Significant Increase in the Incidence of Ventricular Arrhythmic Events After an Intrathoracic Impedance Change Measured With a Cardiac Resynchronization Therapy Defibrillator

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Background: Cardiac resynchronization therapy defibrillator (CRT-D) devices are now capable of monitoring changes in intrathoracic impedance. Intrathoracic impedance monitoring resulting in a fluid index threshold crossing has been proven to predict heart failure (HF) exacerbations. We retrospectively investigated the relationship between changes in intrathoracic impedance and the occurrence of arrhythmic events.

Methods and Results: From 282 patients with New York Heart Association class III or IV HF who were implanted with a CRT-D device with a fluid index feature based on intrathoracic impedance monitoring capabilities, arrhythmic events were retrospectively analyzed in terms of the threshold crossings. The patients were divided into 2 groups: those with fluid index threshold crossings and those without threshold crossings. A total of 4,725 tachyarrhythmic events were reported in 129 patients (46%), and there were 221 fluid index crossing events in 145 patients (51%) during 10.0±3.2 months. Tachyarrhythmic events were more frequently recorded in patients with threshold crossing events than in those who did not experience a threshold crossing (3,241 vs. 1,484 events, P<0.0001). Ventricular tachyarrhythmic events mainly occurred within the first 30 days after the threshold crossing event; however, a similar trend was not observed for the atrial tachyarrhythmic events.

Conclusions: Intrathoracic impedance monitoring may predict arrhythmic events, especially ventricular arrhythmias, in patients with HF and provides an additional management tool. (Circ J 2011; 75: 2614–2620)

Key Words: Arrhythmia; Heart failure; Implantable cardioverter-defibrillator; Intrathoracic impedance

Several studies have suggested that intrathoracic impedance monitoring may be useful for the early detection of cardiac decompensation in patients with heart failure (HF).1–9 Yu et al reported that the intrathoracic impedance correlated inversely with pulmonary capillary wedge pressure and net fluid loss in HF patients hospitalized for fluid overload.1 Cardiac resynchronization therapy defibrillator (CRT-D) devices are now capable of monitoring intrathoracic impedance using a fluid index algorithm that can automatically alert the clinician or patient if the intrathoracic impedance decreases significantly. A decrease in intrathoracic impedance may primarily indicate pulmonary fluid accumulation because of cardiac decompensation. Furthermore, Catanzariti et al showed that a device-based algorithm facilitated the detection of HF deterioration and reduced the number of HF hospitalizations.7

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Intrathoracic Impedance Monitoring Algorithm
The CRT-D device used in the study had several additional diagnostic capabilities for HF management, including intrathoracic impedance monitoring. The details of the intrathoracic impedance monitoring and derived OptiVol fluid index algorithm used in the study device have been described in detail previously. In brief, the intrathoracic impedance was calculated once daily as an average of 64 impedance measurements between the right ventricular defibrillation lead coil and the CRT-D device can, which was measured every 20 min from 12 PM to 5 PM, the best time of day to observe a fluid overload condition, in order to minimize the effects of respiration and posture on impedance. The daily impedance was compared with a reference, which tracked the trends in the preceding daily impedance values. The cumulative difference between the daily and reference impedances was used to calculate the OptiVol fluid index. The device was programmed to store the data if the fluid index increased above a programmed threshold, nominally set at 60 ohm-days, which came from the results of a previous study. The fluid index was inactive for 3,521 atrial events in 90 patients and 1,204 ventricular events in 70 patients. Ventricular arrhythmic events were successfully treated with antitachycardia pacing in 897 (74.5%) and direct current shock deliveries in 107 (8.9%) episodes; 200 (16.6%) ventricular events were not treated because the cycle lengths of most of those events were detected as only being sustained VT (18%) and VF (10%), at baseline. The mean follow-up duration was 10.0 ± 3.2 months.

Device Programming and Definitions
Baseline device programming including arrhythmic event detection and treatment was at the discretion of the implanting physician. A full interrogation of the CRT-D device was performed at each visit. Arrhythmic events involved there were either atrial or ventricular tachyarrhythmias. Atrial tachyarrhythmias included atrial tachycardia (AT), atrial flutter (AFL), and AF. Sustained ventricular tachycardia (VT) or fibrillation (VF) was considered a ventricular tachyarrhythmic event. Non-sustained or self-terminating VT was excluded from the analysis. Arrhythmic events that occurred within the first 34 days after the implant procedure were excluded from the analysis because the thoracic impedance fluid index had not been established. The study patients were classified into 2 groups: with and without OptiVol fluid index threshold crossings. Patient follow-up occurred at 1, 3, 6, and 12 months post-device implantation.

Results

Study Patients
The baseline characteristics of all the study patients were described in detail previously. In brief, 71% were male, 93% had NYHA class III HF, 56% had ischemic cardiomyopathy, and the median age was 68.3 years. The mean QRS duration was 157.0 ± 23.4 ms, and the mean LVEF was 23.3 ± 6.8%. Baseline medications included angiotensin-converting inhibitors or angiotensin receptor blockers (87%), β-blockers (88%), and diuretics (85%). In terms of a history of arrhythmias, 112 patients (40%) had atrial arrhythmias, including AT, AFL, and AF, and 129 (46%) had ventricular arrhythmias, including sustained VT (18%) and VF (10%), at baseline. The mean follow-up duration was 10.0 ± 3.2 months.

Arrhythmic Events
A total of 4,725 arrhythmic events occurred at least 34 days post-device implantation in 129 (46%) study patients, including 3,521 atrial events in 90 patients and 1,204 ventricular events in 70 patients. Ventricular arrhythmic events were successfully treated with antitachycardia pacing in 897 (74.5%) and direct current shock deliveries in 107 (8.9%) episodes; 200 (16.6%) ventricular events were not treated because the cycle lengths of most of those events were detected as only being in the MONITOR zone, which was programmed by each of the investigators.

In the regression analysis, the exploratory variables considered for the analysis were threshold crossing events, patient sex, age at device implantation, baseline NYHA functional class, LVEF, QRS duration, and ischemic vs. non-ischemic HF. As a result, the arrhythmic events were significantly associated with the occurrence of a fluid index threshold crossing, higher NYHA class at baseline, female sex, and age (Table 1). In particular, the occurrence of a fluid index threshold crossing and higher NYHA class at baseline were strongly associated with arrhythmic events during the follow-up period (relative

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All arrhythmias</th>
<th>Atrial arrhythmias</th>
<th>Ventricular arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>1.87 (1.75–1.99)</td>
<td>2.01 (1.86–2.16)</td>
<td>1.55 (1.37–1.74)</td>
</tr>
<tr>
<td>Baseline NYHA</td>
<td>3.01 (2.78–3.26)</td>
<td>2.31 (2.09–2.55)</td>
<td>5.48 (4.79–6.28)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.28 (1.20–1.36)</td>
<td>1.07 (0.99–1.15)</td>
<td>2.08 (1.86–2.34)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (1.00–1.00)</td>
<td>1.01 (1.00–1.01)</td>
<td>1.00 (1.00–1.01)</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; TC, threshold crossing; NYHA, New York Heart Association.

Table 1. RR Analysis of Arrhythmic Episodes
risk (RR) 1.87, 95% confidence interval (CI) 1.75–1.99, P<0.0001; and RR 3.01, 95%CI 2.78–3.26, P<0.0001, respectively). A fluid index threshold crossing and higher NYHA class at baseline were also strongly associated with atrial arrhythmic events (RR 2.01, 95%CI 1.86–2.16, P<0.0001; and RR 2.31, 95%CI 2.09–2.55, P<0.0001, respectively). The multiple regression analysis also suggested that a higher NYHA class at baseline was a risk factor for ventricular arrhythmias (RR 5.48, 95%CI 4.79–6.28, P<0.0001). Patients with fluid index threshold crossing events were 1.55-fold as likely to have ventricular events (RR 1.55, 95%CI 1.37–1.74, P<0.0001) as those without crossing events.

**Association Between Intrathoracic Impedance and Arrhythmias**

All 282 eligible study participants were grouped into 2 analysis cohorts: patients with at least 1 fluid index threshold crossing (TC (+) group, n=145) and those without a fluid index threshold crossing (TC (−) group, n=137). There were no significant differences between the 2 groups in the baseline characteristics (Table 2). Arrhythmic events in the TC (+) group occurred significantly more frequently than in the TC (−) group (P<0.0001) (Table 3). Moreover, a statistically significant association was observed between fluid index threshold crossings and both atrial and ventricular arrhythmic events.

**Time Course of Arrhythmic Events**

In order to determine if intrathoracic impedance monitoring could be used as an indicator of the occurrence of arrhythmic events, the temporal relationship between the fluid index threshold crossings and subsequent arrhythmic events was investigated. Of the TC (+) group patients, 70 (48%) had at least 1 arrhythmic event during the follow-up period. Moreover, 45 of the TC (+) patients experienced arrhythmic events after a threshold crossing. Ventricular arrhythmic events occurred after a threshold crossing in 23 patients (16%) in the TC (+) group (Figure 1). An analysis of the time course of those ventricular arrhythmic events showed that a significantly greater proportion of ventricular arrhythmic events occurred within 1 month of a fluid index threshold crossing than occurred at least 1 month after a fluid index threshold crossing (55.8% vs. 44.2%, P=0.0359) (Figure 2). In contrast, the proportion of atrial arrhythmic events occurring at least 1 month following a threshold crossing was significantly higher than that occurring within 1 month of a fluid index threshold crossing (54.9% vs. 45.1%, P=0.0004) (Figure 3). In summary, vent-

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**Table 2. Characteristics of TC (+) and TC (−) Groups at Enrolment**

<table>
<thead>
<tr>
<th></th>
<th>TC (+) group* (n=145)</th>
<th>TC (−) group† (n=137)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>102 (70)</td>
<td>99 (72)</td>
<td>0.13</td>
</tr>
<tr>
<td>Age, years</td>
<td>68±12</td>
<td>66±11</td>
<td>0.23</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>III</td>
<td>138 (95)</td>
<td>123 (90)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>7 (5)</td>
<td>14 (10)</td>
<td></td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>154.5±21.8</td>
<td>159.7±24.8</td>
<td>0.07</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22.8±6.8</td>
<td>23.7±6.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Ischemic</td>
<td>88 (61)</td>
<td>70 (51)</td>
<td></td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>55 (38)</td>
<td>61 (45)</td>
<td></td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>123 (85)</td>
<td>121 (88)</td>
<td>0.39</td>
</tr>
<tr>
<td>Antiarrhythmic class I</td>
<td>9 (6)</td>
<td>4 (3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Antiarrhythmic class III</td>
<td>35 (24)</td>
<td>32 (23)</td>
<td>0.88</td>
</tr>
<tr>
<td>β-blockers</td>
<td>127 (88)</td>
<td>121 (88)</td>
<td>0.85</td>
</tr>
<tr>
<td>Digitalis</td>
<td>50 (34)</td>
<td>58 (42)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diuretics</td>
<td>119 (82)</td>
<td>122 (89)</td>
<td>0.10</td>
</tr>
<tr>
<td>Complete AV block, n (%)</td>
<td>9 (6)</td>
<td>12 (9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Atrial tachyarrhythmias, n (%)</td>
<td>60 (41)</td>
<td>52 (38)</td>
<td>0.34</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmias, n (%)</td>
<td>68 (47)</td>
<td>61 (45)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Patients with TCs of the fluid index; †Patients with no TCs of the fluid index.
LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; AV, atrioventricular. Other abbreviations see in Table 1.

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**Table 3. Relationship Between TC Episodes and Arrhythmic Events**

<table>
<thead>
<tr>
<th></th>
<th>TC (+) group (n=145)*</th>
<th>TC (−) group (n=137)†</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>753</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>AT/AF</td>
<td>2,488</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3,241</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>451</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>AT/AF</td>
<td>1,033</td>
<td>38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>1,484</td>
<td>59</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Patients who had TCs of the fluid index; †patients who had no TCs of the fluid index; ‡P values were compared between the 2 groups using the number of episodes.
VT, ventricular tachycardia; VF, ventricular fibrillation; AT, atrial tachycardia; AF, atrial fibrillation. Other abbreviations see in Table 1.
left atrial arrhythmic events were more likely to occur within 1 month after a threshold crossing. However, no such trend was observed for the atrial arrhythmic events.

**Discussion**

Sudden cardiac death is often associated with severe HF, presumably because of ventricular tachyarrhythmias. The occurrence of ventricular arrhythmias may increase because of the existence of myocardial mechanoelectrical feedback or the hemodynamic consequences of sympathoadrenergic hyperactivity, concomitant with deteriorating HF. Similarly, the prevalence of atrial tachyarrhythmias, including AF, increases with the severity of HF. HF results in changes to the atrium that predispose it to the development and maintenance of atrial arrhythmias. Decreased atrial refractory periods, slowed atrial conduction, or increased heterogeneity during atrial repolarization can promote the development and maintenance of atrial arrhythmias. Prior studies have focused their attention on intrathoracic impedance as an indicator of HF decompensation. However, consideration has also been given to additional applications of intrathoracic impedance monitoring in the man-

**Figure 1.** Event time assessment. Of 282 patients 145 (51%) had threshold crossing (TC) events. Atrial and ventricular arrhythmic events occurred after TCs in 33 and 23 TC (+) patients, respectively; 11 TC (+) patients experienced both atrial and ventricular arrhythmic events after TCs. AT, atrial tachycardia; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation.

**Figure 2.** Relationship between the proportion of ventricular arrhythmic events after a fluid index threshold crossing (TC) and the period of time from the occurrence of the TC. The proportion of ventricular arrhythmic events within 1 month of a fluid index TC was significantly higher than that after 1 month (55.8% vs. 44.2%, P=0.0359).
Andriulli et al reported a case of repeated VT episodes preceded by an acutely lowered thoracic impedance recorded with a CRT-D device. Moore et al reported that ventricular arrhythmic episodes were preceded by cumulative differences between the averaged daily and reference impedance on the dates leading up to the ventricular arrhythmic events, which was used as a diagnostic indicator rather than the OptiVol fluid index. As for atrial arrhythmic events, Jhanjee et al reported that worsening pulmonary congestion evidenced by fluid index threshold crossings was associated with an increase in the frequency of atrial arrhythmias, and that those arrhythmias may be responsible for triggering episodic pulmonary congestion more often than previously suspected.

Our retrospective observational study both confirmed and extended these findings by demonstrating a relationship between changes in intrathoracic impedance and the occurrence of cardiac arrhythmias within a large patient cohort. We investigated the temporal relationship between ventricular and atrial arrhythmic events and changes in intrathoracic impedance using the OptiVol fluid index. A multiple regression analysis revealed that both the occurrence of a fluid index threshold crossing and a higher NYHA class at baseline were independent predictors of atrial arrhythmic events, ventricular events, and the total number of arrhythmic events. Additionally, the patients with fluid index threshold crossings had significantly more atrial and ventricular arrhythmic events than those without threshold crossings during the follow-up period. These data suggest that cardiac arrhythmias are closely related to the fluid index threshold crossings, which in turn correlates with an increasing severity of HF. We, therefore, propose that changes in intrathoracic impedance can be regarded as a warning for cardiac arrhythmias, which tend to progress in parallel with exacerbation of HF.

Benefits of Early Warning of Cardiac Arrhythmias

Ventricular arrhythmic events sometimes result in the delivery of ICD shocks, which can be painful and increase the patient’s anxiety. Additionally, Poole et al reported that the patients who received ICD shocks for arrhythmias had a substantially higher risk of death than similar patients who did not receive such shocks. If changes in intrathoracic impedance can predict the occurrence of ventricular arrhythmias, effective early medical management may prevent the delivery of ICD shocks, resulting in a significant benefit to the patient.

Additional Considerations

The report by Moore et al and our analysis suggest that the application of intrathoracic impedance monitoring as an indicator of the occurrence of ventricular arrhythmic events may lack specificity. Vollmann et al reported that the fluid index threshold crossing alert detected clinical HF deterioration with a 60% sensitivity (95% CI 46–73) and positive predictive value of 60% (95% CI 46–73) at the nominal threshold setting of 60 ohm-days. Predicting the occurrence of an arrhythmia based on a cardiac overload that may result in HF cannot exceed the accuracy of predicting clinical HF deterioration using the intrathoracic impedance system. Furthermore, arrhythmias do not always appear at the time of HF deterioration. There also might be some prolonged cycle length ventricular events that are undetectable by the device programming, which induce cardiac deterioration and lead to a change in intrathoracic impedance. Thus, the observation that ventricular arrhythmias occurred after the threshold crossing in 16% of the TC (+) group patients in this study was reasonable and potentially clinically meaningful.

Although intrathoracic impedance measurements as currently implemented in implantable devices may not perform ideally
as an indicator of arrhythmic events, tailored use in combination with consideration of the patient’s history and the impedence trend at the time of the event may be useful. However, the hypothesis that changes in intrathoracic impedance predict the occurrence of arrhythmias requires prospective validation.

Study Limitations

This retrospective study is subject to the limitations of all such studies. First, no randomization or blinding was applied. Second, all arrhythmic events used for the analysis were based on the device diagnosis and the programmed settings determined only by the physician’s discretion. The atrial arrhythmia detection criteria of the device requires an atrioventricular conduction of 2:1 or greater for a minimum of 32 ventricular contractions. Atrial arrhythmic events are detected when the median atrial cycle length is less than a minimum value programmed by the physician. Helmut et al reported that the positive predictive value of atrial arrhythmic episodes were 95.3% and 95.7% for previous devices. The ventricular arrhythmia detection algorithm operates to discriminate between supraventricular and ventricular tachyarrhythmias based on atrial and ventricular depolarization timing, ventricular cycle length regularity, AF criteria and far-field criteria. Stadler et al demonstrated a positive predictive accuracy of 91.5% for the detection of ventricular arrhythmia episodes. Third, the data for antitachycardia pacing episodes or direct current shock deliveries were not available for analysis in relation to the fluid index threshold crossings in this study. Finally, in regard to the fluid index setting, the nominal detection threshold value of 60 ohm-days used in this study demonstrated a 76.9% sensitivity in the large-scale observational study by Vollman et al. However, some studies have reported that the positive predictive value of this proposed threshold for the OptiVol index related HF is relatively low. Our data also showed that the fluid index threshold was crossed before atrial and ventricular arrhythmic events with a positive predictive value of 19% and 14%, respectively. The OptiVol index was developed to predict HF deterioration and may be affected by other events (eg, pneumonia, pleural effusion, pocket infection, drinking, etc.). Yenputg et al suggested that the nominal programmed fluid index threshold was not specific for the assessment of HF, and proposed that a threshold value of 120 ohm-days would provide a reasonable balance between sensitivity and specificity. Further prospective studies in larger populations are needed to assess this hypothesis.

Conclusions

In this retrospective study of patients with NYHA class III and IV HF and who were implanted with CRT-D devices, arrhythmic events were associated with a dramatic change in the intrathoracic impedance-derived fluid index. Further prospective clinical trials are required to confirm the relationship between arrhythmic events and intrathoracic impedance monitoring, and to determine whether device-based fluid index monitoring can facilitate preemptive therapy to reduce the occurrence of arrhythmic events in patients with HF.

Acknowledgments

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References


