Chronic Ambulatory Intracardiac Pressures and Future Heart Failure Events

Running Title: Daily Pressures and Heart Failure Events

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ABSTRACT

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

Methods and Results: Median pressures were measured each 24 hours from continuous 8-minute segments for 6 months after implantation of hemodynamic monitors in 261 Class III-IV HF patients in COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure Study). Baseline and chronic daily medians of estimated pulmonary artery diastolic (ePAD), right-ventricular systolic and end-diastolic pressures were compared to HF event rate. The group median for chronic 24-hour ePAD was 28 mmHg (excluding 7 days before and after events). Despite weight-guided management, events occurred in 100/261 (38%) patients. Event risk increased progressively with higher chronic 24 hour ePAD, from 20% at 18 mmHg to 34% at 25 mmHg and 56% at 30 mmHg, with similar relationships for right ventricular pressures. Among patients with baseline day median ePAD ≥ 25mmHg, event risk was 1.10/6 mos if they remained chronically ≥ 25, but risk fell to 0.47 when 24-hour pressures declined to < 25 mmHg for more than half of 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 if more targeted intervention could maintain lower chronic ambulatory pressures and better outcomes.

Key Words: cardiomyopathy, heart failure, hemodynamics, monitoring
INTRODUCTION

Elevated intracardiac filling pressures contribute to the typical symptoms and signs of heart failure. Successful therapy for heart failure 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) Heart failure hospitalizations and death 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 non-invasive correlates are assessed at one 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 elevate dramatically 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 not known.

Recent information from implanted chronic ambulatory monitoring devices has clarified that heart failure events 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 relationship between chronic 24-hour pressures and future heart failure events 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 heart failure events.
We also sought to identify a threshold of 24-hour median filling pressure below which 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 COMPASS-HF trial. (7) Patients were eligible regardless of left ventricular ejection fraction, 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 one HF-related event during the 6 months prior to enrollment. Standard baseline measurements included estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease equation.

Monitoring

The implantable hemodynamic monitoring system (*Chronicle®, Models 9520, 9520B; Medtronic, Inc., Minneapolis) has been described elsewhere (5,7,8). The monitor continuously measured and stored heart rate and physical activity level, right ventricular (RV) systolic pressure (RVSP), RV diastolic pressures (RVDP), an estimated pulmonary artery diastolic pressure (ePAD), previously validated as a reliable estimate of pulmonary capillary wedge pressure and LV diastolic pressure (8) 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 “optivolemic” state for each patient, which was left for each clinician to define. Most attention for this determination was directed toward the nightly minimum ePAD and RVDP pressures at rest without activity, pressures which were assumed to be similar to the familiar resting pulmonary capillary wedge and right atrial pressures in supine patients in the hospital. The focus was on detection of increases in pressures over time. For patients randomized to blinded access, pressure information was transmitted to a central server but 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, pre-determined 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 heart failure events (HFE), defined as unexpected hospitalizations, or any emergency department or urgent clinic visit requiring intravenous therapy for heart failure. An independent Clinical Events Review Committee adjudicated the HFE.

**Analysis of Pressures**

The implantable hemodynamic monitoring system measured intracardiac pressures beat-by-beat and determined a median of all samples over a pre-set storage interval, typically about 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 the
hemodynamic monitoring data was 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 one week for clinical stabilization after the implant procedure. Patients were required to have a minimum of 1 month of data to be included and events occurring within the first week were not included.

Statistical Analyses

Pressures were compared between patients with heart failure events and patients without heart failure events 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 events, 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 prior to the first event, which occurred at a median of 78 days. These “pre-event pressures” were compared to pressures during the first 78 days in patients without events.

Patients with and without heart failure events were compared for baseline characteristics and for intracardiac pressure data during the defined time periods, 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, were used in estimating risk of HFE by applying a Cox proportional hazard regression model, using first events, with the dichotomous variable of chronic 24-hour ePAD pressure above or below 25 mmHg. Survival curves were constructed according to the Kaplan-Meier method. The value of 25 mmHg 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 HFE for the 2 groups. The model assumptions of the Cox regression model were investigated and it was concluded that that assumptions of non-informative 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 rales, 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 to events over a continuous range of ePAD levels that occurred in the study. A Cox regression model with ePAD modeled as a smoothing spline function (9), was used to test for linear and non-linear components of the relationship between ePAD and risk of a HFE, as the relationship was anticipated to be more likely an “S” shape than linear throughout the range. This analysis over the continuous range was also repeated using the multivariate Cox regression model after adjusting for significant covariates, as described above.

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

A hemodynamic monitor was implanted and transmissions received from 274 patients, 261 of whom had a least one month of hemodynamic data for this analysis. Mean age was 58 years, left ventricular ejection fraction was < 50% in 194 patients and ≥ 50% in 67 patients (Table 1). The average duration of heart failure was over 5 years, and the average number of heart failure events in the 6 months prior to enrollment was 1.9± 1.2. Three patients exited the study early: 1 lost to follow up after 3 months, 1 moving away at 5 months, and one withdrawing consent at 3 months. All had stable clinical status at the time of withdrawal.

Patients transmitted their intracardiac pressure data, on average, two 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 access groups (n=134).

During the 6 months, 100 patients (38%) had 191 heart failure events, 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 HF events, the other 13% were emergency department visits or urgent visits during which intravenous therapy was administered. Of the total HF events, 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 pressures during the 6 months was 28 ± 7 mmHg. The distribution of chronic 24 hour pre-event ePAD pressures was shifted to the higher pressures for patients with events (Figure 1), which occurred at a median 78 days. Patients who were event-free had a lower average chronic 24-hour ePAD pressure (p<0.001) during the similar period (Table 2). Using the entire 6 month period (excluding the 7 days before and 7
days after events) showed similar difference between the patients with and without events (Table 2). Parallel differences between patients with events and patients without events were similarly significant for chronic 24-hour RV diastolic pressures (16 ± 7 versus 12 ± 4 mmHg, p < 0.001) and chronic 24-hour RV systolic pressures (55 ± 16 vs 45 ± 13 mmHg, p < 0.001) (Table 2).

The time course of freedom from HF events is shown in Figure 2 for patients with chronic 24-hour ePAD greater than vs less than 25 mmHg (the average ePAD pressure in those patients who did not have HFE). The relative risk of a HFE during the 6 month period was significantly lower in patients with chronic ePAD less than 25 mmHg compared to ≥ 25 mmHg (hazard ratio 0.29 (0.18 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 (0.19 to 0.53, p < 0.0001). Using a log-rank test provided the same result (p< 0.001).

Figure 3 provides evidence of the changing risk of 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 non-linear component (p=0.11) which was slightly greater in the adjusted analysis (p=0.07), limited by the paucity of data at the tapering ends of the curve. The probability of a heart failure event was progressively higher with higher chronic daily ePAD pressures. (For patients with events, this analysis excludes the 7 days prior to clinical heart failure events, because these have shown to have higher pressures(6).) For example, the absolute risk of HFE was 20% with chronic ePAD 18 mmHg, 34% with chronic ePAD 25 mmHg, and 56% with chronic ePAD 30 mmHg. This relationship between chronic filling pressures and events was similar for RVEDP.
(Figure 4A) and RVSP (Figure 4B). With chronic RVDP increased from 10 to 22 mmHg, the probability of an event changed from 27% to 80%. All results were similar whether analyzing 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).

For the entire population, patients with events had higher prevalence of coronary artery disease, more previous HF events, shorter 6 minute walk distance, lower use of ACEI/ARB, and worse MLHF scores at baseline (Table 1). Comparisons were then made for patients with and without events in each of the 2 groups defined by chronic ePAD < 25 mmHg and ≥ 25 mmHg. Among the patients with chronic higher ePAD, 80 (51%) patients had events; these patients with events had more coronary disease and shorter 6MW distance than those with chronic high pressures and no events. Among patients with chronic lower ePAD, only 19% of patients had events; these patients also had more coronary disease and shorter 6MW walk distance compared to patients with chronic low pressures and no events. However, those with events despite low chronic ePAD had worse renal function compared to those with chronic low pressures and no events (eGFR 45 ± 17 cc/min vs 57 ± 22 cc/min, p=0.018), and also compared to patients with high chronic ePAD who had events (eGFR 55 ± 26 cc/min, p=0.056).

**Baseline Day Median and Chronic 24- Hour Pressures**

The relationship 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 less than or ≥ 25 mmHg during this baseline 24- hour
period and subsequently. For those patients whose baseline day median ePAD was $\geq 25$ mmHg, the HFE rate over the next 6 months was 1.02. For patients with the baseline day median ePAD below 25 mmHg, the event rate over the next 6 months was significantly lower (0.42, p<0.001).

Patients were then grouped additionally according to whether they spent more than 50% of the days after the baseline with daily medians $< 25$ mmHg or $> 25$ mmHg. Overall, most patients maintained daily median pressures similar to those initially measured. This lack of change reflects the emphasis during the COMPASS-HF trial on 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.(6) However, 44 patients did switch from their baseline group to spend more than 50% of their days with daily median pressures on the opposite side of 25 mmHg from their baseline (Figure 5). Of the 44 who changed, 25 patients with a baseline day median ePAD below 25 increased to $\geq 25$ mmHg for the majority of their days. The HFE rate for patients moving from this low baseline to high chronic ePAD was 1.10 during 6 months compared to the rate of 0.23 in patients who remained $< 25$ mmHg (p<0.001). Patients going from baseline low to chronic high had the same event rate as seen in patients who began $\geq 25$ mmHg and remained $\geq 25$ mmHg (Figure 5).

Conversely, 19 patients had high baseline day median ePAD that decreased to below 25 mmHg for $> 50\%$ of days. The HFE event rate in this group was only 0.47 HFE/6 months (p=0.042 compared to 1.10 in patients remaining chronically high). The lowest event rate was 0.23 HFE/6 months in those patients who began and remained for a majority of days with median ePAD $< 25$ mmHg (Figure 5).

**Patient Subgroups**
The trial by design studied heart failure with both low and preserved ejection fraction. This analysis included 194 patients with baseline LVEF < 50% and 67 patients with LVEF ≥ 50%. The continuous relationship between risk of HFE and the chronic 24-hour ePAD was seen 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 relationship between chronic ePAD and risk of HFE, although there were fewer events in the open access group (81 versus 110).

**DISCUSSION**

This study reveals that the level of ambulatory filling pressures with which patients live chronically is associated strongly with their rate of future heart failure events. The likelihood of HFE is progressively higher with higher ambulatory chronic filling pressures, without an apparent threshold once the daily median ePAD is over 18 mmHg. Similar relationships were observed for RVDP 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 heart failure has been linked to multiple hemodynamic measurements of filling pressures, including pulmonary capillary wedge pressure, right atrial pressure, and pulmonary artery systolic pressure(2, 3), 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 (10-14). These previous assessments have all been made during supine rest, at one point in time.

The ability to monitor continuous ambulatory filling pressures provides a new window into daily life with chronic heart failure. The 24 hour ambulatory record captures pressures
during all phases of daily living at rest, with exercise, meals, and medications. For example, previous studies with an implantable monitor showed an increase of 16±6 mmHg or 71% increase from baseline in ePAD during a 6 minute walk in 21 patients, although the highest pressures occurred briefly during activity other than formal exercise.(3, 8) 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 the both the chronic plateau levels and the superimposed rising of ambulatory filling pressures. The role of the rising pressures has recently been demonstrated; filling pressures rose an average 12% over baseline during periods of heart failure events, while there was no overall rise during periods without events (6). Rising filling pressures can reflect triggers of fluid retention, such as sodium intake, viral infection, or arrhythmias. While 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 75-80% of patients with chronic heart failure have shown concordance of right and left-sided filling pressure elevations.(15) The right ventricular systolic pressures measured during 24 hours reflect additional factors of intrinsic right ventricular function and afterload. (5). This study was not sized to compare chronic RVEDP, RVSP, and pulmonary artery diastolic pressures either as predictors or risk or targets of intervention.
The 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 suggest any threshold below which risk of events began to 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. As 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 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. The event risks for these patients changed. Specifically, patients who began with 24 hour ePAD ≥ 25 mmHg but then reached a lower plateau had only half the rate of HFE as seen in those patients whose pressures stayed high (Figure 5). Similarly, patients who started at a lower baseline ePAD but subsequently experienced chronic higher ePAD during follow-up experienced a higher HFE rate than predicted by the baseline 24 hour pressures.
The ability to move to a better risk stratum if lower filling pressures can be achieved has been shown acutely after aggressive monitored therapy in hospital (2) and for freedom from clinical congestion assessed in outpatients at one month. (17). This may in part relate 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 focusing on patients with Class III-IV heart failure after recent hospitalization is 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 response 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 contribute 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 Heart Failure 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, 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 than patients with persistently higher ambulatory filling pressures. For individual patients chronically on a high plateau of filling pressures, neither the optimal level of filling pressures 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 heart failure events.
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References


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>Gender (Male)</td>
<td>66</td>
<td>68</td>
<td>65</td>
<td>0.59</td>
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<tr>
<td>Age</td>
<td>58 ± 13</td>
<td>59 ± 13</td>
<td>57 ± 14</td>
<td>0.20</td>
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<tr>
<td>Caucasian (%)</td>
<td>76</td>
<td>78</td>
<td>75</td>
<td>0.66</td>
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<tr>
<td>Coronary artery disease</td>
<td>55</td>
<td>67</td>
<td>47</td>
<td>0.002</td>
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<td>LVEF &lt; 0.50 (%)</td>
<td>74</td>
<td>76</td>
<td>73</td>
<td>0.66</td>
</tr>
<tr>
<td>eGFR cc/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>HF Hosp/ED prior 6 mos</td>
<td>1.9 ± 1.2</td>
<td>2.1 ± 1.4</td>
<td>1.7 ± 1.1</td>
<td>0.035</td>
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<tr>
<td>MLHF</td>
<td>64 ± 24</td>
<td>69 ± 24</td>
<td>61 ± 24</td>
<td>0.007</td>
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<tr>
<td>ACEI / ARB %</td>
<td>84</td>
<td>75</td>
<td>89</td>
<td>0.003</td>
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<tr>
<td>Beta-blocker %</td>
<td>82</td>
<td>77</td>
<td>85</td>
<td>0.14</td>
</tr>
</tbody>
</table>

ACEI = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

ED = emergency department visits

eGFR = estimated glomerular filtration rate

LVEF = left ventricular ejection fraction

MLHF = Minnesota Living with Heart Failure score
Table 2. Continuous Monitoring Results In Relation to Heart Failure Events

<table>
<thead>
<tr>
<th>Baseline Day Median (24 Hours)</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>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 (mmHg)</td>
<td>49 ± 16</td>
<td>53 ± 16</td>
<td>46 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ePAD (mmHg)</td>
<td>28 ± 9</td>
<td>30 ± 9</td>
<td>26 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>RVDP (mmHg)</td>
<td>14 ± 7</td>
<td>16 ± 7</td>
<td>13 ± 7</td>
<td>0.002</td>
</tr>
<tr>
<td>+ dP/dt max (mmHg/s)</td>
<td>404 ± 140</td>
<td>410 ± 152</td>
<td>400 ± 133</td>
<td>0.59</td>
</tr>
<tr>
<td>- dP/dt max (mmHg/s)</td>
<td>-388 ± 135</td>
<td>-412 ± 149</td>
<td>-373 ± 124</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic 24 Hour Measurements Pre-Event *, **</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 (mmHg)</td>
<td>49 ± 15</td>
<td>55 ± 16</td>
<td>45 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ePAD (mmHg)</td>
<td>27 ± 7</td>
<td>30 ± 8</td>
<td>25 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVDP (mmHg)</td>
<td>14 ± 6</td>
<td>16 ± 7</td>
<td>12 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ dP/dt max (mmHg/s)</td>
<td>408 ± 128</td>
<td>420 ± 153</td>
<td>402 ± 111</td>
<td>0.33</td>
</tr>
<tr>
<td>- dP/dt max (mmHg/s)</td>
<td>-390 ± 139</td>
<td>-428 ± 162</td>
<td>-368 ± 119</td>
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</tr>
<tr>
<td>Chronic 24 Hour Measurements (6-Month) ***</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 (mmHg)</td>
<td>49 ± 15</td>
<td>55 ± 15</td>
<td>45 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ePAD (mmHg)</td>
<td>28 ± 7</td>
<td>31 ± 8</td>
<td>26 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVDP (mmHg)</td>
<td>14 ± 6</td>
<td>17 ± 7</td>
<td>13 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ dP/dt max (mmHg/s)</td>
<td>405 ± 131</td>
<td>422 ± 167</td>
<td>394 ± 102</td>
<td>0.13</td>
</tr>
<tr>
<td>- dP/dt max (mmHg/s)</td>
<td>-386 ± 134</td>
<td>-422 ± 151</td>
<td>-363 ± 117</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Chronic pressures pre-event exclude the 7 days before the event in patients with events.
** Chronic pressures “pre-event” 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.

Data are Mean ± SD.

- ePAD = estimated pulmonary artery diastolic pressure,
- HR = heart rate
- RVDP = right ventricular diastolic pressure
- RVSP = right ventricular systolic pressure
**Figure Legends**

Figure 1. Distribution of average of 24 hour chronic daily estimated pulmonary artery diastolic pressure (ePAD) for 261 patients: 100 patients in whom clinical heart failure events did occur (open bars) and 161 patients in whom they did not occur (closed bars). These pressures were obtained from baseline until 7 days before heart failure events for patients with events (which occurred at a median 78 days), and from baseline through 78 days for patients without events.

Figure 2. Kaplan-Meier plots of survival free from heart failure events for patients grouped by chronic 24 hour estimated pulmonary artery diastolic pressure < 25 mmHg or ≥ 25 mmHg, up to the 7 days prior to event for those with events. The plots and hazard ratio represent unadjusted Cox analysis, but analysis done with adjustment for covariates yielded similar hazard ratio of 0.32, p < 0.0001.

Figure 3. Probability of a heart failure event for 261 patients during 6 month period in relationship to chronic daily estimated pulmonary artery diastolic pressures (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 prior to 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 relationships were the same if the entire 6 month period was analyzed. The y-axis was converted from log hazard ratio to probability of a HF event in 6 months based on the event rate observed in this study. The plot represents unadjusted relationship, but the relationship is equivalent using a model adjusted for covariates.
Figure 4. Probability of a heart failure event for 261 patients with heart failure events during 6 month period in relationship to prior chronic daily pressures. (A) depicts chronic right ventricular diastolic pressures (RVDP) and (B) depicts chronic right ventricular systolic pressures (RVSP) in the same format as for Figure 3.

Figure 5. Event rate during 6 months in relation to baseline daily median ePAD < or ≥ 25 mmHg, and whether subsequent daily median ePAD was < or ≥ 25 mmHg for more than 50% of subsequent days during 6 months. Hi-Hi represents 131 patients who had baseline daily median AND more than half of subsequent days ≥ 25 mmHg. Hi-Lo is 19 patients who began with baseline daily median ≥ 25 mmHg but spent more than half of days below 25 mmHg. Lo-Hi is 25 patients who began with baseline daily median ePAD < 25 mmHg but spent more than half of subsequent days ≥ 25 mmHg. Lo-Lo is 86 patients whose baseline daily median AND subsequent majority of days were spent with daily median median ePAD < 25 mmHg. This figure demonstrates that initial risk from the baseline day can be revised if patients establish a different chronic level of filling pressures over time.
FIGURE 1

Distribution of ePAD values in:

- Patients without HF Events
- Patients with HF Events

- 25 ± 6 mmHg
- 30 ± 8 mmHg
FIGURE 2

Freedom from HF Event

![Graph showing the freedom from heart failure event with two curves representing Mean ePAD < 25 mmHg and Mean ePAD ≥ 25 mmHg. The graph illustrates the difference in freedom rate over days from randomization.]

HR: 0.29 (0.18, 0.48)
p < 0.001

# at Risk:
- < 25 mmHg: 105, 104, 90, 82, 80
- ≥ 25 mmHg: 156, 131, 98, 80, 71
FIGURE 3

Mean 24-hour ePAD Pressure (mmHg)

Probability of a HF event in 6 months

10 20 30 40

Circulation
FIGURE 4A and 4B

A. Risk of HF Event Vs. RVDP

B. Risk of HF Event Vs. RVSP

Probability of a HF Event in Six Months

24-hour RVDP (mmHg)

24-hour RVSP (mmHg)
FIGURE 5

Event Rate by Direction of Pressure Change

<table>
<thead>
<tr>
<th>Direction</th>
<th>Event Rate</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi -&gt; Hi</td>
<td>1.10</td>
<td>131</td>
</tr>
<tr>
<td>Hi -&gt; Lo</td>
<td>0.47</td>
<td>19</td>
</tr>
<tr>
<td>Lo -&gt; Hi</td>
<td>1.10</td>
<td>25</td>
</tr>
<tr>
<td>Lo -&gt; Lo</td>
<td>0.23</td>
<td>86</td>
</tr>
</tbody>
</table>

p=0.042

p=0.001
Chronic Ambulatory Intracardiac Pressures and Future Heart Failure Events
Lynne Warner Stevenson, Michael Zile, Tom D. Bennett, Fred J. Kueffer, Mariell L. Jessup, Philip Adamson, William T. Abraham, Ven Manda and Robert C. Bourge

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