Estimation of Central Venous Pressure by Pacemaker Lead Impedances in Left Ventricular Assist Device Patients

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Volume status assessment in left ventricular assist device (LVAD) patients remains challenging. Cardiac resynchronization therapy (CRT) devices are common in LVAD patients, and the impedance across the CRT leads may be associated with hemodynamics and serve as a tool for noninvasive estimation of volume status. Ninety-one sets of measurements including cardiac filling pressures and lead impedances were prospectively obtained during ramp tests from 11 LVAD patients (65.5 ± 9.7 years old; nine male) with CRT devices. Right atrial (RA), right ventricular (RV), and left ventricular (LV) lead impedances were all significantly associated with central venous pressure (CVP) ($p < 0.05$). We derived the following equation: estimated CVP = 47.90–(0.086 × RA lead impedance) + (0.013 × RV lead impedance)–(0.020 × LV lead impedance). The estimated CVP had a significant correlation ($r = 0.795$) and good agreement with the measured CVP (mean difference -0.14 ± 1.77 mmHg). Applying the above equation on the validation cohort of twenty-one patients also maintained a strong association with measured CVP ($r = 0.705$). In conclusion, we have derived a novel equation to estimate CVP using lead impedance measurements. This finding may allow noninvasive monitoring of volume status in LVAD patients. *ASAIO Journal* XXX; XX:00–00.

Key Words: left ventricular assist device; hemodynamics; ramp; cardiac resynchronization therapy

Left ventricular assist devices (LVADs) have become a mainstay of therapy for patients with advanced heart failure (HF), both as destination therapy and as bridge to transplantation.[1] However, the rate of right ventricular failure (RVF) remains high and readmissions for HF continue to impose a significant morbidity burden on LVAD patients.[2,3]

Not only for the diagnosis of RVF but also for the follow-up of the degree of RVF, accurate measurement of CVP is essential. However, repeating invasive hemodynamic measurements, which is a gold standard, may have a risk of complications for LVAD patients with enhanced coagulopathy.

Noninvasive evaluation of CVP for the assessment of RVF includes physical examination,[4] echocardiographic assessment of inferior vena cava (IVC) size and collapsibility,[5] and the recently introduced method of transient elastography.[6] These procedures are semiquantitative, require expert technique, and may lack sufficient reproducibility. Noninvasive methodologies to overcome these demerit are desired thus far.

Cardiac resynchronization therapy (CRT) devices typically contain three intracardiac leads, and changes in the pacing impedances of one or more may be associated with changes in cardiac filling pressures. In this study, we sought to evaluate the usefulness of CRT lead impedance as a predictor of CVP in LVAD patients.

Methods

Patient Selection

We prospectively collected data from clinically stable outpatients with the HVAD LVAD (Medtronic, Minneapolis, MN) or the HeartMate II LVAD (Abbott, Abbott Park, IL) who also had a CRT device. CVP and lead impedances were evaluated during a hemodynamic ramp test according to our institutional protocol. Written informed consent was obtained from all participants before the ramp test. The study protocol was approved by the University of Chicago Institutional Review Board.

Ramp Test Protocol

Hemodynamic ramp tests were performed according to our previously described protocol.[7] Impedances were measured for the right atrial (RA) lead, right ventricular (RV) lead, and left ventricular (LV) lead using each CRT device's specific programmer. Measurements of CVP and impedances of each lead were performed after the devices were turned down to a minimum speed (8,000 rpm for HeartMate II and 2,300 rpm for HVAD); subsequently, measurements were taken at progressively increasing LVAD speeds to a maximal value (12,000 rpm

for HeartMate II and 3,200 rpm for HVAD). After the change of LVAD speed, each measurement was performed after at least 2-minute rest. Measurements of lead impedances were performed three times *via* the baseline programmed pacing configuration and then averaged at each LVAD speed. There were no patients with suspicion of lead insulation failure, conductor fracture, device malfunction, sepsis, or myocarditis.

Variables Evaluated

Patients' preoperative background characteristics before LVAD implantation were obtained. During the ramp test, CVP, and lead impedance data were collected. All data were reviewed by the attending cardiologists. Right atrial and RV lead impedances were measured in a bipolar pacing configuration. Left ventricular lead impedance measurements were taken using a narrow bipoles (one LV electrode to a nearby LV electrode) or a wider bipoles (an LV electrode to the RV lead). Impedance was measured as a single value in ohms. CVP and impedance were measured and recorded simultaneously during the ramp study. A single recording of impedance and CVP were obtained at each LVAD speed.

Validation and Longitudinal Cohorts

For our validation cohort, we collected data from LVAD patients with a CRT device who did not receive the aforedescribed ramp test but underwent measurements of both lead impedance by CRT interrogation[8] and CVP level by right heart catheterization (RHC) at the same timing. For the longitudinal assessment, we collected data from patients who did not receive the ramp test but underwent repeated measurements of both CVP and lead impedance.

Statistical Analyses

Statistical analyses were performed using SPSS Statistics 22 (SPSS Inc, Chicago, IL). A two-tailed p value < 0.05 was considered statistically significant. All continuous variables were described as mean ± standard deviation unless otherwise specified. Relationships between CVP and lead impedances were assessed by Pearson's correlation coefficient. The statistical impact of lead impedance on CVP was analyzed using linear regression analysis. Significant variables with $p < 0.05$ in the univariate analysis were enrolled into the multivariate analysis after confirmation that a variance inflation factor was under 5.0 for each.

Based on the results of the multivariate analysis, an equation to estimate CVP was derived. The agreement between measured CVP and the CVP estimated by the equation was analyzed by the Bland–Altman test. The accuracy of the equation's estimate of CVP in the validation cohort was assessed using Pearson's correlation coefficient and Bland–Altman test. A receiver operating characteristic analysis was used to calculate sensitivity and specificity to estimate CVP ≥ 12 mmHg by using the equation.

Results

Baseline Characteristics

Eleven LVAD patients with CRT devices (65.5 ± 9.7 years old; nine male) were enrolled. Baseline characteristics are shown

Table 1. Baseline Characteristics

	Total (N = 11)
Age (years), mean ± SD	65.5 ± 9.7
Gender (male), n (%)	9 (82)
Race (Caucasian), n (%)	8 (73)
Body mass index, mean ± SD	27.8 ± 5.6
Ischemic etiology, n (%)	7 (64)
Destination therapy, n (%)	9 (82)
LVAD duration before ramp test (days), median (IQR)	859 (246–1,310)
CRT-D support duration (days), median (IQR)	1,219 (939–1,633)
LVAD type, n (%)	
HeartMate II	8 (73)
HVAD	3 (27)
CRT-D type, n (%)	
Boston scientific	3 (27)
Medtronics	6 (55)
St. Jude	2 (18)
Hypertension	5 (45)
Diabetes mellitus	4 (36)
History of stroke	2 (18)
Atrial fibrillation	4 (36)
History of ventricular arrhythmia	3 (27)

CRT-D, cardiac resynchronization therapy defibrillator; IQR, interquartile range; LVAD, left ventricular assist device; SD, standard deviation.

in **Table 1**. The majority of patients (82%) were implanted as destination therapy, and seven patients (64%) had an ischemic etiology of their HF. CRT support duration was 1,219 (interquartile range [IQR], 939–1,633) days.

Correlation of CVP and Lead Impedances

Wide distributions of CVP, RA, RV, and LV lead impedances are observed (**Figure 1A**–D). Variabilities of each three measurements were 0.998, 0.996, and 0.998, respectively. There was a moderate negative correlation between CVP and RA lead impedance ($r = -0.668$); whereas CVP had weak negative associations with both RV lead impedance ($r = -0.374$) and LV lead impedance ($r = -0.222$) (**Table 2**).

Estimation of CVP From Measured Lead Impedances

Univariate and multivariate linear regression analyses showed that RA, RV, and LV lead impedances were independently associated with CVP (**Table 3**; $p < 0.05$ for all). An equation to estimate CVP was subsequently derived (see Appendix for more precise methodology [see Appendix, Supplemental Digital Content, http://links.lww.com/ASAIO/A394]): estimated CVP (mmHg) = 47.9–(0.086 × RA lead impedance [Ω]) + (0.013 × RV lead impedance [Ω])–(0.020 × LV lead impedance [Ω]).

There was a strong linear relationship between the equation to estimate CVP and directly measured CVP, although there was significant scatter around the regression (**Figure 2A**; $r = 0.795$). The results are shown with individual patients identified by colored dots in Appendix Figure 1 (see Appendix, Supplemental Digital Content, http://links.lww.com/ASAIO/A394). Linearity seems to be preserved in each individual. Bland–Altman plots showed that the mean difference between estimated and measured CVPs was –0.14 ± 1.77 mmHg, with no tendency toward systematic bias (**Figure 2B**; $p = 0.85$).
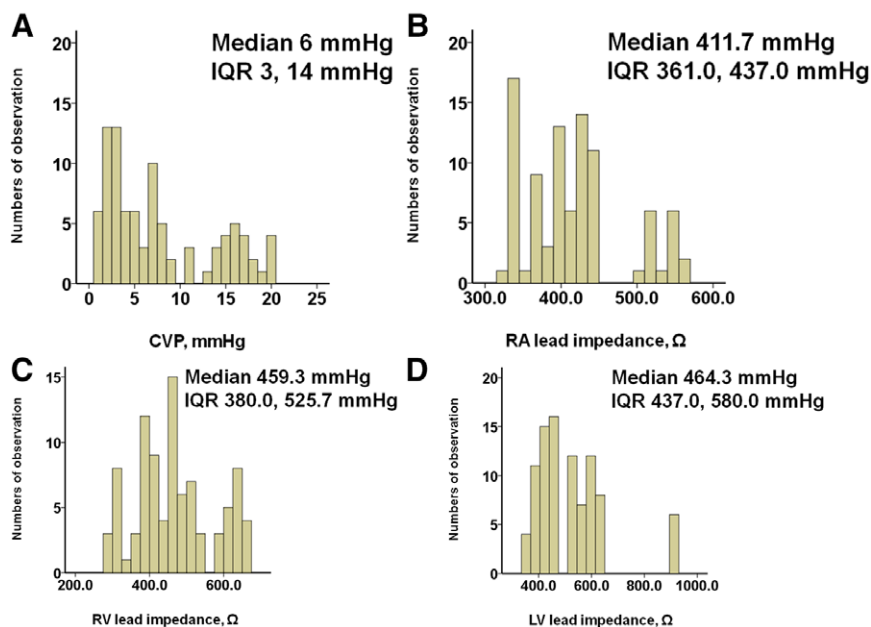
Figure 1. Histograms of the distribution of lead impedances for CVP (**A**), RA (**B**), RV (**C**), and LV (**D**). CVP, central venous pressure; IQR, interquartile range; LV, left ventricular; RA, right atrial; RV, right ventricular.

A receiver operating characteristic analysis showed 0.905 of area under curve, 100% of sensitivity, and 79.1% of specificity to estimate CVP ≥ 12 mmHg by using the equation (Appendix Figure 2 [see Appendix, Supplemental Digital Content, http://links.lww.com/ASAIO/A394]).

As subanalyses, there were still strong linear correlations between estimated and measured CVPs among HeartMate II population ($r = 0.783$, N = 68) and HVAD population ($r = 0.768$, N = 23). Similar trends were observed among Boston scientific device ($r = 0.805$, N = 26), Medtronics device ($r = 0.777$, N = 48), and St. Jude device ($r = 0.980$, N = 17). Strong correlations remained among those with CRT duration shorter than median ($r = 0.659$, N = 55) and those with longer duration ($r = 0.902$, N = 36).

Validation Study for the Derived Equation

Datasets of CVPs directly measured by RHC and lead impedances measured by interrogation were collected from another twenty-one LVAD patients who did not receive the ramp test (63.7 ± 10.6 years old, 15 male) for a validation study.

When the equation was applied to the validation group, estimated CVP still had a strong correlation with directly measured CVP (**Figure 3A**; $r = 0.705$). Bland–Altman plots showed

that the mean difference between estimated and measured CVP averaged 1.15 ± 3.70 mmHg, with no tendency toward systematic bias (**Figure 3B**).

Longitudinal Assessment of the Created Equation

Four patients underwent repeated measurements of both CVP and lead impedance. Second tests were performed at 43, 119, 148, and 154 days, respectively after the first tests. The estimated CVPs changed in parallel with the actually measured CVP in all cases (**Figure 4**).

Discussion

In this prospective study, we analyzed the relationship between invasively measured CVP and noninvasively measured lead impedances in LVAD patients with CRT. The main findings are as follows: 1) there was a moderate negative correlation between CVP and RA lead impedance, and a weak correlation between CVP and RV and LV lead impedances and 2) an equation to estimate CVP based on the results of linear regression analysis demonstrated a strong correlation between measured and estimated CVPs.

Table 2. Correlation Between CVP and Lead Impedances

	p Value	r Value
RA lead impedance, Ω	< 0.001*	−0.668
RV lead impedance, Ω	< 0.001*	−0.374
LV lead impedance, Ω	0.034*	−0.222

*$p < 0.05$ by Pearson's correlation coefficient.
CVP, central venous pressure; LV, left ventricular; RA, right atrial; RV, right ventricular.

Table 3. Linear Regression Analyses for the Estimation of CVP

	Univariate Analysis		Multivariate Analysis		
	B Value	p Value	B Value	p Value	VIF
RA lead impedance, Ω	−0.062	< 0.001*	−0.086	< 0.001*	1.932
RV lead impedance, Ω	−0.021	< 0.001*	0.013	0.009*	1.825
LV lead impedance, Ω	−0.01	0.034*	−0.020	< 0.001*	1.122

CVP, central venous pressure; LV, left ventricular; RA, right atrial; RV, right ventricular; VIF, variant inflation factor.
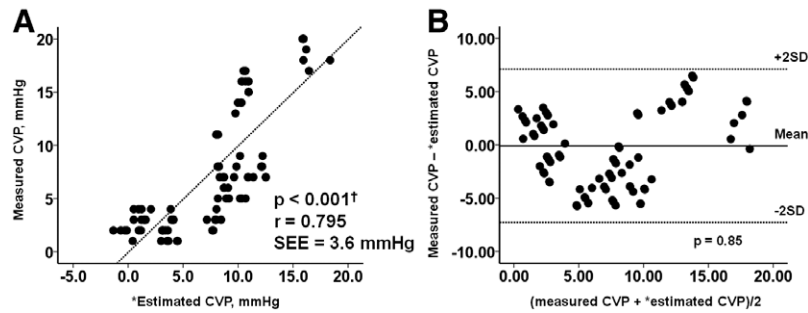*$p < 0.05$ by linear regression analyses.

Figure 2. The correlation between measured CVP and estimated CVP in the derivation cohort are shown in part **A**. The Bland–Altman plot for the comparison of measured CVP and estimated CVP in the derivation cohort is shown in part **B**. There is a moderate positive correlation ($r = 0.795$) and good agreement (mean difference -0.14 ± 1.77 mmHg) between the measured CVP and estimated CVP. *Estimated CVP = $47.90 - 0.086 \times$ (RA lead impedance) $+ 0.013 \times$ (RV lead impedance) $- 0.020 \times$ (LV lead impedance). CVP, central venous pressure; LV, left ventricular; RA, right atrial; RV, right ventricular; SD, standard deviation; SEE, standard error of estimate.

Conventional Noninvasive Estimation of CVP

The most traditional but essential method to estimate CVP remains the physical examination. Jugular venous pressure (JVP), measured at the highest point of oscillation of the internal jugular vein, can be used to estimate CVP.[4] Although convenient and easily performed, JVP estimation may be inaccurate when the jugular vein is constricted or tortuous, and it may be difficult to assess in patients with short necks, with prior neck surgery, or with prior repeated catheter placement in the jugular vein, as is often the case in advanced HF patients. We have previously demonstrated that physical examination had low sensitivity to predict hemodynamics including CVP in the LVAD population.[9]

Another widely-used noninvasive method to predict CVP is transthoracic echocardiography. CVP is estimated using multiple echocardiographic factors, such as the size and respiratory variation of the IVC and RA.[5] However, IVC measurement as a surrogate marker for CVP was never validated in LVAD patients. Echocardiography only offers a semiquantitative assessment of CVP and may lead to inaccurate estimates, particularly in the intermediate range (5–10 mmHg).[10] Furthermore, optimal estimation requires expert technique particularly in LVAD patients.[11]

Use of Impedance Measurements to Reflect Physiology

Impedance measurements derived from cardiac implantable electronic devices (CIEDs) have long been used to assess changes or trends in physiology. Studies have demonstrated correlations between thoracic impedance measurements, measured between the RV lead and pulse generator, and both degree of pulmonary congestion[12–14] and minute ventilation.[15] Such technology is incorporated into some ICD and cardiac resynchronization therapy defibrillator (CRT-D) models (OptiVol; Medtronic, Minneapolis, MN). Changes in LV volume achieved with CRT are also associated with impedance measurements taken between the LV and RV leads.[16] Nevertheless, the accuracy and utility of CIED technology have been questioned in the recent clinical practice.

Localized impedance measurements at the tip of the RV lead have been used as a proxy for ventricular contractility and incorporated in some pacemakers as a closed-loop feedback system for determining heart rate-responsiveness. Given the increase in ventricular contractility with increased sympathetic tone, such a system can increase pacing rate proactively in response to factors like emotional stress, in addition to the more commonly used parameters for heart rate-response such as movement and minute ventilation.[15,17]

There is thus extensive experience with the use of impedance measurements across a variety of intrathoracic spaces to assess physiology and influence therapy. Our data adds the benefit of impedance analysis during the rapidly changing filling pressures seen with routine ramp studies, effectively isolating those changes from other confounding factors.
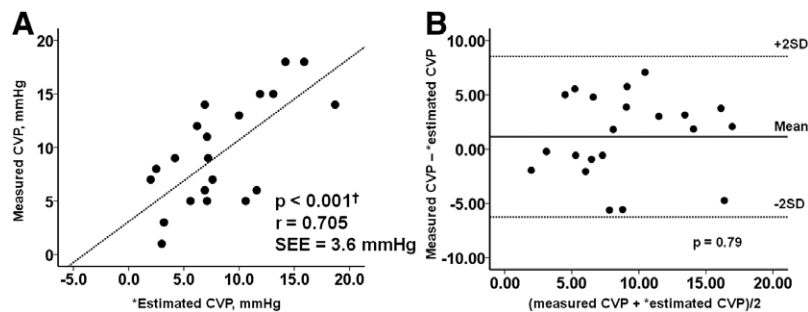

Figure 3. The correlation between measured CVP and estimated CVP in the validation cohort are shown in part **A**. The Bland–Altman plot for the comparison of measured CVP and estimated CVP in the validation cohort is shown in part **B**. There is a moderate positive correlation ($r = 0.705$) and good agreement (mean difference 1.15 ± 3.70 mmHg) between the measured CVP and estimated CVP. *Estimated CVP = $47.90 - 0.086 \times$ (RA lead impedance) $+ 0.013 \times$ (RV lead impedance) $- 0.020 \times$ (LV lead impedance). CVP, central venous pressure; LV, left ventricular; RA, right atrial; RV, right ventricular; SD, standard deviation; SEE, standard error of estimate.
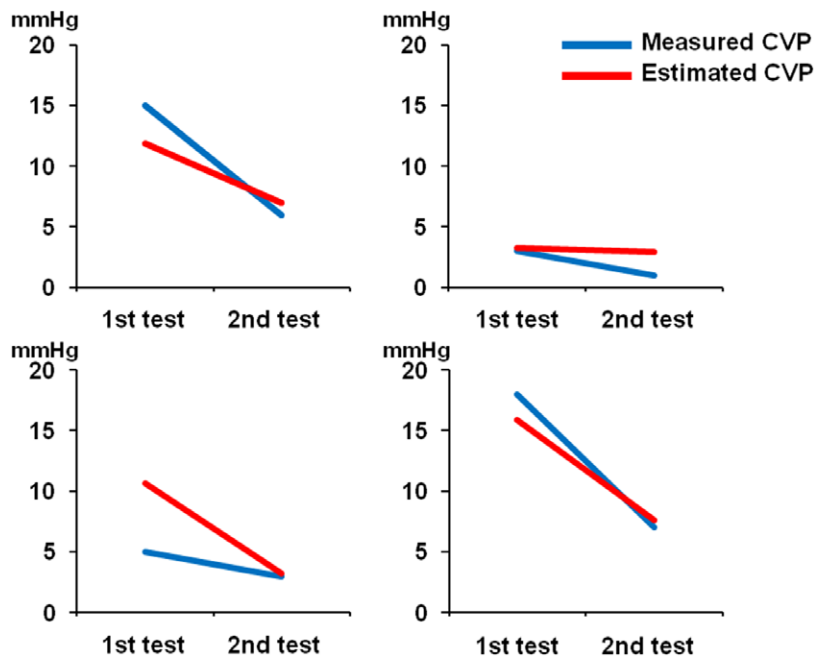
Figure 4. The results of measured CVP and estimated CVP at two different time points are shown for four patients who underwent repeat testing. Decreases in CVP for all four patients were reflected by similar decreases in estimated CVP. CVP, central venous pressure.

Clinical Implications of the Novel Equation Model

Remote measurements of lead impedances (patients are outside of the hospital setting) can be utilized for remote estimation of the CVP using the equation provided in this paper. This remote estimation of CVP may provide the LVAD team the ability to adjust diuretics without physically evaluating the patient and may address fluid accumulation earlier in the course of the disease. Better fluid status control may reduce the high rate of HF readmission associated with LVAD and improve patients' quality of life and exercise performance.

With the recent improvement in device technology and significant reduction in complications such as pump thrombosis and stroke,[3] the next generation of devices—smart pumps—should devote greater focus to improve patient quality of life through the dynamic adjustment of pump speeds in response to hemodynamic cues. These smart pumps will need to take into consideration multiple parameters including 1) patients activity level, 2) LV preload, 3) LV afterload, and 4) RV preload.

Although an easy solution is available only for the first parameters (activity level can be assessed using information derived from permanent pacing devices), the others remain more challenging. Although LV preload can be measured by implantable pulmonary artery monitors such as CardioMEMS (Abbott, Abbott Park, IL),[18] up to 50% of the LVAD patients may experience decoupling between the pulmonary capillary wedge pressure (PCWP) and diastolic pulmonary artery pressure (*i.e.,* diastolic pulmonary pressure overestimates the PCWP).[19] This decoupling could lead to suction events if LVAD speed adjustment is just based on the level of pulmonary artery pressure alone. Recently our group reported a way to estimate PCWP from the HVAD LVAD waveform,[20] and called for further evaluation of waveforms as a source for LV preload assessment.

Currently, we are lacking a way to assess both LV afterload and RV preload in LVAD patients. Measurement of systemic blood pressure in continuous-flow LVAD patients remains challenging. Our team has completed a pilot study of a non-invasive investigational device that can provide continuous blood pressure monitoring of LVAD patients with excellent accuracy in comparison to an invasive arterial catheter.[21] Ongoing studies will further determine the efficacy of this device to provide an accurate measurement of LV afterload. Our current study suggests that lead impedances can provide a reliable estimate of RV preload. The combination of these technologies may provide a comprehensive view of biventricular loading conditions that can be incorporated into a smart pump design.

Although this is the first study describing the significant association between CVP and lead impedance, its precise mechanism remains uncertain. Ultimately, the most likely explanation for these findings are high atrial load resulting in structural and electrical change in RA myocardium, which may impact lead impedance.[22,23] Our next priority is to the impact of atrial load on lead impedance. Other factors, including myocardial properties, fibrosis, and heart rate may also affect pacing lead impedances.

Study Limitations

Several potential limitations of this study should be considered. First, although dataset is moderate size, patient number is small. A prospective multicenter longitudinal study to demonstrate the utility of the lead impedance-guided therapy, in which diuretic dose is adjusted based on the equation, should be pursued. Also, the validity of the equation during longitudinal follow-up of individual patients should be studied further. Second, our equation cannot replicate the pressure waveform of right atrium, which is useful to interpret specific pathology such as constrictive pericarditis. A full invasive hemodynamic

assessment is necessary for complete evaluation in such specific situations. Third, our equation was constructed from LVAD patients and cannot be adapted to patients without LVADs. Fourth, all measurements were made with the patients supine. It is uncertain whether the lead impedances may have differed significantly with posture and activity. Finally, we did not routinely perform echocardiographic IVC measurements during ramp test. We did not demonstrate superiority of our equation over IVC measurements in this study.

Conclusion

We derived a novel equation to estimate CVP levels using lead impedance measurements. This finding may help with the noninvasive monitoring and management of volume status in LVAD patients.

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