Frontiers in Bioscience Elite

Front. Biosci. (Elite Ed) **2023**; 15(2): 12
https://doi.org/10.31083/j.fbe1502012

Original Research

Carotid Artery Corrected Flow Time Measured by Wearable Doppler Ultrasound Accurately Detects Changing Stroke Volume During the Passive Leg Raise in Ambulatory Volunteers

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Academic Editor: Suresh G. Joshi
Submitted: 3 September 2022 Revised: 25 February 2023 Accepted: 16 March 2023 Published: 22 May 2023

Abstract

Background: The change in the corrected flow time of the common carotid artery ($ccFT_{\Delta}$) has been used as a surrogate of changing stroke volume (SV_{Δ}) in the critically-ill. Thus, this relatively easy-to-obtain Doppler measure may help clinicians better define the intended effect of intravenous fluids. Yet the temporal evolution of SV_{Δ} and $ccFT_{\Delta}$ has not been reported in volunteers undergoing a passive leg raise (PLR). **Methods**: We recruited clinically-euvolemic, non-fasted, adult, volunteers in a local physiology lab to perform 2 PLR maneuvers, each separated by a 5 minute 'wash-out'. During each PLR, SV was measured by a non-invasive pulse contour analysis device. SV was temporally-synchronized with a wireless, wearable Doppler ultrasound worn over the common carotid artery that continuously measured ccFT. **Results**: 36 PLR maneuvers were obtained across 19 ambulatory volunteers. 8856 carotid Doppler cardiac cycles were analyzed. The ccFT increased nearly ubiquitously during the PLR and within 40–60 seconds of PLR onset; the rise in SV from the pulse contour device was more gradual. SV_{Δ} by +5% and +10% were both detected by a +7% $ccFT_{\Delta}$ with sensitivities, specificities and areas under the receiver operator curve of 59%, 95% and 0.77 ($p < 0.001$) and 66%, 76% and 0.73 ($p < 0.001$), respectively. **Conclusions**: The $ccFT_{\Delta}$ during the PLR in ambulatory volunteers was rapid and sustained. Within the limits of precision for detecting a clinically-significant rise in SV by a non-invasive pulse contour analysis device, simultaneously-acquired ccFT from a wireless, wearable ultrasound system was accurate at detecting 'preload responsiveness'.

Keywords: carotid artery; corrected flow time; fluid responsiveness; passive leg raise; Frank-Starling

1. Background

A fundamental tenet of cardiac physiology is that of stretch-induced myofibrillar calcium sensitivity [1,2]. That is, when cardiac muscle fibers are lengthened, their subsequent contraction is more forceful because muscle-shortening hinges upon intracellular calcium. Practically, this mechanism is exploited whenever a clinician administers a patient intravenous (IV) fluid to increase stroke volume (SV) [3,4]. In other words, increasing the volume of blood returning to the heart with IV fluid stretches cardiac myocytes and augments blood flow from the heart to the arteries; this is typically done to rectify diminished organ perfusion [3].

However, the relationship between cardiac stretch and its output does not increase linearly without change. As described by the Frank-Starling-Sarnoff curve, there is normally a steep increase in SV for each increment in cardiac filling until a plateau is reached, beyond which further cardiac filling has little effect on SV [5–7]. As well, during acute and chronic illnesses, the slope of this curve can flatten such that cardiac filling (i.e., myocardial stretch) has little effect on SV [6]. In this pathophysiological situation, providing IV fluid is physiologically ineffective and, arguably, harmful [8–11]; this has led clinicians in the intensive care unit (ICU) [8], emergency department (ED) [12,13] and operating room (OR) [14] to test patients for their ability to respond to IV fluid and mitigate the risk of volume overload [8,9].

One commonly-employed maneuver to determine if a patient will increase SV in response to IV fluid, or not, is the passive leg raise (PLR) [15–17]. The PLR involves measuring baseline SV in the semi-recumbent position and then again with the patient supine and legs raised. This positional change mobilizes 200–300 mL of blood towards the heart; a 10–15% increase in SV indicates that the patient will most-likely respond appropriately to IV fluid. While much has been reported on the PLR in critically-ill patients [17–19], relatively little has been described about this maneuver and its time-course in healthy volunteers [20]. Studying healthy subjects is important because roughly 50% of critically-ill patients are preload unresponsive when a PLR maneuver is performed [16,18]. However, the fraction of preload unresponsive patients is much lower early in illness [21,22] suggesting that preload unresponsiveness is a pathological state that evolves during the disease arc. Consistent with this are our observations wherein no healthy subject was unresponsive to preload when performing a squat maneuver [23,24] or undergoing simulated blood transfusion following moderate-to-severe central hypovolemia [25,26]. Furthermore, Søndergaard recently observed that 82% of healthy volunteers were preload responsive by stroke volume as evoked by the passive leg raise [27]. Nevertheless, we have not fully-described the fraction of preload unresponsive, ambulatory volunteers during PLR. Finally, our group [23,25,26,28] and others [29] have successfully used the common carotid artery corrected flow time (ccFT) to assess preload reserve. The ccFT is easily obtained from the Doppler spectrogram; it is the duration of mechanical systole (in milliseconds) corrected for heart rate and the direct relationship between the duration of systole and venous return (i.e., cardiac output) has been known for nearly a century [23,30]. Given the above, in this ambulatory volunteer study, we report on the change in SV and ccFT during a PLR maneuver. We hypothesized that in ambulatory volunteers, preload responsiveness would be nearly ubiquitous and also that the change in ccFT would be an accurate surrogate to detect this state.

2. Materials and Methods

2.1 Clinical Setting

We included ambulatory, volunteers at least 18 years of age who were non-fasted and clinically euvolemic. Euvolemia was determined by normal resting vital signs, the absence of medical comorbidities known to change blood volume (e.g., congestive heart failure, chronic kidney disease), the absence of peripheral edema or dyspnea and no change in baseline body weight by $\pm$5% on the day of examination. The procedures followed were in accord with the ethical standards of the committee on human experimentation at our institution. Written and informed consent was obtained for all subjects, and the study was approved by the Research Ethics Board of Health Sciences North. Exclusion criteria were known cardiovascular history and/or taking regular cardiovascular medications (e.g., anti-hypertensives, diuretics).

2.2 Stroke Volume Monitoring

The Clearsight (Edwards Lifesciences; Irvine, CA, USA) was applied to the subject in the semi-recumbent (i.e., semi-Fowler) position. Clearsight (CS) is a non-invasive pulse contour analysis SV monitor that uses the 'volume clamp' method to provide SV every 20 seconds [31]. CS can track changes in cardiac output and is most accurate in ambulatory volunteers without problems of peripheral perfusion [31]. The protocol did not begin until there was adequate CS signal as measured by the Physiocal calibration metric (i.e., $\geq$30). The third digit was used in all volunteers as recommended by the manufacturer; the subject was instructed to keep his or her arm passively extended throughout the protocol and all subjects were asked to maintain normal, quiet tidal respiration during the PLR maneuver.

2.3 Carotid Doppler Monitoring

A U.S. FDA-cleared, wearable carotid Doppler patch (Flosonics Medical, Sudbury, ON, Canada) was placed over the carotid artery below the angle of the jaw to ensure Doppler sampling below the bifurcation of the common carotid artery (Fig. 1). When an audible Doppler shift was heard and a Doppler spectrum consistent with the common carotid artery visualized, the Doppler patch was adhered in place. As previously described [32], the wearable ultrasound is a 4 MHz, continuous wave (CW) Doppler that does not image the carotid artery. The insonation angle is 60 degrees and generated by a physical 'wedge' on the face of the transducer. Given that it is CW, the Doppler sample volume is the entirety of the vessel lumen which makes uniform insonation [33,34] more likely. The automated maximum velocity trace was used to determine the duration of systole from the systolic velocity upstroke to the dicrotic notch (i.e., flow time); the duration of systole in seconds was used to calculate the ccFT per the equation of Wodey, as previously described [23–26]. Heart rate was used to align the non-invasive pulse contour device and Doppler spectral signals; the calculation of heart rate was standard across participants. Heart rate from the pulse contour device was outputted every 20 seconds and that data was aligned to a 20 second moving average heart rate from the wearable Doppler device. Implemented in Python, the cross correlation of the heart rate signals evaluated the signal similarity for each 20 second time lag. The maximum correlation value between signals was found and the corresponding time lag was used to align signals.

2.4 Passive Leg Raise Protocol

Each protocol consisted of a 60 second resting baseline followed by passive torso lowering to the supine position with legs elevated to no more than 45 degrees, for an additional 3 minutes (i.e., the PLR) [17,18]; thus, each protocol was 4 minutes in total duration. Each volunteer performed 2 PLR maneuvers separated by at least 5 minutes of 'washout' where they remained at resting baseline prior to the second maneuver.

Baseline values for all measures were calculated from the time window at which SV was the lowest during the baseline period and percent change for each 20 second measure was calculated by reference to this resting baseline; this was done to ascertain the greatest hemodynamic effect of the PLR.

2.5 Statistical Analysis

As the non-invasive pulse contour device updates and displays hemodynamic data every 20 seconds, we analyzed

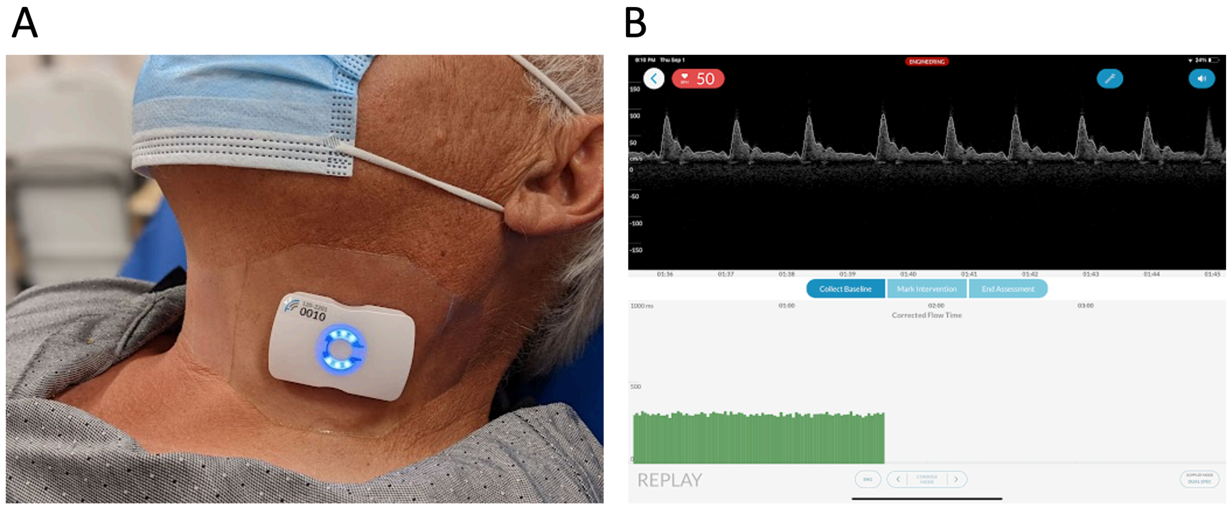

Fig. 1. The wireless, wearable Doppler ultrasound system. (A) The device on the neck of a volunteer. (B) The graphical user interface of the ultrasound system displayed on an iOS device.

the change during the PLR every 20 seconds. Therefore, each 3-minute PLR consisted of 9 data points. To evaluate the ability of the ccFT to detect a 10% change in SV ($SV_\triangle$), sensitivity, specificity and the area under the receiver operator curve were calculated after dichotomizing $SV_\triangle$ into $\geq$10% or $<$10% [4]. Given previous data showing that the percentage error for trending cardiac output by the CS device during PLR is upwards of 40% [35], we performed a secondary analysis whereby we dichotomized $SV_\triangle$ into $\geq$5% or $<$5% and calculated the sensitivity, specificity and the area under the receiver operator curve for detecting this threshold using $ccFT_\triangle$. Mann-Whitney U rank two-sided test was performed with the null hypothesis that the area under the receiver operator curve was 0.5 for both thresholds.

We used a Willcoxon signed-rank two-sided test, comparing baseline stroke volume and heart rate of the first and second passive leg raises to determine if the 5-minute washout period was adequate. We also used Willcoxon signed-rank two-sided test to determine if there was a difference in all measured hemodynamic variables during the passive leg raise. Finally, test-retest reliability for the two passive leg raise maneuvers was assessed by interclass correlation (ICC).

3. Results

21 adult volunteers were studied; 11 were women and 10 were men. One subject was entirely excluded for poor carotid Doppler placement with unusable signal; a second subject was entirely excluded because of low Physiocal on the CS device (i.e., less than 10). A single PLR was excluded as there was a significant Doppler angle change noted during the PLR; another PLR was excluded because of low Physiocal noted during the maneuver. The baseline characteristics of the volunteers included in the final analysis are listed in Table 1.

Table 1. Baseline Hemodynamics. The minimum 20s baseline from SV and corresponding cCFT value was selected.

n = 19	Mean	std
Patient Age	30.95	±7.64
Patient Height (m)	1.71	±0.11
Patient Weight (kg)	82.84	±42.05
BMI (kg/m^2)	27.48	±11
MAP (mmHg)	88.37	±9.54
HR (bpm)	70.21	±10.63
SV (mL/b)	87.87	±17.16
Systolic Blood Pressure (mmHg)	118.37	±13.02
ccFT (ms)	310.69	±10.17

The average between sessions for each subject was used to calculate the mean and standard deviation. M is meters, kg/m^2 is kilograms per meters-squared, mmHg is millimeters of mercury, bpm is beats per minute, mL/b is milliliters per beat, ms is milliseconds.

Effect of PLR on Hemodynamics: There were 36 PLRs performed across 19 subjects. The % $SV_\triangle$ as well as % change in ccFT (% $ccFT_\triangle$) throughout all PLRs are illustrated in Fig. 2. In total, 56% of volunteers achieved $\geq$10% $SV_\triangle$ within the first minute of the PLR, 47% during the second minute, 64% within the third minute and 72% at any time during the PLR. Considering $\geq$5% $SV_\triangle$ as the threshold of interest, 72% of volunteers achieved this within the first minute of the PLR, 81% in the second minute, 86% in the third minute and 92% during anytime in the PLR.

Willcoxon signed-rank two-sided test comparing HR and SV between the baseline periods of the first and second PLR showed no significant difference; that is, p = 0.17 and p = 0.55, respectively.

Wilcoxon signed-rank test was also used to compare baseline, maximal intervention pairs for each PLR

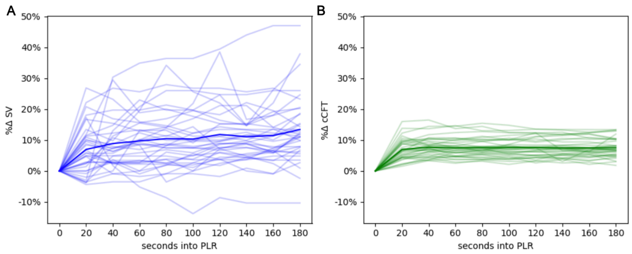

Fig. 2. The hemodynamic evolution of the PLR. (A) The change in stroke volume across the PLR, each faint line represents a single maneuver, the emboldened line is the average of all maneuvers over time. (B) The change in ccFT across the PLR.

across participants. Statistically, all values except heart rate showed a statistically-significant difference in ranked means, though only ccFT was clinically significant. Mean arterial pressure fell by 3.2 mmHg ($p = 0.008$), heart rate fell by 1.8 beats per minute ($p = 0.1$), stroke volume increased by 8.23 mL ($p < 0.001$), systolic blood pressure fell by 2.91 mmHg ($p = 0.4$) and ccFT increased by 26.8 ms ($p < 0.001$).

Test-retest reliability for the two passive leg raise maneuvers was moderate for both percent change SV (ICC = 0.54) and ccft (ICC = 0.54).

Diagnostic Characteristics of Carotid Artery Corrected Flow Time: In total 8856 carotid beats were considered in this analysis. Fig. 3 shows the diagnostic characteristics of % ccFT$_\triangle$ at discriminating both +5% SV$_\triangle$ and +10% SV$_\triangle$ as measured by CS. Mann-Whitney U rank two-sided test ($p < 0.05$), revealed that the AUROC is significantly different from 0.5 ($p < 0.001$ for both thresholds).

4. Discussion

Our results are clinically-important for reasons that flow from the hypotheses described at the outset; that is, that the ccFT$_\triangle$ would be a viable surrogate for detecting a clinically-significant SV$_\triangle$ and that preload responsiveness would be common in this cohort. With regards to our first hypothesis, we observed that (1) the optimal % ccFT$_\triangle$ threshold value (i.e., +7%) was identical whether discriminating a +5% SV$_\triangle$ or +10% SV$_\triangle$ during PLR and, (2) the % ccFT$_\triangle$ accurately detected a $\geq$+5–10% SV$_\triangle$ when measured continuously with a wireless, wearable Doppler ultrasound system. With respect to our second hypothesis, we noted that (3) in this group of non-fasted, euvolemic, ambulatory volunteers, 92% were preload responsive, as defined by a $\geq$+5–10% SV$_\triangle$ measured by the CS during a 3-minute PLR. The clinical and scientific relevance of these points are elaborated upon below, in turn.

First, previous investigators have reported 40% error in the CS device when tracking SV$_\triangle$ as compared to transpulmonary thermodilution [35]. This means that when detecting +10% SV$_\triangle$ by thermodilution, the CS may register % SV$_\triangle$ between approximately +5% and +15%. For this reason, we analyzed both +5% SV$_\triangle$ and +10% SV$_\triangle$

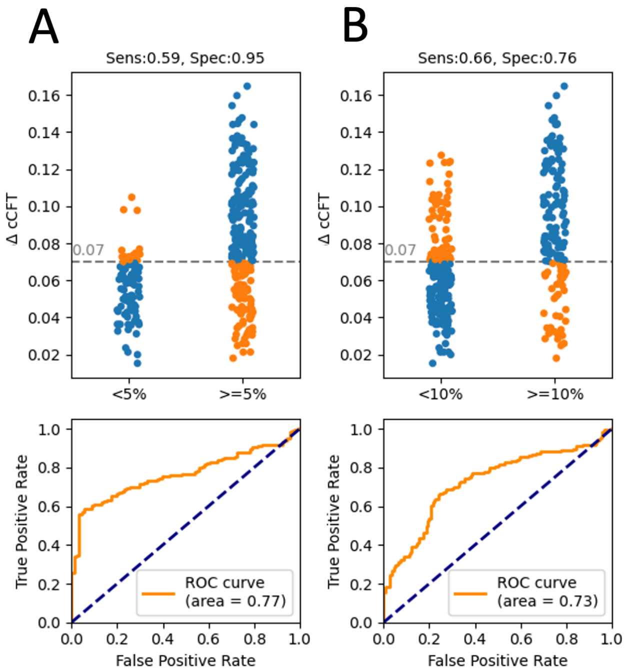

Fig. 3. The diagnostic accuracy of changing ccFT at detecting changing CS SV. (A) shows the characteristics for a +5% change in CS SV. (B) for detecting a +10% change in CS SV.

from the CS as both these values could represent a +10% SV$_\triangle$ by transpulmonary thermodilution. Notably, the optimal % ccFT$_\triangle$ (i.e., +7%) was identical for both SV$_\triangle$ threshold analyses. This observation suggests, but does not prove, that CS precision was diminished, especially for differentiating relatively small % SV$_\triangle$ (i.e., between +5% and +9% SV$_\triangle$). This finding is consistent with error noted by Broch and colleagues in patients undergoing PLR prior to coronary artery bypass grafting [35]. We therefore maintain that a +5–10% SV$_\triangle$ from the CS device likely represents 'preload responsiveness' as defined by transpulmonary thermodilution. The temporal change in ccFT that we report strengthens this supposition. As in Fig. 2, ccFT$_\triangle$ occurs almost immediately after the PLR onset. The average % ccFT$_\triangle$ achieved within 40–60 seconds amongst all volunteers was +8% and remained this high throughout the entirety of the PLR. This time course is consistent with data by Monnet and colleagues in the critically-ill monitored by descending aortic Doppler as the gold standard [18]. They observed that 'fluid responders' were ubiquitously detected within the first 30–60 seconds of the PLR. Therefore, given the early and large % ccFT$_\triangle$ (i.e., >+7%) during the PLR, we suspect that many subjects registering +5–9% SV$_\triangle$ by CS at that time were behaving, hemodynamically, as 'true responders'; that is, they were probably truly above +10% SV$_\triangle$.

Second, we observed that the change in the ccFT$_\triangle$ is a good diagnostic surrogate for detecting a $\geq$+5–10% SV$_\triangle$. These data are congruent with two previous studies performed with the wearable Doppler ultrasound, but with very different preload challenges [23–26]. In the first, healthy volunteers performed a squat maneuver, which diminishes the gravitational pressure gradient between the feet and the right atrium, akin to the PLR. The squat maneuver is easy-to-perform and allows for rapid data collection without additional equipment (i.e., hospital gurney). In the second, healthy volunteers underwent moderate-to-severe central hypovolemia induced by lower body negative pressure (LBNP) followed by rapid, simulated blood transfusion when the LBNP was released—as a resuscitation model. Both paradigms found a similar optimal % $ccFT_{\Delta}$ threshold for detecting a $\geq$+10% SV_{Δ} which were slightly lower than the value found during PLR in this study. The convergence of 3 separate physiological paradigms supports carotid Doppler as a mechanism to capture $\geq$+10% SV_{Δ} with accuracy, at least in healthy volunteers. This is consistent with data in the critically-ill and in those under general anesthesia [29,36–40]. Indeed, we note the similarity between the data presented here and that of Barjaktarevic and colleagues, who studied $ccFT_{\Delta}$ in undifferentiated shock [36]. In their investigation, the sensitivity, specificity and area under the receiver operator curve were 69%, 96% and 0.88 for detecting a 10% SV_{Δ} during PLR. Herein, the same values are 59%, 95% and 0.77 for detecting a +5–10% SV_{Δ}. Nevertheless, the absolute $ccFT_{\Delta}$ observed in our ambulatory volunteer population is greater than that observed by Barjaktaravic *et al*. [36] and in our LBNP model. We do not have a definitive explanation for this difference but postulate that it may be due to adrenergic tone, which shortens flow time for any given SV [41]. Importantly, not all investigators have been able to replicate $ccFT_{\Delta}$ as a surrogate for SV_{Δ} in patients. Given that Doppler ultrasound is subject to human measurement variability [42] and detecting change is sensitive to the number of sampled cardiac cycles [43,44], we suspect that a wearable Doppler system mitigates these confounds.

Third, that such a large fraction of our volunteers was 'preload responsive' provides an important lesson in basic, clinical hemodynamics: the non-fasted, euvolemic, individual is normally preload responsive when assessed by a PLR. In other words, being 'preload responsive' does not mean that a patient has a fluid deficit (i.e., is in a state of hypovolemia), nor does it mean that a patient necessarily requires volume replacement [16]. Being 'preload responsive' simply means that an individual has recruitable stroke volume, which is evolutionarily advantageous during times of stress. This observation, that ambulatory volunteers normally have preload reserve, calls into question resuscitation protocols that encourage IV fluid until 'fluid responsiveness' disappears—which is likely an abnormal state [45,46]. This could explain why some studies that dictated IV fluid administration until fluid responsiveness was extinguished demonstrated no benefit and excessive IV fluid provision [12,46,47]. Our results are also in contradistinction with the finding of Godfrey and colleagues who observed that healthy volunteers were largely fluid unresponsive upon PLR [48]. We note that their study employed transthoracic echocardiography as a gold standard, which is subject to human factors [49], including measurement variability and statistically-limited cardiac cycle sample size [16]. Our study assessed the hemodynamic evolution of the PLR across 4-minutes—comprising thousands of cardiac cycles; our findings are in-line with a more recent investigation by Søndergaard where 82% of healthy subjects were preload responders during a 7-minute passive leg raise [27].

There are limitations to our study. First, we studied ambulatory volunteers, so whether this data can be generalized to hospitalized patients and especially those in the intensive care unit is limited. Nevertheless, it is important to qualify normal physiology so as to better understand departures from it during sickness. As well, other investigators have found that changing carotid Doppler measures can be used in critically-ill populations; this was echoed in a recent systematic review [29,36–40]. As a second limitation, we had to exclude a small minority of our sample due to poor signal from the wearable Doppler and the CS. It is possible that inherent differences in these excluded subjects may skew the data and limit its generalizability. Third, we did not compare our technique to photoplethysmography during PLR, which is also known to detect preload responsiveness [16]. Changes in the perfusion index from wearable photoplethysmography is, therefore, another technology comparable to the wearable Doppler system described above [16]. A potential advantage of the carotid Doppler is that it could be hardy to signal disruption induced by peripheral vasoconstriction, which has been a problem observed in both photoplethysmography and uncalibrated pulse contour analysis transduced via finger-cuff [31]. Fourth, there was a wide distribution of body habitus in this study. We recruited volunteers taking no cardiovascular medications. The diversity in body habitus allowed for testing the Doppler device on a wide range of neck sizes. While this BMI distribution may limit the generalizability of our results, we note that the pre-post paradigm of the PLR should also hold true in the obese population. Fifth, we did not account for exercise training [50] nor did we account for other potential confounds such as caffeine, herbal supplement or dietary intake in this study. It is unclear how these confounds may affect the results of the PLR in our study population and this is not a hypothesis we set out to test, though the response to PLR is related to exercise capacity [50]. We note that studies of critically-ill patients in whom preload responsiveness is measured also do not account for exercise training or other dietary vasoactives such as caffeine. Sixth, we note that the test-retest reliability between the two passive leg raises was only moderate. This might be expected given that the reliability of multiple, successive PLRs has been questioned [20]. It is possible that emptying and redistribution of venous blood from certain capacitance beds (e.g., splanchnic) on the first PLR alters subsequent maneuvers.

5. Conclusions

In this study of non-fasted, clinically-euvolemic, ambulatory volunteers, a clinically-significant % SV_{Δ} change during PLR was common and the rise in SV was gradual during the PLR maneuver. As well, we observed that the $ccFT_{\Delta}$, obtained from a wireless, wearable, Doppler ultrasound system rose rapidly and ubiquitously throughout the PLR and accurately detected SV_{Δ}; this is consistent with previously-published, but entirely different physiological protocols [23–26]. Therefore, we conclude that preload responsiveness is a normal physiological state and is neither indicative of volume status, nor volume need. As well, the $ccFT_{\Delta}$ acquired from wearable, continuous, Doppler ultrasound is a valid surrogate for % SV_{Δ} across a variety of preload challenges, including the passive leg raise.

Availability of Data and Materials

Available upon reasonable request.

Author Contributions

JÉSK—conception, primary drafting, analysis, critical revisions; CH—analysis, critical revisions; ME—analysis, critical revisions; AME—conception, analysis, enrollment, critical revisions; JKE—conception, analysis, enrollment, critical revisions. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The procedures followed were in accord with the ethical standards of the committee on human experimentation at our institution. Written and informed consent was obtained for all subjects, and the study was approved by the Research Ethics Board of Health Sciences North (#19-011).

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

JESK, CH, ME, AME, JKE work for Flosonics Medical, the start-up building the wearable Doppler ultrasound.

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