Continuous and minimally invasive cardiac output monitoring by long time interval analysis of a radial arterial pressure waveform: assessment using a large, public intensive care unit patient database

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Editor’s key points
- The use of minimally invasive cardiac output (CO) monitoring is of interest.
- The relative change in CO can be estimated using long time interval analysis (LTIA) of the arterial waveform.
- LTIA of a public database showed reasonable agreement with thermodilution measurements.
- The accuracy of LTIA improved with greater changes in CO.

Background. A potential practical approach for continuous and minimally invasive cardiac output (CO) monitoring in intensive care unit (ICU) patients is to mathematically analyse an arterial pressure (AP) waveform using an existing radial artery line (‘pulse contour analysis’). We recently proposed a technique to estimate the relative CO change by unique long time interval analysis (LTIA) of an AP waveform. We aimed to test this technique in an ICU patient population and compare its accuracy relative to other techniques.

Methods. We studied a public, electronic ICU patient database. We extracted 1482 pairs of radial AP waveforms and thermodilution CO measurements (via single bolus injections) from 169 patients. We applied the LTIA and previous pulse contour analysis techniques to the AP waveforms. We assessed the calibrated CO estimates against the thermodilution measurements.

Results. The overall root-mean-squared-error of the LTIA technique was 18.8%. This total level of accuracy was not better than the previous techniques. However, the average magnitude of the thermodilution changes was only 12.3% (9.9 SD). When the magnitude of the thermodilution change exceeded 30%, 50%, and 70%, the median squared-error differences between the LTIA technique and the most accurate previous technique were $-45 (−322:69$ quartiles) ($P=0.005$), $-128 (−704:23$) ($P=0.006$), and $−862 (−2871:306)$% ($P=0.055$), respectively. The LTIA technique was therefore superior in detecting clinically important CO changes.

Conclusions. The LTIA technique attained an overall accuracy that may be considered clinically acceptable after taking into account the known thermodilution error and became progressively more accurate than previous techniques with increasing CO changes.

Keywords: arterial pressure; cardiac output; catheterization; Swan–Ganz; critical illness; mathematical model

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(LTIA) technique against reference CO measurements from animals and humans during various physiological settings. However, as recommended in a recent editorial in this journal, the technique has yet to be assessed in a significant ICU patient population.

Recently, Sun and colleagues used their ‘MIMIC (Multi-parameter Intelligent Monitoring in Intensive Care) II’ database, which includes radial AP waveforms and thermodilution CO measurements from a substantial number of ICU patients, to compare eight published pulse contour analysis techniques. They found that pulse pressure times heart rate (HR) normalized by the sum of systolic pressure (SP) and diastolic pressure (DP) \( \text{PP} \times \text{HR}/(\text{SP}+\text{DP}) \) was most accurate in tracking changes in the reference thermodilution CO measurements. They concluded that their electronic database could represent a useful standard for testing pulse contour analysis techniques, with the PP technique serving as a benchmark for comparison, and invited others to assess their own techniques by making the database readily and freely available.

We assessed the LTIA technique using the MIMIC II database. In this way, we were able to demonstrate the relative accuracy of the technique while testing it in a large ICU patient population.

**Methods**

We studied all pairs of radial AP waveforms and reference thermodilution CO measurements in the MIMIC II database that did not meet any pre-defined exclusion criteria. We applied the LTIA, \( \text{PP} \times \text{HR}/(\text{SP}+\text{DP}) \), and other previous techniques to the AP waveforms. These techniques do not yield a value for CO in litre min\(^{-1}\) but estimate CO to within a scale factor (i.e. \( K \times \text{CO} \) or ‘proportional CO’) and may therefore be used to monitor the relative CO changes in a patient. A litre min\(^{-1}\) value for CO may be obtained by determining \( K \) via a calibration procedure such as thermodilution. We accordingly calibrated each technique by scaling its proportional CO estimates using a single value yielded by thermodilution per patient. We then assessed the accuracy of each technique based on the magnitude of the differences between its calibrated CO estimates and the thermodilution CO measurements (‘CO errors’). Finally, we compared the accuracy of the techniques via statistical tests of their magnitudes of the CO error.

**Experimental data**

The MIMIC II database is described in detail elsewhere. Briefly, the database includes anonymized, physiological, and clinical data from ICU patients in a university hospital. At the time of our downloading of the database, data from 2769 patients were available. The physiological data consist of continuous measurements such as invasive radial AP and ECG waveforms sampled at 125 Hz and time aligned, discrete measurements including thermodilution CO. Each of the available thermodilution measurements was obtained using a pulmonary artery catheter and a single bolus injection (rather than multiple bolus injections). The clinical data constitute wide ranging information, including patient characteristics. Our analysis of the database was approved by the Michigan State University IRB (# X05-597).

We extracted all 1 min segments of the radial AP waveforms that coincided with each reference thermodilution CO measurement in the database and included all of these data pairs in the study. A total of 1915 pairs of AP (and ECG) waveform segments and thermodilution CO measurements from 197 patients were available. We then excluded those pairs (i) from patients with only one thermodilution measurement (as relative CO changes within a subject are effectively estimated); (ii) from patients on intra-aortic balloon pumps as indicated by the presence of diastolic augmentation in the AP waveforms (a standard contraindication of pulse contour analysis); and (iii) with obvious artifact in the AP waveform segments as ascertained by visual examination (to evaluate the ability to track CO rather than to detect and suppress artifact). A total of 1482 data pairs from 169 patients remained for analysis.

We applied the LTIA technique to the 1 min radial AP waveform segments to estimate the proportional CO in each patient. Since our data for analysis were not identical to those of Sun and colleagues (who analysed 1164 data pairs from 120 patients), we also likewise estimated the proportional CO with the benchmark \( \text{PP} \times \text{HR}/(\text{SP}+\text{DP}) \) technique and two other previous techniques of particular relevance, namely \( \text{PP} \times \text{HR} \) and MAP. The \( \text{PP} \times \text{HR} \) technique, which tracks CO via the product of pulse pressure and HR, is perhaps the most widely used pulse contour analysis (e.g. two commercial devices are based on this technique).

The MAP technique, which tracks CO via mean AP, is the most basic pulse contour analysis and therefore serves as a useful reference for comparison. In addition, we similarly explored the LTIA technique after normalization [LTIA/(\text{SP}+\text{DP})].

We calibrated each of the five investigational techniques using a single value yielded by thermocilution for each patient. We specifically scaled the proportional CO (i.e. \( K \times \text{CO} \)) estimates of each technique to have the same mean value as the thermocilution measurements in each patient. Thus, for each patient, \( K \) was effectively set to the ratio of the mean value of the \( K \times \text{CO} \) estimates of the technique to the mean value of the thermocilution CO measurements.

We assessed the accuracy of each technique using the differences between its calibrated CO estimates and the thermocilution CO measurements. We quantified the magnitude of these CO errors in terms of two metrics drawn from the Bland–Altman analysis. One metric is the limits of agreement in the absolute errors \( [\mu - 1.96 \sigma, \mu + 1.96 \sigma] \), where \( \mu \) and \( \sigma \) are, respectively, the bias error (i.e. average of all errors) and precision error (i.e. standard deviation of all errors). The use of this metric allowed comparisons with the previous study. The other metric is the root-mean-square of the relative errors \( \text{RMSE} = \sqrt{(\mu^2 + \sigma^2)} \). This metric combines the bias and precision errors into a single
number, as indicated, to reflect the total error. Thus, the RMSE here indicates the typical magnitude or size of the relative CO errors. The use of this metric allowed for comparisons with our previous studies. Further, the use of relative errors permitted assessments that take into account the error in the reference measurements.

We statistically compared the techniques based on the square of their relative errors, which similarly reflect the total error. Since these squared-errors were not normally distributed, we used the Wilcoxon signed-rank test to determine whether the median of the differences between the squared-errors (i.e. median squared-error difference) of the published LTIA technique and the squared-errors of another investigational technique was statistically significant. That is, the median squared-error difference here indicates the typical difference in the sizes of the relative CO errors (after the mathematical squaring operation) of the two techniques. It should be noted that the squared-error differences (i.e. the squared-errors of the LTIA technique minus the corresponding squared-errors of another technique) actually constituted repeated measures rather than truly independent samples with zero correlation. However, we did not make adjustments for the repeated measures for two reasons. First, the adjustment required would be very complicated and therefore difficult to follow (unlike the basic Wilcoxon signed-rank test). Secondly, and most importantly, we tested these data in terms of the extent of the dependence of samples and found little correlation (0.08–0.22). Thus, adjustment for repeated measures would not have materially altered the results.

Results

We used 1482 pairs of 1 min radial AP waveform segments and reference thermodilution CO measurements from 169 patients (age range 37–90 yr, 66% males) (Table 1). Three-quarters of the patients had ischaemic or other forms of heart disease. The patients were mainly in the cardiac surgery recovery unit (70%) but also in the coronary care unit (19%) and medical or surgical ICUs (11%). Their average SAPS (simplified acute physiology score) I was 15.5 (4.4 SD) (Table 1). On average, 9 (6) thermodilution CO measurements made over the course of 1.1 (1.1) days were available from each patient (Table 1). The mean thermodilution CO was similar to that of a healthy adult population, 2 (Table 1).

The CO estimation accuracy of the investigational techniques. LTIA, long time interval analysis; PP, pulse pressure; SP, systolic pressure; DP, diastolic pressure; RMSE, root-mean-squared-error. See Table 1 for remaining abbreviations.

<table>
<thead>
<tr>
<th>Technique</th>
<th>RMSE (%)</th>
<th>Limits of agreement (litre min⁻¹)</th>
<th>Wilcoxon signed-rank test of median squared-error difference (compared with LTIA) (P-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTIA</td>
<td>18.8</td>
<td>−1.96/+1.96</td>
<td>—</td>
</tr>
<tr>
<td>MAP</td>
<td>19.8</td>
<td>−1.90/+1.90</td>
<td>0.85</td>
</tr>
<tr>
<td>PP×HR</td>
<td>18.4</td>
<td>−1.92/+1.92</td>
<td>0.02</td>
</tr>
<tr>
<td>PP×HR/(SP+DP)</td>
<td>14.8</td>
<td>−1.51/+1.51</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LTIA/(SP+DP)</td>
<td>15.0</td>
<td>−1.56/+1.56</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

That is, the PP×HR/(SP+DP) and LTIA/(SP+DP) techniques both showed reductions in RMSE by ~3.7% and in the limits of agreement by ~0.4 litre min⁻¹ (Table 2). The median squared-error difference between the original LTIA technique and each of these techniques was statistically significant (Table 2).

The CO estimation accuracy of the investigational techniques is indicated as a function of the magnitude of the minimum thermodilution CO change (Fig. 1). The y-axis values in the shaded area around Z on the x-axis denote the squared-errors (median (quartiles)) of each technique only when the magnitude of the thermodilution CO change relative to the mean thermodilution CO in the patient exceeded 2%. So, for example, the squared-error values of the techniques at 30 on the x-axis were determined from only those thermodilution CO changes >30%, and at 50 on the x-axis were computed from only those thermodilution changes >50%. This indicates how the magnitude of the thermodilution CO change affects the CO estimation.
The median squared-error of the LTIA technique increased with the magnitude of the minimum thermodilution CO change (Fig. 1). However, the median squared-errors of the PP × HR technique and especially the MAP technique increased at a greater rate. As a result, the median squared-error difference between the LTIA technique and each of these basic techniques became greater with the magnitude of the minimum thermodilution CO change and reached statistical significance when the magnitude of the minimum change was ≥30% (Fig. 1). In particular, the median squared-error differences between the LTIA technique and the PP × HR technique were −45 (−322:69 quartiles), −128 (−704:23), and −862 (−2871:306)%² for magnitudes of the thermodilution CO change exceeding 30%, 50%, and 70%, respectively. Normalization¹⁷ was able to yield modest, statistically significant reductions in the median squared-error for both the PP × HR and LTIA techniques when the magnitude of the minimum thermodilution CO change was 10%, but not any higher. The median squared-errors of these techniques often increased relative to the un-normalized techniques as there was an increase in the magnitude of the minimum thermodilution CO change.

Fig 1  Accuracy of the CO estimation of the investigational techniques (on log scale) as a function of the magnitude of the reference CO change. The y-axis values at Z on the x-axis indicate the calibrated CO squared-errors [median (quartiles)] of each technique when the magnitude of the thermodilution CO change relative to the mean thermodilution CO in the patient exceeded Z%, while the P-values reveal the levels of statistical significance of the median squared-error difference between the pair of techniques with the lowest median squared-errors. MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; SP, systolic pressure; DP, diastolic pressure; LTIA, long time interval analysis. Note that the squared-errors of the LTIA/(SP + DP) technique (Table 2) were similar to those of the PP × HR/(SP + DP) technique for the magnitude of a minimum thermodilution CO change of 10% and generally larger than those of the un-normalized LTIA technique for greater changes.

Accuracy of the techniques. Note that 0 on the x-axis would correspond to the results of all the data (Table 2). The P-values show the levels of statistical significance of the median squared-error difference between the pair of techniques with the lowest median squared-errors, and represent upper bounds on the significance level of the median squared-error difference between the technique with the lowest median squared-error and the remaining techniques (Fig. 1).

The median squared-error of the LTIA technique increased with the magnitude of the minimum thermodilution CO change (Fig. 1). However, the median squared-errors of the PP × HR technique and especially the MAP technique increased at a greater rate. As a result, the median squared-error difference between the LTIA technique and each of these basic techniques became greater with the magnitude of the minimum thermodilution CO change and reached statistical significance when the magnitude of the minimum change was ≥30% (Fig. 1). In particular, the median squared-error differences between the LTIA technique and the PP × HR technique were −45 (−322:69 quartiles), −128 (−704:23), and −862 (−2871:306)%² for magnitudes of the thermodilution CO change exceeding 30%, 50%, and 70%, respectively. Normalization¹⁷ was able to yield modest, statistically significant reductions in the median squared-error for both the PP × HR and LTIA techniques when the magnitude of the minimum thermodilution CO change was 10%, but not any higher. The median squared-errors of these techniques often increased relative to the un-normalized techniques as there was an increase in the magnitude of the minimum thermodilution CO change.

Discussion
In this study, we assessed our previously developed LTIA technique for estimating the proportional CO from an AP waveform using the MIMIC II database.¹⁸ For comparison, we also investigated previous pulse contour analysis techniques of particular relevance. Our results not only provide a first-time indication of the efficacy of the LTIA technique in a significant ICU patient population but also permit comparison with other techniques in the future.
We specifically studied 1482 pairs of 1 min radial AP waveform segments and reference CO measurements from single bolus injection thermodilution from 169 patients. The LTIA technique achieved an overall CO error of 18.8% after a single calibration with thermodilution in each patient. A formula has been recommended that establishes the clinically acceptable level of CO error taking into account the error in the reference measurements. The precision error of the reference measurements used in this study is known to be \( \pm 17\% \). So, based on the formula, a clinically acceptable level of CO error here would be within 19.7%.

The overall calibrated CO errors of the PP×HR technique, which has perhaps been the most widely used pulse contour analysis, and the MAP technique, which represents the most basic analysis, were equivalent to that of the LTIA technique. Further, these simpler, earlier techniques may offer some practical advantages. Importantly, however, in the database, the magnitude of the reference CO change was often small. In fact, approximately three-quarters of the database, the magnitude of the reference CO change was often small. In fact, approximately three-quarters of the magnitudes of the thermodilution CO change (relative to the mean thermodilution CO in the patient) were less than the precision error of the reference measurements. Without significant changes, any reproducible pulse contour analysis technique, when calibrated, will be able to achieve a reasonable level of CO estimation accuracy.

The MIMIC II database did allow for reasonable comparisons of the techniques only during the appreciable reference CO changes. Indeed, as the magnitude of the thermodilution CO change increased, the accuracy of the LTIA technique became increasing and statistically better than the PP×HR and MAP techniques.

Normalization with \( SP + DP \) to correct for any AP-dependent AC changes did afford some improvement in the overall accuracy of the PP×HR technique and the LTIA technique. In particular, the PP×HR/(SP+DP) technique, which was shown to perform the best of the eight pulse contour analysis techniques studied using the same database, and the LTIA/(SP+DP) technique both achieved overall calibrated CO errors of \( \pm 15\% \). However, when the magnitude of the thermodilution CO change increased, the normalization was not helpful and even had a tendency to degrade the accuracy of the PP×HR and LTIA techniques. Thus, the effectiveness of the normalization here may merely be due to blunting the estimated CO change so as to yield better correspondence to the largely unvarying thermodilution CO measurements rather than actually correcting for changes in AC. Consequently, this normalization may not be generally advisable. However, other types of AC correction factors should not be discounted.

Like the pulse contour analysis study with the MIMIC II database, we assessed all of the investigational techniques using 1 min radial AP waveform segments for analysis. However, we initially verified the LTIA technique with 6 min AP waveform segments. We therefore also applied the LTIA technique to AP waveform segments of 6 min durations here, and its performance did not materially improve (e.g. the overall calibrated CO error was 17.8%). This comparative result indicates that the LTIA technique may be applied to a waveform duration that is comparable with those used by conventional techniques without any significant sacrifice in accuracy.

In addition to the assessment of the LTIA technique, there were other differences in methodology and materials between this study and that of Sun and colleagues. First, we had more data for analysis, because the MIMIC II database had increased since their study. Secondly, we excluded \( \pm 22\% \) of the available data (1% for only one reference CO measurement from the patient; 15% for patients on intra-aortic balloon pumps; and 6% for obvious waveform artifact), compared with only \( \pm 15\% \) mainly due to a greater tolerance of artifact in the AP waveforms. Both studies did not exclude data due to unsteady conditions where the thermodilution measurements may be less useful as a CO reference, arterial line damping, or aortic valve regurgitation, all of which may represent sources of error here. Thirdly, we calibrated the proportional CO estimates with the mean thermodilution CO in a patient, rather than an optimal calibration involving all thermodilution CO measurements in a patient and a calibration with one thermodilution measurement per patient. Fourthly, we studied the accuracy of the CO estimation as a function of the magnitude of the relative CO change instead of directional (sign) agreement with the largest reference CO change in each patient as they did. Despite these differences, the results were quite similar in the two studies. Our mean calibration turned out to yield only slightly higher CO errors than their optimal calibration (results not shown). Finally, although the limits of agreement here are a bit tighter due to our more stringent requirements on waveform quality, the relative standing of the previous techniques based on this accuracy metric and the RMSE metric was maintained over all the data.

The main limitation of this study is the non-trivial error in the reference CO measurements available in the MIMIC II database. To compensate for this error, we performed the calibration using the mean, rather than a single, thermodilution CO in each patient. Even with this limitation, we felt that it was sensible to test the LTIA technique using the readily and freely available database for two reasons. First, the study would be efficient and without any risk to human subjects. Secondly, the accuracy of the technique relative to other techniques could be clearly shown, because all developers, including manufacturers of proprietary techniques, have access to the same data.

In conclusion, we have assessed a continuous and minimally invasive technique for estimating the relative CO change by unique LTIA of a radial AP waveform in an ICU patient population using a database that may develop into a standard for testing pulse contour analysis techniques. The technique achieved a CO estimation error that was overall within recommended clinical limits and became increasingly and significantly smaller than previous techniques as the reference CO change became of greater clinical importance. While the ability to continuously monitor the relative CO changes increased, the accuracy of the LTIA technique.
change would be useful for detecting a haemodynamic event or directing therapy in ICU patients, future extensions of the LTIA technique to provide absolute CO via a non-invasive calibration and to effectively correct for any AC change are worthwhile.

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Declaration of interest

R.M. has a patent on the LTIA technique.

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References

4 Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. Chest 2007; 132: 2020–9
6 Cooper ES, Muir WW. Continuous cardiac output monitoring via arterial pressure waveform analysis following severe hemorrhagic shock in dogs. Crit Care Med 2007; 35: 1724–9
14 Lu Z, Mukkamala R. Continuous cardiac output monitoring in humans by invasive and noninvasive peripheral blood pressure waveform analysis. J Appl Physiol 2006; 101: 598–608
17 Liljestrål GZE. Vergleichen die bestimmungen des minutenvolumens des herzens beim menschen mittels der stichoxydulmethode und durch blutdruckmessung. Ztschr ges exper med 1928; 59: 105–22