Echocardiography of Right Ventriculoarterial Coupling Combined With Cardiopulmonary Exercise Testing to Predict Outcome in Heart Failure

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BACKGROUND: Pulmonary hypertension, which is related to right ventricular (RV) failure, indicates a poor prognosis in heart failure (HF). Increased ventilatory response and exercise oscillatory ventilation (EOV) also have a negative impact. We hypothesized that the severity classification of HF and risk prediction could be improved by combining functional capacity with cardiopulmonary exercise testing (CPET) and RV-pulmonary circulation coupling, as evaluated by the tricuspid annular plane systolic excursion (TAPSE)-pulmonary artery systolic pressure (PASP) relationship.

METHODS: Four hundred fifty-nine patients with HF were assessed with Doppler echocardiography and CPET and were tracked for outcome. The subjects were followed for major cardiac events (cardiac mortality, left ventricular assist device implant, or heart transplant). Cox regression and Kaplan-Meier analyses were performed with TAPSE and PASP as individual measures that were then combined into a ratio form.

RESULTS: The TAPSE/PASP ratio (TAPSE/PASP) was the strongest predictor, whereas the New York Heart Association classification and EOV added predictive value. A four-quadrant group prediction risk was created based on TAPSE (<16 mm or ≥ 16 mm) vs PASP (<40 mm Hg or ≥ 40 mm Hg) thresholds and the CPET variables distribution as follows: group A (TAPSE >16 mm and PASP <40 mm Hg) presented the lowest risk (hazard ratio, 0.17) and best ventilation; group B exhibited a low risk (hazard ratio, 0.88) with depressed TAPSE (<16 mm) and normal PASP, a preserved peak oxygen consumption ($\dot{V}O_2$), but high ventilation. Group C had an increased risk (hazard ratio, 1.3; TAPSE ≥ 16 mm, PASP ≥ 40 mm Hg), a reduced peak $\dot{V}O_2$, and a high EOV prevalence. Group D had the highest risk (hazard ratio, 5.6), the worse RV-pulmonary pressure coupling (TAPSE <16 and PASP ≥ 40 mm Hg), the lowest peak $\dot{V}O_2$, and the highest EOV rate.

CONCLUSIONS: TAPSE/PASP, combined with exercise ventilation, provides relevant clinical and prognostic insights into HF. A low TAPSE/PASP with EOV identifies patients at a particularly high risk of cardiac events. CHEST 2015; 148(1):226-234

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ABBREVIATIONS: ANOVA = analysis of variance; CPET = cardiopulmonary exercise testing; EF = ejection fraction; EOV = exercise oscillatory ventilation; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TAPSE/PASP = tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio; $\dot{V}CO_2$ = CO_2 production; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption

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Heart failure (HF) of both systolic and diastolic origin causes pulmonary hypertension (PH) through the increased upstream transmission of elevated pulmonary venous pressure and, in some patients, additional pulmonary vascular remodeling.[1-4] In both cases, PH is associated with decreased survival in proportion to increased pulmonary artery pressure.[5-8] The negative impact of PH on outcome in left ventricular (LV) failure (HF) is related mainly to a coexistent alteration in the indexes of the right ventricular (RV) function.[6,9-12]

The right ventricle basically adapts to increased afterload by an increased contractility. When systolic function adaptation fails, the right ventricle becomes uncoupled from the pulmonary circulation and dilates to preserve flow output at the price of systemic congestion.[13] The right ventricle in HF is exposed to early uncoupling because of the loss of positive systolic interaction with the left ventricle and/or the extension of the LV disease process to RV myocardial tissue.[1,14] A combination of noninvasive measurements of systolic function and pulmonary artery pressure to estimate RV-arterial coupling may be of functional and prognostic relevance.[10] We reported that the evaluation of the RV functional state by using the relationship between the tricuspid annular plane systolic excursion (TAPSE) and the pulmonary artery systolic pressure (PASP) as a surrogate for the RV length-force relationship is of clinical and prognostic relevance.[10] In particular, in a cohort of patients with HF with both reduced and preserved ejection fraction (EF), assessing TAPSE vs PASP as a simple ratio led to an improved prognostic prediction when compared with assessing either variable separately. A TAPSE/PASP ratio (TAPSE/PASP) $\leq$ 0.36 mm/mm Hg identified patients with HF who were at a very high risk irrespective of reduced or preserved EF.[10]

Cardiopulmonary exercise testing (CPET) is essential to the assessment of functional impairment and prognosis in HF.[15] Patients with HF typically present with a decreased peak oxygen consumption ($\dot{V}O_2$) but, even more importantly, an increased minute ventilation ($\dot{V}E$) at any level of metabolic rate, best measured by the $\dot{V}E/CO_2$ production ($\dot{V}CO_2$) slope.[16,17] Furthermore, it has been shown that the presence of exercise oscillatory ventilation (EOV) is an ominous prognostic indicator that is even more accurate than the $\dot{V}E/\dot{V}CO_2$ slope.[18,19]

Based on these premises, we aimed to expand the significance of TAPSE/PASP and studied the associations between echocardiographic measures of right-sided heart function and the ventilatory response assessed by CPET, hypothesizing that differences in exercise ventilation assessed by exercise gas exchange analysis would relate primarily to metrics of the right-sided heart reserve in this population.

Materials and Methods

Patients

From March 2005 to September 2010, 459 consecutive patients with known HF were screened for study enrollment at the time of referral for a clinically indicated hemodynamic and functional assessment. The patients were enrolled at two centers, the Cardiopulmonary Laboratory at San Paolo Hospital, Milan, Italy, and the Cardiac Rehabilitation Institute at Fondazione Maugeri, Veruno, Italy.

The subjects underwent a two-dimensional echocardiographic/Doppler evaluation and CPET. Inclusion criteria were (1) signs and symptoms of HF and (2) adequate echocardiographic windows. The diagnosis of HF was based on the National Health and Nutrition Examination Survey (NHANES) congestive heart failure criteria score[20]; patients were considered to have a preserved EF when the LV ejection fraction (LVEF) was $\geq$ 50% and the additional criteria proposed by the European Society of Cardiology criteria[21] were fulfilled.

The recruited patients were monitored in this prospective observational study, which was approved by the local ethical institutional review board at each institute (San Paolo approval number 09/04 and Fondazione Maugeri approval number 2005). Informed consent was obtained from all subjects prior to enrollment.

Event Tracking and End Points

The subjects were followed for major cardiac events (cardiac mortality, LV assist device implant, or heart transplant) via hospital and outpatient medical chart review for up to 4 years following data collection. They were followed by the HF program at the two institutions included in this analysis, which provided a high likelihood that all events were captured.

Echocardiography: TAPSE and PASP Measurements

Echocardiographic imaging was performed using a Philips IE33 and a 5.2-MHz transducer (Philips Medical Systems). In both centers, an experienced cardiologist obtained echocardiographic measures according to current guidelines.

A two-dimensional Doppler examination was performed using a prespecified echocardiographic protocol using views specifically designed to optimize RV imaging. To obtain TAPSE, the apical four-chamber view was used and an M-mode cursor was placed through the lateral tricuspid annulus in real time. Offline, the brightness was adjusted to maximize the contrast between the M-mode signal arising from the

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