Carotid Flow Time Changes With Volume Status in Acute Blood Loss

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Study objective: Noninvasive predictors of volume responsiveness may improve patient care in the emergency department. Doppler measurements of arterial blood flow have been proposed as a predictor of volume responsiveness. We seek to determine the effect of acute blood loss and a passive leg raise maneuver on corrected carotid artery flow time.

Methods: In a prospective cohort of blood donors, we obtained a Doppler tracing of blood flow through the carotid artery before and after blood loss. Measurements of carotid flow time, cardiac cycle time, and peak blood velocity were obtained in supine position and after a passive leg raise. Measurements of flow time were corrected for pulse rate.

Results: Seventy-nine donors were screened for participation; 70 completed the study. Donors had a mean blood loss of 452 mL. Mean corrected carotid artery flow time before blood loss was 320 ms (95% confidence interval [CI] 315 to 325 ms); this decreased after blood loss to 299 ms (95% CI 294 to 304 ms). A passive leg raise had little effect on mean corrected carotid artery flow time before blood loss (mean increase 4 ms; 95% CI –1 to 9 ms), but increased mean corrected carotid artery flow time after blood loss (mean increase 23 ms; 95% CI 18 to 28 ms) to predonation levels.

Conclusion: Corrected carotid artery flow time decreased after acute blood loss. In the setting of acute hypovolemia, a passive leg raise restored corrected carotid artery flow time to predonation levels. Further investigation of corrected carotid artery flow time as a predictor of volume responsiveness is warranted. [Ann Emerg Med. 2015;■:1-6.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Effective use of intravenous fluid therapy is an essential element of caring for the critically ill.[1] Aggressive fluid resuscitation is encouraged by evidence-based guidelines for the treatment of some shock states, and failure to optimize preload may lead to inappropriate initiation of vasopressor therapy.[2] However, recent evidence has highlighted that overresuscitation with fluid may worsen patient outcomes.[3]

Importance

Approximately 50% of unstable patients in the critical care setting fail to improve their cardiac output in response to an intravenous fluid bolus.[4] Clinical examination and static physiologic measurements, such as mean arterial pressure and central venous pressure, have not proven reliable in identifying patients who will respond to volume expansion.[5] Dynamic predictors of volume responsiveness have demonstrated encouraging results but are not routinely available in many settings in which critical care is provided, including the emergency department. Improved tools to predict which patients will respond to fluid are needed to help balance the goals of optimizing preload, administering intravenous fluids judiciously, and avoiding resource-intensive and potentially harmful invasive procedures.

Goals of This Investigation

Studies of esophageal Doppler monitoring have suggested the value of using changes in aortic flow time to guide fluid therapy.[6] Flow time is the systolic fraction of the cardiac cycle, corrected for pulse rate. Although esophageal Doppler monitoring typically requires intubation, it may be feasible to use flow time through the carotid artery as a substitute, given that the carotid artery is only slightly distal to the aortic outflow tract and has similar flow characteristics.

Editor's Capsule Summary

What is already known on this topic

Invasive hemodynamic monitoring can predict volume responsiveness in some ICU patients.

What question this study addressed

Can noninvasive Doppler measurements of carotid flow time, in conjunction with passive leg raise, identify volume responsiveness in 70 healthy volunteers after a mean 452-mL blood donation?

What this study adds to our knowledge

There was no cut point that successfully differentiated pre– versus post–blood loss states even though there was a significant difference in mean carotid flow time response to passive leg raise between groups.

How this is relevant to clinical practice

This study does not support the clinical utility of this test to detect a 1-unit blood loss in healthy young unstressed volunteers; better noninvasive measures may one day be developed.

To investigate the potential value of corrected carotid artery flow time as a marker of volume responsiveness, we sought to determine whether it changed in response to acute blood loss and to evaluate a passive leg raise maneuver's effect on it. We hypothesized corrected carotid artery flow time would decrease after blood loss and that a passive leg raise maneuver would have no effect on it before phlebotomy but would increase it after blood loss.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective observational study conducted in adult volunteer whole blood donors. We enrolled a convenience sample of donors presenting to the hospital blood donor center. Subjects were recruited from March to September 2013. The institutional review board approved this study.

Selection of Participants

Prospective donors found to be fit for whole blood donation by the blood donor center staff were screened to participate in the study. Subjects were recruited when a study investigator was available. Donors aged 18 to 55 years and with no history of atrial fibrillation or aortic disease were eligible to participate. There were no other exclusion criteria.

Methods of Measurement

Study investigators were 2 emergency physicians with fellowship training in emergency ultrasonography. Investigators completed a series of measurements to standardize approach and technique before enrolling subjects. Study participants' age, height, weight, sex, blood pressure, and pulse rate were recorded from the blood donor center's intake form.

Subjects were seated in a reclining chair for whole blood donation, with their legs parallel to the ground and their back angled at 45 degrees. Before phlebotomy, an investigator acquired an ultrasonographic image of the right common carotid artery in long axis proximal to the carotid bulb and obtained a pulse wave Doppler tracing of flow through the artery. Ultrasonographic images were obtained with a 10-5 MHz linear transducer on a SonoSite M-Turbo (SonoSite, Bothell, WA). The peak velocity, cardiac cycle time, and carotid flow time were recorded. The cardiac cycle time was obtained with electronic calipers in the ultrasonographic machine's software by measuring the distance between heartbeats at the beginning of the Doppler flow upstroke. Carotid flow time was measured between the upstroke of the flow tracing and the dicrotic notch, and it was corrected for pulse rate by dividing flow time by the square root of the cardiac cycle time to calculate corrected carotid artery flow time. Typical times to obtain an image of the artery and a Doppler tracing were 20 to 30 seconds. Figure E1 (available online at http://www.annemergmed.com) illustrates a representative pulse wave Doppler tracing.

After this measurement, a passive leg raise maneuver was performed. In the reclining chair, subjects' feet were elevated 45 degrees above the level of the heart. After 30 seconds in this position, another tracing of Doppler flow through the carotid artery was obtained, and the parameters were measured again. Subjects were returned to a neutral position with their legs at the level of their heart. Blood donor center staff performed phlebotomy according to their protocol. Immediately after the donation, repeated Doppler tracings and measurements were obtained before and after a passive leg raise maneuver.

All images were saved as still pictures, with and without measurements. A third investigator with fellowship training in emergency ultrasonography independently analyzed the image of the Doppler waveform that did not have measurements, blinded to the subject time. This blinded reviewer measured corrected carotid artery flow time measured from the still pictures with an electronic ruler (OndeRulers, version 1.13.1; Ondesoft, http://www.ondesoft.com), calibrated to the measurements on the ultrasonographic image. This was performed to assess that placement of calipers was not subject to bedside sonographer bias.

Outcome Measures

The primary outcome was the difference in supine corrected carotid artery flow time before and after blood loss. Secondary outcomes included the difference in corrected carotid artery flow time after passive leg raise, pre– and post–blood loss.

Primary Data Analysis

Data were summarized with means with SDs. After meeting the normality assumption, differences between values before and after blood donation or between supine and passive leg raise positions were calculated. Sensitivity and specificity of corrected carotid artery flow time and Δcorrected carotid artery flow time after passive leg raise for identification of hypovolemia were calculated. An intraclass correlation coefficient was calculated to assess the agreement between the investigator enrolling subjects and the blinded investigator reviewing the data. The coefficient was calculated with 1-way ANOVA, assuming fixed effects for the evaluator. Data were imported into a Microsoft Excel spreadsheet (version 12.3.3; Microsoft, Redmond, WA), in which descriptive measures were calculated. Analyses were completed in Stata (version 12; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Subjects

Seventy-nine blood donors were screened for participation; 78 gave consent and were enrolled in the study. Of the subjects enrolled, 4 did not complete the blood donation and 4 had incomplete data recorded; they were excluded from the analysis. Seventy completed donation and the study protocol and had complete data for analysis (Figure E2, available online at http://www.annemergmed.com). Donors had a mean blood loss of 452 mL. Table E1 (available online at http://www.annemergmed.com) displays the characteristics of the study population. Two investigators enrolled all subjects (D.C.M., 38; N.A.K., 32).

Main Results

Figure 1 displays the distribution of corrected carotid artery flow time at each study time. Mean supine corrected carotid artery flow time before blood loss was 320 ms (95% confidence interval [CI] 315 to 325 ms). After blood loss, the mean corrected carotid artery flow time decrease was 21 ms (95% CI 17 to 26 ms) to 299 ms (95% CI 294 to 304 ms). Before blood loss, the mean increase in corrected carotid artery flow time after a passive leg raise was 4 ms (95% CI –1 to 9 ms); afterward, it was 23 ms (95% CI 18 to 28 ms) to 322 ms (95% CI 318 to 328 ms). Figure 2 depicts the changes in corrected carotid artery flow time for individual study subjects. The mean percentage change in corrected carotid artery flow time after a passive leg raise before and after blood donation was 1.2% and 8.3%, respectively (Figure 3).

Assuming the pre–blood loss supine position as a standard for euvolemia, we calculated sensitivity and specificity for both corrected carotid artery flow time and Δcorrected carotid artery flow time after passive leg raise to detect hypovolemia. A corrected carotid artery flow time cutoff of 310 ms was 74% sensitive (95% CI 64% to 84%) and 69% specific (95% CI 58% to 79%) for identifying hypovolemia. A Δcorrected carotid artery flow time of 5% was 66% sensitive (95% CI 55% to 77%) and 77% specific (95% CI 67% to 87%) for hypovolemia.

An intraclass correlation coefficient between the blinded reviewer and the measurements obtained by a sonographer at bedside was calculated for each study time. Intraclass correlation coefficient values for the 4 points were pre–blood loss, supine 0.67 (95% CI 0.37 to 0.83); pre–blood loss, with passive leg raise 0.73 (95% CI 0.48 to 0.87); post–blood loss, supine 0.84 (95% CI 0.68 to 0.92); and post–blood loss, with passive leg raise 0.69 (95% CI 0.42 to 0.85).

LIMITATIONS

This study has several limitations. It was performed in a convenience sample of young, healthy volunteers donating whole blood, who were unlikely to have atherosclerosis or cardiovascular dysfunction. Observed changes in carotid flow time may not be generalizable to populations with underlying cardiac or vascular abnormalities, illness-induced organ dysfunction, or medication use.

We assumed that subjects' intravascular volume was replete before blood donation. If subjects were dehydrated before blood loss, the hemodynamic responses to intravascular volume change and passive leg raise may have been altered. We also assumed that the loss of circulating blood volume sustained in whole blood donation represented a transition to a volume-responsive state. Carotid flow time measurements may be influenced by both the amount and acuity of intravascular volume change in this protocol, which may not be representative of physiologic changes and compensations in the critically ill.

In addition, study investigators had advanced ultrasonographic training. Accurate acquisition and interpretation of corrected carotid artery flow time by ultrasonographic users competent in core applications cannot be inferred from these results.

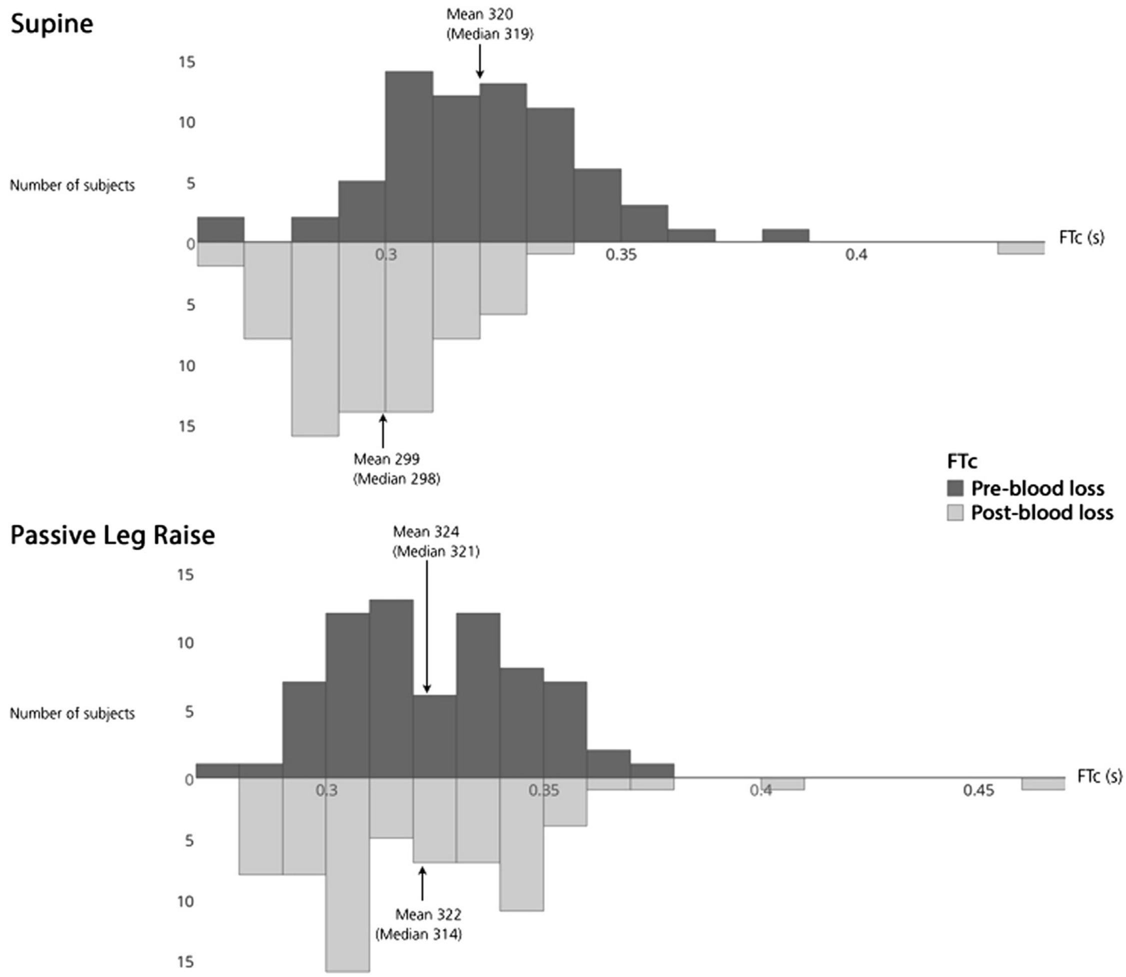

Figure 1. Distribution of corrected carotid flow time at each study time. *FTc*, Corrected carotid artery flow time.

Finally, investigators were not blinded to subject condition when measurements were obtained. The attendant pretest probability raises the potential for bias in how measurements were obtained from the Doppler tracing. However, independent reanalysis of the Doppler tracings by a blinded investigator demonstrated good agreement with the measurements obtained in real time.

DISCUSSION

Studies of patients in the ICU and operating room have demonstrated that dynamic measurements of pulse pressure variation, stroke volume variation, and aortic blood flow can predict volume-responsive patients.[4] However, methods to acquire these measurements typically require mechanical ventilation or invasive monitoring devices.[5] Noninvasive predictors of volume responsiveness are desirable from the perspective of resource use and patient safety.

Our results show that acute blood loss, corresponding to intravascular depletion, was associated with a decrease in mean carotid flow time. A passive leg raise maneuver performed in the volume-depleted state prompted an increase in mean carotid flow time to pre–blood loss levels. These results suggest that measurement of carotid flow time, in conjunction with a passive leg raise maneuver, is a candidate tool to assist in detecting a volume-responsive state or hypovolemia but does not define either a specific corrected carotid artery flow time cutoff or percentage Δcorrected carotid artery flow time indicating volume responsiveness.

The initial studies of aortic flow time showed that it is affected by changes in preload and afterload.[7] Subsequent clinical studies intended to identify a flow time threshold predictive of volume-responsiveness have demonstrated a range of results.[6,8,9] Most of these investigations attempted to define a threshold flow time value predictive of the response to fluid loading. Given the interactions and interventions that may influence preload or afterload, the inconsistent performance of particular flow time thresholds is not necessarily surprising. An isolated corrected carotid

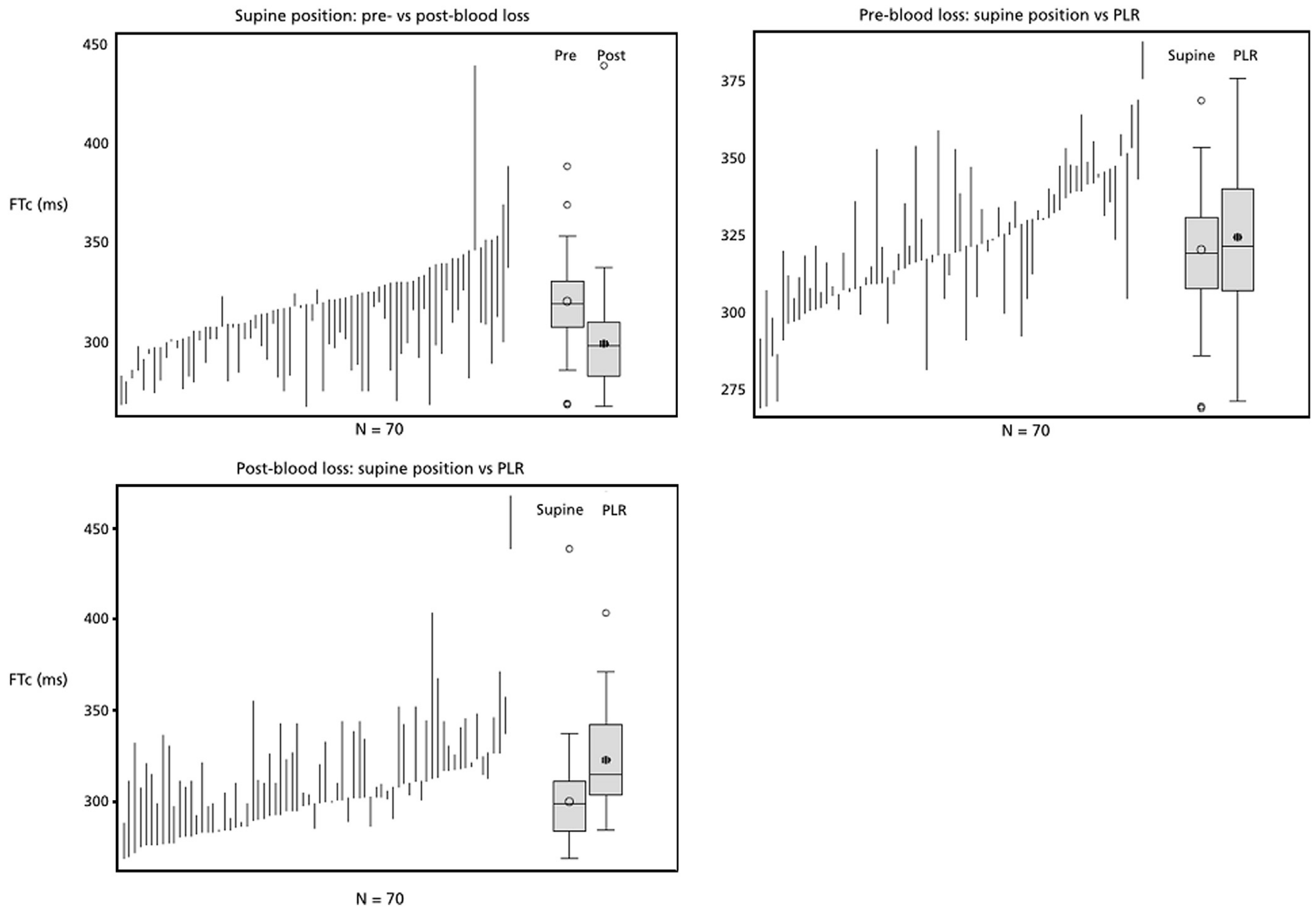

Figure 2. Magnitude and direction of change in corrected carotid artery flow time for individual subjects between study times. Box plots display interquartile range, median, and mean. *PLR*, Passive leg raise.

artery flow time is a static measure, such as mean arterial pressure; dynamic indices, which assess the cardiovascular response to preload variation, are better predictors of fluid responsiveness.

An accumulating body of evidence supports the value of passive leg-raise-induced changes in hemodynamic indices to identify fluid responders.[10] Using a passive leg raise maneuver to determine a threshold Δcorrected carotid

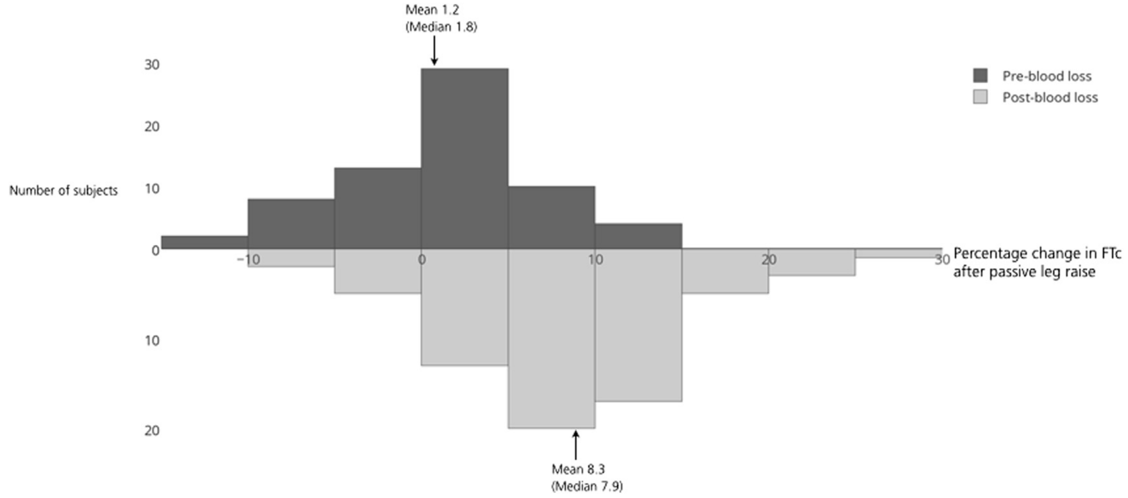

Figure 3. Distribution of percentage change in corrected carotid artery flow time from baseline after passive leg raise.

artery flow time may identify patients who are fluid responsive more accurately than a corrected carotid artery flow time cutoff. A small study suggested that passive leg-raise-induced changes in aortic flow time, but not a threshold flow time value, were predictive of fluid responsiveness.[8] Our data suggest that there are decreases in corrected carotid artery flow time that accompany hypovolemia and that increasing Δcorrected carotid artery flow time after passive leg raise may reflect preload reserve. Although the data provide support for the concept of using a passive leg raise in conjunction with corrected carotid artery flow time measurement, in this healthy experimental population, neither corrected carotid artery flow time nor Δcorrected carotid artery flow time was able to discriminate between euvolemia and mild hypovolemia. Further study in clinical populations with pathophysiologic changes will be necessary to determine whether corrected carotid artery flow time can reliably identify a volume-responsive state.

Predicting the response of cardiac output to a fluid bolus by clinical examination is unreliable, and the adjunctive tests with best supporting evidence are not routinely available to most emergency physicians. Our study shows that corrected carotid artery flow time may have the ability to detect a volume-depleted state and could prove useful in guiding fluid resuscitation. Further investigation of corrected carotid artery flow time, in conjunction with a passive leg raise, is warranted to better define its potential role in guiding fluid management.

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Author contributions: DCM, DB, CPS, VEN, and ASL conceived the study and designed the protocol. DCM and NAK enrolled subjects. DCM, NAK, and SG collected data. YC provided statistical advice and performed the statistical analysis. DCM, VEN, and ASL drafted the article, and all authors contributed to its revision. DCM takes responsibility for the paper as a whole.

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REFERENCES

1. ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370:1683-1693.
2. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41:580-637.
3. Boyd JH, Forbes J, Nakada T, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure increase mortality. *Crit Care Med*. 2011;39:259-265.
4. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. 2009;37:2642-2647.
5. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care*. 2011;1:1-9.
6. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimization and length of hospital stay after repair of femoral fracture: randomized controlled trial. *BMJ*. 1997;315:909-912.
7. Singer M, Allen MJ, Webb AR, et al. Effects of alterations in left ventricular filling, contractility, and systemic vascular resistance of the ascending aortic blood velocity waveform of normal subjects. *Crit Care Med*. 1991;19:1138-1144.
8. Lafanechere A, Pene F, Goulenok C, et al. Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Crit Care*. 2006;10:132-139.
9. Monnet X, Rienzo M, Osman D, et al. Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. *Intensive Care Med*. 2005;31:1195-1201.
10. Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med*. 2010;36:1475-1483.

APPENDIX

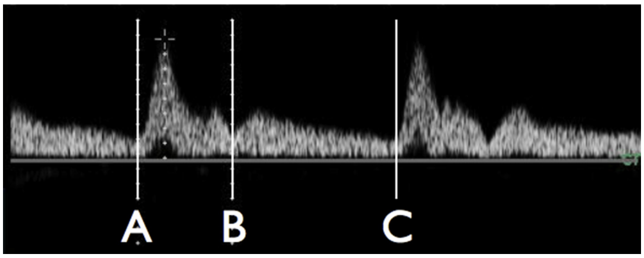

Figure E1. Representative Doppler tracing of carotid artery blood flow. Distance AC, cardiac cycle time. Point B, dicrotic notch. Distance AB, carotid flow time.

Table E1. Characteristics of study subjects.

Characteristic	Median (IQR)*
Age, y	29 (15)
Female sex, No. (%)	43 (61)
Height, cm	170.1 (12.7)
Weight, kg	69.6 (21.3)
BMI, kg/m^2	24.7 (6)
Systolic blood pressure, mm Hg	122 (18)
Diastolic blood pressure, mm Hg	65 (13)
Pulse rate, pre–blood loss, beats/min	70 (17)
Pulse rate, post–blood loss, beats/min	67 (11)
Blood loss, mL	460 (50)

IQR, Interquartile range; *BMI*, body mass index.
*Except age, displaying percentage as noted.

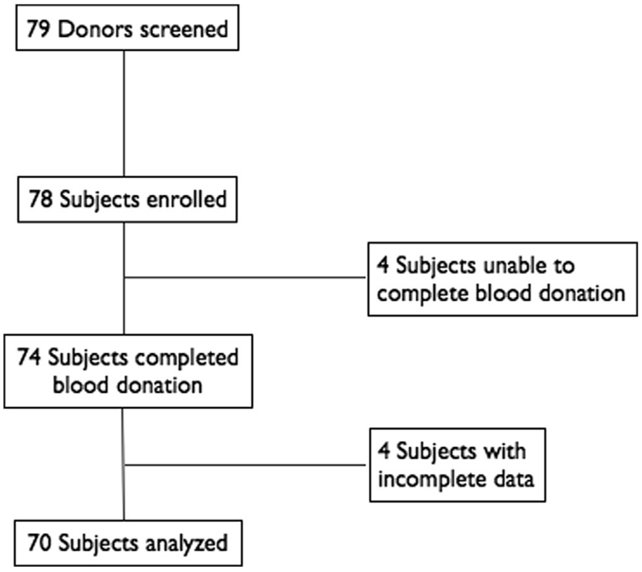

Figure E2. Subject flow diagram.