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A wireless ultrasound patch detects mild-to-moderate central hypovolemia during lower body negative pressure

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BACKGROUND:	We have developed a wireless, wearable Doppler ultrasound system that continuously measures the common carotid artery Doppler pulse. A novel measure from this device, the Doppler shock index, accurately detected moderate-to-severe central blood volume loss in a human hemorrhage model generated by lower body negative pressure. In this analysis, we tested whether the wearable Doppler could identify only mild-to-moderate central blood volume loss.
METHODS:	Eleven healthy volunteers were recruited and studied in a physiology laboratory at the Mayo Clinic. Each participant underwent a lower body negative protocol in duplicate. Carotid Doppler measures including Doppler shock indices were compared with blood pressure and the shock index for their ability to detect both 10% and 20% reductions in stroke volume.
RESULTS:	All carotid Doppler measures were better able to detect diminishing stroke volume than either systolic or mean arterial pressure. Falling carotid artery corrected flow time and rising heart rate/corrected flow time (DSI_{FTc}) were the most sensitive measures for detecting 10% and 20% stroke volume reductions, respectively. The area under the receiver operator curves (AUROCs) for all shock indices was at least 0.86; however, the denominators of the two Doppler shock indices (i.e., the corrected flow time and velocity time integral) had AUROCs ranging between 0.81 and 0.9, while the denominator of the traditional shock index (i.e., systolic blood pressure) had AUROCs between 0.54 and 0.7.
CONCLUSION:	The wearable Doppler ultrasound was able to continuously measure the common carotid artery Doppler pulse. Carotid Doppler measures were highly sensitive at detecting both 10% and 20% stroke volume reduction. All shock indices performed well in their diagnostic ability to measure mild-to-moderate central volume loss, although the denominators of both Doppler shock indices individually outperformed the denominator of the traditional shock index. (*J Trauma Acute Care Surg.* 2022;93: S35–S40. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.)
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KEY WORDS:	Carotid Doppler; velocity time integral; corrected flow time; hemorrhage; hemodynamic monitoring.

D etecting cryptic hemorrhage is challenging.[1] Traditional vital signs such as heart rate (HR) and blood pressure may be deceptively normal following large blood loss as a consequence of robust adrenergic response, especially in young patients.[2] Because hemorrhage decreases venous return, the foremost hemodynamic insult during exsanguination is diminished stroke volume (SV). In response to falling SV, adrenergic tone raises HR to augment blood flow and vascular resistance—both of which help preserve mean arterial blood pressure. Thus, blood pressure is a poor measure of significant blood loss.[3]

In response to the aforementioned limitations, a wireless, wearable Doppler ultrasound that measures beat-to-beat blood flow metrics from the common carotid artery has been developed.[4–12] It has been shown in healthy subjects that this device rapidly and accurately tracks both rising and falling SV as compared with volume-clamp, bioreactance, and descending aortic Doppler ultrasound criterion standards.[4,5,10,12] More specifically, in a human model of increasingly severe hemorrhage, a strong, linear correlation between changing SV and various carotid Doppler measures across roughly 50,000 cardiac cycles was observed, while changing SV and mean arterial pressure had poor correlation.[10]

Furthermore, a novel index, the Doppler shock index (DSI), has been proposed, which is the HR divided by either the maximum velocity time integral (VTI) or corrected flow time (FTc) of the common carotid artery.[9,13] The VTI and FTc were tested in the denominator because they both demonstrated a strong, linear correlation with changing SV in a previous investigation, and it was hypothesized that SV surrogates in the denominator would better detect hemorrhage than the systolic blood pressure. Nevertheless, while the DSI outperformed both systolic blood pressure and mean arterial pressure, it was comparable with the traditional shock index (i.e., HR/systolic blood pressure) for detecting diminished SV in a model of moderate-to-severe human hemorrhage. As noted in that investigation, the diagnostic performance of the traditional shock index was buoyed by the strong, inverse relationship between HR and falling SV;[9,10] both Doppler denominators (i.e., VTI, FTc) better detected central volume loss than the denominator

of the traditional shock index (i.e., systolic blood pressure). Building upon these findings we report the accuracy of common carotid artery measures at detecting less substantial central volume loss in the same lower body negative pressure (LBNP) model. We hypothesized that common carotid artery VTI and FTc would better detect mild-to-moderate volume loss as defined by both 10% and 20% SV reductions than mean arterial and systolic blood pressures. We also hypothesized that the traditional shock index would perform equally well as the DSI given that HR is their shared numerator.

PATIENTS AND METHODS

Clinical Setting

As previously reported, we recruited 11 healthy adult volunteers[9,10,12] in a physiology laboratory. 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. Written and informed consent was obtained for all subjects, and the study was approved by the local Research Ethics Board. This study is reported in accordance with the Standards for Reporting Diagnostic accuracy studies guidelines, and a complete checklist has been uploaded as Supplemental Digital Content (Supplementary Table 6, http://links.lww.com/TA/C581). The number of subjects recruited was based on a power calculation used to detect a repeated measures correlation of at least 0.8, as previously described.[10]

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 seven stages in total, each lasting 5 minutes. The first stage was resting baseline. Following baseline, the next four stages reduced lower body pressure by 15 mm Hg up to and including −60 mm Hg. The next two stages reduced lower body pressure by 10 mm Hg with −80 mm Hg 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 mean arterial pressure >15 mm Hg, HR >150 beats per minute (bpm), and systolic blood pressure <70 mm Hg or if the subject suffered impending syncope symptoms or wanted the procedure to end.[3]

To model mild-to-moderate central hypovolemia, we studied two SV thresholds: 10% and 20% SV reduction from baseline. As described previously, blood volume loss during LBNP may be estimated as 50% of the SV reduction.[14] Accordingly, SV diminished by 10% and 20% model 5% and 10% blood volume loss, respectively; these are mild-to-moderate in severity.[3] As well, these SV thresholds are expected to model a 5-to-10% reduction in thoracic fluid content.[15]

SV and Vital Signs Monitoring

In all protocols, the Nexfin (Bmeye, Amsterdam, the Netherlands) was applied to the subject in the supine position. The protocol did not begin until there was adequate Nexfin signal as measured by the Physiocal calibration metric (i.e., ≥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.

Carotid Doppler Monitoring

A US Food and Drug Administration–cleared, wearable carotid Doppler patch (Flosonics Medical, Sudbury, ON, Canada) was placed over the carotid artery. To place the device, in an axis perpendicular to the plane of the trachea, the face of the ultrasound transducer was moved laterally, away from the trachea, until the strongest carotid Doppler audiovisual signal was noted on user interface. Once obtained, the device was affixed to the neck with a medical adhesive, maintaining a constant angle of insonation.[6] The maximum velocity of the Doppler waveforms was automatically traced using an algorithm based on the approach described by Li et al.[16] The automated maximum velocity was used to determine the duration of systole from the systolic velocity upstroke to the dicrotic notch (i.e., systolic flow time) (Fig. 1). The duration of systole in seconds was used to calculate the FTc using the method of Wodey, as described previously.[4] For a single cardiac cycle, the area under the maximum velocity trace is the maximum VTI and represents the distance, in centimeters, traveled by the fastest moving red blood cells in the artery. Maximum VTI and the FTc were compared in the denominator of the DSI, which is HR/VTI$_{max}$, HR/FTc, respectively.

Statistical Analysis

Values obtained during each stage of the LBNP were compared with baseline using a two-tailed Student *t* test. To evaluate the ability of carotid Doppler metrics to track changes in SV, we quantified the area under the receiver operator curve (AUROC) for each metric using both an absolute value and percent change. From the AUROC, the Youden index was used to choose the best threshold to optimize sensitivity and specificity; we also performed a "gray zone" analysis by reporting the threshold for each measure that yielded a 90% sensitivity and 90% specificity, respectively. Lastly, for each optimal threshold, we calculated the Brier score as a measure of the threshold's ability to detect reduced SV. The Brier score for a model can range from 0 for a perfect model to 0.25 for a noninformative model with a 50% incidence of the outcome.[17] This entire analysis was performed to detect a fall in SV of more than 10% and 20%, separately. All data were compared in 10-second intervals.

RESULTS

The study was performed without any complication. Thirty-nine percent of the volunteers were female, and the average age and body mass index were 29.5 years and 24.0 kg/m^2, respectively. In all subjects, audible Doppler and common carotid spectra were obtained as were adequate SV signals from the pulse contour analysis device.

Hemodynamic Variables During LBNP

Measures at resting baseline, reported as the average ± SD, were as follows: HR, 63.2 ± 6.9 bpm; systolic blood pressure, 127.3 ± 15.6 mm Hg; mean arterial pressure, 97.2 ± 10.8 mm Hg; respiratory rate, 16.2 ± 5.1 breaths per minute; SV, 96.6 ± 12.0 mL;
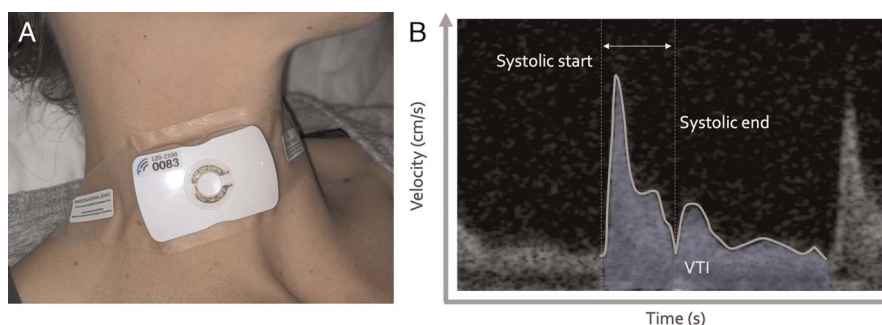
Figure 1. The wearable Doppler and its measures. (*A*) shows the wireless Doppler on a healthy volunteer. (*B*) shows a single cardiac cycle from the Doppler sensor. The area under the maximum velocity trace (VTI$_{MAX}$) is the velocity time integral. The time between systolic start and systolic end is the carotid flow time (double head arrow). This value, in milliseconds, is corrected for HR by the equation of Wodey to give the FTc. The *y* axis is velocity in centimeters per second, and the *x* axis is time in seconds.

carotid artery VTI, 35.5 ± 5.9 cm; and corrected flowtime, 319.5 ± 22.8 milliseconds. Table 1 summarizes the average changes observed during the entire LBNP protocol.

Diagnostic Characteristics

For all measures, Table 2 summarizes the AUROC, best diagnostic threshold, and sensitivity and specificity for detecting a 10% and 20% reduction in SV. The measures and indices are listed in order of highest sensitivity for the percent change threshold. Supplementary Table 3 (http://links.lww.com/TA/C581) lists the measures and indices by the highest specificity for the percent change threshold; supplementary Table 4 (http://links.lww.com/TA/C581) reports the thresholds yielding 90% sensitivity and 90% specificity for each measure and index. Figure 2 shows the receiver operator curves for the denominators of the three studied shock indices. Because the DSI and traditional shock index share the same numerator (i.e., HR), their differences are driven entirely by their denominators; thus, we provide receiver operator curve plots of only the denominators of the two indices.

DISCUSSION

A number of salient points are taken from our data. First, in a human model of hemorrhage, measures and indices from a wireless, wearable Doppler ultrasound device were superior at detecting central hypovolemia than systolic and mean arterial blood pressure. These findings were true whether the SV threshold was 10% or 20%, indicating an advantage for both mild and moderate blood loss. Second, the most sensitive measure for detecting a 10% SV reduction was decreasing carotid artery FTc, whereas the most sensitive measure to detect a 20% fall in SV was rising DSI$_{FTc}$. Third, in general, following percent change of Doppler measures improved accuracy for detecting SV reduction.

Typically, when identifying a serious or life-threatening event, high sensitivity is desired, in other words, a test that minimizes false negatives. Our data suggest that the false-negative rate could be brought down to about 10% to 15% for uncovering even mildly reduced central blood volume by trending the FTc in conjunction with the HR. Thereafter, a specific test may be applied to minimize false positives. Because the DSI$_{FTc}$ has greater specificity, metrics and indices from the wearable patch could be applied successively in a Bayesian approach to help

TABLE 1. Hemodynamic Change During LBNP

Stage/Metric	−15 mm Hg		−30 mm Hg		−45 mm Hg		−60 mm Hg		−70 mm Hg		−80 mm Hg	
	Absolute	**% Δ**	**Absolute**	**% Δ**	**Absolute**	**% Δ**	**Absolute**	**% Δ**	**Absolute**	**% Δ**	**Absolute**	**% Δ**
SV, mL	−3.2*	−3.1	−8.4*	−8.4	−16.9*	−17.4	−25.7*	−26.5	−33.5*	−34.3	−37.9*	−38.2
VTI$_{max}$, cm	−3.4*	−10.7	−5.7*	−18.1	−9.0*	−29.0	−13.1*	−41.5	−15.7*	−50.1	−18.1*	−58.3
FTc, ms	−11.6*	−3.1	−22.1*	−5.9	−32.5*	−8.7	−40.6*	−10.8	−45.1*	−12.0	−44.4*	−11.9
DSI$_{VTImax}$	+0.3*	+13.7	+0.7*	+32.6	+1.5*	+73.3	+3.0*	+150.0	+4.9*	+234.6	+7.5*	+356.2
DSI$_{FTc}$	+0.007*	+3.9	+0.02*	+14.1	+0.05*	+32.0	+0.1*	+58.7	+0.14*	+82.1	+0.18*	+103.1
SI	−0.003**	−0.3	+0.02*	+5.4	+0.09*	+20.0	+0.2*	+43.2	+0.3*	+64.9	+0.4*	+82.0
sBP, mm Hg	+1.0**	+1.2	+2.2†	+2.4	+0.5**	+1.2	−1.1**	−0.1	−2.3‡	−0.9	−1.5**	+0.8
MAP, mm Hg	−0.2**	−0.07	+1.3†	+1.6	+1.6†	+2.0	+2.3*	+2.6	+3.2*	+3.8	+5.2*	+6.6

Absolute value is relative to baseline.
*$p < 0.001$.
**Nonsignificant.
†$p < 0.01$.
‡$p < 0.05$.
MAP, mean arterial pressure; sBP, systolic blood pressure; SI, shock index; VTI$_{MAX}$, maximum velocity time integral.

TABLE 2. Diagnostic Accuracy for Detecting SV Reduction

	Variable	Threshold	Sensitivity	Specificity	AUROC	Brier Score
10% SV Reduction	FTc	297 ms	85%	60%	0.81	0.17
		−7.7%	86%	78%	0.90	0.13
	DSI$_{FTc}$	0.26	74%	88%	0.89	0.14
		+24.0%	84%	87%	0.92	0.12
	DSI$_{VTImax}$	2.75	79%	83%	0.88	0.14
		+44.4%	82%	82%	0.89	0.13
	SI	0.6	67%	89%	0.86	0.15
		+12.6%	81%	90%	0.93	0.12
	VTI$_{max}$	25.1 cm	70%	84%	0.84	0.16
		−25.9%	75%	85%	0.86	0.14
	Systolic pressure	113 mm Hg	16%	92%	0.54	0.21
		−1.7%	53%	77%	0.70	0.19
	MAP	110 mm Hg	80%	7%	0.43	0.20
		−5.9%	14%	92%	0.51	0.21

	Variable	Threshold	Sensitivity	Specificity	AUROC	Brier Score
20% SV reduction	DSI$_{FTc}$	0.28	82%	87%	0.92	0.13
		+36.2%	91%	86%	0.95	0.10
	DSI$_{VTImax}$	3.10	87%	80%	0.91	0.14
		+67.0%	90%	82%	0.92	0.12
	SI	0.6	82%	85%	0.91	0.14
		+21.6%	88%	87%	0.95	0.11
	VTI$_{max}$	24.6 cm	81%	76%	0.87	0.14
		−29.6%	84%	82%	0.90	0.12
	FTc	297 ms	94%	50%	0.80	0.19
		−10.7%	78%	81%	0.89	0.16
	Systolic pressure	119 mm Hg	35%	79%	0.58	0.24
		−2.9%	53%	80%	0.70	0.22
	MAP	110 mm Hg	79%	11%	0.47	0.25
		−6.4%	16%	94%	0.52	0.24

These values are ranked in order of their percent change sensitivity. Each threshold is the optimal as determined by the Youden score. Each measure reports two thresholds: the top row represents an absolute threshold; the bottom row represents a threshold relative to baseline.

MAP, mean arterial pressure; sBP, systolic blood pressure; SI, shock index; VTI$_{MAX}$, maximum velocity time integral.
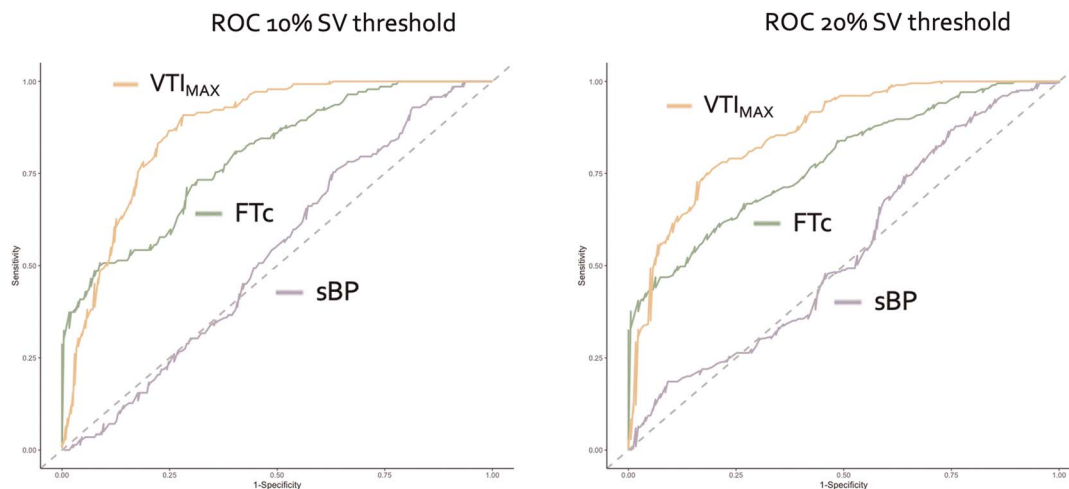

Figure 2. The ROCs for each of the denominators of the studied shock indices. The left panel illustrates detecting a 10% SV reduction; the right panel illustrates detecting a 20% SV reduction. These curves represent the absolute thresholds from Table 2. ROC, receiver operator curve; sBP, systolic blood pressure; VTI$_{MAX}$, velocity time integral under the maximum velocity trace.

refine hemodynamic prediction. Use of carotid FTc to trend blood volume loss is consistent with the findings of previous investigators who measured FTc change following blood donation[18] and in gastrointestinal hemorrhage.[19] Thus, carotid Doppler measures by themselves could minimize both false negatives and positives when detecting mild-to-moderate blood loss. This is especially notable given the simplicity of the wearable Doppler relative to measuring blood pressure in austere medical environments. Furthermore, as the wearable Doppler is lightweight and wireless and has a graphical user interface compatible with any iOS-powered device, this novel biosensor may be useful for medics early in the continuum of care for military and civilian triage and treatment. For example, two patients may have similar traditional vital signs; however, if one were to have a DSI_{FTC} rise by 60%, this patient could be more urgently transported for source control and have blood products at the ready.

We also observed that using percent change (% Δ) generally improved sensitivity; this was true even for the traditional shock index. Clinically, the difference between using an absolute threshold, as compared with a relative one (% Δ), is often expressed as the difference between performing a "snap-shot" assessment versus monitoring across time, respectively. This is consistent with clinical experience in that following hemodynamic change over time typically provides more meaning than a single measurement; we also made this observation in moderate-to-severe central volume loss.[9] An example might be a shock index of 0.5 evolving to 0.7; both absolute values are below the clinically concerning threshold of 1.0; however, the percent rise raises concern. Of interest, in these healthy volunteers, a shock index of 1.0 performed poorly at detecting both SV thresholds with sensitivities less than 10%. In other words, when SV had fallen by more than 20% in these subjects (i.e., approximating a total blood loss of 9 mL/kg), the traditional shock index was above 1.0 in less than 10% of these instances. While the traditional shock index in this evaluation performed well (Table 2), this accuracy was buoyed by the numerator of the shock index (i.e., HR); there is a strong, inverse relationship between HR and SV in this LBNP model.[10] The denominators of each of the shock indices demonstrated clear superiority for Doppler measures, as evidenced in Figure 2.

While our data have more obvious implications for both the military and traumatic civilian populations, we also believe that detecting diminished SV is valuable in other common scenarios such as predicting postintubation hypotension. In the setting of anesthesia, when compensatory rise in vascular resistance is blunted, falling SV is more directly related to systemic blood pressure. Ostensibly, a patient deemed to have mild-to-moderate SV reduction by common carotid Doppler assessment would be at increased risk of hypotension following initiation of mechanical ventilation. Indeed, recent investigations have observed that common carotid artery FTc predicts postinduction hypotension.[20,21]

Our study has limitations. First, we did not study actual hemorrhage; however, the LBNP model does correlate well with blood loss in nonhuman primate studies[14] and diminished thoracic blood volume.[15] More specifically, total blood loss (i.e., in mL/kg) can be estimated as one half the fall in SV in the LBNP model. For example, 10% SV reduction was observed at −20 mm Hg of LBNP and approximated blood loss of 4.5 mL/kg; moreover, 20% SV reduction was observed at −40 mm Hg of LBNP, mim-

icking total blood loss of 9.1 mL/kg. This relationship was linear down to −70 mm Hg LBNP, simulating 18 mL/kg blood loss with a fall in SV of roughly 50%.[14] Second, SV measured by the volume clamp technique is limited when there is digital vasoconstriction. Accordingly, with central hypovolemia and release of adrenaline, SV values may be inexact. Nevertheless, 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% compared with criterion standard, especially in the non–critically-ill population.[22] Supporting the trend in SV change observed in this study are previous investigations[23,24] using volume clamp and others who have used different criterion standards during LBNP, including Doppler ultrasonography,[25] bioimpedance,[26] and bioreactance.[15] The advantages of volume clamp are that it is noninvasive and operator independent. Third, we did not compare the measures from this novel biosensor to the Compensatory Reserve Index (CRI).[27] Briefly, the CRI integrates signals extracted from the digital pressure waveform including HR, respiratory rate and vascular impedance to infer compensatory responses to hemodynamic stress. Unlike the CRI, the wearable Doppler directly assesses blood flow in a major artery. Fourth, the subjects were supine and largely motionless; thus, real-world scenarios that include patient and environmental movement (e.g., ambulance, helicopter vibration) require evaluation. Fifth, the subject sample size was calculated to detect a repeated measures correlation coefficient of at least 0.8 between changing SV and carotid Doppler measures. Thus, the study was not specifically powered to detect statistical differences in the DSI as compared with the traditional shock index. Instead, this observational study considered whether there were clinically meaningful difference between the sensitivities, specificities, and areas under the receiver operator curves of the various measures. A strength of our report is that this data set comprises nearly 50,000 carotid Doppler cardiac cycles compared with a criterion standard, making it to our knowledge the largest such evaluation. Finally, we did not account for differences between the internal and external carotid arteries. While others have found that blood flow in the internal carotid artery tracks changes in SV,[28] the congruence between internal and common carotid artery blood flow in the face of changing cardiac output is an avenue of future study.

CONCLUSION

In summary, a wearable Doppler ultrasound accurately detected diminished SV associated with mild-to-moderate central hypovolemia. Doppler measures from the ultrasound patch demonstrated AUROCs greater than systolic and mean arterial blood pressures. In general, diagnostic accuracy is improved by trending values over time—thresholding based on percent change, rather than absolute cut-offs. While these data intimate that a wearable Doppler monitor can identify and monitor 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.

DISCLOSURE

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