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THE CARDIAC OUTPUT FROM BLOOD PRESSURE ALGORITHMS TRIAL

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THE CARDIAC OUTPUT FROM BLOOD PRESSURE ALGORITHMS TRIAL

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Introduction

Cardiac output (CO) is a cardinal parameter of cardiovascular state, and a fundamental determinant of global oxygen delivery. Historically, clinical measurement of CO has been limited to critically-ill patients, using invasive indicator-dilution methods such as thermodilution (CO_{TD}). Alternative CO measurement strategies have not been widely accepted in critical care, and outside the intensive care unit, rather imprecise metrics are frequently used to assess CO and circulatory adequacy (e.g. blood pressure, urine output, mental status, etc.).

Throughout the past century (and longer (1)), the premise that relative changes in CO could be estimated by analysis of the arterial blood pressure (ABP) waveform has captured the attention of many investigators. Today, peripheral ABP is routinely available in ICU patients, and non-invasive devices exist to measure peripheral ABP in non-critically-ill populations (2, 3). Tracking changes in CO continuously and non-invasively via ABP waveform analysis may be valuable both within and beyond the ICU setting: such a “vital sign” might be a sensitive and specific indicator of circulatory pathology and useful in optimizing therapies such as volume resuscitation and catecholamine infusions. Yet CO-from-ABP monitoring has not been widely adopted in any clinical setting. One can speculate that this is in part because of inadequate validation.

In this investigation, we established an algorithm-testing dataset -- a subset of the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) database (4) --

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3 containing radial artery waveform data and contemporaneous reference CO_{TD}
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5 measurements, collected in an ICU patient population during routine clinical operations.
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7 We used this dataset to evaluate eight previously reported CO-from-ABP algorithms.
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9 Moreover, we are making this dataset publicly available, establishing a standard for the
10
11 meaningful comparison of different CO-from-ABP algorithms using “real-world” (e.g.
12
13 not artificially pristine) ICU physiologic data. Vendors and future developers can apply
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15 their CO-from-ABP algorithms to this public-access dataset and report how they perform
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17 relative to alternative algorithms. The MIMIC II CO_{TD} /ABP dataset is an analog of the
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19 public access arrhythmia databases that have played an indispensable role in the
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21 development, refinement, and – ultimately – widespread acceptance of automated
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23 algorithms for electrocardiogram analysis (5).
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Materials and Methods

Database development: Our CO_{TD}/ABP dataset was extracted from the MIMIC II database (4). The MIMIC II database includes physiologic and wide-ranging clinical data from over 2,500 ICU patients (MICU, CCU, and SICU) hospitalized at the Beth Israel Deaconess Medical Center, Boston, USA between 2001 and 2005. Radial ABP waveform data from the M1006B invasive pressure module and CO_{TD} data (temporally resolved to the nearest minute) were originally sourced from Philips CMS bedside patient monitors (Philips Medical Systems, Andover, MA). Waveforms were sampled at 125 Hz with 8 bit resolution. The patients' gender and age were input by the nursing staff as part of routine clinical operations, using the Philips CareVue system, and these archived data were another component of the MIMIC II database. Additional details about the MIMIC II database are available in (4). A software routine developed using Matlab (Mathworks, Natick, MA) identified and extracted MIMIC II cases with CO_{TD} measurements and contemporaneous one-minute-long segments of radial ABP waveform. All Matlab algorithms used in our analyses, and the MIMIC II CO_{TD}/ABP dataset, have been contributed to PhysioToolkit and PhysioBank, respectively, and are available for review and free public use from the PhysioNet website (6).

ABP Signal Processing: Within each minute-long ABP segment, individual heart beats were identified using a Matlab implementation of an algorithm by Zong (7). The waveform quality of each ABP pulse was assessed automatically using a signal

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3 abnormality index (SAI) algorithm (8). A set of features from each ABP pulse was
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5 computed, including the peak (systolic blood pressure, SBP), trough (diastolic blood
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7 pressure, DBP), MAP, and pulse pressure (SBP minus DBP); see Fig. 1. Each ABP
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9 pulse's average of negative slopes was computed, a metric of spiky, non-physiologic
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11 noise in the ABP pulse waveform. After computing the preceding features for an ABP
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13 pulse, the SAI algorithm checks that all were within normal limits (8). The SAI also
14
15 checks that the features' variation from one ABP pulse to the next is within normal limits.
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18 The SAI algorithm reports a binary 'normal' or 'abnormal' rating for each ABP pulse,
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20 depending if all the normality criteria were met (8). Any abnormal beat was excluded
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22 from further analysis. If a given minute-long ABP segment contained more than 40% of
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24 abnormal beats, the entire segment (and its corresponding CO_{TD}) was excluded from
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26 further analysis.
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34 In addition, we estimated the duration of each entire beat and its systolic interval.
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36 There is no single widely accepted method to identify the systolic interval in a peripheral
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38 ABP pulse (in contrast to a central ABP pulse, the dicrotic notch in a peripheral ABP
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40 pulse does not indicate closure of the aortic valve). Therefore, we chose two alternative
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42 criteria to identify the end of systole. First, we computed a heuristic estimate of systolic
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44 duration, $(0.3 \cdot \sqrt{beat_period})$, originally suggested as an approximation of the QT
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46 interval (9). Second, we identified the point after SBP with the lowest non-negative
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48 slope, as in Fig. 1. In practice, this method located the trough of the dicrotic notch, or
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50 any relative plateau which persisted for two or more ABP samples.
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Investigational CO-from-ABP algorithms:

Mean arterial pressure (MAP) is positively but imperfectly correlated with CO. Of course, variable degrees of systemic vasoconstriction or dilation (which affect peripheral vascular resistance, PVR), as well as variable venous pressure, make MAP an unreliable predictor of CO. ABP waveform analysis assumes that other features in the waveform are less affected by confounders such as peripheral vascular resistance and are thus more reliable correlates of CO. MAP serves as our control method against which eight investigational CO-from-ABP methods are compared. The investigational algorithms are summarized in Table 1. Most algorithms predict stroke volume, and CO is taken as the product of stroke volume and median heart rate over the one minute window. Many of the algorithms were initially intended for a central aortic ABP waveform; in this investigation, we explore their application to a peripheral radial ABP.

(A) Pulse Pressure: In 1904, Erlanger and Hooker suggested that the pulse pressure is a surrogate of stroke volume (10). This notion naturally arises from a basic Windkessel model of the arterial tree, in which the arterial system is considered a single elastic tank, with flow exiting through a distal resistive element. Assuming that forward flow is correlated with pulsatile volume and cardiac ejection is near-instantaneous, then the product of pulse pressure and heart rate is a predictor of CO.

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3 (B) Liljestrand and Zander: Compliance of an artery varies with blood pressure.
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5 The *Liljestrand* algorithm accounts for the dependence of a subject's compliance on
6
7 arterial pressure by scaling its CO estimate to the reciprocal of MAP (11).
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12 (C) Systolic Area: A number of methods treat an artery as a long viscoelastic
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14 tube, a "transmission line" model. Within a transmission line, pressure gradients
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16 accelerate or decelerate flow. By assuming that retrograde (reflected) pressure waves are
17
18 negligible during systole, it is possible to estimate the pressure gradient and the forward
19
20 flow from an ABP waveform. Specifically, flow is proportional to the ABP *systolic area*
21
22 (the area under the systolic portion of the ABP pulse) (12, 13).
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29 (D) Kouchoukos Correction: A potential source of error is the assumption that
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31 cardiac ejection is so rapid that no blood flows out of the arterial tree during systole
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33 ("run-off"). *Kouchoukos* proposed a simple correction factor, related to the ratio of
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35 systolic-to-diastolic duration (14); this was a variation of an earlier method proposed by
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37 Warner (15).
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43 (E) Diastolic Decay: Bourgeois developed an algorithm to quantify systolic run-
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45 off (16). This method leads to an estimation of PVR (CO can then computed from MAP /
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47 PVR, assuming CVP is negligible). Bourgeois' method is based on a constant
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49 compliance Windkessel model. In such an idealized model, a mono-exponential *diastolic*
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51 *decay* (due to the arterial run-off) is expected in the ABP pulse waveform, and that
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53 diastolic curve changes solely as a function of PVR (17). Our *diastolic decay* method
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3 adapts the original Bourgeois method to the radial ABP. We fit a monoexponential curve
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5 to just two points of each ABP pulse, taking the peak of systole as the onset of a mono-
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7 exponential decay, and the trough of diastole as its end (18).
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12 (F) Herd: In theory, systolic blood pressure may be prone to amplification due to
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14 early reflected waves. Herd proposed another empirical method, the difference between
15
16 mean and diastolic pressure, as a more robust surrogate of stroke volume (19).
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21 (G) Corrected Impedance: Wesseling's *Corrected Impedance* method provides an
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23 empiric correction to the systolic area-under-the-ABP curve approach, to account for
24
25 some of the sources of error described above (20).
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30 (H) AC Power: We explored if the stroke volume bore any reliable relationship
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32 with the ABP waveform root-mean-square.
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37 Modelflow, PiCCO, PulseCO, and FlowTrac: The initial investigational plan was
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39 to re-implement the best known commercial algorithms, based on publicly-available
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41 information (21-27). However, we found that insufficient public information was
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43 available to effectively replicate these algorithms. This matter is addressed in detail in
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45 the *Discussion*.
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Calibration: We applied the investigational algorithms described above and summarized in Table 1 to the data of subjects who have at least *two* paired measurements of CO_{TD} and a contemporaneous, minute-long segment of ABP waveform of sufficient quality. Each algorithm was calibrated to each patient, using two different methods. First, the “best-possible calibration factor” was computed, *C1* (fig. 2). *C1* was selected to minimize the root-mean-square of the difference of each pairing of CO_{TD} and CO-from-ABP. Next, each algorithm was calibrated to each patient using a different methodology, *C2* (fig. 2). *C2* was established only by the *first* pairing of the CO estimate and CO_{TD}, so that CO_{TD-initial} = (*C2* * CO estimate). All investigational algorithms were compared against MAP as calibrated predictors of CO. MAP was calibrated exactly like other algorithms, i.e. *C1* and *C2*.

Statistical analysis: Each paired CO-from-ABP and CO_{TD} had an identifiable "error" (their difference). The distribution of errors for each investigational algorithm was computed, for both the *C1* and *C2* calibration methods. From these error distributions, 95% limits-of-agreement were computed for each CO-from-ABP algorithm, per Bland-Altman methodology (28). We tested if the error distribution for an investigational algorithm was statistically different from the error distribution of "calibrated MAP" (using the *C1* data), using the Kolmogorov-Smirnov test (in Matlab).

Results

We excluded 13.7% of the available minute-long ABP data segments (and their paired CO_{TD} measurements) which did not pass our data quality criteria – those were segments that contained more than 40% of abnormal ABP pulses. Table 2 shows the characteristics of the 120 subjects analyzed. Typical of an ICU population, we studied older subjects (age 69 years \pm 12 s.d.), 67% male. The average length of stay in the ICU was slightly over 2 days with an average of ten CO_{TD} measurements per patient. On average, each subjects' CO_{TD} varied by $\pm 46\%$, PVR varied by $\pm 50\%$, and MAP varied by $\pm 32\%$.

In Table 3, we tabulate the 95% limits-of-agreement for all investigational algorithms using both the *C1* and *C2* calibration methods. The Liljestrand algorithm performed the best. Figure 3 plots the differences (“errors”) between the Liljestrand method and CO_{TD} , and subplots in Figure 3 show error plotted as a function of various physiologic parameters. One notable trend is that the Liljestrand error grows larger as peripheral vascular resistance lessens.

The results in Table 3 and Figure 3 are exclusive of the minute-long ABP segments with $>40\%$ abnormal beats. After recomputing the Liljestrand 95% limits-of-agreement for *all* data-segments (i.e. regardless of data quality) the Liljestrand limits-of-agreement grew to $-1.88 / +1.57$ L/min. By contrast, applying more stringent ABP quality criteria (analyzing minute-long ABP waveform segments with no more than 5%

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3 of abnormal beats), the limits-of-agreement were reduced to -1.48 / +1.29 L/min,
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5 although this more stringent ABP quality criteria excluded 40% of the available ABP
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8 data segments.
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13 Some of the algorithms require determining the end-of-systole in a radial ABP
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15 pulse. The results in Table 3 are all based on our heuristic method $0.3 \cdot \sqrt{\text{beat_period}}$.
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17 For select algorithms, subscripts in Table 3 report the results for an alternative method of
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19 identifying the end-of-systole (the “lowest non-negative slope” method), which trended
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21 towards worse results.
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Discussion

A Public Access Database: The ability to monitor CO continuously by analyzing the ABP waveform, wrote Wesseling in 1983, could be used to provide “an early warning signal if cardiac output would rise or fall suddenly, to adjust drug rates and infusion rates...to sense bleeding...to get a true mean cardiac output under arrhythmias, etc. (20)” Yet ABP waveform analysis has not been broadly adopted. Perhaps this is in part because these algorithms haven't been convincingly validated (29). Such validation could be enabled by one or more publicly available “standards” databases. In the 1970's, this Laboratory made the BIH-MIT Arrhythmia database publicly available (5). The BIH-MIT Arrhythmia database, together with other public access databases, e.g. the European ST-T database, promoted the development of automated ECG interpretation algorithms. 30 years later, computerized ECG interpretation has evolved so that it is now standard in bedside monitors and even automated defibrillators.

Academic and commercial developers can freely access and download the MIMIC II CO_{TD}/ABP dataset (www.physionet.org), apply their algorithms, and report their results. This database contains a large number of radial ABP waveforms and contemporaneous measurements of CO_{TD} (over 100 subjects and over 1000 paired data points), archived during routine clinical operations. We observe that the typical record shows distinct intervals of relative stability and other intervals of dynamic physiologic change, as in Fig. 4. The range of physiologic states is summarized in Table 2. The data quality in this dataset -- motion artifacts, incidence of dampened catheters, etc. -- are consistent with routine practice, rather than idealized research conditions. To our

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3 knowledge, there is presently no comparable public database. The performance of a
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5 novel algorithm, including break-down conditions or generally unsatisfactory
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7 performance, can be identified using this testing database. Moreover, the direct
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9 comparisons of different algorithms using a standardized testing database may breed
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11 healthy competition, and promote clear, iterative improvements. Finally, credible
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13 validation using a standard database may encourage adoption of innovative methods by
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15 caregivers, particularly when some methods are proprietary and not fully disclosed to the
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17 public. The usefulness of ancillary algorithms for CO estimation (e.g. generalized
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19 transfer functions to estimate central aortic pressure, or ABP dampening detectors) can
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21 likewise be tested.
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30 Because this CO_{TD}/ABP dataset contains “real-world” ICU data, collected during
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32 routine operations, the CO reference was a single CO_{TD} measurement. This reflects
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34 clinical practice, even though it is an imperfect CO reference method (30, 31). The
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36 difference between an investigational algorithm and the CO reference will be increased
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38 by errors in *either* the CO algorithm *or* errors in CO_{TD} , so the use of single CO_{TD}
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40 measurement as a reference may widen the overall limits-of-agreement (Table 3).
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42 However, in a dataset this large, it is unlikely that random errors in CO_{TD} measurements
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44 will alter whether an individual algorithm is *relatively* better at predicting CO_{TD} than
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46 calibrated MAP, and how it compares *relative* to other algorithms. Moreover, if and
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48 when future investigators collect additional datasets (perhaps using alternative CO
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50 reference methods as in (24), or ABP measured from other anatomic locations such as the
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52 femoral artery), these datasets can also be freely posted on PhysioNet for public access,
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3 permitting further standardized comparisons of different CO estimators. We suggest that
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5 it is beneficial to make available the largest volume of data for the widest range of
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7 populations and physiologic states, rather than idealized, smaller datasets.
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12 *Investigational Algorithms:* We investigated eight CO-from-ABP algorithms,
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14 many of which were originally intended for use with a central ABP waveform. The
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16 notable finding in this trial is the superiority of the CO-from-ABP algorithm described in
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18 1928 by Liljestrand and Zander, which performed significantly better than MAP at
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20 predicting changes in CO, and stood out from the other investigational algorithms. The
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22 performance of the Liljestrand method is all the more notable because the ABP data were
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24 collected during routine ICU clinical operations, during which some degree of motion
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26 artifact, catheter damping, improperly calibrated transducers, etc. are inevitable. We
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28 employed lenient ABP quality criteria (analyzing all data with $\leq 40\%$ abnormal ABP
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30 pulses), which only excluded 13.7% of the noisiest minute-long ABP waveform
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32 segments. To the extent that CO_{TD} is a useful parameter to monitor, the Liljestrand
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34 algorithm may enhance standard vital signs. An example of CO estimated continuously
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36 by the Liljestrand algorithm versus episodic CO_{TD} is given in Fig. 4.
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46 We found that the 95% limits-of-agreement between the Liljestrand CO estimates
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48 and CO_{TD} are a function of ABP waveform quality: as the ABP quality criteria are made
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50 increasingly stringent, the limits-of-agreement grow tighter, although more data are
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52 excluded. Note that we did *not* explicitly exclude dampened ABP waveforms, aside from
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54 requiring that the pulse pressure was > 20 mmHg. Waveform damping (due to air
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3 bubbles, thrombus, partial meatus occlusion, etc.) can subtly reduce the measured pulse
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5 pressure and so it is a potentially serious source of error for the Liljestrand algorithm
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7 which contains pulse pressure in its numerator. All the same, the Liljestrand algorithm is
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9 a better predictor of CO_{TD} than MAP alone, and appears superior to the other algorithms
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11 studied here. If an automated algorithm were able to detect or exclude slightly dampened
12
13 ABP waveforms, or if the clinical staff took special care to avoid dampened intra-arterial
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15 measurements, it is likely that the Liljestrand method, or any of the investigational
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17 methods in Table 1, would prove even more accurate.
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25 The modest performance of the other investigational algorithms requires
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27 discussion. Factors which may explain these results include: use of real-world ABP
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29 waveform data rather than pristine research data (discussed above); use of radial ABP
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31 waveforms rather than central ABP waveforms; one-time calibration rather than repeated
32
33 recalibration; and inclusion of all subjects regardless of cardiac valve function.
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39 Most of the investigational algorithms were originally intended for use with a
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41 central ABP waveform, where the systolic interval of the ABP may have relatively fewer
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43 retrograde components (i.e., reflected waves). Yet measurement of a radial ABP is a
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45 standard clinical practice, where antegrade and retrograde waves are superimposed.
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47 Algorithms which perform suitably using a peripheral ABP may prove more valuable
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49 because radial ABP is more often available, and because non-invasive devices exist to
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51 measure peripheral ABP. Therefore we feel that investigation of these algorithms applied
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53 to a radial ABP is warranted. Indeed, we discovered that the Liljestrand method performs
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3 well when applied to radial ABP. There is precedent for applying an algorithm intended
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5 for a central ABP on a peripheral BP (23, 24).
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9 Many pulse contour methods prescribe recalibration after each new reference CO
10 measurement, though we did not use this methodology in our investigation. It is intuitive
11 that very frequent recalibration leads to more accurate CO estimations, but extremely
12 frequent re-measurement of CO_{TD} obviates the need for CO-from-ABP algorithms.
13
14 Statistics based on a recalibration every time the patient's state changes don't reveal much
15 about the times when continuous CO-from-ABP algorithms would be most valuable:
16 when a patient's state is changing and CO_{TD} is *not* known. Therefore we compared the
17 accuracy of each algorithm through each subject's range of ICU physiology, employing
18 just a single calibration. The calibration methods in this study included *C1*, the "best
19 possible calibration" (a retrospective construct, in which one optimal calibration factor
20 that minimizes the overall estimation error is employed); and *C2*, in which only the *first*
21 pairing of CO-from-ABP and CO_{TD} are employed for calibration, and subsequent
22 pairings are examined for accuracy. Presumably, real-world performances will lie
23 somewhere between the ideal of the *C1* calibration method and the imprecision of the *C2*
24 method.
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45 We did not exclude subjects based on heart valve function. Rather, we trusted
46 that the ICU staff would only measure CO_{TD} in appropriate patients (e.g. without
47 significant tricuspid regurgitation), and that the ideal CO-from-ABP algorithm would
48 tolerate some aortic valve dysfunction. When we studied the subset of cases with
49 documented normal tricuspid and aortic valve function, we did not find improvement in
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3 any of the algorithms' performances. Echocardiograms were available in 56 subjects,
4 and normal cardiac valve function was found in 64% of them (36 subjects). For *all eight*
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any of the algorithms' performances. Echocardiograms were available in 56 subjects, and normal cardiac valve function was found in 64% of them (36 subjects). For *all eight* investigational algorithms, the 95% limits-of-agreement with CO_{TD} were *no better* in this subset of 36 subjects with documented normal valve function.

Commercially-available CO-from-ABP algorithms: The best known CO-from-ABP algorithms are the commercially-available methods, such as PiCCO, ModelFlow, and LiDCO (21-27), which are analytically more complicated than our investigational algorithms in Table 1. In fact, our initial investigational plan was to also re-implement these commercial algorithms, based on publicly-available information (21-27). However, it became apparent it was not feasible to re-implement these commercial methods. Without inspecting the source code of any algorithm, there are many steps (pre-processing, error and outlier trapping, temporal averaging, and many other specific computational steps) that cannot be meaningfully replicated using just the published reports. Our initial attempts to re-implement these algorithms relied on our own judgments whenever the published sources had ambiguous methodological detail, but these implementations did not perform well (18). Our good-faith efforts to re-implement these commercial methods are available for review at www.physionet.org; needless to say, they should not be construed as equivalent to what is deployed in the commercial products.

Ideally, vendors would make the source code for their methods available for public inspection, to bring unreliable methods to light and accelerate acceptance of

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3 rigorous algorithms. However, this is simply not standard practice for commercial
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5 biomedical algorithms. Because most commercial algorithms will remain proverbial
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7 black-boxes to the user community, standard testing databases are all the more essential.
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9 Indeed, testing proprietary ECG arrhythmia detection algorithms using standard testing
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11 databases is a mandatory step in obtaining US FDA approval (5). The MIMIC II
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13 CO_{TD}/ABP dataset is now publicly and freely available. We invite developers and
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15 vendors of CO-from-ABP algorithms to test their methods and report their performance
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20 on this dataset.
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26 **Conclusion**

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29 Public-access testing databases are necessary to determine which CO-from-ABP
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31 algorithms are better than alternatives. Such databases can catalyze the development of,
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33 and public acceptance of, increasingly effective algorithms. Regarding the set of
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35 algorithms that we applied to this testing database, the Liljestrand method is a better
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37 predictor of CO than calibrated MAP in an ICU population, using typical ICU radial
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39 ABP, after filtering out 12% of the noisiest data. It is even more accurate given the
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41 cleanest ABP waveforms. The Liljestrand predictor may be a valuable parameter for
42
43 intelligent monitoring algorithms when a patient's radial ABP is measured. Future work
44
45 should examine the sensitivity and specificity of alarm algorithms which use this
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47 predictor, versus those that use conventional clinical parameters, and establish outcomes
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49 benefits. The corrected impedance algorithm also surpassed MAP as a predictor of CO
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51 changes. Other investigational algorithms failed to surpass calibrated MAP.
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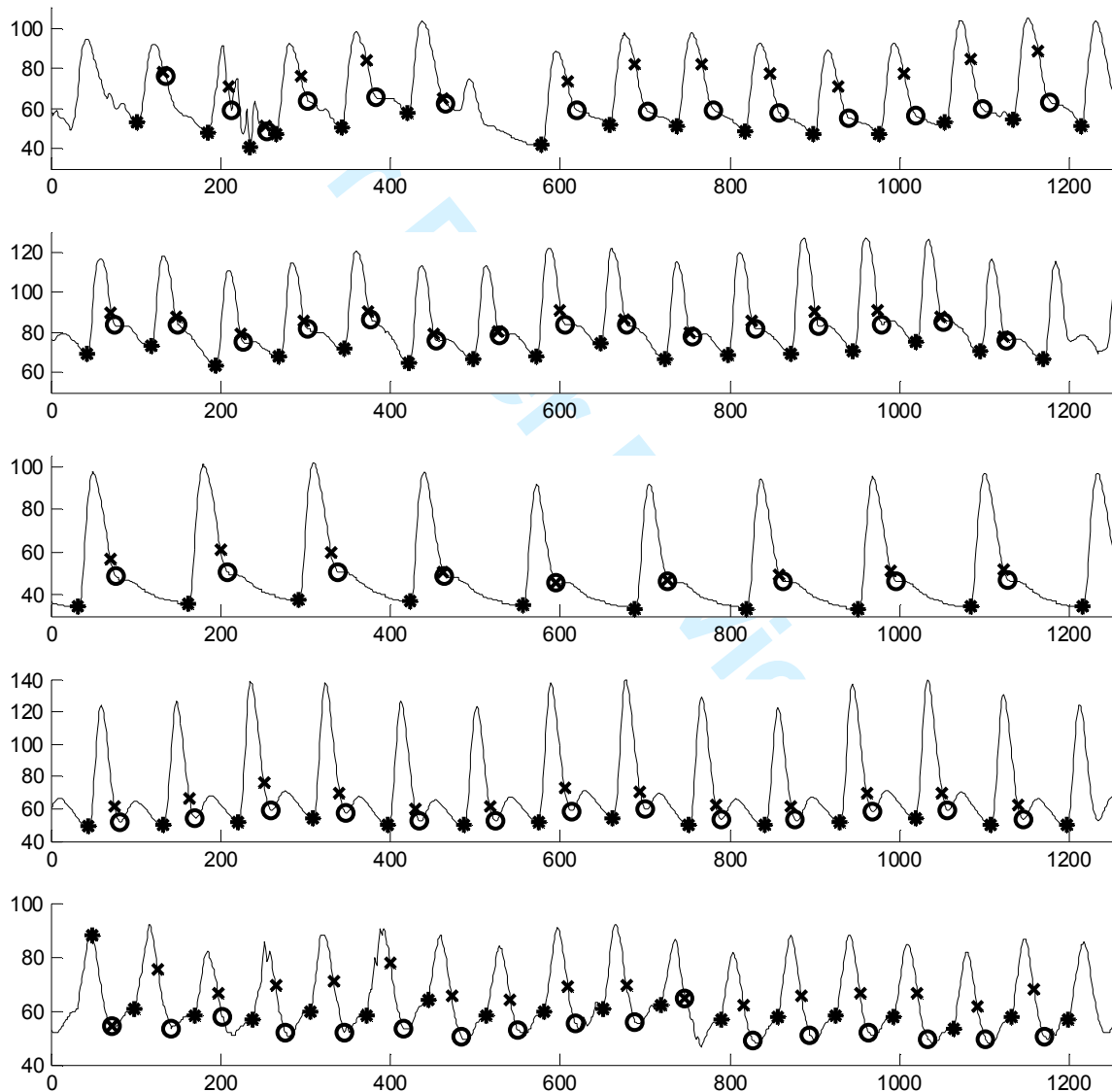
For Peer Review

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Fig. 1: Five examples of ABP waveforms and their key features as identified by our automated algorithms. The horizontal axis is sample number, with 125 samples = one second. *Onset* point of each beat is indicated by a black asterisk “*”; *end of systole*, estimated by $0.3 \cdot \sqrt{\text{beat_period}}$, is indicated by “X”; *end of systole*, estimated by the ‘lowest non-negative slope’ method, is indicated by a “0”. The algorithms also identify systolic (peak), mean, and diastolic (trough) blood pressures (not illustrated). A signal abnormality index (8) checks that all were within physiologic limits and also checks that the features’ variation from one ABP pulse to the next is not excessive.



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Fig. 2: Each investigational algorithm required calibration for each subject. We studied two methods of calibrating the algorithms for a subject. In *C1* (see below, black line), the “best-possible calibration factor” was computed. *C1* was selected to minimize the root-mean-square of the difference of each pairing of CO_{TD} and the corresponding CO-from-ABP estimations. In *C2* (see below, grey line), the first pairing of the CO-from-ABP estimate and CO_{TD} (see below, stem plot) was used to establish the calibration factor, which was then used for all subsequent CO estimation. Note that CO_{TD} is only measured at discrete intervals, while CO-from-ABP is continuous (assuming ABP is measured continuously).

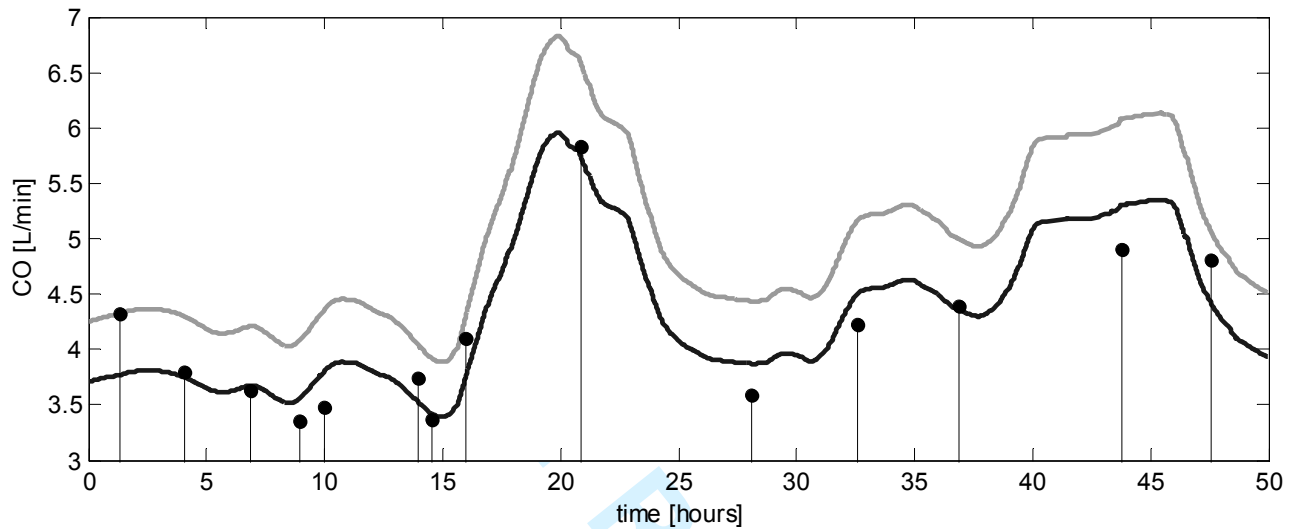


Fig. 3: (a) Bland-Altman plot comparing CO estimated by the algorithm (Liljestrand, using the C1 calibration methodology) with CO_{TD}. 95% limits-of-agreement for this algorithm and the other investigational algorithm are summarized in Table 3. (b) Liljestrand algorithm error as a function of several variables. Each variable is then put into 3 bins of equal quantity. Rectangular bars represent 95% limits-of-agreement for each bin. For example, as shown, CO estimation error decreases as PVR increases.

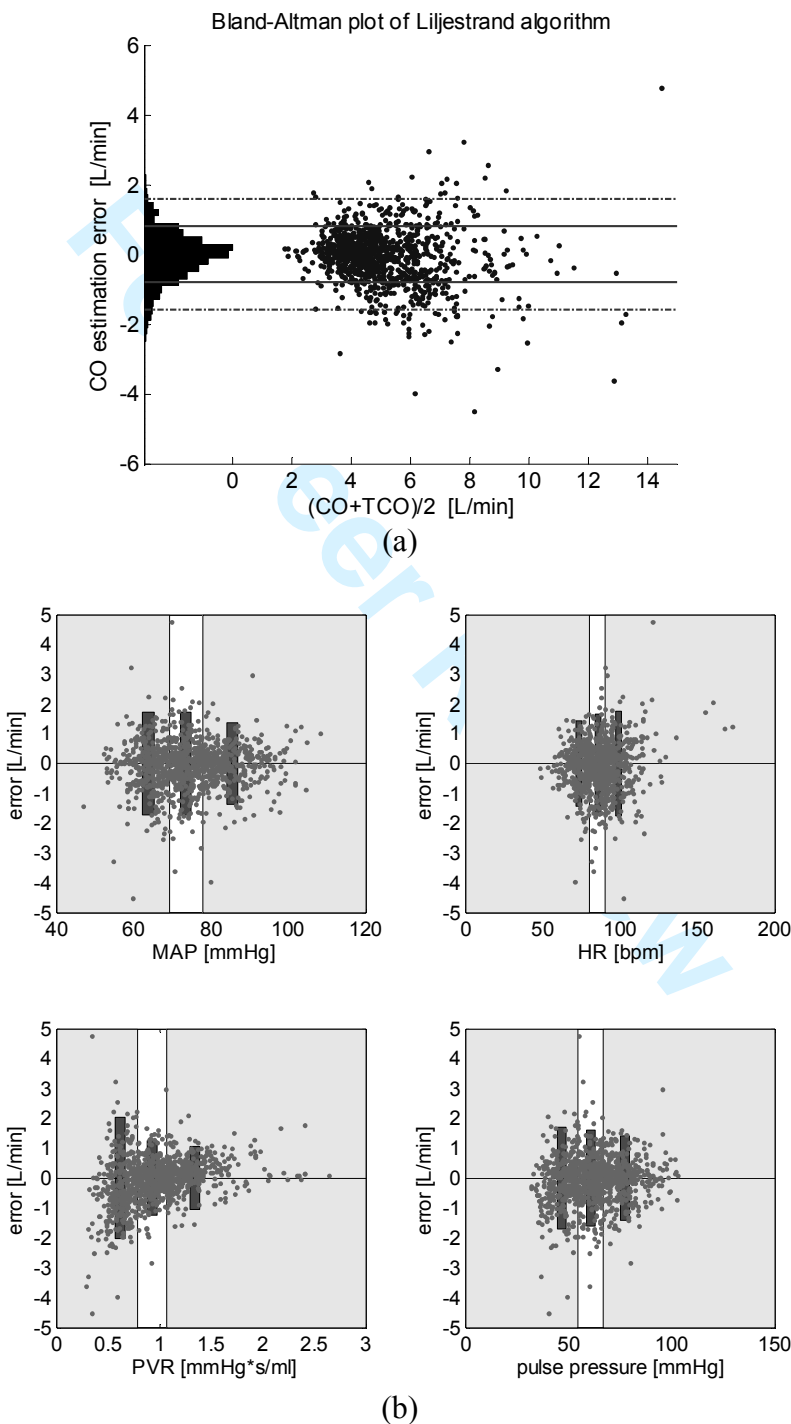


Fig. 4: Example of continuous CO-from-ABP estimated by the Liljestrand algorithm (grey line) versus episodic thermodilution CO measurements (stem plots) for a subject over a 50 hour time interval, using a single calibration (CI , see text for details). Pulse pressure (PP), mean arterial pressure (MAP) and heart rate (HR) through this same temporal window are also shown.

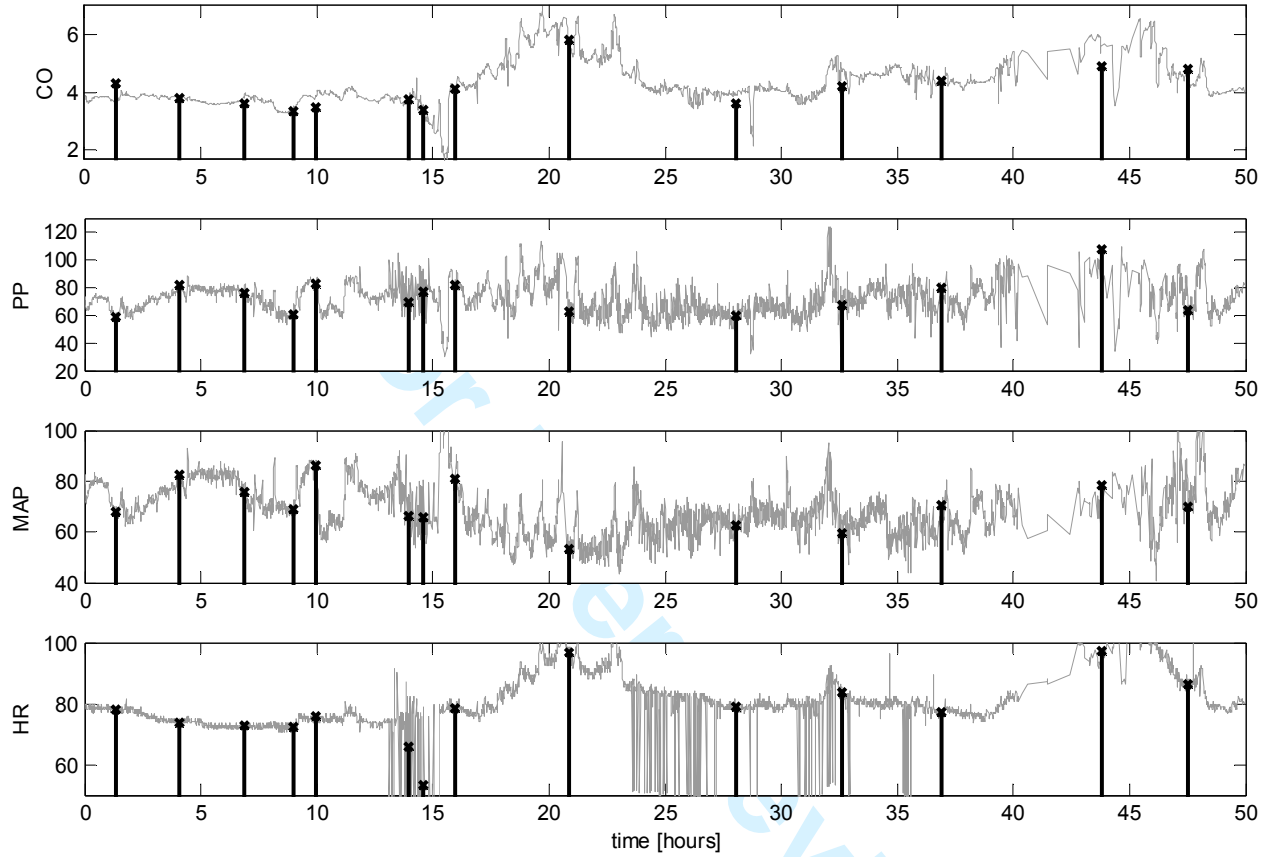


Table 1: Investigational CO-from-ABP algorithms
(CO = Stroke volume * HR)

Pulse Pressure (10)	Stroke volume = $k * (SBP - DBP)$
Liljestrand (11)	Stroke volume = $k * (SBP - DBP) / (SBP + DBP)$
Systolic Area (12, 13)	Stroke volume = $k * \int_{Systole} ABP(t) dt$
Systolic Area with Kouchoukos Correction (14)	Stroke volume = $k * \left(1 + \frac{Duration_{Systole}}{Duration_{Diastole}} \right) * \int_{Systole} ABP(t) dt$
Diastolic Decay [adopted from (16)]	<p><i>Solves for beat-to-beat PVR, fitting a monoexponential curve to each ABP pulse's peak of systole and trough of diastole, where:</i></p> $P_{Diastolic} = P_{Systole} \cdot e^{-k * time / PVR}$
Herd (19)	Stroke volume = $k * (MAP - DBP)$
Corrected Impedance (20)	Stroke volume = $k * (163 + HR - 0.48 * MAP) * \int_{Systole} ABP(t) dt$
AC Power (Root Mean Square)	Stroke volume = $k * \sqrt{(ABP(t) - MAP(t))^2}$

Table 2: Subject and data characteristics

	units	mean \pm sd	N
<i>Study Population</i>			
Age	yr	69 \pm 12	120
Stay duration	day	2.3 \pm 2.2	120
CO_{TD} measurements per patient		10 \pm 8	120
CO_{TD} range per patient	L/min	2.3 \pm 1.2	120
MAP range per patient	mmHg	24 \pm 10	120
PVR range per patient	mmHg·s/ml	0.5 \pm 0.3	120
<i>Pooled Data</i>			
CO_{TD}	L/min	5 \pm 2	1164
MAP	mmHg	75 \pm 10	1164
Heart rate	bpm	88 \pm 17	1164
PVR	mmHg·s/ml	1 \pm 0.4	1164

Table 3: 95% limits-of-agreement between thermodilution CO and investigational CO-from-ABP algorithms

Investigational Predictors of CO _{TD}	"Best Possible Single Calibration" (C1) Lower/Upper Limits (± L / min)	KS test vs. MAP (p-values)	"First Pairing Calibration" (C2) Upper/Lower Limits (± L / min)
Liljestrand	-1.76 / +1.41	0.0001*	-2.81 / +2.04
Corrected Impedance	-1.91 / +1.57[#]	0.009 *	-3.39 / +2.28
Pulse Pressure	-2.07 / +1.73	> 0.05	-3.05 / +2.76
Systolic Area	-2.07 / +1.73	> 0.05	-2.85 / +3.05
Systolic Area with Kouchoukos Correction	-2.08 / +1.71	> 0.05	-3.20 / +2.89
AC Power (RMS)	-2.09 / +1.73	> 0.05	-3.12 / +2.78
Diastolic Decay	-2.23 / +1.77	> 0.05	-3.22 / +2.57
Mean Arterial Pressure	-2.20 / +1.82		-3.19 / +3.42
Herd	-2.66 / +1.89	> 0.05	-3.65 / +3.16

C1 calibration represents a theoretical, retrospective calibration for each algorithm that best matches a subject's set of CO estimates and paired set of thermodilution CO data. For each investigational algorithm, the distribution of errors (estimated CO minus thermodilution CO) was compared with the distribution of errors of 'calibrated MAP' using the Kolmogorov-Smirnov test. C2 calibration uses the first paired CO estimate and thermodilution CO measurement to calibrate each algorithm to each subject, and applies that calibration to all subsequent pairings.

* p less than or equal to 0.05.

[#] When using the alternative "lowest non-negative slope" method to estimate the systolic interval, the lower/upper limits are -1.94 / +1.54 L/min. Results in Table 3 employ $0.3 \cdot \sqrt{\text{beat_period}}$ to estimate systolic interval.

^{##} When using the alternative "lowest non-negative slope" method to estimate the systolic interval, the lower/upper limits are -2.40 / +1.97 L/min.