Ambulatory Monitoring of Congestive Heart Failure by Multiple Bioelectric Impedance Vectors

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Objectives
This study was designed to investigate the properties of multiple bioelectric impedance signals recorded during congestive heart failure (CHF) by utilizing various electrode configurations of an implanted cardiac resynchronization therapy system.

Background
The monitoring of CHF has relied mainly on right-side heart sensors.

Methods
Fifteen normal dogs underwent implantation of cardiac resynchronization therapy systems using standard leads. An additional left atrial (LA) pressure lead sensor was implanted in 5 dogs. Continuous rapid right ventricular (RV) pacing was applied over several weeks. Left ventricular (LV) catheterization and echocardiography were performed biweekly. Six steady-state impedance signals, utilizing intrathoracic and intracardiac vectors, were measured through ring (r), coil (c), and device Can electrodes.

Results
Congestive heart failure developed in all animals after 2 to 4 weeks of pacing. Impedance diminished gradually during CHF induction, but at varying rates for different vectors. Impedance during CHF decreased significantly in all measured vectors: LVr–Can, −17%; LVr–RVr, −15%; LVr–RAr, −11%; RVr–Can, −12%; RVr–Can, −7%; and RA–Can, −5%. The LVr–Can vector reflected both the fastest and largest change in impedance in comparison with vectors employing only right-side heart electrodes, and was highly reflective of changes in LV end-diastolic volume and LA pressure.

Conclusions
Impedance, acquired by different lead electrodes, has variable responses to CHF. Impedance vectors employing an LV lead are highly responsive to physiologic changes during CHF. Measuring multiple impedance signals could be useful for optimizing ambulatory monitoring in heart failure patients. (J Am Coll Cardiol 2009;53:1075–81) © 2009 by the American College of Cardiology Foundation

Heart failure prevalence in the U.S. is estimated at 5 million people and is the leading cause of repeat hospitalization, costing about $35 billion in 2008 alone (1). Reliable monitoring of heart failure patients may help improve their management and cut cost by providing early means for detecting alterations in physiological condition and enabling early therapeutic intervention, thereby reducing hospitalizations.

Ambulatory monitoring of heart failure has relied on right-side heart sensors. Measuring intrathoracic impedance by using right ventricular (RV) lead electrodes to detect pulmonary edema in heart failure patients has been shown to be feasible, but with suboptimal sensitivity (2). Meanwhile, chronic monitoring of RV pressure has been demonstrated to be safe, but the additional sensor has not significantly reduced the rate of heart failure–related events (3).

Measuring bioelectric impedance in a manner that relates well to left ventricular (LV) volumes is preferred and may improve the accuracy of detecting early signs of decompensation due to congestive heart failure (CHF). The LV lead has been shown in a computer model to be superior to the RV lead for monitoring pulmonary edema through intrathoracic impedance (4). Therefore, the study objective was to monitor multiple impedance signals by utilizing both right- and left-sided electrodes of an implanted cardiac resynchronization therapy (CRT) system, and investigate the impedance trends...
in relation to physiologic changes occurring during CHF, induced in dogs by rapid RV pacing.

**Methods**

**Animal preparation.** The study protocol was approved by the animal care and use committees of Methodist Hospital Research Institute and St. Jude Medical. Fifteen adult mongrel dogs were studied (weight 35 to 40 kg). Before any experimental manipulation, each dog was pre-anesthetized by an intramuscular injection of xylazine (0.75 to 1.5 mg/kg) and atropine (0.02 to 0.06 mg/kg), anesthetized by intravenous injection of propofol (5 mg/kg), and continued on isoflurane inhalation (2%) for the remainder of each procedure.

**Implantation procedure.** A CRT system (Promote RF-3107, St. Jude Medical, Sylmar, California) was implanted in each dog. Three standard pacing/defibrillation leads were inserted through the left jugular vein with the tip electrodes fixed in the right atrial (RA) appendage, RV apex, and LV posterolateral epicardial region through the coronary sinus (Fig. 1). The proximal ends of the leads were tunneled subcutaneously to the left pectoral region where the CRT device was connected and permanently implanted. In 5 of 15 dogs, an additional lead carrying a pressure-sensor at the tip (HeartPOD-1011, St. Jude Medical) (5) was fixed at the interatrial septum through a trans-septal puncture, with the sensor oriented to the left atrium as depicted in Figure 1. The sensor was connected to a subcutaneously implanted device that collected and transmitted continuous left atrial (LA) pressure data. After implantation, the dog was allowed to recover for about 4 weeks to establish stable baseline status before any additional interventions.

**Electrical impedance monitoring.** The CRT device delivered between pairs of electrodes a train of current pulses (amplitude 0.5 to 1 mA; frequency 16 kHz), and measured corresponding voltage. Steady-state impedance was determined as the ratio between measured voltage and injected current. Multiple signals were measured through ring (r), coil (c), and device Can electrodes. Impedance was measured along 6 different vectors formed by the following bipolar electrode configurations (Fig. 2): 1) LVr–Can; 2) LVr–RVr; 3) LVr–RAr; 4) RVr–Can; 5) RAr–Can; and 6) RVr–Can. The CRT device sampled impedance every hour, and daily averages were computed. All measurements were made while pacing was temporarily halted. Stored data were automatically transferred through wireless communication.

**Heart failure model.** Once baseline status was established, the CRT system delivered continuous rapid RV pacing (230 to 250 beats/min) for a few weeks until CHF developed, as verified by echocardiography and catheterization (see the following text). Pacing was stopped when advanced CHF developed. The CRT system was not employed to deliver biventricular pacing therapy.

**Echocardiography and catheterization.** Transthoracic echocardiography and LV catheterization were both performed every 2 weeks starting from baseline and were carried out during the same session, under fixed anesthesia, and while pacing was temporarily halted. Thus, effects of anesthesia were uniform throughout the study. Echocardiography was conducted using a color Doppler imaging system with a 1.7 to 3.5 MHz probe (Vivid 7, GE Healthcare, Milwaukee, Wisconsin). Conventional 2-dimensional and Doppler images were obtained for evaluation of LV function, LV volume (biplane Simpson’s method), and LA volume (single-plane, area-length method). Image acquisition and analysis were performed by an investigator blinded to the status of the dog. Meanwhile, LV pressure was measured by a 5-F catheter (SPC-350, Millar Instruments, Houston, Texas) inserted through a femoral artery.

**Statistical analysis.** Continuous data are presented as mean ± SD. Comparisons between data at baseline and CHF were made using paired t tests. All correlations were tested using Spearman rank order. For comparative analysis between LV end-diastolic volume and impedance through each vector, Spearman correlation was performed with the Westfall-Young minP method (1,000 permutations) to control for the family-wise error rate (6). The generalized estimating equation method (7) was used to examine the association between LA pressure and impedance for each vector, and the mathematical model included pressure, impedance by each vector, time, and interactions between pressure and impedance. The analyses were performed using STATA.
version 10 (STATA Corp., College Station, Texas). A value of \( p < 0.05 \) was considered statistically significant, and corrected for multiple comparisons where necessary.

**Results**

**Animals.** Congestive heart failure developed in all 15 dogs within 2 to 4 weeks of rapid RV pacing, as evidenced by deterioration in cardiac function, hemodynamics, or symptoms that included anorexia, lethargy, ascites, tachypnea, and muscle wasting. Three dogs died while in CHF because of experimental complications. Physiologic changes observed in the remaining 12 dogs are summarized in Table 1.

**Impedance trends during CHF.** There was a gradual decrease in impedance through all vectors with progression of CHF (Fig. 3). The onset of increase in LA pressure invariably preceded the onset of decrease in impedance. All impedance signals decreased significantly at CHF in contrast to baseline status (Table 2).

The overall percent change in each impedance vector was computed for each dog, and the results were compared among 15 dogs. There was a trend of increased change in vectors employing an LV lead relative to vectors utilizing only right-sided leads (Fig. 4). In particular, the LV–Can vector was associated with the largest change in impedance in comparison with vectors solely dependent on right-side heart electrodes (\( p < 0.003 \) for all paired comparisons).

To examine the rate of change in each of the impedance vectors, we determined the duration between the onset of rapid pacing and the point of reaching 50% of the overall decline in impedance at CHF. As illustrated in Figure 4, impedance vectors employing an LV lead exhibited more rapid rates of change in comparison with vectors utilizing only right-sided leads (LV–Can, 7 ± 4 days; LV–RV, 10 ± 5 days; LV–RA, 8 ± 4 days; RV–Can, 12 ± 4 days; RV–Can, 13 ± 7 days; and RA–Can, 11 ± 4 days). The LV–Can vector depicted the fastest rate of change in impedance in comparison with vectors solely dependent on right-side heart electrodes (\( p < 0.003 \) for all paired comparisons).

**Impedance changes and hemodynamics.** Analysis of the relationship between LV end-diastolic volume and impedance is summarized in Table 3 for each vector. Impedance measurements through both the LV–Can and LV–RV vectors had statistically significant inverse relationships with LV end-diastolic volume (Fig. 5).

![Figure 2 Electrode Configurations Used for Measuring Impedance](image)

The electrode configurations used for measuring impedance are as follows: 1 = LV–RV; 2 = LV–RA; 3 = RV–Can; 4 = LV–Can; 5 = RA–Can; and 6 = RV–Can. c = coil electrode; r = ring electrode; other abbreviations as in Figure 1.

<table>
<thead>
<tr>
<th>Table 1 Summary of Physiologic Parameters</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>LAV, ml</td>
</tr>
<tr>
<td>LVEDV, ml</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>LAP, mm Hg</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
</tr>
</tbody>
</table>

Maximum left atrial volume (LAV) and left ventricular (LV) end-diastolic pressure (LVEDP) were not measured in 5 dogs with left atrial pressure (LAP) sensor. *Number of dogs.

CHF = congestive heart failure; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

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Khoury et al.
Ambulatory Monitoring of CHF
Analysis of the association between LA pressure and impedance for each vector is summarized in Table 4 on the basis of multiple continuous data pooled from the 5 dogs implanted with the LA pressure sensor, recorded over several time instants from baseline to CHF. Several impedance vectors demonstrated statistically significant dependence on LA pressure, with the LVr–Can exhibiting the strongest negative effect. Figure 6 portrays the relationship in 1 dog between LA pressure and change in impedance through LVr–Can.

**Discussion**

This study measured multiple steady-state impedance signals afforded by various electrode configurations of an implanted CRT system. The responses of the impedance vectors were periodically evaluated during CHF induced in dogs by chronic rapid RV pacing. In all measured vectors, the study found that impedance decreased gradually at varying rates during progression into CHF, and that im-
Impedance was significantly lower during CHF than baseline at different magnitudes of change. Overall, LV-dependent impedance vectors were associated with a faster rate of change, greater reduction in magnitude, better correlation with LV end-diastolic volume, and stronger association with LA pressure than were vectors solely dependent on right-sided cardiac measurements.

Several factors contribute to change in impedance, including cardiac volumes, myocardial thickness, pulmonary edema, and distance between the recording electrodes. Among all vectors measuring impedance, the LVr–Can configuration depicted the fastest rate of change during CHF induction and the largest overall change at CHF in comparison with vectors employing only right-sided heart electrodes. The change in this vector was responsive to the change in LV end-diastolic volume, as evidenced by the high correlation coefficient of the linear regression relationship among all dogs. The LVr–Can vector also exhibited the highest association with LA pressure. These observations suggest that the LVr–Can vector was highly reflective of decreased impedance (improved conductance) due to LV dilation and pulmonary edema during CHF.

Changes in impedance in the setting of pulmonary edema as measured through multiple intrathoracic vectors were previously investigated in a computer model of human anatomy (4). Our animal observations further confirmed the findings of the computer model, with both studies demonstrating improvement in monitoring pul-

### Table 2 Summary of Impedance Trends

<table>
<thead>
<tr>
<th>Impedance Vector</th>
<th>Baseline</th>
<th>CHF</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVr–Can</td>
<td>355 ± 75</td>
<td>294 ± 61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVr–RVr</td>
<td>491 ± 113</td>
<td>417 ± 93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVr–RAr</td>
<td>551 ± 89</td>
<td>487 ± 77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVr–Can</td>
<td>239 ± 64</td>
<td>209 ± 52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVr–Can</td>
<td>58 ± 8</td>
<td>54 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA–Can</td>
<td>289 ± 75</td>
<td>275 ± 77</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Impedance data were collected from 15 dogs. All units are in Ohms.

### Table 3 Relationship Between Change in LV End-Diastolic Volume and Change in Impedance

<table>
<thead>
<tr>
<th>Impedance Vector</th>
<th>r</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVr–Can</td>
<td>-0.88</td>
<td>0.001</td>
</tr>
<tr>
<td>LVr–RVr</td>
<td>-0.73</td>
<td>0.043</td>
</tr>
<tr>
<td>LVr–RAr</td>
<td>-0.55</td>
<td>0.253</td>
</tr>
<tr>
<td>RVr–Can</td>
<td>-0.53</td>
<td>0.235</td>
</tr>
<tr>
<td>RVc–Can</td>
<td>0.08</td>
<td>0.816</td>
</tr>
<tr>
<td>RA–Can</td>
<td>0.13</td>
<td>0.816</td>
</tr>
</tbody>
</table>

Correlation coefficients were determined by Spearman rank order analysis. A value of $p < 0.05$ was considered statistically significant as determined by the Westfall-Young minP method. Data were collected from 12 dogs. Abbreviations as in Tables 1 and 2.

Bar graph (mean ± SD) summarizing changes detected by 6 different impedance signals during deterioration from baseline to congestive heart failure (CHF). Blue indicates overall change in magnitude of impedance during CHF with respect to baseline; red indicates duration from the onset of rapid pacing to the point of reaching 50% of the overall decline in impedance during CHF. **Italicized uppercase letters (top) and lowercase letters (bottom)** indicate paired comparisons of impedance vectors resulting in differences that were statistically significant. A value of $p < 0.003$ was considered statistically significant, taking into account a Bonferroni adjustment for multiple comparisons. Abbreviations as in Figures 1 and 2.
monary edema by the LV lead in comparison with right-sided configurations (computer model: LV r–Can, −25.0%; RV r–Can, −8.3%; RV c–Can, −11.0%; and RA r–Can, −11.7%; animal model: LV r–Can, −16.6%; RV r–Can, −12.1%; RV c–Can, −6.5%; and RA r–Can, −5.3%).

The overall decrease in impedance measured through the RV c–Can vector in our study (6.5 ± 4.8%) was in line with the decrease observed in a previous study utilizing an equivalent vector in a similar animal model (10.6 ± 8.3%) (8), and comparable to the 12.3 ± 5.3% decrease in the same vector seen in heart failure patients hospitalized for worsening symptoms (2). Meanwhile, the decrease in impedance measured through the RV r–Can vector in our study (12.1 ± 7.4%) was consistent with the decrease observed in an equivalent vector in a previous study of pacing-induced CHF in swine (8.4 ± 12.1%) (9).

The utility of the various impedance vectors investigated in this study for monitoring clinical heart failure remains to be determined. Human studies utilizing RV-dependent intrathoracic impedance have observed a moderate rate of unexplained events (false positive) (2). Given the varying responses to CHF by impedance measured through different electrode configurations, we speculate that using multiple impedance vectors, or combining impedance with other hemodynamic sensors, for monitoring CHF may improve the sensitivity to adverse events.

Conclusions

Impedance signals, acquired through different lead electrodes, exhibit variable responses to CHF. Impedance vectors employing an LV lead are highly responsive to physiologic changes during CHF.

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REFERENCES


Key Words: cardiac resynchronization therapy • hemodynamic monitoring • pulmonary edema.