Ambulatory Hemodynamic Monitoring in Pulmonary Arterial Hypertension


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Although an abnormality of pulmonary hemodynamics is the defining characteristic of pulmonary hypertension (PH), there is considerable debate about the optimal method of assessing pulmonary arterial pressure (PAP). Cardiac catheterization is widely accepted as the most accurate and comprehensive technique for measuring PAP and venous pressure. Doppler echocardiography provides a high level of correlation with invasively measured hemodynamics and is free of risk or significant discomfort.

Both of these methods have particular advantages and each has an established vital role in the evaluation and follow-up of patients with suspected or known PH. Catheterization provides crucial information about the impact of pulmonary venous and left heart pressures on PAP; directly measures right atrial pressure and right ventricular end-diastolic pressure; determines pulmonary blood flow; permits calculation of pulmonary vascular resistance; supplements hemodynamic information about valvular heart disease; quantifies shunts; and, with contrast imaging, visualizes pulmonary vascular anatomy. Supine or upright exercise can be performed during catheterization, but exercise testing during catheterization is not widely available and is not well standardized. Doppler echocardiography yields important morphologic, gradient, and quantitative regurgitant data related to valvular heart disease; accurately assesses systolic and diastolic ventricular function, ventricular and atrial chamber size, and myocardial characteristics; identifies congenital lesions definitively; and can estimate relevant hemodynamic data in addition to pulmonary arterial systolic pressure, including cardiac output, diastolic and mean pressure, pulmonary vascular resistance and capacitance, and right ventricular dP/dt.

Each technique, however, also has unique disadvantages. Catheterization is invasive and therefore carries an element of risk and discomfort. Doppler echocardiography is noninvasive. Although data from Doppler echocardiography correlate well with those of more invasive methods, this technique may be imprecise in some patients. Attempts to obtain hemodynamic measures during exercise with echocardiography are limited by the technical issues associated with imaging the tachypneic patient. Both techniques are necessarily performed under controlled circumstances (generally in a supine patient with various degrees of anxiety, discomfort, or sedation), which may not reflect actual conditions of daily living for most patients. Both techniques are done infrequently as dictated by arbitrary follow-up protocols or in defined situations such as clinical deterioration. Furthermore, both entail substantial expense.

Despite the pivotal role of echocardiography and catheterization in evaluating pulmonary hemodynamics, it is interesting that pulmonary hemodynamics per se generally do not emerge as potent indicators of therapeutic effectiveness or of outcome. Criteria of functional status, exercise capacity, and right ventricular

Figure 1. (A) Chronicle device and lead. (B) Appearance of implanted Chronicle on chest X ray. The lead tip is positioned in the right ventricular outflow track.

Key Words—pulmonary arterial hypertension; implantable hemodynamic monitoring; pulmonary arterial pressure; right arterial pressure.
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function have much stronger prognostic content because they tend to distinguish patients in a more advanced and decompensated state from those with equally severe PH who have been able to better adapt physiologically. Hemodynamics may be more predictive of—or may be early indicators of—deterioration in currently stable individuals, but because hemodynamic assessment is infrequent, this remains speculative.

Continuous intravascular pulmonary hemodynamic monitoring may provide a key to understanding the relationship of pulmonary hemodynamics to prognosis, therapeutic effectiveness, and symptoms. Whether the opportunity to have constant access to hemodynamic data can influence clinical decision making and, ultimately, outcome, is worthy of investigation. We elected to obtain a preliminary impression about these issues by performing a pilot study to assess the safety and feasibility of an investigational implantable hemodynamic monitor (Chronicle Model 9520 or 9520B; Medtronic, Inc, Minneapolis, MN; for investigational use only) in patients with pulmonary arterial hypertension (PAH). The initial report of this experience showed that changes in hemodynamics measured by the implantable hemodynamic monitor (IHM) correlated with changes in 6-minute walk distance, exercise tolerance, quality of life, and the brain natriuretic peptide during 12 weeks of treatment with pulmonary vascular-targeted therapy.[1]

While these results are important for validating the relevance of hemodynamic changes, they do not provide immediate insights into the utility of continuous monitoring for clinical management. The limited size of the sample population in our pilot study is not adequate to address this systematically. Nevertheless, during the ongoing experience with these patients, we have made observations that suggest that the use of an IHM may have a clinical role in selected situations. This article briefly describes our study and through illustrative cases summarizes the information that was obtained from the IHM.

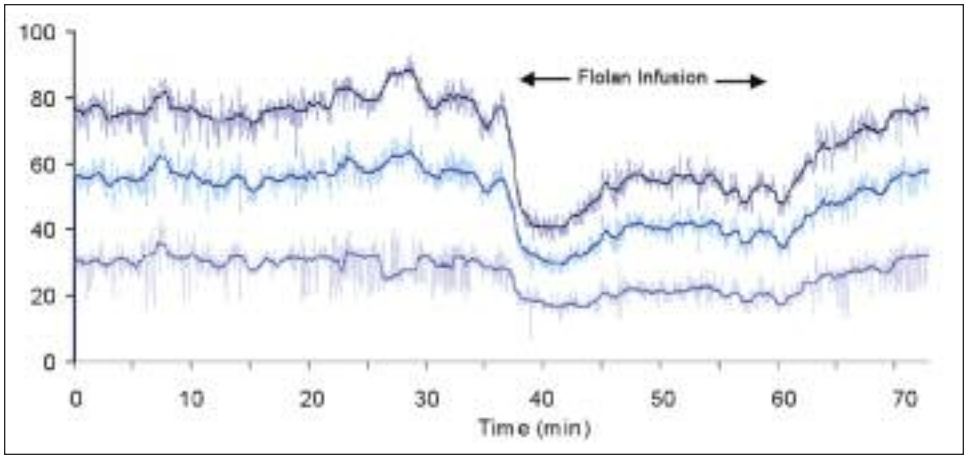

Figure 2. Acute hemodynamic changes.

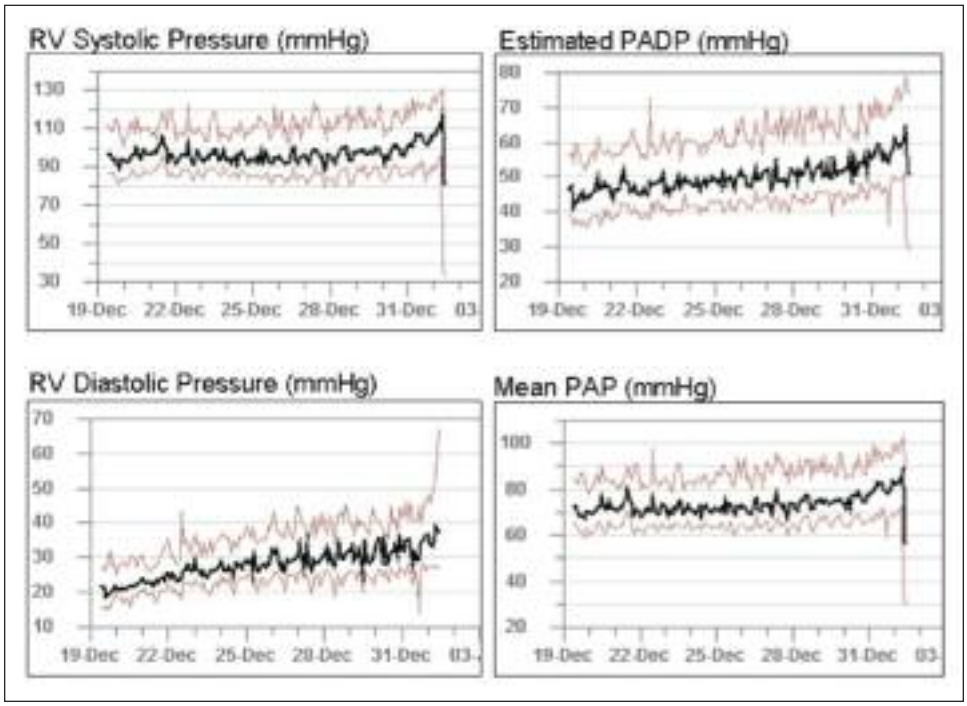

Figure 3. Right ventricular hemodynamics preceding death.

Patient Population

Patients with functional class 2-3 idiopathic PAH, or PAH associated with connective tissue disease or anorexigens were considered for this study. Patients were either newly diagnosed or on stable PAH therapy for at least 3 months, but for whom addition of an approved PAH therapy was clinically indicated. Additional study enrollment criteria were: (1) echocardiogram measurement consistent with PAH with an estimated right ventricular systolic pressure (RVSP) > 50 mmHg; (2) no evidence of obstructive or restrictive lung disease (total lung capacity < 70% predicted); and (3) aged 18 years or older. Exclusion criteria were: (1) left ventricular dysfunction evidenced by pulmonary capillary wedge pressure (PCWP) > 18 mmHg or left ventricular ejection fraction (LVEF) 40 mmHg; (2) 6-minute walk distance < 50 or 450 m; and (3) unable to tolerate a one-week baseline observation period before therapy is added. All centers obtained approval of their institution's ethics committee prior to the study and all patients provided written informed consent.

Study Design

The study was designed as a 12-week, prospective, nonrandomized, multicenter pilot study. All patients received an implanted hemodynamic monitor after enrollment. Baseline tests included physical exam, functional class, echocardiography, brain natriuretic peptide levels, 6-minute walk test, quality-of-life assessment using the Minnesota Living with Heart Failure Questionnaire,[2] and a cardiopulmonary exercise test (CPX, MedGraphics, Minneapolis, USA) using a modified Naughton exercise protocol. Tests were repeated 12-weeks after start of the new treatment for PAH. The drug treatment was initiated a minimum of 7 days after

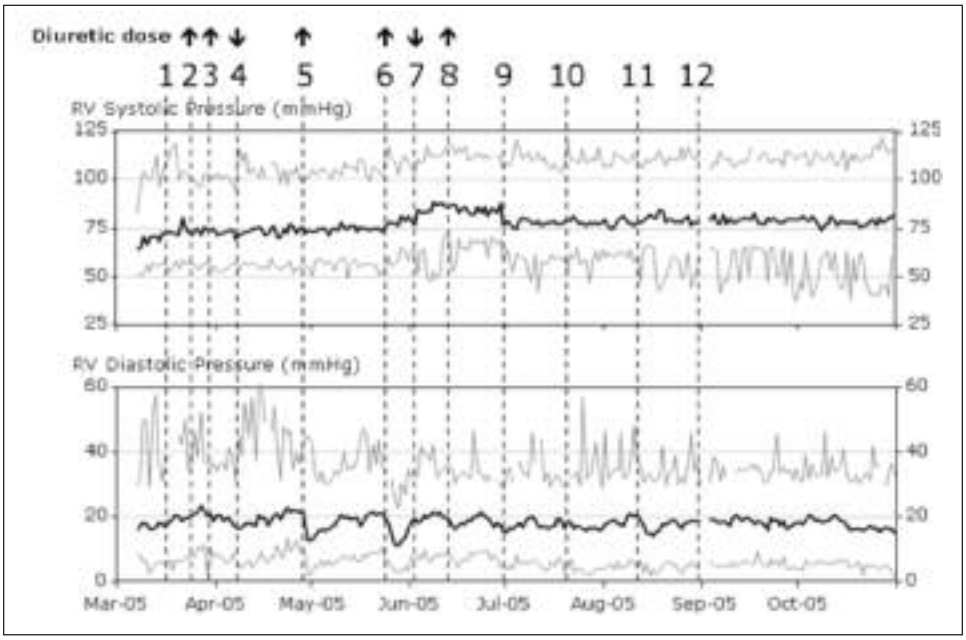

Figure 4. Chronically elevated right ventricular end-diastolic pressure.

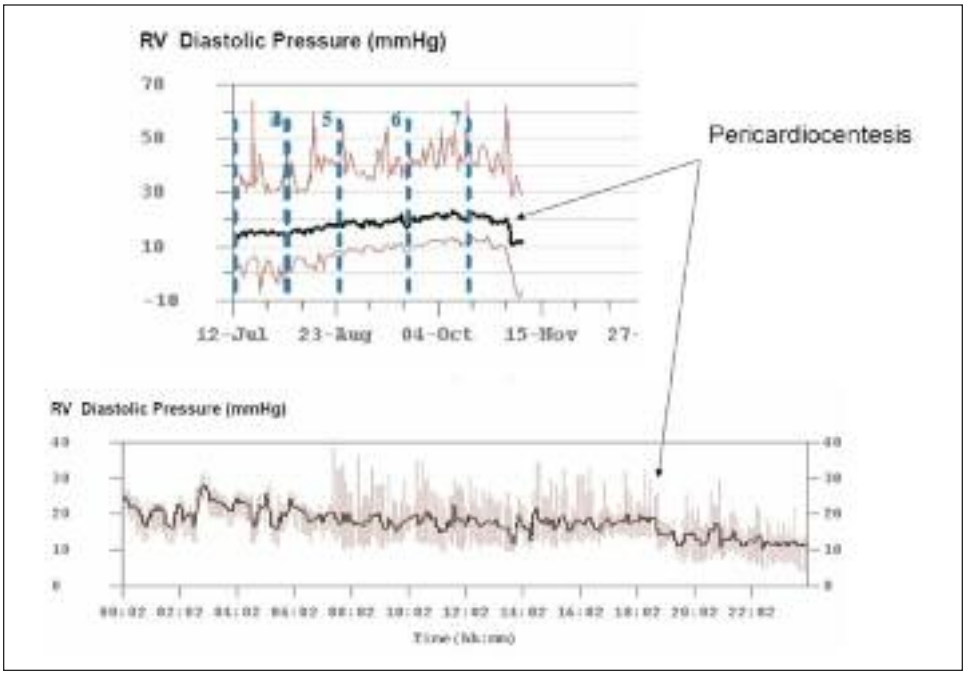

Figure 5. Pericardial effusion and pericardiocentesis.

implantation of the IHM, which permitted the collection of baseline ambulatory hemodynamic measurements. Selection of PAH therapy included intravenous (IV) epoprostenol, subcutaneous treprostinil, oral bosentan, or oral calcium channel blocker. Drug adjustment schedules followed standard guidelines. The IHM hemodynamic data were reviewed regularly by the PAH clinic staff and integrated with patient symptoms reported during telephone follow-up or clinic visits and with other clinically indicated tests to determine adjustments to therapy. Following the 12-week visit, patients continued to upload hemodynamic data at weekly intervals, and were seen in the clinic every 3 months.

Implantable Hemodynamic Monitoring

The Chronicle IHM (**Figure 1**) consists of an implantable hemodynamic monitor (IHM) that continuously stores data from a pressure sensor lead (Model 4328A) positioned in the right ventricular outflow tract.[3] RVSP, right ventricular diastolic pressure (RVDP), estimated pulmonary artery diastolic pressure (ePAD), mean PAP, and heart rate were derived by the IHM from each cardiac cycle.[4] The ePAD was derived from the right ventricular (RV) pressure waveform at maximum dP/dt, the time of pulmonary valve opening.[5,6] Mean PAP was a time-weighted average of RVSP and ePAD. Measured values were stored continuously as the median or median and range (6th and 94th percentiles) over each storage interval (typically 6 to 12 min). Measurements of patient activity levels were provided by an activity sensor mounted inside the IHM.

The pressure sensor required a correction for varying ambient atmospheric pressures by an external pressure reference device (EPR; Model 2805). Patients transmitted stored data from the IHM and EPR by telephone from their homes at least once a week to a password-secured Web site where the data were viewed by the clinical staff.[7]

Results

Twenty-four PAH patients at 3 institutions underwent IHM implantation before a change in PAH therapy. Follow-up duration ranged from 2.5 to 5 years. Fourteen patients were implanted at the Mayo Clinic. None of these patients were lost to follow-up, but 2 patients died. All patients were evaluated on site at regular 6-month intervals or more frequently as clinically indicated. During follow-up, management decisions were made based on clinical presentation, including data obtained via the IHM.

Acute vasodilator response. **Figure 2** illustrates the capability of the IHM to sense, store, and display high-fidelity measurements. The tracing depicts the acute hemodynamic response in the cardiac catheterization laboratory to IV epoprostenol titrated to 9 ng/kg/minute. The pulmonary artery systolic (top tracing), calculated mean (middle tracing), and estimated diastolic pressures (bottom tracing) are represented as median, 94th percentile, and 6th percentile values from every 6 seconds of measurement.

Death. **Figure 3** shows hemodynamic measurements in the days preceding death of a patient with PAH. This patient died 14 days after hemodynamic monitor implant. Approval for therapy with bosentan had been obtained following the baseline catheterization, but the patient died before the arrival of the medication. The patient presented to her local hospital with worsening dyspnea, was admitted to the intensive care unit and seemed to stabilize, but then rather abruptly developed hemodynamic collapse

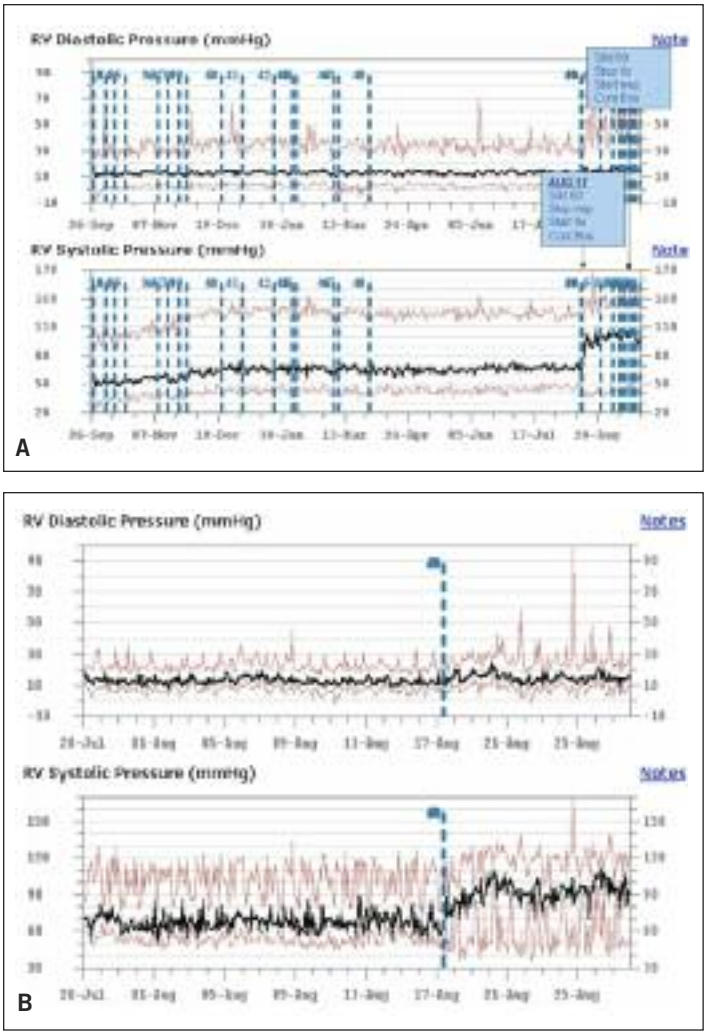

Figure 6. Monitoring hemodynamic effects of treatment adjustments.

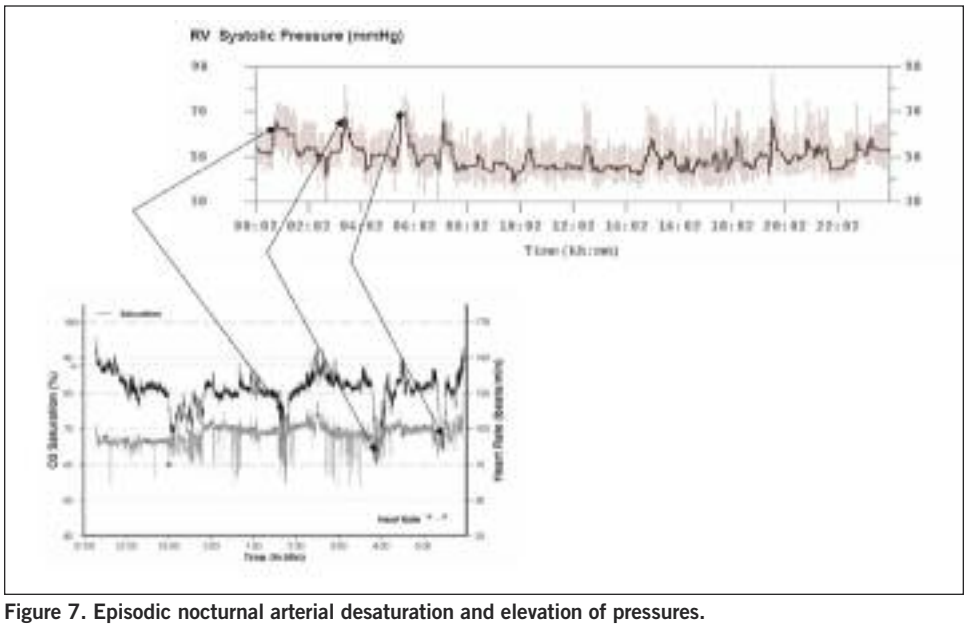

Figure 7. Episodic nocturnal arterial desaturation and elevation of pressures.

and died before arrangement could be made for initiation of prostanoid therapy.

The IHM was removed postmortem and showed that right ventricular pressures had risen dramatically in the days preceding death. Mechanisms are uncertain but could represent in situ thrombosis of smaller pulmonary arterioles or progressive vasoconstriction related to hypoxemia and failure of a marginally compensated right ventricle. Limited autopsy did not demonstrate thrombosis in the major pulmonary arteries.

The disease course in this patient is a sobering reminder of the capricious course of PAH when substantial elevation of right atrial pressure is present before the initiation of treatment. Existence of patients at risk for this accelerated disease course may explain the benefit of epoprostenol in the pivotal randomized trial.

Chronically elevated right ventricular end-diastolic pressure. **Figure 4** shows persistently elevated right ventricular end-diastolic pressure despite aggressive medical therapy. The pressure was repeatedly transiently responsive to augmentation of diuretics. Despite this marked chronic elevation in right ventricular end-diastolic pressure, the patient continues to survive.

Pericardial effusion. Recognition of deteriorating hemodynamics, notably progressively increasing RVDP (**Figure 5**), associated

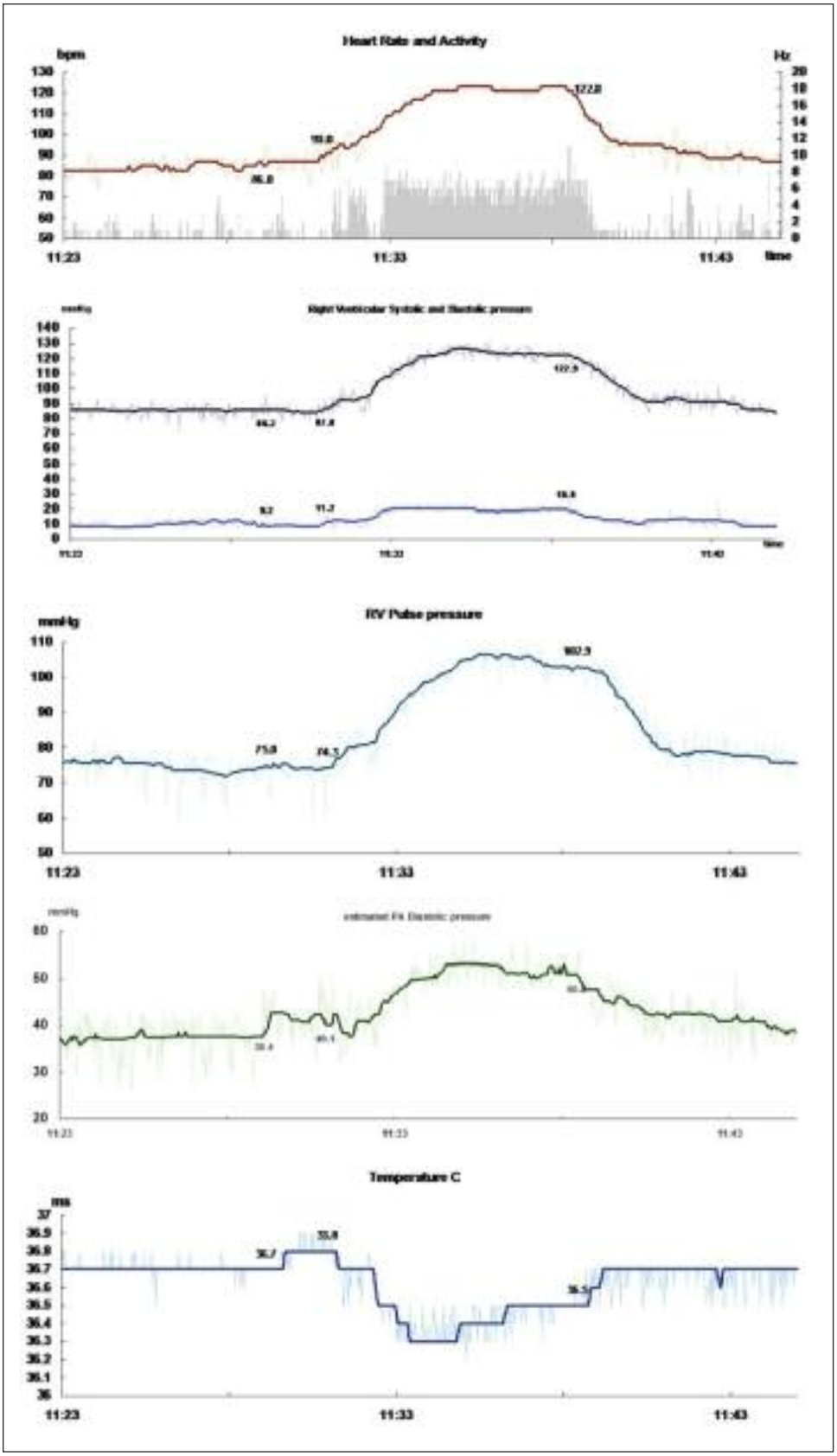

Figure 8. Six-minute walk test.

with increased dyspnea unresponsive to augmented diuretics in a patient with PAH prompted an unscheduled return to the clinic. Echocardiography demonstrated a large pericardial effusion; hemodynamics and symptoms improved immediately with pericardiocentesis.

Response to treatment. **Figure 6** illustrates how treatment modifications were managed by remote evaluation of hemodynamic changes. In this patient, subcutaneous treprostinil was gradually replaced with combined oral agents (bosentan and sildenafil) and inhaled iloprost because of infusion site pain.

(A) Shows the long-term (1-year) view of right ventricular diastolic and systolic pressures. The central black tracing represents the daily median value of each parameter; the red tracings are the 6th and 94th percentiles for each day. The vertical blue dashed lines are markers annotating events—in this case usually dose changes of various medications. Note the worrisome abrupt rise in RVSP with cessation of subcutaneous treprostinil.

(B) Shows the monthly view in which median and percentile values of measurements every 2 hours are displayed. It is evident that RVDP initially rises from a stable baseline of 10 mm Hg and RVSP rises impressively from 60 to 90 mm Hg.

(C) Shows the 1-week view (2-hour values). At this higher resolution the upward trend is visible but appears less dramatic.

(D) Shows the 24-hour view of mean pulmonary artery pressure on 3 consecutive days (values represent median and percentiles every 6 minutes). This level of resolution demonstrates the pattern of response to inhaled iloprost (administration shown by black arrows) in which mean pulmonary artery pressure is substantially but transiently reduced.

IHM data provided timely recognition that hemodynamic values were deteriorating, allowing rescue with resumption of treprostinil.

Nocturnal arterial oxygen desaturation. **Figure 7** shows episodic nocturnal arterial desaturations and simultaneous elevation of pressures that resulted in recognition of presence of sleep disordered breathing causing nocturnal hypoxemia. The episodic pressure elevations illustrate the powerful superimposed vasoconstrictor effects of hypoxemia even in a patient already treated with bosentan.

Response to 6-minute hall walk. **Figure 8** illustrates that even submaximal exercise results in a major increase in pressures. The rise in RVDP suggests decompensation of the right ventricle during activity. A normal response would be maintenance of a normal RVDP. Interestingly, core temperature fell during the walk, perhaps because of an increase in return of cooler blood from the extremities.

Discussion

Ambulatory hemodynamic monitoring provides the ability to examine hemodynamics of PH during activities of daily living, as frequently as necessary. It is a unique tool to study the physiology of PH during rest, activity, and sleep. The longitudinal observations permit recognition of the ongoing effects of treatment, response to change in treatment, and early warning regarding deteriorating hemodynamic compensation.

Since our experience is the result of a nonrandomized pilot study, it is not possible to demonstrate in a statistical fashion that the availability of hemodynamic data altered patient outcome. Anecdotally, both patients and health care providers felt that the availability of the hemodynamic data facilitated decision making, helped monitor disease status, and provided support for evaluating possible substrates for patient symptoms, particularly during remote telephone follow-up. The usefulness of the IHM was borne out by the decision of the majority of patients to proceed with the exchange of the battery pack that powered the IHM to allow for continued monitoring.

We believe that the RVDP is the most critical value to observe, consistent with the recognition that right atrial pressure is the most powerful hemodynamic determinant of patient outcome. Limitations of the device include inability to measure cardiac output. However, preliminary findings indicate that the algorithms using right ventricular pressure waveform to estimate cardiac output with the Chronicle device are accurate. Additional research is still needed.[8]

Other monitoring devices are under development, including a pressure sensor that can be released into the pulmonary artery from a catheter-based system. This device (Cardiomems, Inc) is not actively powered, but can be intermittently checked by an external antenna that pings the device. Correlation with invasive pressure measurements appears to be very good.[9] However, this device measures only the PAP and has no internal memory, so its potential utility in PAH is uncertain.

Selection of the best treatment for PAH, and the best tools to assess treatment response, remain highly complex and controversial.[10] We believe that IHM represents an exciting and novel tool that is highly promising. It may ultimately prove useful to guide treatment decisions, assess important hemodynamic trends to aid prognosis, reduce the need for repeated right heart catheterizations, and serve as an endpoint for investigation of developing therapies.

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