Influence of Intracardiac Pressure on Spontaneous Ventricular Arrhythmias in Patients With Systolic Heart Failure
Insights From the REDUCEhf Trial

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Background—The implantation of a combination hemodynamic monitor-cardioverter-defibrillator in the Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients with Chronic Heart Failure (REDUCEhf) study allowed assessment of the relationship between daily intracardiac pressure and occurrence of ventricular arrhythmic (VT/VF) events.

Methods and Results—Median estimated pulmonary artery diastolic pressures (ePAD) were calculated every 24 hours in 378 subjects with New York Heart Association functional class II-III heart failure who had at least 60 days of hemodynamic data. Forty-six subjects experienced 140 VT/VF events on 80 unique study days in which daily median ePAD was available. The incidence of days with VT/VF events was significantly higher when the daily median ePAD for a subject was elevated, defined as >1 SD above that subject’s average median ePAD for the whole study: (2.8 episode days per patient-year compared with 1.7 episode days per patient-year; \( P = 0.040 \)). However, the incidence of days with VT/VF events was not significantly different on days when ePAD was >25 mm Hg compared with days when ePAD was <25 mm Hg. For all 378 subjects, the risk of VT/VF increased with average median ePAD calculated over the whole follow-up period (odds ratio, 1.072 for a 1-mm Hg increase; 95% confidence interval, 1.023–1.124; \( P = 0.003 \)).

Conclusions—There is significant positive association between average daily median ePAD and risk for VT/VF. Among patients with VT/VF, elevated intracardiac pressures are associated with higher VT/VF risk only when the definition of increased pressure is subject specific. (Circ Arrhythm Electrophysiol. 2013;6:272-278.)

Key Words: devices for heart failure ▪ electrophysiology ▪ heart failure ▪ hemodynamics ▪ ventricular arrhythmia

It is widely held that elevated intracardiac pressures can provoke ventricular arrhythmias. In isolated hearts and in vivo animals and man, acute ventricular dilatation has potentially arrhythmogenic effects.1-3 However, although elevated intraventricular pressure can elicit ventricular arrhythmias in isolated hearts4 and animal models,5 there is limited evidence supporting a comparable effect in humans.

Although ejection fraction, functional class, and N-terminal probrain natriuretic peptide have been shown to be independent predictors of VT/VF occurrence in patients with an implantable cardioverter-defibrillator (ICD),6,7 the influence of volume status and intracardiac hemodynamics on ventricular arrhythmia susceptibility has not been examined in man. Implantable devices, designed to provide long-term hemodynamic measures, offer an opportunity to evaluate directly the relation between intracardiac pressures and ventricular arrhythmia frequency.

The purpose of this study was to assess the relationship between intracardiac hemodynamic pressures and the development of clinical ventricular arrhythmias in the Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients with Chronic Heart Failure (REDUCEhf) trial. We specifically attempted to document whether an increase of intracardiac filling pressure in patients with a history of heart failure (HF) was a determinant of increased risk of spontaneous VT/VF.

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Methods

Patient Population

The REDUCEhf trial was designed to evaluate the effect of hemodynamically guided HF management using an implantable hemodynamic monitoring system combined with a single-chamber implantable cardioverter-defibrillator (IHM-ICD). Planned as a prospective, randomized, single-blinded, multicenter trial, the details of which have been published previously,6,7 REDUCEhf enrolled...
Patients with New York Heart Association (NYHA) functional class II and III HF receiving stable and maximally tolerated medical therapy. Subjects were required to have a HF hospitalization in the 12 months before enrollment and an indication for ICD therapy but no indication for cardiac resynchronization therapy.

**Hemodynamic Monitoring**

Patients were implanted with an ICD device attached to both a single-lead transvenous ICD lead and a second transvenous hemodynamic pressure sensing lead positioned in the right ventricular outflow tract. The ICD continuously measured and stored right ventricular dP/dt, systolic and diastolic pressures, and an estimate of pulmonary artery diastolic pressure (ePAD). Pulmonary artery diastolic pressure was estimated as the pressure in the right ventricle at the time of maximum dP/dt (the time of pulmonary valve opening). All pressures were corrected for ambient atmospheric pressure. ePAD measurements every 8 seconds were used to calculate a median ePAD for an 8-minute period. These were then used to calculate a daily median ePAD for each 24-hour period. Daily median pressures were stored on an Internet information system available for analysis.

In the treatment group, hemodynamic information was used for HF management. Management goals were to maintain a “euvolemic” state, determined individually for each subject by managing physicians, with a recommendation to more aggressively treat increases in ePAD than decreases and, in at least a subgroup, to adjust therapy specifically when daily median ePAD was >1 SD above or >2 SDs below the subject-specific baseline pressure. We considered this definition of hypervolemia and hypovolemia in our initial analysis. In the control group, hemodynamic information was stored but was not available to the managing physician. For the purposes of the present analysis, data from both groups were relevant and used. Patients were in randomized follow-up for 12 months. Although the trial was designed to enroll 1300 patients, enrollment was prematurely stopped after 400 implants because of IHM sensor lead failures.

**Device Settings and Arrhythmia Detection**

ICD detection programming was left to individual investigators with the following recommended settings: VT zone (On or Monitor) <320 ms, detection 18 of 24 intervals; VF zone (On or Monitor) <360 ms or VT CL + 40 ms, detection 16 beats; wavelet matching On; Egm=scan-RV coil. The ICD stored the intervals of detected tachycardias along with electrograms and a QRS snapshot. The device was capable of capturing up to 150 episodes of VT/VF and 50 supraventricular or nonsustained tachycardias for download. Pressure data were not used for VT/VF discrimination.

Spontaneous, stored ventricular episodes defined by therapy delivery (ICD shock in 48, ATP in 71, both in 26) or duration >30 seconds (mean duration, 20 seconds; range, 6–468 seconds) were reviewed and classified initially by the investigators. All episodes were also classified by field clinical engineers for the trial. Episodes were submitted for adjudication by electrophysiologists on the Adverse Events Adjudication Committee if the first 2 classifications were inconsistent. In addition, a subset of episodes was reexamined by 2 of the authors (M.R., D.B.); a consistency of >95% was observed. All consistent episodes were submitted for adjudication by electrophysiologists on the Adverse Events Adjudication Committee. VT/VF episode, our primary analysis considered only the first VT/VF episode, and number of VT/VF episodes were determined. The ePAD was considered hypovolemic for that period. Otherwise, the subject was considered euvolemic based on whether the intracardiac pressure for that day was elevated, normal, or low, respectively. Pressure state was determined in a patient-specific manner: if the daily median ePAD was >1 SD higher than the subject’s average daily median ePAD across the whole study period, then the subject was categorized as hypervolemic for that day; if the daily median ePAD was >2 SDs lower than the subject’s average daily median ePAD, then the subject was considered hypovolemic for that period. Otherwise, the subject was considered euvolemic.

Within each subject and pressure state, the number of days the subject spent in each pressure state, number of days with a VT/VF episode, and number of VT/VF episodes were determined. The ePAD on the day of VT/VF was used to calculate volume status associated with VT/VF. The number of days with at least 1 episode of VT/VF was used to calculate the annualized rate of VT/VF days for all subjects within each pressure state. The number of VT/VF episodes was used to calculate the annualized rate of VT/VF for all subjects within each pressure state. Repeated measures Poisson models were used to compare the annualized rate of days with VT/VF, and annualized rate of VT/VF between pressure states with P values <0.05 was considered significant. In subsequent analyses, hypervolemia, hypovolemia, and euvolemia were defined in an absolute manner, based on daily ePAD in mm Hg.
Results

Baseline Characteristics

Of the 400 patients randomized in the REDUCEhf study, 399 patients were successfully implanted with an IHM-ICD device. The 378 subjects with at least 60 days of ePAD data (mean of 334±74 days with ePAD available) during the 12-month randomized follow-up period were included in the present analysis. There was no difference between the treatment group (194 subjects) and control group (184 subjects) in the risk of VT/VF ($P=0.879$), so data from both groups were included in the analyses. Patients tended to be men (69%) with a mean age of 55±15 (SD) years, and about half (44%) had an ischemic pathogenesis for their HF. The mean ejection fraction was 23%, and the population was evenly divided between functional class II and III symptoms. Forty-nine subjects (13%) experienced a total of 150 VT/VF episodes on 87 distinct days (3.1±4.8 episodes/subject; range 1–23). Six subjects experienced 3 to 5 VT/VF events on ≥1 days. One subject experienced 7 and 12 VT/VF events on 2 different days, and 1 subject experienced 23 VT/VF events on a single day.

Comparison of Patients With and Without VT/VF Events

The 49 subjects with at least 1 VT/VF event had a somewhat higher average baseline daily median ePAD (baseline ePAD was measured 8–14 days after implant) compared with the 329 subjects that were free of VT/VF events (24.4±9.7 mm Hg versus 21.9±7.0 mm Hg), but the difference was not statistically significant ($P=0.080$). Subjects who experienced at least 1 VT/VF event also had a shorter 6-minute hall walk distance, and worse physical health as measured by the SF-12 score at entry, possibly indicating more severe HF (Table 1). There was no difference in HF pathogenesis, left ventricular ejection fraction, or NYHA functional class between the 2 groups. Patients who experienced VT/VF events during the trial were more likely to have a history of PVC, but there was no difference in previous history of sustained VT, nonsustained VT, or VF/cardiopulmonary arrest in the 2 groups.

Average Follow-up Median ePAD as a Predictor of VT/VF Events

The average follow-up median ePAD was a predictor of VT/VF events. The univariate relationship between average follow-up median ePAD and the probability of having at least 1 VT/VF event is shown in Figure 2. The relationship is adequately described as a linear function. Based on a univariate model, the odds ratio for the probability of having at least 1 VT/VF episode during the 12-month randomized period associated with a 1-mmHg increase in average follow-up median ePAD was 1.072 (95% confidence interval, 1.023–1.124; $P=0.003$). Using the propensity score–adjusted logistic regression model, the odds ratio associated with a 1-mmHg increase was similar and remained a significant independent predictor of the likelihood of VT/VF (odds ratio, 1.053; 95% confidence interval, 1.002–1.106; $P=0.043$).

Table 1. Demographic Comparison of the Subjects With at Least 1 VT/VF Event and Subjects Free of VT/VF Events

<table>
<thead>
<tr>
<th>VT/VF Event (n=49)</th>
<th>VT/VF Free (n=329)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age at implant</td>
<td>55.8 (14.5)</td>
<td>54.6 (14.7)</td>
</tr>
<tr>
<td>Men</td>
<td>n=38, 78%</td>
<td>n=223, 68%</td>
</tr>
<tr>
<td>White</td>
<td>n=31, 63%</td>
<td>n=185, 56%</td>
</tr>
<tr>
<td>Ischemic pathogenesis</td>
<td>n=20, 41%</td>
<td>n=148, 45%</td>
</tr>
<tr>
<td>NYHA FC II</td>
<td>n=22, 45%</td>
<td>n=169, 51%</td>
</tr>
<tr>
<td>LVEF %</td>
<td>23.2 (7.7)</td>
<td>23.0 (7.4)</td>
</tr>
<tr>
<td>6-min hall walk, m</td>
<td>258 (116)</td>
<td>312 (126)</td>
</tr>
<tr>
<td>MN living with HF score$^+$</td>
<td>58 (22)</td>
<td>50 (27)</td>
</tr>
<tr>
<td>SF-12 Physical Health Score</td>
<td>31 (9.2)</td>
<td>36 (10.2)</td>
</tr>
<tr>
<td>Baseline ePAD†</td>
<td>24.4 (9.7)</td>
<td>21.9 (7.0)</td>
</tr>
<tr>
<td>History of PVC, %</td>
<td>45</td>
<td>29</td>
</tr>
</tbody>
</table>

ePAD indicates estimated pulmonary artery diastolic pressures; HF, heart failure; LVEF, left ventricular ejection fraction; MN, Minnesota; and NYHA, New York Heart Association.

*p value from t test or Fisher exact test.
†Baseline ePAD calculated as the average daily median ePAD 8–14 days after IHM-ICD implant.

Figure 1. A representative example of the effect of a ventricular arrhythmia on estimated pulmonary artery diastolic pressures (ePAD) is shown. An episode of polymorphic VT/VF with a cycle length ≈190 ms lasting 7 sec is terminated successfully with a 15.3 joule shock. A, Shows the V-V interval over time. The polymorphic VT is preceded by a period of bigeminy. Programmed implantable cardioverter-defibrillator parameters are shown. B, Shows individual ePAD measurements over the same time period. ePAD returns to baseline values (≈13–17 mm Hg in this example) about 60 seconds after tachycardia termination. Vertical lines in both panels indicate tachycardia trigger and represent identical time. Time scales of the 2 panels are intentionally different. Electrograms are not shown.
Of the 49 subjects who experienced at least 1 VT/VF event, 46 (12.2% of the 378 subjects) experienced a total of 140 adjudicated VT/VF events on 80 days when hemodynamic data were available. An additional 10 VT/VF events in 3 subjects occurred on days when hemodynamic data were unavailable and were therefore excluded from this analysis. For the population who had experienced at least 1 VT/VF episode, ePAD was in the hypervolemic range (ie, >1 SD above subject-specific mean) for 15.3% of the follow-up period (6.4 follow-up years; Table 2). Subjects were considered hypovolemic <2% of the follow-up period. The majority of time (83.3%) subject ePAD was considered to be in the euvolemic range.

There were 18 days with at least 1 VT/VF episode during a total of 6.4 patient-years of follow-up categorized as hypervolemic for an annualized rate of 2.80 episode days per year compared with an annualized rate of 1.69 episode days per euvolemic patient-year \( (P=0.040) \). Annualized VT/VF episodes during hypervolemic follow-up were also higher than during euvolemia, but this difference did not reach statistical significance (Table 2).

The annualized days with VT/VF episodes and the annualized number of VT/VF episodes also seemed to be higher during periods of hypovolemia than during periods of euvolemia, but the short duration of time subjects were hypovolemic preclude making a statistical inference. Only 5 episodes of VT/VF on 3 days occurred during periods of hypovolemia. If hypervolemia and hypovolemia are redefined as >1 SD above and >1 SD below subject-specific mean, respectively, the comparison of annualized episode days between hypervolemic and euvolemic periods remains significant (2.80 versus 1.69; \( P=0.047 \)). With this broader definition of hypovolemia, the comparison of hypovolemic and euvolemic periods becomes less dramatic (2.04 annualized days/hypovolemic years versus 1.69 annualized days/euvolemic years; \( P=0.568 \)).

The majority of ventricular events were adjudicated as monomorphic VT, as opposed to polymorphic VT/VF, in both hypervolemic and euvolemic periods (82% of events that occurred during hypervolemia and 67% of events that occurred during euvolemia were adjudicated as monomorphic VT; \( P=0.254 \)).

When hypervolemia was defined by ePAD>25 mmHg (mean ePAD for the whole population), the annualized rate of days with at least 1 episode of VT/VF per year of follow-up was not significantly different compared with periods when ePAD was <25 mmHg (1.83 days with VT/VF per year of follow-up).

### Table 2. Annualized VT/VF Rate by Pressure State (Subject Specific)

<table>
<thead>
<tr>
<th>Subject years in volume status</th>
<th>Hypovolemia</th>
<th>Euvolemia</th>
<th>Hypervolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days with at least 1 VT/VF episode</td>
<td>3</td>
<td>59</td>
<td>18</td>
</tr>
<tr>
<td>Annualized days with VT/VF</td>
<td>5.00</td>
<td>1.69</td>
<td>2.80</td>
</tr>
<tr>
<td>( P ) value*</td>
<td>0.055\†</td>
<td>0.040\†</td>
<td></td>
</tr>
<tr>
<td>Number of VT/VF episodes</td>
<td>5</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>Annualized VT/VF rate</td>
<td>8.34</td>
<td>2.72</td>
<td>6.23</td>
</tr>
<tr>
<td>( P ) value\‡</td>
<td>0.092\†</td>
<td>0.119\†</td>
<td></td>
</tr>
</tbody>
</table>

Hypervolemia is defined as daily median estimated pulmonary artery diastolic pressures (ePAD) 1 SD higher than the subject’s average daily median ePAD for the whole follow-up period. Hypovolemia is defined as a daily median ePAD 2 SDs lower than the subject’s average daily median ePAD.

* \( P \) value from repeated measures Poisson model with number of days with VT/VF as response and volume status as independent variable.
\† \( P \) value compared with euvolemia.
\‡ \( P \) value from repeated measures Poisson model with number of VT/VF episodes as response and volume status as independent variable.
Discussion

This study was designed to ascertain whether there is a correlation between intracardiac pressures and susceptibility to ventricular arrhythmia development over an extended period of observation in an ambulatory, outpatient population with systolic HF. There were 3 principal findings. First, for individual patients, there is a statistically significant relationship between daily ePAD and the risk of a VT/VF event when the definition of increased pressure or volume status is subject specific. On days when the ePAD was higher than the subject mean, the risk of a VT/VF event was approximately twice as high compared with periods of euvolemia. The sensitivity of VT/VF occurrence to relative changes in ePAD may reflect a subject's adaption to chronic pressure. Most patients maintained daily median pressures similar to those initially measured when they tended to be clinically compensated, although initial right-sided pressures varied widely in individual patients. Second, pressure thresholds unrelated to the subject’s specific state were not predictive of increased risk. There was no statistically significant difference in VT/VF incidence when comparing days with pressures >25 mm Hg to days when ePAD was <25 mm Hg. This seems to be different from the relationship of intracardiac pressure and HF exacerbation.

Third, for the whole population, the average ePAD during follow-up correlated with the risk of VT/VF events, and this correlation also parallels other indicators of ventricular dysfunction. Our analysis suggests a progressive risk of VT/VF as the ePAD increases with no apparent threshold below which the risk of VT/VF is zero.

Comparison of Annualized Days With VT/VF Rate and Annualized VT/VF Rates

Although there was a significant difference between days with VT/VF events based on pressure state, when annualized VT/VF rates were compared, the comparison failed to reach statistical significance. A potential explanation for this observation is suggested by Figure 1. A VT/VF event has the potential to transiently elevate ePAD, although pressures quickly tend to return to values preceding the arrhythmic event. An episode of VT/VF occurring during a period of euvolemia could then be associated with a brief period of elevated pressure that transiently increases the risk of arrhythmic events. This scenario could artifactually increase the number of VT/VF events associated with presumed euvolemia if subsequent episodes result from these secondary transient pressure changes. Indeed our data may have been influenced disproportionally by subjects with electrical storm (6 of 9 days on which storm occurred were categorized either as euvolemic or hypovolemic, including 1 subject with 23 VT/VF episodes on a single euvolemic day).

Mechanisms Linking Elevated Ventricular Pressures and Ventricular Arrhythmias

There are several potential mechanisms by which an elevated ventricular pressure could influence the development of ventricular arrhythmias. Elevated ventricular pressure is a neurohormonal activator, increases sympathetic tone, and is associated with aberrant intracellular calcium cycling. Acute diastolic stretch shortens action potential duration and refractoriness, presumably because of activation of stretch-activated channels. Similar phenomena have been described in man. The observation, in the current study, that ventricular events are correlated with patient-specific changes in intracardiac pressure, and not absolute pressure, is consistent with observations in the above studies that show that acute chamber dilatation shortens myocardial refractoriness, whereas chronic dilatation does not.

Recent studies have analyzed the relationship of intrathoracic impedance, as a surrogate for intracardiac pressures, and spontaneous ventricular arrhythmias. Moore et al found that the sum of the daily differences between the average daily and reference impedances (7 days, 2 days, and 1 day before VT/VF) was negative before 66% of VT/VF episodes in 121 patients, only slightly >50% expected if the relationship was random. Although, statistically significant, the difference was small, the study retrospective, and the positive predictive value was low. Ip et al found that VT/VF episodes were more common when the OptiVol fluid index (representing the accumulation of consecutive day-to-day differences between the daily and reference intrathoracic impedance values) was >15, 30, and 45 ohm-days. Again, the predictive value was poor. The OptiVol fluid index does not reflect any specific value or level of HF but rather a change from baseline, and both of the measures these 2 studies used reflect relative and subject-specific changes.
Our study more directly demonstrates a relationship between subject-specific hemodynamic status and VT/VF occurrence. The critical factor seems to be an elevation from median values for a given individual. However, the correspondence between absolute ePAD value and VT/VF events is not tightly linked. Nearly 70% of observed VT/VF episodes occurred when subjects were considered euvolemic. It remains unclear whether elevated pressure is a determinant of ventricular arrhythmic events only in a susceptible subpopulation or whether as yet unidentified influences interact with intracardiac pressures to influence VT/VF events.

Limitations
Although the current study offers a unique approach to assessing the impact of intracardiac pressures on ventricular tachyarrhythmia susceptibility in ambulatory patients with HF, it is nonetheless subject to a number of important limitations. First, although a relatively large population was assessed, the number of VT/VF episodes (event rate) was small. Although the study and data collection were prospectively planned, the analysis was retrospective and the population size and number of VT/VF events were smaller than originally expected. Second, the analysis used daily median ePAD measurements. Intracardiac pressures are dynamic, influenced by activity, posture, medications, and dysrhythmias. Variation of pressure during the day and over shorter periods of time were not available for this analysis. Third, as mentioned, it is possible that a stronger pressure-arrhythmia relationship exists in an, as yet undefined, unique patient population but is diluted out by a population relatively insensitive to elevated intracardiac pressure. Although in the present study, we could discern no notable demographic difference between subjects whose VT/VF events occurred during periods of hypervolemia from those whose VT/VF events occurred during euvolemic periods. Fourth, ePAD may not be the intracardiac pressure best correlated with susceptibility for ventricular arrhythmias. Analysis of this relationship with other measures of intracardiac pressure may be possible in the future. Finally, this analysis could not account for other potentially important data, such as electrolyte status or changes in therapy.

Conclusions
We have demonstrated a significant correlation between days with VT/VF events and preceding subject-specific changes in intracardiac pressures. The risk of a VT/VF occurrence is twice as likely when the daily median estimated PA pressure exceeds the subject mean by 1 SD. This supports the supposition that elevations in intracardiac pressures can influence the development of ventricular arrhythmias in a population with a history of congestive HF. Whether tighter control of intracardiac pressures based on an individual patient’s experience will diminish susceptibility to ventricular tachyarrhythmias remains to be assessed.

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Disclosures
Drs Reiter, Benditt, Adamson, and Gold have served as consultants to Medtronic, Inc and St. Jude Medical. Dr Adamson also serves as consultant to CardioMEMS, Inc and RespiCardia, and has received speaking honoraria from Boston Scientific. Dr Gold has received research support from Medtronic, Inc and St. Jude Medical. Dr Benditt has ownership interest in Medtronic, Inc and St. Jude Medical. Authors Stromberg and Whitman are employees of Medtronic, Inc.

References
Prediction of ventricular arrhythmias (VAs) is a significant, continuing clinical challenge. The relationship between intracardiac pressure and VAs remains controversial. It is often suggested that elevated intracardiac pressure can precipitate VAs (and is a cause of electrical storm), but there is limited direct evidence supporting a connection. Implanted cardioverter-defibrillator devices capable of hemodynamic measurement provide the opportunity to directly examine the association between intracardiac pressure and the occurrence of VAs in humans. In a population of subjects with heart failure, in this study, it was observed that the risk of a VA was almost 2-fold greater on days when the PA diastolic pressure was elevated (ie, at least 1 SD greater than the subject-specific mean). Elevated daily intracardiac pressures were associated with higher VT/VF risk only when the definition of increased pressure was subject specific. The odds ratio associated with a 1-mm Hg increase in PA diastolic pressure over the whole follow-up period was also a significant independent predictor of the likelihood of VT/VF during follow-up (odds ratio, 1.053; 95% confidence interval, 1.002–1.106). Regardless of mechanism or whether elevated pressure is a determinant of VAs only in a susceptible subpopulation, confirmation of this association raises the possibility that stricter control of intracardiac pressure may be an important antiarrhythmic strategy.
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