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Short communication

Association of elevated pulmonary artery systolic pressure with stroke and systemic embolic events in patients with hypertrophic cardiomyopathy☆

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ABSTRACT

Background: Echocardiographically estimated pulmonary artery systolic pressure (PASP) is a non-invasive widely available method that is used to estimate pulmonary arterial pressure. Although elevated PASP predicts mortality in patients with hypertrophic cardiomyopathy (HCM), the relationship between PASP and embolic events is unclear. This study aimed to determine whether elevated PASP is associated with stroke and systemic embolic events in a tertiary referral HCM cohort.
Methods: This study included 374 clinically diagnosed patients with HCM. PASP was estimated from tricuspid regurgitant jet velocity using the modified Bernoulli equation.
Results: The median (interquartile range) PASP was 33 (28–37) mm Hg, and elevated PASP (>40 mm Hg) was observed in 66 (17.6%) patients. Seventeen of the 66 (25.8%) patients with elevated PASP and 24 of the 308 (7.8%) patients without elevated PASP experienced stroke and systemic embolic events during the 10.3 ± 7.4 years of follow-up (log-rank $P < 0.001$). Multivariable analysis showed that age at diagnosis, atrial fibrillation, and PASP >40 mm Hg (adjusted hazard ratio, 2.59; 95% confidence interval, 1.31–5.12; $P = 0.006$) were independently associated with embolic events.
Conclusions: In addition to age and atrial fibrillation, PASP estimated by Doppler echocardiography could help embolic risk stratification in patients with HCM.

1. Introduction

Stroke and systemic embolic events are common complications of patients with hypertrophic cardiomyopathy (HCM), and are associated with adverse clinical outcomes and reduced survival [1–4]. However, HCM is a markedly heterogeneous genetic cardiac disorder with variable clinical presentation [5–8], and the absolute risk of stroke and embolic events in individual patients with different clinical characteristics is relatively unknown. Pulmonary artery systolic pressure (PASP) as estimated by Doppler echocardiography is a non-invasive widely available method. PASP is used to estimate pulmonary hypertension, most commonly by calculating the trans-tricuspid gradient from regurgitant jet velocity, and is already being used in standard echocardiographic studies [9–13]. Elevated PASP can predict mortality and morbidity in the general population and in patients with heart failure [9,11]. Additionally, Ong et al. recently showed that elevated PASP was associated with increased mortality in patients with HCM [12]. Pulmonary hypertension is a common complication of left-sided heart disease and heart failure, and heart failure is a well-known established major risk factor for stroke and embolic events [11,12,14,15]. Therefore, elevated PASP may predict embolic events in patients with cardiovascular disease, especially in patients at high risk of embolization, such as those with HCM. In this study, we aimed to determine whether elevated PASP is associated with embolic events in a tertiary referral HCM cohort.

2. Methods

This retrospective study included 401patients with clinically diagnosed HCM at the Tokyo Women's Medical University Hospital, Tokyo, Japan, from 1994 to 2010. The diagnosis of HCM was made based on 2-dimensional echocardiographic evidence of a hypertrophied (maximal wall thickness of at least 15 mm) non-dilated left ventricle in the absence of any other systemic disease capable of producing a similar hypertrophy [1,2]. We excluded patients who had severe valvular heart disease, severe lung disease, connective tissue disease, and congenital heart disease. The initial evaluation was defined

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as the first clinical assessment at which an echocardiographic diagnosis of HCM was obtained. The most recent evaluation was performed in the outpatient clinic or by telephone interview. This study was conducted based on the principles of the Helsinki Declaration, and the study protocol was approved by the ethics committee in our institute.

Stroke was defined as permanent neurological impairment and disability caused by vascular causes, including ischemic stroke and intracerebral hemorrhage after infarction [3,4,16]. Arterial embolism at sites other than in the central nervous system causing acute ischemia to the kidney, limbs, and other organs was diagnosed based on abrupt onset of localized pain associated with cold, pulseless extremities, or hematuria and confirmed by abnormal angiography, ultrasonography, or computed tomography [3,4]. The presence of atrial fibrillation was documented either by 12-lead resting electrocardiogram or 24 hour ambulatory electrocardiogram, obtained either after the acute onset of clinical symptoms or during routine annual medical examination in patients without symptoms.

Echocardiographic studies were performed with commercially available ultrasound equipment [17]. The peak velocity was quantified by continuous-wave Doppler echocardiography. PASP was estimated from tricuspid regurgitant jet velocity using the modified Bernoulli equation (4 times the peak tricuspid regurgitant velocity squared) and adding the estimated mean right atrial pressure of 10 mm Hg [11]. Sensitivity analyses adopting thresholds for the definition of high PASP (>36, >40, and >50 mm Hg) were performed, and PASP >40 mm Hg showed the most favorable performance for embolic risk stratification [10,12]. Elevated PASP was thus defined according to a PASP cutoff value of >40 mm Hg.

Of the 401 patents, 374 (93.3%) had measureable peak tricuspid regurgitant gradients. The remaining 27 (6.7%) patients with incomplete data on PASP were excluded from the analysis. The excluded patients were similar to the cohort used in this analysis, and no significant differences were observed in embolic events between the 2 groups (11.1% vs. 11.0%, P > 0.999). The Student's *t*-test or the Mann–Whitney *U* test was used for continuous or ordinal variables. The chi-square test or Fisher's exact test was used for nominally scaled variables. The probability of embolic events was estimated by the Kaplan–Meier method, after which the log-rank test was used to compare curves. Multivariable Cox proportional hazards models were used to evaluate the effect of PASP on embolic events. All analyses were performed with the SAS system ver. 9.4 (SAS Institute, Cary, NC) at an independent biostatistics and data center (STATZ Institute, Inc.).

3. Results

The distribution of estimated PASP in the 374 patients with HCM (age at diagnosis: 50.6 ± 15.8 years, men: 64.4%, follow-up period: 10.3 ± 7.4 years) is shown in Fig. 1A. The median (interquartile range) PASP was 33 mm Hg (28–37 mm Hg) and elevated PASP (>40 mm Hg) was observed in 66 (17.6%) patients. Baseline characteristics of the study patients according to PASP are shown in Table 1. There was no significant difference in the rates of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke scores between patients with and without elevated PASP (mean score: 1.31 ± 0.88 versus 1.19 ± 0.89; Mann–Whitney *U* test, P = 0.346) before the embolic events. Twenty of the 66 (30.3%) patients with elevated PASP and 30 of the 308 (9.7%) patients without elevated PASP experienced episodes of progressive heart failure with an increase to ≥3 New York Heart Association functional class during the follow-up period (P < 0.001). Seventeen of the 66 (25.8%) patients with elevated PASP experienced embolic events. Among the 17 patients with events, cerebral ischemic stroke occurred in 15 (88.2%), including 1 patient who had intracerebral hemorrhage after infarction. Two of the 17 (11.8%) patients had embolic events to organs other than the brain (kidney, n = 1; lower limb, n = 1). In contrast, 24 of the 308 (7.8%) patients without elevated PASP experienced embolic events. Among these 24 patients with events, cerebral ischemic stroke occurred in 23 (95.8%), including 1 patient who had intracerebral hemorrhage after infarction, and 1 patient (4.2%) had embolic events to the kidney. The Kaplan–Meier estimate showed that patients with elevated PASP had a significantly greater likelihood of embolic events than those without elevated PASP (log-rank P < 0.001, Fig. 1B). According to multivariable analysis (including age at diagnosis, female sex, left atrial dimension, atrial fibrillation, left ventricular intracavitary obstruction, maximal wall thickness, and elevated PASP), age (adjusted hazard ratio [HR] per 1 increase, 1.03; 95% confidence interval [CI], 1.00–1.05; P = 0.028), atrial fibrillation (adjusted HR, 3.39; 95% CI, 1.63–7.03; P = 0.001) and elevated PASP (adjusted HR, 2.59; 95% CI, 1.31–5.12; P = 0.006) were independently associated with the embolic events.

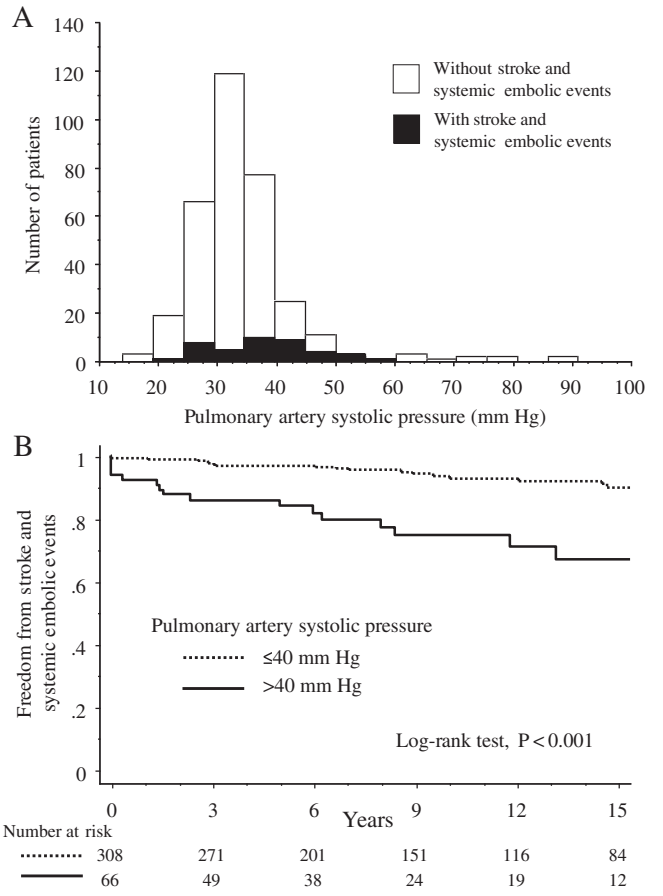

Fig. 1. (A) Distribution of estimated pulmonary artery systolic pressure (PASP) in patients with hypertrophic cardiomyopathy (HCM). Closed bars: patients with a stroke and systemic embolic event; open bars: those without a stroke and systemic embolic event. (B) Kaplan–Meier estimate of stroke and systemic embolic events in HCM patients with or without elevated PASP (>40 mm Hg).

4. Discussion

In this tertiary referral HCM cohort, the median PASP was 33 mm Hg. Patients with elevated PASP were more likely to be female and had a higher prevalence of atrial fibrillation. These PASP values and the characteristics of patients with elevated PASP were almost identical to those in a previous referral cohort [12]. In patients with HCM, diastolic dysfunction secondary to intrinsic myocardial stiffness and hypertrophy can be present. These hemodynamic disturbances predispose to elevation in left atrial pressure and development of post-capillary pulmonary hypertension [1,2]. Therefore, elevated pulmonary pressure represents the cumulative downstream effect of hemodynamic disturbances that increase left atrial pressure, and likely represents a marker of adverse outcome [9,11,18]. A previous study demonstrated that elevated PASP was associated with worse survival in patients with HCM, but the details of adverse events were not available [12].

In this study, echocardiographically estimated PASP was independently associated with stroke and systemic embolic events in patients with HCM. Although the reason for this result is unclear, we also showed that elevated PASP was associated with progressive heart failure events. Elevated PASP predicts hospitalization for heart failure in the general population and various cardiac diseases, and heart failure is a well-known established major risk factor for embolic events [9,11,14,18]. Patients with heart failure have coagulation disorders and a risk of embolic events because all components of Virchow's triad (hypercoagulability, endothelial injury, and stasis) are altered to some extent [15]. These abnormalities could potentially arise from many

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