Continuous Cardiac Output Monitoring in Humans by Non-Invasive Arterial Blood Pressure Waveform Analysis

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Abstract

We have recently introduced a novel technique for continuously monitoring changes in cardiac output (CO) by long time interval analysis of a peripheral arterial blood pressure (ABP) waveform. We have tested the technique with respect to invasive peripheral ABP waveforms obtained from animals and critically ill patients, and our CO estimates showed strong agreement with highly invasive CO measurements. Here, we present a comparison of the application of the technique to non-invasive finger ABP waveforms with reference Doppler ultrasound CO measurements in ten healthy humans during pharmacological and postural interventions. We report an overall CO error of 15.1%.

1. Introduction

The standard clinical method for measuring cardiac output (CO) is currently thermodilution. While this method is relatively simple and inexpensive, it requires an operator and may therefore only be employed intermittently. But, perhaps a more significant drawback of thermodilution is that its high level of invasiveness limits its use to only a minority of all critically ill patients. Although Doppler ultrasound and transthoracic bioimpedance have been introduced as non-invasive CO monitoring methods, neither of them has been able to replace thermodilution. Doppler ultrasound methods require an expert operator to stabilize an external ultrasound transducer as well as expensive capital equipment [1]. Transthoracic bioimpedance may not be sufficiently accurate, especially in critically ill patients who often have excessive lung fluids [2].

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 minimally invasive radial artery catheterization. Moreover, over the past few decades, totally non-invasive methods have been developed and refined to continuously measure peripheral ABP based on finger-cuff photoplethysmography (PPG) [3]. Indeed, commercial finger-cuff PPG systems are available at present (see Finometer and Portapres, Finapres Medical Systems, The Netherlands).

As a result, numerous researchers have sought analysis techniques to compute CO changes from the contour of ABP waveforms so as to permit continuous monitoring and expand the clinical measurement of CO. 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 [4]. However, over such short time scales, peripheral ABP waveforms are dominated by highly complex waves propagating back and forth in the distributed arterial tree [5]. Thus, the previous analysis techniques have generally proven to be too inaccurate for clinical use.

Our ongoing hypothesis is that CO may be accurately monitored from ABP variations 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 [5]. We have recently developed a technique that exploits this hypothesis to monitor changes in CO by mathematically analyzing a single peripheral ABP waveform over long time intervals (approximately six-minutes) [4]. We have tested the technique with respect to invasive peripheral ABP waveforms obtained from open-chest swine and critically ill patients, and our CO estimates showed strong agreement with highly invasive CO measurements [4][6].

In this report, we present an evaluation of the technique with respect to non-invasive peripheral ABP waveforms from humans. Using a previously published data set [7], we specifically compared the application of the technique to non-invasive ABP waveforms obtained via a commercial finger-cuff PPG system with reference Doppler ultrasound measurements made by an expert in ten healthy subjects in which CO was altered through pharmacological and postural interventions.

2. Methods

2.1. The mathematical analysis technique

Our technique for monitoring CO changes by mathematically analyzing a peripheral ABP waveform

was introduced in [4] and is described in detail therein. Here, we review the technique at a conceptual level.

The technique that we have developed builds upon the previous pulse contour analysis work of Bourgeois et al [8]. These investigators assumed that the arterial tree could be well represented by a two-parameter Windkessel model accounting for the lumped compliance of the large arteries (arterial compliance, AC) and the total peripheral resistance (TPR) of the small arteries. According to this model, 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, τ). Since AC may be nearly constant over a wide pressure range and on the time scale of months (see, *e.g.*, [4][6][8]), CO could then be measured to within a constant scale factor by dividing the time-averaged ABP with τ. Thus, the pulse contour analysis of Bourgeois et al involves fitting an exponential function to the diastolic interval of each ABP pulse in order to measure τ.

The above pulse contour analysis is not applicable to peripheral ABP waveforms, because pure exponential diastolic decays are usually not visible in these waveforms (Figure 1). The reason is that the arterial tree is not simply a lumped system like 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 obscured by wave reflections occurring at each site of impedance mismatch.

According to transmission line theory, however, the confounding effects of wave phenomena will diminish with increasing time scale (*i.e.*, as the wavelengths of the propagating waves increase in length with respect to the physical dimension of the arterial tree) [5]. 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). This concept is demonstrated in Figure 1, 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, as the characteristics of the complex wave effects differ at the two measurement sites. In contrast, the long time scale or beat-to-beat variations are much more similar, as the confounding effects of wave phenomena are less significant over these time scales. Thus, the Windkessel model is a more valid representation of the long time scale behavior of the arterial tree. This implies that if pulsatile activity suddenly ceased, then a peripheral ABP waveform may eventually decay like a pure exponential once the faster wave reflections vanish.

Our technique therefore mathematically analyzes a digitized peripheral ABP waveform over long time intervals (approximately six minutes) in order 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 is estimated from the ABP waveform (*h(t)* in Figure 2). Then, the Windkessel time constant τ is determined by fitting a mono-exponential function to the tail end of this response once the faster wave reflections have vanished (Figure 2). Finally, proportional CO is computed via Ohm's law.

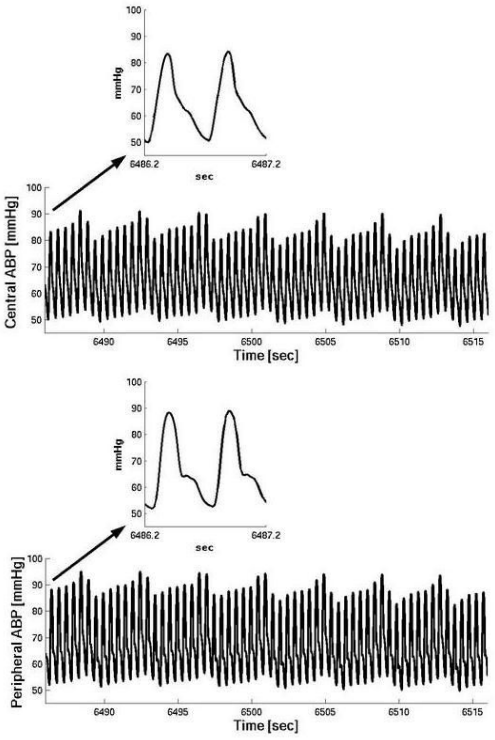

Figure 1. Two arterial blood pressure (ABP) waveforms simultaneously measured centrally in the aorta and peripherally in the radial artery of a swine.

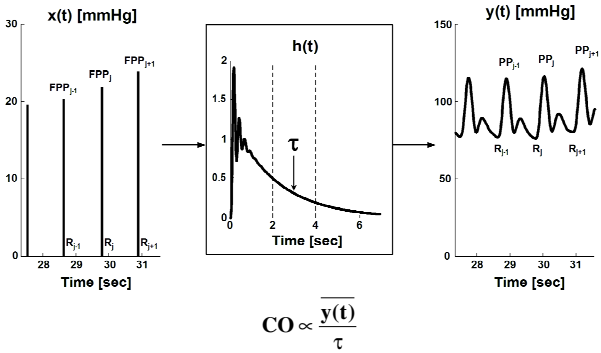

Figure 2. Illustration of the mathematical analysis technique.

Figure 2 illustrates the technique and indicates that the single contraction ABP response *h(t)* is determined in two steps. First, a signal representing the cardiac contractions (*x(t)*) is constructed from the ABP waveform based on 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 and has an area equal to the pulse pressure determined after lowpass filtering the waveform (with a cutoff frequency of 2 Hz) to attenuate the wave effects (FPP, filtered pulse pressure). Then, the impulse response function *h(t)* which when convolved with *x(t)* best fits the (unfiltered) ABP waveform (*y(t)*) in the least squares sense is estimated according to a standard autoregressive exogenous input approach. By definition, the estimated *h(t)* represents the (scaled) ABP response to a single, solitary cardiac contraction. Note that accurate, subsequent determination of τ should be achieved by virtue of *h(t)* coupling the long time scale variations in *x(t)* to *y(t)*.

2.2. Non-invasive hemodynamic data set

The hemodynamic data utilized to evaluate the technique with respect to human non-invasive peripheral ABP waveforms were obtained from previous experiments designed to address different specific aims and are described in detail elsewhere [7]. Here, we briefly present those aspects of the experiments that are relevant to the present study.

Ten healthy human volunteers [five men and five women, age: 25 ± 4 yr (mean±SD)] participated in the experiments. Each subject was instrumented for non-invasive measurement of peripheral ABP, instantaneous CO, and other cardio-respiratory signals. The peripheral ABP waveform was measured with a finger-cuff PPG system (2300 Finapres Continuous Blood Pressure Monitor, Ohmeda; Englewood, CO), while instantaneous CO was measured according to a previously described Doppler ultrasound technique [9] implemented by an expert. Specifically, aortic blood velocity was measured with a bi-directional ultrasound Doppler velocimeter (CFM 750, GE Vingmed; Horten, Norway), which was operated in pulsed mode at 2MHz with the hand-held transducer placed on the suprasternal notch. The area of the rigid aortic ring was determined in a separate session by parasternal sector-scanner imaging (CFM-750, GE Vingmed). Instantaneous CO was then calculated via the product of the measured instantaneous maximum blood velocity and the area of the aortic valve orifice.

Each instrumented subject was studied on two separate days before and after the administration of atropine (0.04 mg/kg) and/or propranolol (14.6 mg) under different postures to vary the experimental conditions. For each experimental condition, approximately six-minute intervals of the non-invasive measurements were continuously recorded at a sampling frequency of 50 Hz. In the present study, we specifically analyzed the digitized recordings from the following six experimental conditions: 1) supine, baseline, 2) supine, propranolol, 3) supine, propranolol+atropine, 4) 30° upright tilt, baseline, 5) 30° upright tilt, atropine, and 6) 30° upright tilt, atropine+propranolol.

Based on these non-invasive recordings, we created a data set for technique evaluation as follows. First, we visually examined each non-invasive finger ABP waveform and instantaneous CO waveform and extracted the longest contiguous, artifact free segment from each waveform. Then, we excluded from the study the four instantaneous CO waveforms that were less than one minute in duration and the three finger ABP waveforms that were less than five minutes in duration or had unreasonably high-pressure values presumably due to prolonged application of cuff pressure. Finally, the reference CO value corresponding to each of the remaining instantaneous CO waveforms was determined by computing its time-average. A total of 57 pairs of simultaneous measurements of artifact-free, non-invasive finger ABP waveforms and reference Doppler ultrasound CO values from the ten healthy subjects remained for technique evaluation. The Table summarizes the hemodynamic data for each of the subjects.

2.3. Statistic analysis

After applying the technique to all of the non-invasive finger ABP waveforms in the data set, we quantitatively compared the resulting, proportional CO estimates with their reference, absolute CO values as follows. First, we scaled the proportional CO estimates to have the same mean value as the Doppler ultrasound CO in each subject. Then, we pooled the data together from all the subjects and computed the root-mean-squared-normalized error (RMSNE) of the calibrated CO estimates (normalized by their reference CO values and given in percent) as a metric for comparison.

3. Results

The Table summarizes the results of evaluating the technique based on the non-invasive human hemodynamic data set. These results indicate that the technique as applied to non-invasive finger ABP waveforms was in strong agreement with Doppler ultrasound measurements made by an expert with an overall CO RMSNE of 15.1% in ten healthy subjects. Figure 3 provides visual examples of the correspondence between the once calibrated CO estimates and their reference Doppler ultrasound CO values in three individuals. Moreover, the CO error was essentially

uncorrelated with CO (ρ=0.17), TPR (ρ=0.10), and HR (ρ=0.19) and only mildly correlated with MAP (ρ=0.37).

Table. Summary of hemodynamic data and results of the mathematical analysis technique in ten healthy subjects.

Subject record	CO range [L/Min]	MAP range [mmHg]	TPR range [PRU]	HR range [BPM]	CO RMSNE [%]
LD	3.6-6.8	82-128	1.0-1.9	43-108	13.0
WP	4.3-6.3	68-93	0.7-1.1	60-113	16.9
CG	4.5-7.7	75-118	0.9-1.3	48-98	20.2
JE	4.5-8.2	85-125	0.9-1.4	51-135	14.6
AE	3.5-5.3	79-124	1.2-1.5	32-72	18.3
DL	3.5-4.7	92-104	1.2-1.9	60-88	14.8
GB	4.6-7.2	65-83	0.6-1.0	56-126	13.3
LB	4.3-7.1	70-95	0.8-1.1	47-100	9.0
MR	4.4-6.8	75-102	0.8-1.2	50-115	12.1
NB	3.7-8.4	72-116	0.8-1.5	48-99	15.3
TOTAL	3.5-8.4	65-128	0.6-1.9	32-135	15.1

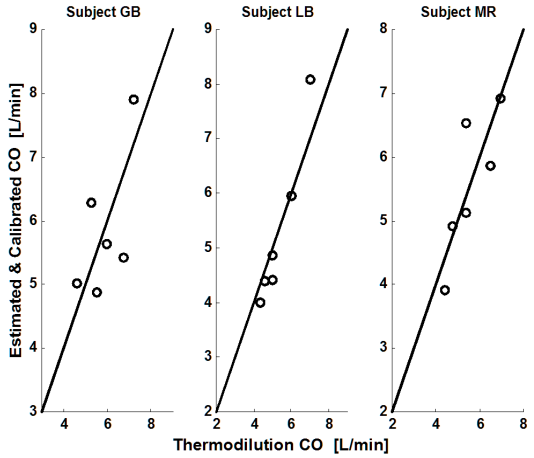

Figure 3. Sample results from three subjects in the Table.

4. Discussion

The CO error reported here may be partly explained by inaccuracies in the reference Doppler ultrasound technique [9]. While errors in measuring peripheral ABP by finger-cuff PPG may have also contributed to the CO error, we note that finger-cuff PPG and radial artery catheterization have been shown to produce similar beat-to-beat ABP fluctuations, which are the very focus of our technique [3]. Other potential sources of the CO error are violations to the assumptions underlying the technique including AC being constant within each subject record and peripheral venous pressure being negligible with respect to ABP. On the other hand, since the CO error was only mildly correlated with MAP, these two assumptions could not have been grossly violated. The CO error for each intervention (atropine, propranolol, and/or a 30° upright shift in posture) ranged from 8.1-20.8%, with the higher errors obtained during the double blockade conditions in which beat-to-beat HR variability was totally abolished. Although the direct effects of atropine and propranolol are cardiac, vascular changes occurred reflexively upon administration of these drugs as well as via the postural shift. Nevertheless, future studies evaluating the technique with respect to non-invasive finger ABP waveforms during interventions that directly act on the vasculature (*e.g.*, phenylephrine) would be worthwhile. With further successful testing, the technique may potentially be employed for continuous CO monitoring in the acute setting such as critical care, emergency care, and even combat casualty care.

Acknowledgements

This work was supported by an award from the American Heart Association and MSU.

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