

Mechanism of Progressive Heart Failure and Significance of Pulmonary Hypertension in Obstructive Hypertrophic Cardiomyopathy

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Background—There are limited data on the prevalence, pathophysiology, and management implications of pulmonary hypertension in patients with obstructive hypertrophic cardiomyopathy and advanced heart failure.

Methods and Results—To assess the clinical significance of measured cardiopulmonary hemodynamics in hypertrophic cardiomyopathy patients with heart failure, we retrospectively assessed right heart catheterization data in 162 consecutive patients with outflow tract gradients (median [interquartile range], 90 mmHg [70–110 mmHg]), 59±11 years old, and 49% men, predominately New York Heart Association class III/IV status. Pulmonary hypertension (mean pulmonary artery pressure, ≥25 mmHg) was present in 82 patients (51%), including 29 (18%) regarded as moderate-severe (mean pulmonary artery pressure, ≥35 mmHg) and 28 (34%) also had increased pulmonary vascular resistance >3.0 WU. The pulmonary artery wedge pressure was ≤15 mmHg in 54%, indicating that left atrial hypertension was absent in a majority of patients. Notably, 9 patients (11%) met hemodynamic criteria for precapillary pulmonary hypertension (mean pulmonary artery pressure, ≥25 mmHg; pulmonary vascular resistance, >3.0 WU; pulmonary artery wedge pressure, ≤15 mmHg). Over a median follow-up of 327 days (90–743 days) after surgical myectomy (or alcohol septal ablation), 92% and 95% of patients with or without preoperative pulmonary hypertension, respectively, were asymptomatic or mildly symptomatic. One postoperative death occurred in a 59-year-old woman with acute respiratory failure and mean pulmonary artery pressure of 65 mmHg.

Conclusions—Pulmonary hypertension was common in obstructive hypertrophic cardiomyopathy patients with advanced heart failure. Although possibly a contributor to preoperative heart failure, pulmonary hypertension did not significantly influence clinical and surgical outcome. Notably, a novel patient subgroup was identified with resting invasive hemodynamics consistent with pulmonary vascular disease. (*Circ Heart Fail.* 2017;10:e003689. DOI: 10.1161/CIRCHEARTFAILURE.116.003689.)

Key Words: cardiomyopathy, hypertrophic ■ hypertension, pulmonary ■ pulmonary artery ■ pulmonary heart disease

Heart failure in hypertrophic cardiomyopathy (HCM) is most common because of mechanical impedance to left ventricular (LV) outflow, present in up to 70% of patients at rest or with physiological provocation, and produced by mitral valve systolic anterior motion with associated mitral regurgitation, resulting in elevated LV pressures and left atrial hypertension.^{1,2} However, the prevalence, clinical significance, and management implications of pulmonary hypertension and the associated risk for adverse outcomes in patients with HCM are incompletely understood. Previous reports characterizing pulmonary artery pressure (PAP) dynamics in patients with obstructive HCM have relied largely on estimates derived from Doppler echocardiography

studies and attributed adverse consequences (ie, all-cause mortality) to pulmonary hypertension.^{3,4} Therefore, in the present analysis, we have revisited clinical issues surrounding pulmonary hypertension in a unique cohort of patients with HCM using hemodynamic data obtained at cardiac catheterization.

See Clinical Perspective

Methods

Study Population

We evaluated 187 consecutive adult patients diagnosed with obstructive HCM who underwent right heart catheterization and subsequent

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septal reduction with surgical myectomy or percutaneous alcohol septal ablation at Tufts Medical Center 2009 to 2015. Diagnosis of HCM was based on echocardiographic or cardiovascular magnetic resonance imaging evidence of LV hypertrophy (wall thickness, ≥ 15 mm) involving ≥ 1 segment of the chamber in the absence of a cardiac or systemic disease capable of producing the extent of hypertrophy evident. Twenty-five patients were excluded from this analysis because of moderate or severe mitral or aortic disease unrelated to HCM, and the final study group comprised 162 patients. This study has been reviewed and approved by Institutional Review Boards of Tufts Medical Center (12019) for retrospective collection of data for this project; the requirement of informed consent was waived for all patients.

Echocardiography

Transthoracic echocardiography was performed using commercially available instruments. Measurements of LV wall thickness and cavity dimensions, ejection fraction, and LV outflow tract gradient (estimated with continuous wave Doppler) were obtained as reported previously.⁵ Mitral regurgitation was graded mild, moderate, and severe using semiquantitative criteria. Left atrial volume was calculated with the biplane area-length method and indexed to body surface area. Patients with LV outflow tract gradient of zero or < 50 mmHg under resting conditions underwent stress echocardiography with upright exercise on a symptom-limited Bruce protocol; subaortic gradient was assessed at baseline and immediately after exercise in the supine position. Measurements of right ventricular (RV) diameter and systolic function including fractional area change and peak systolic tricuspid annular velocity (S') were measured according to standard published guidelines.⁶

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging studies were performed in 118 of the 162 HCM study patients (73%) using a 1.5 T clinical scanner. Cine sequences were performed in standard views with full LV coverage. Late gadolinium enhancement (LGE) images were acquired 10 to 15 minutes after intravenous administration of 0.2-mmol/kg gadolinium-DTPA using breath-held segmented inversion-recovery sequence. LGE quantification was performed by manually adjusting grayscale threshold to visually define LGE, which were summed and expressed as proportion of total LV myocardium.⁷

Cardiac Catheterization

Each patient underwent right heart catheterization in the supine position at rest, either as part of the premyectomy clinical evaluation or at the time of alcohol septal ablation. Most patients continued to take medications that had been administered previously for the purpose of controlling symptoms of heart failure (eg, β -adrenergic receptor blockers or verapamil).

Right atrial, mean PAP (mPAP), and pulmonary artery wedge pressure (PAWP) were measured at end-expiration and averaged over ≥ 3 beats. Cardiac output, measured in 157 patients, was determined by the thermodilution ($n=150$) or assumed Fick ($n=7$) methods, and indexed to body surface area. Pulmonary vascular resistance was calculated as $(\text{mPAP}-\text{PAWP})/\text{cardiac output}$, transpulmonary gradient was calculated as $\text{mPAP}-\text{PAWP}$, and diastolic pressure gradient was calculated as $(\text{diastolic PAP}-\text{PAWP})$.

Statistical Analysis

Continuous data are expressed as mean \pm SD for normally distributed variables or as median (interquartile range) for non-normally distributed variables. Comparisons between normally distributed groups were performed by Student t test. The Mann-Whitney or Kruskal-Wallis tests were used for comparisons between non-normally distributed variables. Exact χ^2 test was used for categorical variables. All tests were 2 tailed, and statistical significance was defined by $P < 0.05$. All analyses were performed using R version 3.2.5.⁸

Results

Study Population

The 162 study patients with obstructive HCM and septal reduction therapy (surgical myectomy in 116 and alcohol septal ablation in 46) were aged 35 to 82 years (mean, 59 ± 11 years) and 79 (49%) were men (Table 1). Maximum LV wall thickness was 19 ± 4 mm and LV outflow obstruction (≥ 30 mmHg) was present at rest ($n=125$) or after physiological provocation ($n=37$) in all patients, with peak systolic gradients of 50 to 160 mmHg (average 90 mmHg).

Patients were severely symptomatic, consistent with New York Heart Association functional class III/IV, and refractory to maximum medical management before septal reduction. Moderate to severe mitral regurgitation was present in 30 patients (19%), associated with increased left atrial volume (≥ 34 mL/m²) in 28 patients; LV ejection fraction ranged from 48% to 80% (mean, 65%). Thirty-six patients (22%) had ≥ 1 episode of symptomatic atrial fibrillation. Obstructive atherosclerotic coronary artery disease was present in 22 patients (14%). The average RV diameter (37 mm [33–42 mm]), RV fractional area change (47 [43–51] % change), and peak tricuspid annulus S' velocity (12.3 cm/s [11.0–14.0 cm/s]) were within the range of normal.

Group Hemodynamic Profile

Among the 162 study patients, mPAP ranged from 11 to 65 mmHg (median 25 [20–31] mmHg); 82 patients (51%) were judged to have pulmonary hypertension with mPAP ≥ 25 mmHg. Of these, 36 had 25 to 30 mmHg, 19 had 31 to 35 mmHg, 9 had 36 to 40 mmHg, and 18 had > 40 mmHg (Figure 1). Of the 82 patients with increased PAP, 28 (34%) also had increased pulmonary vascular resistance (> 3.0 WU). The average pulmonary artery systolic pressure for the entire cohort was 41 mmHg (31–46 mmHg).

The mPAP did not correlate with peak LV outflow tract gradient ($r=0.09$; $P=0.32$; Figure 2). Correlation between systolic PAP measured at catheterization mmHg with that estimated by Doppler echocardiography (28 mmHg [23–32 mmHg]) in 131 patients was $r=0.72$, $P < 0.001$, with Doppler estimate being 9 mmHg (4–16 mmHg) lower than the invasive measure. Using suggested alternative criteria for pulmonary hypertension (mPAP ≥ 20 mmHg),⁹ 132 patients (82%) could be regarded as having increased PAP.

The PAWP at rest ranged from 6 to 41 mmHg (average 16 ± 7 mmHg) and was > 15 mmHg in 74 patients (46%). Cardiac output was measured in 157 subjects and ranged from 2.2 to 12.3 L/min (cardiac index 1.0–5.4 L/min per meter square), normal (> 5.0 L/min) in 73 patients, and reduced (< 3.0 L/min) in 5 patients.

Relation of mPAP to Clinical Variables

Compared with patients with normal mPAP (< 25 mmHg), the 82 patients with pulmonary hypertension (mPAP ≥ 25 mmHg) were older (61.4 versus 56.9 years; $P=0.006$), with higher body mass index (33.2 versus 28.6 kg/m²; $P < 0.001$), maximum LV wall thickness (20.0 versus 18.6 mm; $P=0.024$), and left atrial volume index (45 versus 41 mL/m²; Table 2). Clinically meaningful differences between the groups were not identified for RV diameter (36 mm [32–42 mm] versus 37 mm [34–42] mm;

Table 1. Clinical, Echocardiographic, and Hemodynamic Characteristics in 162 Patients With Obstructive HCM

General Characteristics	
Age, y	59.2 (10.5)
Male sex, n (%)	79 (49)
BMI, kg/m ²	30.9±6.9
Atrial fibrillation, n (%)	36 (22)
Medications at RHC, n (%)	
β-blockers	135 (83)
Calcium-channel blockers	49 (30)
Disopyramide	20 (12)
Diuretics	39 (24)
Echocardiographic variables	
Peak LVOT gradient, mm Hg	90 [70–110]
LVEF, %	65 [61–70]
Maximum LV wall thickness, mm	19.3±3.9
LV end-diastolic volume index, mL/m ²	51 [43–59]
MR moderate or severe, n (%)	30 (19)
Left atrial volume index, mL/m ²	42 [36–52]
Medial E/e' >15, n (%)	108 (72)
RV diameter, mm	37 [33–42]
RV diameter >42 mm, n (%)	36 (22)
RV fractional area change, %	47 [43–51]
Peak tricuspid annulus S' velocity*, cm/s	12.3 [11.0–14.0]
Hemodynamic variables	
PASP, mm Hg	41 [31–46]
Mean PAP, mm Hg	25 [20–31]
mPAP ≥25 mm Hg, n (%)	82 (51)
mPAP 25–34 mm Hg, n (%)	53 (33)
mPAP 35–44 mm Hg, n (%)	17 (11)
mPAP ≥45 mm Hg, n (%)	12 (7)
Right atrial pressure, mm Hg	7 [5–10]
TPG, mm Hg	10 [7–13]
TPG >12 mm Hg, n (%)	45 (28)
PAWP, mm Hg	15 [12–20]
PAWP >15 mm Hg, n (%)	74 (46)
PVR, WU	1.89 [1.31–2.57]
PVR >3.0 WU, n (%)	34 (21)
CI, L/min per m ²	2.51 [2.17–2.91]
DPG ≥7 mm Hg, %	11 (7%)

For continuous data, results are reported as mean±SD. For data not distributed normally, results are reported as median (interquartile range). BMI indicates body mass index; CI, cardiac index; DPG, diastolic pressure gradient; LV, left ventricular; EF, ejection fraction; LVOT, left ventricular outflow tract; MR, mitral regurgitation; mPAP, mean pulmonary artery pressure; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; TPG, transpulmonary gradient; and WU, Wood units.

*Data were available for 92 of 162 patients (57%).

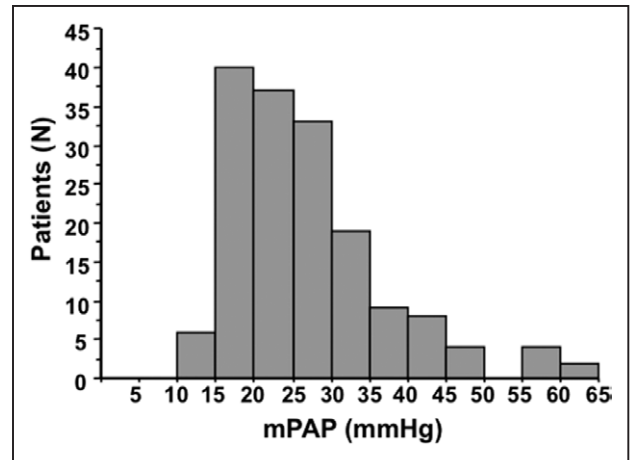


Figure 1. Distribution of mean pulmonary artery pressure (mPAP) in 162 patients with hypertrophic cardiomyopathy undergoing cardiac catheterization.

$P=0.29$) or RV fractional area change (48 [45–51] versus 46 [42–50] % change; $P=0.023$). The prevalence of LGE did not differ between the HCM patients with pulmonary hypertension compared with those without pulmonary hypertension (51% versus 55%; $P=0.51$). In addition, among patients with LGE, there was no significant relationship between extent of LGE and mPAP ($r=0.006$; $P=0.95$). The mPAP was higher in alcohol septal ablation patients than in myectomy patients (30 mm Hg [23–41 mm Hg] versus 24 mm Hg [20–29 mm Hg]; $P<0.02$).

Comorbidities that have been associated with pulmonary hypertension, including chronic obstructive pulmonary disease, obstructive sleep apnea, history of pulmonary embolism, connective tissue, and interstitial lung diseases, were present in 32 patients (20%) and were more common in those with mPAP ≥25 mm Hg than in patients with mPAP <25 mm Hg (27% versus 13%; $P=0.03$).

Evidence for Precapillary Pulmonary Hypertension or Pulmonary Arterial Hypertension

A subgroup of 9 patients (11%) differed from other study patients with pulmonary hypertension by virtue of normal

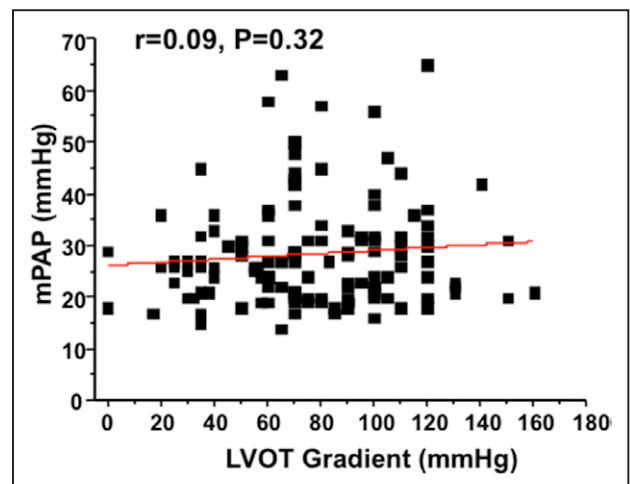


Figure 2. Mean pulmonary artery pressure (mPAP) does not correlate with resting left ventricular outflow tract (LVOT) gradient in patients with obstructive hypertrophic cardiomyopathy.

Table 2. Clinical and Hemodynamic Characteristics With Respect to mPAP

	mPAP <25 mm Hg (n=80)	mPAP ≥25 mm Hg (n=82)	P Value
General characteristics			
Age, y	56.9 (9.6)	61.4 (10.8)	0.006
Male sex, n (%)	42 (52.5)	37 (45.1)	0.43
BMI, kg/m ²	28.6±5.3	33.2±7.5	<0.001
NYHA class III or IV at RHC, n (%)	55 (68.8)	64 (78.1)	0.21
Atrial fibrillation, n (%)	17 (21.3)	19 (23.2)	0.92
Echocardiography			
Peak LVOT gradient, mm Hg	90 [75–105]	88 [70–110]	0.66
LVEF, %	66 [61–71]	64 [60–69]	0.14
Maximum wall thickness, mm	18.6±3.8	20.0±3.9	0.024
Moderate or severe MR, n (%)	12 (15)	18 (22)	0.31
Left atrial volume index, mL/m ²	41 [35–48]	45 [38–54]	0.017
Left atrial volume index ≥34 mL/m ² , n (%)	64 (80)	75 (92)	0.062
LV diastolic E/A ratio ≥2, n (%)	1 (1.3)	9 (11.4)	0.023
LV diastolic medial E/e' >15, n (%)	46 (60.5)	62 (83.8)	0.002
RV diameter, mm	36 [32–42]	37 [34–42]	0.29
RV diameter >42 mm, n (%)	16 (20)	20 (24)	0.57
RV fractional area change, %	48 [45–51]	46 [42–50]	0.023
Cardiopulmonary hemodynamics			
PASP, mm Hg	31 [28–34]	46 [41–56]	<0.001
mPAP, mm Hg	20 [18–22]	31 [28–38]	<0.001
Right atrial pressure, mm Hg	6 [3–8]	9 [7–13]	<0.001
TPG, mm Hg	8 [7–10]	13 [9–16]	<0.001
TPG >12 mm Hg, n (%)	4 (5)	41 (50)	<0.001
PAWP, mm Hg	12 [10–14]	20 [16–24]	<0.001
PAWP >15 mm Hg, n (%)	8 (10.0)	66 (80.5)	<0.001
PVR, WU	1.59 [1.23–2.13]	2.45 [1.66–3.26]	<0.001
CI, L/min per m ²	2.52 [2.21–2.96]	2.51 [2.16–2.85]	0.55
DPG ≥7 mm Hg, %	0 (0)	12 (15)	<0.001

For continuous data, results are reported as mean±SD. For data not distributed normally, results are reported as median (interquartile range). BMI indicates body mass index; CI, cardiac index; DPG, diastolic pressure gradient; LV, left ventricular; EF, ejection fraction; LVOT, left ventricular outflow tract; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; TPG, transpulmonary gradient; and WU, Wood units.

PAWP (≤15 mmHg) in the presence of pulmonary vascular resistance >3.0 WU. The majority did not have concomitant clinical comorbidities or significant mitral regurgitation that could be responsible for increased PAPs. These 9 patients were older (68 versus 61 years; $P=0.042$) than others with pulmonary hypertension, but did not significantly differ from other pulmonary hypertension patients with respect to sex, LV outflow gradient, ejection fraction, maximum wall thickness, left atrial volume, and mPAP. However, a higher percentage of patients in this subgroup had enlargement of the RV cavity, defined by a diameter >42 mm (56% versus 20%; $P=0.03$), and RV systolic function was decreased (43 [40–46] versus 48 [45–51] versus % fractional area change; $P=0.009$) compared with other patients with HCM (Table 3).

Septal Reduction Therapy and Outcome

Preoperative or preprocedural outflow gradients at rest ($n=125$) or with physiological provocation ($n=37$) ranged from 50 to 160 mmHg (median, 90 mmHg). Postoperatively, at rest, each had marked reduction or obliteration of mitral valve systolic anterior motion with zero gradient or a gradient estimated <30 mmHg with Doppler echocardiography. Over a median follow-up of 327 days after myectomy or ablation, the vast majority of patients with preoperative pulmonary hypertension were asymptomatic or mildly symptomatic ($n=71/77$; 92%), similar to patients without pulmonary hypertension ($n=77/80$; 96%).

In addition, myectomy patients with severe pulmonary hypertension (mPAP ≥36 mmHg) preoperatively ($n=12$) did not differ significantly compared with patients with mild to moderate pulmonary hypertension (mPAP <36 mmHg) preoperatively ($n=104$) for relevant postoperative complications, including stroke, myocardial infarction, major bleeding, respiratory failure, acute renal failure or death; prolonged intravenous inotrope use postoperatively ≥3 days; or prolonged inpatient hospitalization (≥10 days) (2/12 [16.7%] versus 14/104 [13.5%]; $P=0.67$). The 1 postoperative death in the group with pulmonary hypertension occurred in a 59-year-old woman who died from acute respiratory failure with severe pulmonary hypertension (mPAP=65 mmHg). A second postoperative death occurred in a 50-year-old man because of mesenteric ischemia (mPAP=22 mmHg).

Discussion

With the decrease in sudden death events in HCM because of penetration of the implantable cardioverter defibrillator into the management of this patient population, heart failure, and its consequences has assumed an enlarging profile.^{10,11} The mechanisms of advanced heart failure in HCM are diverse, including a minority of patients who evolve to the end-stage with or without systolic dysfunction.^{10,12} However, in the vast majority of patients with progressive drug-refractory disability, symptoms are related to dynamic LV outflow tract obstruction resulting in high LV pressure and wall stress.

The role of pulmonary hypertension in this HCM-related heart failure scenario is unresolved, with some investigators attributing deleterious clinical consequences (including an

Table 3. Clinical Characteristics in 9 Patients With Hemodynamics Consistent With Precapillary PH

	Precapillary PH or PAH (n=9)
Clinical characteristics	
Age, y	68.3 (10.3)
Men, n (%)	4 (44)
BMI, kg/m ²	29.3±3
Active smokers, n (%)	1 (11)
NYHA class III or IV, n (%)	8 (89)
Obstructive CAD, n (%)	3 (33)
Hypertension, n (%)	2 (22)
Any PH-related comorbidity, n (%)	1 (11)
Medications at RHC, n (%)	
β-blockers	8 (89)
Calcium-channel blockers	3 (33)
Disopyramide	0 (0)
Diuretics	3 (33)
Echocardiography	
LVOT gradient at rest, mm Hg	70 [60–80]
Peak LVOT gradient, mm Hg	80 [70–110]
LVEF, %	63 [61–72]
Maximum LV thickness, mm	20±4
MR moderate or severe, n (%)	4 (44)
LA volume index, mL/m ²	46 [41–59]
RV diameter (mm)	43 [33–43]
RV diameter >42 mm, %	56
RV fractional area change (%)	43 [40–46]
Cardiopulmonary hemodynamics	
mPAP, mm Hg	28 [27–34]
TPG, mm Hg	18 [14–19]
PAWP, mm Hg	13 [12–14]
PVR, WU	3.44 [3.27–4.75]
CI, L/m ²	2.07 [1.92–2.37]
DPG ≥7 mm Hg, %	4 (44)
Invasive therapy	
Surgical myectomy	n=5
Alcohol septal ablation	n=4
Major complications	n=0
Postoperative NYHA I	n=7
Postoperative NYHA II	n=2

For normally distributed data, results are reported as mean±SD. For data not distributed normally, results are reported as median (interquartile range). BMI indicates body mass index; CAD, coronary artery disease; CI, cardiac index; DPG, diastolic pressure gradient; LV, left ventricular; EF, ejection fraction; LVOT, left ventricular outflow tract; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; and WU, Wood units.

increase in all-cause mortality) to elevations in pulmonary pressures estimated noninvasively with Doppler echocardiography.⁴ On the contrary, we have the unique opportunity to report here the role of pulmonary hypertension in advanced heart failure with cardiopulmonary hemodynamics measured directly at cardiac catheterization.¹³ The study group comprises a consecutive cohort of patients undergoing surgical septal myectomy (or alcohol septal ablation) to relieve outflow tract obstruction and mitigate heart failure symptoms, at a single HCM tertiary referral institution.

We encountered a high frequency of elevated PAPs in about one-half of our study patients using the conventional criterion of mPAP ≥25 mm Hg, including 15% of these patients who had particularly marked PAP >45 mm Hg. Furthermore, recent data in large non-HCM populations suggest that mPAP ≥20 mm Hg is independently associated with adverse clinical outcome; using this cutoff value, >80% of our HCM patients would be considered to have pulmonary hypertension.⁹

Given the high frequency of pulmonary hypertension in this cohort (including moderate to severe levels), we cannot exclude the novel possibility that increased pulmonary pressures played a role in producing advanced heart failure symptoms, in association with LV outflow obstruction. Notably, we found little evidence that abnormal cardiopulmonary hemodynamics, including increased PAP, were associated with adverse clinical consequences in patients undergoing septal myectomy (or alcohol septal ablation) procedures, perioperatively, or over follow-up. For example, >95% of our patients reported improvement in symptoms from New York Heart Association functional class III/IV to absent or only mild symptoms. However, the subgroup of patients with severe preoperative pulmonary hypertension was no more likely to experience many clinically relevant adverse postoperative measures such as major surgical complications, prolonged use of intravenous inotropes, or extended duration of hospitalization compared with patients with mild or moderate pulmonary hypertension. One exception was a 59-year-old woman who died postoperatively because of respiratory arrest with severe preoperative pulmonary hypertension (mPAP, 65 mm Hg). Whether pulmonary hypertension was directly responsible for demise of this patient remains unresolved.

Overall, our observations also suggest that it is unnecessary to consider specific therapeutic pharmacological interventions to mitigate pulmonary hypertension preoperatively in patients with HCM undergoing surgical or percutaneous interventions. Therefore, although pulmonary hypertension is an established risk factor for adverse outcome in patients undergoing most forms of cardiac surgery,¹⁴ our data would suggest that septal myectomy may be an exception in this regard. Nevertheless, the data reported here do not exclude the possibility that pulmonary hypertension could otherwise have a significant role in the presentation, clinical consequences, and natural history of HCM, thereby underscoring the potential value of continued investigations.

Heart failure in HCM differs fundamentally in expression from that of ischemic heart disease or other nonischemic cardiomyopathies by virtue of its characteristic association with preserved ejection fraction and normal cardiac output.

An uncommon exception to this construct in HCM is the end-stage phase with impaired systolic function because of extensive myocardial scarring.^{1,2} The mechanism by which increased PAPs develop and potentially contribute to heart failure symptoms in HCM patients with LV outflow tract obstruction remains incompletely resolved. However, it is likely that on some of our patients, the outflow tract gradient and increased LV cavity pressure, and possibly mitral regurgitation, may cause left atrial pressure to increase (inferred from the increased PAWP), and as a consequence raised PAPs, which in turn contributed to advanced heart failure symptoms (Figure 3).

On the contrary, we should emphasize that we found only an inconsistent relation between PAP and LV outflow tract gradient or mitral regurgitation, allowing for the possibility that in some patients, pulmonary hypertension represented intrinsic pulmonary vascular disease independent of mechanical left-sided obstruction and heart failure.¹⁵ In this regard, we identified a subset of patients ($\approx 10\%$) with pulmonary hypertension associated with increased pulmonary vascular resistance, RV diameter, and diastolic pressure gradient, but normal PAWP. This scenario raises the possibility of coexistent precapillary pulmonary hypertension or pulmonary arterial hypertension in some patients

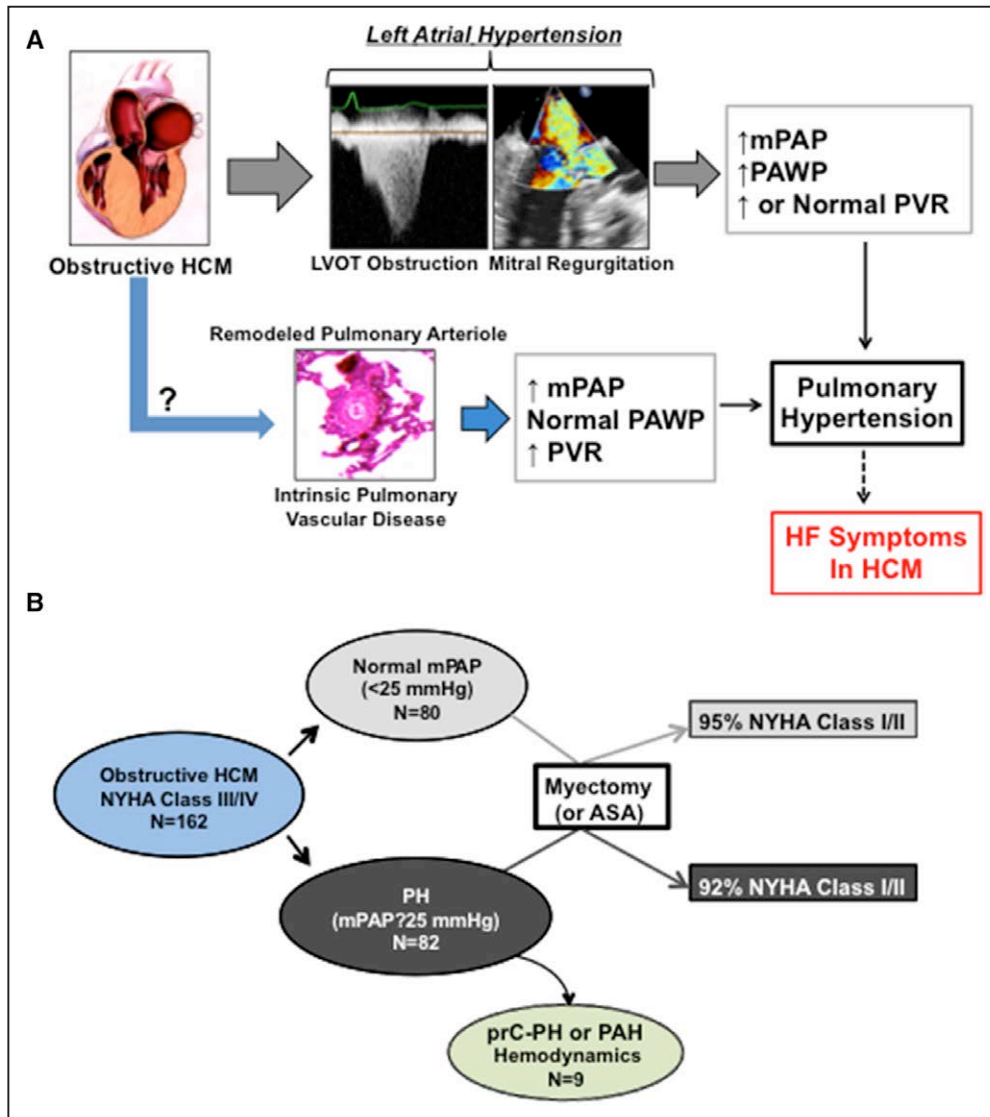


Figure 3. Pulmonary hypertension (PH) and the pathophysiology of heart failure symptoms in obstructive hypertrophic cardiomyopathy (HCM). **A**, Our findings suggest that in patients with obstructive HCM referred for septal reduction therapy, PH is common and may be one pathophysiology underlying heart failure (HF) symptoms in this patient population. Analysis of invasive cardiopulmonary hemodynamics before surgical myectomy or alcohol septal ablation suggests that PH is often associated with left atrial hypertension, which may be because of dynamic left ventricular outflow tract obstruction and mitral regurgitation. However, we also observed in some patients an increase in pulmonary artery pressure (PAP) without left atrial hypertension or other cardiopulmonary diseases commonly associated with PH, raising the possibility that intrinsic pulmonary vascular remodeling was present in this obstructive HCM patient subgroup. **B**, A significant difference in clinical response to septal reduction therapy with surgical myectomy or alcohol septal ablation (ASA) was not observed in patients with preprocedural PH compared with patients with normal preprocedural mean PAP (mPAP). LVOT indicates left ventricular outflow tract; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; NYHA, New York Heart Association; and prC-PH, precapillary pulmonary hypertension. Reprinted from Nishimura et al¹⁶ with permission of the publisher. Copyright ©2003, American Heart Association.

with HCM. However, confirmation and further characterization of pulmonary vascular disease is needed in patients with HCM, which will likely require histopathologic analysis of pulmonary tissue acquired from such patients. This is particularly the case because left atrial enlargement, borderline abnormal PAWP, and diuretic use were observed for patients with HCM within this subgroup, suggesting that provocative maneuvers such as confrontational fluid challenge (which were not performed in this study) could unmask a contribution of left atrial hypertension to pulmonary hypertension in these patients.¹⁴

There are limitations to our study design that justify acknowledgment here. First, clinical care considerations did not allow us to routinely repeat cardiac catheterizations after surgery or alcohol ablation. The right heart catheterization was performed by multiple proceduralists over the span of the study period, likely with some minor variability in measurements. However, a blinded review of the right heart catheterization tracings was performed for the precapillary pulmonary hypertension patients, and this analysis confirmed the accuracy of the reported values. In addition, the limited sample size of certain subgroups, such as subjects fulfilling hemodynamic criteria for pulmonary arterial hypertension, prevented a more detailed characterization of this phenotype. Furthermore, we have resisted solely reporting estimates of PAP with Doppler echocardiography postoperatively, given its relatively poor correlation with these measurements made directly at cardiac catheterization, as reported here and by other authors.^{17,18} Nevertheless, Mayo investigators using Doppler estimates both pre- and postoperatively showed that pulmonary hypertension was reversed by surgical myectomy in most patients with HCM.³ Finally, we are lacking complete data on other possible contributors to pulmonary hypertension, such as the response of mPAP and PAWP to exercise or findings from additional diagnostic testing for the evaluation of pulmonary hypertension, which could be of value in achieving a better understanding of pathophysiology in our novel patient subset considered consistent with pulmonary arterial hypertension.^{19,20}

The number of patients with HCM who underwent genetic testing in this cohort was too small to determine whether specific sarcomere mutations were associated with pulmonary hypertension. However, given the large number of individual mutations now associated with HCM (>1800), many of which are unique to 1 family (private), it is highly unlikely we would have identified a relationship between sarcomere mutation and pulmonary hypertension, similar to previous observations that have demonstrated no clear association between genotype and other aspects of the HCM phenotype (ie, LV wall thickness, extent of fibrosis, obstruction) or outcome.²¹

In conclusion, pulmonary hypertension is common in obstructive HCM patients with severe heart failure. Unexpectedly, our data did not recognize elevated pulmonary pressures as a risk factor for adverse clinical outcome among patients with obstructive HCM undergoing surgical myectomy (or alcohol septal ablation) or do they suggest that such patients require intervention to normalize pulmonary pressures. Nevertheless, this analysis uncovered the distinct

possibility of a new subset of patients with HCM characterized by pulmonary vascular disease.

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CLINICAL PERSPECTIVE

Since the initial description of hypertrophic cardiomyopathy (HCM), left ventricular outflow tract obstruction has been considered a prominent determinant of heart failure. However, the clinical profile and contribution of pulmonary hypertension to limiting symptoms and management of patients with obstructive HCM is incompletely understood. In this report, we analyzed invasive cardiopulmonary hemodynamic and echocardiography data from 162 consecutive patients with obstructive HCM referred for surgical septal myectomy. Pulmonary hypertension, defined as a mean pulmonary artery pressure ≥ 25 mmHg on cardiac catheterization, was present in a majority of patients with HCM and was moderate or severe in 20%. Pulmonary artery pressure did not correlate with magnitude of left ventricular outflow tract gradient and was observed commonly in patients with normal pulmonary artery wedge pressure. In addition, in 11% of patients, cardiopulmonary hemodynamics consistent with precapillary pulmonary hypertension or pulmonary arterial hypertension were present, suggesting that in a subgroup of patients, pulmonary hypertension may be a primary disease manifestation and not because of left heart disease. However, compared with patients with normal pulmonary artery pressure, pulmonary hypertension was not associated with a significant difference in clinical response or short-term outcome after surgical myectomy. Overall, our study shows that pulmonary hypertension is common and may be a novel contributor to heart failure in patients with obstructive HCM but does not seem to influence surgical risk or clinical improvement from myectomy.

Mechanism of Progressive Heart Failure and Significance of Pulmonary Hypertension in Obstructive Hypertrophic Cardiomyopathy

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