Right Ventricular Pressure Waveform and Wave Reflection Analysis in Patients With Pulmonary Arterial Hypertension*

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Background: **Cardiac index is an important determinant of outcome in patients with idiopathic pulmonary artery hypertension (IPAH). An implantable hemodynamic monitor (IHM) [Chronicle; Medtronic; Minneapolis, MN; a system limited to investigational use only] that records right ventricular (RV) pressure waveforms continuously may increase our understanding of IPAH and improve therapeutic selections and outcomes. The aim of this study was to investigate whether the RV pressure waveform utilizing an IHM can be used to estimate the magnitude of pressure wave reflection and cardiac index in patients with IPAH in acute settings.**

Methods: **In eight patients with pulmonary arterial hypertension, RV pressure waveforms were recorded utilizing the IHM, and breath-by-breath cardiac index was recorded during acute IV epoprostenol infusion at 3, 6 and 9 ng/kg/min. Late systolic pressure augmentation and cardiac index were estimated using the RV pressure waveforms and correlated with direct measurement of cardiac index.**

Results: **At baseline, the cardiac index was 2.1 ± 0.2 L/min/m^2, total pulmonary resistance index was 38 ± 2 Wood U/m^2, and RV systolic pressure was 92 ± 4 mm Hg. Wave reflection accounted for 29 ± 1 mm Hg of the RV systolic pressure. During epoprostenol infusion, total pulmonary resistance index and wave reflection decreased (− 15 ± 4 Wood U/m^2, $p < 0.001$, and − 5 ± 2 mm Hg, $p < 0.05$, respectively). The breath-by-breath cardiac index correlated with the RV pressure waveform cardiac index estimates ($r^2 = 0.95$).**

Conclusions: **RV pressure waveform analysis provides continuous hemodynamic assessments including cardiac index in acute settings. Once confirmed in long-term settings, this information may prove useful in optimizing a treatment regimen in patients with IPAH.**

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Key words: cardiac output; epoprostenol; pulmonary arterial hypertension; right ventricular pressure; wave reflection

Abbreviations: AP = augmented pressure; dP/dtmax = maximum derivative of pressure measured over time; dP/dtmin = minimum derivative of pressure measured over time; eCI = estimated cardiac index; eMPAP = estimated pulmonary artery mean pressure; IHM = implantable hemodynamic monitor; IPAH = idiopathic pulmonary arterial hypertension; mCI = cardiac index measured by the breath-by-breath technique; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PCCO = pulse contour cardiac output; PEI = preejection interval; Pes = right ventricular pressure at systolic time interval; Pfirst = early shoulder pressure; Psys = peak RV pressure; $\dot{Q}$max = peak volumetric flow; RV = right ventricular; RVDP = right ventricular diastolic pressure; STI = systolic time interval

Although idiopathic pulmonary arterial hypertension (IPAH), previously termed *primary pulmonary hypertension*, is a rare disease (*ie*, incidence of 2 to 3 persons per million per year), its morbidity and mortality remain high. Over the past decade, the therapeutic options for these patients have increased; however, decisions regarding how to optimize therapy remain difficult.[1]

Medical therapy for pulmonary arterial hypertension (PAH) is targeted directly toward the increased pulmonary artery (PA) pressures and high pulmonary vascular resistance. Typically, before starting treatment, a PAH patient's baseline hemodynamics and acute vasoreactivity are evaluated with invasive monitoring during administration of a short-acting vasodilator such as IV epoprostenol, sodium nitro-

prusside, or inhaled nitric oxide. Fewer than 10% of IPAH patients have acute pulmonary vasoreactivity (*ie*, a decrease in mean PA pressure ≥ 10 mm Hg to ≤ 40 mm Hg with a normal or increased cardiac output during the acute test).[1] The magnitude of the acute response, along with other clinical factors, is used to decide which therapy to initiate for an individual patient.[2] The treatment goal, in addition to improving symptoms, is to reduce PA pressure and increase cardiac output without lowering systemic BP to a symptomatic level. Baseline invasive hemodynamic measurements have been shown to be useful in predicting outcome. The National Institutes of Health Primary Pulmonary Hypertension registry enrolled 194 patients and developed a prognostic equation for patients with IPAH.[3] This equation took the form of $A(x,y,z) = e^{(0.007325x) + (0.0526y) - (0.3275z)}$, where x is mean PA pressure, y is mean right atrial pressure, and z is cardiac index obtained at the diagnostic cardiac catheterization. The probability of survival at 1, 2, and 3 years was $P(1) = 0.75^A$, $P(2) = 0.65^A$, and $P(3) = 0.55^A$. However, this prognostic tool may underestimate survival in the current era following the advent of targeted IPAH therapy. This potential limitation can be overcome by serial invasive hemodynamic assessments to update hemodynamic data following initiation of therapy, although this exposes patients to repeated invasive procedures. An accurate and easily repeated method to follow serial hemodynamic parameters could be useful in assessing response to therapy and prognosis in IPAH. Recent investigations have used an implantable hemodynamic monitor (IHM) [Chronicle; Medtronic; Minneapolis, MN; a system limited to investigational use only] that records high-fidelity right ventricular (RV) pressure waveforms and provides estimates of mean PA pressure and right atrial pressure continuously.[4] This device could be more useful if the tracking of the cardiac index was possible from RV pressure waveform because such development will allow estimation of all the parameters included in the prognostic equation.

It has been shown that not only the steady components (total pulmonary resistance) but also the oscillatory components of the RV afterload (characteristic impedance and pressure wave reflection) are also perturbed in IPAH patients.[5] During acute vasodilator testing, as well as during chronic treatment, the therapy that increases cardiac output might reduce both these steady and oscillatory components of the RV afterload. These changes may or may not be accompanied by a significant decrease in mean PA pressure but may still influence the prognosis.

We have described a method to estimate cardiac output from the high-fidelity RV pressure waveform.[6] Distinctly, this pulse contour cardiac output (PCCO) algorithm is not influenced by the presence of pressure wave reflection. This is important because the oscillatory components of the RV afterload (the amount of pressure wave reflection) could also be estimated through analysis of ventricular pressure waveforms.[7] If accurate in IPAH patients, these techniques could broaden the range of hemodynamic data derived from RV pressure waveforms. In this study, we hypothesized that analysis of high-fidelity RV pressure waveforms might be useful in tracking the magnitude of pressure wave reflection and the cardiac index in patients with IPAH.

Materials and Methods

Patient Population and Inclusion/Exclusion Criteria

A Food and Drug Administration-regulated feasibility study of the potential utility of the Chronicle investigational device exemption in patients with IPAH (n = 24) is currently in process (IDE No. G020303). A subset of eight patients (mean age, 44 ± 5 years [± SD]; seven women and one man) who had a recent diagnosis of IPAH or were receiving stable IPAH therapy for at least 3 months were included in this study. The patients were ≥ 18 years of age, in World Health Organization functional class II-IV, and had an echocardiographically estimated PA systolic pressure > 50 mm Hg. They were enrolled in the study if, by appropriate evaluation, they had low probability of pulmonary embolism and were without parenchymal lung disease.[2] Patients were also excluded if IPAH was related to left to right congenital systemic to pulmonary shunt, sickle-cell disease, HIV infection, schistosomiasis, left-sided valvular heart disease. or left ventricular dysfunction. In addition, patients were excluded from the study if their 6-min walk distance was < 50 m or > 450 m at baseline, or if they had another implantable device (pacemaker or defibrillator), or mechanical right-heart valve. The study was approved by Institutional Review Boards at participating facilities, and all patients provided written informed consent prior to enrollment.

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