Effect of Patent Foramen Ovale in Patients With Pulmonary Hypertension

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Septostomy reduces right ventricular (RV) workload at the expense of hypoxemia in patients with advanced pulmonary hypertension (PH). A patent foramen ovale (PFO) may serve as a "natural" septostomy, but the incidence and impact of a PFO in PH remains uncertain. We prospectively examined echocardiograms in 404 PH patients referred for initial hemodynamic assessment. Patients included had saline bubble injection and if negative repeatinjection after Valsalva maneuver. Echocardiographic and hemodynamic data were examined. Survival was modeled using Kaplan−Meier method. Eisenmenger syndrome or known atrial shunts other than PFO were excluded: 292 patients met entry criteria. A PFO was identified in 16.8% of the entire cohort, 22.9% of pulmonary arterial hypertension (PAH) patients, and 8.6% of Dana Point group 2 PH patients. Right atrial to pulmonary capillary wedge pressure difference was lowest in the latter group (-7.9 ± 7.1 vs -1.7 ± 5.5 mm Hg for all others, $p < 0.01$). Patients with a PFO were younger (53.9 vs 58.6 years, $p = 0.02$). A PFO was more often present with moderately or severely dilated ($p = 0.01$) or dysfunctional ($p = 0.03$) RVs. Six year survival was unchanged by PFO presence for all patients, including those with PAH. Proportional hazards analysis found only age and functional class independently predicted survival ($p < 0.01$). A PFO is identified less often in Dana Point group 2 PH, likely due to inability of Valsalva maneuver to overcome right atrial to pulmonary capillary wedge pressure difference. In conclusion, the incidence of a PFO in the PH population increases with more dilated and dysfunctional RVs, suggesting that the PFO may be stretched open rather than congenital. The presence of a PFO does not impact survival in PH or PAH. **(Am J Cardiol 2018;122:505−510)**

Pulmonary hypertension (PH) remains a severe and life-threatening disease, with limited therapeutic options for those with advanced symptoms. Although medical therapy has greatly impacted patients with pulmonary arterial hypertension (PAH), mortality in this disorder remains high. Current guidelines recommend atrial septostomy as a potential palliative step before or during consideration for lung or heart−lung transplantation in patients poorly responsive to intravenous prostanoid therapy. A patent foramen ovale (PFO) is estimated to occur in 10% to 27% of all patients.[1,2] Although most often a benign entity, several medical problems have been attributed to the presence of a PFO including cryptogenic stroke, migraine headache with aura, and systemic hypoxemia.[3−6] Whether the presence of such a "natural" septostomy could benefit a patient who develops PH is not currently known. In the setting of PH, a right to left shunt through a PFO may theoretically offload the right side of the heart, especially in a patient with more advanced functional class. Interestingly, septostomy is also being studied in patients with heart failure with preserved left ventricular systolic function.[7] Early results have shown a reduction in left atrial pressure and functional improvement.[8] There are little published data evaluating long-term survival in PH with regard to the presence of a PFO. Previous studies looking at idiopathic PH or PAH patients have shown that long-term survival is not affected by PFO presence.[9,10] An atrial septostomy, which serves a similar function as a PFO, has been shown to provide symptomatic improvement to those with severe PAH.[11−13] The aim of this study is to describe the incidence and impact of a PFO, a "natural" septostomy, in patients with PH.

Methods

Patients were identified from a prospective cohort of 404 patients with PH who presented for initial hemodynamic assessment at the Cleveland Clinic or Duke University Hospital academic medical centers between 1998 to 2014 and underwent invasive evaluation by the same operator (RAK). Exclusion criteria included the absence of adequate saline microcavitation (bubble) studies at echocardiographic assessment, known atrial shunt lesions other than a PFO and the presence of Eisenmenger syndrome. Those with atrial level shunt lesions or Eisenmenger syndrome were excluded due to difficulty distinguishing flow through the PFO from other shunt physiology. All patients were categorized by the etiology of their PH using the Dana Point

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See page 509 for disclosure information.

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classification system.[14] The PH classification was determined by referral diagnosis and subsequently reviewed and confirmed by both the primary investigator and an additional investigator. Baseline demographic, clinical, echocardiographic, and hemodynamic parameters were compared between patients with and without PFO.

The presence of a PFO was assessed through administration of saline microbubbles (~0.5 cm^3 of air mixed with 5 cm^3 of saline solution/patient blood). The results of the study were considered to be positive for a right to left intracardiac shunt if bubbles were visualized on echocardiography (either apical 4 chamber view or subcostal view if inadequate apical images) in the left ventricle within 3 cardiac cycles after injection of saline microbubbles. If the initial injection showed no bubbles passing to the left sided chambers, the images were repeated after a Valsalva maneuver to ensure adequate increase in right atrial (RA) pressure with an associated reduction in left atrial pressure to facilitate right-to-left shunting.

Standard echocardiographic images were obtained in the parasternal long- and short-axis views, apical 2- and 4-chamber views, and subcostal view. In addition to calculation of the left ventricular ejection fraction using Simpson's method, right ventricular (RV) size and contractility were visually assessed. RV hypertrophy was defined as an RV free wall thickness of greater than 1 cm. The degree of tricuspid regurgitation was determined using color-flow Doppler and depended on the extent of color flow relative to the RA area. Estimated RV systolic pressure was determined using continuous wave Doppler imaging of the tricuspid regurgitation jet and application of the modified Bernoulli equation. This result was then added to the estimated RA pressure obtained through assessment of the inferior vena cava size and change with inspiration.

Cardiac catheterization was conducted within 1 day of echocardiographic assessment to obtain baseline hemodynamic measurements including RA pressure, pulmonary artery pressure, pulmonary capillary wedge (PCW) pressure, and cardiac index in all patients. Measures were then repeated for all during inhalation of 40 ppm of nitric oxide (Mallinckrodt; Dublin, Ireland). The pressure difference between the right and left atria was calculated by subtracting the mean PCW from the mean RA pressure.

The distance a patient can walk on a flat, hard surface over 6 minutes was measured; this is otherwise known as the 6-minute walk test. Oxygen saturation at rest and during exercise was measured. Oxygen desaturation with exercise was defined as a decrease in pulse oximetry of >4% and a nadir saturation of ≤88%.

Data are presented as percentages for discrete variables and as means ± standard deviations for continuous variables. Comparison of dichotomous variables was performed using the chi-square test or Fisher's exact test whenever appropriate. Comparisons of continuous variables among groups were performed using two-sided *t* tests. Time to last follow-up or death in patients with and without PFO was modeled using Kaplan–Meier survival analysis. Thereafter, patients were compared according to functional status (World Health Organization [WHO] functional class I/II vs III/IV). Survival functions were assessed using the log-rank test. A Cox proportional hazards analysis with covariate adjustments was secondarily used to assess the relation between PFO presence and survival. The proportional hazards assumption for the model was checked using the Schoenfeld test. Statistical significance was assumed for p value <0.05. All analyses were performed using Stata Version 12.1 (StataCorp., College Station, Texas).

Results

Of the 404 patients in the initial cohort, 112 patients were excluded for the following reasons: 78 patients (19.3%) had inadequate PFO assessment, 31 patients (7.7%) had atrial shunt lesion other than a PFO and 8 patients (2%) had Eisenmenger physiology. Two hundred ninty-two patients met the criteria for this study (190 women, 102 men) with a mean age of 57.8 ± 14.8 years (range, 17 to 87). Of these, a PFO was identified in 49 (16.8%) of all patients studied, in 32 patients (22.9%) with PAH and in 5 (8.6%) of Dana Point group 2 PH patients. The distribution of patients with and without PFO by Dana Point classification system is shown in Table 1.

Demographic characteristics were similar between those with and without PFO, except for age (Table 1). Although not significant, a larger proportion of patients with PFO had worse functional class (65.2% without PFO vs 74.5% with PFO were WHO functional class III/IV, p = 0.22).

Echocardiographic and hemodynamic variables are shown in Tables 2 and 3. Echocardiographic findings of systolic flattening of the interventricular septum, dilation of the right ventricle and right ventricular dysfunction, all suggestive of considerable right ventricular pressure overload, was more common in patients with a PFO.

A subgroup analysis of Dana Point classification group 2 patients (left-sided cardiac disease related PH) was done. There were statistically significantly higher RA pressures in those with a PFO (27.0 mm Hg vs 13.3 mm Hg,

Table 1
Baseline demographic and clinical characteristics

Variable	Patent foramen ovale		p value
	No (n = 243)	Yes (n = 49)	
Women	159 (65.4%)	31 (63.3%)	0.77
Age (years)*	58.6 ± 14.6	53.9 ± 15.4	0.02
Race			0.80
White	185 (76.5%)	39 (79.6%)	
Black	49 (20.3%)	8 (16.3%)	
Other	8 (3.3%)	2 (4.1%)	
WHO functional classification†			0.07
I	7 (2.9%)	0 (0%)	
II	76 (31.8%)	12 (25.5%)	
III	126 (52.7%)	22 (46.8%)	
IV	30 (12.5%)	13 (27.7%)	
Dana Point classification			0.03
1	105 (43.2%)	30 (61.2%)	
2	53 (21.8%)	5 (10.2%)	
3	42 (17.3%)	8 (16.3%)	
4	15 (6.2%)	5 (10.2%)	
5	28 (11.5%)	1 (2.0%)	

* Data presented as mean ± standard deviation.
† World Health Organization functional classification.

Table 2
Comparison of echocardiographic parameters

Variable	Patent foramen ovale		p value
	No (n = 243)	Yes (n = 49)	
Right ventricular size			0.01
Normal	81 (33.8%)	6 (12.5%)	
Mild	48 (20.0%)	10 (20.8%)	
Moderate	51 (21.3%)	12 (25.0%)	
Severe	60 (25.0%)	20 (41.7%)	
Right ventricular contractility			0.03
Normal	103 (43.1%)	10 (20.8%)	
Mild	45 (18.8%)	15 (31.3%)	
Moderate	43 (18.0%)	12 (25.0%)	
Severe	48 (20.1%)	11 (22.9%)	
Tricuspid regurgitation			0.28
None	22 (9.2%)	4 (8.5%)	
Trace	66 (27.6%)	13 (27.7%)	
Mild	72 (30.1%)	9 (19.2%)	
Moderate	53 (22.2%)	11 (23.4%)	
Severe	26 (10.9%)	10 (21.3%)	
Right ventricular hypertrophy	43 (18.1%)	4 (8.3%)	0.10
Flattening of interventricular septum	61 (26.4%)	19 (44.2%)	0.02
Left ventricular ejection fraction, %*	55.5 ± 9.4	57.6 ± 6.2	0.13
Right ventricular systolic pressure, mm Hg*	67.4 ± 24.8	75.3 ± 20.0	0.06

* Data presented as mean ± standard deviation.

p <0.01). PCW pressure in this same subgroup was not significantly different (25.6 mm Hg vs 21.7 mm Hg, p = 0.25). The pressure difference between the measured RA pressure and PCW pressure was calculated both overall and in patients with and without a PFO (Table 4). The pressure difference was significantly larger in Dana Point group 2 compared with all other Dana Point groups in those without evidence of a PFO (p <0.01).

Of the patients that underwent a 6-minute walk test with pulse oximetry, there was not a statistically significant difference in distance in patients with and without PFO (326 ± 141 meters vs 295 ± 124 meters, p = 0.34). Furthermore, there was no difference in baseline oxygen saturation (93.7 ± 4.6% with PFO vs 93.8 ± 6.2% without PFO, p = 0.97). Patients with a PFO trended toward having oxygen desaturation with exercise compared with those without a PFO, but this was not statistically significant (53.3% with PFO vs 44.6% without PFO, p = 0.52).

Over a mean follow-up period of 32.6 ± 18.2 months (median: 33.5 months, interquartile range 18.0 to 46.2 months), there were a total of 97 deaths (79 in the no PFO group and 18 in the PFO group). Survival analysis for all patients with PH revealed no significant difference in survival based upon presence of a PFO (Figure 1). This was similarly seen with analysis of patients with solely PAH (Figure 2) or those with WHO functional class III/IV (p = 0.97). A proportional hazards analysis of all patients with PH revealed WHO functional class and age to be the only significant predictors of survival in this cohort (p <0.01, Table 5).

Table 3
Comparison of hemodynamic parameters

Variable*	Patent foramen ovale		p value
	No (n = 243)	Yes (n = 49)	
Right atrial pressure (mm Hg)	10.8 ± 5.9	12.3 ± 7.1	0.12
Right ventricular systolic pressure (mm Hg)	69.8 ± 24.6	75.0 ± 23.6	0.18
Pulmonary artery pressure (mm Hg)	42.9 ± 14.8	47.4 ± 14.7	0.05
Pulmonary capillary wedge pressure (mm Hg)	14.5 ± 7.0	11.8 ± 6.8	0.02
Cardiac index (L/min/m^2)	2.5 ± 0.8	2.3 ± 0.8	0.16

* All variables presented as mean ± standard deviation.

Table 4
Comparison of right atrial to pulmonary capillary wedge pressure differences by Dana Point classification

Pressure difference (mm Hg)	Dana Point classification		p value
	Group 2	All other groups	
Overall	−7.9 ± 7.1	−1.7 ± 5.5	<0.01
Patent foramen ovale: absent	−8.4 ± 6.5	−2.3 ± 5.5	<0.01
Patent foramen ovale: present	−2.0 ± 12.0	0.63 ± 4.5	0.35

Discussion

Our study represents one of the largest cohorts to date to compare characteristics and outcomes of PH patients based upon the presence of a PFO and is one of the first to rigorously assess for PFO presence. The average age of patients with a PFO was younger than those without a PFO. This corroborates with several studies showing an age-related decrease in PFO presence.[1,2,9,15] No physiologic explanation has been found to account for this and some published studies contradict this finding.[16] The incidence of a PFO in our cohort was 16.8%, which is similar to the population incidence described in previous studies.[1,2]

Estimated RV systolic pressure and measured RA and RV systolic pressures appeared higher in patients with a PFO, although none of the differences reached statistical significance. There was, however, a significantly higher incidence of a demonstrable PFO in patients with either right-sided enlargement or RV systolic dysfunction. We postulate that higher right sided pressures and dysfunction may predispose to more right-to-left shunting, possibly due to a previously closed foramen ovale becoming stretched open in patients with advanced disease. No significant difference was seen in the 6-minute walk distance, baseline oxygen saturation or oxygen desaturation with exercise based upon PFO presence. We did not have ambulatory oximetry data available for all patients, and so determination of whether PFO was fully functional in these patients was not possible.

Atrial septostomy is a guideline-based therapeutic approach for patients with PAH, particularly when intravenous prostanoids or other pulmonary vasodilators are not sufficiently effective or as a bridging procedure to lung transplantation.[17,18] Septostomy creates a right to left shunt, which can decompress the right-sided cardiac chambers and increase left ventricular preload and systemic cardiac output. This improves systemic cardiac output, but it also results in arterial desaturation and extreme care must be taken to balance these physiologic effects. It would be

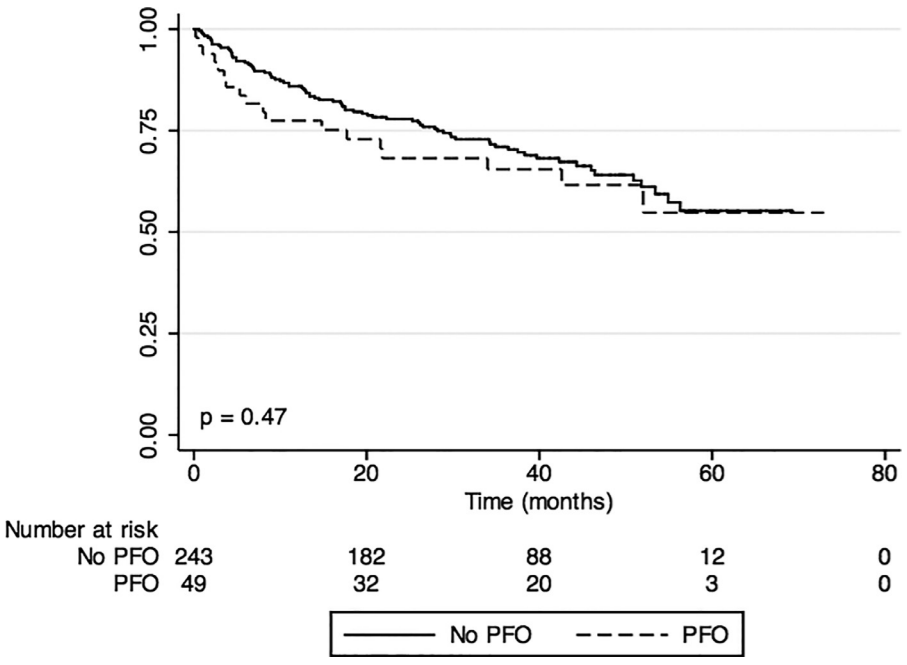

Figure 1. Kaplan–Meier survival analysis by presence of a patent foramen ovale. PFO = patent foramen ovale.

plausible to suspect that the presence of a PFO in patients with PH could provide similar benefits, potentially even positively impacting survival. However, our results do not suggest this to be the case, as we did not see any difference in survival based upon PFO presence. PFO does appear to be a marker of more severe pulmonary hypertension. This is also supported by the greater frequency of PFO seen in patients with worsened functional status. A proportional hazards analysis, however, revealed that the sole clinical predictors of mortality were age and function status, rather than the PFO itself.

Septostomy in PH has been mostly studied in PAH patients; however, few studies have assessed its impact on survival. Furthermore, there have not been any long-term, controlled studies. What we have learned to date is that septostomy improves hemodynamic variables that correlate with clinical improvement.[19] One study examined survival in PAH patients with septostomy plus pharmacologic

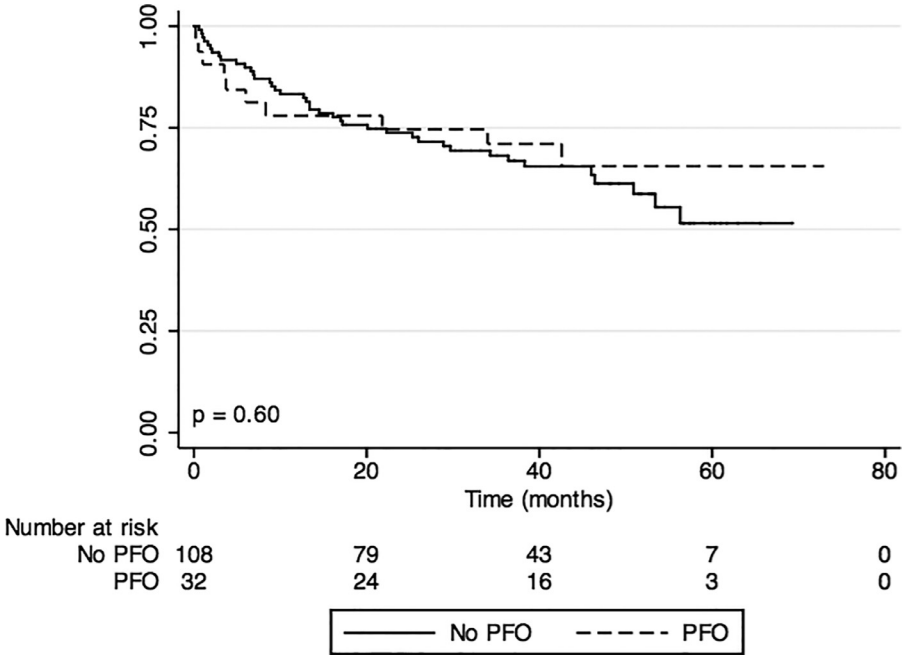

Figure 2. Kaplan–Meier survival analysis of pulmonary arterial hypertension patients by presence of a patent foramen ovale. PFO = patent foramen ovale.

Table 5
Proportional hazards analysis

Variable	Hazard ratio (95% CI)	p value
Age	1.20 (1.10 - 1.30)	<0.01
WHO I/II vs. III/IV*	2.42 (1.41 - 4.16)	<0.01
Patent foramen ovale	1.31 (0.76 - 2.28)	0.33

CI = confidence interval.
* World Health Organization functional classification.

therapy versus septostomy alone. This study showed a survival benefit of combining therapies (median survival with combined treatment was 83 months vs 52 months with septostomy alone).[20] Further controlled studies to assess the impact of septostomy on survival in PAH and in additional PH populations appear warranted.

Several caveats regarding PFO detection are worth mentioning. Patients in our study received transthoracic echocardiography. Transesophageal echocardiography is still considered by some to be the reference standard for PFO diagnosis, because it allows for better imaging of the interatrial septum.[5] It is possible, therefore, that our cohort did not accurately capture all patients with PFO. We postulate that it is harder to detect PFO with echocardiography in Dana Point group 2 patients due to the large pressure difference between the right and left atrium (LA) in this subgroup that needs to be overcome for shunting to occur. There was significantly larger RA-estimated left atrial pressure difference in the Dana Point 2 subgroup in those without PFO in comparison to all other patients without PFO. Under such conditions the Valsalva maneuver may not be able to overcome the high left atrial pressure to open the foramen and allow bubbles to cross. Our study therefore likely underestimates the true incidence PFO in patients with high left atrial pressure and may explain why a smaller percentage of patients in Dana Point group 2 PH had PFO detected compared with the other Dana Point groups (Table 1). Other limitations of our study include incomplete data for some variables given the retrospective nature of this analysis as well a potential for bias in echocardiogram interpretation due to inability for images to be read by a second blinded investigator.

In summary, the incidence of a PFO in patients with PH appears similar to the general population. However, there is an increased incidence in patients with more dilated and dysfunctional RVs, possibly related to RA remodeling and septal stretch leading to opening of the foramen. A PFO is identified less in Dana Point group 2 patients, likely due to the inability of Valsalva to overcome the RA to left atrial pressure difference. Despite the effectiveness of atrial septostomy in the treatment of advanced PAH, the presence of a demonstrable PFO does not appear to impact overall survival.

Disclosures

The following investigators have no financial or nonfinancial disclosures: Lauren Sharan, Kathryn Stackhouse, Jordan Awerbach, and Thomas Bashore.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.04.014.

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