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Original Research

PULMONARY VASCULAR DISEASE

Prognostic Relevance of Pulmonary Arterial Compliance in Patients With Chronic Heart Failure

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Background: **Reduced pulmonary arterial compliance (Ca) is a marker of poor prognosis in idiopathic pulmonary arterial hypertension. We tested the hypothesis that pulmonary arterial Ca could be a predictor of outcome in patients with chronic heart failure (CHF).**

Methods: **We enrolled 306 patients with CHF due to systolic left ventricular dysfunction (sLVD) who underwent a clinically driven right-sided heart catheterization. Pulmonary arterial Ca was measured by the ratio between stroke volume and pulse pressure (SV/PP). The primary end point was cardiovascular death; secondary end point was the composite of cardiovascular death, urgent heart transplantation, and appropriately detected and treated episode of ventricular fibrillation.**

Results: **An inverse relationship was observed between SV/PP and pulmonary vascular resistance, the mean resistance-compliance product (RC-time) being 0.30 ± 0.2 s. In patients with pulmonary capillary wedge pressure (PCWP) < 15 mm Hg, the mean RC-time was 0.34 ± 0.14 s, and in patients with PCWP ≥ 15 mm Hg it was 0.28 ± 0.22 s. Eighty-seven patients died in a follow-up period of 50 ± 32 months. At receiver operating characteristic curve analysis, the optimal prognostic cutoff point of SV/PP was 2.15 mL/mm Hg. An elevated (> 2.15) SV/PP was more strongly associated with survival than any other hemodynamic variable; it was associated with poor prognosis both in patients with high (*P* = .003) and in patients with normal pulmonary vascular resistance (*P* = .005).**

Conclusions: **Pulmonary arterial Ca is a strong prognostic indicator in patients with CHF with sLVD. Most importantly, its prognostic role is retained in patients with normal pulmonary vascular resistance.**

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Abbreviations: Ca = compliance; CHF = chronic heart failure; HR = hazard ratio; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PP = pulse pressure; PVR = pulmonary vascular resistance; RC-time = resistance-compliance product; ROC = receiver operating characteristic; RV = right ventricular; sLVD = systolic left ventricular dysfunction; SV = stroke volume

In patients with chronic heart failure (CHF), the negative impact of pulmonary hypertension (PH) on prognosis seems modulated by right ventricular (RV) function.[1-3] The most plausible explanation to these observations is that RV afterload and RV function are strictly related: PH is one of the main determinants of RV dysfunction, since the right ventricle, because of its specific anatomic characteristics, cannot easily tolerate pressure overload.[4,5] The poor prognosis seems, therefore, related to the unfavorable coupling between the right ventricle and the pulmonary circulation, ultimately leading to RV failure.

From a pathophysiologic point of view, it has to be emphasized that the precise definition of RV afterload is not only difficult to derive but also complex to interpret. Afterload can be defined by an arterial elastance measured as a ratio of end-systolic pressure and stroke volume (SV) on a ventricular pressure-volume loop.[6] This would be estimated by pulmonary vascular resistance (PVR) divided by heart rate, based on the assumption that mean pulmonary artery pressure is equal to RV end-systolic pressure. A more practical and equally valid definition of afterload is hydraulic load calculated from instantaneous pulmonary artery pressure and

flow waves.[7] A few decades ago, Reuben[8] noted an inverse relationship between PVR and pulmonary arterial compliance (Ca) in the normal or diseased pulmonary circulation. This was revisited in a series of studies that showed that the product of PVR and pulmonary arterial Ca, or the time constant (resistance-compliance product [RC-time]) of the pulmonary circulation, remains constant over a wide range of severities, causes, and treatments of PH.[9-11] This remarkable property of the pulmonary circulation has two consequences. The first is that pulmonary arterial Ca becomes a more important determinant of RV afterload than PVR when mean pulmonary artery pressure and PVR are only modestly elevated.[12] The second is that RV oscillatory hydraulic load, or power, remains a constant fraction of total power, irrespective of mean pulmonary artery pressure.[13] The only noticeable exception to the constancy of RC-time is PH secondary to left ventricular failure.[14] In these patients, RC-time is decreased because of a stiffer pulmonary arterial tree caused by increased pulmonary venous pressure.[15,16] A shortened RC-time implies an increased oscillatory component of hydraulic load.

Since in left ventricular failure PVR is usually only modestly elevated and the RC-time is shorter, one would expect pulmonary arterial Ca to be a major determinant of RV afterload. Therefore, we hypothesized that pulmonary arterial Ca would be a major determinant of survival in these patients. Accordingly, we analyzed the prognostic value of pulmonary arterial Ca in comparison with standard right-sided heart hemodynamic variables in a population of patients with CHF due to advanced systolic left ventricular dysfunction (sLVD). In addition, we sought to investigate whether pulmonary arterial Ca had a predictive role both in patients with normal and in patients with elevated PVR.

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Materials and Methods

Study Patients

The study included 306 consecutive patients with CHF with sLVD, referred for heart failure management, heart transplantation evaluation, or both. The inclusion criteria were left ventricular ejection fraction ≤ 35% and etiology due to ischemic or hypertensive heart disease or idiopathic dilated cardiomyopathy. Exclusion criteria were organic valvular heart disease, previous surgery for valvular heart disease, other cardiomyopathies (such as restrictive or hypertrophic cardiomyopathy and arrhythmogenic RV cardiomyopathy), hospitalization due to heart failure in the previous 3 months, implant of a cardiac resynchronization device in the previous 6 months, diagnosis of severe COPD, and history of pulmonary embolism. All patients underwent right-sided heart catheterization as part of the diagnostic protocol for heart failure evaluation and transplantation eligibility assessment. Patients signed an informed consent agreement approved by the Institutional Review Board of Fondazione IRCCS Policlinico S.Matteo for observational, nonpharmacologic, nonsponsored studies, which complies with the Italian legislation on the privacy (Codex on the Privacy, D. Lgs. 30 giugno 2003, n. 196).

Hemodynamic Parameters

Right-sided heart catheterization was performed using a balloon-tipped catheter. The following hemodynamic parameters were measured or calculated: pulmonary capillary wedge pressure (PCWP); systolic, diastolic, and mean pulmonary artery pressure; pulmonary pulse pressure (PP); cardiac output (calculated by thermodilution or by Fick method); cardiac index; SV (obtained by dividing cardiac output by heart rate); right atrial pressure; and PVR, calculated as (mean pulmonary artery pressure − PCWP)/cardiac output. Pulmonary arterial Ca was estimated by dividing the blood volume driven from each heartbeat in the pulmonary vascular tree, namely the SV, by the corresponding change in the pulmonary artery pressure: pulmonary arterial compliance ≈ SV/PP [mL/mm Hg].

Follow-up

The primary end point was cardiovascular death. The secondary end point was the composite of cardiovascular death, urgent cardiac transplantation (United Network for Organ Sharing [UNOS] 1), and appropriately detected and treated episode of ventricular fibrillation. Cardiac transplantation and implantation of a biventricular device were considered censoring events. Survival data were obtained through follow-up visits of patients or, in the case of missed visits, by telephone contact.

Statistical Analysis

Continuous data are presented as mean ± SD. To study the clinical characteristics of patients with normal or reduced Ca, patients were grouped in tertiles of SV/PP, and differences among groups were assessed by *t* test, χ^2, and analysis of variance, as appropriate. Survival and event-free survival were estimated by the Kaplan-Meier method and group differences assessed with the log-rank test. The optimal SV/PP cutoff value for predicting survival was identified from receiver operating characteristic (ROC) curve analysis. All hemodynamic parameters were dichotomized according to literature data. The independent association between SV/PP and prognosis was assess by means of Cox proportional hazard model. Bivariate Cox models were used to avoid multicollinearity among hemodynamic variables; however, results were similar when a full multivariate model was performed, including PCWP, mean pulmonary artery pressure, cardiac index, and PVR (data not