Admittance to detect alterations in left ventricular stroke volume

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BACKGROUND Implantable cardioverter-defibrillators monitor intracardiac electrograms (EGMs) to discriminate between ventricular and supraventricular tachycardias. The incidence of inappropriate shocks remains high because of misclassification of the tachycardia in an otherwise hemodynamically stable individual. Coupling EGMs with an assessment of left ventricular (LV) stroke volume (SV) could help in gauging hemodynamics during an arrhythmia and reducing inappropriate shocks.

OBJECTIVE The purpose of this study was to use the admittance method to accurately derive LV SV.

METHODS Ultrasonic flow probe and LV endocardial crystals were used in canines (n = 12) as the standard for LV SV. Biventricular pacing leads were inserted to obtain admittance measurements. A tetrapolar, complex impedance measurement was made between the Bi-V leads. The real and imaginary components of impedance were used to discard the myocardial component from the blood component to derive instantaneous blood conductance (G_b). Alterations in SV were measured during right ventricular pacing, dopamine infusion, and inferior vena cava occlusion.

RESULTS G_b tracks steady-state changes in SV more accurately than traditional magnitude (ie, |Y|, without removal of the muscle signal) during right ventricular pacing and dopamine infusion (P = .004). Instantaneous LV volume also was tracked more accurately by G_b than |Y| in the subset of subjects that underwent inferior vena cava occlusions (n = 5, P = .025). Finite element modeling demonstrates that admittance shifts more sensitivity of the measurement to the LV blood chamber as the mechanism for improvement (see Online Appendix).

CONCLUSION Monitoring LV SV is possible using the admittance method with biventricular pacing leads. The technique could be piggybacked to complement EGMs to determine if arrhythmias are hemodynamically unstable.

KEYWORDS Shock reduction; Biventricular pacing/defibrillation; Ventricular tachycardia; Ventricular fibrillation; Inappropriate shocks

ABBREVIATIONS **2D** = 2-dimensional; **AICD** = automatic implantable cardioverter-defibrillator; **EGM** = electrogram; **FEM** = finite element method; **G_b** = blood conductance from the admittance method; **HR** = heart rate; **ICD** = implantable cardioverter-defibrillator; **IVCO** = inferior vena cava occlusion; **LCV** = left coronary vein; **LV** = left ventricle; **RA** = right atrium; **RV** = right ventricle; **RVA** = right ventricular apex; **SV** = stroke volume; **Y** = complex admittance (inverse of impedance); **|Y|** = magnitude of admittance; **Z (Ω)** = complex impedance

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Introduction

Automated implantable cardioverter-defibrillators (AICDs) monitor intracardiac electrograms (EGMs) to discriminate between ventricular and supraventricular tachycardias. Hemodynamically unstable arrhythmias are treated with high-energy shocks, whereas benign arrhythmias are treated conservatively. Unfortunately, modern defibrillators cannot always reliably differentiate between these situations and sometimes deliver inappropriate shocks. Spurious shocks result in battery depletion and increased patient morbidity, and can cause degeneration of benign cardiac arrhythmias.[1] An advancement in which AICDs couple EGMs with beat-by-beat assessment of left ventricular (LV) stroke volume (SV) could discriminate between hemodynamically unstable and stable arrhythmias. In such a scheme, AICD shocks would be reserved for

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hemodynamically unstable arrhythmias, which should prevent inappropriate AICD shocks.

The use of electric fields to measure cardiac physiology has been plagued by myocardial noise contaminating the desired LV blood volume signal, limiting clinical applicability. We have derived a new method to remove the myocardium, which we term *admittance*. Admittance inputs a current into the myocardium and takes advantage of the capacitive nature of electrical gradient across myocytes, whereas blood has no capacitive properties. The returning voltage signal has a phase shift that can be used to separate the blood and myocardial components of the signal. In this study of large mammalian hearts, we focused on removing the myocardial signal and obtaining pure blood volume to derive LV SV via commercially available pacemaker and implantable cardioverter-defibrillator (ICD) leads. Future studies will focus on incorporating the pure LV SV obtained by admittance in the classification of arrhythmias as hemodynamically unstable or stable.

By obtaining pure LV SV, we propose that admittance can aid AICD classification of arrhythmias as hemodynamically unstable or stable, through the estimation of LV SV on a beat-by-beat basis.[2,3] In this article, we describe a new technique that measures the impedance between the right ventricular (RV) and lateral coronary vein (LCV) leads by applying a current between the RV and LCV ring electrodes and measuring the returning voltage between the RV and LCV tip electrodes (Figure 1). Although conductance has been used to estimate intraventricular blood volume,[4] the admittance method represents a substantial improvement because it uses the complex nature of tissue's electrical properties to separate and discard the myocardial component, leaving only the LV blood signal.[2] At a frequency of 20 kHz, muscle exhibits significant permittivity,[5] whereas the blood's permittivity (or capacitance) is negligible. The current study demonstrates that admittance can accurately measure SV using commercial leads in large animal hearts. These results were confirmed by finite element modeling analysis (see Online Appendix). The modeling studies explain how admittance can accurately determine LV SV compared with conductance. Algorithms that incorporate LV SV obtained via admittance to assist AICD in differentiating malignant from benign arrhythmias will require future explorations and validations.

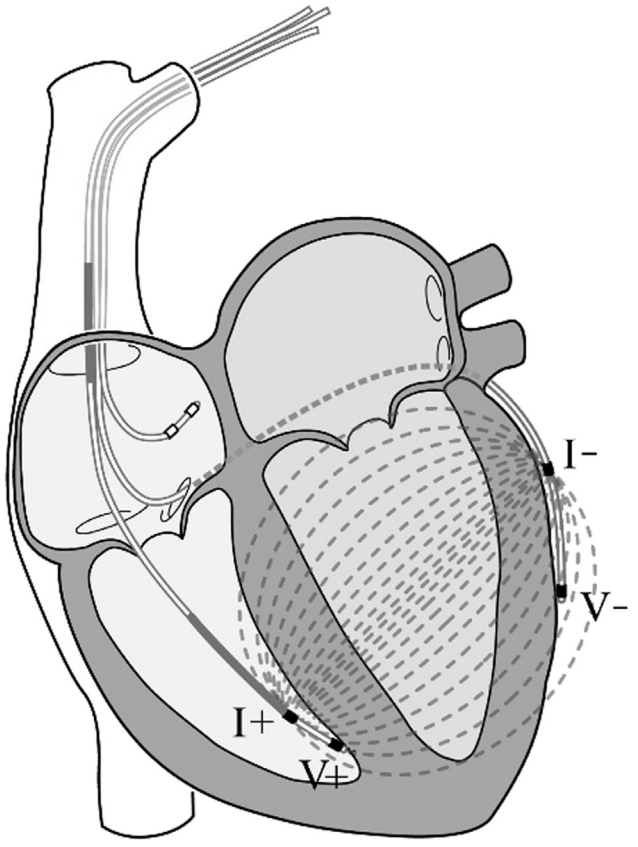

Figure 1 Leads tips were placed across from each other in a configuration with the right ventricular (RV) and left ventricular (LV) electrodes on the RV mid-septal and LV lateral epicardial walls, respectively. Current (I) flows from the RV to the LV ring electrodes and voltage (V) is measured from the corresponding electrode tips. This returning voltage signal and the applied current were used to derive admittance. In this way, admittance was then used to obtain the LV stroke volume (SV) by a cross LV chamber tetrapolar impedance measurement using custom instrumentation. Leads placed in this configuration were ideal for obtaining LV blood volume measurements because blood has 5 times lower resistivity than myocardium and the preferential path for current flow is the LV blood volume, as illustrated by the *dashed lines.*

Methods

Animal preparation

All experiments were approved by the Institute for Animal Care and Use Committee at the University of Texas HSC at San Antonio. Twelve canines (weight 21–35 kg) were anesthetized using a mixture of ketamine and diazepam at a dosage of 1 cc per 5 kg. Anesthesia was maintained with 2.5% isoflurane with 100% oxygen. To obtain blood pressure, a microtip pressure sensor (Transonic, Ithaca, NY) was placed in the femoral artery. Two different accepted methods were used to obtain LV SV and volumes as controls: an aortic ultrasonic flow probe and 2-dimensional (2D) endocardial ultrasonic crystals, respectively.[6] A thoracotomy was performed to place the ultrasonic flow probe (Transonic) around the ascending aorta. Four ultrasonic crystals (Sonometrics, London, Ontario, Canada) were inserted into the endocardium in the anterior–posterior and apex–base planes to measure LV dimensions. For the admittance measurement, commercial pacing leads (QuickFlex, Tendril ST, and Tendril DX, St. Jude, St. Paul, MN) were placed under fluoroscopic guidance into the RV, right atrial (RA) appendage, and lateral coronary vein (LCV).

In order to obtain an isolated LV blood volume signal, epicardial muscle property measurements are required for incorporation into our previously published equations[3] to identify and remove the myocardial component from the combined myocardium–blood admittance signal. LV muscle conductivity and permittivity were obtained with a tetrapolar probe[3,5] placed on the anterior surface of the LV at a location avoiding the left anterior descending artery and its branches,

and data were collected over 3 heartbeats. Five measurements were taken, and the average conductivity-to-permittivity ratio was used. Blood was removed from the canine, and the tetrapolar probe was used to measure blood conductivity. To assure constant blood conductivity throughout the experiment, intravenous fluids were given at the replacement rate, and hematocrit was measured at baseline and at the end of the experiment.

Methods to alter LV SV

Several methods were used to vary LV SV. They included (1) atrial (AOO) pacing, (2) ventricular (VOO) pacing, and (3) dopamine infusion to achieve steady-state SV. Instantaneous alterations in SV were obtained during transient inferior vena cava occlusion (IVCO).

Pacing protocol

Atrial and ventricular pacing were performed to decrease SV. Data were acquired at baseline and while pacing at several rates in increments of 20 bpm until capture became intermittent.

Dopamine protocol

Dopamine infusion was performed to increase LV SV. Measurements were performed at baseline and at infusion rates of 1.25, 2.5, 5, 7.5, and 10 μg/kg/min. Measurements were taken 10 minutes after the start of each dose.

Transient IVCO

In a subset of 5 subjects, IVCO was performed to determine the effect of instantaneous changes in LV volume on G_b (conductance of blood with the muscle component removed). Umbilical tape was looped around the inferior vena cava to perform transient occlusion for up to 5 seconds, then released to allow blood return to the heart.

Admittance-derived blood conductance (G_b) measurement to obtain LV SV

The admittance method was used to obtain LV SV by a cross-chamber tetrapolar impedance measurement using custom instrumentation. Admittance was obtained from the LV epicardium between the RV and LCV leads. Real and imaginary components of impedance were used to calculate G_b with the admittance method.[3] Only myocardium has imaginary properties derived from the capacitive electrochemical gradient across myocytes. It is this unique property that we used to identify the real-time muscle component from the measured signal. Because the electrodes reside on the LV epicardium, a series electrical model of myocardium–blood–myocardium was required to obtain the combined myocardium–blood signal. LV blood volume and SV signals were then extracted from the combined signal. Traditional magnitude, or |Y|, without removal of the muscle signal, was also obtained for comparison.

Data analysis

RVA pacing to simulate ventricular tachycardia

The pacing data for each subject were searched for incidents of beat-to-beat variations in LV SV. Fluctuations during RVA pacing provide a means of showing the ability of G_b to track hemodynamics in real time. LV volume was calculated from 2D sonomicrometry using a prolate ellipsoid model.[7,8] G_b and |Y| were compared to crystal volume during irregular cardiac contractions. Ventricular fibrillation was induced in 1 subject by applying DC voltage to the surface of the RV.

SV monitoring

The ability of G_b and |Y| to track SV was analyzed using results from the pacing and dopamine protocols. G_b and |Y| were compared to SV derived from the ultrasonic flow probe.

The relationship between peak-to-peak blood conductance, ΔG_b, and SV was assumed to be linear. Baan's equation[9] was not used because it only applies to fixed electrodes, and in this study the electrodes were in motion with respect to one another. SV was calculated as $SV = m \cdot \Delta G_b + b$, where ΔG_b is the peak-to-peak blood conductance. Constants m and b are derived from the acquired data using the linear mixed-effect model results for the mean slope. Baseline SV from each dataset determined the offset, b, such that the baseline measurement was forced to the correct SV. This same method was also applied to the traditional peak-to-peak magnitude, Δ|Y|.

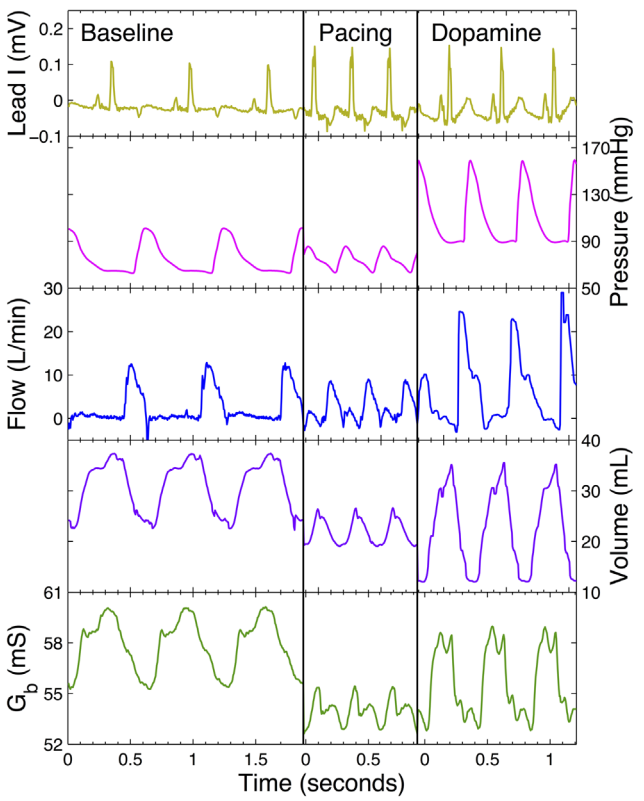

Figure 2 Typical signals showing G_b is in phase and has a similar morphology with crystal-derived volume; and G_b tracks stroke volume (SV) changes from baseline (heart rate 96 bpm) to AOO pacing at 200 bpm, and 7.5 μg/kg/min dopamine infusion.

Volume tracking during transient IVCO

Maximum and minimum G_b and |Y| were compared to diastolic and systolic LV crystal volume during IVCOs. G_b and |Y| were converted to volume similarly to ΔG_b and $\Delta|Y|$ conversion to SV. A linear relationship was again assumed, only the conversion results in LV volume rather than SV.

Statistical analysis

We contrasted the scatter derived with SV from ΔG_b, and traditional $\Delta|Y|$, both versus SV from the flow probe using a repeated measures linear model for paired data. To determine during RVA pacing whether ΔG_b or $\Delta|Y|$ more closely tracks crystal-derived LV volume, we rescaled ΔG_b, $\Delta|Y|$, and crystal volume from 0 to 1. After alignment with the ECG signal, we had 2100 data-points (out of a total of 2500) for each subject for each signal (ΔG_b, $\Delta|Y|$, and crystal volume). We then computed the area between each rescaled and aligned test signal (ΔG_b, $\Delta|Y|$) and the rescaled and aligned gold standard crystal volume signal and expressed the area as the percentage of the maximum possible area (A_{max}) by multiplying by 100 and dividing by A_{max}. For these signals, 2100 time-points were used so that A_{max} is 2100 (realized by the rescaled and aligned test signal being identically 1.0 and the rescaled and aligned crystal volume signal being identically 0 at every time-point). The unit of the resulting normalized area is thus percent. For each of the subjects, we computed $D = A_{\Delta Gb} - A_{\Delta|Y|}$, where $A_{\Delta Gb}$ is the normalized area between ΔG_b and the crystal volume signal, and $A_{\Delta|Y|}$ is the normalized area between $\Delta|Y|$ and the crystal volume signal after rescaling and alignment. We then tested the hypothesis that the mean of D is zero using a paired *t* test with n–1 degrees of freedom. We used the same methodology for the IVCO data. All statistical testing was 2-sided

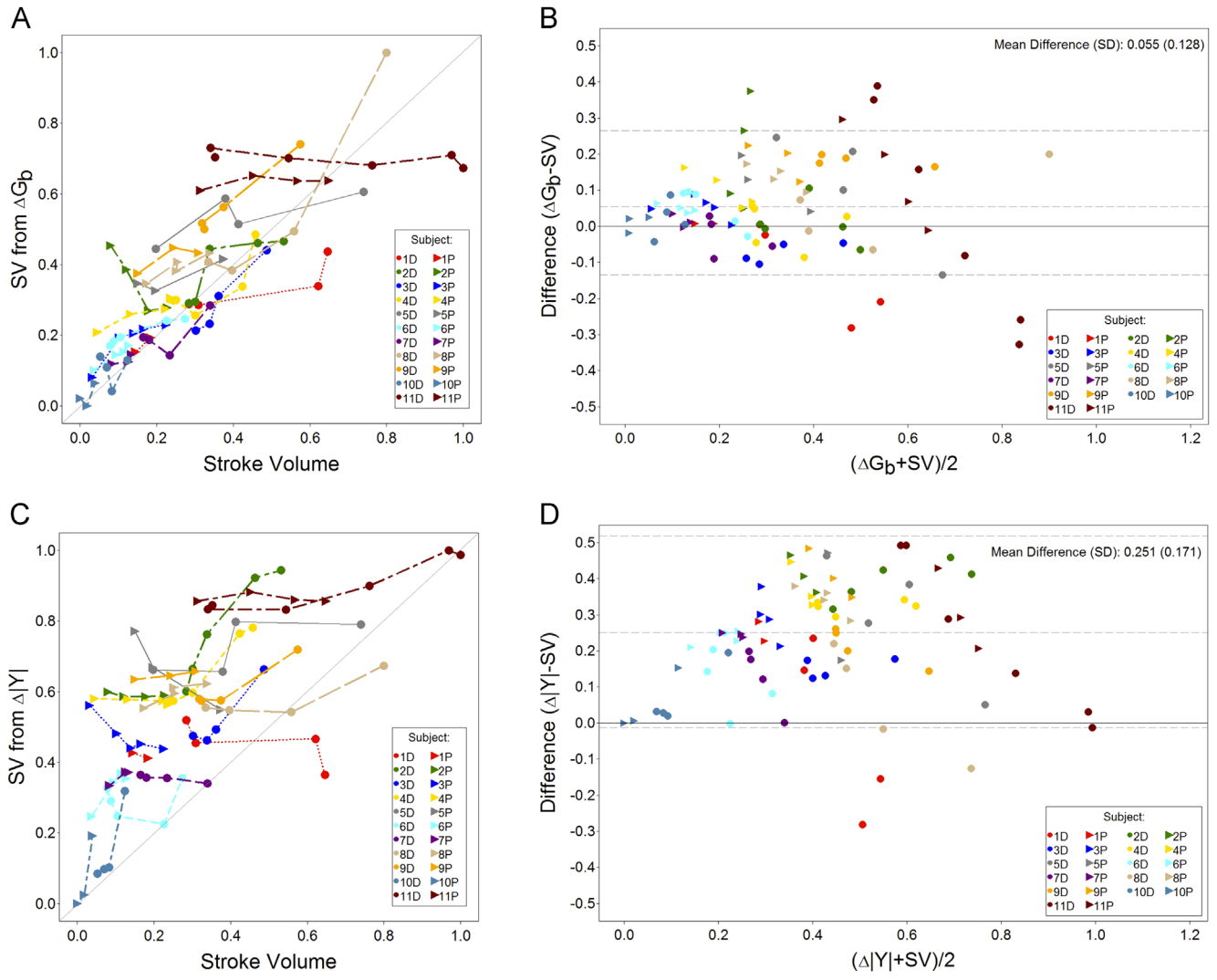

Figure 3 For each subject, during right ventricular pacing and dopamine infusion, the plot of stroke volume (SV) obtained by flow probe (*horizontal axis*) against SV obtained via admittance (ΔG_b, *perpendicular axis*) (**A**), with corresponding Bland-Altman plot (**B**), and SV obtained by flow probe against SV obtained via conductance ($\Delta|Y|$) (**C**) with its corresponding Bland-Altman plot (**D**). These data demonstrate that admittance tracks crystal SV more accurately than traditional conductance. Based on a repeated measures linear model for paired data, ΔG_b was significantly closer to true SV than $\Delta|Y|$ ($P = .001$). *Triangles* indicate pacing (P), and *dots* indicate dopamine infusion (D). *Dotted lines* in the Bland-Altman plot indicate m-1.96SD, m, and m + 1.96SD, where m and SD are the mean and standard deviation of ΔG_b−SV and $\Delta|Y|$–SV. SV indicates the gold standard stroke volume flow probe signal.

with a significance level of 5%. SAS (version 9.3, SAS Institute, Carey, NC) and MATLAB R2013a (Mathworks, Natick, MA) were used throughout.

Results

Baseline hemodynamics

Studies were completed in n = 12 subjects; 1 subject excluded from analysis because of crystal noise. Mean hemodynamics at baseline were heart rate (HR) of 120 ± 18 bpm, LV SV of 30 ± 12 mL (determined by flow probe), systolic femoral pressure of 99 ± 12 mmHg, diastolic femoral pressure of 56 ± 11 mmHg, and end-diastolic and end-systolic volumes of 43 ± 17 mL and 30 ± 14 mL (determined by endocardial crystals), respectively.

Surface property measurements were recorded and used to remove the myocardial component of the combined blood–muscle signal because only the pure LV volume signal was desired. Mean myocardial conductivity was 0.27 ± 0.02 (S/m), mean relative muscle permittivity was 20,900 ± 2,300, and mean sigma-to-epsilon ratio was 1,492,000 ± 154,000 (S/F) (n = 10). Mean blood conductivity was 0.73 ± 0.08 S/m before the dopamine protocol and 0.70 ± 0.09 S/m afterward (P = NS). Hematocrit also was stable, with a mean value of 38% ± 3% before dopamine and 40% ± 5 % afterward (P = NS).

Steady-state SV monitoring

Example data from RA pacing and dopamine infusion in a single subject are shown in Figure 2, which demonstrates that the changes in steady-state LV volume derived with admittance track the more traditional hemodynamic measures of blood pressure, SV, and LV volume. Specifically, the decreases and increases in SV with RA pacing and dopamine infusion, respectively, were detected with G_b. Furthermore, G_b detected the anticipated decrease in end-systolic volume with dopamine infusion.

The individual G_b and |Y| SV data for both pacing and dopamine infusion for every subject are color coded and plotted against the line of identify in Figures 3A and 3C, respectively. Corresponding Bland-Altman plots are shown in Figures 3B and 3D Based on a repeated measures linear model for paired data, ΔG_b was significantly closer to flow probe–derived SV than $\Delta|Y|$ ($P = .001$), demonstrating that ΔG_b tracks SV more accurately than $\Delta|Y|$. This holds true even though there was biologic variability for both ΔG_b and |Y| measurements.

RVA pacing to simulate ventricular tachycardia

RVA pacing was performed to determine whether admittance could also detect instantaneous beat-by-beat variations

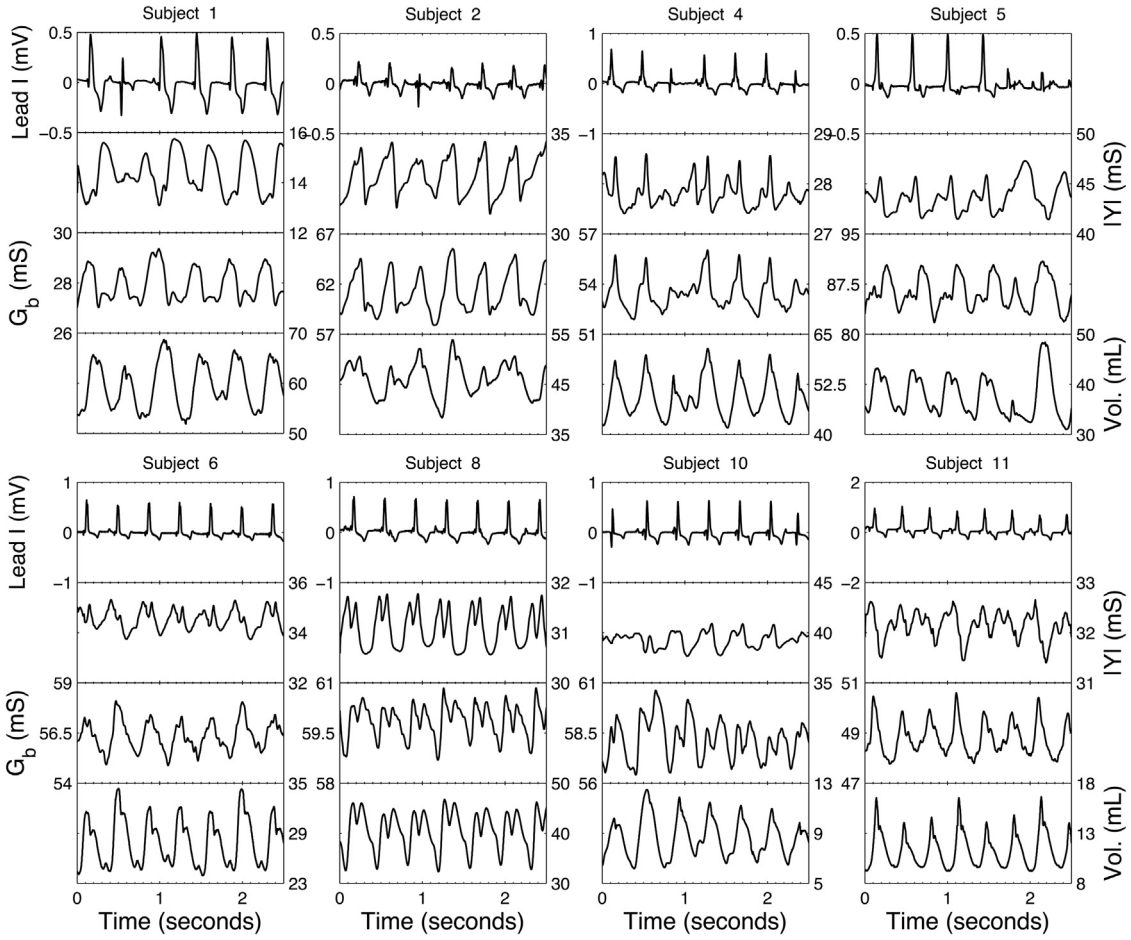

Figure 4 Simulated ventricular tachycardia examples demonstrating that G_b (where the myocardial signal has been removed) tracks endocardial crystal volume (Vol.) more consistently than |Y|, without removal of the muscle signal.

in SV. Among the 11 subjects, 8 exhibited beat-by-beat variations in LV SV and were the basis of further analysis. The ECG, |Y|, G_b, and crystal-derived LV volume for pacing rates of 140 or 160 bpm are shown in Figure 4. G_b and LV volume waveforms show similar morphologies, whereas additional noise was present in |Y|. This noise is visualized as double spikes in Figure 4 |Y|data. The significance of the noise is quantitated with ΔG_b signal being significantly closer to the crystal volume signal than the $\Delta|Y|$ signal ($A_{\Delta Gb}$: 14.9 ± 4.7, $A_{\Delta|Y|}$: 27.3 ± 7.0, $P = .004$; Figure 4).

Ventricular fibrillation

Hemodynamic signals before and after inducement of ventricular fibrillation are shown in Figure 5. G_b correctly reduced to negligible amplitude during fibrillation, as did |Y| (data not shown).

Instantaneous volume tracking during transient IVCOs

IVCOs were successful in all 5 subjects in whom it was attempted. A representative measurement is shown in Figure 6A. End-diastolic and end-systolic G_b consistently tracks crystal volume, including the greater decrease in end-diastolic volume than end-systolic volume and fall in SV on a beat-by-beat basis in 4 of 5 subjects. Analysis of all subjects derived from the end-systolic and end-diastolic volumes is shown in Figure 6B. ΔG_b is significantly closer to the crystal volume signal than the $\Delta|Y|$ signal [mean ± SD $A_{\Delta Gb}$: 14.8 ± 5.0, $A_{\Delta|Y|}$: 24.9 ± 6.2, $P = .046$].

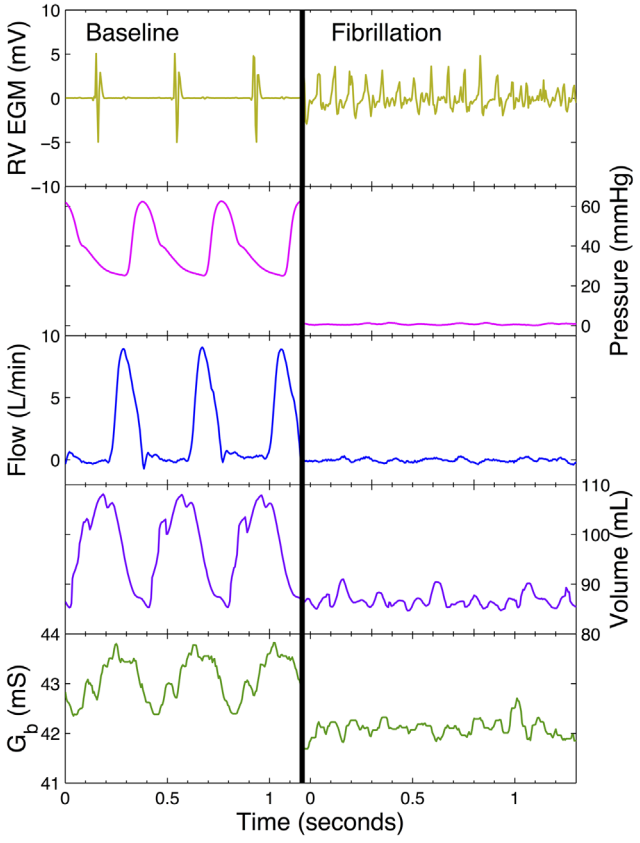

Figure 5 Hemodynamic signals before and during ventricular fibrillation demonstrating that G_b also detects the absence of stroke volume (SV).

Discussion

For the first time, SV was obtained with the admittance method through RV and LCV leads. Our results demonstrate that (1) G_b tracks LV volume obtained by flow probe and 2D ultrasonic crystals, including beat-to-beat variations in LV SV more consistently than traditional |Y|; (2) the relationship between ΔG_b and true LV SV is statistically superior to that of $\Delta|Y|$ and LV SV; (3) G_b correctly tracks LV volume physiology during IVCOs; and (4) finite element models show that the admittance method shifts the weight of the measurement toward the LV blood pool (see Online Appendix). It is clearly advantageous to remove the LV myocardium from the signal, which results in improved reliability in monitoring LV hemodynamics.

The purpose of this study was to determine if admittance could accurately track fluctuations in SV using commercial leads. We were interested in the ability of admittance to identify the drop in SV that is expected during unstable arrhythmias. Our method using admittance expresses SV as LV SV G_b. LV SV G_b is the total conductance minus the myocardium, yielding only the blood component. This measurement accurately tracked changes in SV from normal to low volumes as measured using 2 well-accepted traditional methods: an aortic ultrasonic flow probe and 2D endocardial ultrasonic crystals.[6] LV SV G_b appropriately followed alterations in SV during both steady-state and acute beat-by-beat measurements better than traditional conductance. This relationship holds true despite the biologic variability noted in both G_b and |Y| measurements. Coupling a reliable assessment of LV SV, obtained through the admittance method, with EGMs should aid AICDs in differentiating between hemodynamically unstable and stable arrhythmias. Reserving AICD shocks for unstable arrhythmias would potentially reduce inappropriate AICD shocks.[10–13]

The biologic variability mentioned is the reason that all of the data do not follow unity. Specifically, dogs 1 and 6 had improved correlation with the line of identity when analyzed with admittance compared with conductance. This is evident in both the plots of SV flow and probe versus SV admittance or conductance and the Bland-Altman plots (Figure 3). On the other hand, in dog 11, although a slight fall in SV occurred with pacing, the subject never regained baseline SV before dopamine infusion. Thus, the health of the preparation may be a factor. Despite this variability LV SV, G_b appropriately followed alteration in SV during both steady-state and acute beat-by-beat measurements better than traditional conductance.

The rate of inappropriate AICD shocks ranges from as low as 10% to as high as 30% in different studies.[10,14–16] Inappropriate therapy remains the most frequent complication in patients with ICDs resulting in clinical and psychological distress.[10,14,17,18] Atrial fibrillation, supraventricular

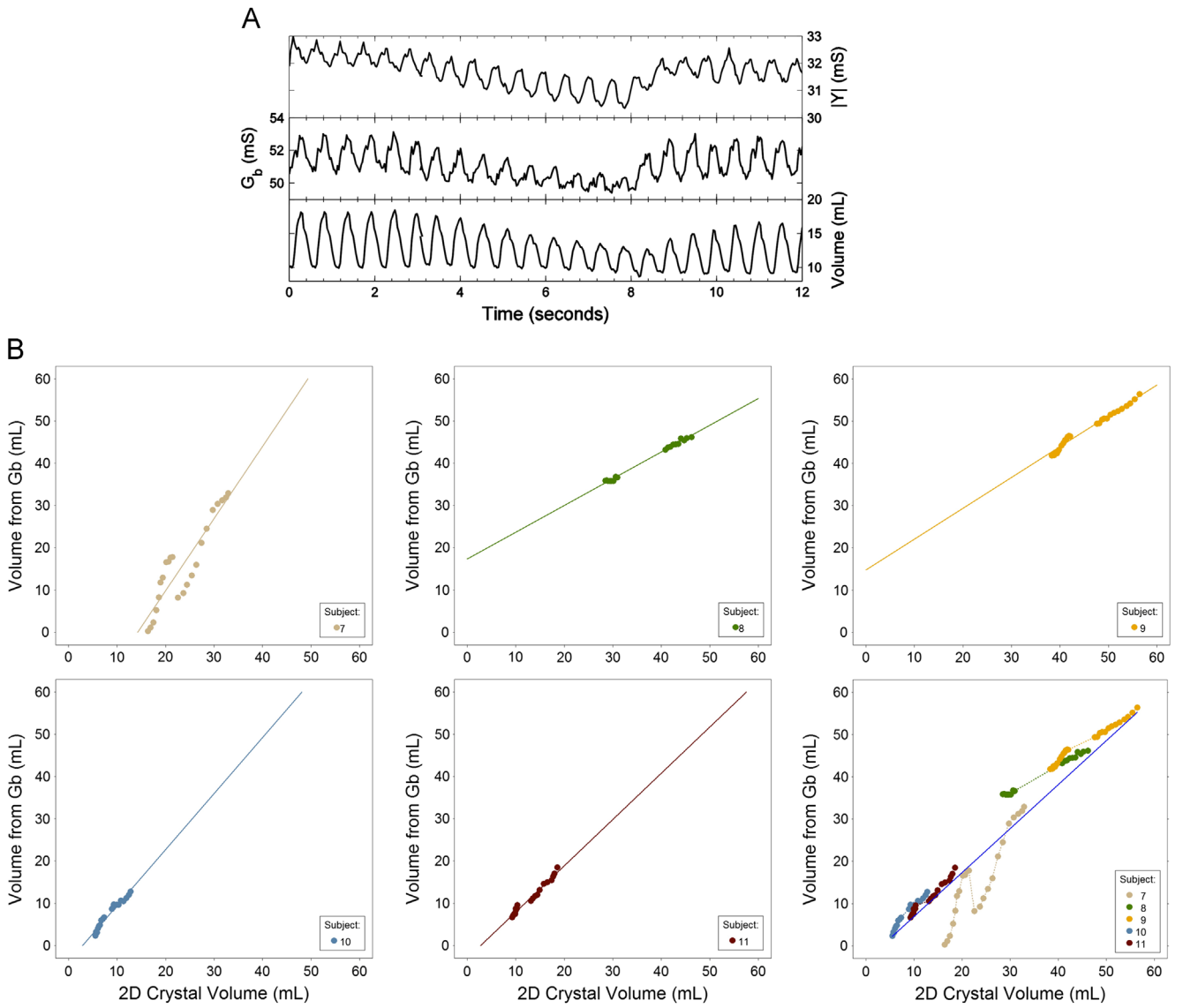

Figure 6 **A:** Example of the recorded change in beat-by-beat stroke volume (SV) during inferior vena cava occlusion as obtained from |Y|, G_b, and crystal left ventricular (LV) volume measurements. The expected physiologic decrease in LV SV is seen in the **bottom two panels** (G_b and crystal volume), but not the **top panel** (|Y|). **B:** Plots of end-diastolic and end-systolic G_b against crystal LV volume in the 5 subjects (panels 1–5) that underwent inferior vena cava occlusion clearly demonstrate excellent correlation between the beat-by-beat LV SV obtained by admittance (G_b) and the ultrasonic crystals. Data from all 5 experiments are shown in the **last panel.**

tachycardia, and abnormal sensing are the most prevalent causes of inappropriate shocks.[17] These causes of inappropriate shocks usually do not result in hemodynamic instability. Thus, we propose the addition of hemodynamic monitoring with G_b to current algorithms to reduce the number of inappropriate shocks in patients through sequential testing to increase specificity (Figure 7A).

Our proposed algorithm is shown in Figure 7B. We propose adding SV detection following accepted AICD algorithms.[13] SV testing would thus be invoked once an AICD shock is indicated based on presently used AICD algorithms. In this manner, sequential testing would be performed to differentiate hemodynamically significant from stable arrhythmias. Thus, EGM signals would continue to be the initial method for indicating the presence of an arrhythmia.[1] Only when EGM results suggest delivery of a shock will G_b be analyzed. Analysis of ΔG_b for SV as well as HR from G_b will determine whether to observe or to deliver a shock. The algorithm will continue as follows. (1) HR is determined from G_b and compared to HR from EGMs. If the rate from EGMs is twice the rate from G_b, the activity will be noted as double counting (oversensing), and no therapy will be delivered. (2) If the SV is normal, no therapy will be delivered. (3) If SV is critically low, therapy will be provided. (4) If the SV is moderately reduced, therapy will be withheld and a counter will be incremented. If the EGM continues to indicate a shock is necessary, the algorithm will repeat. Once the counter reaches as few as 4 (which can be performed in 4 heartbeats), therapy will be delivered. If EGM analysis does not advise a shock, the counter will be reset.

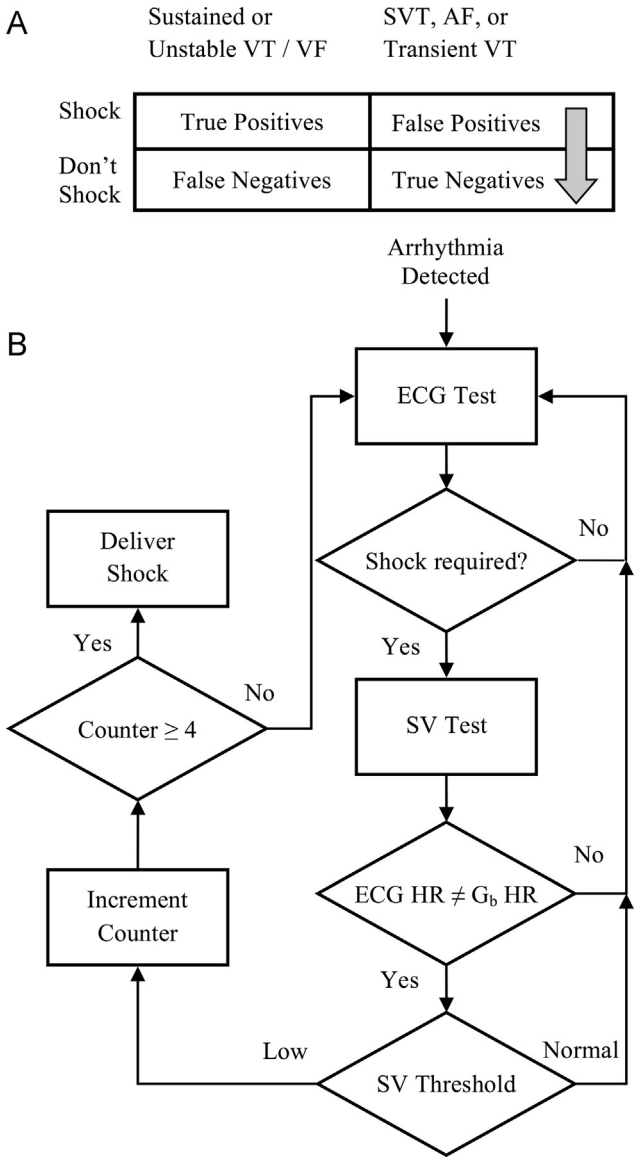

Figure 7 Graphic display of how sequential testing of ΔG_b with current EGM algorithms could potentially be used to shift the false positives to true negatives in order to reduce inappropriate shocks (**A**) and the proposed algorithm to incorporate G_b (**B**). See text for details.

Study limitations

In this study, we only tested the utility of the admittance method for tracking alterations in SV with Bi-V AICDs. Only 10% to 16% of all patients who require an AICD for prevention of sudden death are candidates for Bi-V AICDs.[15] Thus, testing the admittance method in single- and dual-chamber AICDs is important. We provide proof of concept that the admittance method can follow changes in SV through RV and LV leads. We can now begin to extend our findings to single- and dual-chamber devices.

These studies were performed in normal canine hearts. Our current model is limited by the absence of dyssynchrony, LV dilation, scar, lead fibrosis,[19,20] and a chronic model with permanent implantation. Future validation of the admittance technology is needed for these more complex models. Experiments to assess the effect of cardiac geometry on G_b are being proposed. Such research will provide insight into the utility of G_b not only in chronically implanted fibrosed leads but also in structurally abnormal hearts. Studies also will be necessary to establish that incorporation of SV into AICD algorithms is safe and superior to current SV/ventricular tachycardia discrimination algorithms.

Modeling results outlined in the Online Appendix show that application of the admittance method to biventricular leads focuses measurement sensitivity toward the LV blood pool through reduction of signal components outside of the LV. Electrical measurements are inherently weighted toward electrical property changes in close proximity to the electrodes where the current density is highest, near the myocardium. The admittance method is unable to completely remove the muscle signal because of the complex geometry of the electric current densities. However, despite this limitation, the admittance method is able to reduce the contribution of the myocardium in the area closest to the electrodes and to track changes in LV SV better than traditional conductance. The reduction in signal components is most significant near the electrodes, likely the largest source of artifact in the magnitude signals.

Conclusion

LV epicardial cross-chamber measurement of G_b using the admittance method provides a new technique for monitoring cardiac hemodynamics. The technique can be piggybacked onto ICD technology and uses standard leads.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2014.06.034.

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