Chronic Ambulatory Intracardiac Pressures and Future Heart Failure Events

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Background—Intracardiac pressures in heart failure (HF) have been measured in patients while supine in the hospital but change at home with posture and activity. The optimal level of chronic ambulatory pressure is unknown. This analysis compared chronic intracardiac pressures to later HF events and sought a threshold above which higher pressures conferred worse outcomes.

Methods and Results—Median pressures were measured every 24 hours from continuous 8-minute segments for 6 months after implantation of hemodynamic monitors in 261 patients with New York Heart Association class III-IV HF in the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure Study. Baseline and chronic daily medians of estimated pulmonary artery diastolic, right ventricular systolic, and right ventricular end-diastolic pressures were compared with HF event rate. The group median for chronic 24-hour estimated pulmonary artery diastolic pressure was 28 mm Hg (excluding 7 days before and after events). Despite weight-guided management, events occurred in 100 of 261 (38%) patients. Event risk increased progressively with higher chronic 24-hour estimated pulmonary artery diastolic pressure, from 20% at 18 mm Hg to 34% at 25 mm Hg and 56% at 30 mm Hg, with similar relations for right ventricular pressures. Among patients with baseline day median estimated pulmonary artery diastolic pressures of ≥25 mm Hg, event risk was 1.10/6 mo when they remained chronically ≥25 mm Hg, but risk fell to 0.47 when 24-hour pressures declined to <25 mm Hg for more than half of the days.

Conclusions—Despite current management, many patients with advanced HF live on a plateau of high filling pressures from which later events occur. This risk is progressively higher with higher chronic ambulatory pressures. It is not known whether more targeted intervention could maintain lower chronic ambulatory pressures and better outcomes. (Circ Heart Fail. 2010;3:580-587.)

Key Words: cardiomyopathy ■ heart failure ■ hemodynamics ■ monitoring

Elevated intracardiac filling pressures contribute to the typical symptoms and signs of heart failure (HF). Successful therapy for HF treats the causes of myocardial injury, inhibits activity of the renin-angiotensin-aldosterone and sympathetic nervous systems, and maintains fluid balance through surveillance and intervention for changes in volume status.1 HF hospitalizations and deaths are predicted by multiple parameters that reflect elevated filling pressures, such as invasively measured pulmonary artery wedge and right atrial pressures, natriuretic peptide levels, and estimated jugular venous pressures.2-4 These pressures and their noninvasive correlates are assessed at 1 point in time, usually at rest. However, filling pressures are dynamic, changing with upright posture, daily activity, oral intake, and medications. Pressures that do not cause symptoms at rest may become dramatically elevated with exercise or other stressors.5 On the other hand, reduction of filling pressures to a goal that seems optimal during supine rest may compromise perfusion of kidneys and other organs during upright posture or activity. The optimal level of chronic 24-hour pressures during the usual day out of the hospital is unknown.

Clinical Perspective on p 587

Recent information from implanted, chronic ambulatory monitoring devices has clarified that HF events (HFEs) are generally preceded by elevations in 24-hour filling pressures, which return to baseline after acute therapy.6 These episodic events may be driven by unpredictable external factors and/or by insidious daily increments of volume retention. Outside the window of the
acute event, the relation between chronic 24-hour pressures and future HFEs remains a fundamental unanswered question.

We hypothesized that patients who maintain lower continuous ambulatory filling pressures during clinical stability would be at lower risk of progression to HFEs. We also sought to identify a threshold of 24-hour median filling pressure below which a further decrease in risk was no longer apparent.

Methods

Population

The population and methods used for collection of chronic ambulatory intracardiac pressures have been previously reported in the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure Study (COMPASS-HF). Patients were eligible regardless of left ventricular ejection fraction (LVEF), with New York Heart Association functional class III or IV symptoms while receiving optimal standard medical therapy in centers specifically selected for active HF management programs. Patients had at least 1 HF-related event during the 6 months before enrollment. Standard baseline measurements included estimated glomerular filtration rate according to the modification of diet in renal disease equation.

Monitoring

The implantable hemodynamic monitoring system (Chronicle models 9520 and 9520B; Medtronic, Inc, Minneapolis, Minn) has been described elsewhere.5,7,8 The monitor continuously measures and stores heart rate and physical activity level, right ventricular (RV) systolic pressure (RVSP), RV end-diastolic pressures (RVEDP), and an estimated pulmonary artery diastolic pressure (ePAD), previously validated as a reliable estimate of pulmonary capillary wedge pressure and left ventricular diastolic pressure (LVSP). These measurements were transmitted to a central server once a preset storage interval, typically 8 minutes. The daily median of each ventricular diastolic pressure8 in the absence of significant intrinsic pulmonary disease (which was an exclusion criterion). The institutional review board of each participating center approved the study protocol, and all patients provided written, informed consent.

Management

All patients transmitted pressure information at least weekly, but only half were randomized to have this information available to their physicians during the first 6 months ("open access"). For these patients, clinicians reviewed hemodynamic information at least weekly to determine volume status. The goal was to maintain an "optivoletic" state for each patient, which was left for each clinician to define. Most attention for this determination was directed toward the nightly minimum ePADs and RVEDPs at rest without activity, pressures that were assumed to be similar to the familiar resting pulmonary capillary wedge and right atrial pressures in supine patients in the hospital.9 The focus was on the detection of increases in pressures over time. For patients randomized to blinded access, pressure information was transmitted to a central server but was not available to clinicians.

Patients were asked to chart daily weights and to document and respond to weight changes. To ensure comparable frequency of contact between study nursing staff and patients in each arm of the study, predetermined call schedules were used to contact patients whose hemodynamic information was not open to the investigators.

The primary outcome was as defined for the original trial: all HFEs, defined as unexpected hospitalizations or any Emergency Department or urgent clinic visit requiring intravenous therapy for HF. An independent clinical events review committee adjudicated the HFEs.

Analysis of Pressures

The implantable hemodynamic monitoring system measured intracardiac pressures beat by beat and determined a median of all samples over a preset storage interval, typically ~8 minutes. The daily median of each measured pressure parameter was determined as the median of the 180 8-minute storage intervals during the 24 hours (midnight to midnight). Data from hemodynamic monitoring were analyzed in cooperation with engineering and statistical staff at Medtronic, Inc. Investigators had full access to all data and directed all analyses.

Baseline pressures were calculated on the eighth day after implant, to allow 1 week for clinical stabilization after the implant procedure. Patients were required to have a minimum of 1 month of data to be included, but events occurring within the first week were not included.

Statistical Analyses

Pressures were compared between patients with HFEs and patients without HFEs during 3 time periods for each patient: (1) baseline day median of 24 hours of recorded pressures; (2) chronic 24-hour pressures as the average of the daily medians collected from baseline until 6 months (for patients with HFEs, 6-month data excluded the 7 days before and after events); (3) in patients with events, the pre-event pressures included only those pressures up to 7 days before the first event, which occurred at a median of 78 days. These “pre-event pressures” were compared with pressures during the first 78 days in patients without events.

Patients with and without HFEs were compared for baseline characteristics and for intracardiac pressure data during the defined time periods by using the appropriate unpaired t tests, Wilcoxon rank-sum test, or Fisher’s exact test. The average of the chronic 24-hour pressures (pre-event or 78 days), excluding 7 days before an event, was used in estimating risk of an HFE by applying a Cox proportional-hazards regression model from first events and with the dichotomous variable of chronic 24-hour ePAD pressure above or <25 mm Hg. Survival curves were constructed according to the Kaplan-Meier method. The value of 25 mm Hg was selected because it was the mean chronic 24-hour ePAD in patients without events and a common clinical integer. Both the Cox model and the log-rank test were used to compare the freedom from HFEs for the 2 groups. The model assumptions of the Cox regression model were investigated, and it was concluded that assumptions of noninformative censoring and of proportional hazards were reasonable.

The Cox analyses were done both with unadjusted models and with models adjusted for covariates. For adjusted analyses, univariate Cox regression models were used to determine which covariates were significantly related to risk of HFE; those significant at a 0.05 level were included, 6-minute hall walk distance, therapy with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, estimated glomerular filtration rate, ischemic heart disease, quality of life score, atrial fibrillation, and QRS duration. These covariates were then included in a multivariate Cox regression model to compare the risk of events for the 2 ePAD groups.

The risk of HFE was also compared for events over a continuous range of ePAD levels that occurred in the study. A Cox regression model with ePAD modeled as a smoothing spline function9 was used to test for linear and nonlinear components of the relation between ePAD and risk of an HFE, as the relation was anticipated to be more likely an "S" shape than linear throughout the range. This analysis over the continuous range was also repeated in the multivariate Cox regression model after adjusting for significant covariates, as described earlier.

Among patients whose baseline day median pressures were initially low (ePAD <25 mm Hg), event rates were compared between those whose daily median pressures remained low during follow-up (>50% of their days) and those whose pressures increased during follow-up such that >50% of their daily median ePAD values were ≥25 mm Hg. Similar analysis of event rates was done for those patients with initially high baseline day median pressures (ePAD ≥25 mm Hg). Differences in these event rates were compared with a negative binomial regression model. All probability values are 2 sided and nominal.

Results

A hemodynamic monitor was implanted in and transmissions were received from 274 patients, 261 of whom had a least 1 month of hemodynamic data for this analysis. Mean age was 58 years, and LVEF was <50% in 194 patients and ≥50% in 67 patients (Table 1). The average duration of HF was >5 years, and the average number of HFEs in the 6 months before enrollment was 1.9 ± 1.2. Three patients exited the study early: 1 was lost to follow-up after 3 months, 1 moved away at 5 months, and 1 withdrew consent at 3 months. All had stable clinical...
Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (N=261)</th>
<th>Patients With Events (n=100)</th>
<th>Patients Without Events (n=161)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No.</td>
<td>66</td>
<td>68</td>
<td>65</td>
<td>0.59</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>58±13</td>
<td>59±13</td>
<td>57±14</td>
<td>0.20</td>
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<tr>
<td>White, %</td>
<td>76</td>
<td>78</td>
<td>75</td>
<td>0.66</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>55</td>
<td>67</td>
<td>47</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF &lt;50, %</td>
<td>74</td>
<td>76</td>
<td>73</td>
<td>0.66</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>56±24</td>
<td>53±25</td>
<td>59±23</td>
<td>0.065</td>
</tr>
<tr>
<td>6-minute walk, m</td>
<td>236±120</td>
<td>208±120</td>
<td>252±118</td>
<td>0.005</td>
</tr>
<tr>
<td>Years with heart failure</td>
<td>5.5±5.1</td>
<td>5.6±4.8</td>
<td>5.5±5.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Hospitalization/ED for HF in prior 6 mo</td>
<td>1.9±1.2</td>
<td>2.1±1.4</td>
<td>1.7±1.1</td>
<td>0.035</td>
</tr>
<tr>
<td>MLHF score</td>
<td>84</td>
<td>75</td>
<td>89</td>
<td>0.003</td>
</tr>
<tr>
<td>ACEI/ARB use, %</td>
<td>82</td>
<td>77</td>
<td>85</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* eGFR indicates estimated glomerular filtration rate; ED, Emergency Department visits; MLHF, Minnesota Living with Heart Failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. Other abbreviations are as defined in text.

status at the time of withdrawal. Patients transmitted their intracardiac pressure data, on average, 2 times weekly. During the 6-month follow-up period, there was an average of 1 clinical contact weekly for patients in both open- (n=127) and blinded- (n=134) access groups.

During the 6 months, 100 patients (38%) had 191 HFEs, and 161 patients (62%) were event-free. The median time to first event was 78 days after implantation. Hospitalizations accounted for 87% of the total HFEs; the other 13% were Emergency Department visits or urgent visits during which intravenous therapy was administered. Of the total HFEs, 175 were adjudicated as volume-overload events and the other 16 were volume-depletion events, 14 of which followed treatment for volume-overload events.

### Chronic 24-Hour Pressures and Event Risk

The average of the chronic 24-hour ePAD during the 6 months was 28±7 mm Hg. The distribution of chronic 24 hour pre-event ePADs was shifted to the higher pressures for patients with events (Figure 1), which occurred at a median of 78 days. Patients who were event-free had a lower average chronic 24-hour ePAD (P<0.001) during a similar period (Table 2). Using the entire 6-month period (excluding the 7 days before and 7 days after events) showed similar differences between the patients with and without events (Table 2). Parallel differences between patients with events and those without events were similarly significant for chronic 24-hour RVEDPs (16±7 vs 12±4 mm Hg, P<0.001) and chronic 24-hour RVSPs (55±16 vs 45±13 mm Hg, P<0.001; Table 2).

The time course of freedom from HFEs is shown in Figure 2 for patients with chronic 24-hour ePAD ≥25 versus <25 mm Hg (the average ePAD in those patients who did not have an HFE). The relative risk of an HFE during the 6-month period was significantly lower in patients with a chronic ePAD <25 mm Hg compared with ≥25 mm Hg (hazard ratio=0.29; 95% CI, 0.19 to 0.48; P<0.001). When adjusted for covariates, the ePAD group was still strongly related to the risk of HFE (hazard ratio=0.32; 95% CI, 0.19 to 0.53; P<0.0001). A log-rank test provided the same result (P<0.001).

Figure 3 provides evidence of the changing risk of an HFE over the spectrum of ePAD levels seen, as opposed to a specific threshold. As the slope of the smoothing spline function illustrates, there is a consistent and monotonic increase in the risk of HFE with higher chronic ePAD. The linear component is highly significant (P<0.001). When adjusted for covariates, the curve has the same shape and significance. There is a trend for significance of the “S”-shaped nonlinear component (P=0.11), which was slightly greater in the adjusted analysis (P=0.07) but limited by the paucity of data at the tapering ends of the curve. The probability of an HFE was progressively higher with higher chronic daily ePAD. (For patients with HFEs, this analysis excludes the 7 days before clinical HFEs, because these have been shown to have higher pressures.6) For example, the absolute risk of an HFE was 20% with a chronic ePAD of 25 mm Hg compared with 45±13 mm Hg, P<0.001; Table 2).

![Figure 1. Distribution of average 24-hour chronic daily ePAD for 261 patients, for 100 patients in whom clinical HFEs did occur (open bars) and for 161 patients in whom HFEs did not occur (closed bars). These pressures were obtained from baseline until 7 days before HFEs for patients with events (which occurred at a median of 78 days) and from baseline through 78 days for patients without events.](http://circheartfailure.ahajournals.org)
Table 2. Continuous Monitoring Results in Relation to Heart Failure Events

<table>
<thead>
<tr>
<th></th>
<th>All (N=261)</th>
<th>Patients With Events (n=100)</th>
<th>Patients Without Events (n=161)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline day median (24 h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>79±13</td>
<td>78±13</td>
<td>80±13</td>
<td>0.36</td>
</tr>
<tr>
<td>Activity, counts</td>
<td>1.0±0.8</td>
<td>0.9±0.6</td>
<td>1.1±0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>49±16</td>
<td>53±16</td>
<td>46±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ePAD, mm Hg</td>
<td>28±9</td>
<td>30±9</td>
<td>26±9</td>
<td>0.001</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>14±7</td>
<td>16±7</td>
<td>13±7</td>
<td>0.002</td>
</tr>
<tr>
<td>+dP/dt(_{max}), mm Hg/s</td>
<td>404±140</td>
<td>410±152</td>
<td>400±133</td>
<td>0.59</td>
</tr>
<tr>
<td>−dP/dt(_{max}), mm Hg/s</td>
<td>−388±135</td>
<td>−412±149</td>
<td>−373±124</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic pre-event 24-h measurements*†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>79±12</td>
<td>79±12</td>
<td>79±12</td>
<td>0.81</td>
</tr>
<tr>
<td>Activity, counts</td>
<td>1.1±0.7</td>
<td>0.9±0.6</td>
<td>1.1±0.8</td>
<td>0.012</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>49±15</td>
<td>55±16</td>
<td>45±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ePAD, mm Hg</td>
<td>27±7</td>
<td>30±8</td>
<td>25±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>14±6</td>
<td>16±7</td>
<td>12±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+dP/dt(_{max}), mm Hg/s</td>
<td>408±128</td>
<td>420±153</td>
<td>402±111</td>
<td>0.33</td>
</tr>
<tr>
<td>−dP/dt(_{max}), mm Hg/s</td>
<td>−390±139</td>
<td>−428±162</td>
<td>−368±119</td>
<td>0.003</td>
</tr>
<tr>
<td>Chronic 24-h measurements (6 mo)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78±11</td>
<td>78±11</td>
<td>78±12</td>
<td>0.96</td>
</tr>
<tr>
<td>Activity, counts</td>
<td>1.0±0.7</td>
<td>0.9±0.6</td>
<td>1.2±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>49±15</td>
<td>55±15</td>
<td>45±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ePAD, mm Hg</td>
<td>28±7</td>
<td>31±8</td>
<td>26±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVDP, mm Hg</td>
<td>14±6</td>
<td>17±7</td>
<td>13±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+dP/dt(_{max}), mm Hg/s</td>
<td>405±131</td>
<td>422±167</td>
<td>394±102</td>
<td>0.13</td>
</tr>
<tr>
<td>−dP/dt(_{max}), mm Hg/s</td>
<td>−386±134</td>
<td>−422±151</td>
<td>−363±117</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*Chronic pre-event pressures exclude the 7 days before the event in patients with events.
†Chronic “pre-event” pressures for comparison include 78 days in patients without events, selected because the median time to first event was 78 days.
‡Chronic pressures for the entire 6-month period exclude the 7 days before and 7 days after the event in patients with events.

18 mm Hg, 34% with a chronic ePAD of 25 mm Hg, and 56% with a chronic ePAD of 30 mm Hg. This relation between chronic filling pressures and events was similar for RVEDP (Figure 4A) and RVSP (Figure 4B). When chronic RVEDP increased from 10 to 22 mm Hg, the probability of an event changed from 27% to 80%. All results were similar whether the pre-event comparison interval or the chronic daily pressures from the entire 6-month monitored period (excluding 7 days before and 7 days after events) were analyzed.

For the entire population, patients with events had a higher prevalence of coronary artery disease, more previous HFEs, shorter 6-minute walk distance, lower use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and worse Minnesota Living With Heart Failure scores at baseline (Table 1). Comparisons were then made for patients with and without events in each of the 2 subgroups defined by chronic ePAD <25 mm Hg and ≥25 mm Hg. Among the patients with chronically higher ePAD, 80 (51%) patients had events; these patients with events had more coronary disease and a shorter 6-minute walk distance than those with chronically higher ePAD and no events. Among patients with chronically lower ePAD, only 19% of patients had events; these patients also had more coronary disease and a shorter 6-minute walk distance compared with patients with chronically low pressures and no events. However, those with events despite a low chronic ePAD had worse renal function compared with those with chronic low pressures and no events (estimated glomerular filtration rate=45±17 vs 57±22 mL/min, P=0.018) and also compared with patients with a chronically high ePAD who had events (estimated glomerular filtration rate=55±26 mL/min, P=0.056).

Baseline Day Median and Chronic 24-Hour Pressures

The relation between chronic 24-hour pressures and events during the 6-month period includes important separate contributions of the baseline day median of 24 hours of measurements and of the level of chronic 24-hour pressures experienced for the rest of the study. The baseline day median pressures were higher in patients with later events than in patients without events (Table 2). Activity levels on the baseline day were also lower (Table 2). Patients were grouped according to ePAD <25 mm Hg or ≥25 mm Hg during this baseline 24-hour period and subsequently. For those patients whose baseline day median ePAD was ≥25 mm Hg, the HFE rate during the next 6 months was 1.02. For patients with a baseline day median ePAD
<25 mm Hg, the event rate during the next 6 months was significantly lower (0.42, \(P<0.001\)).

Patients were then also grouped according to whether they spent >50% of the days after baseline with daily medians <25 mm Hg or \(\geq 25\) mm Hg. Overall, most patients maintained daily median pressures similar to those initially measured. This lack of change reflects the emphasis during the COMPASS-HF trial of detecting and responding to changes in volume status, as demonstrated by changes in weight or symptoms for both groups, and changes in intracardiac pressures for the group randomized to open access to monitored information. However, 44 patients did switch from their baseline group to spend >50% of their days with daily median pressures on the opposite side of 25 mm Hg from their baseline (Figure 5). Of the 44 who changed, 25 patients with a baseline day median ePAD <25 mm Hg experienced an increase to \(\geq 25\) mm Hg for the majority of their days. The HFE rate for patients who changed from this low baseline to high chronic ePAD was 1.10 during 6 months compared with the rate of 0.23 for patients who remained at <25 mm Hg (\(P<0.001\)). Patients who switched from a low baseline to a chronically high pressure had the same event rate as those whose initial pressures were \(\geq 25\) mm Hg and

Figure 2. Kaplan-Meier plots of survival free from HFEs for patients grouped by chronic 24-hour ePAD <25 mm Hg or \(\geq 25\) mm Hg up to 7 days before event for those with events. The plots and hazard ratio represent unadjusted Cox analysis, but analysis done with adjustment for covariates yielded a similar hazard ratio of 0.32 (\(P<0.0001\)).

Figure 3. Probability of an HFE for 261 patients during a 6-month period in relation to chronic daily ePAD. The vertical dashes on the x axis indicate the median chronic 24-hour pressures in individual patients, excluding pressures obtained from the 7 days before events. To provide a comparable sampling interval for patients without events, the pressures were included for the first 78 days (the median period from enrollment to event in patients with events). The relations were the same when the entire 6-month period was analyzed. The y axis was converted from a log hazard ratio to probability of an HFE in 6 months, based on the event rate observed in this study. The plot represents an unadjusted relation, but the relation was equivalent in a model adjusted for covariates.
remained at ≥25 mm Hg (Figure 5). Conversely, 19 patients had a high baseline day median ePAD that decreased to <25 mm Hg for >50% of days. The HFE event rate in this group was only 0.47 HFE/6 mo (P = 0.042, compared with 1.10 for patients who remained at chronically high pressure). The lowest event rate was 0.23 HFE/6 mo in those patients who began with and remained at, for a majority of days, a median ePAD <25 mm Hg (Figure 5).

**Patient Subgroups**

The trial by design studied HF with both low and preserved LVEF. This analysis included 194 patients with a baseline LVEF <50% and 67 patients with an LVEF ≥50%. The continuous relation between risk of HFE and chronic 24-hour ePAD was observed for patients in both low and preserved LVEF groups. In addition, there was no independent effect of randomization to open-access or blinded-access groups on the relation between chronic ePAD and risk of HFE, although there were fewer events in the open-access group (81 vs 110).

**Discussion**

This study reveals that the level of ambulatory filling pressure with which patients live chronically is associated strongly with their rate of future HFEs. The likelihood of an HFE is progressively higher with higher ambulatory chronic filling pressures, without an apparent threshold once the daily median ePAD is ≥18 mm Hg. Similar relations were observed for RVEDP and RVSP. However, this risk became lower in patients who started with high baseline pressures and subsequently moved to a lower plateau of chronic filling pressures.

Prognosis in HF has been linked to multiple hemodynamic measures of filling pressure, including pulmonary capillary wedge pressure, right atrial pressure, and pulmonary artery systolic pressure, all measured during supine rest. Echocardiographic measures of inflow patterns and mitral and tricuspid regurgitation often reflect elevated ventricular filling pressures and predict worse outcomes. These previous assessments have all been made during supine rest at 1 point in time.

The ability to monitor continuous ambulatory filling pressures provides a new window into daily life with chronic HF. The 24-hour ambulatory record captures pressures during all phases of daily living at rest, with exercise, during meals, and while taking medications. For example, previous studies with an implantable monitor showed an increase of 16±6 mm Hg, or a 71% increase, from baseline in ePAD during a 6-minute walk in 21 patients, although the highest pressures occurred briefly during activity other than during formal exercise. These components of daily life integrate into the filling pressures measured during the entire 24-hour period, for which optimal levels have not previously been described.

This study establishes the importance of both the chronic plateau levels and the superimposed rising of ambulatory filling pressures. The role of rising pressures has recently been demonstrated: filling pressures rose an average 12% over baseline during periods of HFEs, whereas there was no overall rise during periods without events. Rising filling pressures can reflect triggers of fluid retention, such as sodium intake, viral infection,
or arrhythmias. Although these triggers are unpredictable, they are more likely to lead to events when starting from a higher plateau. Events occurred in 51% of patients with high chronic pressures. Among patients with lower chronic daily pressures, events occurred in only 19% of patients, in whom renal function was significantly worse than in patients with low pressures and no events or in patients who had events from higher chronic filling pressures.

The congruence of the risk curves for chronic right- and left-sided filling pressures is not surprising, as 75% to 80% of patients with chronic HF have shown a concordance of right- and left-sided filling pressure elevations.13 The RVSPs measured during 24 hours reflect additional factors of intrinsic right ventricular function and afterload.9 However, this study was not sized to compare chronic RVEDP, RVSP, and pulmonary artery diastolic pressures either as predictors of events or targets of intervention.

Consideration of targets for filling pressures in ambulatory patients has raised concern regarding excessive therapy. The hazard for the whole patient group analyzed in this study did not increase. This is further supported by the low rate of hypovolemic episodes in the COMPASS-HF trial.16 The small number of patients with preserved LVEF and low filling pressures in this study precludes analysis, but previous work suggests that the window for tolerable filling pressures may be narrower in this population.6

Changes Between Baseline 24-Hour Pressures and Chronic Pressures

Continuous ambulatory pressure monitoring can integrate a single 24-hour day at home and then provide ongoing trends over time. During the COMPASS trial, the emphasis was on intervention for changes in volume status. Because most patients had recently undergone adjustment of therapy in the hospital, baseline pressures at enrollment were assumed to be “reasonable” as long as symptoms were stable.7 Thus, most patients spent most of their time on a plateau of high chronic filling pressures similar to that on the baseline day. Although this can now be associated in hindsight with a higher risk of events, there were no target levels established for chronic 24-hour ambulatory pressures at the time of the COMPASS-HF trial.

However, chronic ambulatory pressures did change from baseline in some patients, and the event risks for these patients also changed. Specifically, patients who began with a 24-hour ePAD ≥25 mm Hg but then reached a lower plateau had only half the rate of HFEs as those patients whose pressures stayed high (Figure 5). Similarly, patients who started at a lower baseline ePAD but subsequently experienced a chronically higher ePAD during follow-up experienced a higher HFE rate than predicted by the baseline 24-hour pressures.

The ability to progress to a better risk stratum if lower filling pressures can be achieved has been shown in the short term after aggressive monitored therapy in hospital2 and for freedom from clinical congestion assessed in outpatients at 1 month.17 This may in part be related to the effective reduction of mitral regurgitation.18 This study provides the first evidence that a reduction in chronic risk can be detected at home during ambulatory monitoring. The level of ambulatory filling pressures where patients spent the majority of days revised the risk conferred by the pressures on their baseline day.

Limitations

This study focused on patients with class III-IV HF after recent hospitalization and was neither wholly a “natural history” study nor a study of intervention. Therapy during this study was guided by the general principle of treating evidence of increasing filling pressures. Because the trial design emphasized responses to monitored changes, patients tended to remain with daily median pressures close to those with which they began until events occurred. When adjustments were made, they were usually on the basis of minimum values measured during supine rest at night, which resulted in chronic 24-hour pressures now seen in retrospect to have been too high.

The extensive and unique data collected during this study can be analyzed in many ways. The overlap in chronic pressures between patients with and without events indicates the challenge of identifying which patients will develop the rising pressures that lead to events. The challenges of analysis are further confounded by the overlap between the chronic filling pressure elevations that contribute to ongoing risk, the smaller incremental pressure increases that constitute the event itself, and the decreases during acute therapy. We addressed this by excluding the 7 days before and after an event. Within this relatively small population, it is not possible to test how chronic filling pressures integrated over time should be scored in combination with standard baseline risk factors for events. The complexity of factors, both intrinsic and extrinsic, that contributes to ePAD changes over time prevented construction of a relevant longitudinal model to take into account baseline and changing ePAD values. This study was not intended to determine which pressure parameter (ePAD, RVEDP, or RVSP) would be most useful to detect an important change in time to prevent a developing HFE.

Implications for Chronic HF Management

This study of chronic 24-hour filling pressures suggests that high chronic ambulatory filling pressures may merit more intense intervention, even in patients who appear to be clinically stable or improved after recent hospitalization. For patients staying or moving early to a plateau of lower filling pressures, the subsequent risk of events was low.

The possibility remains that those patients who have near-normal levels of intracardiac filling pressures and those who can be brought down to near-normal levels are intrinsically different from patients with persistently higher ambulatory filling pressures. For individual patients chronically on a high plateau of filling pressures, neither the optimal level of filling pressure nor the surveillance necessary to avoid events has been established. However, this demonstration of the risk associated with chronically elevated filling pressures may stimulate more intensive intervention and surveillance in the hope of decreasing the frequency of HFEs.

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**CLINICAL PERSPECTIVE**
Intracardiac pressures in heart failure (HF) measured in the supine position at 1 time have long been known to predict outcomes after discharge. Out of the hospital, filling pressures vary during the day with posture, activity, meals, and medications. The optimal level of chronic ambulatory pressures is unknown. This analysis linked HF events to information obtained from weekly transmission of chronic ambulatory hemodynamic monitoring in 261 patients with New York Heart Association class III–IV HF with both low and preserved ejection fraction. Continuous measurement included estimated pulmonary artery diastolic (ePAD) pressures and right ventricular pressures during 6 months of management at experienced HF centers. The 24-hour chronic ePAD was 28±7 mm Hg (excluding pressures within 7 days before and after events). The risk of HF events during 6 months was progressively higher as chronic 24-hour ePAD exceeded 18 mm Hg, for which risk was 20%, compared with 34% at an ePAD of 25 mm Hg and 56% at an ePAD of 30 mm Hg. Patients who started with a 24-hour ePAD ≥25 mm Hg but then experienced lower pressures also transitioned to a lower risk of future events. Patients with HF can be envisioned to live on a plateau of filling pressures from which further rises lead to events. Despite current management, many HF patients live on a plateau that is too high. Even when they appear to be clinically stable, these patients may benefit from more intensive therapy to lower filling ambulatory filling pressures. However, it is not known whether more targeted intervention could maintain lower chronic ambulatory pressures and improve outcomes.