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EDITORIALS

Academic assessment of arterial pulse contour analysis: missing the forest for the trees?

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In this issue of the *British Journal of Anaesthesiology*, Montenij and colleagues[1] provide a thoughtful review of analytic methods for comparing cardiac output measurement methods, with focus on arterial pulse contour analysis methods that are intended to measure cardiac output. This review is a welcome addition to the literature, as such comparative investigations are commonplace, and often without optimal rigor.

At the same time, I hold a concern about another deficiency in pulse contour investigations. Despite 414 'pulse contour' AND 'cardiac output' articles currently indexed by PubMed, a century of academic reports describing various pulse contour methods[2] and decades of commercial sales, it remains uncertain whether pulse contour methods provide more sensitive and specific indicators about circulatory decompensation than routine use of blood pressure (bp) and heart rate monitoring – let alone whether such technology leads to improved patient outcomes. It can be argued that conducting future studies that continue to merely compare one cardiac output measurement technique against another, risks missing the forest for the trees.

To be sure, management of the tenuous patient – stable but with minimal physiological reserve, and with a high risk of decompensation, as might occur after haematemesis from esophageal varices, or during an invasive procedure – is a challenge. The vigilant clinician monitors tenuous patients carefully, to respond to any deterioration while avoiding unnecessary and excessive intervention. A conundrum may occur when the arterial bp drifts down, which might indicate deterioration, such as new, dangerous blood losses. Yet as often as not, this is relatively benign, a lessening of vasoconstriction as the patient becomes more relaxed as a result of medication or time. The vigilant clinician must distinguish between these two very different physiological circumstances, and the stakes are high. Accordingly, there has been interest in techniques for non-invasive monitoring cardiac output, such as pulse contour analysis, as cardiac output is a cardinal metric of circulatory adequacy and, as the dividend of the bp–to–central venous pressure gradient, also yields total peripheral resistance (TPR), a measure of vasoconstriction.[3]

If pulse contour analysis for measuring cardiac output is truly reliable, then it should be uniformly used as the standard-of-care for tenuous patients. If the technique is inaccurate, then it is only an illusion that the patient's cardiac output and vascular tone are being carefully monitored, unreliable information that gives a false – and possibly dangerous – sense of security when managing tenuous patients.

The rationale behind pulse contour analysis

For a masterly treatment of the principles underlying pulse contour analysis, one may consult the textbook 'McDonald's Blood Flow in Arteries'.[4] The vast majority of pulse contour methods estimate volumetric flow in the aortic root, which equals cardiac output. As a matter of basic physics, note that it is not the pressure wave but the *pressure gradient* that impels fluid to flow in blood vessels. In other words, it is the *difference* of pressures in a segment of artery, upstream vs downstream, that accelerates/decelerates the pulsatile blood within that segment. It is simply

impossible to compute flow with only one pressure wave: computing the gradient cannot be done precisely without a second pressure measurement. Most pulse contour methods address this conundrum by relying on probabilistic relationships between the upstream pressure wave and the downstream pressure wave. For instance, one method of calculating flow would be to assume that the downstream pressure waveform is similar to the upstream pressure, aside from a small time delay. From this assumption, pressure gradients can be estimated and flow computed.

The first challenge for pulse contour analysis is that the downstream waveform is not, in fact, the same shape as the upstream waveform, because the entire pressure waveform is not wholly moving downstream. Instead, there is a primary wave moving downstream, while there are smaller pressure waves that move upstream: reflected pressure waves from distal vascular junctures that travel in the retrograde direction. These reflected waves increase the amplitude of an arterial waveform, but they actually create retrograde pressure gradients that decelerate the blood and retard flow. Larger bp waveforms do not always correspond to greater forward flow! This is one fundamental challenge to pulse contour analysis, and different pulse contour methods use different techniques, usually statistical corrections based on either patient characteristics or some property of the shape of the bp waveform, to try to circumvent this complication.

There is a second challenge. While the gradient of pressure determines the magnitude of acceleration/deceleration, it is the diameter of the vessel that dictates the actual volume of blood. Pulse contour methods must use some technique to address this complication, such as a calibration of volume against another reference, or relying on probabilistic relationships between age and gender and the likely size and pulsatile compliance of the arterial vessel.

There is also a third major analytic challenge. It is only within the aortic root that flow equals cardiac output, whereas the arterial waveform is usually measured somewhere in the periphery. Pulse contour methods must use some technique to estimate flow in the proximal aorta using a pressure waveform measured in the periphery. Again, a common approach is to use probabilistic relationships between those waveforms. (One approach is to use a generalized transfer function, which is a mathematical manipulation based entirely on probabilistic relationships between peripheral and central waveforms[5]).

The crux of the matter

There is indeed a physical causal relationship between the arterial pressure waveform and cardiac output. However, taking the three analytic challenges together, it is also clear than quantifying cardiac output from pulse contour analysis must rely on probabilistic relationships (e.g. the *likely relationship* between the central and peripheral arterial waveform; the *likely relationship* between the patient's age, gender, etc. and the size and compliance of the patient's aorta; or the *likely relationship* between the upstream and downstream pressure waves that determine the flow-determining pressure gradient). These 'likely relationships' are purely probabilistic; they are observed in the majority of cases, but not all cases. Conceptually, it is no different from relying on a patient's weight to estimate her height: a reasonable estimate can be made for many individuals, but there is likely a subset for whom the relationship will be invalid. Which means that the estimated cardiac output by pulse contour may be accurate, except when it isn't.

This doesn't invalidate pulse contour analysis. We clinicians are accustomed to relying on probabilistic relationships when we assess our patients' haemodynamics. When mean arterial pressure (MAP) is falling, we know that it typically represents failing circulation. Or when the patient has a large pulse pressure, we assume that the patient probably has a large stroke volume. Yet sometimes these probabilistic relationships are invalid (e.g. patients with low MAP who are not in shock but are merely vasodilated). It is because our routine measures, such as MAP and pulse pressure, can be clinically ambiguous that we seek superior, less ambiguous non-invasive measures.

Returning to pulse contour analysis: the motivation to incorporate this technology into our practice is because we know that routine bp is not always reliable in assessing circulatory state. Yet pulse contour cardiac output also relies on a set of probabilistic relationships that may be invalid for some subset of clinical situations. Is pulse contour analysis superior to routine vital signs monitoring? Or does it provide false reassurance by continuously displaying a cardiac output estimate that is not always reliable? Is it indeed superior to routine monitoring? In my opinion, after more than several decades, this question is not answered.

Open questions within the literature

The academic literature regarding pulse contour analysis is dominated by method comparison studies (i.e. comparing cardiac output from pulse contour analysis vs a reference method). Method comparison studies do not answer the following question: 'should I use technology X for patient Y.' The emphasis on '95% confidence intervals' can mask serious problems that can occur under certain circumstances: pulse contour method, overly reliant on probabilistic relationships, might yield wildly and systematically inaccurate cardiac output in a subset of patients with atypical physical or physiological properties. Focus on the majority of cases who, by definition, fall within the 95% confidence interval, and treating errors as if they are just 'random', means that major failures of these techniques are treated as nothing more than 'outliers' (i.e. unpredictable statistical flukes).

Yet it is very possible that pulse contour analysis fails in a predictable way under predictable conditions (and those conditions may or may not be commonplace in any given published study). It would be valuable to determine if there are patients in whom pulse contour analysis predictably fails so that we may learn the most about the technologies' true capabilities and pitfalls. Consider pulse oximetry, by analogy: we know not to rely on pulse oximetry if there are haemoglobinopathies or after methylene blue, and we know it is less reliable given poor skin perfusion or bright ambient lights. We must focus on defining any non-random sources of error for each and every investigational cardiac output method that we hope to use on patients.

Method comparison studies[1] are only a rudimentary way of assessing pulse contour analysis. Other essential questions include, how frequently does clinical management change when guided by pulse contour analysis rather than routine monitoring, and are overall prospective outcomes improved? Or, can pulse contour analysis predict the patient's future physiological state better than routine methods involving bp and heart rate alone? (A useful schema for diagnostic test assessment includes technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, clinical outcome efficacy, and societal efficacy[6]).

There are a relatively small number of published prospective outcomes trials involving pulse contour analysis for cardiac output monitoring. Of those outcomes trials, many are suboptimal, comparing management using pulse contour analysis vs *ad hoc* care. *Ad hoc* care, in which there are no explicit expectations in how the control group is managed, is often inferior to *any* rigorous protocol. Consider that the bispectral index monitor (for anaesthesia monitoring[7]) and the continuous fiber optic central venous oximetry monitor (for sepsis resuscitation[8]) were both associated with significantly superior outcomes than *ad hoc* care. However, when those technologies were later compared against alternative monitoring methodologies, neither novel technology was found to be superior.[9 10]

A second problem with many outcomes trials involving pulse contour analysis is that they use a *bundle* of technologies from the vendor, such as pulse contour cardiac output and stroke volume variation metrics for predicting volume responsiveness. Certainly, if using a bundle of technologies can be shown to improve patient outcomes, that finding is noteworthy and may be practice-changing. However, study designs involving bundles do not reveal which technologies within the bundle are reliable and which are not.

Overall, there exist a rather limited number of studies investigating whether or not patients experience superior outcomes using pulse contour analysis monitoring of cardiac output, and not nearly enough is known about a technology that has been sold and used in patient care for decades. Searching the Cochrane Library, there is only one meta-analysis involving pulse contour analysis (which concluded 'an absence of evidence that fluid optimization strategies improve outcomes for participants undergoing surgery for [proximal femur fracture' and 'length of hospital stay may be improved, but lack of good quality data leaves uncertainty').[11] Additional outcomes investigations, including replication of successful pilot studies without industry-sponsorship, should be encouraged for anyone interested in the academic assessment of pulse contour methods.

Closing remarks

The current landscape is a generally poor understanding of pulse contour analysis products' clinical value. Searching the Pulsion.com website,[12] I cannot find any detailed explanation for their pulse contour analysis algorithm that addresses the analytic challenges that were discussed above. The FloTrac website[13] is similarly vague, merely stating broadly that: 'Cardiac output is correlated with the variance between systolic and diastolic pressure. Real-time analysis of waveform characteristics is also integrated, compensating for changes in vascular physiology affecting the pressure waveform.' Retia Medical offers a different approach to pulse contour analysis, seeking to estimate the rate at which blood drains from the arterial tree by looking at the arterial pressure over long time intervals (rather than estimating volume of each systole)[14] but their website does not provide substantial detail, either.[15] We clinicians would never treat patients with pharmacologic agents with active ingredients so poorly described and understood.

There is insufficient published evidence that pulse contour methods, which offer cardiac output estimates based on a set of probabilistic assumptions, are safe, or that they offer significant advantage over careful monitoring using routine haemodynamic parameters. Nor is it clear which commercially sold methods are superior to the others. There is generally weak understanding about the specific conditions under which each method is reliable vs erroneous. The fact that pulse contour analysis generally correlates well with cardiac output references measurements (as demonstrated by many cardiac output method comparison studies) is not, to me, adequately encouraging, because changes in MAP also generally correlate well with changes in cardiac output.[16] Therefore, correlation with cardiac output is not in-and-of-itself evidence that pulse contour analysis is better than routine use of bp and heart rate monitoring.

The promise of pulse contour analysis is clear: there is a wealth of information within the waveform, and it seems reasonable that rigorous analysis should yield superior information for decision-making than rudimentary metrics such as systolic bp and MAP. In the near future, one hopes that these open questions can be addressed with trials that unambiguously affirm the clinical value of pulse contour analysis for patient management, while clinicians will use the technologies with a deep understanding of its underlying principles and the evidence that it is useful for a given clinical application.

Declaration of interest

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Applied cardiovascular physiology in theatre: measuring the cardiovascular effects of propofol anaesthesia

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Cardiovascular homeostasis is a complex and beautiful interplay between the functional differences between various vascular circuits in the body and their tissue's metabolic demand, the physical nature of the endothelial barrier to fluid flux, the circulating blood volume, and reflex-mediated autonomic tone. When at rest, as occurs during anaesthesia, basal metabolic demand is both constant and low. Thus, impairments in autoregulation or sudden decreases in blood volume, as may happen during surgery, are thankfully less detrimental to tissue wellness than might otherwise be the case under conditions of metabolic stress. However, such physiologic reserve though comforting to the anaesthetist and forgiving to the patient, has clearly defined limits. Anaesthesia by its nature decreases central nervous system activity and by default, impairs autonomic responsiveness and at high enough concentrations impairs vascular tone and cardiac contractility. These concepts form the basis for anaesthetic selection in specific patient groups. But mostly all these considerations have focused on the left ventricle (LV) and arterial tone, ignoring venous return by simply placating it with increased fluid resuscitation, vasopressor infusion and/or decreased concentration of anaesthesia if the patient becomes hypodynamic.

However, the circulation is much more interactive in its components defining cardiac output than those described by left ventricular preload and contractility and arterial pressure and arterial vasomotor tone. Fundamental principles of cardiovascular physiology, as originally described by Guyton and colleagues[1] more than 50 yr ago,[1] identified venous return as the primary determinant of cardiac output and that LV function is remarkably insensitive in defining this level of flow, only the required backpressures needed for that flow. We collectively argued these points relative to cardiopulmonary bypass surgery in a physiologic commentary.[2] Until recently, just knowing that venous return was the primary determinant of cardiac output did little to help the bedside clinician manage complex and changing surgical patients. One understood that mean circulatory filling pressure (Pmcf) was the best surrogate for effective circulating blood volume, but its measure and its own determinants were difficult to ascertain at the bedside and nearly impossible to measure repeatedly over time. The effective circulating blood volume represents a balancing act between total circulating blood volume, blood flow distribution amongst various organs with varying degrees of capacitance and unstressed volume, and the resistance to venous return (RVR), which has more of a conductance determinant to its value that actual physical resistive.[3] Importantly, multiple lines of investigation have led to the development of several methods to quantify Pmcf at the bedside using only arterial pressure, central venous pressure (CVP), and cardiac output. A detailed review of these various techniques is found elsewhere.[4] However, presently three techniques are readily available and can be used for the bedside assessment of venous return.

The first approach uses an analogue estimate of Pmcf by assuming a constant proportion of compliance and resistances within the arterial and venous circuit.[5] We recently validated this breath-by-breath analogue approach in a canine model during normal and endotoxic shock state.[6] Using this analogue approach Cecconi and colleagues[7] examined the effect of fluid boluses on Pmcf, the driving pressure for venous return (Pmcf-CVP), and cardiac output in a large postoperative surgical patient population. They showed that fluid loading universally increased Pmcf, if only transiently, and unaltered RVR. However, for cardiac output to increase the driving pressure for venous return also needed to increase. Thus, if fluid loading did not increase cardiac output, CVP increased, whereas in those whose cardiac output increased CVP remained stable. The observation that volume loading does not alter RVR has been known for more than 30 yr,[8] and is the basis for increases in CVP during fluid loading being a 'stopping rule' for fluid infusion therapy.[9]