A Carotid Doppler Patch Accurately Tracks Stroke Volume Changes During a Preload-Modifying Maneuver in Healthy Volunteers

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Objectives: Detecting instantaneous stroke volume change in response to altered cardiac preload is the physiologic foundation for determining preload responsiveness.

Design: Proof-of-concept physiology study.

Setting: Research simulation laboratory.

Subjects: Twelve healthy volunteers.

Interventions: A wireless continuous wave Doppler ultrasound patch was used to measure carotid velocity time integral and carotid corrected flow time during a squat maneuver. The Doppler patch measurements were compared with simultaneous stroke volume measurements obtained from a noninvasive cardiac output monitor.

Measurements and Main Results: From stand to squat, stroke volume increased by 24% while carotid velocity time integral and carotid corrected flow time increased by 32% and 9%, respectively. From squat to stand, stroke volume decreased by 13%, while carotid velocity time integral and carotid corrected flow time decreased by 24% and 10%, respectively. Both changes in carotid velocity time integral and corrected flow time were closely correlated with changes in stroke volume ($r^2 = 0.81$ and 0.62, respectively). The four-quadrant plot found a 100% concordance rate between changes in stroke volume and both changes in carotid velocity time integral and changes in corrected flow time. A change in carotid velocity time integral greater than 15% predicted a change in stroke volume greater than 10% with a sensitivity of 95% and a specificity of 92%. A change in carotid corrected flow time greater than 4% predicted a change in stroke volume greater than 10% with a sensitivity of 90% and a specificity of 92%.

Conclusions: In healthy volunteers, both carotid velocity time integral and carotid corrected flow time measured by a wireless Doppler patch were useful to track changes in stroke volume induced by a preload-modifying maneuver with high sensitivity and specificity.

Key Words: carotid ultrasound; corrected flow time; fluid responsiveness; stroke volume; velocity time interval

Tracking changes in stroke volume (SV) during a fluid challenge is the reference method to detect fluid responsiveness (1). Patients experiencing a significant (e.g., > 10%) rise in SV are considered fluid responders, whereas other patients are classified as nonresponders. Predicting fluid responsiveness is useful to identify patients who may benefit from fluid administration and, maybe more importantly, to prevent unjustified fluid administration in nonresponder patients (2). A recent meta-analysis suggests that predicting fluid responsiveness is useful to rationalize perioperative fluid management and to improve the postoperative outcome of surgical patients (3). Predicting fluid responsiveness is also one of the recommendations of the Surviving Sepsis guidelines when treating patients with suspected or confirmed sepsis (4).

Several preload-modifying maneuvers have been proposed to predict fluid responsiveness before fluid administration. The passive leg raising (PLR) maneuver mobilizes one part of the blood volume from the legs to the abdomen and the right side of the heart, mimicking the hemodynamic effects of a fluid challenge (5). Assessing SV changes during a PLR maneuver is useful to predict fluid responsiveness without the need to give a single drop of fluid (6). Other methods such as the quantification of changes in SV during a lung recruitment maneuver or during an end-expiratory occlusion test have been proposed as well to predict fluid responsiveness (7, 8). These methods have their own advantages and
limitations, but all have in common the need for continuous SV monitoring. Unfortunately, many patients are not equipped with a cardiac output monitoring system. This is particularly true in the emergency department and in the operating room. Even in the ICU, a minority of patients are monitored with cardiac output measurement systems, which are usually cumbersome, invasive, and expensive.

During preload-modifying maneuvers, echocardiography-Doppler is an alternative to cardiac output monitoring systems for quantifying changes in SV, or its main surrogate, the velocity time integral (VTI) of aortic blood velocity (9, 10). However, using echocardiography-Doppler requires a specific training, is time consuming and operator dependent. Sometimes, ultrasound measurements are simply not doable when clear images of the left ventricular outflow tract are impossible to obtain. Therefore, there is a need for a simple and easy way to track changes in SV during preload-modifying maneuvers.

An adhesive Doppler patch was recently developed for the continuous monitoring of carotid blood velocity. When positioned on the neck, it enables a real time quantification of the carotid VTI and corrected flow time (FTc) (Fig. 1). It is light and wireless and could represent an appealing solution for tracking changes in SV during preload-modifying maneuvers. Therefore, in healthy volunteers, we investigated whether it could be used to track changes in SV during a squat maneuver, that is known to induce a rise in cardiac preload and SV (11–13). We hypothesized that the rise in SV during squat and the drop in SV when standing back could be detected by the wearable Doppler patch.

MATERIALS AND METHODS

Clinical Setting
We recruited 12 healthy adult volunteers with no known cardiovascular history and on no regular cardiovascular medications. The study was conducted in the Simulation Laboratory at Health Sciences North (Sudbury, ON, Canada). Written informed consent was obtained for all subjects, and the study was approved by the Research Ethic Board of Health Sciences North.

The Squat Maneuver
The entire protocol was 3 minutes in duration (i.e., 180 s); the protocol began with 60 seconds of quiet standing followed by 60 seconds of passive squat and a subsequent 60 seconds return-to-stand (Fig. 2). Each subject performed the protocol twice separated by at least 3 minutes of rest. Blood pressure, heart rate (HR), and symptoms of orthostasis were monitored throughout.

Stroke Volume Measurements
All subjects were monitored with a noninvasive, U.S. Food and Drug Administration-approved, pulse contour method (Clearsight; Edwards Lifesciences, Irvine, CA) enabling measurements of SV every 20 seconds. Briefly, this cardiac output monitoring system uses the “volume clamp” method for transducing the digital artery
waveform. The digital artery waveform is transformed into a brachial artery waveform and then analyzed using pulse contour analysis to derive SV (14, 15).

Carotid VTI and Carotid FTc Measurements
The carotid ultrasound patch (Flosonics Medical, Sudbury, ON, Canada) was placed by palpation over the carotid artery below the angle of the jaw in an effort to ensure Doppler sampling below the bifurcation (Fig. 1). Once an adequate spectrogram signal was visualized in an open-access audio-recording program (Audacity; https://audacityteam.org) the protocol was initiated. The maximum velocity of the Doppler waveform was automatically traced using an algorithm based on the approach described by Steinman et al (16). The waveform analysis was done off-line on a personal computer. The automated maximum velocity estimation for each time point in the waveform was used to calculate the VTI as the area under the curve. The duration of systole (i.e., from systolic velocity upstroke to the dicrotic notch, in ms) was recorded from the Doppler signal and corrected for HR using Wodey’s formula (17) to obtain the carotid corrected flowtime (FTc). In the equation below, FTc and systolic flowtime are in milliseconds (ms), HR is in cycles per minute and 1.29 is a correction factor with the units of ms × (min/cycle).

\[
\text{FTc} = \text{systolic flow time} + (1.29 \times [\text{HR} - 60])
\]

Figure 1C describes the carotid metrics derived from the continuous wave Doppler patch.

Data Analysis
Because the cardiac output monitor provides SV averaged over 20 seconds time intervals, we averaged VTI and FTc measurements over the same time period to ensure the synchronization of measurements. The following time intervals were considered for analysis: 20 to 40 seconds for baseline measurements in the stand position, 80 to 100 seconds for measurements done during squat and 140 to 160 seconds for measurements done after return to the stand position (Fig. 2). Changes in carotid VTI, carotid FTc, and SV measurements were compared using a two-tailed Student t test. The ability of VTI and FTc measurements to track changes in SV values during the squat maneuver was investigated. To do so, we computed four-quadrant plots and performed a concordance analysis, as previously described (18). The four-quadrant plot shows the relationship between changes in VTI or changes in FTc (y-axis) and changes in SV (x-axis) in a scatter plot. We defined a 10% change exclusion zone at the center of the plot to exclude changes in SV which are not clinically relevant. Based on the data points outside the exclusion zone, we calculated the concordance rate as the proportion (percentage) of concordant data pairs to all data pairs. Finally, we quantified the sensitivity and specificity of changes in VTI and changes in FTc to detect significant changes in SV (> 10%).

RESULTS
Twelve healthy volunteers were recruited to complete the squat maneuver. Eleven of the 12 volunteers were included in the study results. In one volunteer, we did not obtain reliable measures of SV with the cardiac output monitor (autocalibration failure). Baseline characteristics of the 11 healthy subjects studied are described in Table 1. Each subject performed the protocol twice.

Hemodynamic Effects of the Squat Maneuver
From stand to squat, there was a significant increase in SV (+24%; \( p = 0.0003 \)), in carotid VTI (+32%; \( p = 0.001 \)), and in carotid FTc (+8.5%; \( p = 0.002 \)). From squat back to stand, there was a significant decrease in SV (–12.9%; \( p = 0.0296 \)), in carotid VTI (–24%; \( p = 0.0013 \)), and in carotid FTc (–10%; \( p = 0.0005 \)). Figure 3 demonstrates the individual and averaged changes in SV, carotid VTI, and FTc.

Evaluating Agreement Between Changes in SV, Carotid VTI, and Carotid FTc
Figure 4, A and B shows the four-quadrant plot comparing changes in SV and changes in carotid VTI and FTc; the concordance rate was 100% for both carotid metrics. Figure 4, C and D shows the change in VTI and in FTc dichotomized by the presence or absence of a 10% change in SV. A 15% change in carotid VTI revealed a sensitivity of 95% and specificity of 92% for detecting a 10% change in SV. A 4% change in carotid FTc revealed a sensitivity of 90% and specificity of 92% for detecting a 10% change in SV.

DISCUSSION
Our study done in healthy volunteers shows that both changes in carotid VTI and in carotid FTc measured by a wireless Doppler patch are useful to track changes in SV induced by a preload-modifying maneuver.

From a physiologic standpoint, carotid blood flow depends on global blood flow (i.e., on cardiac output) but also on the distribution of global flow through the different regional circulations. It depends as well on cerebral autoregulation, a mechanism ensuring that cerebral blood flow does not increase if the brain metabolic demand does not change. As a result, several studies have shown that carotid blood flow cannot be used to estimate SV or cardiac output in steady state conditions (19–21). In contrast, acute and transient changes in SV, as those induced by a preload-modifying maneuver, have been shown to induce proportional changes in the common carotid artery Doppler signal (17, 22–26). In 34 critically

### Table 1. Characteristics of Healthy Volunteers \( (n = 11) \)

| Characteristic                        | Value            |
|--------------------------------------|------------------|
| Average age, yr, median (IQR)        | 32.1 (23–38)     |
| Percent female, %                    | 45               |
| Average body mass index, median (IQR)| 23.4 (19–32.4)   |
| Mean heart rate and range, beats/min, median (IQR) | 81 (59–98) |
| Systolic blood pressure and range, mm Hg, median (IQR) | 117 (92–135) |
| Diastolic blood pressure and range, mm Hg, median (IQR) | 69 (60–78) |

IQR = interquartile range.
ill patients, Marik et al (25) observed a strong correlation ($r^2 = 0.59$) between the percent change in SV assessed using a bioreactance technique and the concomitant percent change in carotid blood flow during a PLR maneuver. In 22 medical ICU patients, Jalil et al (26) compared changes in carotid FTc and changes in SV assessed with an invasive pulse contour method during a PLR maneuver, and reported a fair agreement between the two methods. Barjaktarevic et al (17) quantified the carotid FTc in 77 patients with undifferentiated shock before and after a PLR maneuver. They showed that changes in carotid FTc during the PLR maneuver were predictive of changes in SV measured with bioreactance.

As far as we know, this is the first study to simultaneously measure the sensitivity and specificity of carotid VTI and carotid FTc for predicting clinically significant changes in SV. Our findings suggest that tracking changes in VTI may be more clinically relevant. Indeed, the magnitude of changes in FTc was much smaller than the magnitude of changes in VTI and was therefore more prone to measurement errors. In addition, changes in VTI were more closely correlated with changes in SV than changes in FTc (Fig. 4). These findings make sense from a physiologic standpoint since VTI is directly related to blood flow (blood flow = VTI × carotid area × HR), whereas FTc is only indirectly related to SV (the ejection time depends on the ejected volume, or SV, but also on contractility and afterload). On the other hand, the concordance rate was 100% (Fig. 4) and the sensitivity and specificity to detect a significant change in SV has been shown to provide reliable estimations of changes in blood pressure and flow (14, 15, 30, 31). This method had the major advantage to be noninvasive and nonoperator dependent. Third, we did not perform fluid challenges. Future studies are therefore needed to investigate the ability of the new Doppler patch to predict fluid responsiveness before fluid administration. Fourth, we did not account for differences between the internal and external carotid arteries. The internal carotid artery has a lower resistance in its downstream arterial bed and, consequently, has higher diastolic velocities than the relatively high resistance external carotid artery (32). The common carotid artery, which we measured, is a hybrid between the aforementioned. An increase in blood flow to the internal carotid artery is normally met with auto-regulatory changes that increase downstream resistance and, accordingly decrease diastolic velocity; the degree to which this is transmitted to the common carotid artery is an avenue of future study in both healthy volunteers and the critically ill. Finally, we did not measure total carotid artery flow but rather VTI. We believe that this is an adequate surrogate for flow in

Figure 3. Results of preload-modifying maneuver. A, Individual percent changes in stroke volume, carotid velocity time integral (VTI), and carotid corrected flow time (FTc) during the squat maneuver ($n = 22$); B, averaged absolute values for changes in stroke volume, VTI, and FTc during the squat maneuver (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).
this study because the cross-sectional diameter of the carotid artery is known to change minimally in healthy volunteers within the normal range of mean arterial pressures (33). Change in carotid artery cross-sectional area is likely more important at lower mean arterial pressures, as observed in septic shock patients by Marik et al (25).

In conclusion, we describe the use of a novel hands-free continuous wave ultrasound patch placed over the common carotid artery to track changes in SV during a preload-modifying maneuver. Both changes in carotid VTI and in carotid FTc were useful to track changes in SV and detect potential fluid responders. Further evaluations are now needed in surgical or critically ill patients and during fluid challenges.

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Figure 4. Comparative statistics for stroke volume and carotid Doppler metrics. A and B, Four-quadrant plots comparing percent change in stroke volume on x-axis to percent change in carotid velocity time integral (VTI) and carotid corrected flow time (FTc) on y-axis, respectively. C and D, Optimal thresholds for changes in carotid VTI and changes in carotid FTc, respectively, to detect a change in stroke volume greater than 10% (delta stroke volume [SV]).

Drs. Kenny, Andrew M. Eibl, Parrotta, Long, and Joseph K. Eibl are working with Flosonics, a start-up developing a commercial version of the Doppler patch. Dr. Michard is the founder and managing director of MiCo, a Swiss consulting firm. MiCo does not sell any medical products, and Dr. Michard does not own shares nor receive royalties from any MedTech company. Dr. Barjaktarevic has disclosed that he does not have any potential conflicts of interest.

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