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Mismatch between right- and left-sided filling pressures in heart failure patients with preserved ejection fraction☆

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ABSTRACT

Background: Mismatch between right- and left-sided filling pressures is poorly understood in heart failure with preserved ejection fraction (HFpEF).
Methods and results: We retrospectively analyzed 170 patients with HFpEF (EF ≥ 40%) who underwent right heart catheterization. Low match (right atrial pressure [RAP] < 10 mm Hg and pulmonary capillary wedge pressure [PCWP] < 10 mm Hg) was 76%, high match (RAP ≥ 10 mm Hg and PCWP ≥ 22 mm Hg) was 6.5%, high-R mismatch (RAP ≥ 10 mm Hg and PCWP < 22 mm Hg) was 12%, and high-L mismatch (RAP < 10 mmHg and PCWP ≥ 22 mm Hg) was 5.9%. Elevated PCWP was a significant predictor of the composite endpoint of death or HF hospitalization within 12 months (hazard ratio 5.40, 95% confidence interval 2.17–12.5, $p < 0.001$). Elevated RAP was not significantly associated with worse outcomes. Pulmonary artery systolic pressure (PASP) and diastolic pressure (PADP) showed strong correlations with PCWP (PASP, $r = 0.738$, $p < 0.001$; PADP, $r = 0.834$, $p < 0.001$; RAP, $r = 0.638$, $p < 0.001$, respectively).
Conclusions: Discordance exists between right- and left-sided filling pressures in HFpEF. Physicians may utilize pulmonary artery pressure to evaluate left-sided filling pressure, which is a significant predictor of prognosis.

1. Introduction

Decongestion is a crucial component of heart failure (HF) treatment, because many symptoms of HF arise from congestion, which is associated with elevated left-sided filling pressure. Jugular venous pressure (JVP) is one of the most reliable physical signs for elevated left-sided filling pressure [1–3]. The relationship between JVP and left-sided filling pressure is predicated upon concordance between right- and left-sided filling pressure, although dissociation between right- and left-sided pressure has been reported [4,5], in which right- and left-sided pressures are not tightly coupled and decongestion therapy guided by JVP can result in over- or under-treatment. This dissociation, termed right–left (R–L) mismatch, has been primarily investigated in severe grade HF patients, such as patients being considered for heart transplantation. However, little is known about R–L mismatch and its prognostic impact in the general HF population, especially in HF patients with preserved ejection fraction (HFpEF) [6].

The present study aimed to investigate the prevalence of R–L mismatch in HFpEF patients and to determine whether R–L mismatch is a predictor of worse clinical outcomes.

2. Methods

2.1. Study population

Consecutive patients who underwent right heart catheterization (RHC) have been prospectively registered in our institutional database since January 2012. Patients without acute coronary syndrome (ACS) or hemodialysis were retrospectively analyzed from January 2012 to September 2015. The indications for RHC were patients with suspected HF who had typical HF symptoms, chest X-ray showing congestion, elevation of brain natriuretic peptide (BNP) or echocardiography abnormalities. All patients underwent RHC during hospitalization. Patients with BNP level <100 pg/ml and patients without echocardiography data were excluded. Of these, patients with EF ≥40% were included in the study.

Patient characteristics and medical history were obtained on admission. Ischemic heart disease as the etiology of HF was defined as the presence of at least one of the following: prior myocardial infarction, prior percutaneous coronary intervention or prior coronary bypass grafting. Hypertension (blood pressure ≥ 140/90 mm Hg or the use of antihypertensive medications), diabetes mellitus (hemoglobin A1c ≥ 6.5% or the use of oral hypoglycemic agents or insulin) and dyslipidemia (fasting serum low-density lipoprotein

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cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or the use of medications for dyslipidemia) were recorded. Left ventricular ejection fraction (LVEF) was calculated by the modified Simpson method. Ultrasonographers performed echocardiography and specialists of the Japanese Society of Echocardiography approved the findings. Vital signs, laboratory data and medication at the time of RHC were also collected.

All patients provided written informed consent and all data were anonymized throughout the study and analysis. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Right heart catheterization and match/mismatch hemodynamic characteristics

RHC was performed after the optimal treatment of diuresis, vasodilators, and other pharmacologic therapies based on the treating physician's discretion. RHC was performed in the supine position and was measured by a 6F balloon-tipped fluid-filled catheter (Swan Ganz Thermodilution Catheter, Edwards Lifesciences, California, USA). Transducers were zeroed at the mid-axilla and measured by callipers in each case. RHC was placed under fluoroscopic guidance through a femoral vein to a pulmonary artery. We confirmed the wedge position of the catheter by fluoroscopy and the presence of typical wave forms. Hemodynamic data were measured at the end of expiration and represent the mean of ≥3 beats. Cardiac output was measured by the thermodilution method, and indexed to body surface area (cardiac index, CI). Right ventricle stroke work index (RVSWI) was calculated as follows: (CI/heart rate) × (mean pulmonary artery pressure [PAP] − mean right atrium pressure [RAP]) × 13.6. Pulmonary artery resistance index (PARI) was determined as follows: PARI = (mean PAP − pulmonary capillary wedge pressure [PCWP])/CI.

Patients were divided into four match or mismatch groups based on the following definitions: low match group, RAP <10 and PCWP <22 mm Hg; high match group, RAP ≥10 and PCWP ≥22 mm Hg; high-R mismatch group, RAP ≥10 and PCWP <22 mm Hg; high-L mismatch group, RAP <10 and PCWP ≥22 mm Hg.

2.3. Study endpoints

The endpoint was the composite of death or first HF hospitalization within 12 months. HF hospitalization was defined as an unexpected hospitalization with at least one of the following symptoms: increasing dyspnea on exertion, worsening orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue/worsening exercise tolerance, or altered mental status and at least two of the following symptoms: peripheral edema, elevated jugular venous pressure, radiologic signs of HF, increasing abdominal distension or ascites, pulmonary edema or crackles, rapid weight gain, hepatojugular reflux, S3 gallop or elevated BNP. These endpoints were observed by retrospective medical record review.

2.4. Statistical analysis

Normally distributed continuous variables were described as mean ± standard deviation and non-normally distributed data were expressed as medians and interquartile ranges. Categorical variables were described as percentages. The prevalence of the four match/mismatch groups (low match, high match, high-R mismatch, and high-L mismatch) was investigated. To compare characteristics among the four match/mismatch groups, we used the one-way ANOVA test for continuous variables and the chi-square test for categorical variables. We conducted multiple comparisons using Tukey–Kramer method. Kaplan–Meier curves and 12-month event rates of the composite endpoint were estimated. The log-rank test was used for comparisons among the four match/mismatch groups. A p value of <0.05 was considered significant. Cox proportional hazards regression analysis was performed to investigate whether PCWP ≥22 mm Hg or RAP ≥10 mm Hg predicted 12-month clinical outcomes. Factors with a p value <0.05 by univariate analysis were included in the multivariate analysis. Because the composite events occurred in 23 patients, PCWP ≥22 mm Hg or RAP ≥10 mm Hg was adjusted by each confounding factor separately to avoid over-fitting. All statistical analyses were performed using JMP version 12.0.1 for Windows (SAS, North Carolina, USA).

3. Results

3.1. Study population

During the study period, 456 patients without ACS or hemodialysis underwent RHC in our institution. We excluded 12 patients without BNP data, 106 patients with BNP < 100 pg/ml, and 34 patients without echocardiography. We also excluded 134 patients with EF < 40%. A total of 170 HFpEF patients were included in the final analysis. Mean age was 73 ± 11 years, 63% were male, and 31% had ischemic HF etiology. Mean EF was 58 ± 12%, median creatinine was 0.93 (0.76, 1.26) mg/dl, and median BNP was 331 (174, 581) pg/ml. ACE-Is or ARBs were prescribed in 74% and β-blockers were prescribed in 49%.

3.2. Match and mismatch groups

Fig. 1A shows the prevalence of match and mismatch groups. The match group represented 83% (low match, 76%; high match, 6.5%) and the mismatch group represented 18% (high-R mismatch, 12%; high-L mismatch, 5.9%). Table 1 reports patient characteristics of match/mismatch groups. Demographic characteristics, including age, sex, HF etiology and past medical history were not different among the groups. BNP was higher in the high match and high-L mismatch groups than in the low match and high-R mismatch groups. Regarding echocardiography, the high match and high-L mismatch groups had higher E wave and tricuspid regurgitation peak gradient (TRPG) than the low match and high-R mismatch groups. Hemodynamic data, such as pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), and RVSWI were also higher in the high match and high-L mismatch groups than in the low match and high-R mismatch groups.

3.3. Clinical outcomes

The composite endpoint of death or HF hospitalization occurred in 14 patients (11%) in the low match, 3 patients (27%) in the high match, 1 patient (5%) in the high-R mismatch, and 5 patients (50%) in the high-L mismatch groups (Table 2A). Kaplan–Meier estimates showed that the composite endpoint was more frequently observed in the high match and the high-L mismatch groups than in the low match and high-R mismatch groups (Fig. 1B). Patients with PCWP ≥22 mm Hg were more frequently associated with the composite endpoint than patients with PCWP <22 mm Hg (Fig. 1C). These relationships were not observed in RAP (Fig. 1D). In multivariate analysis, PCWP ≥22 mm Hg was a significant predictor of the composite endpoint (Table 2B).

3.4. Relationships between PCWP and other characteristics

Fig. 2 shows the relationships between PCWP and other factors. EF were not significantly related to PCWP ($r = -0.035$, $p = 0.652$). BNP and E/e′ showed significant but weak correlations with PCWP (BNP, $r = 0.256$, $p < 0.001$ and E/e′ $r = 0.199$, $p = 0.015$, respectively). Hemodynamic characteristics including PASP and PADP showed strong correlations with PCWP (PASP, $r = 0.738$, $p < 0.001$; PADP, $r = 0.834$, $p < 0.001$; RAP, $r = 0.638$, $p < 0.001$, respectively).

4. Discussion

The present study revealed that: 1) R–L mismatch exists in HFpEF patients; 2) elevated left-sided pressure was a significant predictor of worse clinical outcomes; and 3) hemodynamic characteristics, including PASP and PADP, strongly correlate with PCWP.

Dranzer et al. analyzed hemodynamic data of 4079 HFrEF patients over 3 years (1993 to 1997, 1998 to 2002, and, 2003 to 2007) [4], in which the frequency of concordant hemodynamics were 74%, 72%, and 73%, respectively. Campbell et al. analyzed hemodynamic data of 537 patients with advanced HF [5]. Among these patients, the frequency of concordant hemodynamics was 72%. In another study of patients with HFpEF, 11 HF patients with EF > 50% underwent RHC at rest and under loading conditions by lower body negative pressure and saline infusion [6]. Match or mismatch of RAP and PCWP was investigated among 66 paired measurements. The frequency of concordant hemodynamics was 79% (low match was 67% and high match was 12%) and high-R mismatch was more prevalent than high-L mismatch (21% vs. 0%). In the present study with HF patients with EF ≥ 40%, concordant hemodynamics were present in 84%, and high-R mismatch was also more frequently observed than high-L mismatch (11% vs. 5.6%). We also analyzed patients with EF > 50% (117 patients). The match group was 85% (low match, 77%; high match, 7.7%) and the mismatch group was 15%