Continuous cardiac output monitoring in humans by invasive and noninvasive peripheral blood pressure waveform analysis

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Lu, Zhenwei, and Ramakrishna Mukkamala. Continuous cardiac output monitoring in humans by invasive and noninvasive peripheral blood pressure waveform analysis. J Appl Physiol 101: 598–608, 2006; doi:10.1152/japplphysiol.01488.2005.—We present an evaluation of a novel technique for continuous (i.e., automatic) monitoring of relative cardiac output (CO) changes by long time interval analysis of a peripheral arterial blood pressure (ABP) waveform in humans. We specifically tested the mathematical analysis technique based on existing invasive and noninvasive hemodynamic data sets. With the former data set, we compared the application of the technique to peripheral ABP waveforms obtained via radial artery catheterization with simultaneous thermodilution CO measurements in 15 intensive care unit patients in which CO was changing because of disease progression and therapy. With the latter data set, we compared the application of the technique to noninvasive peripheral ABP waveforms obtained via a finger-cuff photoplethysmography system with simultaneous Doppler ultrasound CO measurements made by an expert in 10 healthy subjects during pharmacological and postural interventions. We report an overall CO root-mean-squared normalized error of 15.3% with respect to the invasive hemodynamic data set and 15.1% with respect to the noninvasive hemodynamic data set. Moreover, the CO errors from the invasive and noninvasive hemodynamic data sets were only mildly correlated with mean ABP (ρ = 0.41, 0.37) and even less correlated with CO (ρ = −0.14, −0.17), heart rate (ρ = 0.04, 0.19), total peripheral resistance (ρ = 0.38, 0.10), CO changes (ρ = −0.26, −0.20), and absolute CO changes (ρ = 0.03, 0.38). With further development and successful prospective testing, the technique may potentially be employed for continuous hemodynamic monitoring in the acute setting such as critical care and emergency care.

Doppler ultrasound; Finapres; pulse contour analysis; radial artery catheterization; thermodilution

THE STANDARD CLINICAL METHOD for measuring cardiac output (CO) is currently thermodilution. After insertion of a pulmonary artery catheter, this method involves injecting a bolus of cold saline in the right atrium, measuring temperature downstream in the pulmonary artery, and computing the average CO on the basis of conservation laws (9). Because an operator is required to administer the bolus injection, thermodilution measurements may only be obtained intermittently. However, perhaps a more significant shortcoming of thermodilution is that its high level of invasiveness limits its use to only a minority (e.g., 10–20%) of all critically ill patients (32). In fact, thermodilution usage may decline to even lower levels because of recent reports indicating that the invasive pulmonary artery catheter may not improve patient outcome (e.g., Ref. 35). Thus the need for a less invasive CO monitoring method may become even more urgent in the future. Although Doppler ultrasound and transthoracic bioimpedance have been introduced as noninvasive CO monitoring methods, neither of them has been able to replace thermodilution. Doppler ultrasound methods, which measure the Doppler shift in the frequency of an ultrasound beam reflected from the flowing aortic blood (9), require an expert operator to stabilize an external ultrasound transducer as well as expensive capital equipment (19). Transthoracic bioimpedance, which involves measuring changes in the electrical impedance of the thorax during the cardiac cycle (9, 19), may not be sufficiently accurate, especially in critically ill patients who often have excessive lung fluids (7).

On the other hand, peripheral arterial blood pressure (ABP), which is related to CO through the arterial tree, may be measured reliably and continuously via radial artery catheterization, which is less invasive than pulmonary artery catheterization. Indeed, this relatively safe procedure is performed in a majority (e.g., 50–80%) of all critically ill patients (33). Moreover, over the past few decades, totally noninvasive methods have been developed and refined to continuously measure peripheral ABP on the basis of finger-cuff photoplethysmography (16) and arterial tonometry (17). These noninvasive methods are even available as commercial systems at present (see, for example, the Finometer and Portapres, Finapres Medical Systems, The Netherlands and the T-Line Blood Pressure Monitoring System, Tensys Medical, San Diego, CA).

Beginning with the seminal work of Frank in 1899 (13) and Erlanger and Hooker in 1904 (12), numerous cardiovascular researchers have sought analysis techniques to compute CO to within a constant scale factor from the contour of ABP waveforms so as to permit continuous (i.e., automatic and without the need for an operator), quantitative measurements of relative changes in CO and expand the clinical monitoring of CO. (Note that some researchers have also sought to calibrate the proportional CO estimates via empirical formula.) Although a wide variety of “pulse contour analysis” techniques have been proposed, they are all conceptually the same to the extent that the waveform analysis is performed only over time scales within a cardiac cycle (e.g., see Fig. 1) (26). However, over such short time scales, peripheral ABP waveforms are domi-
nated by highly complex waves propagating back and forth in the distributed arterial tree (28). Thus the previous analysis techniques have generally proven to be too inaccurate (in terms of estimating proportional CO) for clinical use.

Our ongoing hypothesis is that proportional CO may be more accurately monitored from all ABP variations, especially those occurring over time scales greater than a cardiac cycle. This novel hypothesis originates from transmission line theory, which predicts that the confounding effects of wave phenomena will diminish with increasing time scale (28). We have recently developed a technique that exploits this hypothesis to quantitatively monitor relative changes in CO by mathematically analyzing a single peripheral ABP waveform over long time intervals (about 6 min) (26). We have previously tested the technique in a set of acute swine experiments, and our CO estimates showed strong agreement with gold standard aortic flow probe CO measurements over a wide physiological range (26).

In this paper, we present an evaluation of the technique in humans based on previously published invasive and noninvasive hemodynamic data sets (10, 24, 25, 27). With these data, we were specifically able to compare the application of the technique to 1) invasive peripheral ABP waveforms obtained via radial artery catheterization with reference thermodilution measurements in 15 intensive care unit (ICU) patients in which CO was changing because of disease progression and therapy, and 2) noninvasive peripheral ABP waveforms obtained via a commercial finger-cuff photoplethysmography system with reference Doppler ultrasound measurements made by an expert in 10 healthy subjects in which CO was altered through pharmacological and postural interventions.

METHODS

Mathematical Analysis Technique

Our technique for monitoring relative CO changes by mathematically analyzing a peripheral ABP waveform was introduced in Ref. 26 and is described in detail therein. Here, we review the background, underlying concepts, and implementation of the technique from a physiological perspective while including its mathematical steps.

Background and underlying concepts. The technique that we have developed builds on the previous pulse contour analysis work of Bourgeois et al. (6) as well as Osborn et al. (31). These investigators assumed that the arterial tree could be well represented by a two-element windkessel model accounting for the lumped compliance of the large arteries (arterial compliance, AC) and the total peripheral resistance (TPR) of the small arteries (see electrical analog in Fig. 1). They further assumed that TPR does not vary within a diastolic interval [as justified by the relatively slow local and autonomic nervous mechanisms responsible for modulating TPR (3, 14)] and that AC is approximately constant over a wide pressure range and on the time scale of days to months (see experimental evidence in Refs. 5, 6, 15, 26, 31, and DISCUSSION). On the basis of these assumptions, these investigators predicted that ABP should decay like a pure exponential during each diastolic interval with a time constant equal to the product of TPR and AC (windkessel time constant, \(\tau\)). Thus their pulse contour analysis involved first fitting a monoeponential function to each diastolic ABP interval to measure \(\tau\) and then dividing the time-averaged ABP (MAP) with \(\tau\) to estimate proportional CO. Figure from Ref. 26; © 2006 IEEE.

This pulse contour analysis proved to be successful when applied to ABP waveforms measured centrally in the aorta, because the diastolic interval of these waveforms can resemble an exponential decay after incisura (see Fig. 2). However, central ABP is rarely measured clinically because of the risk of blood clot formation and embolization. Moreover, in readily available peripheral ABP waveforms, an exponential diastolic decay is usually not apparent (see Fig. 2). Indeed, it is well known that the contour of the arterial pulse changes significantly as it traverses through the arterial tree (30). The reason is that the arterial tree is not simply a lumped system as the windkessel model suggests, but rather a complicated distributed system with impedance mismatches throughout due to vessel tapering, bifurcations, and caliber changes. Thus the diastolic (and systolic) intervals of peripheral ABP waveforms are corrupted by complex wave reflections that occur at each and every site of impedance mismatch. [Note that the complexity of these sites and their varying distances from the aorta result in reflected waves with large phasic differences, which can tend to mitigate the cumulative effects of these waves on the central ABP waveform, i.e., destructive interference (28).] The above pulse contour analysis therefore cannot be applied to readily measured peripheral ABP waveforms.

According to transmission line theory, however, the confounding effects of wave phenomena will diminish with increasing time scale. That is, the wave effects significantly obscure peripheral ABP waveforms over short time scales (high frequencies) without complicating the waveform over longer time scales (low frequencies). For example, consider the limiting case in which the time scale is sufficiently long such that the wavelengths of the propagating waves are much larger than the dimension of the arterial tree. At such time scales, the arterial tree acts as a single blood reservoir, and the windkessel model is therefore valid. So, for example, if pulsatile activity abruptly ceased, then peripheral ABP may eventually decay like a pure exponential as soon as the faster wave reflections vanish. This concept is demonstrated in Fig. 2, which illustrates two ABP waveforms measured at the same time but at different sites in the arterial tree. The short time scale or within-beat variations are different in the two ABP waveforms (Fig. 2, A and B, top, inset), as the characteristics of the highly complex wave effects differ at the two measurement sites. In contrast,
the long time scale or beat-to-beat variations are much more similar (Fig. 2, A and B, bottom), as the confounding effects of wave phenomena are less significant over these time scales. This implies that, if pulsatile activity were to abruptly cease, then peripheral ABP would eventually decay like a pure exponential (according to the time constant $\tau$ of the windkessel model of Fig. 1) once the faster wave effects vanished. Figure from Ref. 26; © 2006 IEEE.

Implementation steps. Our technique therefore mathematically analyzes a digitized peripheral ABP waveform over long time intervals (~6 min) to determine the pure exponential decay that would eventually result if pulsatile activity abruptly ceased. More specifically, the ABP response to a single, solitary cardiac contraction $[h(t)]$ in Fig. 3] is estimated from the ABP waveform. Then, the windkessel time constant $\tau$ is determined by fitting a monoexponential function to the tail end of this response once the faster wave reflections have vanished (Fig. 3). Finally, proportional CO is computed via Ohm’s law. Figure 3 illustrates the technique, which is specifically implemented in four steps as follows.

First, a signal representing the cardiac contractions $[x(t)]$ is constructed from the ABP waveform on the basis of a slightly modified impulse ejection model. That is, $x(t)$ is formed as an impulse train in which each impulse is located at the onset of upstroke of an ABP pulse (resulting from a normal or ectopic beat) and has an area equal to the ensuing pulse pressure (PP; maximum ABP value minus the ABP value at the onset of upstroke) determined after low-pass filtering the ABP waveform (with a cutoff frequency of 2 Hz) to attenuate corruption due to high-frequency wave phenomena in the waveform (filtered PP).

Then, the impulse response function $[h(t)]$ is estimated that, when convolved with $x(t)$, best fits the (unfiltered) ABP waveform $[y(t)]$ in the least squares sense. [Note that, whereas ~6-min intervals of $x(t)$ and $y(t)$ are utilized to estimate $h(t)$, only a few seconds of $x(t)$ and $y(t)$ are shown in Fig. 3 for the purpose of clarity.] By definition, the estimated $h(t)$ represents the (scaled) ABP response to a single, solitary cardiac contraction. The impulse response function is specifically estimated according to the following autoregressive exogenous input equation:

$$y(t) = \sum_{k=1}^{m} a_k y(t-k) + \sum_{k=1}^{m} b_k x(t-k) + e(t)$$  \hspace{1cm} (I)
CARDIAC OUTPUT MONITORING BY BLOOD PRESSURE ANALYSIS

where \( e(t) \) is the unmeasured residual error, \( a_k, b_k \) are unknown parameters, and \( m \) and \( n \) limit the number of these parameters (model order) \( 21 \). For a fixed model order, the parameters are estimated from \( x(t) \) and \( y(t) \) through the least squares minimization of the residual error, which has a closed-form solution \( 21 \). The model order is determined by minimizing the minimum description length (MDL) criterion, which penalizes for unnecessary parameters \( 21 \). [For the invasive hemodynamic data set below in which \( x(t) \) and \( y(t) \) were sampled at 90 Hz, the minimum MDL value was specifically identified over the model orders ranging from \( m = n = 1 \) to \( m = n = 15 \), with the final selected model order typically being no less than \( m = n = 12 \). For the noninvasive hemodynamic data set below in which \( x(t) \) and \( y(t) \) were sampled at 50 Hz, the minimum MDL value was identified over the model orders ranging from \( m = n = 1 \) to \( m = n = 10 \), with the final selected model order generally being no less than \( m = n = 8 \). These model order ranges were established on the basis of our previous swine study \( 26 \).] With the estimated parameters \( \{a_k, b_k\} \), \( h(t) \) is computed as follows:

\[
   h(t) = \sum_{k=1}^{m} b_k \delta(t-k) + \sum_{k=1}^{n} a_k h(t-k)
\]

where \( \delta(t) \) is the unit impulse function.

Next, \( \tau \) is determined over the interval of \( h(t) \) ranging from 2 to 4 s after the time of its maximum value on the basis of the following exponential equation:

\[
   h(t) = Ae^{-t/\tau} + w(t)
\]

That is, the technique is not just trivially extrapolating the ABP waveform at the end of diastole.

Finally, CO is computed to within a constant scale factor equal to \( 1/AC \) by dividing the time-averaged ABP with \( \tau \). Note that the above mathematical steps can easily be implemented in near real time with only a delay on order of a few seconds with a standard home personal computer.

Invasive Human Hemodynamic Data Set

The hemodynamic data utilized to evaluate the mathematical analysis technique with respect to human invasive peripheral ABP waveforms were obtained from the MIMIC (Multiple-parameter Intelligent Monitoring for Intensive Care) database, which is described in detail elsewhere and freely available on the web \( 23-25 \). Briefly, this database includes 72 ICU patient records, typically ranging from 24 to 48 h in duration, that were archived from patient monitors in the medical, surgical, and cardiac intensive care units of the hospital formerly known as the Beth Israel Hospital, Boston, MA. Each of these records consists of continuous waveforms sampled at 125 Hz, such as invasive peripheral ABP via radial artery catheterization and surface ECG leads, as well as 1-min trends, such as thermodilution CO, mean ABP (MAP), and heart rate (HR). Sixteen of the 72 patient records were applicable to the present evaluation study, as they included \( J \) radial ABP waveforms, and \( 2 \) more than one reference thermodilution CO measurement. Within each of these records, CO was changing because of disease progression and therapy.

On the basis of these 16 MIMIC patient records, we created a data set for technique evaluation as follows. First, we downloaded from these records all of the distinct, 1-min thermodilution CO measurements and 6-min contiguous segments of the corresponding radial ABP waveforms (from 2.5 min preceding the 1-min CO measurements to 2.5 min after these measurements). Then, we visually examined each of the radial ABP waveforms and extracted the longest contiguous, artifact-free segment from each of these waveforms (see DISCUSSION). Finally, we excluded from the study all radial ABP waveforms that were less than 5 min in duration, had a significant

![Fig. 3. Our technique for monitoring CO from a peripheral ABP waveform \( 26 \). The measured ABP waveform \( y(t) \) is analyzed over long time intervals \( (6\text{-min}) \) so as to mathematically estimate the ABP response to a single cardiac contraction \( h(t) \). [Note that, although \( 6\text{-min} \) intervals of \( y(t) \) are utilized to estimate \( h(t) \), only a few seconds of \( y(t) \) are illustrated for the purpose of clarity.] Then, the time constant \( \tau \) of the windkessel model of Fig. 1 is determined by fitting a monoeponential function to the tail end of \( h(t) \) once the faster wave reflections have vanished. Finally, proportional CO is computed by dividing the time-averaged ABP \( \langle y(t) \rangle \) with \( \tau \). In principle, \( \tau \) is accurately determined by analysis of the subtle, beat-to-beat ABP variations in which the complex wave effects cease to be a significant factor (see Fig. 2). PP, pulse pressure; FPP, PP determined after low-pass filtering \( y(t) \); R, onset time of upstroke of each ABP pulse; \( j \), beat number; \( x(t) \), a constructed cardiac contractions signal corresponding to the \( 6\text{-min} \) interval of \( y(t) \); and \( h(t) \), an estimated impulse response coupling \( x(t) \) to \( y(t) \). Figure adapted from Ref. 26; \( \odot 2006 \) IEEE.](image131x519 to 491x721)
linear trend (≥20 mmHg change), or represented the only waveform segment within a patient record (because the technique estimates changes in CO). Note that radial ABP waveforms with significant linear trends were removed from the study, because the corresponding thermodilution measurements, which strictly represent average CO over intervals of typically less than 1 min, are unlikely to provide an adequate reference CO to the entire 5- to 6-min period of unsteady ABP. A total of 101 pairs of simultaneous measurements of artifact-free, invasive radial ABP waveforms and reference thermodilution CO values from 15 ICU patients [10 men and 5 women; age: 67 ± 12 yr (mean ± SD)] remained for technique evaluation. Table 1 summarizes the clinical class and hemodynamic data for each of these patients.

Noninvasive Human Hemodynamic Data Set

The hemodynamic data utilized to evaluate the mathematical analysis technique with respect to human noninvasive peripheral ABP waveforms were obtained from previous experiments designed to address different specific aims and are described in detail elsewhere (10, 27). Here, we briefly describe those aspects of the experiments that are relevant to the present study.

Ten healthy human volunteers [5 men and 5 women, age: 25 ± 4 yr (mean ± SD)] participated in the experiments. Each subject was instrumented for noninvasive measurement of a peripheral ABP waveform, instantaneous CO, and other cardiorespiratory signals. The peripheral ABP waveform was measured with a commercial finger-cuff photoplethysmography system (2300 Finapres continuous blood pressure monitor, Ohmeda; Englewood, CO), and instantaneous CO was measured according to a previously described Doppler ultrasound technique (11) implemented by an expert. Specifically, aortic blood velocity was measured with a bidirectional ultrasound Doppler velocimeter (CFM 750, GE Vingmed; Horten, Norway), which was operated in pulsed mode at 2 MHz with the hand-held transducer...
Cardiac output (CO) root-mean-squared normalized error (RMSNE) of 15.3% with respect to reference thermodilution measurements. MAP, mean arterial blood pressure.

Corresponding supine data, the overall results reported below would have the same mean value as the corresponding reference CO within each patient or subject. Then, we pooled the data together from all the patients or subjects in each data set and performed Bland-Altman analysis to comprehensively visualize the CO error (difference between calibrated CO estimate and reference CO value normalized by the reference CO value and given in percent), including its bias ($\mu$) and precision ($\sigma$) (4). We also computed the CO root-mean-squared normalized error (RMSNE = $\sqrt{\mu^2 + \sigma^2}$) as a scalar metric indicating artifact-free, noninvasive finger ABP waveforms and reference Doppler ultrasound CO values from 10 healthy subjects remained for technique evaluation. Table 2 summarizes the hemodynamic data for each of the subjects.

### Statistical Analysis

After applying the mathematical analysis technique to all of the invasive and noninvasive peripheral ABP waveforms in the two human data sets, we quantitatively compared the resulting, proportional CO estimates with their reference, absolute CO values in each data set as follows.

On the basis of these noninvasive recordings, we created a data set for technique evaluation as follows. First, we visually examined each noninvasive finger ABP waveform and instantaneous CO waveform and extracted the longest contiguous, artifact-free segment from each waveform. Then we excluded from the study all instantaneous CO waveforms that were less than 1 min in duration and all finger ABP waveforms that were less than 5 min in duration or had unreasonably high-pressure values (see DISCUSSION).

### Table 1. Summary of the intensive care unit patient records and results of the invasive human hemodynamic data set

<table>
<thead>
<tr>
<th>Patient Record</th>
<th>Clinical Class</th>
<th>Number of Comparisons</th>
<th>CO Range, l/min</th>
<th>MAP Range, mmHg</th>
<th>TPR Range, PRU</th>
<th>HR Range, beats/min</th>
<th>CO RMSNE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>041</td>
<td>Bleed</td>
<td>2</td>
<td>8.5–9.5</td>
<td>74–81</td>
<td>0.5–0.6</td>
<td>78–104</td>
<td>0.5</td>
</tr>
<tr>
<td>055</td>
<td>Respiratory failure</td>
<td>7</td>
<td>3.9–5.2</td>
<td>78–106</td>
<td>0.9–1.4</td>
<td>88–106</td>
<td>6.9</td>
</tr>
<tr>
<td>281</td>
<td>NA</td>
<td>4</td>
<td>3.7–4.9</td>
<td>94–99</td>
<td>1.2–1.6</td>
<td>100–114</td>
<td>6.8</td>
</tr>
<tr>
<td>410</td>
<td>Sepsis</td>
<td>7</td>
<td>4.3–9.4</td>
<td>74–97</td>
<td>0.6–1.1</td>
<td>60–94</td>
<td>22.3</td>
</tr>
<tr>
<td>411</td>
<td>Respiratory failure</td>
<td>6</td>
<td>3.2–4.6</td>
<td>84–94</td>
<td>1.2–1.7</td>
<td>50–61</td>
<td>14.4</td>
</tr>
<tr>
<td>451</td>
<td>CHF</td>
<td>5</td>
<td>4.1–5.8</td>
<td>51–58</td>
<td>0.5–0.9</td>
<td>74–84</td>
<td>15.0</td>
</tr>
<tr>
<td>453</td>
<td>Post-op valve</td>
<td>12</td>
<td>3.4–4.8</td>
<td>60–79</td>
<td>0.9–1.3</td>
<td>50–89</td>
<td>10.7</td>
</tr>
<tr>
<td>454</td>
<td>Post-op valve</td>
<td>5</td>
<td>3.7–4.8</td>
<td>67–74</td>
<td>0.9–1.1</td>
<td>49–70</td>
<td>5.4</td>
</tr>
<tr>
<td>456</td>
<td>Post-op CABG</td>
<td>8</td>
<td>3.8–8.5</td>
<td>57–100</td>
<td>0.6–1.0</td>
<td>67–108</td>
<td>22.5</td>
</tr>
<tr>
<td>474</td>
<td>NA</td>
<td>5</td>
<td>3.8–4.4</td>
<td>72–79</td>
<td>1.1–1.2</td>
<td>86–94</td>
<td>15.6</td>
</tr>
<tr>
<td>476</td>
<td>Post-op CABG</td>
<td>6</td>
<td>4.2–4.6</td>
<td>58–71</td>
<td>0.8–0.9</td>
<td>90–105</td>
<td>11.2</td>
</tr>
<tr>
<td>477</td>
<td>Post-op CABG</td>
<td>6</td>
<td>4.5–6</td>
<td>54–75</td>
<td>0.6–0.8</td>
<td>79–111</td>
<td>10.6</td>
</tr>
<tr>
<td>480</td>
<td>Post-op CABG</td>
<td>6</td>
<td>5–6.7</td>
<td>63–75</td>
<td>0.6–0.8</td>
<td>85–112</td>
<td>11.1</td>
</tr>
<tr>
<td>484</td>
<td>NA</td>
<td>9</td>
<td>5.1–7.5</td>
<td>62–78</td>
<td>0.6–0.8</td>
<td>79–96</td>
<td>12.4</td>
</tr>
<tr>
<td>485</td>
<td>NA</td>
<td>13</td>
<td>2.9–4.7</td>
<td>60–87</td>
<td>1.0–1.8</td>
<td>94–126</td>
<td>23.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>101</td>
<td>2.9–9.5</td>
<td>51–106</td>
<td>0.5–1.8</td>
<td>49–126</td>
<td>15.3</td>
</tr>
</tbody>
</table>

The technique of Fig. 3 as applied to 101 invasive radial arterial blood pressure waveform segments from 15 intensive care unit patients achieved an overall cardiac output (CO) root-mean-squared normalized error (RMSNE) of 15.3% with respect to reference thermodilution measurements. MAP, mean arterial blood pressure; TPR, total peripheral resistance; HR, heart rate; CHF, congestive heart failure; CABG, coronary artery bypass graft; NA, not available; Post-op, postoperative.

### Table 2. Summary of the healthy young adult records and results of the noninvasive human hemodynamic data set

<table>
<thead>
<tr>
<th>Subject Record</th>
<th>Number of Comparisons</th>
<th>CO Range, l/min</th>
<th>MAP Range, mmHg</th>
<th>TPR Range, PRU</th>
<th>HR Range, beats/min</th>
<th>CO RMSNE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD</td>
<td>5</td>
<td>3.6–6.8</td>
<td>82–128</td>
<td>1.0–1.9</td>
<td>43–108</td>
<td>13.0</td>
</tr>
<tr>
<td>WP</td>
<td>6</td>
<td>4.3–6.3</td>
<td>68–93</td>
<td>0.7–1.1</td>
<td>60–113</td>
<td>16.9</td>
</tr>
<tr>
<td>CG</td>
<td>6</td>
<td>4.5–7.7</td>
<td>75–118</td>
<td>0.9–1.3</td>
<td>48–98</td>
<td>20.2</td>
</tr>
<tr>
<td>JE</td>
<td>6</td>
<td>4.5–8.2</td>
<td>85–125</td>
<td>0.9–1.4</td>
<td>51–135</td>
<td>14.6</td>
</tr>
<tr>
<td>AE</td>
<td>6</td>
<td>3.5–5.3</td>
<td>79–124</td>
<td>1.2–1.5</td>
<td>32–72</td>
<td>18.3</td>
</tr>
<tr>
<td>DL</td>
<td>4</td>
<td>3.5–4.7</td>
<td>92–104</td>
<td>1.2–1.9</td>
<td>60–88</td>
<td>14.8</td>
</tr>
<tr>
<td>GB</td>
<td>6</td>
<td>4.6–7.2</td>
<td>65–83</td>
<td>0.6–1.0</td>
<td>56–126</td>
<td>13.3</td>
</tr>
<tr>
<td>LB</td>
<td>6</td>
<td>4.3–7.1</td>
<td>70–95</td>
<td>0.8–1.1</td>
<td>47–100</td>
<td>9.0</td>
</tr>
<tr>
<td>MR</td>
<td>6</td>
<td>4.4–6.8</td>
<td>75–102</td>
<td>0.8–1.2</td>
<td>50–115</td>
<td>12.1</td>
</tr>
<tr>
<td>NB</td>
<td>6</td>
<td>3.7–8.4</td>
<td>72–116</td>
<td>0.8–1.5</td>
<td>48–99</td>
<td>15.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>57</td>
<td>3.5–8.4</td>
<td>65–128</td>
<td>0.6–1.9</td>
<td>32–155</td>
<td>15.1</td>
</tr>
</tbody>
</table>

The technique of Fig. 3 as applied to 57 noninvasive finger arterial blood pressure waveform segments from 10 healthy young adults achieved an overall CO RMSNE of 15.1% with respect to reference Doppler ultrasound measurements made by an expert.
from the past samples of the actual form by the mathematical analysis technique. Note that the (actual) and fitted (predicted) human peripheral ABP waveform segments from 15 intensive care unit patients achieved an overall CO error bias of μ = 0.60% and precision of σ = 15.28% with respect to the reference thermodilution measurements.

the size of the overall CO error. [Note that, because the bias component will be small (but not exactly zero) here because of the scaling, the CO RMSNEs reported below are mainly due to its precision component.] These metrics indicate the ability of the technique to measure changes in CO relative to its mean value within an individual. We also computed the correlation coefficients (ρ) between the pooled CO error. The corresponding values of CO, MAP, TPR, HR, and CO change with respect to its mean value within each patient or subject (ΔCO), and the magnitude of these CO changes (ΔΔCO) in each data set to determine the extent to which the hemodynamic conditions affected the performance of the technique.

RESULTS

Figure 4 illustrates a representative example of a measured (actual) and fitted (predicted) human peripheral ABP waveform by the mathematical analysis technique. Note that the figure includes two predicted ABP waveforms. Each sample of the ABP waveform indicated with the dotted line is predicted from the past samples of the actual y(t) and the input x(t) in Fig. 3 (i.e., one-step ABP prediction), whereas each sample of the ABP waveform indicated with the dashed line is predicted from only the input x(t) (i.e., full ABP prediction) (21). Because one-step ABP prediction is what is optimized by the technique (to obtain a closed-form solution; see Eq. 1) and is an easier task than full ABP prediction, the one-step prediction ABP waveform is more accurate and, in fact, virtually imposable on the actual ABP waveform indicated with the solid line. Nevertheless, the correspondence between the actual and full prediction ABP waveforms is quite good, especially on a beat-to-beat basis. As discussed above, because both predicted ABP waveforms correspond closely to the actual ABP waveform over time scales greater than a cardiac cycle, the subsequent estimation of the windkessel time constant τ and proportional CO via Ohm’s law (see Fig. 3) should, in principle, be accurate.

Figures 5 and 6, respectively, illustrate the overall results of evaluating the technique with respect to the invasive and noninvasive hemodynamic data sets in terms of Bland-Altman plots of the CO error. (Note that the x-axis of these plots is reference CO rather than the average of reference CO and calibrated, estimated CO.) Tables 1 and 2, respectively, summarize the CO RMSNE of the technique with respect to each patient in the invasive hemodynamic data set and each subject in the noninvasive hemodynamic data set. Indeed, these tables and figures indicate that the technique as applied to invasive radial ABP waveforms was in strong agreement with thermodilution measurements in 15 ICU patients with an overall CO RMSNE of 15.3%, whereas the technique as applied to noninvasive finger ABP waveforms was in equally strong agreement with Doppler ultrasound measurements made by an expert in 10 healthy subjects with an overall CO RMSNE of 15.1%. Moreover, the CO error resulting from the invasive hemodynamic data set was essentially uncorrelated with CO (ρ = −0.14), HR (ρ = 0.04), ΔCO (ρ = −0.26), and |ΔCO| (ρ = 0.03) and only mildly correlated with MAP (ρ = 0.41) and TPR (ρ = 0.38), whereas the CO error resulting from the noninvasive hemodynamic data set was essentially uncorrelated with CO (ρ = −0.17), TPR (ρ = 0.10), HR (ρ = 0.19), and ΔCO (ρ = 0.20) and only mildly correlated with MAP (ρ = 0.37) and |ΔCO| (ρ = 0.38). Finally, in the noninvasive hemodynamic data set in which the interventions were known (see DISCUSSION), the CO RMSNE for each intervention (atropine, propranolol, and/or a 30° upright shift in posture) ranged from 8.1 to 20.8%, with the higher errors obtained during the double blockade conditions.

Fig. 5. Bland-Altman plot comprehensively illustrating the results of the invasive hemodynamic data set specifically in terms of the CO error of the technique of Fig. 3 vs. the reference thermodilution CO. The CO error here is defined to be the difference between a calibrated CO estimate and the reference thermodilution CO value and given in percent. The technique as applied to 101 invasive radial arterial blood pressure waveform segments from 15 intensive care unit patients achieved an overall CO error bias of μ = 0.60% and precision of σ = 15.28% with respect to the reference thermodilution measurements.

Fig. 6. Bland-Altman plot comprehensively illustrating the results of the noninvasive hemodynamic data set specifically in terms of the CO error of the technique of Fig. 3 vs. the reference Doppler ultrasound CO measurements made by an expert. The CO error here is defined to be the difference between a calibrated CO estimate and the reference Doppler ultrasound CO value normalized by the reference Doppler ultrasound CO value and given in percent. The technique as applied to 57 noninvasive finger ABP waveform segments from 10 healthy young adults achieved an overall CO error bias of μ = 0.57% and precision of σ = 15.08% with respect to the reference Doppler ultrasound measurements.
DISCUSSION

In summary, we have recently introduced a new technique for continuous [i.e., automatic and without the need for an operator] monitoring of relative changes in CO by long time interval analysis of a peripheral ABP waveform (see Ref. 26 and Figs. 1–4 herein). We have previously demonstrated the validity of the technique with respect to intra-arterial femoral and radial ABP waveforms obtained from open-chest swine instrumented with aortic flow probes over a wide physiological range (26). Here, we present an evaluation of the technique in humans based on previously published invasive and noninvasive hemodynamic data sets (10, 24, 25, 27). Although the evaluation described herein was retrospective, it is noteworthy that neither of these data sets was designed for the evaluation of our technique or any other pulse contour analysis technique. With the former data set, we compared the application of the technique to invasive radial ABP waveforms with reference thermodilution measurements in 15 ICU patients in which CO was changing because of disease progression and therapy. With the latter data set, we compared the application of the technique to noninvasive finger ABP waveforms with reference Doppler ultrasound measurements made by an expert in 10 healthy subjects during pharmacological and postural interventions. We report an overall CO estimation error of about 15% with respect to each of these human data sets (see Tables 1 and 2 and Figs. 5 and 6).

Potential Sources of CO Error

The CO errors reported here could be partly explained by inadequacies in the quality and accuracy of the hemodynamic measurements within the studied invasive and noninvasive data sets. However, as described below, we excluded from the study all data segments of poor quality (e.g., corrupted by significant noise artifact) so as to benchmark technique performance. On the other hand, nothing could be done in this retrospective study to improve on the accuracy of the measurements, which is largely intrinsic to the employed transducers.

The radial ABP waveforms in the invasive data set were measured with generally accurate, intra-arterial catheters. However, in the MIMIC database on which this data set was based, ABP waveform artifact was sometimes present. The artifact may have been due, for example, to patient movement, arterial line flushing, catheter obstruction, loss of signal, and proximal ABP cuff inflation. We excluded from the study all radial ABP waveforms that were significantly corrupted by such artifact (~11% of the available, simultaneous pairs of radial ABP waveforms and thermodilution measurements). Although we identified ABP artifact here by visual means, it may be possible to automatically and reliably detect ABP artifact in real time [e.g., with a simultaneous surface ECG measurement based on an algorithm recently introduced by Zong et al. (39)] so as to warn the clinician that the CO estimate derived from the ABP analysis may not be valid or preclude the output of such a CO estimate. Note that, for reasons described above, we also excluded from the study all radial ABP waveforms with linear trends of ≥20 mmHg (~13% of the available, simultaneous pairs of radial ABP waveforms and thermodilution measurements).

In contrast to the radial ABP waveforms in the invasive data set, it was not possible to assess the quality of the correspond-
Other potential sources of the CO errors reported here are any violations to the assumptions on which the technique is based. These assumptions include the following: 1) AC is constant within each individual; 2) peripheral venous pressure is negligible with respect to ABP; 3) ABP exceeds the critical closing pressure; and 4) the time constant governing arterial viscoelastic effects is negligible with respect to the windkessel time constant (26). The first of these assumptions is perhaps the most controversial, because there is currently no generally accepted, gold-standard method for measuring in vivo AC. Nevertheless, we believe that in vivo AC must be nearly constant over a wide hemodynamic range in at least some animals on the basis of the success of the pulse contour analysis of Bourgeois et al. (5, 6) and Osborn et al. (31) with respect to canine central ABP waveforms and the present mathematical analysis technique with respect to swine peripheral ABP waveforms (26). We are unaware of any existing in vivo data likewise demonstrating constancy of the human AC. However, Hallock and Benson (15) did show that, although the compliance of excised human aortas of various ages at autopsy (ranging from young adults to the elderly) decreased with increasing pressure, in vitro aortic compliance could be approximated as constant over a wide pressure range. If in vivo AC sharply changed in the opposite direction of MAP within each individual record of our study, then our technique would have grossly overestimated CO at high MAP levels and underestimated CO at low MAP levels (i.e., a strong, positive correlation between CO error and MAP). Although the correlation between CO error and MAP is positive, the degree of correlation is mild (see above), suggesting that in vivo AC within each of the 15 ICU patient and 10 healthy young adult records may have been approximately constant.

Comparison to Intrabeat Pulse Contour Analysis Techniques

In a previous paper introducing our mathematical analysis technique (26), we used signal-to-noise theory to argue that estimating the average windkessel time constant \( \tau \) (and thus average, proportional CO via Ohm’s law) by analyzing a peripheral ABP waveform over time intervals greater than a cardiac cycle should be more accurate than analyzing the ABP waveform over individual cardiac cycles and then averaging the beat-to-beat results. To support this theoretical argument, we fitted complex exponentials function(s) to individual diastolic decay intervals of swine peripheral ABP waveforms to estimate \( \tau \) on a beat-to-beat basis, averaged the resulting individual \( \tau \) estimates, and then computed average, proportional CO via Ohm’s law. The best result we were able to achieve with this intrabeat analysis was an overall CO RMSNE that was 52% larger than that obtained by our technique. We repeated this intrabeat analysis with respect to the human invasive and noninvasive hemodynamic data sets here and obtained overall CO RMSNEs that were, respectively, 23 and 81% higher than those obtained by our technique. (Note that one possible reason that this intrabeat analysis is much less effective with respect to the noninvasive hemodynamic data set is that, as described above, the noninvasive ABP waveforms may suffer from high-frequency distortion due to the employed Finapres system). We believe that these comparative studies confirm the theory that important information is indeed present in beat-to-beat ABP variations and that analysis of these subtle variations leads to improved average, proportional CO estimation in practice. However, we note that future studies should also be conducted to compare our technique with the recent intrabeat techniques of Wesseling et al. (38) and Linton and Linton (20), which also require a single peripheral ABP waveform for analysis.

Limitations of the Long Time Interval Analysis Technique

Two limitations of the current form of the long time interval analysis technique are: 1) beat-to-beat CO monitoring is not feasible and 2) artifact is a more significant problem (compared with beat-to-beat pulse contour analysis techniques such as the aforementioned). With respect to the former limitation, we feel that attempts to improve the accuracy of average, proportional CO estimation, even at the cost of temporal resolution, are worthwhile from a clinical point of view. For example, although many recent pulse contour analysis techniques can offer beat-to-beat proportional CO monitoring, they have still not been widely adopted in clinical practice, presumably because of accuracy concerns. Moreover, automatic estimation of proportional CO at intervals on the order of seconds but representing the last 6 min (i.e., boxcar moving average) would represent a significant improvement over discrete, operator-required determinations of CO by the clinical thermodilution method (assuming similar accuracy). With respect to the second limitation, the requirement of \(~6\) min intervals of relatively artifact-free ABP waveforms does not substantially limit the practical applicability of the technique. For example, only \(~11\)% of the invasive radial ABP waveforms from the real-world MIMIC database were discarded in our study because of artifact. Moreover, the 6-min intervals of analysis may be reduced to smaller intervals (e.g., 1 min) without materially affecting the accuracy of the estimates (e.g., CO RMSNE of 16.1% in the invasive hemodynamic data set and 15.7% in the noninvasive hemodynamic data set). Future formal studies are needed to determine the minimum interval for analysis that does not significantly compromise the accuracy of the technique.

Limitations of the Human Evaluation Study

In the invasive hemodynamic data set, CO was naturally changing within each ICU patient record because of disease progression and therapy. Typical ICU therapy is known to include medications such as dobutamine, dopamine, intravenous fluids, and nitroprusside (i.e., both cardiac and vascular interventions) (22). However, because time-stamped annotations were not available here, we were not able to evaluate the technique in the ICU patients with respect to each of these common therapeutic interventions. In contrast, in the noninvasive hemodynamic data set, CO was changing in each healthy subject because of precisely known interventions of atropine, propranolol, and/or a 30° upright shift in posture. As described above, the CO RMSNEs were largest during the double blockade conditions, presumably because beat-to-beat HR variability was totally abolished. Although vascular changes (TPR and fluid shifts) occurred reflexively on administration of atropine and propranolol as well as via the postural shift (see Table 2), we were not able to test the technique with respect to noninvasive ABP waveforms during interventions that directly act on the vasculature (e.g., phenylephrine, nitroprusside). Finally,
because the reference thermodilution CO in the invasive hemodynamic data set could not be assumed to be valid during unsteady conditions (e.g., ABP waveform segments with significant trends) and the noninvasive ABP waveforms were only recorded during steady conditions (Invasive Human Hemodynamic Data Set). We were not able to evaluate the technique in humans during unsteady conditions (i.e., rapid changes in CO). However, we have previously shown that the technique performs quite accurately during unsteady conditions in swine instrumented with aortic flow probes measuring instantaneous flow (26). Moreover, in the present human study, we were at least able to show that the technique performed approximately the same regardless of the size or direction of the CO change, as the correlations between the CO error and ΔCO and |ΔCO| were only mild (Noninvasive Human Hemodynamic Data Set).

**Potential Applications of the Mathematical Analysis Technique**

Our technique mathematically analyzes a single peripheral ABP waveform over long time intervals to continuously (i.e., automatically and without the need for an operator) measure CO to within a constant scale factor. The technique may therefore be utilized to quantitatively monitor relative changes in CO. The proportional CO may be calibrated, if desired, with a single, absolute CO measurement (e.g., thermodilution). For normal individuals, it may be possible to determine the proportionality constant from a nomogram. However, we believe determination of the proportionality constant is unnecessary in the context of continuous monitoring in the acute setting in which only CO changes are clinically relevant.

The results of this retrospective human evaluation study indicate that the technique may be sufficiently accurate in terms of estimating relative changes in CO with respect to invasive radial ABP waveforms from critically ill patients and noninvasive finger ABP waveforms from healthy subjects. With further mathematical analysis development (including the incorporation of an automated artifact detector) and successful prospective testing, the technique may potentially be applied to continuously monitor CO in the acute setting. The most prominent such application is in critically ill patients in the ICU and operating and recovery rooms. In critically ill patients instrumented with both pulmonary and radial artery catheters, the technique could be calibrated with a single thermodilution measurement to permit subsequent continuous monitoring of absolute CO. In the numerous critically ill patients with only radial artery catheters installed (see Introduction), the technique could provide continuous, quantitative monitoring of relative changes in CO. Other such applications in which noninvasive peripheral ABP transducers would be most appropriate include patients in the emergency room and the hospital ward, trauma patients in transport, as well as soldiers in combat. The human evaluation study described herein represents an initial step toward the realization of such applications.

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**REFERENCES**