ASAIO Journal 2016 Clinical Critical Care

Dynamic Limb Bioimpedance and Inferior Vena Cava Ultrasound in Patients Undergoing Hemodialysis

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Assessment of volume status in critically ill patients poses a challenge to clinicians. Measuring changes in the inferior vena cava (IVC) diameter using ultrasound is becoming a standard tool to assess volume status. Ultrasound requires physicians with significant training and specialized expensive equipment. It would be of significant value to be able to obtain this measurement continuously without physician presence. We hypothesize that dynamic changes in limb's bioimpedance in response to respiration could be used to predict changes in IVC. Forty-six subjects were tested a hemodialysis session. Impedance was measured *via* electrodes placed on the arm. Simultaneously, the IVC diameter was assessed by ultrasound. Subjects were asked to breathe spontaneously and perform respiratory maneuvers using a respiratory training device. Impedance (dz) was determined and compared with change in IVC diameter (dIVC; $r = 0.76$, $p < 0.0001$). There was significant relationship between dz and dIVC ($p < 0.0001$). Receiver-operator curves for dz at thresholds of dIVC (20% to70%) demonstrated high predictive power with areas under the curves (0.87–0.99, $p < 0.0001$). This evaluation suggests that real-time dynamic changes in limb impedance are capable of tracking a wide range of dynamic dIVC. This technique might be a suitable surrogate for monitoring real-time changes in dIVC to assess intravascular volume status. *ASAIO Journal* 2016; 62:463–469.

Keywords: bioelectrical impedance analysis, hemodialysis, ultrasound

Monitoring and assessment of a patient's volume status and fluid responsiveness is an integral part of the management plan of critically ill patients as well as others for whom volume management has significant outcome implications. Rapid and accurate volume determinations are important for preventing under or over resuscitation of critically ill and injured patients that can result in higher rates of secondary injury and mortality. These same considerations also extend to patients with chronic conditions such as heart failure and chronic kidney disease.[1–6] Development of noninvasive and easy to use tools to make these assessments would be a welcome addition to the management of these patients.

The dynamic relationship between venous return, the function of the right ventricle, and its interaction with lung mechanics are key determinants of estimating intravascular volume status and more importantly, the patient's functional response to addition or removal of volume.[7,8] The use of real-time ultrasound to view the collapse or distention of the inferior vena cava (IVC) during respiration is a useful tool to estimate volume responsiveness and guide intravenous fluid management.[9–18] Inferior vena cava ultrasound requires physicians with significant training and specialized expensive equipment. Inferior vena cava measurements are difficult to obtain in obese patients and patients with significant amounts of bowel gas. Inferior vena cava measurements require a physician to be present at the bedside for each measurement making frequent measures to follow treatment logistically challenging. It would be of significant value to be able to obtain this measurement on a continuous basis without physician presence for each measurement. Bioimpedance—a measure of a tissue's resistance to an induced current or voltage[19,20]—has been used to monitor fluid status, nutritional status, and lung water. When applied to either the whole body or a portion thereof, bioimpedance becomes the cumulative effect of the individual impedances of components under examination. These components in the body consist of muscle tissue, fat, intracellular and extracellular fluid, and blood. Blood, as a good conductor of electricity, has a distinct effect on limb impedance as the respiratory cycles significantly shift blood volume in the limb. That is, the impedance of a limb increases with decreased blood volume in the limb—as occurs during spontaneous inspiration as blood return is increased to the thorax through the mechanism of enhanced intrathoracic negative pressure—and decreases with increased blood volume in the limb—as is the case during spontaneous expiration. These effects are exaggerated with respiratory maneuvers like deep inspiration. Furthermore, because venous compliance is up to 30 times greater than its arterial counterpart,[21,22] volume change occurring within a limb during respiration will largely be a function of venous blood return.

Aim

We tested a new noninvasive technique to assess volume status. Our approach was to utilize single-frequency

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Submitted for consideration November 2015; accepted for publication in revised form February 2016.

MHT, KRW, BB, MH, NT, RDH, and AJP have received grant funding support from Baxter Healthcare Corporation for this study.

Disclosures: MHT and KRW have submitted a patent application (61/859,615). Filed on July 29, 2014 and published on January 29, 2015. AJS, CMF, GTD, and BCC declare no conflict of interest.

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DOI: 10.1097/MAT.0000000000000355

bioimpedance measurements of the upper arm as a method to determine intravascular volume status by assessing dynamic changes in the peripheral venous volume in response to respiration and compare it to changes in IVC diameter due to the same respiration in spontaneously breathing patients. We hypothesize that dynamic bioimpedance changes measured in the upper arm during respiration would predict IVC collapsibility changes (dIVC). We chose to examine patients with renal failure undergoing hemodialysis because of the typically large volume status changes that can occur over the course of a dialysis treatment thus affording us the chance to examine dynamic changes on time.

Materials and Methods

This pilot study was approved by the University of Michigan Institutional Review Board to consent and enroll patients 18 years or older receiving hemodialysis as a part of their routine care. Prisoners and pregnant women were excluded from the study. Limb bioimpedance was continuously measured throughout a hemodialysis session, while the IVC diameter was assessed using ultrasound at the beginning (before) and then at the end (after) of hemodialysis. Dialysis prescription, including amount of ultrafiltration, were determined by the primary team using standard measures (such as a patient's established dry weight). Study data were not available to any members of the treating team and no clinical decision making was performed based on either the ultrasound or bioimpedance measures.

Continuous bioimpedance monitoring of the limbs was performed using a tetrapolar lead system (MB150, Biopac Inc. Goleta, CA). A tetrapolar electrode arrangement was placed on the arm (**Figure 1**), with the outer two electrodes injecting low amplitude alternating current (0.1–1 mA, at 50 kHz) and the inner two detecting voltage changes (at a rate of 200 samples/second). The ratio of these two was calculated and represented the raw bioimpedance data. This raw data was then low-pass filtered (with a cutoff frequency of 0.6 Hz) to isolate the respiratory signal. The peak-to-trough amplitude of the respiratory impedance signal was used as the metric of impedance in this study. Impedance was not measured in the arm with either an A–V fistula or dialysis catheter. Concurrently, a standard curvilinear or phased array ultrasound probe was used to visualize the IVC in a subxiphoid view using commercially available devices (Mindray M7, Mindray North America, Mahwah, NJ). The IVC was examined with patients in the supine position subcostally in a longitudinal view. All IVC measurements were made after identifying the point of maximal collapse, approximately 2 cm caudal to the hepatic vein inlet, in B-mode imaging using frame by frame analysis to identify the point of maximal and minimal diameter. Measuring at this location has been previously validated.[23] Although some sonologists have studied M-mode imaging to calculate IVC collapsibility or distensibility,[9] others have suggested that respiration results in caudal displacement of the IVC which may make M-mode measurements less accurate.[23,24] Video clips 10–15 seconds in length of the ultrasound images were recorded and saved in the DICOM format for later processing and analysis. Ultrasound was performed by one of three members of the team (NT, CF, and RDW) with special ultrasound training and credentialing. Ultrasound was performed and interpreted without simultaneous knowledge of the bioimpedance measurements.

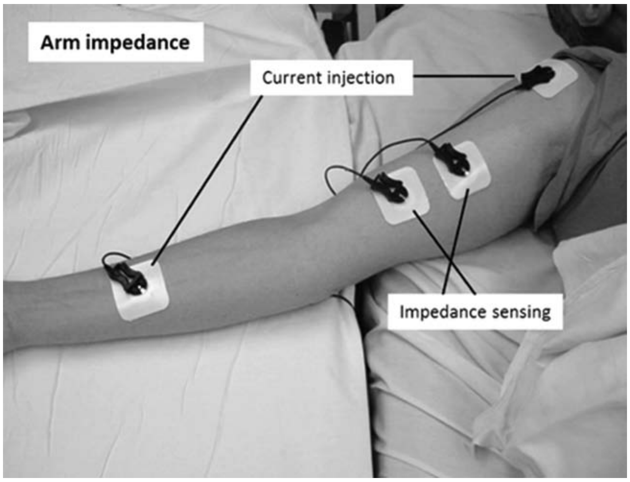

Figure 1. Tetrapolar arrangement of bioimpedance electrodes on the upper limb.

To take advantage of the dynamic changes in the IVC in response to respiration and to control for respiration efforts among subjects, measurements of IVC diameter and bioimpedance were also made during a forced respiratory exercise (deep inspiration) using an inspiratory muscle trainer (IMT) device (Respironics New Jersey). The IMT is a small respiratory adapter that incorporates flow-independent, one-way valve to ensure consistent resistance. It features adjustable specific pressure settings and are regularly used to provide consistent and specific inspiratory pressure regardless of how quickly or slowly patients breathe. Subjects were asked to inhale through the IMT using 20 and 40 cmH_2O pressure thresholds.

Since this study was not a traditional outcome testing study, it is not possible to determine a discrete power. However a study population of 40–50 subjects was deemed sufficient to test the hypothesis that bioimpedance is a suitable surrogate for dIVC. Furthermore, a sample population, particularly with a focus on patients with high fluid removal requirements, was targeted to provide sufficient exposure to a range of dynamic changes in physiology and therefore enough signal variance, to utilize the below stated techniques.

Statistical Analysis

For each inspiratory maneuver, dIVC was measured as ultrasound changes in IVC diameter normalized to the maximum diameter (as used in various collapsibility indices) $(IVC_{max} - IVC_{min}/IVC_{max})$. Peak-to-trough (dz) limb impedance change for each respiratory maneuver was calculated then normalized to the baseline spontaneous breathing $(dz_{maneuver}/dz_{spontaneuos})$. The normalized dz was then compared with dIVC as described in references 10, 25. Descriptive statistics including means, standard deviations, and Pearson correlation were performed to allow for visual inspection across a range of values. A linear regression model of the form $dIVC = \beta_0 + \beta_1(dz) + \varepsilon$ was used to fit the data for a linear response between dIVC and dz to determine if they are related. In this model, β_0 is baseline dIVC when dz is zero, while β_1 is the rate of change in dIVC over time.

Receiver-operator characteristic (ROC) curves were plotted for dz to predict different IVC collapsibility thresholds (20%,

Table 1. Demographics and Ultrafiltration Fluid Amount

Age	Gender		Race			Fluid Ultrafiltrated (ml)
Mean (SD)	Male n (%)	Female n (%)	White n (%)	Black n (%)	Other n (%)	Mean (SD)
58.1 (12.2)	28 (61%)	18 (39%)	23 (50%)	21 (46%)	2 (4%)	1,934 (929)

30%, 40%, 50%, 60%, and 70%) which have been used to assess volume status and fluid responsiveness.[11,26] In this analysis, the ROC curve depicts the relation between dz true positive and false positive results (dz at a lower or higher than a certain dIVC threshold). An area under the curve (AUC) along with confidence interval was calculated to determine how well dz predicted each threshold level of dIVC. Sensitivity and specificity of the bioimpedance method at different levels of dIVC thresholds were calculated as well. SAS9.3, MATLAB 8.3.0, and GraphPad-Prizm6 were used to facilitate this analysis.

Results

Sixty-one patients were consented. Fifteen patients were excluded. Ten due to scheduling issues (discharged before testing or rescheduled dialysis time), four due to the inability of the ultrasound physicians to visualize the IVC, and one due to patient's noncompliance during the use of the IMT device (did not use the device as directed). In addition, two data points from one patient were excluded due to noncompliance as well. Data presented for forty-six patients. **Table 1** lists patients' demographics and average of fluid amount removed. The two metrics used in this comparison are 1) the peak-to-trough value of the bioimpedance respiration signal was found for the breathing maneuver and normalized to a subject's normal premaneuver breathing then transformed by natural log and 2) the distensibility index of the IVC (dIVC) during spontaneous respiration.[25] **Figure 2** demonstrates IVC diameter changes before and after the hemodialysis session as well as corresponding bioimpedance changes

Through the respiratory maneuvers, we obtained a range of dIVC between 1% and 100%. There was a strong, positive, linear relationship comparing dz with dIVC at different respiratory maneuvers ($r = 0.76$, $p < 0.0001$). A linear regression model showed significant relationship between dz and dIVC ($p < 0.00001$, $R^2 = 0.58$). When considering the time elapsed between the tests before and after dialysis, there was no significant effect due to the time elapsed between the tests from before and after dialysis on the relationship between dIVC and dz ($p = 0.318$). The ROC for dz was plotted at different thresholds of dIVC (20% to 70%) and AUCs were calculated for the entire period of the test and for the beginning and end

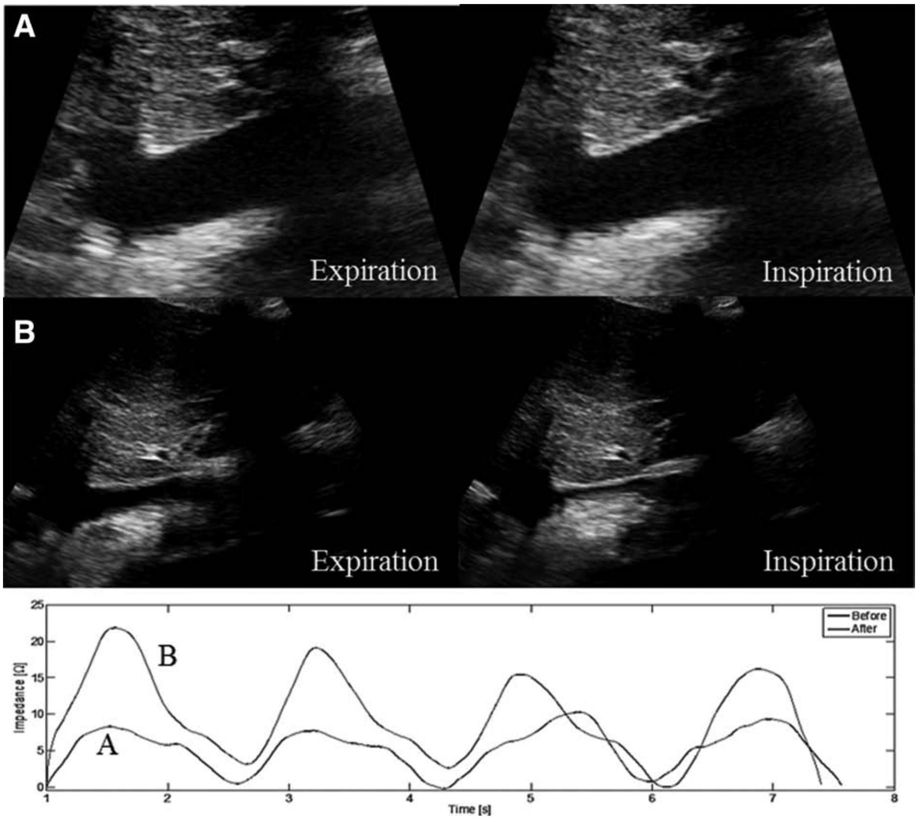

Figure 2. Changes in IVC diameter during (**A**) before hemodialysis, (**B**) at the end of hemodialysis, and corresponding bioimpedance changes. **A**: before and (B) after hemodialysis. IVC, inferior vena cava.

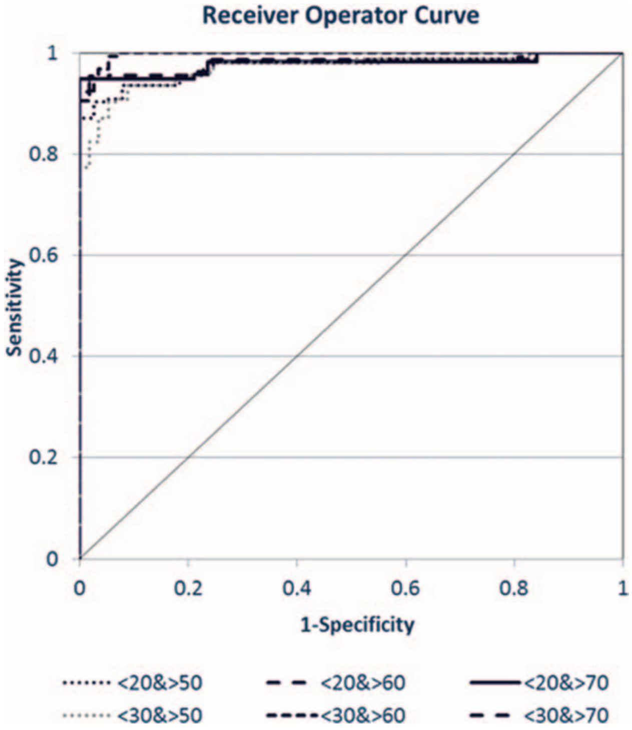

Figure 3. Receiver operator curve of dz. Receiver operator curve of dz was constructed at different thresholds of dIVC between 20% and 70%. dIVC, inferior vena cava diameter.

of dialysis separately. dz was shown to have a high predictive power with areas under the curve between 0.87 and 0.99 ($p < 0.0001$) when looking at the test in its entirety and when considering pre- and posthemodialysis separately. The sensitivity of the impedance method associated with the above thresholds varied between 87% and 96%, while the specificity varied between 89% and 100%. **Figure 3** shows the ROC curves for dz at dIVC threshold combinations with highest AUCs when considering the entire test, while **Figure 4** shows a visual representation of the relationship between an expanded lower and upper bound dIVC threshold (10–90%) and corresponding ROC values. The figure illustrates AUC values between 0.86 and 0.98. **Tables 2 and 3** list various dIVC thresholds, corresponding AUCs, sensitivity, and specificity.

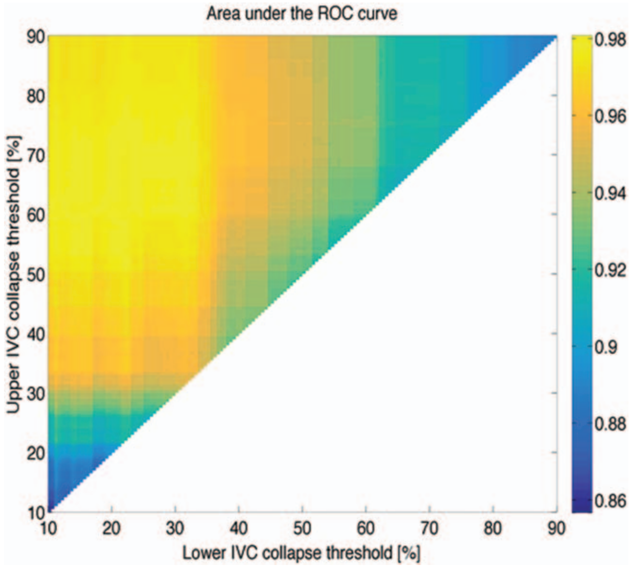

Figure 4. The relationship between the lower and upper bound dIVC threshold and corresponding ROC values. dIVC, inferior vena cava diameter; ROC, receiver operator curve. full color online

Discussion

Technologies and methods for assessment and management of a patient's volume status continue to evolve moving away from such static measures as central venous and pulmonary artery pressure to more dynamic and functional measures such as pulse pressure variation, stroke volume variation, cardiac output, and others.[27,28] Respirophasic changes in IVC diameter are being used as a method to assess volume status and to predict fluid responsiveness in an increasing number of settings including sepsis, trauma, heart failure, and dialysis. It has also been assessed and found to be of value in both spontaneously breathing and mechanically ventilated patients.[9,11–14,29,30] As opposed to techniques such as pulse pressure and stroke volume variation, the value of the technique lies in the physiology of venous return and the transient and reversible volume or preload challenges produced by a ventilatory maneuver such as a sniff or deep breath during which intrathoracic pressure is decreased enhancing venous return and thus pulling greater blood volume into the thorax. The degree of IVC collapse is contingent upon circulatory blood volume, and cardiac function (particularly right heart function).[7,8] The greater the degree of IVC collapse in spontaneously breathing individuals, the greater degree the individual will respond favorably or at least be tolerant to fluid administration. General values for volume responsiveness in spontaneously breathing patients include dIVC values of greater than 40%.[15] dIVC values of less than 15–40% have been reported in heart failure and dialysis patients to indicate a state of fluid surplus or overload.[10,11,31] For mechanically ventilated patients, the reverse relationship exists since intrathoracic pressure increases during ventilation. Thus a greater degree of IVC expansion during positive pressure ventilation is associated with fluid responsiveness to administration of intravenous fluids.[9]

The use of IVC ultrasound has several drawbacks. Ultrasound is operator dependent. A physician who is trained in ultrasound must be at the bedside for each measurement. This means frequent measurements especially in multiple patients can pose logistical challenges. Adequate views often cannot be obtained in as many as 10% of patients.[23,32] In fact in this study the IVC of four individuals could not be visualized. Our impedance technique was designed in an attempt to overcome these issues with IVC ultrasound while providing a similar degree of accuracy as well as the ability to make more frequent measures conveniently. The use of limb bioimpedance changes in response to respiratory maneuvers leverages the same physiology of venous return as does IVC ultrasound. While overall tissue impedance is known to change over time, varies greatly among individuals, and is affected by other variables such as type and placement of electrodes,[33,34] our method negates these issues by indexing the changes in impedance to a respiratory maneuver that changes the venous volume of the limb thus allowing each individual to be used as their own control. The use of the IMT device was incorporated in an attempt to

Table 2. Area Under the Curve for dz with Standard Error, 95% CI and *p* Value

dIVC Threshold	<20% and >30%	<20% and >50%	<20% and >60%	<20% and >70%	<30% and >40%	<30% and >50%	<30% and >60%	<30% and >70%	<40% and >50%	<50% and >60%	<60% and >70%
Entire data (before and after)											
AUC for dz	0.942	0.972	0.979	0.978	0.963	0.969	0.978	0.978	0.943	0.945	0.935
Std. err	0.015	0.010	0.001	0.011	0.011	0.011	0.010	0.011	0.015	0.015	0.017
(95% CI)	(0.913–0.971)	(0.952–0.993)	(0.960–0.999)	(0.956–0.999)	(0.941–0.986)	(0.949–0.990)	(0.959–0.997)	(0.956–0.999)	(0.914–0.971)	(0.916–0.974)	(0.901–0.969)
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Sensitivity	0.884	0.935	0.955	0.949	0.922	0.935	0.947	0.945	0.870	0.902	0.923
Specificity	0.921	0.921	0.947	1.000	0.912	0.912	0.947	0.965	0.899	0.891	0.894

AUC, area under the curve; dIVC, inferior vena cava diameter; 95% CI, 95% confidence intervals.

Table 3. Area Under the Curve for dz with Standard Error, 95% CI and *p* Value for Measurements Before and After Dialysis Separately

dIVC Threshold	<20% and >30%	<20% and >50%	<20% and >60%	<20% and >70%	<30% and >40%	<30% and >50%	<30% and >60%	<30% and >70%	<40% and >50%	<50% and >60%	<60% and >70%
Before dialysis											
AUC for dz	0.925	0.964	0.969	0.963	0.949	0.959	0.964	0.964	0.946	0.943	0.927
Std. err	0.024	0.019	0.019	0.022	0.020	0.019	0.019	0.021	0.020	0.022	0.028
(95% CI)	(0.878–0.972)	(0.927–1.000)	(0.931–1.000)	(0.919–1.000)	(0.909—0.988)	(0.923—0.996)	(0.928—1.000)	(0.923–1.000)	(0.906–0.990)	(0.901–0.986)	(0.872–0.982)
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Sensitivity	0.860	0.933	0.941	0.931	0.915	0.933	0.927	0.931	0.880	0.882	0.931
Specificity	1.000	1.000	1.000	1.000	0.941	0.942	0.941	1.000	0.918	0.893	0.921
After dialysis											
AUC for dz	0.955	0.971	0.990	0.989	0.975	0.977	0.992	0.991	0.932	0.937	0.942
Std. err	0.019	0.016	0.008	0.009	0.012	0.012	0.007	0.007	0.027	0.024	0.021
(95% CI)	(0.917—0.993)	(0.940–1.000)	(0.975–1.000)	(0.972–1.000)	(0.952–0.999)	(0.954–1.000)	(0.979–1.000)	(0.977–1.000)	(0.880–0.985)	(0.890–0.984)	(0.901–0.984)
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Sensitivity	0.859	0.866	0.970	0.966	0.939	0.937	0.969	0.966	0.873	0.893	0.880
Specificity	0.938	0.938	1.000	1.000	0.870	0.870	1.000	1.000	0.867	0.833	0.880

AUC, area under the curve; dIVC, inferior vena cava diameter; 95% CI, 95% confidence intervals.

control for inspiratory effort among individuals in this initial experiment and to produce various levels of dIVC. While not shown, the use of a simple sniff in our patients is being demonstrated to provide equivalent results and should thus allow for easier implementation of the bioimpedance technique in the future.

It was not the intent of this study to examine the new bioimpedance method's ability to predict fluid responsiveness. This pilot study was designed to simply compare the dynamic impedance changes of the upper arm to the dynamic changes of the IVC as measure by ultrasound. The high AUC values, however, over the course of intravascular fluid removal indicates the potential of the bioimpedance technique to predict a wide range of dIVC changes as measured by ultrasound, which are associated with a wide range of intravascular volume states as previously assessed and reported by the use of ultrasound measured dIVC. These high AUC values over a wide range of dIVC also indicate the potential for the technique to be studied alongside IVC ultrasound as new precision targets or thresholds of IVC collapse are developed for various patient cohorts.

Several philosophical and physiologic limitations exist with the current study. We made IVC collapsibility the "gold standard" for comparison with the assumption that dIVC reflects an important part of a closed cardiovascular system consisting of the components of preload, afterload, contractility, and heart rate that while isolated and each capable of being individually manipulated, certainly can impact each other. Since limb impedance changes are based on volume movement into and out of the arm and that they also closely parallel changes in dIVC, this may further support that dIVC is a reflection of venous return and volume and not just a reflection of central venous pressure.[7,8] However, while data are suggesting that dIVC may be a sensitive measure of functional preload capable of predicting volume responsiveness, it may simply be an indicator of volume tolerance.[7,8] Such a measure would still probably have high value. We did not measure the use of limb impedance and dIVC in the setting of vasopressor or ionotropic therapy with or without mechanical ventilation so we cannot yet know how the use of such therapeutics will impact limb impedance and its comparison with dIVC. Similarly, we did not record the presence of chronic pulmonary hypertension in our subject population. The effect of pulmonary hypertension on the usefulness of dIVC and thus limb impedance will need to be examined. Current studies are being undertaken and future studies designed to compare the technique to the ultrasound measure of dIVC in critically ill and injured mechanically ventilated patients as well as its use on other patient groups, such as those with sepsis, heart failure, and trauma. We are currently developing a small wearable version of the device, which could be used for more ubiquitous monitoring in both the inpatient and ambulatory setting. Such a device might allow patients and their health care providers to manage volume sensitive conditions in a more continuous and precision manner.

Conclusions

Limb bioimpedance changes due to respiration-induced intrathoracic pressure–volume changes reflect dynamic changes in the diameter of the IVC as measured by ultrasound with a high degree of performance. The potential of the technique for continuous or semicontinuous volume assessment as an alternative to ultrasound of the IVC deserves future study.

Acknowledgment

The authors acknowledge and thank the University of Michigan Fast Forward Medical Innovations (FFMI) and the Michigan Economic Development Corporation's MTRAC funding program for their support.

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