The right ventricle in heart failure with preserved ejection fraction

Gorter, Thomas Michiel

Measuring Pulmonary Artery Pressures in Heart Failure: A New Useful Diagnostic Tool?

Thomas M. Gorter
Michiel Rienstra
Dirk J. van Veldhuisen

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Editorial

Heart failure (HF) is still one of the largest health problems in the Western world which caused an estimated 37.6M hospitalizations in the U.S. between 2001 to 2009.[1] After an insult to the myocardium, cardiac output drops which will lead to impairment of the systemic circulation, and ultimately signs and symptoms of HF. Indeed, tissue and organ perfusion generally decrease in HF, unless local compensatory mechanisms are activated. To maintain sufficient perfusion of vital organs and peripheral tissues, vasoconstrictor mechanisms in the systemic arterial bed are activated in response to stimulation of the sympathetic nervous and renin-angiotensin system.[2] This has paved the way for the use of arterial vasodilators in HF, since long-term systemic vasoconstriction leads to left ventricular hypertrophy and failure, and – ultimately – refractory HF. As a consequence of left-sided heart failure, pulmonary congestion may occur. Previously, pulmonary congestion was considered mainly a marker of severity of left-sided HF, but there is increasing evidence that pulmonary congestion may also be actively contributing to the HF syndrome, and impair prognosis.[3]

Along with previous attempts of monitoring indirect signs related to pulmonary congestion to improve outcomes in HF,[4] there is a (renewed) interest in more directly measuring pulmonary artery (PA) pressures in HF and elevated PA pressures have been shown to strongly associate with an adverse prognosis and increased risk for hospitalization in patients with HF (**Figure 1**).[5] Consequently, the pulmonary circulation as therapeutic target in HF has gained increasing interest.

In 2011, the results of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) Trial were reported.[6] In the CHAMPION trial, 550 patients with moderate HF were randomized to management of their HF with either usage of the wireless PA hemodynamic monitoring system (CardioMEMS, St Jude Medical), or to control treatment. For patients in the active treatment arm, clinicians used daily measurements of PA pressures to guide their HF treatment. The treatment goal was to lower PA pressures when elevated, using neurohormonal, diuretic, or vasodilator drugs.[6] The control group continued to receive standard treatment and any changes in medication were based on patients' signs and symptoms.[6] Pulmonary artery pressures decreased to a larger extent in the treatment group than in controls (-156 mmHg·days vs. 33 mmHg·days,

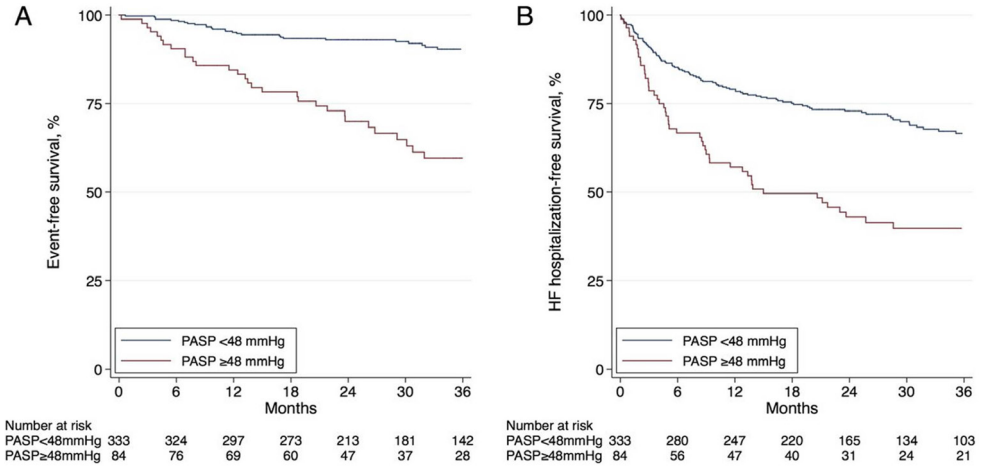

Figure 1: Association between pulmonary pressures and outcomes in outpatients with heart failure (HF). Event-free survival from (A) major clinical events (death, left ventricular assist device implantation or urgent heart transplantation) and (B) major clinical events or hospitalization for HF, according to echocardiography-derived pulmonary artery systolic pressure (PASP) at baseline (24.9% of the patients had HF with preserved ejection fraction). Reproduced from Kalogeropoulos *et al.*[5] with permission from the American Heart Association. Copyright 2014.

p=0.008, respectively), and this was associated with a 28% reduction in HF-related hospitalizations. This CHAMPION study has thus provided promising data and in the most recent 2016 European Society of Cardiology Heart Failure Management Guidelines, wireless PA monitoring received a class IIb-B recommendation in order to reduce recurrent HF hospitalizations.[7] Nevertheless, additional data, for example in other patients' groups, are clearly welcome.

In the present issue of the Journal, Heywood *et al.* describe their experience with 2,000 U.S. patients from the general HF community, who were implanted with the same wireless PA pressure monitoring system, after this device received market approval in the United States.[8] The study shows a significant reduction in PA pressures during a follow-up of 333±125 days. When comparing the present study population with the patients in the CHAMPION trial, patients in the present study were older and there was a higher proportion of patients with left ventricular ejection fraction (LVEF) ≥40%, while PA pressures were slightly but not significantly higher. During six months of the study, the reduction in PA pressures was higher in these general-use patients, compared to the patients in the CHAMPION trial (-434.0 mmHg·days versus -150.1 mmHg·days, respectively). In the 1,024 patients in the present study of whom LVEF was available at baseline, the decrease in PA pressure was the same in

HF patients with reduced ejection fraction and those with preserved ejection fraction (p=0.81).[8] The strength of this study is clearly the large number of patients, and also the apparent good clinical use of this device in a large spectrum of patients with HF. Limitations of this study include the relatively sparse documentation of the patient population, the lack of safety data, and also the fact that clinical endpoints (e.g. hospitalizations and deaths) were not collected. Indeed, this study was a registry and not a randomized clinical trial in which an intervention was investigated.

Despite these limitations, the study by Heywood *et al*. does provide important novel information about the diagnostic use of PA pressures in HF patients, both for those with HF with reduced ejection fraction as with preserved ejection fraction. In patients with HF with reduced ejection fraction, major progress in the last 20 to 25 years has been made in the management of these patients. Big steps forward have been made in HF with reduced ejection fraction patients in the field of pharmacological treatment, but also with device therapy (in particular cardioverter defibrillator and cardiac resynchronization therapy), to improve quality of life and to reduce mortality.[7] As a result, this has led to large-scale use of drugs, but also devices in HF patients in many countries.[7,9] With regard to patients with HF with preserved ejection fraction however, very little – if any – improvement has been achieved in recent years. Yet, patients with HF with preserved ejection fraction have the same dismal prognosis as patients with HF with reduced ejection fraction.[10] For this reason, the present findings of Heywood *et al.*,[8] which are in line with earlier similar findings from CHAMPION in HF with preserved ejection fraction,[11] may particularly be relevant for HF with preserved ejection fraction patients, because ~68% of them suffer from pulmonary hypertension, and the risk of mortality increases with 30% for every 5 mmHg increase in PA pressure.[12] The finding that PA pressures can be significantly reduced in patients with HF with preserved ejection fraction by using the wireless monitor as a diagnostic tool to adjust individual medical treatment, is therefore very interesting, because several randomized trials that aimed at reducing PA pressures with specialized drugs in HF with preserved ejection fraction were unsuccessful.[13] Thus, the concept of acting on continuous monitoring of PA pressures seems to be the key to a successful treatment strategy – in both patients with HF with reduced and with preserved ejection fraction.

Having said this, it must be noted that although pulmonary hypertension and resulting right sided decompensation is strongly associated with hospitalization for HF, a significant number of hospitalizations for HF are due to other cardiac and non-cardiac comorbidities.[14] Consequently, other targets such as optimizing heart rate and controlling systemic blood pressure, remain equally important.

Furthermore, a clear diagnostic algorithm would seem useful to guide clinicians and HF specialized nurses to act on changes in PA pressure recorded by a wireless monitor in the general HF community. From the CHAMPION trial the exact diagnostic algorithm is unknown, but conventional loop and thiazide diuretics seemed mainly responsible for the important reduction in PA pressures and hospitalization rates in the intervention group: 64.9% of all medication changes in HF with reduced ejection fraction and 73.5% of all changes in HF with preserved ejection fraction.[11] It is known that a specific subgroup of HF patients with longstanding pulmonary venous hypertension may develop a pre-capillary component of pulmonary hypertension. Especially in HF patients with 'disproportional' high PA pressures – suggesting the presence of additional pre-capillary PH – information from actual PA pressures recorded by the wireless pressure monitor may help to develop better therapies targeting the pulmonary vasculature. Clearly, further research in other well-defined HF cohorts with combined post- and pre-capillary pulmonary hypertension is needed, to test such other PA-pressure informed therapeutic concepts.

Although there are still significant challenges to overcome, the present study by Heywood et al. adds to the growing evidence that closely monitoring of PA pressures may be a key strategy for both HF with reduced and preserved ejection fraction.

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