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Pulmonary hypertension and clinical correlates in hypertrophic cardiomyopathy

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ABSTRACT

Background: Pulmonary hypertension (PH) in patients with hypertrophic cardiomyopathy (HCM) has been investigated in a small number of studies. Purpose of this study was to assess the prevalence and its association with outcome in a population of consecutive HCM outpatients.
Methods: We retrospectively analyzed data of 361 consecutive HCM outpatients in whom echocardiographic measurements of pulmonary artery systolic pressure (PASP) were available at initial and most recent evaluation. Four different clinical groups were specifically investigated: patients without left ventricular outflow tract obstruction (group A, 165), with obstruction (group B, 126), patients diagnosed at the age ≥ 65 (group C, 50) and patients with end stage (ES) HCM (group D, 20).
Results: PH was identified in 41 (11.4%) of the 361 patients at initial evaluation while it has been recognized in 25 (7,8% [1.1%/year]) during a median follow-up of 3.4 years. Analysis of subgroups showed that prevalence of PH increased from patient group A to D (8%, group A, 19%, group B, 28% group C, 70%, group D, respectively, $p < 0,01$). During follow-up, patients with PH showed a significant higher HCM-related mortality ($p = 0.01$) and morbidity ($p < 0.001$) as compared with those without PH, but in multivariable analysis, PH resulted an independent risk factor only for HCM-related morbidity (HR = 2.50, 95% CI 1.08–5.79, $p = 0.03$).
Conclusion: PH affects a significant proportion of patients with HCM. Its prevalence varies according to different clinical profiles. It is associated with an unfavorable clinical outcome and is an independent predictor of morbidity.

1. Introduction

Pulmonary hypertension (PH) is a known complication of any cardiac disease in which left ventricular (LV) filling pressure is increased, including LV systolic dysfunction, LV diastolic dysfunction and left-side valvular heart disease [1–3]. In these disease conditions, PH results in more severe symptoms and worse exercise tolerance and exerts a negative impact on outcome [4–6]. PH may develop in patients with hypertrophic cardiomyopathy (HCM) due to elevated left-sided diastolic pressures, secondary to diastolic dysfunction, LV outflow tract (LVOT) obstruction with mitral regurgitation and in a minority of cases to systolic dysfunction [7–9]. To date, few studies have investigated the prevalence and the role of PH in HCM [7–9]; moreover, most of these analyses were conducted in a highly selected population from an HCM Centre of Excellence [8,9].

The aim of our study was to assess how PH is prevalent in a population of consecutive HCM outpatients, according to different clinical profiles, and to evaluate its prognostic impact.

2. Methods

2.1. Study population

From January 2002 to January 2014, 441 consecutive patients aged >18 years old with HCM were evaluated and periodically followed in the HCM outpatient clinic at Azienda Ospedaliera Sant'Andrea (Rome, Italy). We retrospectively analyzed data of all patients who had

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echocardiographic recordings of pulmonary artery systolic pressure (PASP) at initial evaluation and during follow-up. We excluded from our analysis 26 patients lost at follow-up, 39 patients who did not have good quality echocardiographic images and 15 patients with comorbidities that may contribute to cause PH such as lung disease (e.g. chronic obstructive pulmonary disease) and autoimmune disease. Three hundred-sixty-one patients met the study inclusion criteria. To evaluate whether the occurrence of PH varies among different clinical phenotypes of HCM, we divided patients in four groups: patients diagnosed before 65 years of age without LVOT obstruction (group A, 165), and with LVOT obstruction (group B, 126), patients diagnosed at age of 65 or above (group C, 50) and patients with end stage (ES) HCM (group D, 20). The mean duration of follow-up from the first to the most recent evaluation or event was of 4.1 ± 2.8 years (range 1–12 years). At each visit, patients underwent a complete clinical and echocardiographic assessment; sudden cardiac death (SCD) risk stratification was performed according to the established risk factors at first visit and periodically re-evaluated during follow-up [10–12]. All patients consented to retrospective anonymized participation into clinical surveys, by signing an informed consent. The consent was administered by paramedic practitioners trained for this procedure, and it was later verified by medical doctors involved in the study. The consent was not designed for the purpose of the present study but a template approved and validated by the local Ethical Committee to process personal data for both hospital procedures and clinical researches and analysis. Confidentiality of the data has been protected through encrypted electronic medical records with reserved limited access.

2.2. Definitions

The diagnosis of HCM was based on echocardiographic demonstration of a hypertrophied and non-dilated left ventricle (LV wall thickness > 15 mm in adults) in the absence of any other cardiac or systemic disease capable of producing the magnitude of wall thickening evident [10,12]. Pulmonary hypertension was defined as PASP >35 mmHg, detected at >1 evaluation during follow-up [13]. End stage HCM was defined in the presence of a LV ejection fraction <50% at rest [14]. Sudden cardiac death was defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute symptoms. Death was also classified as sudden if it occurred unexpectedly but was unwitnessed, such as in bed overnight [15]. Heart failure-related death was defined as death occurring in the context of long-standing cardiac decompensation with progression of disease during the previous year, with the development of pulmonary oedema or evolution to end-stage disease [16]. Implantable cardioverter-defibrillator (ICD) interventions (shocks or anti-tachycardia pacing) were considered appropriate when triggered by ventricular fibrillation or rapid ventricular tachycardia (rate > 200 per minute) documented by stored electrographic or cycle length data [17]. Appropriate ICD interventions and heart transplantation were considered as a surrogate of sudden cardiac and heart failure-related death, respectively.

2.3. Echocardiography

Echocardiograms were performed with commercially available instruments. In all patients LV diameter, maximal wall thickness, left atrial end-systolic diameter and LV ejection fraction were assessed in the standard fashion [18]. LVOT obstruction under basal conditions was considered present when a peak gradient ≥30 mmHg was identified by Doppler [10,19]. Mitral regurgitation was graded semiquantitatively and classified as mild, moderate and severe [20]. LV filling patterns were assessed by pulsed-wave Doppler at the mitral tip level, from the 4-chamber echocardiographic apical view in a standard manner [21–22]. We identified 4 LV diastolic dysfunction grades: none = normal; mild = abnormal relaxation LV filling pattern; moderate = pseudonormal LV filling pattern; severe = restrictive LV filling pattern.

PASP was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, where v is the velocity of the tricuspid regurgitation jet in m/s. Right atrial pressure, estimated based on echocardiographic characteristics of the inferior vena cava and assigned a standardized value, was then added to the calculated gradient to give PASP [23].

3. Statistics

Continuous data are presented as mean ± SD. Categorical data are presented as frequency and percentages. Differences between continuous variables were assessed using Student's *t*-test. Categorical variables were compared among groups by the chi-square test or Fisher's test, as appropriate.

To assess the role of clinical and echocardiographic features as determinants of developing PH, a univariable and multivariable Cox regression analysis was performed. We have performed a LASSO analysis for selecting the variables to be included in the multivariable model. Reliable confidence intervals around the penalized estimates can be obtained using the standard Cox model theory. Thus, we re-fitted the model with the retained predictors (from Lasso regression) using standard Cox regression. Forty-one patients who had PH at first evaluation were excluded from this analysis.

In order to estimate the impact of PH on prognosis, two specific end-points were evaluated.

HCM-related mortality end-point was considered as any occurrence of SCD or heart failure-related death and/or appropriate ICD intervention or heart transplantation. HCM-related morbidity end-point was considered as progression to NYHA functional class III-IV and/or to ES HCM. HCM-related mortality and morbidity incidence rate was calculated by dividing the number of new events by the total number or person-years accumulated during follow-up in the study population. To evaluate the role of PH as an independent predictor of HCM-related mortality and morbidity, a set of univariable and multivariable Cox proportional-hazard models were fitted to the data. Variables not significantly associated with outcome were removed from multivariate models using a step-up procedure.

Survival curves for HCM-related mortality and morbidity were constructed according to the Kaplan-Meier method and differences in survival were compared using the log-rank test.

Statistical analysis was performed using SPSS statistical software. A p-value less than or equal to 0.05 was considered as statistically significant.

4. Results

4.1. Patient characteristics and PH distribution among the 4 clinical groups

PH was documented in 66 (18,3%) out of 361 study patients. Forty-one (11.4%) patients presented PH at first evaluation, while 25 (7.8% [1,1%/year]) developed it during a mean follow-up of 4.1 ± 2.8 years (median 3.4 years). Clinical characteristics of patient without PH and with PH at baseline or during follow-up are presented in Table 1. At first evaluation patients with PH were older ($p < 0.001$), more likely female ($p = 0.001$) and had more severe symptoms ($p < 0.001$) and higher prevalence of atrial fibrillation (AF) ($p < 0.001$) compared with HCM patients without PH. At echocardiographic evaluation, patients with PH had increased left atrial diameter ($p < 0.001$), and presented more frequently with ES HCM ($p < 0.001$), moderate/severe LV diastolic dysfunction grade ($p < 0.001$) and moderate/severe mitral regurgitation ($p = 0.001$).

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