Right Isovolumic Contraction Velocity Predicts Survival in Pulmonary Hypertension

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Background: Right ventricular function is a strong determinant of prognosis in severe pulmonary hypertension.

Methods: The aim of this study was to evaluate the prognostic value of estimates of right ventricular function obtained by echocardiography and Doppler tissue imaging and of functional class and 6-min walk distance (6MWD) in 142 patients with either pulmonary arterial hypertension (n = 104) or chronic thromboembolic pulmonary hypertension (n = 38). Echocardiography was prospectively performed, and demographics, medications, associated medical conditions, New York Heart Association class, and 6MWD at inclusion in addition to vital status, transplantation, and hospital admission related to pulmonary hypertension at follow-up were then collected by review of the medical records.

Results: Variables associated with overall survival by univariate analysis were 6MWD (P = .009), functional class (P = .024), tricuspid annular plane systolic excursion (P = .03) and isovolumic peak velocity at the tricuspid annulus (IVCv) (P = .003). On multivariate analysis, IVCv (P = .015) and 6MWD (P = .016) were the only independent predictors of survival. Kaplan-Meier estimates of survival at 1 year were 95% in patients with IVCv > 9 cm/sec and 80% in those with IVCv ≤ 9 cm/sec (P = .002). Intraobserver and interobserver variability of IVCv measurement were 5% and 9%, respectively.

Conclusions: Measurement of right ventricular function by Doppler tissue imaging, an easy, noninvasive, and reproducible method, is an independent predictor of clinical outcomes in patients with severe pulmonary hypertension. (J Am Soc Echocardiogr 2013;26:297-306.)

Keywords: Pulmonary hypertension, Prognosis, Echocardiography, Right ventricular function

Despite major advances achieved with the introduction of targeted medical therapies, the prognosis of pulmonary arterial hypertension (PAH) remains poor, with a 3-year survival rate of approximately 65%.[1,2] The prognosis of medically treated inoperable chronic thromboembolic pulmonary hypertension (CTEPH) is also poor, with a reported median survival time of 5 to 6 years.[3] In both PAH and CTEPH, predictors of outcomes have been shown to be related to the functional state of the right ventricle and cardiac index rather than to the severity of pulmonary vasculopathy as defined by pulmonary artery pressure (PAP) or pulmonary vascular resistance.[4-6] However, right ventricular (RV) function measurements during standard right-heart catheterization are limited to right atrial pressure, cardiac output, and PAP or pulmonary vascular resistance, which are imperfect surrogates of preload, contractility, and afterload.[4]

Recent studies have shown that RV function adaptation to pulmonary hypertension is initially systolic, with further diastolic and dimensional changes when contractility fails to remain coupled to afterload.[4] This has been illustrated by magnetic resonance imaging coupled to RV pressure measurements showing increased end-systolic elastance (contractility) to match increased arterial elastance (afterload) for the preservation of RV-arterial coupling in patients with advanced PAH but no clinical signs of RV failure.[7]

Several indices of both systolic and diastolic function of the right ventricle can be obtained by echocardiography with or without Doppler tissue imaging (DTI).[8] Many of these indices have shown sensitivity to prognosis[9-17] and to therapeutic interventions[18,19] in PAH. Awaiting further validation, only two of them are recommended for the definition of therapeutic goals in guidelines: tricuspid annular plane systolic excursion (TAPSE) as an index of systolic function and pericardial effusion, presumably as an index of failed diastolic function with increased filling pressures.[20]

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Abbreviations

CI = Confidence interval

CTEPH = Chronic thromboembolic pulmonary hypertension

DTI = Doppler tissue imaging

ε_{mean} = Mean peak systolic longitudinal strain of the right ventricular free wall

HR = Hazard ratio

IVA = Isovolumic acceleration

IVCv = Isovolumic contraction peak velocity at the tricuspid annulus

IVRT = Isovolumic relaxation time

NYHA = New York Heart Association

PAH = Pulmonary arterial hypertension

PAP = Pulmonary artery pressure

RV = Right ventricular

6MWD = 6-min walk distance

TAPSE = Tricuspid annular plane systolic excursion

In an attempt to identify novel noninvasive predictors of outcomes related to RV function, we evaluated the prognostic relevance of echocardiographic and DTI measurements of systolic function, compared with previously reported functional, exercise capacity, and standard echocardiographic predictors of survival, in medically treated patients with PAH and CTEPH in a cohort with predominantly severe disease. We focused on isovolumic contraction phase measurements, because they have been proposed as relatively load independent indices of RV contractility,[21,22] and on longitudinal strain, an indicator of global RV contractility.[23] Our hypothesis was that these indices of RV systolic function would emerge as predictors of outcomes and survival.

METHODS

Study Population

One hundred forty-two patients who underwent echocardiography for the evaluation of pulmonary hypertension were prospectively screened at two institutions: Louis Pradel University Hospital, Lyon, France (91 patients), and Erasme University Hospital, Brussels, Belgium (51 patients). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

In all patients, a diagnosis of PAH or inoperable CTEPH had been made following the currently recommended stepwise approach, with right-heart catheterization confirming a mean PAP $\geq$ 25 mm Hg at rest and a pulmonary capillary wedge pressure $<$15 mm Hg.[20] Inoperability of CTEPH was evaluated on the basis of pulmonary angiographic results and expert multidisciplinary advice.

Entry into the cohort was defined as the date of echocardiography. Echocardiography was prospectively performed, and demographics, medications, associated medical conditions, New York Heart Association (NYHA) class, and 6-min walk distance (6MWD) at inclusion in addition to vital status, transplantation, and hospital admission related to pulmonary hypertension at follow-up were then collected by review of the medical records. Because of the observational nature of this study, right-heart catheterization was not repeated at inclusion.

Exclusion criteria were as follows: age $<$18 years, unstable severe pulmonary hypertension, arrhythmia, pulmonary hypertension associated with lung diseases and/or hypoxemia, left-heart disease including severe valvular heart disease and systolic dysfunction (defined as a left ventricular ejection fraction $<$45%), terminal malignancies, and poor acoustic window.

Echocardiography

Transthoracic echocardiography was performed using similar commercially available ultrasound systems at both centers (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). Acquisitions were digitally stored in raw data format for offline analysis (EchoPAC; GE Vingmed Ultrasound AS). Analysis was performed at a single core lab (Louis Pradel Hospital) by two observers, who were blinded to the patients' clinical status.

Left ventricular dimensions were measured according to the current guidelines. Left ventricular ejection fraction was calculated using the modified Simpson's biplane method. RV basal diameter[24] and left ventricular diameter were measured at end-diastole in the apical four-chamber view to calculate the ratio of RV to left ventricular diameter. The left ventricular diastolic eccentricity index was measured from the parasternal short-axis view at the mid left ventricular level.[25] Left and right atrial areas were measured by planimetry on the apical four-chamber view. Right atrial area was indexed to height as previously described.[12]

Using pulsed Doppler, we measured cardiac output using aortic time-velocity integral, mitral inflow velocities (E and A), early mitral annulus velocity (e′) at the lateral site of the mitral annulus and pulmonary acceleration time using the RV outflow tract velocity profile. Left ventricular filling pressure was assessed on the value of left atrial area in addition to the E/A and E/e′ ratios.[26] In addition, the presence or absence of midsystolic pulmonary notching was noted.

Systolic PAP was calculated by adding the systolic transtricuspid pressure gradient assessed on peak tricuspid regurgitation velocity and right atrial pressure. Evaluation of right atrial pressure was estimated from the size of the inferior vena cava and its inspiratory collapsibility.[27] Finally, the presence of pericardial effusion was noted.

Study of RV Function

The study of RV function is summarized in Figure 1. TAPSE was measured on the M-mode tracing obtained from the apical four-chamber view.[14] Pulsed DTI at the lateral site of the tricuspid annulus was acquired from the apical four-chamber view to measure the following parameters: isovolumic contraction peak velocity at the tricuspid annulus (IVCv), isovolumic acceleration (IVA),[21] systolic velocity (S′), isovolumic relaxation time (IVRT), and early diastolic (E′) and atrial contraction (A′) peak velocities. The instantaneous IVA was measured on the same velocity profile obtained by pulsed DTI at the lateral site of the tricuspid annulus as the difference between the baseline and the peak velocity divided by their time interval during the isovolumic period.[21,24] DTI recording of the right ventricle was performed using an apical four-chamber view centered on RV free wall with a high frame rate (240 frames/sec). Peak systolic longitudinal strain of the RV free wall was measured at the basal, mid, and apical segments. The average of these three values (ε_{mean}) was calculated. All measurements were performed on three consecutive cycles, and the mean value was calculated.

Angle-dependant parameters, including TAPSE, velocity profile using pulsed DTI at the lateral site of the tricuspid annulus, and longitudinal strain, were obtained with the optimal angle of incidence available (with a predetermined range of angle of incidence $<$20° off angle).

To define the reproducibility of RV functional parameters, 20 patients were randomly selected. RV functional analysis was repeated three months apart by the same observer and was performed by a second blinded observer. Interobserver and intraobserver variability were calculated as the difference between the two observations divided by the means of the observations and expressed as percentages. Intraobserver and interobserver variability were 6% and 7% for S′, 9%