Clinical Investigation

Pulmonary Vascular Resistance During Exercise Predicts Long-Term Outcomes in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Background: In heart failure with preserved ejection fraction (HFpEF), the prognostic value of pulmonary vascular dysfunction (PV-dysfunction), identified by elevated pulmonary vascular resistance (PVR) at peak exercise, is not completely understood. We evaluated the long-term prognostic implications of PV-dysfunction in HFpEF during exercise in consecutive patients undergoing invasive cardiopulmonary exercise testing for unexplained dyspnea.

Methods: Patients with HFpEF were classified into 2 main groups: resting HFpEF (n = 104, 62% female, age 61 years) with a pulmonary arterial wedge pressure (PAWP) >15 mmHg at rest; and exercise HFpEF (eHFpEF; n = 81) with a PAWP <15 mmHg at rest, but >20 mmHg during exercise. The eHFpEF group was further subdivided into eHFpEF + PV-dysfunction (peak PVR ≥80 dynes/s/cm^{-5}; n = 55, 60% female, age 64) group and eHFpEF – PV-dysfunction (peak PVR <80 dynes/s/cm^{-5}; n = 26, 42% female, age 54 years) group. Outcomes were analyzed for the first 9 years of follow-up and included any cause mortality and heart failure (HF)-related hospitalizations. The mean follow-up time was 6.7 ± 2.6 years (0.5–9.0).

Results: Mortality rate did not differ among the groups. However, survival free of HF-related hospitalization was lower for the eHFpEF + PV-dysfunction group compared with eHFpEF – PV-dysfunction ($P = .01$). These findings were similar between eHFpEF + PV-dysfunction and the resting HFpEF group ($P = .774$). By Cox analysis, peak PVR ≥80 dynes/s/cm^{-5} was a predictor of HF-related hospitalization for eHFpEF (hazard ratio 5.73, 95% confidence interval 1.05–31.22, $P = .01$). In conclusion, the present study provides insight into the impact of PV-dysfunction on outcomes of patients with exercise-induced HFpEF. An elevated peak PVR is associated with a high risk of HF-related hospitalization. (*J Cardiac Fail 2018;24:169–176*)

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Heart failure (HF) is a clinical syndrome characterized by dyspnea, fatigue, and fluid retention. The presence of preserved left ventricular ejection fraction (i.e., >50%) is common, affecting nearly half of all patients with HF-related symptoms.[1–3] In this context, the diagnosis of HF with preserved ejection fraction (HFpEF) is defined as the presence of typical signs and symptoms of HF in patients with a normal left ventricular ejection fraction and no significant valvular abnormalities by echocardiography.[4]

HFpEF is associated with exercise intolerance, poor quality of life, frequent hospitalization, and reduced survival in a similar fashion to HF with reduced EF (HFrEF).[5] However, treatment strategies effective for HFrEF have not been found to be beneficial for HFpEF.[6–9] The combination of high prevalence and lack of evidence-based treatments makes HFpEF a challenging clinical syndrome.[5] Therefore, diagnosing HFpEF early and/or identifying relevant subgroups at risk of a poorer prognosis is of major clinical relevance and may allow new therapeutic interventions aiming to improve patients' outcomes.

Exercise testing with invasive hemodynamic monitoring aids in earlier diagnosis of HFpEF[10–12] and can promote the identification of patients that have elevated pressures exclusively during exercise. For the purpose of the current study, these patients will be designated as having exercise HFpEF (eHFpEF), and those with elevated pressures at rest will be designated as having resting HFpEF (rHFpEF).

In group II pulmonary hypertension (PH), the presence of pulmonary vascular dysfunction (PV-dysfunction) and pulmonary vascular remodeling, is associated with poor outcomes.[13] However, the prognostic value of PV-dysfunction in eHFpEF remains unclear.[12] Additionally, the predictive value of PV-dysfunction diagnosed during exercise in eHFpEF remains uncharacterized. In the current study, therefore, we aimed to evaluate the long-term prognostic implications of PV-dysfunction diagnosed during exercise in eHFpEF.

Methods

Study Population and Design

Consecutive patients evaluated for unexplained exertional intolerance at the Massachusetts General Hospital and Brigham and Women's Hospital between January 2001 and March 2010 using invasive cardiopulmonary exercise testing (iCPET), and with hemodynamically proven HFpEF, were retrospectively analyzed.

In the context of echocardiographically normal left ventricular ejection fraction and no significant valvular abnormalities,[4] HFpEF subgroups were hemodynamically defined as follows: (1) rHFpEF group: pulmonary arterial wedge pressure (PAWP) >15 mmHg at resting right heart catheterization (RHC); (2) eHFpEF group: PAWP <15 mmHg at resting RHC, but >20 mmHg at peak exercise during iCPET. The eHFpEF patients were further subdivided per the presence or absence of elevated peak pulmonary vascular resistance (PVR), using the previously published cut–off value of 80 dynes.s.cm^{-5}:[14] eHFpEF with peak PVR ≥80 dynes/s/cm^{-5} were designated as the eHFpEF + PV-dysfunction group, and those with PVR <80 dynes/s/cm^{-5} as the eHFpEF – PV-dysfunction group.

Exclusion criteria included HFrEF (left ventricular ejection fraction <50%), moderate or severe mitral and/or aortic valve disease based on resting echocardiographic criteria, severe obstructive lung disease (forced expiratory volume in 1 second [FEV_1] <65% predicted, and a ratio with forced vital capacity < .65), or acute coronary syndromes defined by ST elevation myocardial infarction, non–ST elevation myocardial infarction, and/or unstable angina. The Partners Human Research Committee approved this study and waived the need for informed consent.

iCPET

The iCPET methods used in this study have been described previously.[15] Briefly, after placement of a pulmonary artery catheter via the internal jugular vein and a radial artery catheter, patients underwent a symptom-limited incremental CPET using an upright cycle ergometer and breath-by-breath gas exchange assessment with a metabolic cart (CPE 2000, Medical Graphics Corporation, St Paul, MN). Heart rate, radial arterial blood pressure, right atrial pressure, and pulmonary arterial pressure were continuously measured throughout the test. PAWP was measured at rest and at the end of each minute of exercise after passive exhalation.[15] When respirophasic changes persisted, an electronic average over 3 respiratory cycles was used.[16] Arterial and mixed venous blood samples were simultaneously collected at rest and at the end of each minute of exercise. Oxygen saturation, hemoglobin concentration, and arterial-mixed venous oxygen content differences were assessed. Fick cardiac output (CO) was calculated using simultaneously measured oxygen consumption (VO_2). PVR was calculated using mean pulmonary arterial pressure (mPAP) minus PAWP, divided by CO (mPAP – PAWP/CO).

Follow-up and Outcomes

The date of the patient's initial visit for evaluation of exertional intolerance was designated as day 0. Data collection for each patient continued until the patient either died or reached the end of the study (May 2015) and was performed by the identification of events on the patient-linked electronic medical record at the Partners Healthcare System. Outcome events were analyzed for the first 9 years of follow-up and included mortality from any cause, HF-related