Risk of Death and Need for Transplantation in Chronic Pulmonary Hypertension

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Abstract: *Background:* Echo-Doppler parameters that exemplify right ventricular (RV) outflow dynamics and measures of annular tissue Doppler imaging to assess left ventricular (LV) and RV diastolic function, known to be affected in chronic pulmonary hypertension (cPH), have never been studied to determine if they could be predictive of mortality or need for transplantation 1-year after follow-up. *Methods:* Numerous echo-Doppler parameters of RV and LV performance were recorded from 120 patients. This patient population was divided into 3 groups. Group I had no PH, group II had cPH but no documented death or need for either lung or heart transplantation, at 1-year follow-up after their initial echocardiogram whereas group III had cPH and patients had either died or required heart and/or lung transplantation during the same time period. *Results:* Analysis of variance was first used to identify which echo-Doppler variables were significant among the studied groups. A logistic regression analysis was then performed to identify predictive variables of the occurrence death and need for transplantation. Finally, a multiple regression analysis was used between groups II and III to identify which echo-Doppler variables were most useful in identifying severe cPH patients at risk of the prespecified events. *Conclusions:* Even though older patients with worse RV fractional area change might be considered at risk of worse prognosis in patients with severe cPH, only a low mitral annular early diastolic velocity was useful in identifying which of those individuals were at highest risk of death or in need of transplantation.

Key Indexing Terms: Age; Echocardiography; Doppler echocardiography M-mode echocardiography; Mortality; Pulmonary hypertension; Right ventricular function; Tricuspid annular plane systolic excursion; Tissue Doppler imaging. **[Am J Med Sci 2014;347(2):106–111.]**

Chronic pulmonary hypertension (cPH) is a devastating disease with relentless progression of dyspnea and fatigue culminating in right ventricular (RV) failure and death in the majority of patients. Assessment of pulmonary artery pressures is not only essential for diagnosis of PH and treatment and follow-up but also necessary to calculate pulmonary vascular resistance. Increased pulmonary arterial pressures and pulmonary vascular resistance are known to trigger secondary abnormalities of right heart structure and function that contribute significantly to the morbidity and mortality associated with this disease.[1,2] It has been reported that as many as 2/3 of the deaths in idiopathic pulmonary arterial hypertension may be attributed to RV failure.[2–6]

Numerous reports have documented the correlation existing between cPH and the development of specific echocardiographic findings such as RV dilatation, hypertrophy and decreased contractility, in addition to varying degrees of tricuspid regurgitation, abnormal motion of the interventricular septum and presence of a pericardial effusion.[1,7–10] Furthermore, some of these echocardiographic findings have also been shown to be predictive of adverse outcomes.[11] With the exception of the severity in pulmonary artery systolic pressures (PASP), none of these echocardiographic parameters clearly assess the hemodynamic burden of cPH.

Recent data seem to suggest that assessment of right ventricular outflow tract (RVOT) spectral Doppler signals is useful because these signals correlate with pulmonary vascular resistance and RV systolic function.[12–14] Furthermore, assessment of the diastolic properties of both the left and right ventricles, known to be affected in cPH patients,[15–17] is easily attained by the use of annular tissue Doppler imaging (TDI). However, none of these measurements have been studied in this population to determine if any of these variables is predictive of mortality or need for transplantation of heart, lung or both.

METHODS

Study Group

This was a retrospective analysis of our echocardiographic database. Inclusion criteria for this study required that all patients had a complete echocardiogram including pulsed Doppler spectral signals across the RVOT, discernible tricuspid regurgitation signal, good endocardial border resolution of both RV and left ventricular (LV) chambers for tracing of end systole and end diastole in addition to M-mode and TDI of the lateral mitral and tricuspid annuli. In addition, all the patients included for analysis were in normal sinus rhythm and had normal LV systolic function. In terms of exclusion criteria, no atrial or ventricular ectopy were present at the time of the study, none of the patients had a pacer or defibrillator wire in the RV or any significant left-sided valvular diseases.

Based on the aforementioned predefined criteria, a total of 120 patients were included for analysis. The population was then divided according to absence of PH, determined by echocardiography, with normal PASP in group I. The rest of the population ($n = 78$) with documented cPH were then divided into group II if they had no documented death or need for either lung or heart transplantation, at 1-year follow-up after their initial echocardiogram used for inclusion in this study or into group III if they had died or required heart and/or lung transplantation during the same time period. The University of Pittsburgh's Institutional Review Board approved the study.

The definition of pulmonary hypertension for this study was based on a tricuspid jet velocity greater than 2.8 m/s.[18] Echocardiograms of patients on this study were collected from the University of Pittsburgh Medical Center's echocardiographic database.

Echocardiographic Examination

Two-dimensional echocardiographic (Vivid 7; GE Medical Systems, Milwaukee, WI) images were digitally acquired with a 1.5/3.1-MHz phased array transducer using standard harmonic imaging, in gently held end-expiration, for subsequent

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Submitted June 28, 2012; accepted in revised form October 31, 2012.

The author has no financial or other conflicts of interest to disclose.

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offline analysis using the Acuson Syngo system (version 6.0 Diagnostic Workstation; Siemens, Mountain View, CA). Examinations were performed in accordance with the recommendations of the American Society of Echocardiography.[19] LV ejection fraction was assessed using the biplane method of disks (modified Simpson's rule) and maximal excursion of the mitral annulus (MA).[20,21]

RV fractional area change and maximal excursion of the tricuspid annulus (TA) were used to determine global RV systolic function.[20,21]

To assess ejection of the right ventricle, the RVOT pulsed Doppler signal was obtained by placing a 1- to 2-mm pulsed-wave Doppler sample volume just within the pulmonary valve from the parasternal short axis view. The sample volume was placed so that the closing but not opening click of the pulmonary valve was visualized.[22,23] Pulsed-wave Doppler was used rather than continuous-wave Doppler to eliminate cases with increased pulmonary velocities secondary to either pulmonary valve or peripheral pulmonary artery stenosis and assess more accurately the duration of the signal.[14,22]

Velocity time integral values were obtained by tracing the RVOT spectral pulsed Doppler signals, as previously described.[22]

Continuous-wave Doppler was used to record the tricuspid regurgitation jet from multiple windows, and the highest velocity was then used to estimate PASP using the modified Bernoulli equation and an estimate of mean right atrial pressure using the diameter and collapse index of the inferior vena cava and the hepatic venous flow pattern.[24]

Tissue Doppler interrogation of the TA was performed by placing the sample volume (gate length of 0.6 cm) of the ultrasound cursor on the lateral aspect of TA at the junction of the RV free wall in the apical 4-chamber view, parallel to the direction of annular motion.[25] A similar approach was used to interrogate the MA and determine systolic and diastolic annular velocities as previously described.[26] Peak velocities during systole and early (Ea) and late diastole (Aa), along with simultaneous electrocardiograpy displayed at a sweep rate of 50 mm/s were recorded.

Statistical Analysis

Three measurements were obtained for each studied variable and individual mean ± standard deviation values were compared using the 2-tailed Student's *t* test for unpaired data. The reported measures in this study represent an average of 3 different measurements obtained for each variable. A single experienced investigator performed all analysis.[12–17,21,25] Univariate analysis was performed when appropriate. Analysis of variance (ANOVA) with repeated measures was used to test statistical significance of the studied variables. When ANOVA showed statistically significant differences among groups, post hoc analysis with the Student-Newman-Keuls test was then performed to assess differences among these groups. A multivariate logistic regression analysis was performed to determine which variables were predictive of categorical variables such as death or need for transplantation. A stepwise multiple linear regression analysis was then performed between groups II and III to determine the independent predictive value of those identified variables that were significant on univariate analysis to identify the presence of hard end points between groups II and III. *P* values of less than 0.05 were considered to be statistically significant.

RESULTS

Distribution of World Health Organization classification[27] for all 78 cPH patients included in both groups II and III is shown in Table 1.

Important characteristics of the study group are listed in Table 2. Group I consisted of 42 individuals (mean age, 52 ± 9 years) with no PH and mean PASP of 30 ± 6 mm Hg (range, 18–40 mm Hg). Group II included 52 patients (mean age, 55 ± 14 years) and mean PASP of 73 ± 22 mm Hg (range, 45–130 mm Hg). Group III encompassed 26 patients (mean age, 63 ± 11 years) and mean PASP of 78 ± 29 mm Hg (range, 40–140 mm Hg). As expected, group I individuals had a statistically lower PASP than patients in both groups II and III ($P < 0.001$); but most importantly, there was no statistical difference between PASP measurements between groups II and III (P = NS). Group III patients were older than patients in either group I or II ($P = 0.005$). Finally, group I patients had a relative slower heart rate (66 ± 14 beats per minute; $P = 0.004$) than either group II (75 ± 15 beats per minute) or group III (77 ± 14 beats per minute) patients.

As seen in Table 2, group I patients had larger LV end systolic (27 ± 11 mL; $P = 0.001$) and end diastolic (101 ± 29 mL; $P < 0.001$) volumes than group II (18 ± 12 mL and 70 ± 38 mL, respectively) and group III (16 ± 12 mL and 59 ± 30 mL, respectively); however, LV volumes were not different between groups II and III. There was no difference among the 3 groups in terms of maximal mitral annular plane systolic excursion ($P = 0.120$) or LV ejection fraction ($P = 0.907$). In terms of RV areas, as expected, group I patients had smaller RV end systolic (6 ± 2 cm^2; $P < 0.001$) and end diastolic (17 ± 4 cm^2; $P < 0.001$) areas than group II (16 ± 8 cm^2 and 18 ± 9 cm^2, respectively) and group III (26 ± 9 cm^2 and 26 ± 9 cm^2, respectively), but, again, RV areas were not different between groups II and III. Not surprisingly, group I patients had a higher tricuspid annular systolic plane excursion (2.5 ± 0.3 cm) than group II (2.0 ± 0.5 cm) and group III (1.8 ± 0.5 cm); but, again, there was no difference between groups II and III for this measurement of RV systolic performance. Similarly, RV fractional area change was larger in group I (64% ± 8%; $P < 0.001$) than group II (41% ± 17%) or group III (34% ± 17%) patients.

In terms of Doppler measures, there was no difference among the 3 groups regarding RV outflow tract velocity ($P = 0.632$). Pulmonary vascular resistance values were significantly lower in group I (0.13 ± 0.03) when compared with group II (0.29 ± 0.12) and group III (0.34 ± 0.16), but again, we found no difference in terms of pulmonary vascular resistance between groups II and III.

Mitral annular TDI systolic velocity values were no different among the 3 groups ($P = 0.458$); however, group III had lower mitral annular early diastolic (Ea) wave (0.08 ± 0.03 cm/s) velocities than group I (0.11 ± 0.03 cm/s) and group II (0.11 ± 0.04 cm/s; $P = 0.007$). With regard to the late diastolic mitral annular TDI (Aa) wave velocity, a significant difference was only found between group I (0.10 ± 0.03 cm/s) and group III (0.12 ± 0.04 cm/s; $P = 0.054$). Late diastolic (Aa) wave velocities were no different between groups III and II (0.11 ± 0.04 cm/s, P = NS) patients. Only group III patients had a statistically lower mitral annular E/A diastolic ratio (0.77 ± 0.37) than group I (1.22 ± 0.53) and group II (1.05 ± 0.47) patients.

In terms of tricuspid annular TDI signals, group I patients had higher systolic velocities (0.13 ± 0.02 cm/s; $P = 0.001$) than either group II (0.12 ± 0.03 cm/s) or group III (0.11 ± 0.03 cm/s) patients with no difference noted between groups II and III. Group I patients also had higher early diastolic tricuspid annular (Ea) wave velocities (0.13 ± 0.03 cm/s; $P = 0.001$) than either group II (0.10 ± 0.06 cm/s) or group III (0.09 ± 0.03 cm/s) patients. However, no differences were seen in either late diastolic (Aa) velocities ($P = 0.994$) or tricuspid annular TDI E/A diastolic ($P = 0.196$) ratio among any of the 3 groups of patients.