Brief Communication

The Correlation between Carotid Artery Corrected Flow Time and Velocity Time Integral during Central Blood Volume Loss and Resuscitation

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Abstract

Background: Doppler ultrasound of the common carotid artery is used to infer central hemodynamics. For example, change in the common carotid artery corrected flow time (ccFT) and velocity time integral (VTI) are proposed surrogates of changing stroke volume. However, conflicting data exist which may be due to inadequate beat sample size and measurement variability – both intrinsic to handheld systems. In this brief communication, we determined the correlation between changing ccFT and carotid VTI during progressively severe central blood volume loss and resuscitation. **Methods:** Measurements were obtained through a novel, wireless, wearable Doppler ultrasound system. Sixteen participants (ages of 18–40 years with no previous medical history) were studied across 25 lower body-negative pressure protocols. Relationships were assessed using repeated-measures correlation regression models. **Results:** In total, 33,110 cardiac cycles comprise this analysis; repeated-measures correlation showed a strong, linear relationship between ccFT and VTI. The strength of the ccFT-VTI relationship was dependent on the number of consecutively averaged cardiac cycles ($R_{1\ cycle} = 0.70$, $R_{2\ cycles} = 0.74$, and $R_{10\ cycles} = 0.81$). **Conclusions:** These results positively support future clinical investigations employing common carotid artery Doppler as a surrogate for central hemodynamics.

Keywords: Carotid artery, corrected flow time, Doppler ultrasound, functional hemodynamic monitoring, velocity time integral, wearable technology

Introduction

Doppler ultrasound of the common carotid artery is used to infer central hemodynamics.[1] For example, the change in the carotid artery corrected flow time (ccFT) – the systolic time corrected for heart rate (HR) – tracks volume loss and administration in various patient populations.[2] Specifically, two groups found that the ccFT fell with hemodialysis.[3,4] Furthermore, one of these investigations reported that ccFT increased back to predialysis baseline with passive leg raise (PLR);[4] the PLR is a maneuver well known to increase central blood volume. Similarly, Mackenzie *et al*. noted falling and rising ccFT with blood donation and PLR,[5,6] respectively, whereas Barjaktarevic *et al*. observed that ccFT augmentation during PLR predicted the change in stroke volume (SV) in undifferentiated shock.[7]

In addition to ccFT, changing carotid artery flow by Doppler ultrasound has been used as a surrogate for SV during resuscitation.[8,9] Carotid blood flow is calculated by multiplying the velocity time integral (VTI) by the area of the carotid artery; thus, VTI is directly related to the volume of blood pumped through the carotid per cardiac cycle. Nevertheless, while conflicting data exist for both carotid flow and ccFT as SV surrogates,[10-13] many of these investigations suffer from diminished measurement precision due to human factors[14] and do not report the least significant change for the number of cardiac cycles sampled before and during a hemodynamic intervention.

Received: 09-07-2023 **Revised:** 18-08-2023 **Accepted:** 01-09-2023 **Available Online:** 07-12-2023

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_80_23

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How to cite this article: Kerrebijn I, Munding CE, Horner C, Atwi S, Elfarnawany M, Eibl AM, *et al*. The correlation between carotid artery corrected flow time and velocity time integral during central blood volume loss and resuscitation. J Med Ultrasound 2023;31:309-13.

To clarify these discrepant observations, we have previously reported that both carotid VTI and ccFT require averaging multiple cardiac cycles to confidently detect change;[15] we have also shown that both changing VTI and ccFT correlate with SV during various preload modifying maneuvers in healthy subjects.[16,17] However, we did not correlate changing carotid VTI with ccFT during these maneuvers which represents a noteworthy gap in our knowledge, given that one group found a poor relationship between ccFT and carotid blood flow.[18]

In this study, therefore, we correlated changing ccFT with carotid artery VTI during lower body-negative pressure (LBNP) and release as a model of central blood volume loss and resuscitation in participants with no previous medical history. LBNP is a well-validated paradigm wherein central blood volume falls as blood is drawn by vacuum to the lower body; then, upon the release of the negative pressure, central blood volume returns to baseline.[19] Our investigations were enabled by a novel, wireless, wearable Doppler ultrasound patch capable of measuring ccFT and VTI simultaneously. We hypothesized that there would be a strong, linear correlation between changing ccFT and carotid VTI and that the correlation would strengthen with the number of averaged cardiac cycles.

Methods

Clinical setting

Adults with no prior medical history were recruited; none were taking cardiovascular medications. The study was approved by the Research Ethics Board of the Mayo Clinic (IRB number 19-010136); written informed consent was obtained from all participants.

Doppler system

The US Food and Drug Administration cleared, wireless, wearable, 4 MHz Doppler ultrasound patch (Flosonics Medical, Sudbury, Canada) was placed, and the ccFT and VTI were captured as described previously.[17,20]

Lower body-negative pressure

Each stage of the LBNP protocol was 5 min long, beginning with resting baseline. LBNP was reduced by 15 mmHg per stage down to and including − 60 mmHg and then by 10 mmHg down to and including − 80 mmHg, as tolerated. The final stage was release of LBNP to atmospheric pressure. All subjects underwent this seven-stage protocol in duplicate with a 30-min washout period in between sessions.

Statistical analysis

Cardiac cycles with artifacts or during LBNP stage transition were excluded. Artifacts were detected by HR discordance of <0.8 or >1.3-fold change between devices and visual inspection of the Doppler spectra for phonation or deglutition signatures. Both ccFT and VTI were referenced to resting baseline to model increasingly severe hypovolemia. The change from the lowest-achieved LBNP stage back to atmospheric pressure is used as a model of rapid blood transfusion. Data were analyzed over two temporal windows – a 10-beat average and a whole-stage average. To account for multiple measurements per subject, the relationship between ccFT and VTI was assessed using repeated-measures linear correlation (R_{rm}) across negative pressure stages. To detect an R_{rm} of 0.8, with a power of 0.8 and a significance level of 0.05, we calculated a required minimum sample size of approximately 11 for each stage for a multilevel model with 7 stages.

Results

The baseline characteristics and vital signs of all included subjects are listed in Table 1.

In total, 39,958 cardiac cycles were captured; 17.14% of the beats were excluded for the following reasons: 7.61% stage transition, 2.55% misaligned HR between the Doppler and traditional HR vital sign monitor (i.e., <0.8 or >1.3-fold change as compared to vital sign monitor), and 6.98% Doppler feature detection (e.g. dicrotic notch) failure as determined by either ccFT or VTI value more than two standard deviations as compared to the respective mean values for any given LBNP stage. 33,110 cardiac cycles comprised the analysis including 4380 release-stage beats. The correlations for changing ccFT and VTI are shown in Figure 1. The strength of the ccFT-VTI relationship was dependent on the number of consecutively averaged valid cardiac cycles ($R_{1\ cycle} = 0.70$, $R_{2\ cycles} = 0.74$, and $R_{10\ cycles} = 0.81$). Release phase R was 0.38 and slope was 4.93 for % ccFT change and R was 0.35 and slope was 1.88 for absolute ccFT change.

Discussion

Our results demonstrated a number of clinically important findings. First, during progressive central blood volume loss, there was a strong linear correlation between falling ccFT and carotid VTI. Second, ccFT and VTI both also increased during central blood volume resuscitation, but the strength of their direct correlation was diminished. Finally, the correlation between changing ccFT and VTI was weaker and quite variable when fewer than six consecutive cardiac cycles were averaged; the correlation coefficient became stronger and stabilized beyond the mean of at least 20 consecutive cardiac cycles in this model.

Table 1: Demographics and sample characterization at baseline

Demographic variable ($n=16$)	Mean±SD
Average age (years)	27±4.2
Percentage female	44
Average BMI	25.9±4.6
Mean heart rate (bpm)	63.6±8.1
Systolic blood pressure (mmHg)	132.6±8.9
Diastolic blood pressure (mmHg)	78.3±5.3
Mean arterial pressure (mmHg)	98.1±6.2

BMI: Body mass index, SD: Standard deviation

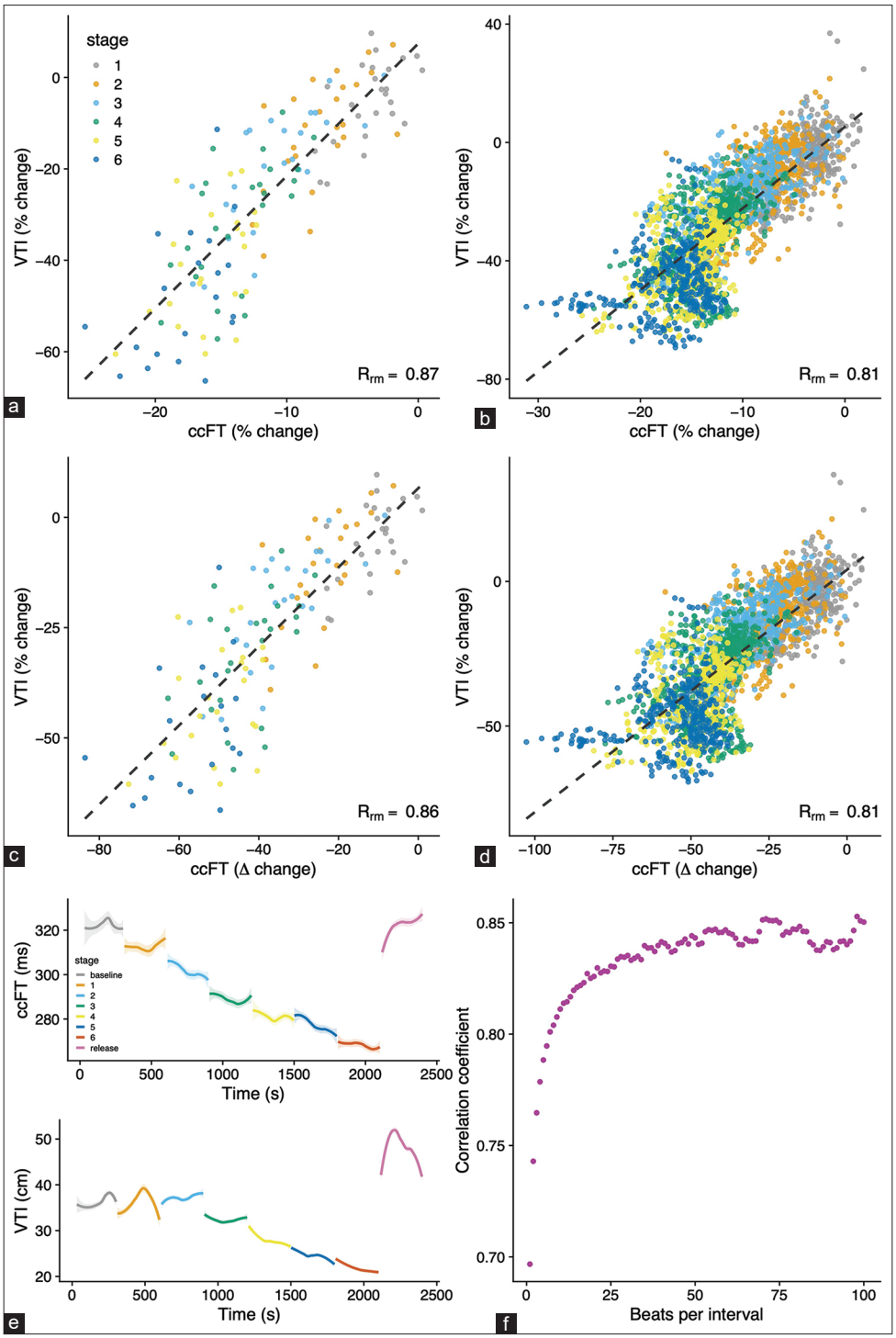

Figure 1: The relationship between change in common ccFT and VTI in models of central blood volume loss and resuscitation. (a) Across decreasing pressure stages, the Rrm is 0.87 and the slope is 2.82, using whole-stage average % changes. (b) Across decreasing pressure stages, the Rrm is 0.81 and the slope is 2.79, using 10-beat average % changes. (c) Across decreasing pressure stages, the Rrm is 0.86 and the slope is 0.88, using whole-stage average absolute ccFT and VTI % change. (d) Across decreasing pressure stages, the Rrm is 0.81 and the slope is 0.87, using a 10-beat average absolute ccFT and VTI % change. (e) Sample of raw ccFT (top) and VTI (bottom) values during the lower body-negative pressure protocol. Shown with smooth trend lines per stage. (f) The effect of the number of consecutively averaged cardiac cycles on repeated-measures correlation coefficient. ccFT: Carotid artery corrected flow time, VTI: Velocity time integral

The relationship between ccFT and carotid VTI is consistent with our previous work where we related each of these measures to changing SV during LBNP and release in healthy volunteers.[16,21] In this particular investigation, we observed that during central volume loss, the slopes of the relationship between percent change in ccFT and absolute change in ccFT

with percent change in carotid VTI were approximately 3.0 and 1.0, respectively. Clinically, this means that a falling ccFT of 2%–4%[17,21] or 7–10 ms[7] would correlate with decreased carotid VTI of 6%–12% and 7%–10%, respectively. Conversely, the slope of the relationship between changing ccFT and carotid VTI was essentially double when central blood volume was replenished upon LBNP release. Based on this, a 7-ms rise in ccFT correlates with an 11%–13% carotid VTI augmentation; however, this relationship was not statistically significant. We are curious, specifically, about a + 7-ms change in ccFT because this was the optimal threshold for predicting at 10% SV change reported by Barjaktarevic *et al*. in undifferentiated shock.[7]

Our data may partially explain the report by Judson *et al*. who found a poor relationship between carotid blood flow and ccFT in septic patients receiving intravenous fluids.[18] Although there are many differences between their investigation and ours, we suspect that at least one key mediator is the number of consecutive cardiac cycles considered in their study, which was only 3. This number of sampled heartbeats is common in Doppler studies, but our data illustrate why this could be problematic. Fewer than six consecutive cycles led to a poorer correlation between ccFT and carotid VTI [Figure 1f]. Our current analysis is consistent with our previous report using the coefficient of variation of the carotid Doppler signal to establish least significant change;[15] we found that, on average, a minimum of six carotid Doppler cycles should be averaged to detect VTI change with statistical confidence. Notably, in Figure 1f, the correlation coefficient relating VTI to ccFT becomes strong (i.e. >0.8) when six cardiac cycles are averaged.

The slope difference between ccFT and VTI change during volume loss versus volume repletion in this model is unexplained, though we hypothesize that it could be due to changing vascular impedance downstream to the common carotid relative to the rest of the body during hemodynamic stress. For example, during progressive volume loss, release of adrenaline and noradrenaline shifts blood away from the extremities and toward the vital organs such as the brain; thus, the impedance of the brain relative to the body falls.[21,22] Accordingly, during the release stage of the LBNP, a transient "rush" or "overshoot" of blood to the carotid is observed as an "inverted U" pattern of the VTI [Figure 1e]. This phenomenon would raise the slope of changing carotid VTI relative to ccFT and diminish their correlation. We have also observed this phenomenon in healthy subjects performing standardized Valsalva maneuvers.[23] Further investigation relating the change in ccFT and carotid VTI to ascending aortic Doppler as a surrogate for SV is ongoing.

There are limitations to our analysis. First, this was a relatively small sample of adult participants in a physiology laboratory. Thus, these results cannot be definitively applied to ill patients in the hospital. Nevertheless, our observations are similar to a previous LBNP investigation that we reported, as well as in a study changing preload by squat maneuvers.[16,17,20,21] Second, we do not report SV in this dataset, a key variable when considering central hemodynamics. SV data have been collected in this LBNP model by both ascending aortic Doppler and noninvasive pulse contour analysis; however, it is outside of the present analysis, and it will be reported in a future investigation. The question raised in this analysis was the quantitative relationship between ccFT and carotid VTI during volume depletion and resuscitation. Third, we did not measure total carotid blood flow, which depends on common carotid artery area. We did not do so because the wearable Doppler patch does not measure carotid diameter and human measurement variability in a 6.5-mm vessel leads to a 30% flow error if the diameter is misjudged by only 1 mm. Fourth, the release phase of our model was statistically underpowered to make definitive conclusions about the relationship between changing ccFT and VTI during volume resuscitation. Nevertheless, in all subjects and in all protocols, both ccFT and VTI increased from the lowest LBNP stage, consistent with our previous reports and the anticipated physiology.[16,21]

Conclusions

We investigated 16 healthy, adult volunteers during central volume depletion and resuscitation induced by LBNP and release. This study comprised 33,110 cardiac cycles which is quite large compared to most clinical studies that often sample fewer than three cardiac cycles per patient. There was a strong linear correlation between changing ccFT and VTI during central blood volume loss; the strength of this relationship was dependent on the number of consecutively averaged cardiac cycles; fewer than 6 is likely to result in a poorer correlation between ccFT and VTI. These results are important for planning future clinical investigations employing common carotid artery Doppler as a surrogate for central hemodynamics.

Ethics approval and consent to participate

All data collection was initially performed after the approval of the local Institutional Ethics Committee. Informed written consent was obtained from all the participants of the studies included in the analysis at the time of enrollment.

Financial support and sponsorship

This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Congressionally Directed Medical Research Program under Award No. W81XWH1910591. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense; JL Taylor is supported by the National Institute on Aging (1R21AG073726).

Conflicts of interest

IK, CEM, CH, SA, ME, AME, JKE, and JESK are employees of Flosonics, a start-up developing a commercial version of the Doppler patch.

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