Echocardiographic estimation of pulmonary arterial systolic pressure in acute heart failure. Prognostic implications

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Abstract

Background: Prognostic implications of echocardiographic assessment of pulmonary hypertension (PH) in non-selected patients hospitalized for acute heart failure (AHF) are not clearly defined. The aim of this study was to evaluate the association between echocardiography-derived PH in AHF and 1-year all-cause mortality.

Methods: We prospectively included 1210 consecutive patients admitted for AHF. Patients with significant heart valve disease were excluded. Pulmonary arterial systolic pressure (PASP) was estimated using transthoracic echocardiography during hospitalization (mean time after admission 96 ± 24 h). Patients were categorized as follows: non-measurable, normal PASP (PASP ≤ 35 mm Hg), mild (PASP 36-45 mm Hg), moderate (PASP 46-60 mm Hg) and severe PH (PASP > 60 mm Hg). The independent association between PASP and 1-year mortality was assessed with Cox regression analysis.

Results: At 1-year follow-up, 232 (19.2%) deaths were registered. PASP was measured in 502 (41.6%) patients with a median of 46 [38–55] mm Hg. The distribution of population was: 708 (58.5%), 76 (6.3%), 147 (12.1%), 190 (15.7%) and 89 (7.4%) for non-measurable, normal PASP, mild, moderate and severe PH, respectively.

One-year mortality was lower for patients with normal PASP (1.32 per 10 person-years), intermediate for patients with non-measurable, mild and moderate PH (2.48, 2.46 and 2.62 per 10 persons-year, respectively) and higher for those with severe PH (4.89 per 10 person-years). After multivariate adjustment, only patients with PASP > 60 mm Hg displayed significant adjusted increase in the risk of 1-year all-cause mortality, compared to patients with normal PASP (HR = 2.56; CI 95%: 1.05–6.22, p = 0.038).

Conclusions: In AHF, severe pulmonary hypertension derived by echocardiography is an independent predictor of 1-year mortality.

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1. Introduction

Risk of mortality following an admission for acute heart failure (AHF) is high and risk stratification in this context still remains a challenge [1]. Heart failure (HF) is one of the main causes of pulmonary hypertension (PH), and is classified as type 2 PH by the World Health Organization [2]. Both systolic and diastolic dysfunction, as well as valvular heart disease, can increase left ventricular filling pressures and, consequently, cause elevated pulmonary artery pressures [3].

Although invasive measurement of pulmonary pressure is considered to be the gold standard, it is not routinely recommended due to its invasive nature [1]. Therefore, echocardiography has become a useful non-invasive technique for estimating the systolic pulmonary artery pressure (PASP) using the Doppler-derived velocity of the tricuspid regurgitation jet [4].

In chronic HF, the deleterious effect of PH is well established [4–10], nevertheless there are few data regarding its prognostic value following an admission for AHF [11]. Hence, the objective of this study was to evaluate the relationship between echocardiography-derived PASP and 1-year all-cause and cardiovascular mortality in a consecutive cohort of patients admitted for AHF.

2. Methods

2.1. Patients and study design

We prospectively studied a cohort of 1638 patients who were consecutively admitted for AHF to the cardiology department of a third level centre from January 1st 2004 to August 1st 2011. AHF was defined by rapid onset of symptoms and signs secondary to abnormal cardiac function, together with the presence of objective evidence of structural
or functional abnormality of heart at rest (such as cardiomegaly, third heart sound, cardiac murmur, echocardiographic abnormalities or elevated natriuretic peptides) [1]. Patients with significant left-sided valve disease (n = 428) were excluded, therefore 1210 patients formed the study population. Demographic information, medical history, vital signs, 12-lead laboratory data, and drug utilization were routinely determined on admission and during the hospital course, using pre-established registry questionnaires. All patients received intravenous treatment with furosemide for at least the first 48 h after admission.

Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonist, anticoagulants, diuretics, and other therapeutic strategies were individualized following established guidelines [1].

2.2. Echocardiographic examinations

M-mode, two-dimensional, and Doppler echocardiographic examinations (Agilent Sonos 5500-Phillips) were performed during index hospitalization after initial stabilization (mean time after admission 96 ± 24 h). Left ventricular ejection fraction (LVEF) was measured using the Simpson method. For PASP estimation, the Doppler-derived velocity of the tricuspid regurgitation jet was measured, and used to estimate the right ventricular to atrial pressure gradient during systole using the modified Bernoulli equation (4v²), where v is the velocity of the tricuspid regurgitation jet. Then, this gradient was added to the right atrial pressure (estimated on the basis of echocardiographic characteristics of the inferior vena cava and assigned a standardized value) in order to calculate the right ventricular systolic pressure which, in the absence of pulmonary stenosis, is equal to PASP [12].

PH was defined as PASP >35 mm Hg. Patients were categorized according to the following categories: non-measurable, normal PASP (PASP ≤ 35 mm Hg), mild (PASP 36–45 mm Hg), moderate (PASP: 46–60 mm Hg) and severe PH (PASP >60 mm Hg).

2.3. Endpoints and follow-up

The primary endpoint of the study was all-cause mortality. Cardiovascular mortality was chosen as the secondary endpoint. The survival status was ascertained by review of electronic medical records. The cause of death was extracted from patients' clinical charts, adjudicated by an investigator blinded to PASP values, and further categorized according to the American Heart Association classification [13]. Deaths were considered as non-cardiovascular, if a specific non-cardiovascular cause was identified. Otherwise, those deaths were considered to be of cardiovascular aetiology and included sudden death, death due to progressive HF or due to other cardiovascular causes (such as myocardial infarction, stroke, etc.) and unknown cause of death.

This study conforms with the principles outlined in the Declaration of Helsinki, was approved by an institutional review committee, and patients gave informed consent.

2.4. Statistical analysis

Baseline characteristics were compared among the PASP categories. For continuous, normally distributed variables, comparisons were calculated with ANOVA, using the Kruskal–Wallis rank test for highly skewed variables. The χ² test was used for the comparison of discrete variables. Cumulative mortality curves and their differences were estimated with the Kaplan–Meier method and the Log rank test for all-cause mortality and the cumulative incidence function and Gray test for cardiovascular mortality.

The independent effect of PASP categories on long-term all-cause and cardiovascular mortality was assessed using standard Cox regression analyses, as well as Cox regression analyses adapted for competing risk events [14], respectively. All variables listed in Table 1 were tested for prognostic purposes. Candidate covariates for multivariable analyses were chosen based on previous medical knowledge, independently of their p-value. A backward stepwise selection that keeps the nominal type I error at 0.05 was used [15]. The covariates included in the final simplified Cox model were: age, gender, first admission for AHF, prior hypertension, ischemic etiology, the interaction LVEF <50% with systolic blood pressure, hemoglobin, urea, brain natriuretic peptide, plasma carbohydrate antigen 125, treatment with angiotensin-converting-enzyme inhibitor, angiotensin receptor blockers and betablockers. For both the primary and the secondary endpoint, the proportionality assumption was tested. The model discriminations were assessed by the Harrell's C-statistic. Cox model calibration was tested by the Gronnesby and Borgan test [16]. A 2-sided p-value of <0.05 was considered statistically significant for all analyses. All analyses were performed using STATA 11.1 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

3. Results

In total, 1210 patients were included in the study. The mean age was 72.6 ± 11.6 years and 54.1% were male. On echocardiography, 52.4% of the patients exhibited a LVEF <50% and PASP could be estimated by transthoracic echocardiography in 41.5% of patients.

The distribution of patients according to PASP categories was as follows: non-measurable [708 patients (58.5%)], normal PASP [76 patients (6.3%)], mild [147 patients (12.1%)], moderate [190 patients (15.7%)] and severe PH [89 patients (7.4%)].

Overall, there was a positive association of PASP with clinical variables related to the severity of the disease (Table 1). Thus, patients with higher PASP were older, exhibited higher prevalence of congestion (pleural effusion, peripheral oedema, previous use of diuretics and plasma antigen carbohydrate 125), atrial fibrillation and higher mean BNP and left atrial diameter. Similarly, mean systolic and diastolic blood pressure as well as haemoglobin were found in patients with higher PASP. Of note, LVEF was not significantly different across PASP categories (Table 1).

At 1-year follow-up, 232 patients (19.2%) reached the primary endpoint. PASP was positively associated with 1-year all-cause mortality, with lower mortality rates found in patients with normal PASP (1.32 per 10 persons-year), intermediate for those with non-measurable PASP (2.48 per 10 persons-year), mild (2.46 per 10 persons-year) and moderate PH (2.62 per 10 persons-year) and higher for patients with severe PH (4.89 per 10 persons-year) (p-value for trend <0.001). As illustrated in Fig. 1, these differences were highly significant and evident from the first months of follow-up, especially in the case of severe PH, with similar trajectories in those with preserved systolic function and systolic dysfunction (Fig. 2a and b, respectively).

In a multivariate analysis, after adjusting for established prognostic covariates and potential confounders, only patients with a PASP >60 mm Hg displayed a significant increase of risk of 1-year all-cause mortality, compared to patients without PH (HR = 2.56; CI 95%[1.05–6.22], p = 0.038). Adjusted HRs for all PASP categories are shown in Table 2. The Harrell's C-statistics of the multivariate Cox models with and without PASP were 0.783 and 0.774, respectively. The Gronnesby and Borgan test of goodness-of-fit showed a good calibration of the final model (p = 0.916).

In a sensitivity analysis, forcing chronic obstructive pulmonary disease (as binary) into the multivariate model regardless of the association with the endpoint, similar estimates were obtained; thus, only those patients with PASP >60 mm Hg showed an increased risk of 1-year all cause mortality (HR = 2.58; CI 95% [1.06–6.27], p = 0.037).

The adjusted interactions between PASP >60 mm Hg and LVEF (<50% or ≥50%) were not significant (p = 0.623), revealing a
homogeneous prognostic effect of PASP in both populations of HF (preserved systolic and systolic dysfunction).

The secondary endpoint, 1-year cardiovascular mortality, was reached by 183 patients (15.1%). Similarly to all-cause mortality, patients with severe PH showed a higher cumulative incidence of cardiovascular mortality, while simultaneously accounting for non-cardiovascular mortality as a competing event (Fig. 3). In multivariate competing risk analysis, adjusting for the same set of covariates and for non-cardiovascular mortality as a competing event (Fig. 3), we observed that echocardiography-derived PASP, after intensive treatment, identified a non-negligible subset of patients, PASP > 60 mm Hg, with a significant adjusted increased risk for all-cause and cardiovascular mortality at 1-year.

4.1. PASP in heart failure

The prevalence of PH in HF is heterogeneous and ranges from 46 to 83% [10]. This disparity in prevalence possibly stems from the fact that these patients were either highly selected or very heterogeneous.

4. Discussion

In the present study of non-selected patients admitted for AHF, we observed that echocardiography-derived PASP, after intensive treatment, identified a non-negligible subset of patients, PASP > 60 mm Hg with a significant adjusted increased risk for all-cause and cardiovascular mortality at 1-year.
prospective studies which enrolled non-selected patients [4,7,8]. Regardless of the success of echocardiographic measurements of PASP, our study, in accordance with previous studies, found a high prevalence of PH (85%).

### 4.2. Prognostic implications

Although there are abundant data on the prognostic value of PASP in idiopathic PH, data on the prognostic value in type 2 PH are scarce and restricted to very selected chronic HF populations [5–9]. Abramson et al. [5] showed a worse prognosis in 108 patients with dilated cardiomyopathy in the presence of high velocities of tricuspid regurgitation (2.5 m/s). Later, Lam et al. [9] demonstrated that PASP predicted mortality in patients with chronic heart failure with preserved ejection fraction selected from a community study (HR = 1.3 per increase in 10 mm Hg, p < 0.001). Other studies, both in systolic or diastolic heart failure, have shown similar results [4,7,8].

In contrast to these previous studies, our cohort included a non-selected cohort of consecutive patients with AHF and estimates of risk were obtained after a thoroughly multivariate adjustment,
including the most important prognostic parameters in the acute setting, as natriuretic peptides, renal function, pharmacological treatment and potential confounders highly prevalent in this population such as chronic obstructive pulmonary disease.

More recently, Bursi et al. [10] reported in 1049 non-selected community HF patients that higher PASP was a strong predictor of death and provided incremental prognostic information. Similarly to our findings, these authors found that patients with an elevated PASP (PAPS > 54 mm Hg) showed an adjusted 2-fold increased risk of death. In addition, the prognostic implications attributable to PASP were uniform according to LVEF.

5. Conclusions

Echocardiographic assessment of PAPS, after initial stabilization in patients admitted for AHF, identifies a subgroup of patients (PASP > 60 mm Hg) with an adjusted increased risk of 1-year mortality.

Learning points

• Pulmonary hypertension is a frequent finding in patients admitted with acute heart failure.
• In patients hospitalized for acute heart failure, echocardiographic estimation of severe pulmonary hypertension pressure is associated to an independent increased risk of 1-year mortality.

Conflict of interests

No conflict of interest to declare.

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