Ambulatory Hemodynamic Monitoring in the Management of Pulmonary Arterial Hypertension

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Background: Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling, rise in pulmonary arterial pressures, and if left untreated, right heart failure. Invasive hemodynamic assessment with right heart catheterization (RHC) has been the gold standard for the diagnosis and serial assessment of patients with PAH. However, RHC has important limitations and might be supplemented by newer technologies in the management of PAH patients.

Implications for Clinicians: Implantable hemodynamic monitors (IHM) hold the promise of being able to provide accurate pulmonary artery pressure measurements, with frequent or continuous remote monitoring in the home or ambulatory setting. As such, IHMs may provide a more complete understanding of a patient’s hemodynamic profile and burden of disease. IHM data may also help to provide ongoing feedback in terms of a PAH patient’s response to medical therapy and other interventions and might be valuable in specific subsets of patients with borderline or exercise-induced PAH.

Conclusions: Though clinical studies using IHMs in PAH patients have been limited to small series and case reports, these devices hold a great deal of promise to supplement RHC in the management of PAH patients and warrant further investigation and clinical experience.

Pulmonary arterial hypertension (PAH) is an insidious disease characterized by progressive hemodynamic derangements in the pulmonary arterioles and microvasculature. Pulmonary vascular remodeling in PAH leads to a gradual increase in right ventricular (RV) afterload, elevation in pulmonary artery (PA) pressure, and ultimately to RV dysfunction and RV failure.

In early studies evaluating the prognosis of PAH such as the National Institutes of Health registry, mean PA pressure was found to be an independent predictor of survival.1,2 Conversely, newer studies from large contemporary registries in the United States and Europe have suggested that of hemodynamic variables, severely elevated pulmonary vascular resistance (PVR) and right atrial pressure better predict mortality than mean PA pressure per se.3-5 This does not imply, however, that PA pressures are not important, and from a patient and clinician’s perspective, PA pressures remain a frequent focus of interest.

To date, invasive hemodynamic assessment with right heart catheterization (RHC) has been considered the gold standard for the diagnosis of PAH, to assess severity of disease and to gauge response to PAH-specific therapies. As such, RHC forms the cornerstone of the evaluation of PAH patients and is included in current PAH management guidelines.6 As with any gold standard test, however, it is also important to acknowledge the limitations and technical challenges of RHC, some of which are user-dependent, and some of which are inherent to the test itself, when making treatment decisions. Moreover, newer technological developments such as the advent of implantable hemodynamic monitors (IHM) afford an alternative approach to the diagnosis and management of PAH patients and the potential use of this technology in patients with pulmonary hypertension (PH) will form the basis of this article.

LIMITATIONS OF RHC

Though RHC can be performed very safely with low complication rates,7 accurate assessment of invasive hemodynamics requires rigorous attention to detail. This starts with equipment setup to ensure accurate leveling of pressure transducers and the zero line, as misleveling in and of itself can lead to inaccurate pressure measurements.8

In many PAH patients, especially those with some degree of associated lung disease, hemodynamic pressure recordings are subject to significant respiratory variation in PA pressures and wedge pressure. This requires careful scrutiny of each measured parameter by an experienced clinician, with measurements ideally taken consistently at end expiration.8 Errors in measurement of the wedge pressure using mean rather than end-expiratory wedge pressure, for example, can lead to the misclassification of pulmonary venous hypertension as PAH, and similarly, underwedging of the PA catheter can lead to an erroneous diagnosis of left heart–related PH in patients with PAH.

Key Words—pulmonary arterial hypertension, hemodynamic monitoring, diagnosis, management

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In many centers, RHC for the evaluation of PAH is also typically performed at rest and in the recumbent, supine position. This is a somewhat artificial situation and is clearly not the hemodynamic state that most patients spend the majority of their lives in. Hemodynamics obtained in this condition may underestimate the severity of PAH and functional limitations with activity.

Indeed, the biggest limitation inherent to RHC is that it only provides a snapshot of a patient’s hemodynamics at a single time point, akin to a solitary office blood pressure recording. In patients necessarily reflected by a solitary office blood pressure over the course of a 24-hour period and from day to day, which is not obtainable in this condition. Hemodynamics may be underestimated by resting hemodynamics on PH-specific therapy can develop progressive RV dilatation and dysfunction on cardiac MRI.

Close Monitoring During Medication Titration or Changes in Therapy
The intermittent pulmonary hemodynamic information provided by RHC makes optimization of treatment more challenging, particularly in assessing response to specific therapies such as parenteral prostacyclins. In many PAH referral centers, parenteral prostacyclins are often titrated slowly to a fixed “target” dose as tolerated by patients’ clinical symptoms, before reassessment of hemodynamics with RHC and consideration of further titration. Use of an IHM in these patients might allow for more ready and rapid reassessment of response to therapy and potentially of more rapid titration to an effective dose. Similarly, IHM data might help to inform the need to augment existing oral therapies or the impact of changes in PAH-specific therapy. There has already been limited but promising experience using IHM data to gauge response to changes in medical therapy.13,14

Remote Monitoring and Reduction in Heart Failure Hospitalization
Another potential advantage of IHM monitoring is the ability to monitor PA pressures remotely. Patients with impending decompensated heart failure (HF) can be identified by a rise in PA pressures on IHM prior to worsening clinical symptoms, and the same holds true for patients with HF and associated World Health Organization (WHO) Group 2 PH.15

Managing congestive heart failure patients with knowledge of PA pressures from IHM data has been shown to reduce HF hospitalizations, and PA pressures have been shown to rise before the onset of worsening symptoms, allowing a window for early intervention by a clinician.16,17 In addition, many PAH patients live significant distances away from tertiary PAH referral centers. Through remote monitoring, PAH patients may be able to enjoy a greater sense of autonomy, self-control, and work productivity through reduction in the number of visits to the tertiary care center and by preventing hospitalizations by recognizing clinical decline before the onset of symptoms. In addition, the reduction in invasive procedures such as RHC with their associated risk and discomfort could help to improve quality of life for PAH patients by reducing associated morbidity, anxiety over the procedure, and loss of time.

Assessment of Borderline PH or Exercise-Induced Symptoms
Lastly, another clinical scenario in which IHM data might inform treatment decisions is in patients who have borderline PH at rest or those who have predominantly exercise-induced symptoms. In patients with PH related to left heart disease in the CHAMPION trial, the baseline resting RHC significantly underestimated the prevalence of PH when compared to the average mean PA pressure from IHM data over the first week at home post implant.18 In many centers and in the community, exercise hemodynamics are often not routinely performed in PAH patients, and even in those centers that do undertake rigorous exercise evaluation, the exercise protocol may not mirror the hemodynamic changes seen with daily activities.

In patients with scleroderma-related PAH, survival is improved with early initiation of therapy,19 and screening algorithms in this patient population have identified a group of patients with “borderline PH,” defined as a mean PA pressure between 20–25 mm Hg. This patient population has a 40% to 60% chance of progressing to clinically relevant PAH over the next 4 to 5 years, and use of IHM data may again identify early disease progression before severe symptoms develop.20

EXPERIENCE WITH CURRENT AMBULATORY HEMODYNAMIC MONITORING SYSTEMS
At present, 2 IHM systems have been studied in patients with congestive heart failure with left heart-related PH (WHO Group 2), and one system has
been evaluated in a limited number of PAH patients. A comparison of these systems is illustrated in Table 1.

The Medtronic Chronicle system (Medtronic, Minneapolis, MN) is an implanted device similar in appearance to a pulse generator of a pacemaker with a transvenous lead and associated pressure sensor, which is positioned in the RV (Figure 1). This system can provide an RV systolic pressure, an estimated PA diastolic pressure, and a calculated mean PA pressure. In patients with left-sided HF, IHM data have been shown to provide accurate RV and PA pressure measurements vs simultaneous RHC hemodynamics,21,22 as well as in a limited number of patients with PAH.23

In the COMPASS-HF study of 274 New York Heart Association (NYHA) functional class III or IV HF patients, the IHM was shown to be safe with no pressure sensor failures and very rare system-related complications. Patients treated based on IHM data had a nonsignificant trend to reduction in HF-related hospitalizations, which failed to meet the efficacy endpoint.24 A subsequent study demonstrated that patients who maintained lower intracardiac pressures on long-term monitoring had lower risk of future hospitalization.25 Despite these data, the Medtronic Chronicle system has not received FDA approval in the United States for hemodynamic monitoring in HF patients. This is somewhat unfortunate, because clinical data using IHM in patients with PAH remains limited to small clinical studies and case series mainly with the Medtronic Chronicle system. The clinical data that do exist have revealed intriguing findings concerning the severity of PAH and the effects of medical therapy.

Use of the Medtronic Chronicle in 5 patients with PAH treated with inhaled iloprost revealed that the reduction in PA pressures with iloprost was much shorter-lived than previously thought, and the vasodilator effect was achieved for only 13% of the entire monitoring span.26 In addition, though iloprost consistently reduced PA pressure at rest, it did not change PA pressures at peak exercise and workload.27 In 2 PAH patients transitioned from iloprost to bosentan, IHM data allowed clinicians to see the acute efficacy of bosentan therapy, which was sustained and indeed more pronounced over a week of therapy, allowing for successful discontinuation of iloprost therapy.14 In a multicenter study of 24 patients with PAH who had the Medtronic Chronicle implanted prior to change in PAH therapy, IHM data identified 13 of 15 patients who improved 6-minute walk distance greater than 30 meters, and change in mean PA pressure on IHM monitoring correlated with change in 6-minute walk.13

The second IHM device that has been used extensively in HF patients is the CardioMEMS sensor (St. Jude’s Medical, St. Paul, MN). This system uses a wireless pressure sensor (Figure 2), which is a passive implant placed in a distal branch of the pulmonary artery during an RHC procedure via a delivery catheter. The external measurement system is designed to acquire pressure information from the sensor implanted within the pulmonary artery. It is composed of a main unit, a detachable antenna, and the connectivity to export the pressure data to an external database.

| Table 1. Comparison of Medtronic Chronicle and CardioMEMs Hemodynamic Monitors |
|--------------------------------|-------------------------------------|
| **Sensor Placement** | **Medtronic Chronicle** | **CardioMEMS** |
| Sensor at tip of transvenous lead in RV | Entire sensor placed in distal branch of PA |
| **Power Source** | Via implanted battery similar to pacemaker generator | Powered by RF energy from remote patient electronic module |
| **Size** | Overall system similar to typical implanted pacemaker | Entire implanted system smaller than AAA battery |
| **Implant Technique** | Battery placed subcutaneously; transvenous lead tunneled typically to subclavian vein and then positioned in RV | Placed in distal PA in conjunction with femoral RHC |
| **Frequency of Recording** | Continuous recording and storage | Data transmitted only when sensor placed on remote patient electronic module |
| **Hemodynamic Parameters Provided** | RV systolic, diastolic pressure, estimate PA diastolic pressure, RV dp/dt | Direct PA systolic and diastolic pressure, calculated PA mean pressure |

Figure 1: Medtronic Chronicle System Including Transvenous RV Lead and Pressure Sensor.
though the device showed a significant reduction in hemodynamics (HR 0.74, 95% CI 0.55 to 0.99, P=0.04). Moreover, a recent substudy of the CHAMPION trial suggested that WHO Group II PH was underdiagnosed by a baseline RHC when compared to the mean PA pressure on IHM monitoring over the first week of the study, and that patients with occult PH had higher hospitalization rates than those without any PH. Based on results of the CHAMPION trial, the CardioMEMS device has received FDA approval for the management of NYHA functional class III HF with HF hospitalization in the past year.

Though there is relatively little experience with use of the CardioMEMS device in the PAH population, the clinical rationale for using this device is similar to that with the Medtronic Chronicle with the potential advantage of a cardiac output assessment, though the cardiac output algorithm is yet to be fully validated. In patients with PAH and presumable normal wedge pressure, knowledge of mean PA pressure and cardiac output could thus give the clinician insight into PVR on an ongoing basis. Certainly larger clinical studies using IHM data in PAH patients are warranted before their use is adopted in routine clinical practice, and IHM data might be used as a surrogate endpoint in future PAH clinical trials. In light of this, the National Heart, Lung and Blood Institute has recently funded a “proof of concept” study utilizing the CardioMEMS device in conjunction with cardiac MRI in 20 PAH patients to explore the feasibility and safety of using these combined modalities as a means to improve outcome prediction and monitoring of treatment efficacy in this disease state.

SAFETY OF DEVICE IMPLANTATION

Limited safety data exist for the use of IHM in patients with PAH. In the small case series and case reports of the use of IHM in patients with PAH, no safety concerns were reported with IHM implantation. In the CHAMPION trial of the CardioMEMS IHM in 550 patients with congestive heart failure, 48 (9.2%) patients had PH with a significant pulmonary vascular component, a clinical profile similar to that encountered in PAH.

In this patient subset, there was only a single device/system-related complication: an atrial tachyarrhythmia associated with the implantation RHC procedure. The device/system-related adverse event rate in this subgroup with PH with a significant pulmonary vascular component was not statistically different than the established rate of adverse events for RHC in PH (n=76 of 7218, 1.1%, P=0.401), and is also not statistically different than what was observed in the remaining CHAMPION cohort with NYHA class III Heart Failure (n=7 of 508, 1.4%, P=0.517). This acceptable safety record in CHAMPION, in patients with comparable pulmonary vascular hemodynamic characteristics as PAH patients, provides a reasonable basis to expect an acceptable safety profile in PAH patients. In the COMPASS-HF study, which used the Medtronic Chronicle IHM in patients with NYHA class III or IV HF, some of whom had PH, there were no pressure sensor failures, and system-related complications occurred in only 8% of patients, of which all but 4 were resolved.

IMPLICATIONS AND FUTURE DIRECTIONS

Ambulatory hemodynamic monitoring holds great promise for the management of patients with PAH. IHM data might provide further insight into a given patient’s physiology and response to pharmacological therapy, while potentially allowing for remote monitoring and decreasing the requirement for office visits and invasive hemodynamic assessment. Despite these potential advantages, there has been very limited efficacy and safety data in PAH patients with IHM monitoring strategies to date. With FDA approval of the first IHM for use in HF patients and growing experience at major centers with this technology, this is an ideal opportunity to evaluate this technology in a larger clinical trial in PAH patients.

Figure 2: CardioMEMS HF System Including Pressure Sensor and External Measurement Unit.

References
1. D’Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary...