Real-Time Ventricular Volume Measured Using the Intracardiac Electromyogram

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Left ventricular end-diastolic volume (EDV) is an important parameter for monitoring patients with left ventricular assist devices (LVADs) and might be useful for automatic LVAD work adaptation. However, continuous information on the EDV is unavailable to date. The depolarization amplitude (DA) of the noncontact intracardiac electromyogram (iEMG) is physically related to the EDV. Here, we show how a left ventricular (LV) volume sensor based on the iEMG might provide beat-wise EDV estimates. The study was performed in six pigs while undergoing a series of controlled changes in hemodynamic states. The LV volume sensor consisted of four conventional pacemaker electrodes measuring the far-field iEMG inside the LV blood pool, using a novel unipolar amplifier. Simultaneously, noninvasive measurements of EDV and hematocrit were recorded. The proposed EDV predictor was tested for statistical significance using a mixed-effect model and associated confidence intervals. A statistically significant \( p = 3 \times 10^{-7} \) negative correlation was confirmed between the DA of the iEMG and the EDV as measured by electric impedance at a slope of \(-0.069 (-0.089, -0.049) \) mV/mL. The DA was slightly decreased by increased hematocrit \( p = 0.039 \) and moderately decreased with the opening of the thorax \( p = 0.003 \). The DA of the iEMG proved to be a significant, independent predictor of EDV. The proposed LV volume sensor is simple to integrate into the inflow cannula of an LVAD and thus has the potential to inform the clinician about the state of LV volume in real time and to automatically control the LVAD. ASAIO JOURNAL 2021; 67:1312–1321

Key Words: electrocardiogram, 3D echocardiography, ventricular volume sensor, preload, LV end-diastolic volume, heart failure, left ventricular assist device, heart pump

State-of-the-art continuous flow left ventricular assist devices (LVADs) are limited in reacting to various hemodynamic states as they largely run at a constant operating speed. At a constant pump speed, the patient may experience a reduced exercise capacity and suction, followed by adverse events such as septum shift or hemolysis. Manual titration of pump speed can improve exercise performance, but generally only minimal improvements are achieved. Automatic adaptation of pump speed is an intriguing concept but requires monitoring volume status of the patient to ensure safe operation. The end-diastolic volume (EDV) has been proven as a robust parameter of LVAD state to inform the clinician about the hemodynamic state of the patient to ensure safe operation. The EDV predictor was tested for statistical significance using a mixed-effect model and associated confidence intervals. A statistically significant \( p = 3 \times 10^{-7} \) negative correlation was confirmed between the DA of the iEMG and the EDV as measured by electric impedance at a slope of \(-0.069 (-0.089, -0.049) \) mV/mL. The DA was slightly decreased by increased hematocrit \( p = 0.039 \) and moderately decreased with the opening of the thorax \( p = 0.003 \). The DA of the iEMG proved to be a significant, independent predictor of EDV. The proposed LV volume sensor is simple to integrate into the inflow cannula of an LVAD and thus has the potential to inform the clinician about the state of LV volume in real time and to automatically control the LVAD. ASAIO JOURNAL 2021; 67:1312–1321

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Because EDV is difficult to measure, researchers have sought other ways to estimate EDV. The time point of the EDV should be influenced by a change in the intracavitary blood pool, as stated by Brody already in the 1950s. Hence, the maximum of the R-wave amplitude or the QRS complex is determined not only by physiologic mechanisms, such as stress, heart rate (HR), and temperature, but also by physical factors, such as the EDV. The DA is preferably measured inside the LV blood pool through a unipolar noncontact intracardiac electromyogram (iEMG). A unipolar measurement is required to capture the far-field response. Such a unipolar amplifier was not available until recently. We hypothesize that electrodes that are integrated in the cannula of an LVAD can measure beat-to-beat
EDV and thus provide additional means to monitor LV function continuously during LVAD support.13

In this study, we developed an LV volume sensor prototype encompassing four electrodes, which were integrated into a placeholder LVAD cannula and connected to a custom-built unipolar amplifier. Each electrode independently measured the far-field iEMG inside the LV cavity during experimentally induced, controlled hemodynamic interventions in six pigs. We report the correlation of the iEMG DA and gold-standard noninvasive measures of EDV such as echocardiography and electric impedance. Additionally, we assessed the effect of different hematocrit (HCT) levels and the effect of an open chest as potential confounders to the measurement.

Materials and Methods

Left Ventricular Volume Sensor

Four off-the-shelf pacemaker electrodes (Biotronik 25539254 IS-1 BI, Germany) were integrated into a placeholder cannula to measure the intracardiac DA in real time with no flow through it. The design of the cannula was optimized to fit with the HVAD (Medtronic, Minneapolis, MN) suture ring to facilitate surgical implantation (see Figure 1). The three-dimensional (3D) printed cannula was manufactured from polyamid 12 (PA12) in a selective laser sintering (SLS) process to a diameter of 20.6 mm and a length of 35 mm. The electrodes were integrated into the cannula, with two of the electrodes, B3 and B4, being shielded from the myocardium by a casket of 0.8 mm thickness. The insertion points of the electrodes were sealed with silicone (DowCorning 732).

The design of the unipolar amplifier was adapted from the recently published design of Gargiulo et al.14 and tested successfully against the gold standard.15,16 A pseudo-infinite potential is generated from a low-pass filtered signal of the reference electrodes, which can be arbitrarily chosen among the electrodes B1–B4. All four signals are then referenced to this pseudo-infinite potential, rendering a pseudo-unipolar electromyogram. A schematic of the electronic circuit is shown in Figure 2. The main advantage of using this unipolar amplifier is that the unipolar measurement is obtained from two implanted electrodes, rather than referenced to a data acquisition unit.16

In this study, the reference electrode was chosen per animal as the one which proved the most stable at the beginning of each trial.

Experimental Setting

The cannula prototype was tested in acute pig models (n = 6, female, Swiss large white; see Table 1). The animal housing and all procedures and protocols were approved by the Cantonal Veterinary Office (Zurich, Switzerland) under the license number 219/2016. Animal housing and all experimental procedures were in accordance with Swiss animal welfare protection law, and conform to European Directive 2010/63/EU of the European Parliament and the Council on the Protection of Animals used for Scientific Purposes, and to the Guide for the Care and Use of Laboratory Animals.

After loss of postural reflexes following premedication with ketamine (15 mg/kg), midazolam (0.5 mg/kg), and atropine (0.1–0.2 mg/kg) anesthesia was deepened by an intravenous bolus injection of propofol (1–2 mg/kg body weight) and the animals were intubated. General anesthesia was maintained with propofol (2–5 mg/kg/h, i.v.) in combination with isoflurane (1–2.5%) by positive pressure ventilation in an air-oxygen mixture (1:1, 4–6 L/min) with an inspired oxygen fraction (FiO₂) of 0.5, tidal volume of 6–8 ml/kg, a frequency of 10–15 bpm and a positive end-expiratory pressure (PEEP) of 5 cmH₂O. For intraoperative analgesia, buprenorphine (0.01 mg/kg body weight) was administered intravenously approximately 30 minutes before the first skin incision and was continued throughout anesthesia. During surgery, animals received a continuous intravenous infusion of crystalloids (5–7 ml/kg/h).

For maximum control of hemodynamics, a modified cardiopulmonary bypass (CPB) was installed without oxygenator. A shunt connected the outlet and inlet line of the CPB, which could be clamped according to whether it was intended to decrease or increase volume load. Drainage and inlet were performed via a single femoral vein access realized by inserting a venous CPB-cannula in the animal’s femoral vein. The circuit was used to rapidly load or unload the animal’s circulation. After lower hemi-sternotomy was performed for access, the cannula prototype was implanted into the LV at the apex.

![Figure 1. Surgical implantation. A: A cannula encompassing four electrodes (B1–B4) was implanted in the left ventricular cavity. The electrodes measured the intracardiac electromyogram (iEMG). B: Explanted heart showing the attachment with an HVAD suture ring. C) Intracavity view of the cannula showing the shielded (B3, B4) and unshielded electrodes (B1–B2).](image-url)
using an HVAD suture ring (Medtronic), and thus mimicking an LVAD implant. After completion of both surgical steps, the thoracic spreader was removed, and the suprasternal tissue closed using sutures, whereas the pericardium and the sternum were left open. The thorax was opened only if necessary, to stabilize or resuscitate the animal. A balloon catheter (Medtronic, Reliant 12 Fr Balloon) was inserted in the descending aorta to allow for temporary partial or full aortic occlusion to control for afterload. After the acute trial the animal was euthanized with pentobarbiturat 75 mg/kg Esconarkon (Streuli Pharma AG, Uznach, Switzerland).

Four types of experimentally induced hemodynamic interventions were performed to simulate changes in pre- and afterload and hence, changes in EDV: Small ΔV, Large ΔV, Occlusion of the descending aorta using a balloon catheter, and Hemorrhage (see Figure 3). The sequence of interventions performed per animal was randomly assigned (see Table 1). The amount of blood in the circulation was altered by draining or infusing blood into the venous system using the CPB followed by a 5 minutes stabilization period to allow for steady-state conditions. The small ΔV consisted of steps of 200 ml; the large ΔV were randomized with a maximum step of 1,500 ml. The interventions with small ΔV were designed to keep HCT values in a range of ±2.5% from baseline. Dynamic measurements were recorded during the occlusion intervention. In three animals, we aggressively reduced the HCT by inducing a hemorrhage and subsequent infusion of NaCl 0.9% at the last intervention.

**Data Acquisition and Analysis**

At each intervention a breath-hold was initiated and the measured DA from the intracardiac electrodes was compared with the EDV measured through electric impedance (EDVimp) and transesophageal echocardiography (EDVecho). All continuous electrophysiologic data were recorded with the SIGMA A-M signal conditioner at 2 kHz and acquisition was triggered manually at each intervention for synchronization.

### Table 1. Experiments Conducted

| No. | Intervention | Thorax | n  | HCT (mV/%) | HR (bpm) | CVPsys (mmHg) | Femsys (mmHg) |
|-----|--------------|--------|----|------------|----------|---------------|---------------|
| Animal 1 | I | Small ΔV | closed | 6  | 24.5 ± 1.0 | 90.8 ± 4.3 | 13 ± 1 | 45 ± 15 |
| Animal 2 | I | Small ΔV | open | 14 | 29.1 ± 2.6 | 93.2 ± 9.1 | 16 ± 3 | 51 ± 8  |
|          | II | Hemorrhage | closed | 5  | 19.8 ± 3.9 | 83.9 ± 23.0 | 14 ± 1 | 49 ± 11 |
| Animal 3 | I | Small ΔV | closed | 18 | 24.6 ± 1.6 | 46.8 ± 2.8 | 19 ± 2 | 75 ± 7  |
|          | II | Occlusion | closed | 10 | 23.8 ± 1.0 | 79.8 ± 10.0 | n/a  | n/a     |
|          | III | Large ΔV | closed | 6  | 23.0 ± 1.5 | 98.0 ± 3.3 | 19 ± 2 | 60 ± 14 |
|          | IV | Hemorrhage | closed | 6  | 20.2 ± 4.1 | 87.8 ± 16.0 | 20 ± 2 | 45 ± 13 |
| Animal 4 | I | Small ΔV | closed | 16 | 25.4 ± 1.6 | 56.2 ± 9.6 | 18 ± 3 | 64 ± 19 |
|          | II | Occlusion | open | 7  | 24.1 ± 0.4 | 52.7 ± 1.2 | 18 ± 2 | 41 ± 16 |
|          | III | Large ΔV | open | 2  | 22.0 ± 0.0 | 50.4 ± 2.7 | 17 ± 3 | 41 ± 23 |
| Animal 5 | I | Small ΔV | closed | 17 | 27.5 ± 1.5 | 74.3 ± 12.0 | n/a  | 70 ± 11 |
|          | II | Occlusion | closed | 8  | 24.0 ± 0.0 | 90.5 ± 3.8 | n/a  | 70 ± 15 |
|          | III | Hemorrhage | closed | 9  | 17.4 ± 5.4 | 67.5 ± 22.0 | 19 ± 4 | 46 ± 21 |

n, number of interventions performed; HCT, hematocrit; HR, heart rate; CVP, central venous pressure; Fem, femoral pressure; sys, systolic; mean +/- standard deviation.
Potentials from the intracardiac electrodes were recorded alongside with continuous measurements of all three main leads of the surface electrocardiogram (ECG). LV pressure and LV impedance were measured by a pig-tail catheter (CL-71083-PL; BP Hengelo, The Netherlands) (see Figure 3B) and were recorded via a Windows machine running the Leycom conduct NTV3.18 data logger (Leycom; BP Hengelo) at 250 Hz. The echocardiographic transesophageal probe (Philips CX50; Philips, The Netherlands) was positioned inside the pericardium posterior to the heart and served for two-dimensional (2D) echocardiographic measurements of LV EDV and LV end-systolic volume (ESV). The HCT was measured at each intervention using a Statspin Multi-purpose centrifuge (Stat Spin MP, Provet, Switzerland). The blood sample was centrifuged at 15,800 rpm for 120 seconds and the packed cell volume was determined using a micro HCT tube reader.

All data were postprocessed and filtered in MATLAB (R2019a; The Mathworks Inc., Natick, MA). The resulting signal quality is shown in two exemplary waveforms in Figure 4 accounting for high and low preload conditions. The QRS complex was detected in Lead I of the surface ECG and used to cut all continuous signals into heartbeats. Per beat, we identified EDV and ESV in the electric impedance signal as maximum and minimum. The DA in the signals acquired by each intracardiac electrode was found by relating it to the isoelectric level. The isoelectric level was taken as the median value of a 315 ms long segment occurring after the P-wave and before the depolarization. The DA was found in a specified time interval as the negative peak, defined by a threshold and the peak prominence. Per intervention, we report the median of the beat-wise data over a period of 15 seconds.

**Statistical Methods**

All summary statistics in Table 1 are reported as mean ± standard deviation.

A mixed-effect model was used to describe the relationship between DA and the EDV in MATLAB (see Equation 1). The linear relationship is described by two parameters: an offset, or y-axis intercept, \( \mu \), and the slope (\( \beta \)). A mixed-effect model assumes a fixed underlying relationship (\( \mu, \beta \)), while it allows for subject-specific variation in parameters (\( \mu_i, \beta_i \)), also known as random intercept–random slope model:

\[
DA_{ij} \sim (\mu + \mu_i) + (\beta + \beta_i) EDV_{ij}
\]

(1)

The residual variance and all estimated parameters are reported with 95% confidence intervals (CIs).

The model was fit using small \( \Delta V \) and large \( \Delta V \) at the same time. One separate model was fit for EDV based on echocardiography and electric impedance. The most stable intracardiac electrode was chosen per animal for analysis of the DA and reported in the analysis. The electrodes were electrode B4 for animals 1, 2, 5, 6; electrode B3 for animal 2; and electrode B3 for animal 3. The estimated subject-specific parameters were subsequently validated in real time for the occlusion interventions, if available.

An extended mixed-effect model estimated the effect of potential confounders (open chest, change of HCT, and HR).
For this analysis, data from small $\Delta V$ and large $\Delta V$ as well as hemorrhage were used.

Results

$DA$ and $EDV$

Per animal, the observed range of $DA$ was up to 6 mV, whereas the $EDV$ range was up to 80 ml during small $\Delta V$ and large $\Delta V$. Using the novel LV volume sensor, the $EDV$ was found to be a significant predictor of the $DA$. This was true for the $EDV$ measurement for both the electric impedance ($p = 3e^{-07}$) and echocardiographic volume measurement ($p = 1e^{-04}$) and showed excellent agreement ($R^2 = 0.85$ and $R^2 = 0.83$, respectively) (see Table 2). The mean estimation error was found to be 14.6 and 15.9 ml, respectively, with CIs of 29.2 and 31.8 ml. Animal 2 showed an increased mean-square error, compared with the other animals (26.9 ml vs. [15.2, 5.0, 12.7, 2.3, 4.1 ml]; see Figure S1, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A630). In animal 2, the surface ECG showed high waveform variability and electric impedance volume measurement was unreliable compared with echocardiography. Also, the iEMG recordings showed high variability of $DA$ across one 15 second segment and the waveforms between electrodes and beats were distinctly different. Excluding animal 2, the mean-square error reduces to 7.9 and 7.6 ml, for $EDV_{imp}$ and $EDV_{echo}$, respectively, resulting in CIs of 15.8 and 15.2 ml, respectively.

The estimated slopes and intercepts of the fixed model are comparable between echocardiography and electric impedance (see Table 2). The estimated offset ($\mu$) shows high variability in the animal-specific models (colored line) compared with the fixed model (black line), as can be observed in Figure 5. For electric impedance, the estimated slope shows low variability between animals, observable by the parallel slopes of the fixed and animal-specific models in Figure 5. In contrast, the variability in animal-specific slopes is higher for volume estimated by echocardiography (see Figure S2, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A630). The results per animal can be found in Table S1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A630).

Position of the Electrode

All electrodes recorded the iEMG electrogram well, independent of their position on the cannula. Example waveforms can be found in Figure 6. We found up to 75% of the continuous signals to be permissible (see Figure 6A). In 6% of cases, the heart rhythm of the animal was unstable, in 17% we observed large jumps in the $DA$ amplitude and the remaining signals were excluded due to technical issues. Electrodes B1 and B2 were not shielded from interaction with the myocardium. The measured DAs were highly correlated between the electrodes across the four positions B1–B4 (see Figure 6B). The electrode position affected the offset of the $DA$, but not its relationship with the $EDV$ (see Figure 6C).

Impact of Open Chest, HCT, and the HR

The impact of different HCT levels and open chest are reported in Table 1. The HCT was recorded during each intervention, in order to assess its influence on the $DA$. The levels of HCT remained stable during the small $\Delta V$. During the large $\Delta V$ and especially during hemorrhage, higher changes in HCT were expected and recorded. In animals 2, 3, and 6, the HCT was reduced to 16%, 16%, and 10%, respectively, at the end.
of the experiment. Using data from the small ΔV and large ΔV as well as hemorrhage in these three animals, the HCT was found to be a significant predictor (p = 0.039) of the DA with an estimated effect of 0.06 mV/% (see Table 3). However, if only data from the hemorrhage intervention were considered, both EDV and HCT did not show significant correlation with the DA. The intracardiac DA was further confounded by the chest being open or closed. Opening of the chest was found to decrease the measured DA by 2.1 mV in the extended mixed-effect model. The HR did not significantly affect the DA.

Dynamic Response to Occlusion Maneuver

The animal-specific models obtained from the observations during the small ΔV and large ΔV interventions (Table 2) were used to estimate volumes (EDV_{iEMG}) based on the DA during an occlusion maneuver performed in three out of the six animals. Figure 7 shows the dynamic response to the occlusion maneuver for the three animals 3, 4, and 5, for animal 4 the thorax was open. The estimated volumes from the intracardiac EDV_{iEMG} can detect changes in EDV_{imp} well during acute occlusion of the descending aorta (see Figure 7). No time delay is observed between the intervention-based increase in EDV and the decrease in the DA of the iEMG signal.

Discussion

The intracardiac DA was found to be a strong predictor of beat-wise EDV, when measured by the proposed LV volume sensor. The CIs of estimating EDV using the LV volume sensor were found to be 16 mL. Hence, the accuracy is comparable with the intraobserver variability reported for clinical 2D/3D echocardiography (18/12 mL).\textsuperscript{17,18} The effect was observable in all four electrodes, with variable sensitivity.

Large variation in subject-specific parameters implies that subject-specific calibration is necessary. Every subject requires independent calibration of the LV volume sensor, due to blood composition, electrode placement, and heart size. The EDV measured by the LV volume sensor can discern sudden changes in hemodynamics, for example, filling of the heart

| Table 2. Mixed-Effect Model Parameters |
|----------------------------------------|
| Estimate | CI– | CI+ | SE | p value |
| EDV_{imp} Intercept, μ (mV) | 15.5 | 13.0 | 17.9 | 1.45 | 2e–17 |
| EDV, β (mV/mL) | –0.069 | –0.089 | –0.049 | 0.013 | 3e–07 |
| Animal residual SD | 0.99 | 0.84 | 1.17 | – | – |
| EDV_{echo} Intercept, μ (mV) | 14.4 | 11.9 | 16.9 | 1.41 | 9e–17 |
| EDV, β (mV/mL) | –0.072 | –0.104 | –0.040 | 0.018 | 1e–04 |
| Animal residual SD | 1.05 | 0.90 | 1.23 | – | – |

CI, confidence interval; EDV_{imp}, end-diastolic volume measured by electric impedance; EDV_{echo}, end-diastolic volume measured by echocardiography; SD, standard deviation; SE, standard error.

Figure 5. The depolarization amplitude and the end-diastolic volume (EDV). A mixed-effect model relates the depolarization amplitude of the intracardiac electromyogram with the end-diastolic volume measured by electric impedance. Each measurement point represents the median of a steady-state segment of 15 seconds.
Easily achieved. Additionally, experience of the community but the interface of the sensor with the blood has not been attempted the integration of pressure sensors into the cannula, to integrate a sensor within an LVAD. Various groups have the conduct of surgery. This study is not the first to attempt that could either put the patient at additional risk or delay additional surgical trauma. Full integration of sensors into hemodynamics.

LVAD, might inform patients and clinicians on beat-to-beat configuration on the LV volume sensor measurement. Integration of the LV volume sensor into implantable devices, such as an LVAD, might inform patients and clinicians on beat-to-beat upon occlusion of the descending aorta. The study was further able to quantify the effect of the HCT as well as chest configuration on the LV volume sensor measurement. Integration of the LV volume sensor into implantable devices, such as an LVAD, might inform patients and clinicians on beat-to-beat hemodynamics.

Electrodes can be integrated into medical devices without additional surgical trauma. Full integration of sensors into an LVAD is key to prevent any additional surgical maneuver that could either put the patient at additional risk or delay the conduct of surgery. This study is not the first to attempt to integrate a sensor within an LVAD. Various groups have attempted the integration of pressure sensors into the cannula, but the interface of the sensor with the blood has not been easily achieved. Additionally, experience of the community remains limited with drift in readings from implantable pressure sensors over long periods of time. Some well-established pressure sensors such as CardiMEMS allow only for discontinuous data recording, making them unsuitable for LVAD control. In contrast, the proposed LV volume sensor relies on established implantable sensor technology, that is, pacemaker electrodes. This study provides evidence, that due to their small size and off-the-shelf availability, pacemaker electrodes can be integrated into the cannula of an LVAD.

Alternative, integrated measurement technologies for preload in LVADs are scarce. End-diastolic pressure is a valid estimate of preload. However, end-diastolic pressure is less sensitive than EDV to changes in preload measured in relative terms. Alternatively, intracardiac ultrasound is capable of directly measuring distances inside the heart, which is at once/on the one hand a highly desirable measure. At the same time, such a sensor is technically complex and generates large amounts of data, because of the high-resolution. Haines et al. have been able to use pacemaker leads in patients to measure bipolar impedance, and thereof estimate EDVs and ejection fractions with high accuracy. The technology requires a pacemaker to be implanted and is not yet clinical standard. Impedance has also been integrated into the cannula of an LVAD and successfully tested in vivo. The measurement was, however, limited to measuring apical blood volumes, as the electric field for measurement is only spanned in the apex. On the contrary, the unipolar amplifier measures the far-field and thus enables the measurement to also be sensitive to changes in volume in the mid-ventricle. The LV volume sensor further takes advantage of the electric field spanned by the heart's own activity. Like with impedance, the proposed methodology requires a subject-specific calibration.

In clinical practice, the LV volume sensor constitutes an excellent complement to echocardiography. Echocardiography is the established method to measure left- and right-sided volumes, useful to titrate the speed of an LVAD. Theoretically, measurement of geometry using speed of ultrasound is highly accurate. But transthoracic echocardiography is sensitive to patient echogenicity, requires experience in effective probe placement, and is especially difficult in patients with an LVAD due to artifacts from shadowing. Still, it remains the only non-invasive measurement for hemodynamics at the bedside to date. Transeosophageal echo shall be used for patient-specific calibration post-LVAD implantation. Transthoracic echocardiography will remain the go-to technology for recalibration after early ventricular remodeling in the first 4 weeks. During this time, the LV volume sensor needs to be frequently recalibrated using echocardiography to find the patient-specific offset and slope. Once, the patient is stable and at home, the LV volume sensor can provide continuous information on EDV even in the remote setting.

In heart failure patients, physiologic variation in QRS amplitude measured in the surface ECG were previously reported to be ±0.3 mV. Based on the sensitivity of 0.07 mV/mL found in this study, the proposed technology can discern volume changes as small as 4 mL. The same study reported that

### Table 3. Confounders to the Depolarization Amplitude in Animals 2, 3, and 6

|                     | Estimate | Cl−   | Cl+   | SE     | p value |
|---------------------|----------|-------|-------|--------|---------|
| Intercept (mL)      | 17.1     | 14.52 | 19.6  | 1.285  | 7.49e−22|
| EDV (mV/mL)         | −0.0661  | −0.080| −0.052| 0.007  | 1.93e−14|
| HCT (mV/%)          | −0.0609  | −0.118| −0.002| 0.029  | 0.039   |
| Open chest (mV)     | −2.1     | −3.4  | −0.7  | 0.687  | 0.003   |

The model was fitted with data from the small and large changes in volume as well as the hemorrhage intervention. EDV, end-diastolic volume; HCT, hematocrit; CI, confidence interval; SE, standard error.
variability in QRS amplitude in the surface ECG remained unaffected by pacing. As is evident, the LV volume sensor is likely to detect and report severe adverse events such as extreme LV emptying or overload conditions.

Electrode positioning, opening of the chest, and HCT have been shown to confound the Brody effect in previous studies and are therefore addressed extensively in this study. The reliability of electrodes shielded from the blood pool was not different from the unshielded electrodes. Potentially the shielded electrodes were less likely to be exposed to the myocardium, but blood clotting might have affected the measurement. Although the positioning of the electrode altered the overall levels of the DA, the slope was sustained. Based on the findings in this study, the exact positioning is not critical, and how electrodes shall be shielded needs further investigation.

One previous study in dogs found a relationship between the endocardial EMG measurements and EDV which was negative for the endocardium, positive for the surface ECG and showed no effect in the epicardium. Changes in epicardial DAs were around 20%, following pharmacologically induced increases in HR and without reporting the HCT. In our study, volume changes were induced solely by infusion of blood to keep blood conductivity constant. HCT levels remained within 5%. The relative changes in DA were comparable (~30% per animal). Another study in pigs also found sensitivities of 0.03–0.09 mV/mL in an open chest configuration. Our study did not include the effect of the RV blood volume nor blood flow in the LV, but this aspects should be addressed in the future.

In summary, beat-to-beat volume measurement might provide critical information in the management of patients with an LVAD. The current study provides evidence that an LV volume sensor can be easily integrated into an LVAD inflow cannula and provide information on acute changes in LV volume and is indicative for adverse events such as extreme LV emptying or overload. Using the LV volume sensor to automatically and physiologically adapt the pump speed to the patient’s need is highly desirable. Given the manifold determinants of the QRS amplitude, the LV volume sensor signal should be preferably used in combination with a mechanical signal such as pump flow, LV pressure or ultrasound distances to further increase robustness. Furthermore, the effects of long-term drift need to be accounted for in the interpretation of such a signal. Future research should also investigate whether similar measurements could be obtained from pacemaker leads to measure right and left ventricular volumes. As the physical origin of the observed effect remains incompletely understood, the current study assumes a linear relationship between the DA and the EDV. More detailed modeling studies can help elucidate the underlying relationship. In the next step, this LV volume sensor will be tested in interaction with an LVAD and in a heart failure model.

Figure 7. The intracardiac electromyogram (iEMG) during dynamic change in afterload during occlusion of the descending aorta (dashed line). One out of three representative occlusion maneuver is depicted per column for animal 3, animal 4, and animal 5. The beat-wise end-diastolic volume (EDV) was estimated using the iEMG and compared against the EDV_iEMG derived from the left ventricular volume (LVV) signal measured by electric impedance.
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