Continuous Monitoring of Intrathoracic Impedance and Right Ventricular Pressures in Patients With Heart Failure

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Background—Hemodynamic monitoring using implantable devices may provide early warning of volume overload in patients with heart failure (HF). This study was designed to prospectively compare information from intrathoracic impedance monitoring and continuous right ventricular pressure measurements in patients with HF.

Methods and Results—Sixteen patients with HF (age, 63.5±13.8 years; left ventricular ejection fraction, 23.2±11.3%; New York Heart Association, II and III) and a previous HF decompensation received both a cardiac resynchronization therapy defibrillator providing a daily average of intrathoracic impedance and an implantable hemodynamic monitor providing an estimate of the pulmonary artery diastolic pressure. At the end of a 6-month investigator-blinded period, baseline reference hemodynamic values were determined over 4 weeks during which the patient was clinically stable. A major HF event was defined as HF decompensation requiring hospitalization, IV diuretic treatment, or leading to death. Sixteen major HF events occurred in 10 patients. Within 30 days and 14 days before a major HF event, impedance decreased by 0.12±0.21 Ω/d and 0.20±0.20 Ω/d, respectively, whereas estimated pulmonary arterial diastolic pressure increased by 0.10±0.20 mm Hg/d and 0.16±0.15 mm Hg/d, respectively. During these periods, impedance decreased by 3.8±5.4 Ω (P<0.02) and 4.9±6.1 Ω (P<0.007), respectively, whereas estimated pulmonary arterial diastolic pressure increased by 5.8±5.7 mm Hg (P<0.002) and 6.8±6.1 mm Hg (P<0.001), respectively, compared with baseline. In all patients, impedance and estimated pulmonary arterial diastolic pressure were inversely correlated (r = −0.48±0.25). Within 30 days preceding a major HF event, this correlation improved to r = −0.58±0.24.

Conclusions—Decompensated HF develops based on hemodynamic derangements and is preceded by significant changes in intrathoracic impedance and right ventricular pressures during the month prior to a major clinical event. Impedance and pressure changes are moderately correlated. Future research may establish the complementary contribution of both parameters to guide diagnosis and management of patients with HF by implantable devices. (Circ Heart Fail. 2010; 3:370-377.)

Key Words: heart failure | intrathoracic impedance monitoring | hemodynamic monitoring | ePAD

Congestive heart failure (HF) represents a major public health problem that affects close to 7 million Europeans and 5 million North Americans each year. Despite new and more effective pharmacological and nonpharmacological therapeutic strategies, the prognosis of patients with HF remains poor. Because of its progressive and unstable nature, many patients develop recurrent episodes of decompensated HF, requiring frequent hospital admissions. These recurrent episodes of decompensation result most often from volume exacerbations with concomitant high cardiac filling pressures and are associated with a high risk for rehospitalization or death.

Clinical Perspective on p 377

The primary focus of the therapeutic management in chronic HF is the maintenance of an optimal volume status and low filling pressures to prevent hemodynamic deterioration. However, clinical signs and symptoms of HF usually occur late in the course of decompensation and are largely unreliable in the routine follow-up of patients with HF. Daily body weight, a mainstay of HF outpatient management as an indicator of fluid retention, has poor sensitivity to predict clinical deterioration. Alternatively, it has been suggested that continuous monitoring of right ventricular (RV) pressures with use of implantable hemodynamic monitors (IHM) or daily measurements of intrathoracic impedance (ePAD) may be used to improve volume management. Preliminary data suggest that both methods may provide helpful tools for the early detection of an imminent cardiac decompensation because hospitalizations for decompensated HF commonly are

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preceded by a gradual increase in filling pressures or a decrease in intrathoracic impedance over several days or weeks. However, before introducing this technology into daily clinical practice, there is a need to better characterize the complex pathophysiological relationship between RV pressures and intrathoracic impedance in the context of volume overload decompensation. Accordingly, this observational study was designed to prospectively compare the diagnostic information derived from implantable hemodynamic and intrathoracic impedance monitoring in patients at increased risk to be hospitalized for decompensated HF.

Methods

Study Population
Patients with moderate to severe HF due to either ischemic or idiopathic dilated cardiomyopathy were eligible for the study if they were in New York Heart Association functional class II to IV and had at least 1 hypertrophic HF-related hospitalization within the past 12 months that required IV administration of diuretics or vasoactive drugs. All patients had a cardiac resynchronization therapy defibrillator (CRT-D) implanted in the pectoral region, preferably at the left side. After CRT-D implantation, the IHM was implanted in the contralateral region. Patients with moderate-to-severe chronic obstructive lung disease with a 1-month forced expiratory volume <1.0 L/s, HF and preserved ejection fraction, severe primary pulmonary hypertension, any known atrial or ventricular septal defect, and life expectancy <1 year were excluded.

Study Protocol
At baseline, patients were assessed by standard echocardiography, serum N-terminal pro-brain natriuretic peptide level, and 6-minute walk test. During the first 6 months, investigators were blinded to the RV pressure and fluid status (OptiVol) data, and patients were treated based on routine clinical assessment with monthly follow-up visits. After 6 months, patients had monthly visits, and the investigators had access to the monitoring information to support clinical HF management. During the study, remote access through the Carelink network was not available, and the devices were interrogated only at a time of routine outpatient visits or when the patient developed symptoms. Measurements obtained during the first 3 months after device implantation (stabilization phase) were excluded from analysis to avoid interference of the impedance measurements by postoperative fluid resorption in the device pocket. In addition, during these 3 months, medical therapy was optimized. Baseline reference values were determined as the median of daily average values taken during the last 4 weeks in the blinded phase (ie, during the sixth month) when the patient was in stable clinical condition (reference month). In 2 patients with clinical events during the sixth month, baseline device parameters were obtained the month before.

Major events were defined as decompensated hypertensive HF-related events necessitating hospitalization, IV therapy with diuretics or vasodilators, or events leading to cardiac death. Minor events were defined as HF-related episodes requiring only adjustment of oral diuretics. All other clinical events were defined as non-HF related. Critical data on hospitalization, changes in clinical status, and HF-related medication as well as device- and nondevice-related events were prospectively collected in an electronic database (TrialXS). The study protocol was approved by the local ethics committees, and all patients provided written informed consent.

Intrathoracic Impedance and RV Pressure Monitoring
In brief, intrathoracic impedance was measured between the CRT-D and the RV coil. For calculation of the daily impedance value, 64 instantaneous measurements were taken between 1200 and 1700 hours and averaged, as previously described. Each impedance value is used to update a reference multiday-weighted rolling trend, which is then compared to the daily value to measure the daily deviations. Negative deviations are summed day after day to form the OptiVol Fluid Index (OFI). Whenever the daily impedance is higher than the reference value, the OFI is reset to 0 Ω. If deviations continue to be negative day after day, the OFI will exceed the physician-established standard OptiVol threshold of 60 Ω.

The IHM continuously stores heart rate, RV systolic and diastolic pressure, estimated pulmonary artery diastolic pressure (ePAD), RV pulse pressure, and maximum positive and negative rate of rise in left ventricular pressure, together with physical activity. The ePAD is derived from RV pressures at the time of maximum rate of rise in left ventricular pressure coinciding with the moment of pulmonary valve opening. This concept was validated previously by Ohlsson et al. The device is implanted similar to a VVI pacemaker with the pressure sensor located on an RV lead inserted in the RV outflow tract position. A time-synchronized external pressure reference corrects cardiac pressures for changing ambient pressures.

The programmer allows adjustment of settings and retrieves data from the IHM and external pressure reference for storage and generation of summarizing reports. The IHM device was programmed for storage of median, p6, and p94 for all parameters every 34.15 minutes.

Data Analysis
Changes in intrathoracic impedance and RV pressure were assessed within time periods of 14 and 30 days before major and minor HF

### Table 1. Baseline Clinical Characteristics and Device-Derived Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Patients With Major HF Events</th>
<th>Patients Without Major HF Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>16</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>16</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.5 ± 13.8</td>
<td>59.8 ± 15.4</td>
<td>67.0 ± 10.2</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23.2 ± 11.3</td>
<td>23.4 ± 13.2</td>
<td>22.8 ± 4.0</td>
</tr>
<tr>
<td>HF cause, %</td>
<td>Ischemic</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Valvular</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>NYHA class, %</td>
<td>II</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>0</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>363 ± 109</td>
<td>362 ± 116</td>
<td>367 ± 105</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>3250 ± 2248</td>
<td>3847 ± 2603</td>
<td>2253 ± 1027</td>
</tr>
<tr>
<td>Medication use, n (%)</td>
<td>β-blockers</td>
<td>13 (81)</td>
<td>8 (80)</td>
</tr>
<tr>
<td></td>
<td>ACEI or ARBB</td>
<td>15 (94)</td>
<td>9 (90)</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>15 (94)</td>
<td>9 (90)</td>
</tr>
<tr>
<td></td>
<td>Aldosterone antagonists</td>
<td>14 (88)</td>
<td>8 (80)</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>38</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise indicated. 6MWT indicates 6-minute walk test; ACEI, angiotensin converting enzyme inhibitor; ARBB, angiotensin-II receptor blocker; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

is compared to the daily value to measure the daily deviations. Negative deviations are summed day after day to form the OptiVol Fluid Index (OFI). Whenever the daily impedance is higher than the reference value, the OFI is reset to 0 Ω. If deviations continue to be negative day after day, the OFI will exceed the physician-established standard OptiVol threshold of 60 Ω.

The IHM continuously stores heart rate, RV systolic and diastolic pressure, estimated pulmonary arterial diastolic pressure (ePAD), RV pulse pressure, and maximum positive and negative rate of rise in left ventricular pressure, together with physical activity. The ePAD is derived from RV pressures at the time of maximum rate of rise in left ventricular pressure coinciding with the moment of pulmonary valve opening. This concept was validated previously by Ohlsson et al. The device is implanted similar to a VVI pacemaker with the pressure sensor located on an RV lead inserted in the RV outflow tract position. A time-synchronized external pressure reference corrects cardiac pressures for changing ambient pressures.

The programmer allows adjustment of settings and retrieves data from the IHM and external pressure reference for storage and generation of summarizing reports. The IHM device was programmed for storage of median, p6, and p94 for all parameters every 34.15 minutes.

Data Analysis
Changes in intrathoracic impedance and RV pressure were assessed within time periods of 14 and 30 days before major and minor HF
events. Daily median values of the individual impedance and RV pressures 30 and 14 days preceding HF events were compared, with values obtained during the reference month. Furthermore, the estimation of pressure trends was done by a first order (linear) fit (least squares criterion) with use of all the data in a window of 30 and 14 days before each major and minor HF event. For the reference month, 30 days were used. For each event, the slope of the fitted line was taken as the trend of the parameter. The mean and SD of the slopes obtained for each major and minor event were calculated separately for the 14- and 30-day windows.

For impedance, the daily median was calculated by taking the median of the 64 impedance values produced by the CRT-D device. For pressure parameters, the IHM device produces 1 value each 34.15 minutes. Median was calculated within 24 hours each day.

**Statistical Analysis**

Statistical analysis was performed with SPSS version 16.0 and Matlab version 2008a. All data are expressed as mean±SD for continuous data and as counts, percentages, or both for categorical data. A normal distribution of data was tested by Kolmogorov-Smirnov test. The student paired t test was used for comparisons of hemodynamic and impedance parameters. Daily values of intrathoracic impedance and ePAD were analyzed by linear regression analysis, and Pearson correlation coefficients were calculated accordingly. To estimate the ensemble-averaged impedance and pressure trends, a moving average of each parameter was calculated. Statistical significance was set at a 2-tailed probability level of <0.05.

**Results**

**Baseline Characteristics**

Nineteen patients (all men) were enrolled in the study. The CRT-D and IHM systems were successfully implanted in all patients. However, in 2 patients, IHM data could not be used after 1 month because of instability of the pressure lead in the RV outflow tract, and both patients refused lead repositioning. One patient underwent heart transplantation because of drug refractory HF within 2 months after implantation. In the remaining 16 patients, HF was due to ischemic heart disease (n=13), idiopathic dilated cardiomyopathy (n=2), or valvular heart disease (n=1). All patients were >80% of time paced in the atrium. Baseline characteristics are summarized in Table 1.

**HF-Related Adverse Events**

During a cumulative follow-up period of 351 months (21.9±7.5 months per patient), a total of 36 HF-related clinical events were observed in 11 patients (1.2 per patient-year). There were 16 major HF events in 10 patients, including 1 death, 14 hospitalizations for HF (10 patients) with IV diuretic treatment, and 1 IV diuretic treatment without hospitalization. In addition, a total of 20 minor HF events occurred in 8 patients. Five patients remained without any major or minor HF event during the study. Twenty-seven non-HF-related events, including stroke, atrial fibrillation, sepsis, and renal failure, occurred in 11 patients.

Compared with patients with at least 1 major event (n=10), patients without major events (n=6) had lower NT-proBNP levels, but no difference in New York Heart Association functional class, ejection fraction, 6-minute walk test, heart rate, medication use, or underlying disease was found. Furthermore, patients with a major event had higher RV systolic pressures during the reference month (54±13 mm Hg versus 41±10 mm Hg; P<0.04), although RV diastolic pressure, ePAD, and intrathoracic impedance were similar compared with patients with no major events (Figure 1).

**Impedance and RV Pressure Before Major Events**

Data from before major events are summarized in Tables 2 and 3. Thirty and 14 days before patients had a major HF event, mean RV systolic and diastolic pressures and ePAD had significantly increased, whereas intrathoracic impedance had significantly decreased compared with the reference month. In addition, 14 days before major HF events, these changes were associated with a significant decrease in patient activity.

During the reference month, the impedance and pressure trends were very small, consistent with optimal hemodynamic control. However, within the month before the major HF events, ePAD increased at a rate of 0.1±0.2 mm Hg/d (P=0.41 versus reference month), whereas intrathoracic impedance dropped by 0.12±0.21 Ω/d (P=0.06 versus reference month). Within 14 days, these trends were significantly
higher (0.16±0.15 mm Hg/d [P<0.01] and −0.2±0.2 Ω/d [P<0.003]) compared with the reference month, indicating that most variation took place within the last 14 days before the event (Tables 2 and 3).

During the entire study period, 15 of 16 patients showed an inverse correlation between daily averages of ePAD and intrathoracic impedance (median r=−0.51), with 8 of 16 patients showing a correlation >0.50. Interestingly, this correlation became more prominent during the 30 days preceding a major or minor HF event (median r=−0.63). Figure 2 shows the correlations between ePAD and intrathoracic impedance in 2 patients during the entire study period (−0.31 and −0.51, respectively) and within 30 days before a major event (−0.77 and −0.81, respectively).

**Impedance and RV Pressures Before Minor Events**

Data from before minor events are summarized in Tables 2 and 3. Thirty and 14 days before patients had a minor HF event, mean RV systolic and diastolic pressures and ePAD had significantly increased, whereas intrathoracic impedance was not different compared with the reference month. In addition, 14 days before minor HF events, these changes were associated with a significant decrease in intrathoracic impedance.

Furthermore, the corresponding ePAD and RV systolic and diastolic pressures were even higher compared with the 30-day average. The ePAD increased by 0.14±0.23 mm Hg/d, whereas impedance dropped by 0.12±0.15 Ω/d within the month before the minor HF events. Fourteen days before the event, significant differences were noted in the impedance trends but not in the ePAD trends.

**Ensemble-Averaged Impedance and Pressure Trends**

In Figure 3, the 30-day ensemble average trends of intrathoracic impedance and ePAD before and after major, minor, and non-HF events are presented. The ePAD started to increase 18 days before major HF events in synchrony with a consistent decrease of impedance. Interestingly, significant differences in ePAD and impedance trends occurred only during the last 14 days before the event and were not observed at 30 days. After admission to the hospital and IV diuretic treatment, impedance increased within 2 days, whereas ePAD decreased more gradually, falling back to the baseline level 15 days after hospitalization. In contrast to major events, the ePAD increase before minor HF events started from a lower level of filling pressures, whereas impedance started to decrease 19 days before the event (Figure 3, middle). Thus, pressure increase before minor events occurred over a longer period of time and was smoother. Of note, opposite to what happened before major events, only ePAD increased significantly during the 30-day period, and differences in ePAD rise were not observed during the last 14 days preceding the event. In addition, ePAD at the time of the event was lower compared with major HF events. Likewise, the impedance decrease occurred over a longer period of time.

After minor HF events, oral diuretic dose adjustments did not lead to a similar prompt impedance and ePAD response as observed after major HF events. Of note, in contrast to the marked treatment response after IV diuretic therapy given in the context of major events, ePAD was only slightly reduced after oral adjustment of diuretics. Finally, before non-HF

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**Table 2. Absolute Difference Before Major and Minor HF Events**

<table>
<thead>
<tr>
<th>Reference Month</th>
<th>30 Days (Delta)</th>
<th>14 Days (Delta)</th>
<th>1 Day (Delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;sub&gt;syst&lt;/sub&gt;, mm Hg</td>
<td>54.9±16.1</td>
<td>5.9±7.1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>7.4±7.1&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ePAD, mm Hg</td>
<td>31.0±11.3</td>
<td>3.0±4.0†</td>
<td>4.6±4.5&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>P&lt;sub&gt;dias&lt;/sub&gt;, mm Hg</td>
<td>13.9±6.8</td>
<td>2.8±3.9&lt;sup&gt;*&lt;/sup&gt;</td>
<td>3.9±4.5&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Activity, au</td>
<td>201±49</td>
<td>−29±42&lt;sup&gt;*&lt;/sup&gt;</td>
<td>7±91</td>
</tr>
<tr>
<td>Impedance, Ω</td>
<td>70.6±11.2</td>
<td>−2.9±6.5</td>
<td>−4.3±7.8</td>
</tr>
</tbody>
</table>

**Table 3. Trends Before Major and Minor HF Events**

<table>
<thead>
<tr>
<th>Reference Month</th>
<th>30 Days</th>
<th>14 Days</th>
<th>Reference Month</th>
<th>30 Days</th>
<th>14 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;sub&gt;syst&lt;/sub&gt;, mm Hg/d</td>
<td>0.1±0.1</td>
<td>0.09±0.15</td>
<td>0.14±0.21</td>
<td>0.1±0.1</td>
<td>0.10±0.17</td>
</tr>
<tr>
<td>ePAD, mm Hg/d</td>
<td>0.0±0.1</td>
<td>0.14±0.22</td>
<td>0.15±0.18&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.0±0.1</td>
<td>0.15±0.25&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>P&lt;sub&gt;dias&lt;/sub&gt;, mm Hg/d</td>
<td>0.0±0.1</td>
<td>0.07±0.11</td>
<td>0.04±0.18</td>
<td>0.0±0.0</td>
<td>0.10±0.09&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Impedance, Ω/d</td>
<td>0.0±0.0</td>
<td>−0.14±0.25</td>
<td>−0.16±0.23&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.0±0.0</td>
<td>−0.13±0.11&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table 3. Trends Before Major and Minor HF Events**

Trends were calculated during periods 30 and 14 days before the major and minor HF events. Paired t test were used for significance testing (1-tailed equal variance) (see Table 2). <sup>*</sup>P<sub>syst</sub> indicates systolic pressure; <sup>*</sup>P<sub>dias</sub> diastolic pressure.

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events, ePAD did not increase significantly and, accordingly, impedance did not decrease (Figure 3, right).

**OFIG Crossings and RV Pressures**

Figure 4 summarizes the ensemble-averaged RV pressure parameters within a time window of 30 days before and after an OFIG threshold crossing. Twenty OFIG threshold crossings were followed by either a major (n=10) or minor HF event (n=10). In 3 major HF events, the OFIG threshold was reached within 2 days after hospital admission, whereas in 6 minor HF events, fluid index was rising and reached the threshold immediately (within 48 hours) after the event.

For OFIG threshold crossings followed by a major or minor HF event, RV diastolic and systolic pressure and ePAD were higher compared with baseline reference values (P<0.01). Moreover, after OFIG threshold crossings, RV diastolic and systolic pressures and ePAD continued to increase when followed by a major HF event, whereas they remained unchanged when followed by a minor HF event.

**Discussion**

This study reports data from the continuous monitoring of intrathoracic impedance and RV pressures in patients with chronic HF. The main findings are that (1) impedance and

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**Figure 2.** Correlation between daily medians of ePAD and intrathoracic impedance. Examples are given in 2 patients with major HF events. Correlations are shown during whole follow-up period (r=−0.31 and −0.51) (left) and within the 1-month period before a major HF event (r=−0.77 and −0.81) (right).

**Figure 3.** Thirty-day ensemble averages of intrathoracic impedance (top) and ePAD (bottom) before (red) and after (blue) HF and non-HF events. The dashed line (0) indicates clinical events.
pressure values show a significant inverse relationship; (2) the correlation between intrathoracic impedance and RV pressures becomes more pronounced during periods leading up to clinical HF events; and (3) once filling pressures exceed a critical level, intrathoracic impedance gradually declines, suggesting accumulation of interstitial pulmonary fluid. Thus, our findings confirm the pathophysiological link between cardiac filling pressures and pulmonary fluid content and indicate that both methods may be useful in providing early warning on an impending hypervolemic HF decompensation.

Impedance and Pressure Monitoring for Early Detection of Congestion

Strategies using implanted sensor technology to detect changes in volume load have recently gained increasing attention. Early clinical experience suggested that an IHM may facilitate the clinical management of patients with HF and reduce HF-related hospitalizations.8,12 Recently, this concept was tested in a randomized trial.13 Although the main end point of all HF-related events was not significantly reduced by the guidance with the IHM, retrospective analysis suggested a significant risk reduction of time to the first HF hospitalization. Yu et al9 demonstrated that intrathoracic impedance can be a useful alert to an impending volume overload decompensation. Our study extends these findings by simultaneously testing both monitoring strategies. Significant changes of either monitoring parameter preceded major and minor HF events and started before the clinical event in a time interval similar to the one previously reported.9 Importantly, this pattern was not present in the context of non-HF–related events.

Figure 4. Ensemble-averaged RV systolic and diastolic pressure and ePAD before and after OFI threshold crossings (60 Ω/d). Parameter trends before and after OFI crossings followed by a major (n=10) or minor (n=10) HF event are presented in red and blue, respectively.

So far, the algorithm proposed for intrathoracic impedance showed a reasonable diagnostic accuracy in the pivotal validation study and in a recent European observational registry.9,14 Interestingly, in our study, only OFI crossings paralleled by an increase in ePAD resulted in HF-related cardiac events. Although speculative and not within the scope of this study, this finding might suggest that combining information derived from the fluid index algorithm with raw pressure measurements may improve the diagnostic accuracy and be helpful to alert clinicians about patients who are at increased risk for a subsequent HF decompensation. However, whether combining the OFI measurements with IHM hemodynamic measurements may improve the prediction of HF-related events should be validated in a randomized controlled study.

Major Versus Minor HF-Related Events

In our study, major HF events were characterized by a steeper slope in impedance and ePAD as compared with minor HF-related events. Furthermore, pressure levels 30 days before a major event showed a greater difference from reference values than the corresponding values 30 days before a minor event, with ePAD changes almost twice as high in major HF-related events compared with minor HF-related events. The decrease in patient activity suggests that the higher ePADs observed during major clinical events also had direct clinical impact. Filling pressures at the time of major clinical events were higher than those noted before minor events, with ePAD pressures of 38 mm Hg and 36 mm Hg, respectively. These values are in line with the critical value of 35 mm Hg for ePAD reported by Zile et al15 at the time of hypervolemic HF-related events. In contrast to major HF-related events, the ePAD increase preceding minor events started from lower levels for a longer time. Only when ePAD reached a critical value did impedance start to decrease. These data strongly support the importance of cardiac filling pressures as the driver of HF decompensation. During the major HF-related events, significant differences in pressure rise could be detected only 14 days before the event. However, during minor HF-related events, pressure changes, although smaller in the extent, could be detected 30 days before the event, which might suggest that not only the absolute pressure, but also the rate of pressure rise determine the severity of the upcoming HF-related event.

Hydrostatic Pressure and Interstitial Fluid Accumulation

The equilibrium between interstitial fluid accumulation and lung water clearance is well maintained until a critical ePAD is reached. Above a critical ePAD, compensatory mechanisms that regulate the equilibrium between interstitial fluid accumulation and lung water clearance are exhausted, and fluid filtered into the alveolar interstitial tissue no longer will
be cleared from the peribronchovascular space by the lymphatics. A rapid increase in hydrostatic pressure in the pulmonary capillaries leading to increased transvascular fluid filtration is the hallmark of volume overload edema. Our data corroborate these observations. The higher correlation between the intrathoracic impedance and ePAD measurements during or immediately before episodes of decompensated HF suggests that changes in filling pressure play a pivotal role in the underlying pathophysiology of acute decompensated HF. Interestingly, when looking at the ensemble-averaged ePAD, fluid accumulation evidenced by a drop in impedance occurred at ePAD values higher than those reported in the literature. However, this finding is consistent with the clinical observation that patients with chronic HF may only occasionally develop pulmonary edema despite the presence of chronically elevated filling pressures, suggesting that alternative mechanisms, such as increased lymphatic and alveolar fluid clearance, might partially compensate for the alveolar fluid accumulation. Further studies are needed to explore the interaction between hydrostatic pressure and interstitial accumulation in detail.

Implications
Our data indicate that both intrathoracic impedance and RV pressures are useful parameters to monitor fluid status in patients with HF. Both measurements were instrumental in the warning of an imminent major or minor decompensation, depicting a distinct time course of respective rise and decrease. However, the correlation between these 2 variables remained modest, suggesting that they do not provide identical information and, therefore, may play a complementary role in predicting HF decompensation rather than being replaceable by each other.

We speculate that the integration of multiple monitoring features offered by implantable devices, such as arrhythmia incidence, heart rate, and heart rate variability, may facilitate a gradual differentiation of alerts depending on the concordance of the diagnostic data. Such an algorithm may give a higher priority to an alert based on significant deviation of each monitored parameter than one based on changes of only one parameter. Furthermore, when an HF decompensation episode is preceded by more pronounced relative changes in ePAD than impedance, one could speculate that the pressure information might act as the primary monitoring parameter, which needs to be confirmed by impedance changes and vice versa.

Limitations of the Study
Due to its small sample size and frequent follow-up visits, our study was unable to create and validate multimodal HF detection algorithms and, therefore, should be regarded as a pilot exploration. However, for the first time, we were able to measure RV pressures and intrathoracic impedance over an extended period in patients with compensated and acute decompensated HF, providing the rationale for further testing. During the last part of the protocol, investigators were aware of the diagnostic information that might have interfered with the clinical course of the patients. However, we observed a relatively large number of major and minor events, reflecting appropriate recruitment of patients at risk for HF decompensation. In addition, the investigators did not have remote access to patient data and were, therefore, unable to spot a trend of unfavorable changes in either RV pressure or impedance. Finally, no differences in absolute change, trends in cardiac pressures, and impedance could be noted between those occurring in the blinded phase versus those occurring in the unblinded phase.

Conclusions
This observational study demonstrates that both ePAD and intrathoracic impedance are correlated and that changes in either parameter precede imminent HF episodes. Whether patient management strategies that incorporate device-based hemodynamic sensors have a beneficial impact on morbidity and mortality outcomes and whether the diagnostic accuracy of proactive fluid detection can be increased by a combined use of impedance and RV pressure monitoring remain to be investigated in large clinical randomized trials.

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Disclosures
Dr. Braunschweig received research funding from Medtronic and St Jude Medical. He is a consultant to Medtronic and Boston Scientific and has received speaker honoraria from different pacemaker manufacturers. Dr. Kessels, Mr. Houben, and Mr. Reiters are employees of Medtronic.

References


**CLINICAL PERSPECTIVE**

This study prospectively compared intrathoracic impedance and continuous right ventricular pressure measurements in patients with heart failure. It demonstrated that decompensated heart failure develops based on medium-term hemodynamic derangements and is preceded by significant changes in intrathoracic impedance and right ventricular pressures during the month before a major clinical heart failure event. In general, intrathoracic impedance and pressure changes are moderately correlated, but the correlation increases within the month before a major and minor heart failure event. Whether patient management strategies that incorporate device-based hemodynamic sensors have a beneficial impact on morbidity and mortality outcomes and whether the diagnostic accuracy of proactive fluid detection can be increased by a combined use of impedance and right ventricular pressure monitoring remains to be investigated in large clinical randomized trials.
Continuous Monitoring of Intrathoracic Impedance and Right Ventricular Pressures in Patients With Heart Failure
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