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Carotid Doppler Measurement Variability in Functional Hemodynamic Monitoring: An Analysis of 17,822 Cardiac Cycles

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OBJECTIVES: Carotid Doppler ultrasound is used as a measure of fluid responsiveness, however, assessing change with statistical confidence requires an adequate beat sample size. The coefficient of variation helps quantify the number of cardiac cycles needed to adequately detect change during functional hemodynamic monitoring.

DESIGN: Prospective, observational, human model of hemorrhage and resuscitation.

SETTING: Human physiology laboratory at Mayo Clinic.

SUBJECTS: Healthy volunteers.

INTERVENTIONS: Lower body negative pressure.

MEASUREMENTS AND MAIN RESULTS: We measured the coefficient of variation of the carotid artery velocity time integral and corrected flow time during significant cardiac preload changes. Seventeen-thousand eight-hundred twenty-two cardiac cycles were analyzed. The median coefficient of variation of the carotid velocity time integral was 8.7% at baseline and 11.9% during lowest-tolerated lower body negative pressure stage. These values were 3.6% and 4.6%, respectively, for the corrected flow time.

CONCLUSIONS: The median coefficient of variation values measured in this large dataset indicates that at least 6 cardiac cycles should be averaged before and after an intervention when using the carotid artery as a functional hemodynamic measure.

KEY WORDS: carotid Doppler; corrected flow time; fluid responsiveness; measurement variability; velocity time integral

Functional hemodynamic monitoring (FHM) in the ICU has gained traction over the last 2 decades (1). A requisite for FHM is stroke volume (SV) assessment—or some surrogate—following a change in cardiac preload (2). FHM is superior to commonly used static indices such as filling pressure, ejection fraction, or absolute cardiac output when predicting SV response to preload (3).

Quantitative Doppler ultrasonography of the descending aorta, left ventricular outflow tract (LVOT), and peripheral arteries such as the common carotid have been used, successfully, to measure the impact of altered cardiac preload on ventricular output (3). Importantly, however, detecting change in the Doppler waveform with statistical confidence depends upon the change threshold as well as variation introduced by physiology (e.g., respiratory-induced changes in SV) *and* measurement (e.g., human factors). Accordingly, the coefficient of variation (CV) partly determines beat sample size. For example, if the Doppler

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velocity time integral (VTI) CV is 5% and a change threshold of 10% is desired, then measuring 3–4 cardiac cycles before and after preload modification affords statistical confidence; this is the assumption for the LVOT VTI (4).

Given that the flow profile in a peripheral artery like the carotid is generally "blunted parabolic" (i.e., mixed velocities) and not "plug" (i.e., near uniform velocity, as in the ascending aorta) and that changing preload mediates SV variation, assuming a constant CV of 5% may be inaccurate. Using a novel, wireless, wearable Doppler ultrasound patch, we quantified the CV of commonly employed Doppler measures at resting baseline and during altered preload induced by lower body negative pressure (LBNP). Establishing the CV of carotid Doppler metrics establishes the number beats sampled to detect change with statistical confidence.

METHODS

Clinical Setting

We recruited 11 healthy, adult volunteers with no known cardiovascular history on no regular cardiovascular medications. Written informed consent was obtained for all subjects, and the study was approved by the Research Ethics Board of the Mayo Clinic, Institutional Review Board number 19-010136.

Adherent Doppler System

The U.S. Food and Drug Administration (FDA) cleared Doppler ultrasound patch (Flosonics Medical, Sudbury, ON, Canada) is a wireless, wearable, continuous wave 4 MHz ultrasound. It was placed by palpation below the angle of the jaw; when an audible Doppler shift and spectrogram consistent with the common carotid artery were obtained, the patch was adhered to the neck. The duration of systole, in seconds, was used to calculate the corrected flow time (FTc), as described previously (5, 6).

Lower Body Negative Pressure and Stroke Volume

All subjects underwent a seven-stage protocol in duplicate. Each stage was 5 minutes beginning with resting baseline. LBNP was reduced by 15 mm Hg per stage down to and including −60 mm Hg and then by 10 mm Hg down to and including −80 mm Hg, as tolerated. The final stage was a 5-minute recovery following release of LBNP to atmospheric pressure. For this investigation, we restricted analysis to data at resting baseline (T1), the lowest stage tolerated for each subject (T2), and return to atmospheric pressure (T3). Accordingly, T1 to T2 diminished cardiac preload while T2 to T3 increased cardiac preload. The Nexfin (Bmeye, Amsterdam, The Netherlands) was applied to subjects in the supine position; Nexfin is a U.S. FDA cleared noninvasive SV monitor that uses "volume clamp" to calculate SV.

Coefficient of Variation

Doppler cardiac cycles with artifact or during LBNP stage transition were excluded. For each subject, the CV was calculated as the SD divided by the mean of all cardiac cycles within a given stage.

RESULTS

The average age of the subjects was 29.5 years and 39% were female. The average body mass index was 24.0 kg/m^2. **Table 1** lists vital signs, SV, carotid Doppler measures, and their change during decreased (T1 to T2) and increased (T2 to T3) cardiac preload. A representative example of Doppler variation and the CV values for all subjects for each stage are shown in **Figure 1**.

DISCUSSION

In total, 17,822 cardiac cycles were analyzed to measure the CV of commonly employed carotid Doppler metrics. As the average carotid VTI_{max} CV was greater than 5% and changed significantly with preload, simply averaging 3–4 cardiac cycles before and after an intervention may not be statistically adequate. For example, given a VTI_{max} CV of 9%, a change threshold of 15% (5), a type I error of 0.05, and power 0.80 (7), roughly six cardiac cycles should be obtained before and after preload modification to confidently capture change. Importantly, the number of beats sampled varies as a function of CV and the threshold to detect. For example, detecting a 3% change in FTc (6) with a CV of 4.5% demands roughly 36 beats sampled before and after an intervention.

TABLE 1.
Average Hemodynamic Changes Across Three Stages for All Protocols

	Baseline (T1)	↓Preload (T2)		↑Preload (T3)	
Measure	Mean (SD)	Mean (SD)	% Δ From T1	Mean (SD)	% Δ From T2
Heart rate (beats/min)	63.2 (6.9)	109.6 (14.2)	+73.4%[a]	60.4 (7.9)	−44.9%[a]
Systolic blood pressure (mm Hg)	127.3 (15.6)	120.9 (16.6)	−5.0%[a]	136.9 (15.9)	+ 13.2%[a]
Diastolic blood pressure (mm Hg)	79.0 (8.5)	86.9 (12.3)	+10.0%[a]	85.3 (8.8)	−1.8%[a]
Mean arterial pressure (mm Hg)	97.2 (10.8)	98.8 (13.8)	+1.6%[a]	105.8 (12.3)	+7.1%[a]
Respiratory rate (breaths/min)	16.2 (5.1)	18.8 (6.8)	+16.0%[a]	16.4 (5.6)	−12.3%[a]
Stroke volume (mL)	96.6 (12.0)	59.1 (8.2)	−38.8%[a]	98.0 (12.4)	+65.7%[a]
Velocity time integral (cm)	35.5 (5.9)	15.8 (4.4)	−55.5%[a]	36.6 (7.3)	+132.0%[a]
Corrected flow time (ms)	319.5 (22.8)	270.0 (19.3)	−15.5%[a]	320.6 (23.7)	+18.7%[a]
Cardiac cycles	5,610	7,702		4,510	

[a]$p \leq 0.0001$.

Importantly, the aforementioned pertains to assessing carotid Doppler before and after a relatively prolonged hemodynamic stimulus (e.g., passive leg raising [8], preload administration) rather than when the respiratory cycle itself is the stimulus used to infer functional state (e.g., peak velocity variation) (9). In general, respiratory cycle-induced FHM is limited to patients completely passive with the mechanical ventilator, receiving relatively large tidal volumes, free from left ventricular dysfunction, and in sinus rhythm (3). Nevertheless, even though our subjects were spontaneously breathing, when cardiac preload was lowest (i.e., T2), variation was greatest for both VTI and FTc.

In a previous investigation, we found that carotid VTI slightly outperformed FTc at detecting a 10% SV change in healthy volunteers (5). In that study, data were averaged over 10-second windows, capturing roughly 10–15 cardiac cycles before and after cardiac preload change. Based on the CV values reported herein, this sample size could partly explain the smaller false negative rate of VTI relative to FTc (i.e., 5% vs 10%, respectively) for detecting increased SV.

Notably, our current findings approximate inherent, physiologic variation devoid of human factors because the Doppler ultrasound patch is adherent. That is, the presented CVs are likely "best-case" given that manual manipulation of an ultrasound probe introduces additional error. Angle error and sample volume selection can increase the CV by four- to five-fold even in expert technicians (10). Errors introduced by manual manipulation of the ultrasound probe are important in peripheral arteries like the carotid for a few reasons. First, at 60° insonation, a 5° error engenders 15% velocity error (10). Second, the carotid typically has blunted parabolic flow; that is, a greater velocity gradient across the vessel lumen that amplifies sampling error (11). Finally, compressible neck tissue might accentuate geometric spectral broadening by changing aperture-to-depth ratio (12). These limitations are in contradistinction to the LVOT where the angle of insonation is low, the velocity profile is uniform (i.e., "plug"), and the depth of insonation is more constant; thus, 5% CV for the LVOT VTI is understandable.

The relatively small number of healthy volunteers without cardiovascular disease are limitations of this research correspondence; it was performed as a convenience sample in a physiology laboratory. However, the large number of cardiac cycles captured, absent human measurement error, are clear advantages; the reported intrinsic variation of the carotid Doppler pulse informs beat sample size calculations for recently initiated studies in patients.

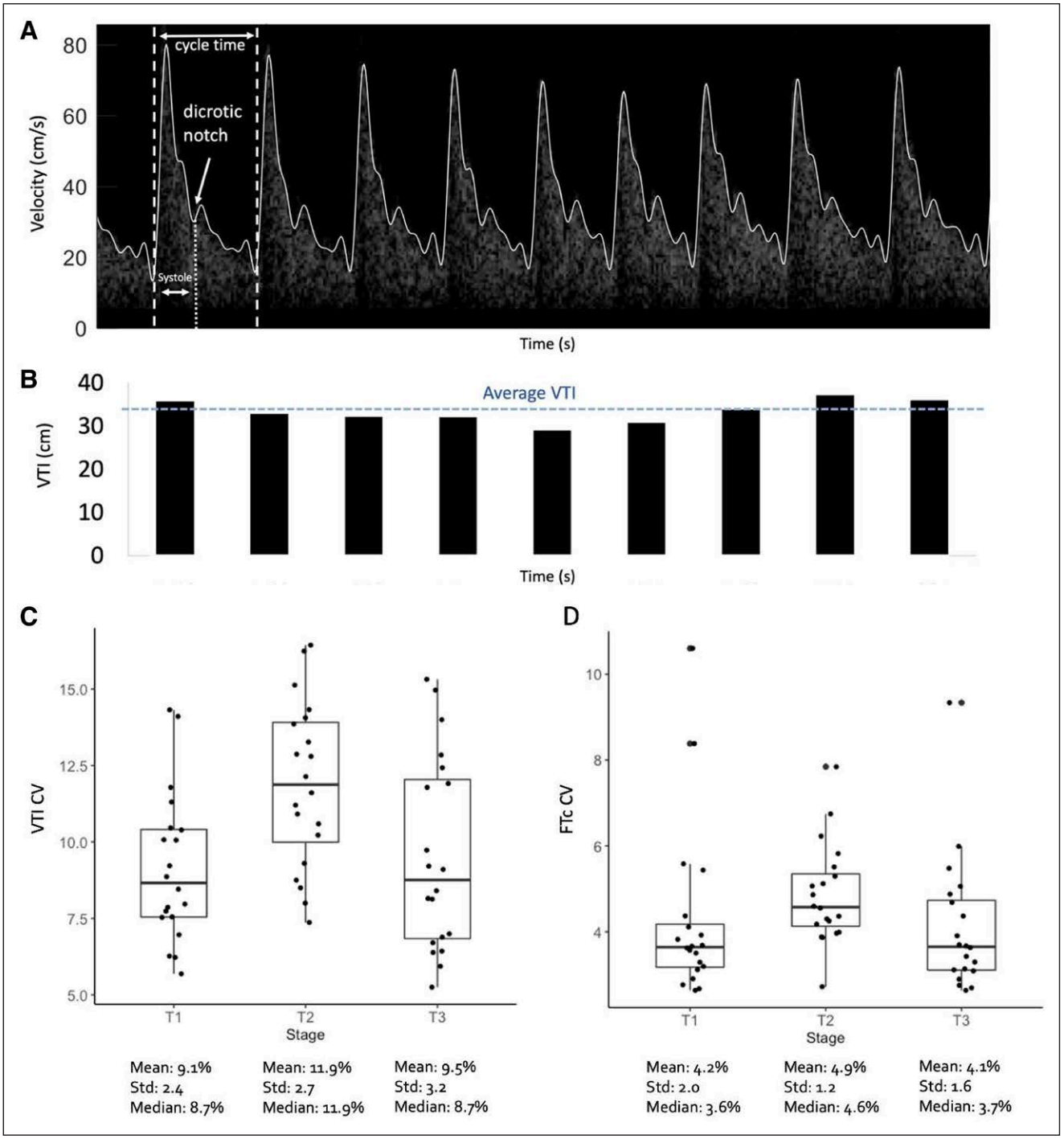

Figure 1. Inherent variation of carotid Doppler. **A**, Representative spectrogram across a respiratory cycle. **B**, Corresponding velocity time integral (VTI) across the respiratory cycle, each *bar* represents a single beat VTI, *horizontal dashed line* shows average VTI across the nine pictured beats. **C**, Coefficient of variation (CV) of the maximal VTI across two preload changes during lower body negative pressure. **D**, CV for the corrected flow time (FTc) for the same changes in preload. In (**C**) and (**D**), each *point* represents the CV from a single subject during the indicated stage; each subject performed the protocol in duplicate. Std = SD of the CV about its mean.

In conclusion, our results are anticipated based on the underlying physiologic principles of FHM (1). Preload dependent subjects are expected to increase SV variation with changes in venous return. While this has physiologic implications, the *statistical* consequences might be ignored; increased Doppler variation in a peripheral artery demands a larger sample size to detect change with confidence.

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