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Ongoing Right Ventricular Hemodynamics in Heart Failure

Clinical Value of Measurements Derived From an Implantable Monitoring System

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OBJECTIVES This study examined the characteristics of continuously measured right ventricular (RV) hemodynamic information derived from an implantable hemodynamic monitor (IHM) in heart failure patients.

BACKGROUND Hemodynamic monitoring might improve the day-to-day management of patients with chronic heart failure (CHF). Little is known about the characteristics of long-term hemodynamic information in patients with CHF or how such information relates to meaningful clinical events.

METHODS Thirty-two patients with CHF received a permanent RV IHM system similar to a single-lead pacemaker. Right ventricular systolic and diastolic pressures, heart rate, and pressure derivatives were continuously measured for nine months without using the data for clinical decision-making or management of patients. Data were then made available to clinical providers, and the patients were followed up for 17 months. Pressure characteristics during optimal volume, clinically determined volume-overload exacerbations, and volume depletion events were examined. The effect of IHM on hospitalizations was examined using the patients' historical controls.

RESULTS Long-term RV pressure measurements had either marked variability or minimal time-related changes. During 36 volume-overload events, RV systolic pressures increased by 25 ± 4% ($p < 0.05$) and heart rate increased by 11 ± 2% ($p < 0.05$). Pressure increases occurred in 9 of 12 events 4 ± 2 days before the exacerbations requiring hospitalization. Hospitalizations before using IHM data for clinical management averaged 1.08 per patient year and decreased to 0.47 per patient-year (57% reduction, $p < 0.01$) after hemodynamic data were used.

CONCLUSIONS Long-term ambulatory pressure measurements from an IHM may be helpful in guiding day-to-day clinical management, with a potentially favorable impact on CHF hospitalizations. (J Am Coll Cardiol 2003;41:565–71) © 2003 by the American College of Cardiology Foundation

Optimal day-to-day management of patients with chronic heart failure (CHF) requires accurate clinical assessment of volume by a physical examination. Changes in volume or ventricular performance often cause cardiac decompensation, leading to severe symptoms and, many times, the need for hospitalization. Strategies to prevent such events include frequent physician examinations and close monitoring of the patient's clinical status to maintain optimal volume and adjust CHF medications (1), but physical findings of high filling pressures are frequently absent in established CHF, even when filling pressures are high (2,3). Repeated right heart catheterizations may help tailor CHF therapy (4), but they are inconvenient for patients and associated with significant risks. Furthermore, traditional invasive evaluations assess patients only while they are resting supine. What is lacking is a means to continuously measure ongoing ventricular filling pressures to monitor individual responses to medical management of the disease.

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Continuous hemodynamic monitoring with an implantable device is technically feasible and can provide information during normal activity (5–10). Newer device designs have long-term accuracy (5), providing information over a variety of physiologic conditions (5) and during short-term

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Abbreviations and Acronyms

CHF = chronic heart failure
ePADP = estimated pulmonary artery diastolic pressure
HF = heart failure
HR = heart rate
ICD = implantable cardiac defibrillator
IHM = implantable hemodynamic monitor
RV = right ventricle or ventricular
RVDP = right ventricular diastolic pressure
RVSP = right ventricular systolic pressure

medication changes (6). This study is the first to examine the long-term characteristics of ongoing hemodynamics measured from a permanently implanted device in patients with CHF and to correlate changes to clinical events. These data help develop the hypothesis that incorporation of long-term hemodynamic data in heart failure (HF) management has the potential to affect meaningful outcome measures in patients with CHF.

METHODS

This clinical investigation was a multicenter, prospective, nonrandomized study with three goals: 1) to examine the long-term characteristics of cardiovascular parameters derived from an implantable hemodynamic monitor (IHM) in patients with CHF; 2) to determine changes in those parameters that occur during meaningful clinical events; and 3) to investigate whether incorporating hemodynamic information in long-term management impacts hospitalizations in HF care. During the first nine months of the trial, hemodynamic data were collected but not made available to the investigators for clinical decision-making. When device accuracy was demonstrated (5), hemodynamic information was included in the clinical management, and the patients were followed up for 17 months. The first two goals were examined during the blinded phase. Information about hospitalizations was analyzed using historical controls, comparing hospitalization rates from 12 months before implantation, combined with the blinded phase of the trial (9 months), with the 17 months after hemodynamic information began to be used.

Patient inclusion criteria. Patients between the ages of 21 and 75 years, with New York Heart Association class II/III CHF, were enrolled in the trial if they were able to provide informed consent. Subjects were excluded if they had an existing indication for a pacemaker or an implantable cardiac defibrillator (ICD). Additionally, patients with known atrial or ventricular septal defects, tricuspid or pulmonic stenosis, or mechanical right heart valves, as well as those with a terminal illness unrelated to HF with a life-expectancy of <12 months, were excluded. Institutional review boards at each site approved the study design, and patients gave informed consent to be involved in this investigational protocol.

Device design and implantation. The Chronicle IHM (Medtronic, Inc., Minneapolis, Minnesota) is a long-term implanted device designed to record ongoing right ventricular (RV) pressures, heart rate (HR), and pressure derivatives. The implantation procedure was similar to a single-lead permanent pacemaker system with a programmable memory device (128-K random-access memory) placed in the pectoral area and a transvenous electrode carrying a pressure sensor in the RV outflow tract. The device continuously measured RV systolic and diastolic pressures (RVSP and RVDP), estimated pulmonary artery diastolic pressure (ePADP), maximum change in pressure over time (dP/dt), HR, activity, and temperature. The ePADP was derived from RV pressures at the time of maximum dP/dt, the moment of pulmonary valve opening. This concept was validated in previous work (11,12).

Absolute pressure values were obtained directly from the pressure sensor, and HR was determined from a unipolar electrogram recorded at the tip of the lead. Long-term performance of the IHM sensor was recently established (5). The sensor provides a continuous pressure trace for analysis by the IHM (Fig. 1) and is known to be stable over time (5,7,8). A brief pre-insertion calibration procedure was performed immediately before implantation. Once the sensor was implanted, no additional or repeated calibration was required. Previous validation of the sensor's accuracy and precision was performed by using serial right heart catheterizations and comparing IHM signals with simultaneously acquired balloon-tipped catheter values at 3, 6, and 12 months after implantation (5). These studies revealed a small baseline error at 12 months that was similar to the error at the time of implantation (<1.0 mm Hg). This indicated that no significant drift occurred in the sensor (5). Although the sensor's response is linear to >100 Hz, the IHM signal was low-pass filtered at 60 Hz to minimize noise. An external device that patients kept with them recorded ambient barometric pressure once per minute. When stored hemodynamic information was interrogated from the monitor, the external pressure reference information was subtracted from monitor data to provide relative pressures in the RV.

Long-term information stored in the monitor was retrieved using a PC-based program with specialized software that allowed users to verify proper device function by visual inspection of real-time ventricular pressure waveforms. The median value ± 5% and 95% ranges were derived from the data depending on the duration of recordings, which ranged from 1 h to two months based on planned follow-up. To address the possibility that IHM pressures may vary as a function of body position, a previous study (5) demonstrated that IHM pressures were not different from simultaneously obtained balloon-tipped pulmonary artery catheter pressures in the supine/rest, sitting/rest, and sitting/exercise positions (5). Therefore, IHM pressures are accurate and precise over a variety of physiologic conditions. Nevertheless, cardiac filling pressures may vary as a function of body position,

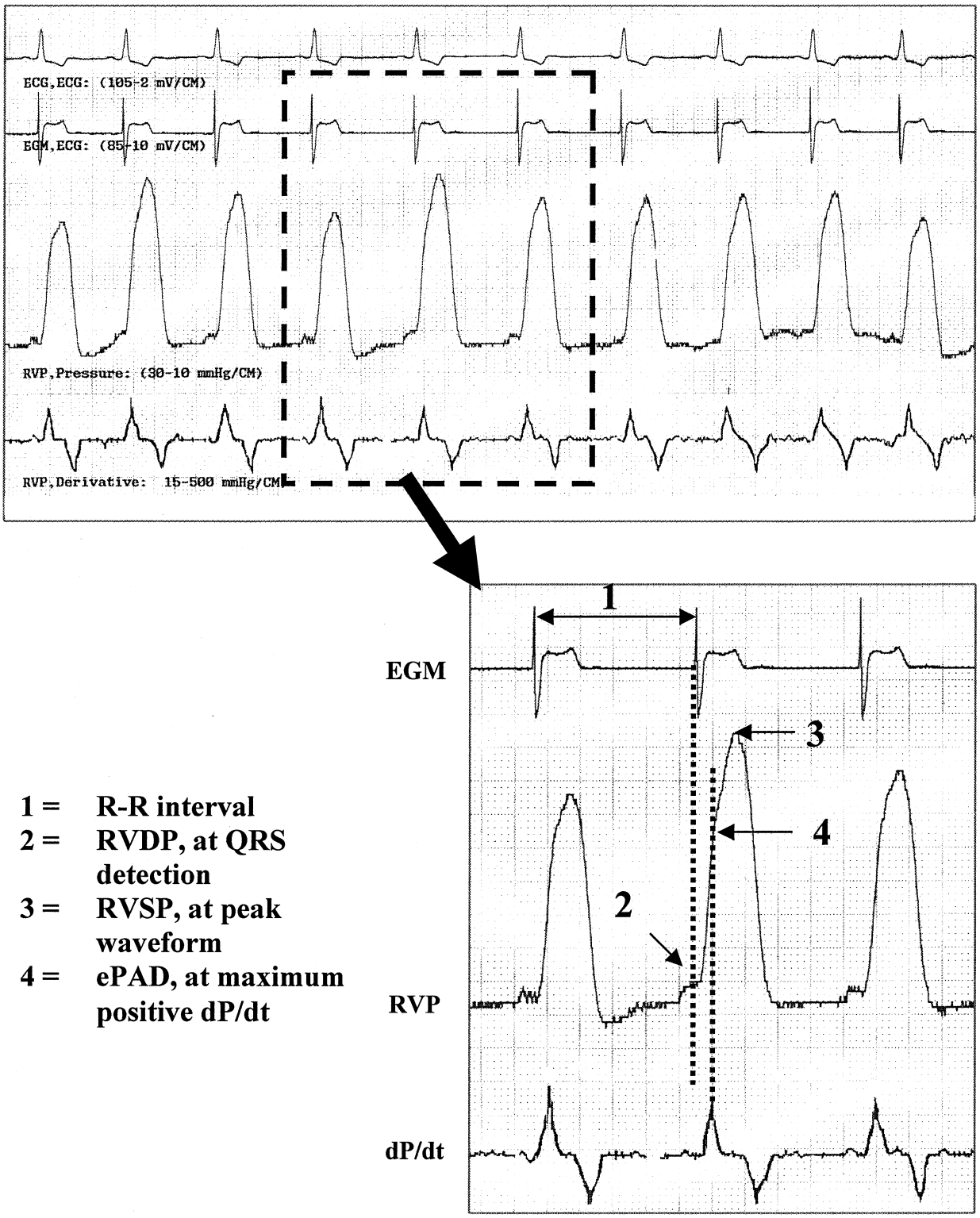

Figure 1. Actual right ventricular pressure waveforms derived from an implantable hemodynamic monitor (IHM) system, with an illustration of how the IHM determines the pressure values. dP/dt = contractility as measured by change in pressure over change in time; EGM = electrogram; ePAD = estimated pulmonary artery diastolic pressure; RVDP = right ventricular diastolic pressure; RVSP = right ventricular systolic pressure.

which may reflect differences in activity or body position between individual patients. To decrease the potential effects of differences in activity or body position on the results in this study, pressures from nighttime rest values were collected between midnight and 4 AM when there was zero activity detected by the device.

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Table 1. Patient Characteristics (n = 32)

Age (yrs)	59 ± 10
Gender (M/F)	12 (38%)/20 (62%)
LVEF	29 ± 11%
Etiology	
Ischemic	19 (59%)
Idiopathic	11 (34%)
Valvular	2 (7%)
NYHA class	
I	1
II	14
III	17

Data are presented as the mean value ±SD or number (%) of patients.
LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Long-term monitoring and clinical end points. The daily maximum, minimum, median, and range of pressures were analyzed, along with nighttime values between midnight and 4 AM, when no activity was sensed. During the blinded phase of the trial, HF physicians determined volume-overload exacerbations on the basis of elevated jugular venous pressure, rhonchi on lung auscultation, and abdominal-jugular reflux. Volume-overload events were considered *major* if hospitalization was required and *minor* if outpatient adjustments in therapy treated the exacerbation. Volume depletion was reported on the basis of an orthostatic drop in systolic blood pressure and typical signs and symptoms of dehydration that resulted in discontinuation of diuretic therapy or volume infusion. Individual baseline pressure parameters were determined at times when the patient had optimal volume control. Percent changes in pressures were calculated for each day during the week before the event. A sustained change of >20% above baseline for any pressure parameter before a clinical event was considered meaningful.

The CHF hospitalization data (verified by ICD-9 and DRG codes) collected from 12 months before IHM placement, and during the 9-months blinded phase, were compared with the 17-months of follow-up that began when information was made available for management decisions. Hospitalization incidence was expressed in patient-years to reduce the statistical impact of patients who underwent transplantation or died during follow-up.

Statistics. The two-tailed paired Student *t* test was used to determine a difference between baseline values and peak pressure values. Hospitalization rates were evaluated using an unpaired *t* test comparing pre-hemodynamic management rates to post-hemodynamic rates. An alpha level of $p < 0.05$ was considered statistically significant. Data are reported as the mean value ± SD, unless otherwise noted in the text.

RESULTS

The characteristics of the 32 patients enrolled are reported in Table 1. Three patients required lead replacement due to calibration or sensor problems. Two patients died during follow-up due to causes unrelated to the device. One patient withdrew consent for subsequent invasive hemodynamic evaluations. One patient had the system explanted during heart transplantation. One patient had a small pneumothorax after implantation, and one patient developed complete heart block requiring permanent pacemaker implantation.

Characteristics of ongoing pressures. Pressure values and their variability had individual characteristics, as illustrated in Figure 1. The RVSP and RVDP nighttime minimum pressures with zero activity averaged 54 ± 17 and 2.3 ± 4 mm Hg, respectively, and ePADP averaged 28 ± 8 mm Hg during optimal volume conditions. The HR averaged 75 ± 20 beats/min when optimal volume was maintained.

Volume-related exacerbations. Thirty-six volume-overload events occurred in 14 patients, and 12 events (major) were severe enough to require hospitalization. Sustained increases (>20%) in at least one pressure parameter were observed in nine of the 12 events 4 ± 2 days before exacerbations, leading to hospitalizations (Fig. 2, left panel). In contrast, early pressure increases occurred in only 9 of 24 events with minor exacerbations. In all exacerbations, pressures increased 24 h before clinical intervention (Fig. 2). The RVDP increased by 265 ± 16% (2.3 ± 4 to 8.4 ± 4 mm Hg), whereas RVSP increased by 25 ± 4% (54 ± 17 to 67 ± 10 mm Hg), and ePADP rose 26 ± 4% (28 ± 8 to 35 ± 9 mm Hg), when comparing baseline values with peak events (all $p < 0.05$). The HR increased by 11 ± 2% during the peak of exacerbations ($p < 0.05$).

Eight volume-depletion episodes occurred in seven patients, and all pressure measurements decreased. The RVSP decreased by 17 ± 4%, RVDP decreased by 63 ± 4%, and ePADP decreased by 23 ± 8% (all $p < 0.05$). The HRs were lowest at the peak of volume-depletion events (−14 ± 2%) and highest at the peak of overload events (11 ± 2%, $p < 0.05$). All hemodynamic parameters measured returned to baseline levels with successful treatment of clinical events.

Hospitalizations. Hospitalization data were examined in 28 patients, as one patient died, two underwent heart transplantation, and one was lost to follow-up before hemodynamic data were used for clinical management. A total of 52 CHF-related hospitalizations occurred before use of hemodynamic information for management had begun. After hemodynamic data were available to help manage patients, six patients received a transplant and five died. There were 18 CHF-related hospitalizations in 14 of the 28 patients in the 17 months of follow-up. When expressed in patient-years, there were 1.08 admissions per patient-year in the 21 months before hemodynamic information was used and 0.47 hospitalizations per patient-year in the 17 months after data were made available (57% reduction, $p < 0.01$) (Fig. 3).

DISCUSSION

Findings from this study indicate that continuous hemodynamic monitoring provides detailed information on CHF patients' status that may be helpful in day-to-day volume

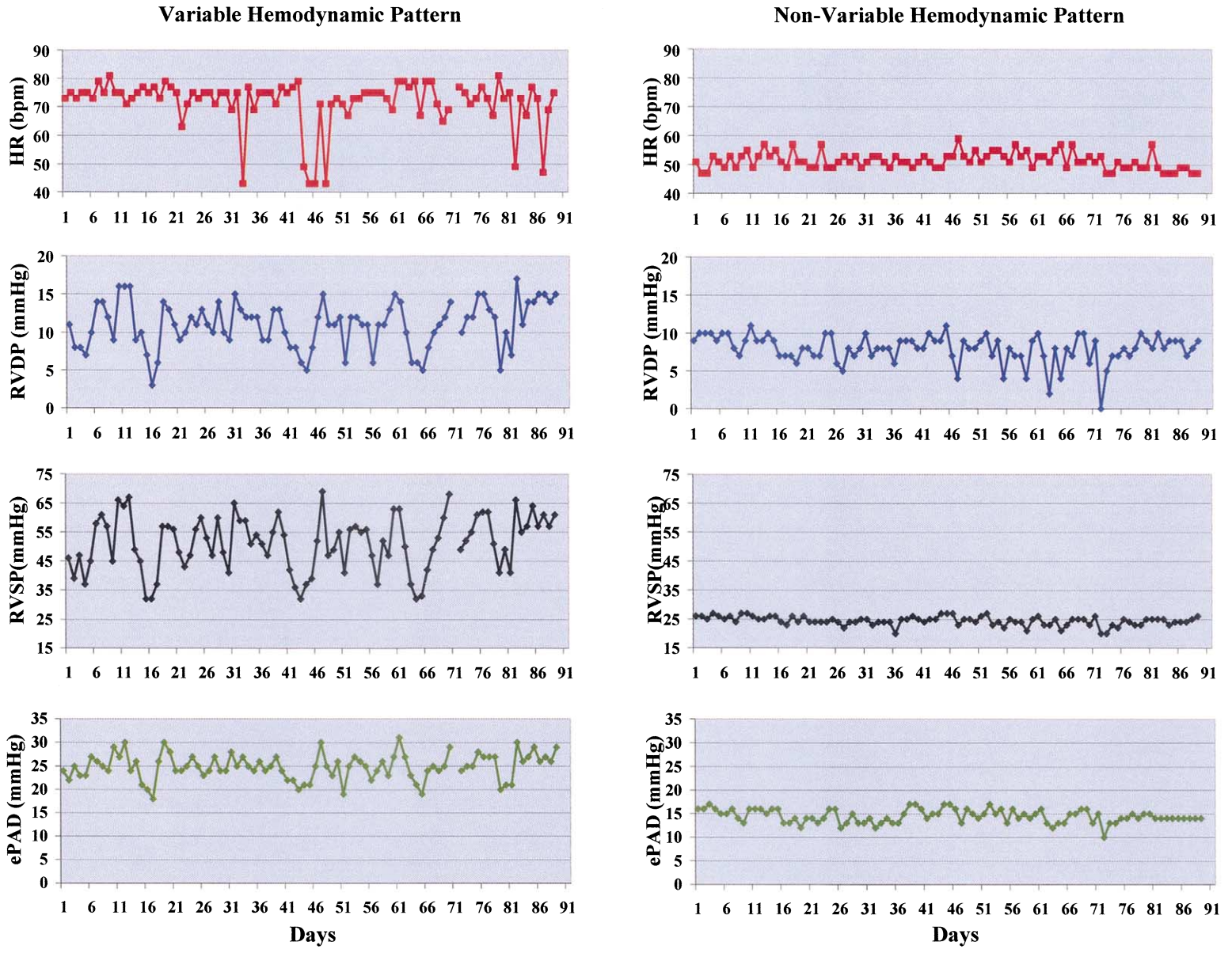

Figure 2. Right ventricular pressure values from a patient with *variable* pressure **(left panel)** and a patient with *nonvariable* pressure **(right panel)** characteristics. (See text for details.) Nighttime minimum values are shown for heart rate (HR), RVSP, ePAD, and RVDP values. Abbreviations as in Figure 1.

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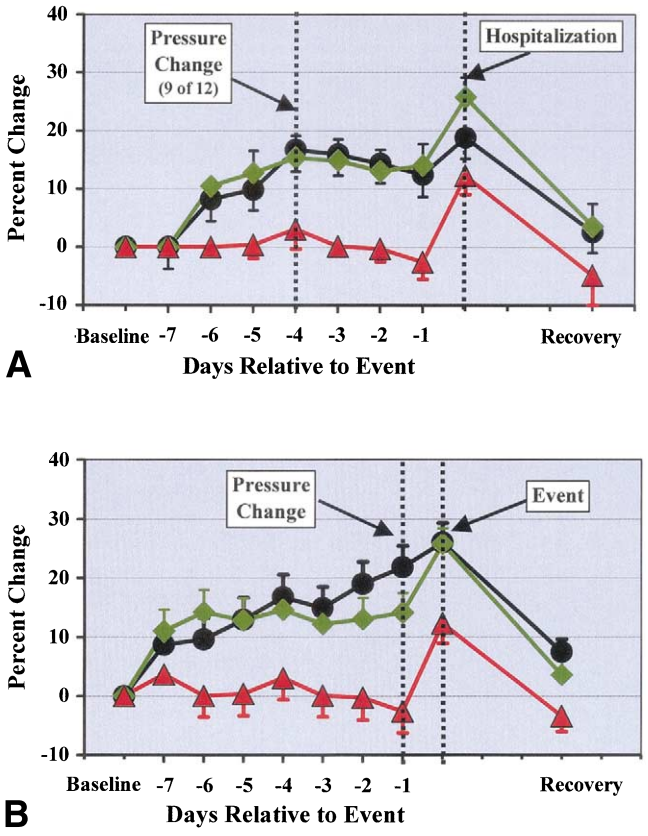

Figure 3. **(A)** Pressure changes occurred in 9 of 12 events 4 ± 2 days before hospitalization (major). **(B)** Pressure changes before minor exacerbations (n = 24) that did not require hospitalization. Percent changes in right ventricular systolic pressure **(black circles)**, estimated pulmonary artery diastolic pressure **(green diamonds)**, and heart rate **(red triangles).**

management of the disease. Based on the current findings, the hypothesis can be generated that long-term hemodynamic monitoring may decrease CHF hospitalizations, but this hypothesis must be tested in a prospective, randomized trial designed to specifically address this question. Finally, data from this study expand the concept that invasive RV hemodynamic monitoring in patients with CHF provides important information on left ventricular filling (13), with a favorable impact on meaningful outcomes. Application of this technology to other important diseases, such as pulmonary hypertension and diastolic left ventricular dysfunction, may describe important pathophysiologic features of those diseases and improve therapeutic intervention.

Individual characteristics of ongoing pressures. The individual characteristics of ongoing pressures were unique, which required using the patient's values as their own control. Many patients had large pressure variability, whereas others had less variable measurements with a similar clinical course (Fig. 1). This observation may be important, as highly variable systemic arterial pressures cause more end-organ damage than higher mean, but less variable pressures (14). Whether RV pressure variability carries the same risk remains to be determined. Furthermore, inherent pressure variability may increase the possibility of inappropriate volume assessment, unless monitoring algorithms account for individual changes. Other markers of physiologic control systems, such as HR variability, which indirectly quantifies autonomic HR control, may be important parameters to include in continuous hemodynamic monitoring systems.

This study established that long-term pressures have individual variability, but it was not designed to examine the exact predictive value of continuous hemodynamic monitoring, as there were no control subjects in the phase of the trial in which hemodynamic information was used for management. However, these observations will provide a means to develop future monitoring algorithms that may facilitate processing of continuously acquired data. This is important because pressures changed beyond their normal variability when volume-overload exacerbations were severe enough to require hospitalization. Often the pressure changes occurred several days before clinical intervention. Pressures further increased in the 24 h before hospitalization. This pattern suggests that the earlier changes possibly reduced the patient's "tolerable reserve" but did not produce severe symptoms until pressures increased further. Therapy guided by information from IHM systems could thus be useful by providing early warning of an impending, severe exacerbation or, in the case of minor volume overload, confirming the patient's status and guiding therapy. This may result in a substantial reduction in the need for health care utilization, especially with the advent of trans-telephone data transmission. Furthermore, when hospitalization cannot be avoided, the presence of an IHM may reduce the need for invasive hemodynamic monitoring using traditional balloon-tipped catheters. Prospective studies designed to specifically evaluate how an IHM may reduce costs of CHF care are still required.

Implications for future use. Device therapy to treat CHF now includes biventricular pacemakers in patients with significant conduction delays (15,16) and ICDs in those with ischemic heart disease (17). Because biventricular pacemakers reduce hospitalizations (16) and ICDs tend to increase them (17), combination devices, such as biventricular pacemakers with ICDs, may provide therapy that has a favorable impact on morbidity as well as mortality. Similarly, combining IHM capability with ICDs or other devices may have a favorable, meaningful impact clinical outcomes. A device that combines IHM information with ICD capability will potentially result in more cost-effective, device-based, disease management systems. Furthermore, value may be added to other interventions such as ventricular assist devices or artificial hearts and may offer a way to reduce costs while enhancing therapeutic benefits.

The patients in this study already benefited from organized CHF treatment programs, which significantly reduce hospitalizations (1). Although this study was not designed to examine the effect of IHMs on health care utilization, the results provide substantial background to more fully examine the hypothesis that IHMs use may have a broad range of

applications and will likely have a significant impact on disease morbidity, even beyond those benefits of an organized system. The device used in this study continuously measures hemodynamic information. This is theoretically superior to one-time "spot measurements," typically used in CHF management and diagnosis, such as body weight and B-type natriuretic protein. Validation of this concept will require prospective trials specifically designed to compare other modalities with IHM information.

Conclusions. Continuous monitoring of ambulatory RV pressures is feasible, accurate, and safe. Furthermore, RV pressure changes reflect the patient's volume status, which provides meaningful information to guide day-to-day management of CHF. Long-term management of patients with CHF, guided by ambulatory hemodynamic information, promises to have an effective impact on the severe morbidity associated with this syndrome.

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