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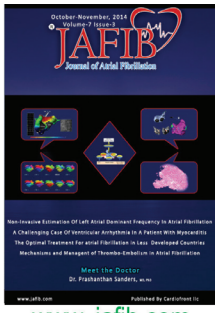

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Left Atrial Diastolic Dysfunction And Pulmonary Venous Hypertension In Atrial Fibrillation: Clinical, Hemodynamic And Echocardiographic Characteristics

J. Thomas Heywood, MD[1], FACC, Srikanth Seethala, MD[1], Tariq Khan, MD[1], Allen Johnson MD, FACC[1], Michael Smith, MD[1], David Rubenson, MD, FACC[1], Eric Reynolds, RDCS

[1]*Division of Cardiovascular Disease, Scripps Clinic, La Jolla, CA.*

Abstract

Background: Left ventricular diastolic dysfunction has been well described; diastolic abnormalities of the LA are less frequently recognized and poorly understood.

Objective: The purpose of this study was to investigate the clinical, hemodynamic and echocardiographic features of left atrial (LA) diastolic dysfunction.

Methods: Patients with atrial fibrillation (AF), severe LA enlargement, and pulmonary venous hypertension (PVH, Group 1) were compared to patients with pulmonary arterial hypertension (PAH), normal LA size and sinus rhythm (Group 2). All underwent right heart catheterization and transthoracic echo to evaluate hemodynamics and LA function. Mitral regurgitation was evaluated by transesophageal echocardiography. LA diastolic function was measured by comparing filling fraction, pulmonary venous flow and compliance.

Results: Right atrial, pulmonary artery systolic and mean pressures were similar. Mean wedge pressure were increased in Group 1, 20.8±2.6 versus 9.7±2.8 mm of Hg ($p<0.0001$). The most striking hemodynamic difference was large V wave in Group 1 without significant mitral regurgitation. LA filling fraction was abnormal in Group 1, 11.4%±8.5 compared to Group 2, 111.5%±44 ($p<0.0001$). LA compliance was 0.39±0.27 ml/m2/mmHg in Group 1 versus 6.8±4.54 ml/m2/mmHg in Group 2 ($p=0.001$). There was a strong negative correlation between the V wave and LA filling fraction ($r= 0.756$, $p<0.001$). The ratio of the height of the transmitral E wave divided by the S/D ratio (the LA diastolic dysfunction index) correlated very strongly with the V wave ($r=0.907$, $p<0.001$).

Conclusion: LA diastolic dysfunction is present in some patients with long standing AF and PVH. LA diastolic dysfunction, in addition to left ventricular diastolic dysfunction, may contribute to the syndrome of heart failure with preserved left ventricular systolic function.

Introduction

There has been increased awareness on the association of left atrial size and prognosis.[1] As the left atrium enlarges there is the attendant risk of the development of atrial fibrillation, which independently increases overall mortality and stroke.[1,2] The left atrium plays a complex role in cardiac physiology; functioning as a booster pump, reservoir and conduit for blood entering the left ventricle.[3] The contractile function of the left atrium has been extensively evaluated, and much effort and expense is deployed to maintain sinus rhythm, often with unclear benefit.[4] There has been less consideration of the reservoir or diastolic function of this chamber, although models predict that impaired left atrial compliance could result in increased pulmonary venous pressures and an overall decrease in cardiac output.[5,6]

In 1988, Pilote et al. reported a case of pulmonary hypertension and severe right ventricular failure in patient following mitral valve replacement. Invasive hemodynamics and ventriculography revealed normal prosthetic valve function without regurgitation or stenosis.[7] The most striking finding was a large V wave in the pulmonary artery wedge position, confirmed by a direct transeptal measurement. They speculated that these findings were the result of impaired filling of a very noncompliant left atrium, naming it the stiff left atrial syndrome. Since that time there have been a few reports confirming their findings, most often in patients with prosthetic mitral valves or mitral stenosis. In these cases the patients had enlarged left atria and large V waves in the pulmonary artery wedge position.[8,9]

Left atrial dysfunction and enlargement is common with mitral valve disease, especially in association with atrial fibrillation.[10] Indeed, atrial fibrillation may play a key role in reducing left atrial compliance simply because with atrial fibrillation there is no active atrial emptying (no pump function) so that the chamber is by necessity more full when blood enters from the pulmonary veins.[5] Hence, loss of pump function may significantly impair reservoir function. Left atrial dysfunction associated with atrial fibrillation may be associated with left atrial noncompliance even in the absence of mitral valve disease. To test this hypothesis we evaluated hemodynamic and echocardiographic parameters of left atrial function in patients undergoing right heart catheterization for characterization of pulmonary hypertension.

Disclosures:
None.

Corresponding Author:
J. Thomas Heywood, M.D., F.A.C.C.
10666 N. Torrey Pines Road
La Jolla,
CA 92037.

Table 1: Hemodynamic differences between groups

	Group 1 (Pulmonary Venous Hypertension)	Group 2 (Pulmonary Arterial Hypertension)	p-value
Right Atrial (mmHg)	13.8±4.9	12.3±6.8	NS
RV Systolic	58.8±9.4	67.7±23.9	NS
RV Diastolic	13.7±3.7	15.7±5.5	NS
Pulmonary Artery Systolic	58.8±9.5	67.7±21.4	NS
Pulmonary Artery Diastolic	24.4±5.2	36.3±14.8	0.043
Pulmonary Artery Mean	36.6±6.0	47.5±15.3	0.072
Mean PA Wedge	20.8±2.6	9.7±2.8	<0.0001
Peak V Wave Pressure	33.7±3.5	14.7±4.8	<0.0001
V Wave Height	14.6±4.3	2.2±0.7	<0.0001
Cardiac Index (L/min/m2)	2.1±0.6	1.8±0.4	NS
LVEF (%)	57.8±16	70.2±9.8	NS
LA Size (ml/m2)	55.7±15	24.8±10.8	0.001
TAPSE	1.5±0.4	1.7±0.8	NS
LA Filling Fraction (%)	11.4±8.5	111.5±44	<0.0001
LA Compliance (ml/m2/mmHg)	0.39±0.27	6.73±4.54	0.001
Pulmonary Vein (cm/sec)			
S-Wave	26.2±7.0	58.8±10.8	<0.0001
D-Wave (cm/sec)	91.7±18.4	39.3±17.3	<0.00017
S/D	0.29±0.06	1.8±0.99	<0.0001
Mitral E-Wave (cm/sec)	116±21	78±0.33	0.018
E-Wave/S/D (cm/sec)	415±94	58±41	<0.0001
Tricuspid Regurgitation	2.6±1.0	1.0±1.5	0.034

Methods

Consecutive patients scheduled for right heart catheterization for the evaluation of elevated pulmonary artery pressure were screened. Patients underwent transthoracic echocardiography and transesophageal echocardiography to assess hemodynamics and cardiac structure. They then underwent right heart catheterization on the same day. Patients were subsequently divided into two groups. Group 1 consisted of patients with pulmonary venous hypertension with a mean pulmonary capillary wedge pressure >15 mmHg, and non-valvular atrial fibrillation.

Group 2 patients had pulmonary arterial hypertension by the standard criteria, with a mean pulmonary capillary wedge pressure <15 mmHg and a mean pulmonary artery pressure >25 mmHg.

All patients provided written informed consent, and the study was approved by the Institutional Review Board of the Scripps Office for the Protection of Research Subjects.

Transthoracic Echocardiography

Transthoracic echocardiography was performed using an IE33 system (Philips Medical Systems, Bothell, Washington), with an S5-1 probe. This study included a comprehensive transthoracic echocardiogram utilizing 2D, Doppler, and M-mode imaging. The data from three to six consecutive beats was averaged for all Doppler measurements. The pulmonary vein flow velocities were measured using a pulsed-wave Doppler sample volume placed approximately 1 cm into the ostium of the right upper pulmonary vein. The highest pulmonary velocity during systole (S wave) and diastole (D wave) were measured in each patient.

In addition, a detailed analysis of the size and function of the left atrium (LA) was undertaken. Left atrial biplane volumes were derived from traced apical 4 chamber (Ap4C) and apical 2 chamber (Ap2C) areas at both end systole and end diastole.[11]

LA volume index (LAVi) was calculated using the standard formula:

LAVi (ml/m2) = 0.85 (Ap4c area x Ap2c area)/shortest long-axis dimension/Body Surface Area

LA volume calculation was performed at both end atrial diastole and end atrial systole. End-atrial diastole was defined as the frame immediately before MV opening while end-systole corresponded to the frame immediately before MV closure. In Group 1 patients since all were in AF, "atrial systole" per se did not exist but defined as above. A minimum of three end-systolic and end-diastolic biplane volumes were performed and averaged.

The resulting volumes were then used in the calculation of the LA filling fraction, or difference in indexed LA volume between atrial systole and diastole volume indexes divided by volume at end-atrial systole x100. In other words, the maximum LA volume-minimum LA volume/ minimum LA volume x100 was defined as the left atrial filling fraction.[12]

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) was performed using an IE33 system with an X7-2T probe (Philips). A standard, comprehensive TEE was performed on each patient according to institutional protocol. Particular attention was paid to assessing the degree of mitral regurgitation, if present, and to rule out pulmonary venous pathology. Patients were excluded from the study that had greater than mild mitral regurgitation using accepted qualitative and quantitative criteria obtained during the transthoracic and transesophageal Doppler exams. These criteria included the mitral regurgitation color flow jet area, continuous wave jet density, vena contracta width and effective regurgitation orifice area based upon the proximal isovelocity surface area (PISA) method.[13]

Right Heart Catheterization

Right heart catheterization was performed in the standard fashion via right femoral vein access, using a Swan-Ganz catheter under direct fluoroscopic guidance. Intracardiac and pulmonary artery

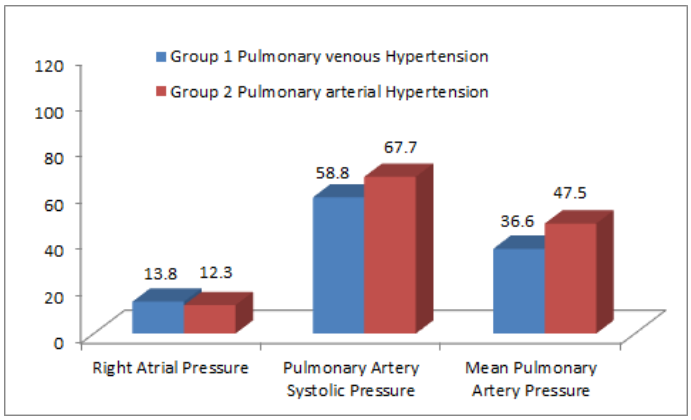

Figure 1: Right atrial, systolic pulmonary artery and mean pulmonary artery pressure (mean and standard deviation) in Group 1 (Pulmonary venous hypertension) and Group 2 (Pulmonary arterial hypertension).

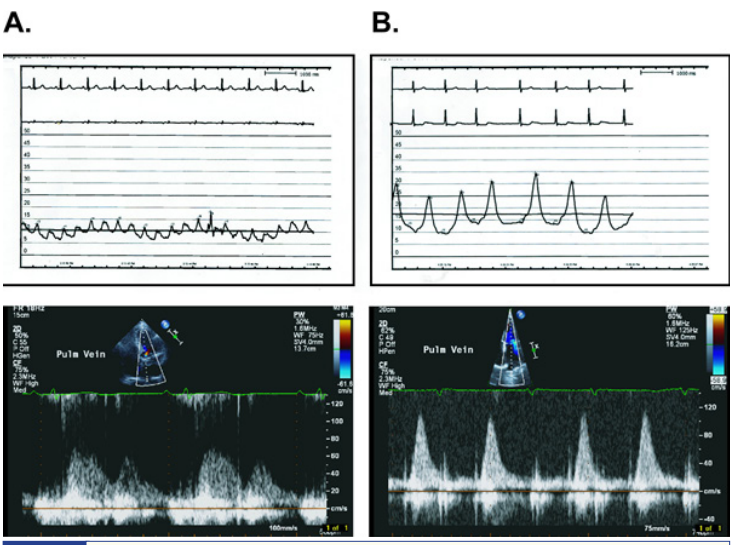

Figure 2: **Panel A. The right panel is a representative tracing from a patient in Group 1 with a prominent V wave. The left panel is from a patient in Group 2 with normal and V waves.**
Panel B. The right panel shows the pulmonary vein flow from a patient in Group 1 demonstrating reduced systolic (S) velocity and proportionally increased diastolic velocity (D wave). The left panel is the pulmonary vein tracing from a patient in Group 2 with more normal systolic velocity

pressures were documented. Pulmonary artery wedge pressures were measured and the height of the systolic pressure wave (V wave), when present, was measured. For patients in AF the pressures of 5 consecutive beats were measured and averaged. Oxygen saturation in the pulmonary artery wedge position was obtained and used to verify that the pressures reflected a true wedge position (LA saturation >95%). The cardiac outputs were calculated using the estimated Fick and thermodilution methods, but only the estimated Fick cardiac outputs are reported because of the severity of tricuspid regurgitation in many of the study patients.[14]

The change in pressure from between the beginning of the pulmonary capillary wedge pressure V wave to the maximum height of the V wave was then measured, and used to determine left atrial compliance.

This was defined as the change in echocardiographically-derived LA volume index divided by difference in the catheter-derived pressure from the nadir to the peak of the V wave.[15]

Statistical Analysis

All data are presented as mean ± SD. The means for variables were compared by an unpaired Student's t test. The Fisher exact test was used to compare categorical data. Correlations between variables were determined by Pearson's correlation. Data was analyzed using Statistics for Social Sciences (SPSS) version 17, Chicago, Illinois. A p-value <0 05 was considered statistically significant.

Twenty-one patients were enrolled in the study, but six were excluded because of prosthetic mitral valve disease (one), more than mild mitral regurgitation (four) or absence of atrial fibrillation (one) (in those with pulmonary venous hypertension). The remaining patients and were divided into two groups. Group 1 (n=9) patients had pulmonary hypertension with elevated pulmonary artery wedge pressure, >15 mmHG (termed pulmonary venous hypertension, PVH). In addition they had evidence of LA enlargement and AF. Group 2 patients (n=6) had pulmonary arterial hypertension (PAH) with elevated mean pulmonary artery pressures, >25 mmHg with a pulmonary artery wedge pressure <15 mmHg.

Group 1 consisted of seven men and two women with an mean age of 81.1±4.4; all but one patient in Group 2 were women, average age 64.8±15.5 years p=0.01. Whereas all patients in Group 1 had atrial fibrillation with an average duration of this rhythm of 5.3±4.7 years, all patients in Group 2 were in sinus rhythm. Eight of nine patients in Group 1 had been admitted for heart failure whereas only two patients in Group 2 had been, p=0.088. The left ventricular ejection fraction was not different between the groups, 57.8±16% versus 70.2±9.8%, p=ns. However, the left atrial size differed significantly, 55.7±15 ml/m2 in Group 1 and 24.8±10.8 ml/m2 in Group 2, p=0.001.

Hemodynamic Findings

The mean right atrial pressures was elevated in both groups indicating some degree of right ventricular failure, 13.8±4.9 mmHg for Group 1 and Group 2, 12.3±6.8 mmHg, p=ns. Similarly RV systolic, diastolic, pulmonary artery systolic and diastolic pressures were not statistically different between the two groups (Table 1 and Figure 1). The mean pulmonary artery wedge pressures were significantly different however, 20.8±2.6 mmHg in Group 1 and 9.7±2.8 mmHg for Group 2, p<0.0001. More strikingly in Group 1 there was a V wave present, often quite large, despite the fact that no patient had more than mild mitral regurgitation. Large V waves (defined as an increase of ≥10 mmHg from nadir to peak) were present in eight patients in Group 1 versus none in Group 2 (Figure 2). The absolute V wave pressure was 33.7±3.5 mmHg (Group 1) compared to 14.7 ± 4.8 mmHg in Group 2, p<0.0001 (Figure 3). The average change in wedge pressure from the beginning of the V wave to its peak was 14.6±4.3 mmHg in Group 1 and 2.2±0.7 mmHg in Group 2, p<0.0001. The V waves represented a greater proportion of pulmonary artery systolic pressure in Group 1, 59% versus 24% for Group 2, (p<0001). The cardiac index by estimated Fick was reduced in both the groups, 2.1 L/min/m2 in Group1 and 1.8 p=L/min/m2 in Group 2, p=ns.

Left Atrial Filling and Diastolic Function

The LA filling fraction (change in LA volume index from end atrial systole to end atrial diastole divide by end atrial systolic volume x100) was very low in Group 1, 11.4±8.5% whereas it was much larger in Group 2, 111.5±44%, p<0.0001. As would be expected pulmonary venous Doppler measures of inflow velocity were greatly reduced during atrial filling (ventricular systole) in Group 1. The peak velocity of the S wave (ventricular systole, atrial diastole) was 26±7.0 cm/sec compared to 59±10.8 cm/sec in Group 2, p<0.0001. Since atrial filling during diastole was so impaired in Group 1, inflow increased with the opening of the mitral valve with a corresponding increase in the D wave velocity, 91.7±18.4 cm/sec compared to only 39.3±17.3 cm/sec in Group 2, p=0.00017 (Table 1).

Left atrial compliance, the change in diastolic volume/change in pressure during atrial diastole was greatly reduced in Group 1, 0.39±0.27 ml/m2/mmHg as compared to 6.8±4.54 ml/m2/mmHg in Group 2, a 15-fold reduction in compliance, p=0.001. There was a good correlation between the size of the V wave (base to peak) and left atrial filling fraction, r=-0.756, p=0.001 (Figure 4) or the ratio of S/D, r=-0.699 p=0.004. Since a large V wave indicates increased LA pressure this should increase flow into the left ventricle in early

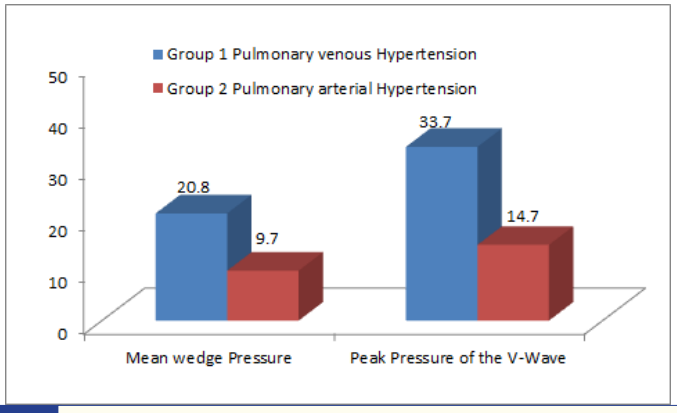

Figure 3: Significant differences exist between the mean pulmonary artery wedge pressure and the peak V wave pressure between the two groups.

diastole, there should be a correlation between E wave peak velocity and the size of the V wave which was found, r=0.64, p=0.01. An improved relationship was found by dividing the peak E wave velocity by an index of impaired atrial filling, the ratio of the S/D waves. This parameter termed the "left atrial diastolic dysfunction index" clearly separated the two groups and produced a very strong correlation with the size of the V wave, r=0.907, p<0.001 (Figure 5). This index when above 250 cm/sec is associated with a moderate to large V wave in this limited data set and thus may be a useful noninvasive marker of impaired LA diastolic filling or LA diastolic dysfunction. A larger series of patients will be required to establish the clinical predictive power of this index.

Discussion

As the population ages the development of AF will be a growing health care burden.[3] The role of AF as a strong and independent risk factor for stroke and mortality has been well described.[1, 4] AF is also risk factor for the development of congestive heart failure.[16] The loss of sinus rhythm may lead to a reduction in cardiac output when the "booster pump" function of atrial contraction is lost.[17] However, it appears that diastolic properties of the left atrium may be also important in the development of increased LA pressure leading to pulmonary venous hypertension.

A small number of patients with left atrial noncompliance or "stiff left atrial syndrome" have been described previously.[7, 8] Blood entering the noncompliant left atrium results in a steep pressure rise in a similar fashion to the left ventricle with diastolic dysfunction. Fitchett created an electronic analog model of cardiac function in which left atrial compliance could be varied to study the effect on hemodynamics.[18] The model predicted a marked increase in atrial pressure following the onset of ventricular systole (atrial diastole) with blood moving into the atrium from the pulmonary veins when LA compliance was reduced.

In the current study, the mean wedge pressure in Group 1 patients was 20.8±2.6 mmHg indicating some degree of left ventricular diastolic dysfunction. However, the most striking hemodynamic finding was a large V wave in the pulmonary artery wedge tracing (Figure 2 and Table 1). Although a V wave may be indicative of severe mitral regurgitation, the patients had no more than mild mitral regurgitation by both transthoracic and transesophageal echocardiography. Fuchs et al have shown that large V waves are neither sensitive nor specific for mitral regurgitation.[19] Eight out of nine patients in the pulmonary venous hypertension group had large V waves (≥10 mmHg). In a study of patients with rheumatic mitral stenosis, the strongest predicator of the pulmonary artery systolic pressure was the height of V wave.[9] Undoubtedly there is a complex interplay between LV and LA diastolic dysfunction. LV diastolic dysfunction begets left atrial enlargement and the predisposition to AF. Higher LV filling pressures increase LA pressure. Nonetheless poor left atrial compliance manifested by a large V wave further increases systolic loading of the right ventricle due to increased pulmonary venous hypertension.

Echocardiography has been a powerful tool for evaluating both LV diastolic and LA function. Left atrial pumping function has been the major focus, but diastolic properties of this chamber have also been reported.[5, 11] Indeed, they are intimately related because if the atrium loses pumping function and cannot empty then, by necessity, its volume will increase for the next diastolic filling period. Normal filling fraction for the left atrium has been reported by Shin et al to vary from 171% in normals to 95% in patients with hypertrophic cardiomyopathy.[12] This value was somewhat higher than the range of 58 to 134% seen in Group 2 patients with pulmonary arterial hypertension and normal left atrial size and sinus rhythm. Group 1 patients had a mean atrial filling fraction of 11% indicating very little change in volume during atrial diastole and very much less than the 95% filling fraction reported by Shin whose patients had hypertrophic cardiomyopathy but were in sinus rhythm.

Pulmonary venous flow is another means to evaluate atrial and ventricular diastolic function.[20, 21] Up to four distinct waves may normally be seen. S1 which occurs in atrial systole, S2 later in atrial diastole and is thought to be produced blood moving into the LA from the pulmonary veins as a result of right ventricular contraction.[18] The D wave which begins with the opening of the mitral valve and the movement of blood passively from the pulmonary vein, through the LA and into the left ventricle. The D wave represents the conduit function of the LA. Finally, the AR wave (A reversal wave) which is the retrograde movement of blood backward into the pulmonary vein with atrial systole. In AF with the loss of atrial systolic function the S1 and the AR waves are not seen. Moreover, the S2 or just S wave is typically attenuated, although there was no difference in the D wave

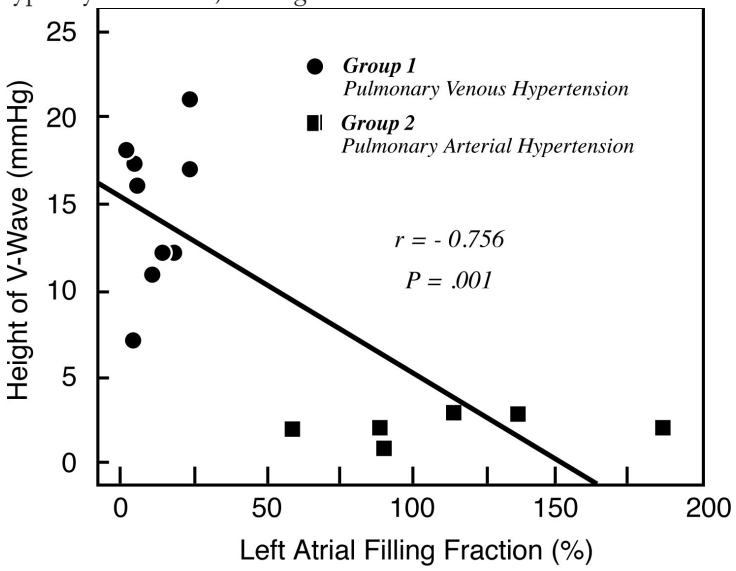

Figure 4: Correlation between the filling fraction of the left atrium and the height of the V wave from its base to the peak in Group 1 and 2 patients.

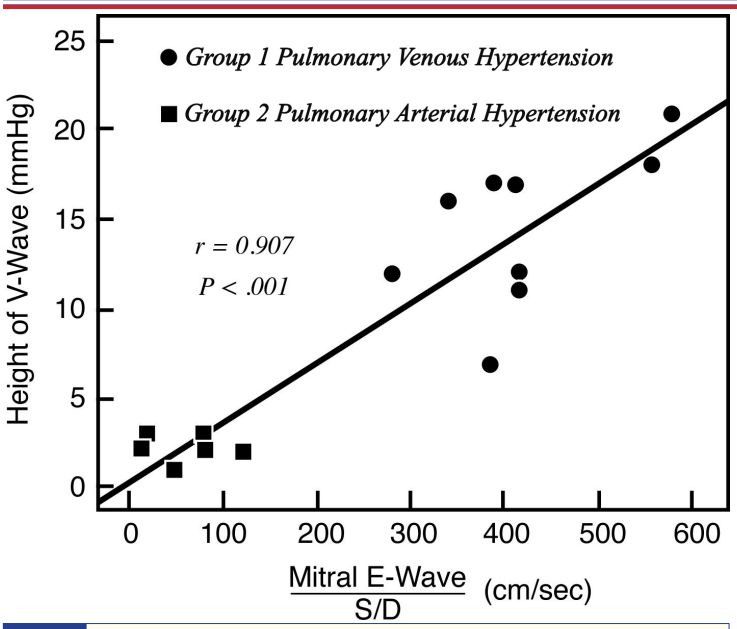

Figure 5: Correlation between the left atrial diastolic dysfunction index (E wave peak velocity divided by the ratio of the pulmonary vein S wave to D wave) for Group 1 and Group 2. Patients with significant V waves had values above 250 cm/sec.

height.[22] There was a marked reduction in the S wave in the Group 1 compared to Group 2 (26 versus 59 cm/sec); however, there was also a compensatory increase in the D wave in Group 1 compared to Group 2 (92 versus 39) suggesting a relative increase in LA conduit function when the reservoir function was impaired.

Left atrial compliance was quite different between Group 1 and 2, (0.39 versus 6.8 mmHg/ml/m2, p=0.002) LA compliance has been evaluated by several groups. Baxley determined average LA compliance in patients with rheumatic mitral regurgitation (5.14 ml/mmHg/m2) versus those with ruptured chordae (1.61 ml/mmHg/m2).[23] Arakawa and colleagues found LA pressure to rise exponentially with increased volume, similarly to the left ventricle.[15] The LA compliance in a group of patients half of whom had coronary artery disease was 1.03 ml/mmHg/m2 at a pressure of 13.5 mmHg. The compliance of the LA was about three times less that the left ventricle.[24] The LA compliance in Group 1 is significantly less than previously reported. There are several possible explanations for this finding. The mean wedge pressure was higher in Group1 so that LA was filling at a steeper portion of its pressure volume curve. Secondly, the lack of atrial systole in Group 1 reduced atrial emptying and would again shift the pressure volume curve upward. Thirdly, AF is associated with calcium overload within in atrium, which may cause tissue injury and reduce dispensability.[25] With the onset of AF, left atrial filling pressures are known to increase.[26] Enlarged left atrial are fibrotic with increased collagen content which would further decrease compliance.[27,28]

In our patients with AF LA noncompliance appears to have had significant clinical repercussions. There were significant V waves in eight out of nine patients, the absolute size of the V wave was a significant fraction of the peak pulmonary systolic pressure. It is clear that pulmonary systolic pressure must exceed the V wave LA filling to occur during ventricular systole. This V wave increases the loading of the right ventricle. All patients in Group 1 had an elevated right ventricular end diastolic pressure, indicating right heart failure. Tricuspid regurgitation was common and often moderate to severe. These patients were on diuretics and the majority had been hospitalized at some point for congestive heart failure. Their left ventricular systolic function was in the normal range, with the exception of one patient with a mean ejection fraction of 57.8±16%. Thus left atrial, in addition to left ventricular, diastolic dysfunction may be a contributor to the syndrome of heart failure with preserved systolic function. In the ADHERE database, those admitted with heart failure and normal ejection fraction were significantly more likely to be in AF at the time of admission.[29] The majority of subjects in Group 1 had been admitted to hospital for heart failure and only one patient had an ejection fraction below 40%. With high central venous pressure Group 1 patients would meet Framingham criteria for heart failure.[30] Right ventricular failure is being increasingly recognized as a contributor to heart failure with normal left ventricular systolic function.[31]

If left atrial diastolic dysfunction associated with atrial fibrillation can have such important hemodynamic consequences, why is it not recognized more often? Several reasons are possible.1) Although left atrial size is routinely measured by echocardiography, left atrial function is not. Therefore there are few studies evaluating left atrial diastolic function.[15, 23, 32] 2) Perhaps only severe loss of atrial compliance in LA results in large V waves and secondary pulmonary venous hypertension. The patients in Group 1 had longstanding AF with severe chamber dilation and dysfunction. 3) The significance of the pulmonary artery V wave as a marker of left atrial noncompliance has not been widely appreciated and can be only recorded invasively. Our data suggest that left atrial diastolic dysfunction index (E/(s/d)) may provide a noninvasive marker of reduce LA compliance and V

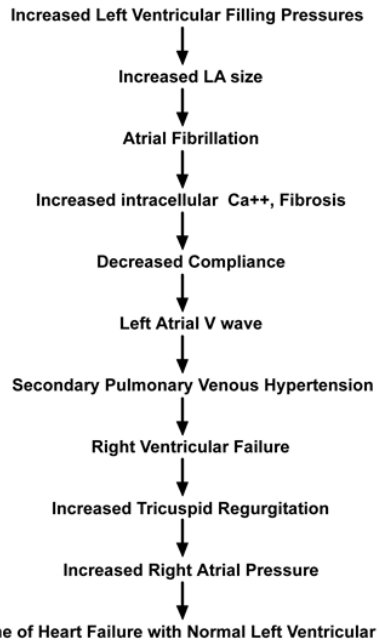

Figure 6: A proposed schema for the development of heart failure with normal systolic function in patients with atrial fibrillation and left atrial diastolic dysfunction. Poor compliance and reduced filling fraction of the left atrium produces the major hemodynamic abnormality of LA diastolic dysfunction-a large V wave. This marked increase in LA pressure coupled with an increase in left ventricular end diastolic pressure results in pulmonary venous hypertension and right heart failure.

wave. Unfortunately studies attempting to maintain sinus rhythm in patients with episodes of AF do not show clinical benefit. It may be that the LA is already so abnormal so that left atrial diastolic dysfunction already exists with its detrimental hemodynamic consequences.

Limitations

Left atrial compliance was measured at two points rather than more rigorously using micromanometer catheters and the construction of pressure volume loops. Furthermore the left atrial pressure was inferred via the pulmonary artery wedge tracing rather than directly measured with a transeptal puncture. Because pulmonary artery wedge tracings are a reasonable estimate of LA pressure it was not felt to be ethical to expose the patients to an unnecessary transeptal puncture. The wedge tracing was confirmed via its waveform and by demonstrating that the oxygen saturation was at the arterial level when measured with the balloon inflated.

Conclusion:

Patients with pulmonary venous hypertension and AF may have evidence of marked left atrial diastolic dysfunction with large V waves in the pulmonary artery wedge tracing, markedly reduced LA filling fractions and compliance. This in turn appears to augment pulmonary venous hypertension and may result, as in our patients, in right heart failure. We believe this is an under recognized cause of the syndrome of heart failure with preserved systolic function. The peak velocity of the E wave divided by the ration of the pulmonary S to D wave velocities may identify patients with pulmonary venous hypertension with a large V wave due to LA diastolic dysfunction. Thus efforts to preserve left atrial function, both systolic and diastolic, may have important implications beyond stroke reduction.

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