analysis when used to estimate SV and CO provides significant help in assessing rapid CO changes, as may occur with passive leg raising [51,52,70–73], an end-expiratory occlusion test [70,73,74], or a fluid bolus challenge. There are multiple devices that can be applied in a minimally invasive or noninvasive fashion to measure CO.

Practice points:

- The arterial waveform can be used to estimate CO to further guide therapy, though looking at the arterial waveform alone is not adequate.
- The limitations of these devices include decreased accuracy in the setting of aortic insufficiency and large changes in afterload must be taken into account.
- The calibration of instruments is generally through thermodilution, either with lithium or with known-temperature saline.
- There are clinically defined targets for SVV and CO therapies.

Less, minimally, and noninvasive devices to measure arterial pressure

There exists a complex relationship between the MAP and the CO. As a result, multiple algorithms have been used to calculate the CO based on assumptions of central arterial compliance, resistance, and impedance. The electric current analogy indicates that the systemic vasculature acts as the resistance to the current or pressure, supplied by the heart [32]. Ohm's law ($V = IR$) can then be used to calculate the flow. However, this is not especially accurate for pulsatile flow within arteries, but for flow averaged over time. The Windkessel model [75,76] is more accurate to describe the relation between pressure and flow accounting for pulsatile flow. Further, the arteries act as a capacitor because they hold a significant amount of blood, which have by their vessel wall nature an inherent impedance to a change in volume. The Liljestrand and Zander method [32,77] assumes that arterial capacitance varies as a function of pressure in that as arterial pressure increases, the arterial walls stiffen and capacitance is reduced.

The major issue with these models is that the arterial tree is distributed into multiple branches with effects including impedance and wave reflection. Most models and all commercially available device models presume a “lumped parameter” estimate of resistance, compliance, and impedance. The present-day approaches to estimating SV from the arterial pressure profile have their roots in 1950s studies documenting that the SV is proportional to the area under the curve of the systolic portion of the arterial waveform [78] and a correction factor for calculation of CO. The Godje nonlinear compliance model [32,79] added on to the Windkessel model and made the heart a source of pressure, not a source of flow. It takes into account arterial compliance. The Wesseling Modelflow [32,80] further takes into account that the entire vasculature is nonlinear. This group used systemic arterial pressure in humans to compute aortic flow. They found that aortic impedance is a function of arterial compliance, compliance is a function of pressure, and resistance is a function of pressure divided by flow. As a result of these observations, formulae were created allowing accurate estimates of CO from the direct analysis of the arterial pressure waveform in real time.

In 2001, a new method of CO estimation, called the pulse contour CO algorithm (PulseCO), was devised based on frequency analysis from arterial systems [81]. This study compared PulseCO with transpulmonary thermodilution and found that CO can be estimated accurately. Based on the principles of the conservation of mass and power, the PulseCO algorithm calculates SV from an analysis of the SV-induced pulsatile change in the pressure waveform. The advantage of the PulseCO algorithm over the original Modelflow approach is that its estimates of CO are less sensitive to artifactual changes in the arterial pressure waveform contour, especially in the instance of vasopressor administration or catheter tip clot formation [82].

Present-day Food and Drug Administration (FDA)-approved devices can analyze the arterial waveform and pressure curve from a peripheral artery such as the radial or femoral artery, compute CO, and if present quantify SVV and PPV. Because all devices use different algorithmic approaches, as described above, the devices display different levels of accuracy depending on the pathologic states studied. Still, to be useful clinically, all the devices must be able to:

1. Analyze the geometry of the arterial pressure curve, especially the systolic portion. Recall that SV is proportional to the amplitude of the pressure curve.
2. Estimate arterial compliance while accounting for arterial tone. There is a constant, *k*, that is inversely proportional to arterial compliance and *k* is a multiplication factor proportional to the amplitude of the pressure curve. Additionally, pulse amplification is dependent upon arterial resistance.
3. Estimate aortic pressure from peripheral pulse pressure understanding the concept of distal amplification, already described.

Two types of devices utilize the arterial waveforms that have been developed. One type requires external calibration so that it can then calculate the patient's specific compliance and impedance, and the other type is uncalibrated, assuming a standard compliance and impedance based on known normal age-, sex-, and size-specific values. In general, the calibrated devices are more accurate immediately following calibration but their accuracy degrades over time. It is not clear if the uncalibrated devices change their accuracy over time more than the variation in the physiologic state. For the calibrated devices (Table 1), depending on the brand, transpulmonary dilution can be accomplished with the use of cold saline or lithium.

The following are calibrated devices (alphabetical order): LiDCOplus (LiDCO, Ltd., London, UK), PiCCO plus (Pulsion Medical Systems, Munich, Germany), and VolumeView/EV1000 (Edwards Lifesciences, Irvine, CA, USA). The following minimally invasive devices do not require calibration (alphabetical order): FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA, USA), LiDCOrapid (LiDCO Ltd., London, UK), Mostcare (VytechHealth, Padua, Italy), and ProAQT/Pulsioflex (Pulsion Medical Systems, Munich, Germany).

Calibrated devices (Table 1)

These devices are considered “less invasive” because of the use of a central venous catheter for calibration instead of a PAC. Using the lithium transpulmonary dilution technique to calibrate the analysis of the pressure waveform, the LiDCOplus uses the PulseCO algorithm to analyze the arterial waveform. The reliability of the LiDCOplus device has been reliably and successfully compared to thermodilution methods in multiple studies [83–87]. In addition to being less sensitive to arterial curve morphology changes, it is also supposed to be less sensitive to arterial catheter pressure dampening.

Table 1
Calibrated devices that measure cardiac output.

Device	Calibration	Algorithm	Special features	Disadvantages
LiDCOplus	Lithium transpulmonary dilution	PulseCO	- Less sensitive to arterial morphology changes - Less sensitive to arterial pressure dampening	- Less invasive
PiCCO	Transpulmonary thermodilution	Analyzes pulse contour and integrates area under systolic portion of the curve, dividing it by aortic compliance	- Estimates arterial compliance and SVR - CO based on real-time hemodynamics - Valid against PAC	- Less invasive - Requires multiple recalibrations - Questionable accuracy in hypothermic states
VolumeView/ E1000	Transpulmonary thermodilution	Langewouters'	- Validated with hyperdynamic and vasoplegic patients - Possible improved precision over PiCCO	- Less invasive

Calibrated by transpulmonary thermodilution (making it a "less invasive device" as compared to a "minimally invasive device"), the PiCCO device analyzes the pulse contour and then estimates CO by integrating the area under the systolic part of the arterial curve and dividing it by the aortic compliance [88]. The geometric properties of the curve, including the dicrotic notch, are accounted for. Multiple, separate algorithms are required to estimate the arterial compliance and systemic vascular resistance (SVR), which in this approach is defined as the MAP divided by the CO. Recalibration of all externally calibrated devices is often required to estimate arterial compliance as well as SVR, if the physiologic state changes markedly. This continuous reassessment allows the systems to adapt to CO estimation based upon the patient's real-time hemodynamics. Multiple studies have reliably validated that the PiCCO plus device estimation of CO as compared to the PAC is acceptable [82,88–95], though one study [94] indicated that measurements are better when they are performed closer to the calibration period. In fact, the same study indicated that measurements were unreliable if a prior calibration was not performed more than an hour before, secondary to dynamic changes in the patient's arterial SVR. This has been cited as a disadvantage to the PiCCO plus device. Further, though studies have attempted to use the PiCCO plus device in patients with hypothermia [96], it should be validated against more proven techniques [97]. Further, from the same study, it has also been suggested that a non-temperature or metabolism-independent calibration needs to be used, as temperature may not be as precise for hypothermic patients. Ultrasound approaches spot estimates of CO would fulfill this requirement.

The VolumeView/E1000 is another calibrated device that requires transpulmonary thermodilution and is rather similar to the PiCCO system. Based on the Langewouters method [98], the SV is estimated by pulsatility and a constant *k*, which quantifies arterial resistance and compliance. This method has been supported by a large database of pressure tracings recorded in hyperdynamic and vasoplegic patients [99]. It has been validated to be reliable in a recent study, which has appeared to indicate that not only is it as reliable as the PiCCO but also an improved precision over that of the PiCCO was seen with this device [100].

Uncalibrated devices (Table 2)

These devices are considered minimally invasive because they only require an arterial catheter.

The FloTrac/Vigileo has an algorithm by the Langewouters method [98], similar to the VolumeView/EV1000. This device consists of a standard arterial catheter and a standard arterial line, which is connected to a disposable specific pressure transducer ("FloTrac"). The latter is connected to the Vigileo device, which performs analysis and displays CO.

Table 2
Uncalibrated devices that measure cardiac output.

Device	Algorithm	Special features	Disadvantages
FloTrac/Vigileo	Langewouters	- Most studied - Reliable in perioperative period	- Controversial reliability outside of perioperative period - Reliability decreases with variations of vasomotor tone - Less invasive
LiDCOrapid	PulseCO	- Height, age, and weight nomograms infer arterial compliance - Can measure CO by separate technique	- Less invasive - When compared to esophageal Doppler, reliability is poor
ProAQT/Pulsioflex	Confidential, using height, weight, age, MAP, HR for autocalibration	- Can measure CO by separate technique - Analyze waveform 250 times/second	- Still requires validation - Less invasive
MostCare	PRAM	- No calibration required - Acceptable reliability in cardiac surgical population - Can use with IABP - Can use with critically ill patients	- Less invasive

The reliability of the FloTrac/Vigileo, or any uncalibrated device, is debated in the literature, more than for calibrated devices. The first uncalibrated device, FloTrac/Vigileo, has been the most studied. Multiple studies show a good reliability when compared to PAC thermodilution studies [99,101–106]. However, there are as many number of studies that demonstrate that it is not accurate [92–119]. Good reliability was shown in the perioperative setting [92–94,96]. However, the reliability of the FloTrac/Vigileo seems to decrease if there are vasomotor tone changes to a large extent [107,113,114,116,117] such as in patients who are critically ill [111,115–117] or patients undergoing liver surgery [107–110,112,118,119]. An example of this was demonstrated by Monnet et al., who found that the reliability of a recent version of the FloTrac/Vigileo was much poorer to track the changes in CO when they were induced by changing the dose of norepinephrine than by administering a volume expansion [116].

In general, any uncalibrated pulse contour analysis device is subject to poor reliability when the arterial pressure is modified. The cases include aortic valvular regurgitation [113], aortic stenosis [120], intra-arterial balloon counterpulsation [121], and simple dampening of the arterial waveform from air bubbles in the pressure tubing or kinks in the catheter or tubing.

The LiDCOrapid uses the same PulseCO algorithm as already described. Further, the patient's age, height, and weight are used to infer the arterial compliance through established nomograms. While it does not require any calibration, the CO, measured from an independent technique, can be entered. Its reliability is not considered to be as good as an esophageal Doppler [122]. Whether this was due to using a poor reference technique, descending aortic flow as a measure of total CO or actual errors in PulseCO, is unclear [123].

The ProAQT/Pulsioflex incorporates height, weight, age, MAP, and heart rate for the use of its own autocalibration algorithm, and from these values, the CO is inferred from a company-specific and confidential analysis, which is not based on the Windkessel model discussed before. Pulse contour analysis is then accomplished by the analysis of the arterial waveform 250 times per second [124]. Similar to the LiDCOrapid, one can enter the CO from another independent technique to avoid drift. This device still requires study and validation.

The MostCare is another uncalibrated device that utilizes the pressure-recording analytical method (PRAM) [125], which is based on the principle that, in a given vessel, variations in pressure cause responsorial radial expansion [126]. The process involves the force of left ventricular ejection, arterial impedance and compliance, and peripheral small vessel resistance. This is the only device that does not require any calibration and is independent of the baseline characteristic data of the patients [127]. Its reliability appears to be acceptable in cardiac surgery patients [126]. In contrast to the LiDCO, even in critically ill septic patients, receiving norepinephrine and compared to the PAC, the PRAM system exhibited an acceptable percentage of error [128]. Interestingly, patients with an intra-aortic balloon pump using this device had an acceptable percentage of error [121,129,130], though one study showed a large difference between the PRAM and PAC estimates of CO [131].

The Nexfin device (BMEYE, Amsterdam, the Netherlands) uses a completely noninvasive method of measuring patient hemodynamics. Connected to the patient by wrapping an inflatable cuff around the middle phalanx of the finger, “the pulsating finger artery is clamped to a constant volume by applying a varying counter pressure equivalent to the arterial pressure.” [124] This is called the volume-clamp method. The resulting brachial waveform, which is reconstructed based on an algorithm, serves as the basis to measure CO. The Windkessel model is also used, incorporating arterial pressure, height, weight, and gender regarding the vascular properties [132]. Multiple studies have validated this for the measurement of arterial pressure [133–140]. The reliability of this estimation of CO, similar to the LiDCO device, provided conflicting results, with some positive [134,141–147] and negative studies [140,148,149]. Once again, critically ill patients with possible poor perfusion of the extremities, in septic shock, may impede a correct measurement of the curve described above. Thus, this device may be better suited for the operating theater or other healthy subjects.

In summary, the calibrated devices tend to give more accurate trending data but often are more invasive. Thus, they are more likely indicated in those patients who are critically ill requiring vasopressor support, or in those patients in whom the vasomotor tone is rather unstable, such as septic shock. Uncalibrated devices can be set up quickly and tend to be less expensive and thus may be more useful in healthier subjects, presenting to the operating theater or within the perioperative period.

Practice points:

- There are multiple systems that can be used to measure CO from the arterial waveform. Some require calibration and others do not.
- There is one system that is completely noninvasive, which is the Nexfin.
- Systems that require calibration require central venous catheterization. While uncalibrated systems are less invasive, they may not be as accurate or reliable as the calibrated devices.
- Calibrated devices may require multiple recalibrations to guarantee the best accuracy.
- The accuracy and reliability of less invasive and noninvasive devices within the context of the disease state of the patient and the therapy and temperature required for the patient.

Research points:

- Further research is warranted regarding the interactions between MAP and CO/PPV/SVV, in the context of vasomotor tone, that is, the septic patient.
- Further research is warranted regarding the interactions of different modes of therapy and how to define the goals of resuscitation
- Further research is warranted regarding how to use the information given by the arterial waveform to recognize early onset of instability for early therapy

Conflicts of interest

Stephen A. Esper: None declared.

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