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ORIGINAL RESEARCH

Trauma

The Doppler shock index measured by a wearable ultrasound patch accurately detects moderate-to-severe central hypovolemia during lower body negative pressure

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Abstract

Objective: Moderate-to-severe hemorrhage is a life-threatening condition, which is challenging to detect in a timely fashion using traditional vital signs because of the human body's robust physiologic compensatory mechanisms. Measuring and trending blood flow could improve diagnosis of clinically significant exsanguination. A lightweight, wireless, wearable Doppler ultrasound patch that captures and trends blood flow velocity could enhance hemorrhage detection.

Methods: In 11 healthy volunteers undergoing simulated hemorrhage and resuscitation during graded lower body negative pressure (LBNP) and release, we studied the relationship between stroke volume (SV) and common carotid artery velocity time integral (VTI) and corrected flow time (FTc). We assessed the diagnostic accuracy of 2 variations of a novel metric, the Doppler shock index (ie, the DSI_{VTI} and DSI_{FTc}), at capturing moderate-to-severe central hypovolemia defined as a 30% reduction in SV. The DSI_{VTI} and DSI_{FTc} are calculated as the heart rate divided by either the VTI or FTc, respectively.

Results: A total of 17,822 cardiac cycles were analyzed across 22 LBNP protocols. The average SV reduction to the lowest tolerated LBNP stage was 40%; there was no clinically significant fall in the mean arterial pressure. Correlations between changing SV and the common carotid artery VTI and FTc were strong (R^2 of 0.87, respectively) and concordant. The DSI_{VTI} and DSI_{FTc} accurately detected moderate-to-severe central hypovolemia with values for the area under the receiver operator curves of 0.96 and 0.97, respectively.

Conclusion: In a human model of hemorrhage and resuscitation, measures from a wearable Doppler ultrasound patch correlated strongly with SV and identified moderate-to-severe central hypovolemia with excellent diagnostic accuracy.

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KEYWORDS
carotid Doppler, corrected flow time, hemodynamic monitoring, hemorrhage, velocity time integral

1 | INTRODUCTION

1.1 | Background

Hemorrhage is a common cause of death in both military and civilian populations.[1,2] Despite its significant human cost, methods to detect evolving hemorrhagic shock are generally insensitive.[3] Often low blood pressure is used as a marker of blood volume loss, yet its diagnostic value is poor, and this has been known since World War II.[1] Indexes such as the shock index (ie, heart rate [HR] divided by the systolic blood pressure) have been proposed to improve hemorrhage detection; however, nearly one-third of patients in a trauma cohort who required massive transfusion were missed by the shock index.[4] Although newer approaches, such as the compensatory reserve index (CRI)[5] are promising, CRI is still dependent on classical vital signs, which are all at least one step removed from blood flow. Because diminished venous return and, therefore, stroke volume (SV) are the *primum movens* of hemorrhagic shock, monitors that directly measure flow, or some surrogate, may be more sensitive at detecting impending hemodynamic collapse.

1.2 | Importance

We have previously shown that a wireless, wearable Doppler ultrasound patch worn over the common carotid artery accurately tracks changing SV in healthy subjects.[6] Furthermore, a novel metric—the Doppler shock index (DSI)—better detected falling SV than mean arterial pressure (MAP) in a feasibility study of healthy volunteers performing a standardized Valsalva maneuver.[7] The DSI is defined as the HR divided by the maximum velocity time integral (VTI_{max}) of the common carotid artery. Given this, we further investigated the ability of a wearable Doppler ultrasound to detect both the onset of severe central hypovolemia and its response to simulated blood transfusion in a cohort of healthy volunteers undergoing lower body negative pressure (LBNP) in a physiology lab. As cardiac cycle time is truncated by increased HR,[8] we studied an additional variation of the DSI, the HR divided by the corrected flow time (DSI_{FTc}) of the carotid artery.

1.3 | Goals of this investigation

We hypothesized that both forms of the DSI would accurately detect severe central hypovolemia induced by LBNP. As well, we hypothesized that a simulated blood transfusion—by release of LBNP to atmospheric pressure—would be correctly followed by the DSI and other Doppler metrics from the common carotid artery.

2 | MATERIALS AND METHODS

2.1 | Clinical setting

We recruited 11 healthy, adult volunteers. Exclusion criteria were known cardiovascular history and/or taking regular cardiovascular medications. The procedures followed were in accord with the ethical standards of the committee on human experimentation at the Mayo Clinic. Written and informed consent was obtained for all subjects, and the study was approved by the Research Ethics Board of the Mayo Clinic.

2.2 | Lower body negative pressure

The subjects were supine in the LBNP chamber. Simulated central hypovolemia was induced by applying progressively greater degrees of LBNP. There were 7 stages in total, each lasting 5 minutes. The first stage was resting baseline. Following baseline, the next 4 stages reduced lower body pressure by 15 mmHg up to and including −60 mmHg. The next 2 stages reduced lower body pressure by 10 mmHg with −80 mmHg being the lowest achievable stage. Finally, there was a recovery stage when the chamber pressure was returned to atmospheric pressure. Each subject underwent the above in duplicate.

The protocol was terminated immediately in the event of a drop in MAP >15 mmHg, HR >150 beats per minute (bpm), or systolic blood pressure < 70 mmHg or if the subject suffered impending syncope symptoms or wanted the procedure to end.[1]

To model moderate-to-severe central hypovolemia, we studied SV reduction during the LBNP protocol as observed in a previous publication including 117 subjects.[9] By stages 5 and 6 (ie, −70 to −80 mmHg), about 15%–20% total blood volume loss[1,9] or a 10% reduction in thoracic fluid content[10] is expected. We compared resting baseline data (T1) with the subject's lowest achieved LBNP (T2) as a model of severe central hypovolemia. Conversely, we compared the lowest achieved LBNP (T2) with recovery (T3), which took place upon immediate release of LBNP to atmospheric pressure. Thus, T2 to T3 simulated a rapid blood transfusion. Figure 1 is a schematic of the LBNP protocol.

2.3 | SV and vital signs monitoring

In all protocols, the Nexfin (Bmeye, Amsterdam, Netherlands) was applied to the subject in the supine position. Briefly, Nexfin is a US Food

The Bottom Line

Hemorrhagic shock can be difficult to identify early because of the body's ability to compensate for volume loss. In this study of simulated hemorrhage and resuscitation in 11 healthy volunteers using graded lower body negative pressure and release, the authors demonstrated that measurements from a wearable Doppler carotid ultrasound patch correlate with stroke volume and may be able to assist with the identification of hemorrhagic shock.

and Drug Administration (FDA)–cleared non-invasive SV monitor that uses a "volume clamp" method to transduce the digital artery waveform. Using an algorithm, the digital artery waveform is transformed into a brachial artery waveform and then analyzed using pulse contour analysis to provide SV for each beat.[11] A number of studies have evaluated the ability of volume clamp devices to track changes in cardiac output with agreement values ranging between 84% and 100%.[11] The protocol did not begin until there was adequate Nexfin signal as measured by the Physiocal calibration metric (ie, ≥30). The third digit was used in all volunteers as recommended by the manufacturer, and all subjects' arms remained passively extended throughout the protocol so as not to change upper extremity arterial resistance. All subjects maintained normal, quiet tidal respiration during the maneuver. Blood pressure for this study was obtained from the volume clamp device. Respiratory rate was also recorded.

2.4 | Carotid Doppler monitoring

A US FDA-cleared, wearable carotid Doppler 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 of the common carotid artery. 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. The maximum velocity of the Doppler waveforms was automatically traced using an algorithm based on the approach described by Li and colleagues.[12] The automated maximum velocity trace was used to determine the duration of systole from the systolic velocity upstroke to the dicrotic notch (ie, flow time) (Figure 2). The duration of systole in seconds was used to calculate the corrected flow time (FTc) using the formula of Wodey, as described previously.[13] For a single cardiac cycle, the area under the maximum velocity trace is the velocity time integral (VTI) and represents the distance traveled by the fastest moving red blood cells per cardiac cycle in centimeters. As an exploratory analysis, we measured the common carotid artery resistance index calculated as the peak systolic velocity less the end diastolic velocity divided by the peak systolic velocity during the mid-point of each subject at T1, T2, and T3.

2.5 | Statistical analysis

All calculations were carried out using R statistical software. Values obtained for SV during the LBNP were compared using a 2-tailed Student *t* test. To evaluate the ability of carotid Doppler metrics to track changes in SV during simulated hemorrhage (ie, T1 to T2) and simulated blood transfusion (ie, T2 to T3), we quantified the sensitivity and specificity of carotid Doppler measurements to detect a 30% decrease in SV to mimic a 15%–20% reduction in total body blood volume,[9] which approximates moderate-to-severe hemorrhage.[1] Area under the receiver operator curve (AUROC) was calculated for measures of interest; the optimal threshold to detect a 30% SV reduction was determined by Youden's index. To calculate the true positive and false positive rates, 10-second averages were compared between the synchronized volume clamp and Doppler measures for T1, T2, and T3 across all 22 protocols. As well, with these data, we computed 4-quadrant plots and performed a concordance analysis.[14] The 4-quadrant plot shows the relationship between changes in the Doppler metric of interest (*y* axis) and changes in SV (*x* axis) in a scatterplot. We defined a 10% change exclusion zone at the center of the plot to exclude changes in SV that 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 for each Doppler metric. Simple linear regression was performed on the 4-quadrant plot using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

The study was performed without any complication. The average age of the volunteers was 29.5 years and 39% were women. The average body mass index was 24.0 kg/m^2. In all subjects, audible Doppler and

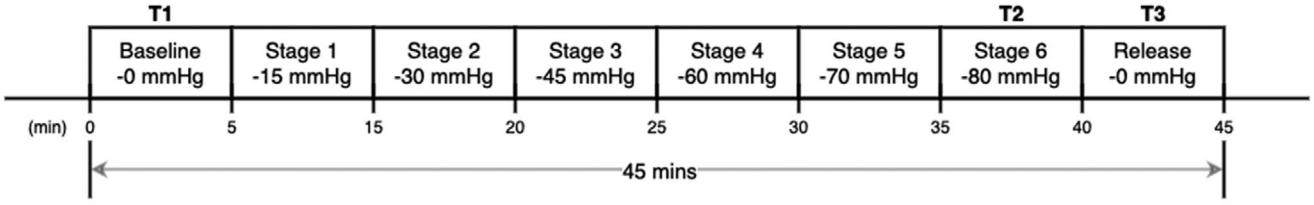

FIGURE 1 Schematic of lower body negative pressure protocol. T1 is the resting baseline, T2 is the lowest tolerated stage, and T3 is recovery

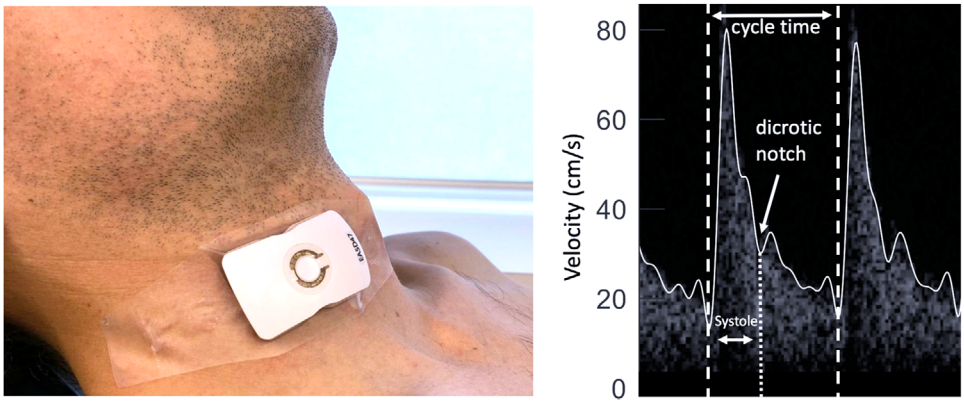

FIGURE 2 The wearable Doppler ultrasound patch with Doppler waveforms

common carotid spectra were obtained, and all subjects had adequate SV signals from the pulse contour analysis device. A total of 17,822 cardiac cycles were recorded across the 11 participants for simulated moderate-to-severe hemorrhage and resuscitation with a mean number of 1620 cycles per participant.

3.1 | Simulated severe hemorrhage

On average, SV fell by 37.5 milliliters or 38.8% ($P \leq 0.0001$) from T1 to T2 across the 22 protocols; there was no clinically-significant difference in the SV fall from T1 to T2 when comparing the first versus second LBNP protocol. In aggregate, the 95% confidence interval for SV change was between −39.13% and −37.88%. Mean arterial blood pressure changed minimally from T1 to T2 from 97.2 mmHg to 98.8 mmHg ($P \leq 0.0001$). HR increased significantly from 63 bpm to 110 bpm ($P \leq 0.0001$) and the shock index (ie, HR/systolic blood pressure) rose significantly by 0.42 or +85.7% ($P < 0.001$). The mean respiratory rate in breaths per minute increased from 16.2 to 18.8, and this was not statistically significant.

Carotid Doppler VTI significantly fell during simulated moderate-to-severe hemorrhage from 35.5 cm to 15.8 cm or −55.5% ($P \leq 0.0001$), so too did the FTc from 319.5 milliseconds to 270.0 milliseconds or −15.5% ($P \leq 0.0001$). Both variations of the DSI rose significantly from T1 to T2. The DSI_{VTI} and DSI_{FTc} rose by 5.7 (+317%) ($P < 0.0001$) and 0.2 (+102%) ($P < 0.0001$), respectively.

3.2 | Simulated blood transfusion

SV increased by 38.9 milliliters (ml) or +66% from T2 to T3; there was no clinically significant difference in the SV rise from T2 to T3 when comparing the first versus second LBNP protocol. Mean arterial blood pressure rose significantly from T2 to T3 from 98.8 mmHg to 105.8 mmHg ($P \leq 0.0001$). HR fell from 110 bpm to 60 bpm ($P \leq 0.0001$), and the shock index (ie, HR/systolic blood pressure) also decreased significantly by 0.47 (−51.%) ($P \leq 0.0001$). The absolute respiratory rate fell from 18.8 to 16.4, and this was not significant.

Carotid Doppler VTI increased during simulated blood transfusion, from 15.8 cm to 36.6 cm ($P \leq 0.0001$). The FTc increased from 270.0 milliseconds to 320.6.7 milliseconds ($P \leq 0.0001$). Both variations of the DSI significantly fell during simulated blood transfusion. The DSI_{VTI} and DSI_{FTc} decreased by 5.7, −76.9% ($P \leq 0.0001$) and 0.2, −53.2% ($P \leq 0.0001$), respectively. The resistance index decreased from 0.81 to 0.74 from T1 to T2; the resistance index increased back to 0.80 at T3. Both changes were statistically significant ($P \leq 0.0001$).

3.3 | Diagnostic characteristics of hemodynamic measurements

In total, 17,822 carotid beats were analyzed between T1, T2, and T3 in all volunteers. Table 1 summarizes the best diagnostic threshold for detecting a 30% reduction in SV as well as the sensitivity, specificity, and AUROC of all studied metrics. Figure 3 shows the receiver operator curves for the measures in Table 1, and Figure 4 shows the 4-quadrant plots and regression coefficients for SV versus maximum VTI and FTc. All 44 preload changes are plotted (ie, 22 simulated hemorrhages from T1 to T2 and 22 simulated blood transfusions from T2 to T3). For the VTI and FTc 4-quadrant plots, no data points were discordant with SV. The correlations between changing SV and the common carotid artery VTI and FTc were strong (R^2 of 0.87, respectively). The 2 variations of the DSI, the DSI_{VTI} and DSI_{FTc}, detected moderate-to-severe central hypovolemia with values for the AUROCs of 0.96 and 0.97, respectively.

4 | LIMITATIONS

Our study has several limitations. First, we did not study actual exsanguination. Nevertheless, the LBNP model does correlate well with blood loss in non-human primate studies[9] and decreased thoracic blood volume.[10] Second, the volume clamp technique used to measure SV is limited when there is peripheral vasoconstriction (eg, Raynaud's syndrome, vasopressors, adrenergic tone),[11] which may degrade the accuracy of SV as central hypovolemia progressed. However, the

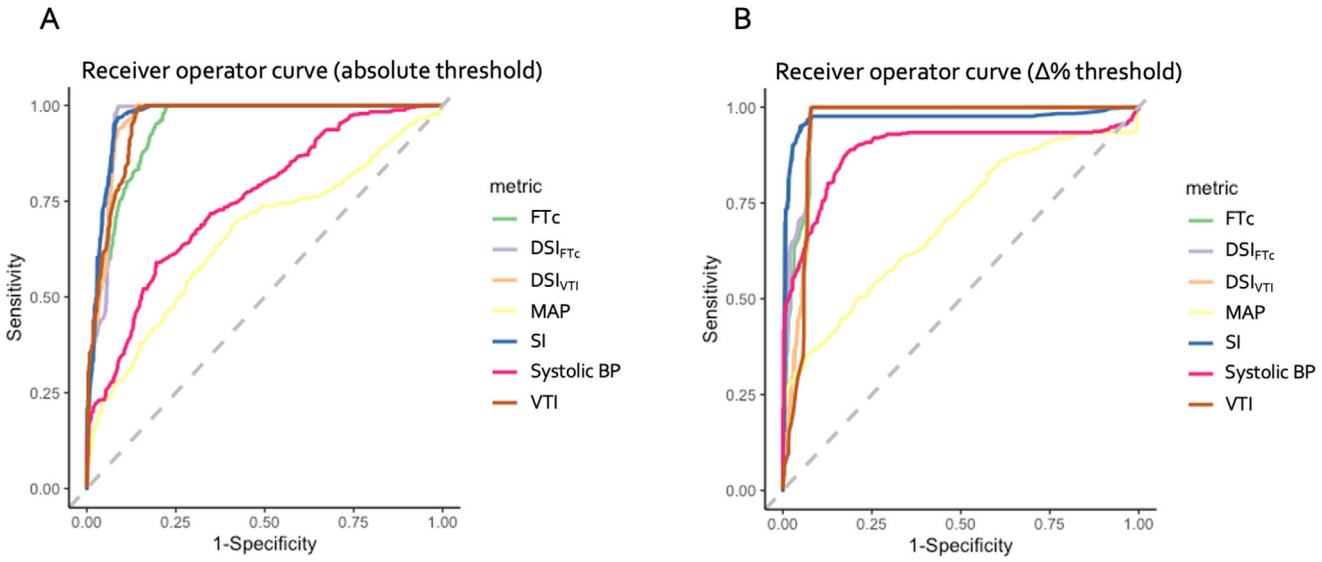

FIGURE 3 Receiver operator curves for measures reported in Table 1: (A) data for absolute threshold and (B) Δ% thresholds. Δ%, percent change; BP, blood pressure; DSI$_{FTc}$, Doppler shock index with FTc in the denominator; DSI$_{VTI}$, Doppler shock index with VTI in the denominator; FTc, corrected flow time; MAP, mean arterial pressure; SI, shock index; VTI, velocity time integral

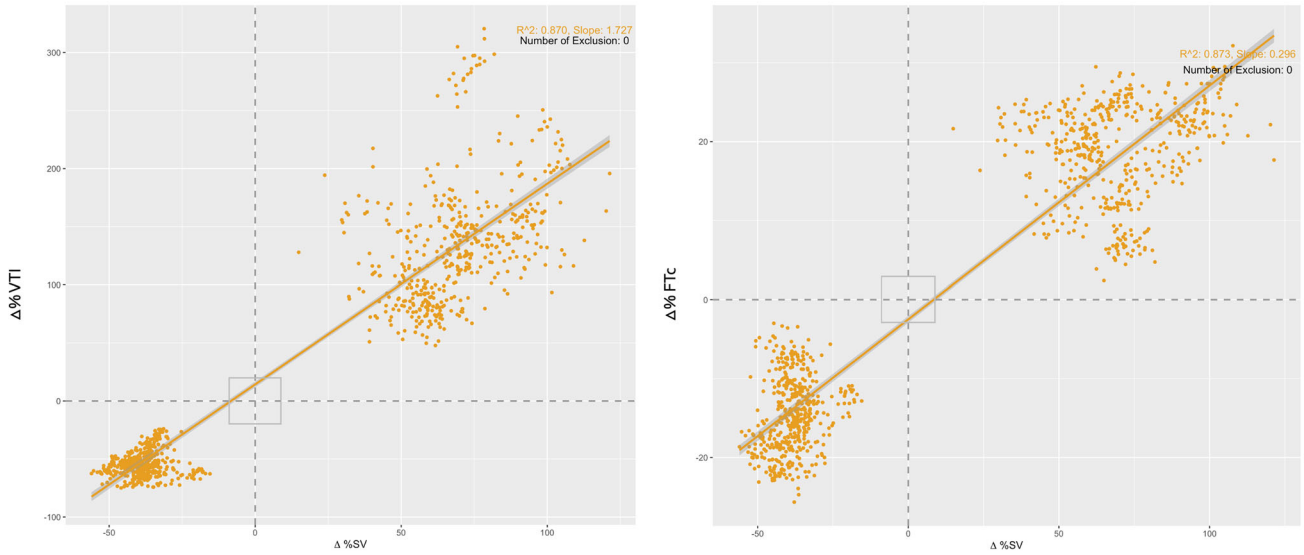

FIGURE 4 Four quadrant plots for Δ% SV versus Δ% carotid VTI and FTc. For both measures, no data fell within the zone of exclusion, and there were no discordant beats. Each data point represents a 10-second average of SV and carotid Doppler data. These data are accumulated from 22 lower body negative pressure protocols and 17,822 cardiac cycles. Δ%, percent change; FTc, corrected flow time; SV, stroke volume; VTI, velocity time integral

decrease in SV measured by the volume clamp technique in this study and others[15,16] is remarkably consistent with other gold standards employed during LBNP, including left ventricular outflow tract VTI,[17] bioimpedance,[18] and bioreactance.[10] The advantages of the volume clamp method are that it is continuous, non-invasive, and non-operator dependent. Third, the accuracy of the shock index in this study depends on the accuracy of the volume clamp device used to measure systolic blood pressure. As compared with invasive blood pressure readings, the mean bias of systolic blood pressure from volume clamp technology is small (ie, 2 mmHg) and arguably valid in this population of young, healthy volunteers.[11] Nevertheless, repeating this study in patients, especially those on vasoactive medications, would best be performed with an invasive gold standard. Fourth, the Doppler angle of insonation employed by the ultrasound patch is estimated to be 60°. In vitro, we have shown that this estimation introduces a clinically small, fixed error into the VTI calculation that is mitigated when the VTI is referenced

TABLE 1 Diagnostic characteristics of hemodynamic variables for detecting 30% reduction in stroke volume

Metric	Threshold	Sensitivity	Specificity	AUROC
Mean arterial pressure	103.1 mmHg	0.70	0.58	0.66
	+1.06%	0.51	0.78	0.70
Systolic blood pressure	121.5 mmHg	0.60	0.80	0.76
	+5.76%	0.86	0.83	0.89
VTI	28.4 cm	1.0	0.85	0.95
	−23.5%	1.0	0.92	0.95
FTc	301.8 milliseconds	1.0	0.78	0.94
	−3.0%	1.0	0.92	0.97
Shock index	0.62	0.97	0.91	0.96
	+31.4%	0.97	0.95	0.97
DSI_{VTI}	2.7	1.0	0.86	0.96
	+46.5%	1.0	0.92	0.96
DSI_{FTc}	0.26	0.99	0.91	0.96
	+15.9%	1.0	0.92	0.97

Abbreviations: AUROC, area under the receiver operator curve; FTc, corrected flow time; VTI, velocity time interval. DSI_{VTI}, Doppler Shock Index-velocity time integral; DSI_{FTC}, Doppler Shock Index-corrected flow time.

to its baseline value.[19] Because the ultrasound patch is adhered to the neck, the angle of insonation remains relatively constant throughout the study and small, absolute velocity error is accounted for. Importantly, however, should the carotid artery move relative to the adhered transducer face (eg, significant head and neck movement), erroneous VTI change is introduced.[19] Finally, we did not account for differences between the internal and external carotid arteries. Although others have found that blood flow in the internal carotid artery tracks changes in SV,[20] the congruence between internal and common carotid artery blood flow in the face of changing cardiac output is an avenue of future study.

5 | DISCUSSION

In a human model of moderate-to-severe central hypovolemia, measurements obtained from a wireless, wearable Doppler ultrasound accurately detected diminished SV with greater accuracy than either MAP or systolic blood pressure. Two variations of the DSI had similar sensitivity and specificity for detecting the fall in SV induced by moderate-to-severe central hypovolemia; concordance and correlation between carotid Doppler VTI, FTc, and SV were excellent during simulated moderate-to-severe hemorrhage and transfusion.

These data are consistent with an earlier feasibility study first describing the DSI using a standardized Valsalva maneuver[7]; the directional change in carotid Doppler metrics observed during simulated hemorrhage and transfusion was similar to a simulated end-inspiratory, end-expiratory occlusion test in healthy volunteers.[21] Although raising intra-thoracic pressure during a Valsalva maneuver leads to central hypovolemia, the average SV reduction was only about 25% and relatively transient. To better study the effects of moderate-to-severe hypovolemia over many minutes, LBNP was employed for the present study. LBNP is a good model of hemorrhage in humans. In an evaluation of 117 subjects, SV consistently fell during LBNP, culminating in a 60% SV reduction at −80 mmHg.[9] The authors also noted that the percent blood volume contraction is estimated as one-half the percent fall in SV (eg, a 60% fall in SV corresponds to 30% blood volume loss). Given that the average SV decrease noted in our subjects was roughly 40%, we surmise an average blood volume loss of approximately 20%, which is moderate to severe.

In addition to accurately detecting moderate-to-severe central hypovolemia, indexes from the wearable Doppler ultrasound followed simulated blood volume resuscitation upon release of LBNP. With correction of central hypovolemia, both variants of the DSI rapidly returned to baseline. We observed an "over-shoot" in the VTI immediately upon release of LBNP in some volunteers, consistent with our observations in standardized Valsalva maneuvers.[21] This might reflect intra-cerebral vasodilation that occurs with diminished cerebral perfusion.[22] Indeed, as an exploratory analysis, we compared the common carotid artery resistive index from the wearable Doppler across T1, T2, and T3. In all 22 protocols, the resistance index fell from baseline to the onset of the lowest tolerated LBNP stage, consistent with downstream vasodilation; the resistance index increased back to baseline in all subjects upon release of LBNP. On the other hand, respiratory rate increased slightly during T2, which might produce hypocapnia and induce cerebral vasoconstriction, which is expected to increase cerebrovascular resistance. Regardless of the underlying physiology, continuous common carotid Doppler may provide information on both changing SV and downstream autoregulatory effects; this is an avenue of ongoing investigation.

The clinical relevance of these data is, first, we have demonstrated that Doppler indexes obtained from the common carotid can detect, with excellent accuracy, moderate-to-severe central volume loss. Ostensibly, elevated DSI in a patient injured by trauma facilitates triage; further, normalization of the DSI in response to volume resuscitation might indicate adequacy of central volume repletion. As the DSI is trended by a wireless, wearable Doppler ultrasound, these data are easily obtained in a wide range of prehospital and inpatient settings. Second, nevertheless, the AUROC of the DSI was comparable with the traditional shock index at detecting moderate-to-severe central volume loss in this investigation. We believe that this equivalence was driven primarily by changing HR, which is the shared numerator of both the DSI and shock index. The AUROC curves and values illustrated in Figure 3 and Table 1, respectively, reveal that the DSI denominators (ie, VTI and FTc) outperformed the shock index denominator (systolic blood pressure) for detecting a 30% reduction in SV. Thus, the very strong relationship between changing HR and falling SV in these young, healthy volunteers nullified the difference between the DSI and shock index. In an expanded analysis of these data, we demonstrated that HR, VTI, and FTc all strongly correlated with changing SV.[23] Third, although the AUROC of the shock index was high at a threshold of 0.62, the traditionally taught threshold of 1.0 performed poorly with a

sensitivity of only 25%, meaning that 75% of subjects with a SV reduction of 30% in this study did not achieve a traditional shock index of at least 1.0. Fourth, for all studied measures, trending the value across time (ie, using a percent change threshold rather than an absolute threshold) improved the specificity or diminished the false positive rate. This finding makes intuitive sense and should be kept in mind when interpreting similar studies in the literature. Because there is a range of normal values for all baseline hemodynamic variables, it is anticipated that some will naturally fall on the other side of an absolute threshold and be labeled abnormal. Referencing each individual metric to itself and following it temporally mitigates this diagnostic error. Finally, we note that based on the slope of the regression equations presented in Figure 2, a 10% change in SV relates to an 17% change in carotid Doppler VTI and 3% change in carotid FTc. Significantly, these regressions are based on roughly 18,000 cardiac cycles and are consistent with our previous healthy volunteer studies and clinical data and an expanded analysis of this LBNP data set.[6,23–25] Accordingly, in addition to evolving hypovolemia, the physiology observed herein might extrapolate to other clinical scenarios where diminished venous return and SV are culpable for hemodynamic instability (eg, peri-intubation).

In conclusion, 2 variations of the DSI measured by a wearable Doppler ultrasound accurately detected diminished SV in a model of moderate-to-severe central hypovolemia. There was strong association between both VTI and FTc and changing SV during both simulated hemorrhage and volume resuscitation. Although this suggests that a wearable Doppler monitor is useful for identifying and monitoring cryptic hemorrhage, other clinical scenarios typified by diminished SV may also benefit from this technology. Future studies in patients at risk for cryptic hemorrhagic shock and in the peri-intubation period are planned.

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CONFLICT OF INTEREST

Jon-Émile S. Kenny, Mai Elfarnawany, Matt Meyers, Zhen Yang, Andrew M. Eibl, and Joseph K. Eibl work for Flosonics Medical, a start-up building the wearable Doppler ultrasound. Jenna L. Taylor, Chul Ho Kim, and Bruce D. Johnson declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Jon-Émile S. Kenny,Andrew M. Eibl, Joseph K. Eibl, and Bruce D. Johnson conceived the study, designed the trial, and obtained research funding. Chul Ho Kim and Bruce D. Johnson supervised the conduct of the trial and data collection. Chul Ho Kim and Bruce D. Johnson undertook recruitment of participating centers and patients and managed the data, including quality control. Mai Elfarnawany, Zhen Yang, Matt Meyers, and Jenna L. Taylor provided statistical advice on study design and analyzed the data. Jon-Émile S. Kenny drafted the manuscript, and all authors contributed substantially to its revision. Jon-Émile S. Kenny takes responsibility for the paper as a whole.

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