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THE ROLE OF LEFT ATRIAL COMPLIANCE IN THE DEVELOPMENT OF PULMONARY HYPERTENSION IN PATIENTS WITH PURE MITRAL STENOSIS AND SINUS RHYTHM

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Abstract

In patients with mitral stenosis, there is poor correlation between the severity of mitral stenosis, as measured by the mitral valve area and the magnitude of pulmonary hypertension. We tested the hypothesis that left atrial compliance is a major factor determining the height of pulmonary artery pressure in patients with pure mitral stenosis and sinus rhythm.

The right sided and left atrial trans-septal catheterization data was analyzed in 84 patients (67 females, 17 males) with pure MS and sinus rhythm. Pulmonary artery peak systolic, diastolic and mean pressures were obtained through right sided catheterization. The magnitude of the LA a and v waves and the mean (m) LA pressure were measured directly through trans-septal catheterization. A non-compliant LA was considered to exist if the LA v_m pressure difference equaled to or exceeded 10 mmHg. The mitral valve area was determined by echocardiographic and Doppler methods, as were the LA size, LV systolic and diastolic dimensions, and the LV ejection fraction. Multiple regression analysis was performed to determine the most important factor in the determination of pulmonary artery pressure.

Fifty four patients had PAPs≥50 mmHg, 41 of whom had non- compliant LA. Of the 30 patients with PAPs<50 mmHg, 9 had non compliant LA (P<0.0005).There was no significant difference in the mitral valve area between the two groups with and without severe pulmonary hypertension (0.64±0.18 versus 0.73±0.14 cm2, P=0.13). Analysis of the 30 patients with PAPs<50 mmHg showed significantly higher systolic and mean PA pressure in the 9 patients with non-compliant LA (PAPs 40.55±4.64 vs 35.58±7.46 mmHg, P<0.01; PAPm 30.24±3.56 versus 23.15±5.68 mmHg, P<0.01).

In conclusion, impaired LA compliance contributes at least in part to the development of pulmonary hypertension, and may well be the major mechanism responsible for the development of pulmonary hypertension in patients with pure mitral stenosis and sinus rhythm.

Key words: (mitral stenosis, LA compliance, pulmonary hypertension).

Introduction

Pulmonary hypertension develops in patients with mitral stenosis and may dominate the clinical picture of these patients. It also has adverse effect on the functional status, exercise tolerance and prognosis[1].

The mechanism of pulmonary hypertension with mitral stenosis is known to be a complex process. Pulmonary hypertension may result from: 1- Passive backward transmission of the elevated LA pressure; 2- Pulmonary arterial constriction, which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); 3- Organic obliterative changes in the pulmonary vascular bed[2] . Vasoactive substances like endothelin and adrenomedullin have also been linked to the development of pulmonary hypertension[3,4].

It is generally thought that the severity of mitral stenosis and the resultant increase in the left atrial pressure are important

factors affecting the development of secondary pulmonary hypertension. However, there is a wide spectrum of pulmonary pressure in patients with severe mitral stenosis, despite the similar severity of mitral stenosis[5,6]. It was once thought that coexisting pulmonary disease might contribute to the excessive elevation in the pulmonary arterial pressure[2]. Alternatively, it was suggested that the duration of mitral stenosis is a contributing factor for the development of pulmonary hypertension. This explanation remains far from complete, since the actual mechanism of pulmonary hypertension is still unexplained.

The effect of left atrial compliance was raised as an important determinant of cardiovascular performance and pathophysiology of mitral stenosis. In contrast to the mitral valve area, which is frequently measured, left atrial compliance is seldom measured[1,5-7]. Compliance is defined as the change in pressure per unit change in volume or dp/dv[8,9]. In practice, LA compliance is measured during left atrial catheterization and is defined as the difference between the height of the left atrial v wave and the mean LA pressure or simply the peak value of the v wave[7].

In this study we tested the already existing hypothesis that LA compliance is the main determinant of PA pressure in patients with pure mitral stenosis and sinus rhythm.

Patients and methods

Study population: From November 2001 till August 2004, all patients who underwent PTMC were included in this study. Data of all patients were reviewed, including the history and physical examination, CXR, and ECG. The echocardiographic studies, both trans-thoracic and trans-esophageal, were carefully reviewed; specifically, the mitral valve area was determined by one or both of two methods, i.e. direct planimetry of the mitral valve and/or pressure half-time of the continuous wave Doppler signal of the LV inflow[2].

As a prerequisite for PTMC, all patients had their heights and weights measured and body surface areas calculated immediately before the procedure.

Exclusion Criteria: Excluded from the study were patients with atrial fibrillation, those who had associated coronary artery disease, and those with any degree of mitral regurgitation. Patients with mild aortic insufficiency who were eligible for PTMC were not excluded.

Catheterization Technique: After obtaining the patient's informed consent, both the arterial and venous circulations were accessed via the femoral route according to a standard protocol[10,11]. The pulmonary artery pressure was measured directly during catheterization using a catheter inside the main pulmonary artery, as were the aortic, LV systolic, and LV end diastolic pressures. The left atrium was entered by the trans-septal technique[10], which permitted direct measurement of pressure during the various phases of the cardiac cycle, as well as the mean LA pressure, and elucidation of the pressure waveform pattern, which was recorded on graphic paper. The mean diastolic pressure gradient across the mitral valve was calculated by subtracting the LVEDP from the simultaneously recorded mean LA pressure. The LA pressure waveform was analyzed offline, the height of the v-wave and the mean LA pressure were averaged for 5 cardiac cycles.

Calculation of LA compliance: LA compliance was calculated by subtracting the mean LA pressure from the height of the v-wave[7]. According to a predefined convention, a non compliant LA was considered to be present if the peak v-wave-mean LA pressure difference was≥ 10mmHg[12]. The patients were divided into two groups according to the PAPs (≥50mmHg or <50mmHg), with 54 patients with PAPs ≥50mmHg and 30 patients with PAPs<50mmHg.

Statistical Analysis: All continuous variables were presented in mean (±SD) and all absolute variables were presented in numbers and percent.

A univariate logistic regression analysis was done using the correlation coefficient (r), looking for the correlation between pulmonary arterial systolic pressure (PAPs) as a dependant variable and measures of severity of mitral stenosis (LA peak v wave pressure, LA mean pressure, mitral valve area, mean pressure gradient by catheterization). A multivariate analysis was done to verify which of the measures of mitral stenosis severity correlates most with pulmonary hypertension.

The hypothesis was considered significant when the P value is <0.05.

Results

The total number of patients was 84. They were divided into two groups according to the pulmonary artery systolic pressure, 54 patients (64.3%) had PASP ≥50 mmHg; and 30 (35%) had PASP < 50 mmHg. There was no significant difference in mean age, the male: female ratio, left ventricular dimensions, or the ejection fraction between the two groups (table I). As is shown in table II, there was no significant difference in LA diameter and mitral valve area between the two groups. On the other hand, the two groups differed significantly regarding the mean pressure gradient across the mitral valve, mean LA pressure, and the height of the LA v wave (P<0.0005) (figures 1,2&3).

Of the 54 patients with severe pulmonary hypertension, 41 had large LA v_m difference exceeding 10 mm Hg. On the other hand, of the 30 patients with PASP < 50 mm Hg, 9 had LA v_m ≥10mm Hg (table III). In the latter group, the mean values of systolic and mean PA pressures were significantly higher in those patients with LA v_m ≥10 mmHg (P< 0.01 for each) but there was no significant difference in mitral valve area and mean trans-mitral pressure gradient between the two subgroups (P=0.3 &0.6 respectively).

Relation between PAPs and measures of mitral stenosis severity: there was a strong correlation between the severity of pulmonary hypertension and peak left atrial v-wave pressure, mean left atrial pressure and mean pressure gradient through the mitral valve by catheterization (P<0.0005 for each). From the multivariate analysis, LAPv was the most important factor correlating with PAPs, followed by the LAPv_m, LAP, and MPG. Of note, there was no significant correlation between the MVA and the degree of pulmonary hypertension (P=0.22).

Table I: Baseline Characteristics of 84 Patients with Mitral Stenosis Before They Underwent BMV

Characteristics	PAPs ≥50mmgh	PAPs<50mmgh	P value
Number (%)	54 (64.3)	30 (35.7)	0.005
Age mean (SD)	30.8±9.4	28.75±8.9	0.3
Female sex (%)	49 (90.1)	28 (90.3)	0.9
LVIDD (mm)	46.5±5.36	48.4±8.5	0.3
LVIDS (mm)	32±6.44	31.5±5.9	0.5
EF (%)	61.2±2.4	63.1±3.2	0.5

LVIDD: left ventricular internal diameter in diastole, LVIDS: left ventricular internal diameter in systole, and EF: ejection fraction

Table II: Comparison of Different Measures of Mitral Stenosis Severity in 84 Patients with Mitral Stenosis Before They Underwent BMV.

Measure	PAPs≥50mmgh	PAPs<50mmgh	P value
Number (%)	54 (64.3)	30 (35.7)	0.005
LAD (±SD)	47.3±6.4	45.9±7.2	0.17
MVA/m2 (cm2/m2)	0.64±0.18	0.73±0.14	0.13
LVEDP (mmHg)	9.27±3.67	9.33±3.37	0.25
PAPs (±SD)	69.8±20	37.47±6.75	<0.0005
PAPm (mmHg)	49±15.6	24.16±6.69	<0.0005
LAPm (mmHg)	30.4±6.7	20.4±5	<0.0005
LAPv (mmHg)	42.75±10.3	28.34±6.5	<0.0005
LAP v-m (mmHg)	12.3±5.0	8.08±3.6	<0.0005
LAP v-m ≥10mmHg	41 (76.0)	9 (30.0)	<0.0005
MPG (mmHg)	20.4±7.19	11.27±5	<0.0005

LAD: left atrial diameter, MVA: mitral valve area, PAPs: systolic pulmonary artery pressure, PAPm: mean pulmonary artery pressure, LAPm: mean left atrial pressure, LAPv: peak v wave left atrial pressure, MPG: mean pressure gradient through the mitral valve.

Table III: Comparison of PAP, MVA and MPG in 30 Patients with PAPs ≤ 50mmHg according to the LAP v-m.

Characteristic	LAP v-m ≥10, (no 9)	LAP v-m<10, (no 21)	P value
PAPs (mmHg)	40.55±4.64	35.38±7.46	<0.01
PAPm (mmHg)	30.24±3.56	23.15±5.68	<0.01
MVA (cm2/m2)	0.73±0.13	0.73±0.15	0.3
MPG (mmHg)	11.44±6.04	10.19±3.72	0.6
LAPm (mmHg)	22.11±4.65	20.15±4.2	0.15
LAD (mm)	46.54±5.12	45.86±6.48	0.2

LAD: left atrial diameter, MVA: mitral valve area, PAPs: systolic pulmonary artery pressure, PAPm: mean pulmonary artery pressure, LAPm: mean left atrial pressure, MPG: mean pressure gradient through the mitral valve

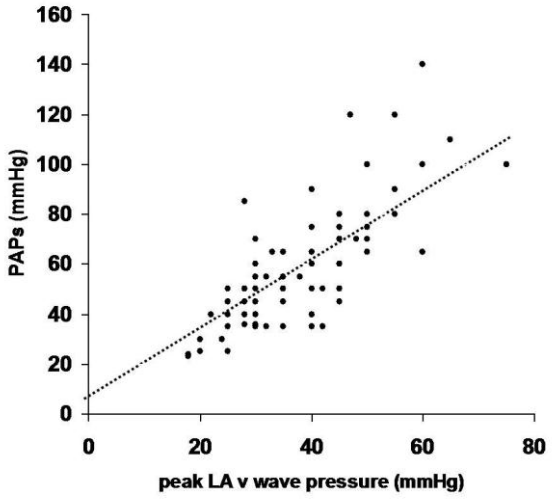

Figure 1: Correlation between PAPs and peak LA v wave pressure

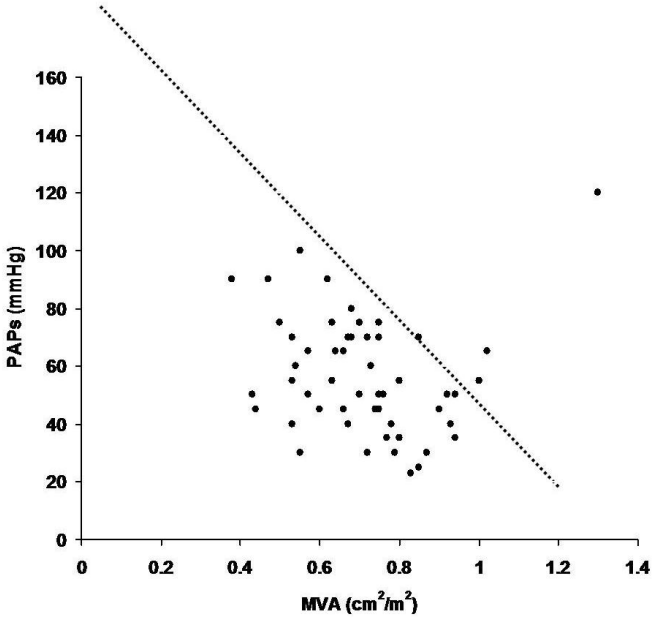

Figure 2: Showing the correlation of pulmonary artery pressure as an independent factor with the MVA

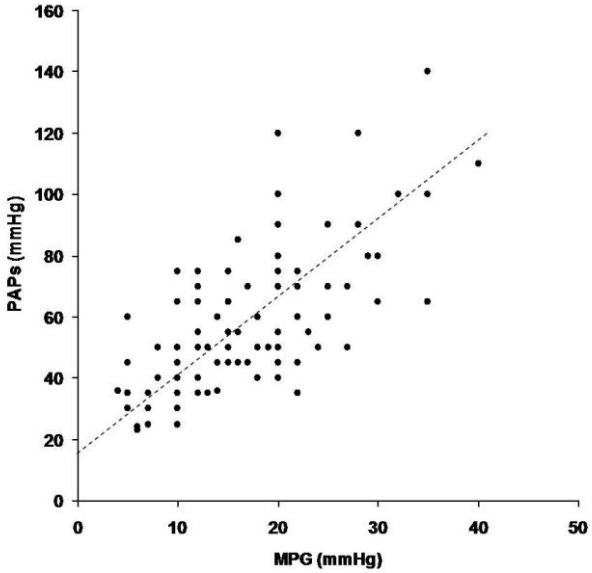

Figure 3: Correlation of PAPs and MPG

Discussion

In the current study, we have confirmed other investigator's findings that in patients with mitral stenosis, the development of pulmonary hypertension is largely independent of the mitral valve area[1,7,12,13]. The lack of positive correlation between mitral valve area and the magnitude of PA pressure is a well known phenomenon, although it has long intrigued scientists. It has been postulated that coexisting pulmonary parenchymal disease may play a role in the development of pulmonary hypertension[14], but this remains a presumptive explanation, since it defies

the law of parsimony, and since many patients with milder forms of mitral stenosis and no evidence of pulmonary vascular disease still display high pulmonary arterial pressures[5].

It is generally agreed that pulmonary arterial hypertension reflects raised LA and pulmonary venous pressures[1,5,6,9,15]. In this study, patients with pulmonary hypertension had significantly higher mean LA pressures than those without pulmonary hypertension. According to the pressure-volume curve of the LA[16,17], pressure is determined by the volume of blood inside the LA and the chamber's stiffness. It is conceivable that in tight MS, there is little egress of blood outside the LA, leading to its expansion, thereby elevating the intra-chamber pressure. However, in this study, there was little correlation between LA diameter and PA pressure. If the echocardiographically obtained left atrial diameter can be considered a measure of the chamber's volume, it follows that left atrial dilatation caused by mitral valve stenosis is not the entire explanation for the magnitude of pulmonary hypertension in these patients. Rather, it is the LA compliance that plays the major role in determining PA pressure. A non-compliant LA would fail to dilate in tight MS and the intra-chamber pressure rises more readily than in a compliant, dilated LA.

Why should the left atrium become less compliant in mitral stenosis? The LA wall may become fibrotic and less distensible as a consequence of chronic, recurrent, or current rheumatic activity[18,19]. The rheumatic inflammatory process, which is the underlying pathology in mitral stenosis, may extend to the left atrial wall and cause fibrosis and disorganization of muscle bundles in the left atrial wall[2]. In this study, we did not strictly exclude recent rheumatic activity. However, this remains to be examined in detail in further studies. The other possible explanation is that the increased left atrial volume due to the obstruction by MS causes shift of the pressure-volume curve upward, this is reflected by an increased left atrial diameter. However, in this study there was no correlation between the echocardiographically obtained LAD and PAPs, making this an unlikely explanation.

To avoid the effect of body size and its known direct relation to the blood volume, we have indexed the mitral valve area to body surface area; this would be expected to enhance the accuracy of the results and reflect more accurately the relation between MVA and PAPs.

For this study, we considered the value of 50mmHg as a cut-off for pulmonary hypertension. This is a generally accepted value since any rise of PA pressure beyond that figure is poorly tolerated by the right ventricle[2,7].

Not clarified in the study of Ha et al however, is the relation of PA pressure to LA compliance in patients whose PA pressure does not exceed 50 mm Hg[7]. Subgroup analysis of the patients with PAPs<50 mmHg casts further light on the pathophysiology of pulmonary hypertension in MS. In this group, patients with non-compliant left atria had significantly higher PA pressures than those with compliant left atria (table 3, $P<0.01$), and there was a significant correlation between LA v wave and systolic PAP (figure 1, $r=0.777$, $P<0.0005$), whereas the two subgroups did not differ significantly in terms of mean LA pressure or mean pressure gradient (table 3). It is possible that this represents a chronological sequence in the development of severe pulmonary hypertension. Apparently, it is the phasic variation in LA pressure (producing large v waves) that is responsible for the early development of pulmonary hypertension, and as LA compliance declines with time, LA pressure and MPG start to rise. Large v waves will cause temporary rise of pressure in the pulmonary venous system. Interestingly, pulsed-wave Doppler

assessment of the pulmonary venous flow by TEE has shown temporary interruption of flow during systole in patients with MS and pulmonary hypertension[20] (unpublished data), producing a blunted s wave on the Doppler signal. It appears that this phasic interruption of pulmonary venous flow, with its attendant phasic rise in pressure in the pulmonary venous system, is the initial step in the development of pulmonary hypertension in patients with mitral stenosis. This issue is still complicated and deserves further studies to verify this finding and to look into the effect of pressure and flow wave reversal on the pulm. microcirculation to produce pulmonary hypertension.

Conclusions

In this study, we confirmed the finding that left atrial compliance is a major determinant of pulmonary artery pressure in patients with mitral stenosis. The relation between the two variables was strong, consistent, and continuous over a wide range of PA pressures. This relation was independent of other factors like MPG, mean LA pressure, and mitral valve area, and sheds light on the pathophysiology of pulmonary hypertension in these patients.

Referrences

1. Ko YG, Ha JW, Chung N, et al. Effects of Left Atrial Compliance on Left Atrial Pressure in Pure Mitral Stenosis. Catheter Cardiovasc Interv 2001; 52: 328-33
2. Braunwald E. Valvular Heart Disease. In Heart Disease, a textbook of cardiovascular medicine, 6th ed. Philadelphia, PA: WB Saunders, 2001; ch 46, pp1643-1704.
3. Yamamoto K, Ikeda U, Mito H, et al. Endothelin Production in Pulmonary Circulation of Patients with Mitral Stenosis. Circulation 1994; 89: 2093-2098.
4. Nishikimi T, Nagata S, Tomimoto S, et al. Plasma Concentration of Adrenomedullin Correlate with the Extent of Pulmonary Hypertension in Patients with Mitral Stenosis. Heart 1997;78:390-395.
5. Kapoor A, Kumar S, Shukla A. et al. Determinants of Left Atrial Pressure in Rheumatic Mitral Stenosis: Role of Left Atrial Compliance and "Atrial Stiffness". Indian Heart J. 2001; 56: 27-31.
6. Sato S, Kawashima Y, Hirose H, et al. Clinical Study of Left Atrial Compliance and Left Atrial Volume in Mitral Stenosis. Jpn Circ J. 1991; 55: 481-6.
7. Ha JW, Chung N, Jang Y, et al. Is the Left Atrial V wave the Determinant of Peak Pulmonary Artery Pressure in Patients with Pure Mitral Stenosis? Am J Cardiol. 2000, 85: 986-91.
8. Elizabeth JB. Monitoring Pulmonary Artery Pressures: Just the fact. Crit Care Nurs. 2000; 20: 146-192
9. Vascular Distensibility and Function of Arterial and Venous Systems. In Textbook of Medical Physiology, Guyton AC, Hall JE. 9th Ed. Philadelphia: WB Saunders, 1996: 171-182.
10. Baim SD. Percutaneous Approach, Including Trans-septal and Apical Puncture. In Grossman's Cardiac Catheterization, Angiography and Intervention, Baim SD, Grossman W. 6th Ed. Philadelphia. Lippincott William's and Wilkin's, 2000: 69-100.
11. Skibo KL, Wexler L. Pulmonary Angiography. In Grossman's Cardiac Catheterization, Angiography and Intervention, Baim SD, Grossman W. 6th Ed. Philadelphia. Lippincott William's and Wilkin's, 2000: 271-291.
12. Park S, Ha JW, Ko YG, et al. magnitude of left atrial v wave is the determinant of exercise capacity in patients with mitral stenosis. Am J Cardiol 2004; 94: 243-5.
13. Korewicks J, Pogorzelska H, Madeja G. Pulmonary venous compliance. Indirect evaluation based on pulmonary capillary pressure registration. Kardiol Pol 1993; 39: 267-72.
14. Otto CM, Davis KB, Reid CL, Slater JN, Kronzon I, Kisslo KB, Bashore TM. Relation between pulmonary artery pressure and mitral stenosis severity in patients undergoing balloon mitral commissurotomy. Am J Cardiol 1993;71:874-878.
15. Abbo K, Carroll JD. Hemodynamics of mitral stenosis: a review. Cathet Cardiovasc Diagn 1994;2:216-225.
16. Alexander J Jr, Sungawa K, Chang N, Sagawa K. Instantaneous pressure-volume relation of the ejecting canine left atrium. Circ Res 1987;61:209-219.
17. Suga H. Importance of left atrial compliance in cardiac performance. Circ Res 1974;35:39-43.
18. Moreyra AE, Wilzon AC, Deac R, et al: Factors associated with atrial fibrillation in patients with mitral stenosis: A cardiac catheterization study. Am Heart J 1998;135:138–45.
19. Keren G, Etzion T, Sherez J, et al: Atrial fibrillation and atrial enlargement in patients with mitral stenosis. Am Heart J 1987;114:1146.
20. Ha JW, Namsik C, Goh CW, Kang SM, Rim SJ, et al : Pulmonary venous flow in pure mitral stenosis and sinus rhythm- does pulmonary hypertension alter pulmonary venous flow velocity? ECHOCARDIOGRAPHY 2003;20:129-135.