Continuous and less invasive central hemodynamic monitoring by blood pressure waveform analysis

Ramakrishna Mukkamala and Da Xu
Department of Electrical and Computer Engineering, Michigan State University, East Lansing, Michigan

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Mukkamala R, Xu D. Continuous and less invasive central hemodynamic monitoring by blood pressure waveform analysis. Am J Physiol Heart Circ Physiol 299: H584–H599, 2010. First published July 9, 2010; doi:10.1152/ajpheart.00303.2010.—Blood pressure waveform analysis may permit continuous (i.e., automated) and less invasive (i.e., safer and simpler) central hemodynamic monitoring in the intensive care unit and other clinical settings without requiring any instrumentation beyond what is already in use or available. This practical approach has been a topic of intense investigation for decades and may garner even more interest henceforth due to the evolving demographics as well as recent trends in clinical hemodynamic monitoring. Here, we review techniques that have appeared in the literature for mathematically estimating clinically significant central hemodynamic variables, such as cardiac output, from different blood pressure waveforms. We begin by providing the rationale for pursuing such techniques. We then summarize earlier techniques and thereafter overview recent techniques by our collaborators and us in greater depth while pinpointing both their strengths and weaknesses. We conclude with suggestions for future research directions in the field and a description of some potential clinical applications of the techniques.

arterial tree; cardiac output; intensive care unit; modeling; signal processing

The proportion of the elderly population is growing as the clinical staff per capita declines (36). By 2020, a ~30% shortfall in nurses is projected (36). These demographic changes accentuate the importance of effective, continuous (i.e., automated), and less invasive (i.e., safer and simpler) patient monitoring systems. Such systems are especially needed for the hemodynamic monitoring of cardiovascular disease.

Today, hemodynamic monitoring often entails the continuous measurement of blood pressure (BP) waveforms. Indeed, each year, minimally invasive catheters are used in at least 10 million intensive care unit (ICU) and surgery patients to measure the peripheral arterial BP (ABP) waveform from, typically, the radial artery (59a). Invasive catheters are also used, although to a lesser degree, in these and other patients to monitor BP waveforms from the right heart and pulmonary artery (66). Moreover, the Food and Drug Administration (FDA)-approved systems for noninvasive measurements of the peripheral ABP waveform are now commercially available (14a, 35a), whereas implantable devices for chronic measurements of the right ventricular pressure (RVP) waveform or other BP waveforms may follow (19a, 63, 80). These newer sensors could potentially be used in the ICU in addition to other settings. However, while these systems are continuous and afford a level of invasiveness safe enough for regular monitoring, they are ineffective in the sense that the measured BP levels are imprecise indicators of circulatory status.

One reason is that BP levels in the right heart and peripheral arteries are not as relevant as their counterparts in the left heart and central aorta. That is, the left heart is more prone to disease than the right heart, whereas central ABP truly indicates cardiac afterload and perfusion and is more predictive of patient outcome than peripheral ABP (see Fig. 1A) (95, 113).

A second reason is that BP levels do not provide an early indicator of a hemodynamic event. For example, in the initial stages of a bleed, the cardiovascular control system maintains mean ABP at the cost of cardiac output (CO; see Fig. 1B) (13, 40). While frank hypotension may eventually occur (see Fig. 1B), it is often too late to intervene at this point (13, 40). Thus, it is CO monitoring that would give an early enough indication of the need for therapy.

A third reason is that BP levels alone do not permit diagnosis. For example, when the cardiovascular control system eventually fails so as to result in hypotension, the root cause could be sepsis, systolic or diastolic dysfunction, or hypovolemia (see Fig. 1C). To reveal the root cause, CO, left atrial pressure (LAP) [or other left ventricular (LV) filling pressure (LVFP) measures], and LV ejection fraction (EF) must also be monitored (see Fig. 1C) (55, 84). Note that EF has also proven to be a powerful predictor of outcome in heart failure patients (27).

A fourth reason is that BP levels are not sufficient for directing therapy during obvious hypotension of known etiology. Other measurements that more adequately reflect global oxygen delivery, especially CO, are also needed to implement the recently celebrated “goal-directed therapy” and thereby improve patient outcomes (see Fig. 1D) (71, 83).

Several methods are available for measuring CO, LAP, EF, and central ABP (see Table 1). The most commonly used methods for monitoring CO and LAP in clinical practice both require the insertion of a pulmonary artery catheter (66). In particular, CO has been estimated with the bolus thermodilu-
tion method, and LAP has been approximated with the pulmonary capillary wedge pressure (PCWP) method. However, these two methods require an operator to inject a fluid bolus through a catheter side port and inflate a catheter-tip balloon and are thus not continuous. Moreover, the PCWP method is not easy to implement, as exemplified by the frequent occurrence of partial wedging and balloon overinflation (59, 74). Similarly, proper implementation of the thermodilution method is hindered by variations in injectate volume, rate, and temperature, which introduce 10–15% error in the measurement (26, 48, 72, 103). Perhaps due in part to these limitations along with the moderate level of invasiveness of the pulmonary artery catheter, this longstanding ICU device has yet to reveal a clinical benefit (see, e.g., Refs. 43 and 97), and its use has declined (118). The standard clinical method for monitoring EF [i.e., the ratio of stroke volume (SV) to end-diastolic volume (EDV)] is by imaging the ventricular volume via, e.g., echocardiography or contrast angiography (93). However, non-invasive imaging methods require an expert operator and capital equipment. Alternative methods for measuring CO, LAP, and EF suffer from even more severe disadvantages that have limited or precluded their use in clinical practice. Finally, the conventional method for measuring central ABP is to place a catheter in the aorta. However, this method is rarely performed for regular monitoring due to its high level of invasiveness, carrying risks of thromboembolism (e.g., stroke).

Fig. 1. Central hemodynamic variables are clinically significant. A: central arterial blood pressure (ABP) is a superior predictor of coronary artery disease (CAD) severity than peripheral ABP. *P < 0.05; **P < 0.01; ***P < 0.001. B: cardiac output (CO) provides an earlier indicator of a bleed than ABP. TPR, total peripheral resistance; HR, heart rate; BP, blood pressure; RAP, right atrial pressure. C: CO, left atrial pressure (LAP), and left ventricular ejection fraction (EF) permit diagnosis. D: CO helps direct therapy so as to improve postcardiac surgery outcomes. [Adapted from Refs. 13, 71, and 113.]
Thus, while these methods are effective in terms of monitoring vital central hemodynamic variables, they are not both continuous and less invasive, and, as a result, their application is limited today and likely to be even more so hereafter.

One potential solution for overcoming the aforementioned limitations of conventional hemodynamic monitoring systems is to estimate essential central hemodynamic variables by the mathematical analysis of BP waveforms (see Fig. 2). The main advantage of this solution is that hemodynamic monitoring systems may become simultaneously effective, continuous, and less invasive without requiring any instrumentation beyond what is already in use or available.

In this article, we review BP waveform analysis techniques for central hemodynamic monitoring that have appeared in the literature. We first summarize earlier techniques and then highlight recent techniques by our collaborators and us. We conclude by providing a summary, suggesting future research avenues, and describing possible applications in the ICU and beyond.

**Summary of Earlier BP Waveform Analysis Techniques**

Central hemodynamic monitoring by BP waveform analysis has attracted the attention of many for decades. The earlier techniques span the estimation of several cardinal central hemodynamic variables from different BP waveforms, with particular emphasis on tracking CO through ABP waveforms.

**CO monitoring by BP waveform analysis.** ABP WAVEFORM ANALYSIS. Over a century ago, Frank (37) first suggested that CO could be measured from ABP waveforms. Shortly thereafter, Erlanger et al. (34) introduced the first specific analysis technique. They observed that pulse pressure [PP; i.e., systolic pressure (SP) minus diastolic pressure] in the aorta was positively correlated to SV. Thus, their technique simply involved detecting PP from the central ABP waveform to determine SV for each beat and CO (via PP × heart rate) to within constant scale factors. In this way, the technique could be used to monitor the relative changes in these variables or their absolute values after one calibration. (Note that tracking changes is most relevant in acute settings such as the ICU.) However, this PP technique assumes that cardiac ejection occurs instantly when it actually occurs over finite time in which a portion of the ejected blood passes through the aorta.

Among the numerous ensuing studies (e.g., Refs. 61, 67, 90, 102, 112, 114, and 115), Bourgeois et al. (16, 17) performed one of the most compelling. These investigators developed a central ABP waveform analysis technique that made no cardiac ejection time assumptions. They represented the arterial tree with a Windkessel model accounting for the lumped compliance of the large arteries (AC) and the total peripheral resistance (TPR) of the small arteries (see Fig. 3A). According to this model, central ABP should decay like a pure exponential during diastole with a time constant (τ) equal to TPR × AC. By assuming constant AC, their technique involved fitting an exponential to each diastolic interval of the waveform to measure τ and then dividing mean ABP by τ to compute CO to within a 1/AC scale factor (see Fig. 3B). Their technique also yielded proportional SV for each beat via the dynamic model equation (see Fig. 3B). This Windkessel technique proved to be highly accurate (see Fig. 3C), because the diastolic intervals of the central ABP waveform indeed resemble pure exponential decays (see Fig. 3B).

**CHALLENGE OF WAVE REFLECTIONS.** However, as discussed above, central ABP is seldom measured for monitoring. Moreover, unlike the central ABP waveform, the analysis of a readily available peripheral ABP waveform is complicated by wave reflection phenomena (85). That is, when the heart ejects blood, pressure and flow waves are initiated, which travel through the arterial tree. Whenever the waves reach a site of impedance mismatch, especially the high-resistance arteries (68, 77, 117), they are in part reflected back toward the heart. The pressure (or flow) at a given arterial site is thus equal to the sum (or difference) of the forward- and backward-traveling waves at that site (117). As a result, the ABP waveform becomes progressively distorted with increasing distance from...
the heart (see Fig. 4) (68). Most notably, PP and SP become more and more amplified, whereas exponential diastolic decays become less apparent. Furthermore, the magnitude and timing of wave reflections are not unvarying. For example, reflected waves, and thus PP and SP amplification, are augmented by vasoconstriction and blunted by vasodilation (117). Thus, a peripheral ABP waveform may not be well represented with the Windkessel model or other lumped parameter models, as these models ignore confounding wave reflections.

Consequently, the Windkessel and PP techniques do not produce the same results when applied to a peripheral ABP waveform. Even so, three PP- or Windkessel-based techniques are now commercially available for continuous and minimally invasive CO monitoring (30). These techniques have shown overall accuracies good enough for the FDA. But, the techniques have not proven reliable during hemodynamic instability (23, 49, 98), when monitoring is most needed, and can even predict increases in CO during progressive hypovolemia (see Fig. 5B) (14, 82). This wrong prediction occurs because the hypovolemia-induced vasoconstriction augments the wave reflections so as to buffer the decrease in peripheral PP via SV.

ANALYSIS OF OTHER BP WAVEFORMS. A few teams have applied techniques designed for ABP waveforms to the pulmonary artery pressure (PAP) waveform to try to improve CO estimation reliability (but at the cost of increased invasiveness) (22, 32, 111, 126, 127). Bennett and coworkers (50) have more recently tailored one of these techniques to the RVP waveform to track CO with their implantable RVP monitor for heart failure patients (63, 80). However, these PAP and RVP waveform analysis techniques may not yield greater accuracy (22, 111), as the waveforms are similarly confounded by wave reflections in addition to inertial effects in the low-resistance pulmonary circulation [see, e.g., complex PAP diastolic decays in Fig. 2 (111)].

LESSONS LEARNED. Much has been gained from the earlier studies on CO monitoring by BP waveform analysis (often called “pulse contour analysis”). For example, two important insights can be drawn from the studies of Bourgeois et al. (16, 17).

First, these studies demonstrate that, from the perspective of the aorta, the arterial tree can be regarded simply as a single reservoir (or Windkessel) rather than spatially dispersed, infinitesimal reservoirs of different pressures. Indeed, the long and varying distances between the aorta and the main reflection sites at the high-resistance arteries result in forward and backward waves in the aorta with large phasic differences (77). So, waves with relatively short wavelengths, which correspond to high-frequency ABP changes, destructively interfere so as to lessen their buildup in the aorta. On the other hand, waves with longer wavelengths, which correspond to low-frequency ABP changes, constructively add and are felt by the aorta. The key point is that, as the wavelengths of the propagating waves increase, the pressures at
the various arterial sites converge to the same level such that the arterial tree behaves more like a single reservoir (77). [Note that this point also implies that low-frequency ABP variability can be well represented with the Windkessel model regardless of the measurement site (73, 77, 87, 88).]

Second, the studies indicate that AC is approximately constant. Indeed, AC is mainly due to the aorta, which is relatively sparse in smooth muscle (19, 69). So, changes in vasomotor tone should only have a small effect on AC. Furthermore, AC is not very sensitive to ABP changes, as wave travel delay
time, which is determined by AC, varies only modestly with large ABP changes (86). Thus, the well-known inverse relationship between AC and ABP (41) may only become a major factor during extreme ABP perturbations. However, AC does significantly decrease with aging (41). Consequently, and more precisely, AC is approximately constant over a wide ABP range and on the time scale of months to years. Nevertheless, correcting CO estimates for AC change would be useful, particularly at the limits of the ABP range. Wesseling and colleagues have developed an accurate curve relating AC to ABP (57) and have applied it for ABP-dependent calibration of their Windkessel-based CO-monitoring technique (115).

**LAP monitoring by BP waveform analysis.** Far fewer techniques have been introduced for estimating LAP from BP waveforms. Over half a century ago, Cournand (24) helped establish the classic technique of monitoring LAP through end-diastolic PAP (42) that is sometimes used in clinical practice (66). Bennett and coworkers (21, 79, 92) recently showed that end-diastolic PAP may be well estimated from the value of RVP at the time of its maximal derivative and may therefore be tracked with their implantable RVP monitor. However, end-diastolic PAP is not as accurate as PCWP (47) and is contraindicated for following LAP during pulmonary hypertension (46, 66). Within the past two decades, researchers have proposed techniques to predict LAP from a BP waveform via formulas derived from a training data set of LVFP mea-

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**Fig. 4.** The ABP waveform becomes progressively distorted from the central aorta to the peripheral arteries due to wave reflections in the arterial tree. [Adapted from Ref. 68.]

**Fig. 5.** Recent technique for monitoring CO by analysis of a peripheral ABP waveform. A: estimation of relative CO change by circumventing the confounding wave reflections via long-time interval analysis. Here, the cardiac contraction signal \( x(t) \) and the peripheral ABP waveform segment \( P_p(t) \) are actually 1–6 min in duration. \( P_p \) and \( R_p \) are the pulse pressure and the onset time of ABP upstroke of the \( j \)th beat. \( h(t) \), impulse response. B: group-averaged human lower body negative pressure (LBNP) results (means ± 2SE). The CO estimates correctly decreased with LBNP, whereas classic \( (P_p \times HR) \) estimates of CO did not. [Adapted from Refs. 76 and unpublished observations of A. T. Reisner, D. Xu, K. L. Ryan, V. A. Convertino, C. A. Rickards, and R. Mukkamala.]
sures and BP waveforms. In particular, McIntyre and colleagues (70, 100) led the development of a technique to monitor LV end-diastolic pressure from the peripheral ABP response to a Valsalva maneuver. This technique is now available on the market with FDA clearance (27a). Marik and others (65, 125) formulated a technique to monitor PCWP from peripheral SP variations induced by mechanical ventilation. Most recently, deBoisblanc et al. (29) conceived a technique to predict PCWP from the PAP waveform specifically using a neural network. The former two techniques, which extract LVFP information from the induced intrathoracic pressure variations, provide an attractive minimally invasive or noninvasive means to sensitively monitor LAP but do require a hemodynamic perturbation. On the other hand, the latter, more invasive technique is continuous and may be more specific, as PAP is directly determined by LAP, whereas ABP is not. For all of these techniques, accuracy is reliant on the availability of comprehensive training data sets, which may be very difficult to obtain.

**EF monitoring based on BP waveform analysis.** Most of the earlier BP waveform analysis techniques do not explicitly model the ventricle and therefore cannot estimate EF. However, Guarini et al. (39) and Xiao et al. (121) have proposed techniques based on ABP waveform analysis that account for the LV and could be extended to monitor EF. These techniques specifically estimate the ventricular parameters needed for EF computation. However, the techniques also require a CO measurement for the estimation.

**Central ABP monitoring by peripheral ABP waveform analysis.** Starting with the work of O’Rourke and colleagues (53) over a decade and a half ago, there has been considerable interest in techniques for estimating the central ABP waveform from a peripheral ABP waveform. Nearly all of the techniques that have been introduced involve developing an average transfer function from simultaneous peripheral ABP and central ABP measurements in a group of subjects and then applying this transfer function to a peripheral ABP waveform measured from a new subject to estimate the central ABP waveform (e.g., Refs. 20, 35, 51, and 52). One such “generalized transfer function” technique is commercially available with FDA clearance (11a). While the accuracy of this technique has not been proven in a diverse patient population, it has been shown to determine some clinical outcomes better than the raw peripheral ABP waveform (120). Even so, the transfer function relating peripheral ABP to central ABP is not invariant, as wave reflection phenomena are known to change over time due to, e.g., neurohumoral modulation of TPR, and vary among subjects due to, e.g., age-related AC differences (see above). With this recognition, Sugimachi et al. (105) and Westerhof et al. (116) have recently proposed a technique to adapt the transfer function by defining it through an arterial tube model with a personalized value for a model parameter reflecting the wave travel delay time. However, the technique uses population averages for the remaining parameters.

**Overview of Our Recent BP Waveform Analysis Techniques**

The earlier studies have laid the foundation for further research in the field. In a series of recent investigations, we, along with our collaborators, have attempted to build on this seminal body of work by accounting for additional facets of physiology.

**CO monitoring by long-time interval analysis of a peripheral ABP waveform.** We (76) developed a technique for continuous and minimally invasive or noninvasive monitoring of CO by analysis of a peripheral ABP waveform. The idea is to circumvent the confounding arterial wave reflections by exploiting the fact that they diminish with decreasing frequency or increasing time scale (see above). Thus, the Windkessel model (see Fig. 3A) becomes a more valid representation of the arterial tree with longer time scales (73, 77, 87, 88). So, for example, if the heart suddenly stopped beating, then peripheral ABP would eventually decay like a pure exponential once the faster wave reflections vanished.

The technique therefore analyzes a peripheral ABP waveform over long time intervals to determine the pure exponential decay that would eventually result if the heart abruptly ceased to beat. More specifically, the ABP response to one heart beat is estimated from a 1- to 6-min segment of the waveform [see h(t) in Fig. 5A]. Then, τ is determined by fitting an exponential to the tail end of this single-contraction ABP response once the faster wave reflections have dissipated (see Fig. 5A). Finally, proportional CO is computed (see Fig. 5A).

**Steps.** The single-contraction ABP response is determined in two steps (see Fig. 5A). First, a cardiac contraction signal [s(t)] is constructed by forming an impulse train in which each impulse is located at the onset of upstroke of an ABP pulse and is scaled by the ensuing PP. An impulse response [h(t)] is then estimated, which, when convolved with s(t), optimally fits the ABP waveform [p(t)] segment. By definition, h(t) represents the (scaled) ABP response to one heart beat. In principle, reliable determination of τ is then achieved by virtue of h(t) accurately coupling the beat-to-beat variations in s(t) to p(t).

**Evaluation.** We evaluated this long-time interval analysis technique against independent CO measurements from swine and humans over a wide range of physiological conditions (44, 62, 75, 76). The overall relative CO error was ~15% after a single calibration in each subject. For comparison, the Windkessel technique (see Fig. 3B) yielded a corresponding error that was, on average, ~50% higher. We also assessed the technique as applied to a noninvasive peripheral ABP waveform from humans using lower body negative pressure (LBNP), a popular hemorrhage model (A. T. Reisner, D. Xu, K. L. Ryan, V. A. Convertino, C. A. Rickards, and R. Mukkamala; unpublished observations). We specifically tested the technique in terms of its ability to predict reductions in CO that occur with LBNP. For comparison, we likewise evaluated the PP technique, with thoracic bioimpedance (see Table 1) as a reference. Consistent with early bleeding, mean ABP was maintained, whereas the reference CO decreased, with increasing LBNP (see Fig. 5B). The CO estimates of our technique correctly decreased with escalating LBNP and then returned to baseline after recovery from LBNP (see Fig. 5B). In contrast, for the reasons mentioned above, the CO estimates of the classic technique erroneously increased during LBNP (see Fig. 5B).

**Limitations.** Unlike earlier techniques, this technique cannot detect rapid CO changes. The technique also does not account for any AC changes in its present form and, as with the Windkessel technique, would monitor total rather than forward flow during aortic regurgitation.
CO and LAP monitoring by long-time interval analysis of the PAP or RVP waveform. **IDEA.** We extended the preceding technique to PAP and RVP waveforms so as to monitor LAP in addition to CO and thereby potentially realize continuous monitoring with the pulmonary artery catheter and chronic monitoring with the aforesaid implantable device (122, 123). The ideas are to include a constant term in the analysis to account for the major contribution of LAP to PAP in the low-resistance pulmonary circulation and to invoke the fact that RVP is normally close to PAP during the ejection intervals.

**STEPS.** The extended PAP waveform analysis technique is performed in four steps (see Fig. 6A). First, a cardiac contractions signal \(x(t)\) is constructed from a PAP waveform segment \([p_{pa}(t)]\) as described above. An impulse response \([h(t)]\)

![Diagram A](https://www.ajpheart.org/)

Fig. 6. Recent extended techniques for monitoring CO and LAP by analysis of the PAP or RVP waveform. 
*A:* estimation of LAP in addition to the relative CO change from the PAP waveform by including a constant term in the long-time interval analysis, \(p_{pa}(t)\), the PAP waveform segment. 
*B:* estimation of the relative CO change and LAP from the RVP waveform by further invoking the fact that RVP is nearly equal to PAP during ejection intervals, \(p_{rv}(t)\), the RVP waveform segment; \(z(t)\), complete PAP waveform segment; \(t_{MPDj}\), the time of the maximal derivative of the \(j\)th RVP beat. 
*C:* exemplary canine results. [Adapted from Refs. 122 and 123.]
and an additive constant term are then estimated so as to optimally couple \(x(t)\) to \(p_{pr}(t)\). The constant term represents PAP attained in the absence of cardiac contractions and is thus indicative of average LAP, whereas \(h(t)\) represents the PAP-LAP response to a single heart beat. Next, the Windkessel time constant of the pulmonary arterial tree (\(\tau = PAR \times PAC\), where PAR is pulmonary arterial resistance and PAC is pulmonary artery compliance) is determined by fitting an exponential to the tail end of \(h(t)\) once the faster wave reflections and inertial effects vanish. Finally, since PAC may also be approximately constant over a wide PAP range (56, 101), proportional CO is computed by dividing mean PAP minus LAP with \(\tau\) and readily calibrated with a single thermodilution measurement. (This latter measurement can be made more accurate by averaging a number of carefully repeated measurements, which may be feasible for a one-time calibration in the ICU.)

The extended RVP waveform analysis technique is executed as follows (see Fig. 6B). First, each ejection interval of an RVP waveform segment \([p_{pa}(t)]\) is detected from the time of the maximal derivative (see above) to shortly after the peak value. The technique then proceeds similarly to the PAP waveform analysis technique with the formation of a cardiac contraction signal \([x(t)]\) and the subsequent estimation of average LAP (constant term) and the single-contraction PAP-LAP response [impulse response \(h(t)\)] by optimally coupling \(x(t)\) to only the detected ejection intervals of \(p_{pa}(t)\) (i.e., an incomplete PAP waveform segment specifically lacking diastolic intervals). Next, after \(\tau\) is determined from \(h(t)\), the complete PAP waveform segment \([z(t)]\) is constructed by adding average LAP to the convolution between \(x(t)\) and \(h(t)\). Finally, proportional CO is determined by dividing mean \(z(t)\) minus LAP with \(\tau\).

EVALUATION. We evaluated these extended long-time interval analysis techniques against gold standard aortic flow probe CO and LAP catheter measurements from dogs during drug and volume interventions (122, 123). The overall relative calibrated CO error and absolute LAP error from the PAP waveforms were 15.2\% and 1.7 mmHg, whereas the corresponding errors from the RVP waveforms were 16.0\% and 2.0 mmHg (excluding one outlier; see Fig. 6C). For comparison, classic end-diastolic PAP estimates resulted in LAP errors that were almost three times larger. These initial results suggest that continuous monitoring may be achieved with right ventricular catheterization rather than the more risky pulmonary artery catheterization.

LIMITATIONS. These techniques carry weaknesses similar to the initial long-time interval analysis technique. The extended techniques also do not account for intrathoracic pressure changes that are directly transmitted to PAP and the vascular waterfall effect (13, 40). Furthermore, the RVP waveform analysis technique is contraindicated during pulmonic valve disease.

EF monitoring by lumped parameter model-based analysis of the central ABP waveform. IDEA. We (106) developed a technique for the continuous monitoring of beat-to-beat EF (along with CO and beat-to-beat SV) by analysis of only the central ABP waveform. The idea is to extend the Windkessel technique (17) by modeling the LV so as to split a proportional SV estimate into likewise scaled end-systolic volume and EDV components. Absolute EF is then computed by cancellation of the common scale factor.

STEPS. The technique is performed in three steps. First, the entire central ABP waveform is represented with a lumped parameter model of the LV and arterial tree (see Fig. 7A). In particular, the LV is characterized by the well-known variable elastance (reciprocal of compliance) model in which the ventricular elastance (VE) oscillates over time \([E(t)]\) so as to drive blood flow and the ventricular unstressed volume (VUV) is nonzero (96, 104), the aortic valve is modeled with an ideal diode, and the arterial tree is embodied by the Windkessel model.

The lumped model parameters are then estimated to within AC scale factors from each beat of the central ABP waveform \([p_{pa}(t)]\) via the following discretized equation governing model behavior during the ejection interval:

\[
\frac{p_{pa}(t_{be})}{AC \times E(t_{be})} - \frac{p_{pa}(t)}{AC \times E(t)} = \frac{p_{pa}(t) - p_{pa}(t_{be})}{AC \times E(t)} + \frac{T}{2 \times T_{\text{be} - t_{ee}}} \sum_{k=t_{be}+1}^{t_{ee}} \left[ p_{pa}(k) + p_{pa}(k-1) \right], t_{be} \leq t \leq t_{ee},
\]

where \(T\) is the sampling period and \(t_{be}\) and \(t_{ee}\) are the beginning and end times of the ejection interval. Both \(T\) and \(p_{pa}(t)\) for \(t_{be} \leq t \leq t_{ee}\) are known, whereas the proportional model parameters, \(\tau = TPR \times AC\) and \(AC \times E(t)\) for \(t_{be} \leq t \leq t_{ee}\), are unknown. Thus, Eq. 1 represents a set of \(N\) equations with \(N + 2\) unknowns (where, e.g., \(N = 80\) for \(T = 4\) ms). To arrive at a set of equations with a unique solution, a parametric raised cosine function is used to succinctly characterize the variable VE as justified by previous studies (45, 99) [see \(E(t)\) in Fig. 7B]. Substituting this parametric function into Eq. 1 reduces the number of unknowns to \(\tau\), \(AC \times \text{maximum elastance (}E_{\text{max}}\text{)}\), \(AC \times E(t_{be})\), and \(T_{s}\) where \(T_{s}\) is the time duration to reach \(E_{\text{max}}\) from minimum elastance (see Fig. 7B). Initially, \(\tau\) is estimated by fitting an exponential to the diastolic interval of \(p_{pa}(t)\) (see Fig. 7B). This \(\tau\) is then substituted into Eq. 1, and the remaining three parameters are estimated from \(p_{pa}(t)\) over the ejection interval by optimally matching both sides of this equation.

Finally, \(AC \times E(t)\) for \(t_{be} \leq t \leq t_{ee}\) and \(p_{pa}(t)\) are used to compute beat-to-beat absolute EF (by cancellation of the AC scale factor) as well as beat-to-beat proportional SV (and thus proportional CO) via the following variable VE model equation:

\[
EF = \frac{SV}{EDV} = \frac{p_{pa}(t_{be})}{AC \times E(t_{be})} - \frac{p_{pa}(t_{ee})}{AC \times E(t_{ee})} + \frac{VUV}{AC}.
\]

Note that VUV/AC here is not estimated. Normally, however, this parameter is relatively small (28, 54) and may thus be neglected or set to a nominal value. Alternatively, especially for stiff, dilated hearts, VUV/AC may be periodically determined from imaging measurements of EF.

EVALUATION. We evaluated this lumped parameter model-based analysis technique against standard transthoracic echocardiography EF measurements from dogs during drug and volume interventions (106). The overall uncalibrated absolute EF error was 5.6\%. Furthermore, unlike the refer-
ence measurements, these estimates offer continuous monitoring (see Fig. 7).

LIMITATIONS. This technique ignores the arterial characteristic impedance, which may be important for fitting the ejection interval (77). The technique as described is also contraindicated during aortic valve disease. More significantly, the central ABP waveform is rarely available.

Central ABP monitoring by analysis of multiple peripheral ABP waveforms via adaptive multichannel blind system identification. IDEA. We (107, 108) developed a technique for minimally invasive or noninvasive monitoring of the central ABP waveform by analysis of multiple peripheral ABP waveforms. The idea is to derive central ABP in a fully adaptive manner by finding the commonality in two or more peripheral ABP waveforms via multichannel blind system identification (1).

STEPS. The technique is executed as follows. First, $m$ peripheral ABP waveforms $[p_{pi}(t), 1 \leq i \leq m]$ are modeled as outputs of $m$ unknown systems driven by the common unknown central ABP waveform $[p_{c}(t)]$ input (see Fig. 8A). Each of the systems relating the common input to the distinct outputs characterizes wave reflection phenomena in different arterial paths. These systems are represented with finite impulse responses $[h_i(t), 1 \leq i \leq m]$ that are different from each other (or, more precisely, coprime) (124). In this way, all of the similarity in the outputs may be attributed to only the input. Then, $h_i(t)$ ($1 \leq i \leq m$) values are estimated from $p_{pi}(t)$ ($1 \leq i \leq m$) by optimally matching the cross relations [e.g., $p_{pi1}(t) \otimes h_2(t) = p_{pi2}(t) \otimes h_1(t)$ for $m = 2$, where $\otimes$ is convolution] (124). Note that the scale factor of $h_i(t)$ ($1 \leq i \leq m$) is determined by invoking the fact that mean ABP is similar throughout the arterial tree due to Poiseuille’s law (66, 77, 81). Finally, $p_{c}(t)$ is determined by optimally deconvolving the estimated $h_i(t)$ ($1 \leq i \leq m$) from $p_{pi}(t)$ ($1 \leq i \leq m$) (1).

EVALUATION. We (108) evaluated this adaptive multichannel blind system identification technique as applied to two peripheral ABP waveforms from the radial and femoral arteries against central ABP catheter measurements from swine during several interventions. The overall absolute central ABP sample-to-sample and PP errors were 3.5 and 5.6 mmHg (see Fig. 8B). For comparison, the corresponding errors between the raw peripheral ABP waveforms and time-aligned central ABP waveforms were, on average, 8.6 and 14.3 mmHg (see Fig. 8B).

ADDITIONAL IDEA. The preceding lumped parameter model-based analysis technique may then be applied to the derived central ABP waveform, which is less complicated by wave reflections than peripheral ABP waveforms (see Fig. 9A). The
idea is to attenuate (rather than circumvent) the confounding wave reflections so as to estimate beat-to-beat EF and proportional SV in addition to proportional CO.

**EVALUATION.** We (108) evaluated the preceding technique as applied to the aforesaid derived central ABP waveforms against gold standard aortic flow probe SV measurements. The overall relative calibrated beat-to-beat SV error was 12.9% (see Fig. 9B).

**LIMITATIONS.** The main concern for this technique is that any wave reflection dynamics shared by the different arterial paths will be erroneously attributed to the central ABP waveform. In addition, only one peripheral ABP waveform is commonly measured in clinical practice.

**Central ABP monitoring by analysis of one peripheral ABP waveform via an adaptive transfer function.** IDEA. We (109) developed another technique for minimally invasive or noninvasive monitoring of the central ABP waveform, but this time by analysis of one peripheral ABP waveform. The idea is to derive central ABP in a fully adaptive manner by defining the transfer function relating peripheral ABP to central ABP through a distributed model of arterial pressure and flow to account for the confounding wave reflections (105, 116) and then estimating all model parameters by exploiting the pre-knowledge of aortic flow.

**STEPS.** The technique is implemented as follows. First, the arterial tree is modeled as \( m \) parallel, uniform tubes terminated by lumped parameter loads (see Fig. 10A). The \( i \)th tube represents the path between the aorta and the \( i \)th peripheral artery. Consistent with Poiseuille’s law, each tube is frictionless and thus has constant characteristic impedance \( Z_{ci} = \sqrt{\frac{l_i}{c_i}} \), where \( l_i \) and \( c_i \) are the large artery inertance and compliance and allows waves to travel with constant time delay \( T_{di} = \sqrt{\frac{l_i}{c_i}} \). The \( i \)th terminal load represents the arterial bed distal to the \( i \)th peripheral artery. Each terminal load has a frequency-dependent impedance \( Z_i(\omega) \) characterized by two parameters that are dependent on the peripheral resistance and compliance (\( A_i \) and \( B_i \) and \( Z_{ci} \) (105, 116). Waves traveling along each tube are reflected at the terminal load in a frequency-dependent manner so as to mimic the progressive distortion that actual arterial pressure and flow waveforms undergo with increasing distance from the heart (see Fig. 4).

According to this model, a peripheral ABP waveform \( p_{pi}(t) \) is related to the central ABP waveform \( p_{ca}(t) \) through a transfer function in terms of \( T_{di} \), \( A_i \), and \( B_i \) (see the pressure → pressure transfer function in Fig. 10B). These three unknown parameters are estimated as follows.

First, the wave travel delay time \( T_{di} \) is first measured noninvasively via any of the known methods (see, e.g., Refs. 105 and 116). Only one such measurement is made for a subject over a period of months to years, as \( T_{di} \) may not greatly vary over this time period (see above).

All three parameters are then estimated from a 15- to 60-s segment of \( p_{pi}(t) \) and the initial \( T_{di} \) value by exploiting the fact that aortic flow is negligible during diastole. Thus, the flow at each tube entrance in the model (central arterial flow) may likewise be small during this time interval (as indicated in Fig.
In particular, according to this model, \( p_{\text{ppi}}(t) \) is related to the central arterial flow waveform \( q_{\text{a}}(t) \) through a transfer function also in terms of \( T_{\text{di}}, A_i, \) and \( B_i \) (see the pressure–flow transfer function in Fig. 10B). These common parameters are estimated by finding the pressure–flow transfer function that, when applied to \( p_{\text{ppi}}(t) \), optimally fits \( q_{\text{a}}(t) \) (scaled by \( Z_{ci} \)) to zero over its diastolic intervals [as approximated via heart rate (64); see Fig. 10B].

Finally, the estimated parameters are substituted into the pressure–pressure transfer function. This transfer function is then applied to \( p_{\text{ppi}}(t) \) so as to derive \( p_{\text{pa}}(t) \).

**Evaluation.** We (109) evaluated this adaptive transfer function technique against central ABP catheter measurements from dogs during various interventions. The overall absolute central ABP sample-to-sample and PP errors were 3.7 and 3.4 mmHg, whereas the parallel errors of the time-aligned peripheral ABP waveforms were 8.6 and 20.3 mmHg (see Fig. 10C). For comparison, the analogous errors of totally or partially generalized transfer function techniques (35, 105, 116) were, on average, 63% higher than the technique (see Fig. 10C), even though they had the advantage of being developed with a subset of the reference central ABP waveforms.

**Limitations.** This technique disregards wave reflections caused by arterial tapering, stiffening, and branching. The technique is also contraindicated during aortic regurgitation.

**Conclusions**

**Summary.** BP waveform analysis provides a practical approach for achieving the much-needed continuous and less invasive monitoring of vital central hemodynamic variables. As a result, investigation of this approach has been longstanding. Various techniques for estimating CO, LAP, or central ABP from more readily available ABP, PAP, or RVP waveforms were developed earlier. Some of these techniques are now commercially available with FDA clearance. However, the techniques generally neglect key facets of physiology, which has left room for further research. These efforts allowed us to recently conceive ideas to (1) overcome the challenge of wave reflections by circumventing their confounding effects (via long-time interval analysis) or attenuating these effects upfront, (2) estimate LAP without training data by identifying PAP attained in the absence of cardiac contractions, (3) derive EF by modeling the LV, and (4) estimate central ABP in a fully adaptive manner by exploiting the commonality in multiple peripheral ABP waveforms or preknowledge of aortic flow.

**Future directions.** Although much progress has been made in the field, future investigations are warranted. First, there will always be a need for the development of more accurate and simpler techniques. Such development efforts could, for example, help overcome the limitations of our work revealed herein. In this regard, we believe that the development of an effective and convenient AC correction factor for CO estimation is particularly worthwhile. We also advocate subsequent focus on realizing minimally invasive or noninvasive monitoring of specific markers of LVFP and extending the analysis to even more readily available pulse oximeter waveforms. Second, compelling verification of both existing and new techniques is a must for widespread clinical adoption. Such validation efforts should show that the techniques are generally accurate enough, which means that they should yield overall errors that are within the 10–15% relative and absolute errors of thermodilution and transathoracic echocardiography measurements (11, 18, 26, 38, 48, 103), the 1- to 2-mmHg error of valid PCWP measurements (47, 58), and the 5 ± 8-mmHg FDA limits for ABP measurement (78) in a broad patient population. The validation should also indicate that the techniques do not have critical failure modes such as hemodynamic instability.
Furthermore, demonstrations that the techniques, when coupled with defined therapeutic protocols, can improve patient outcomes would be of tremendous value.

Potential applications. Established BP waveform analysis techniques have a number of potential clinical applications. First and foremost, the techniques could be readily used in the ICU and other settings where invasive catheters are broadly in use. The continuous and/or less invasive central hemodynamic monitoring capabilities of the techniques would offer several advantages over the methods that have been used in these settings. These advantages include 1) reducing patient risk, 2) avoiding the technical problems associated with the implementation of PCWP and thermodilution methods, 3) saving precious time in the busy clinical environment, 4) obtaining an early indication of a hemodynamic event, 5) guiding therapy more effectively, and 6) permitting remote monitoring. In addition, the techniques could be used, for example, with noninvasive systems for 1) early detection of circulatory shock in patients entering the emergency room and during transport of combat and civilian trauma casualties, 2) identification of patients who become unstable during convalescence, 3) risk stratification of outpatients, and 4) home healthcare; the techniques could also be used in implantable devices for chronic heart failure management.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
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Review


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