VALUE OF LEFT ATRIAL FUNCTION ON HEMODYNAMIC RESPONSE IN PATIENTS WITH MITRAL STENOSIS: A DOBUTAMINE STRESS ECHOCARDIOGRAPH STUDY

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Summary

The mechanisms of different hemodynamic and clinical responses to dobutamine infusion in mitral stenosis are not clearly established. The aim of this study was to evaluate the relation between left atrial (LA) function and hemodynamic response in patients with mitral stenosis to dobutamine infusion and to explain this response related to this parameter.

Forty-two consecutive moderately symptomatic patients (33 women, 9 men; mean age 46 ±9, range from 26 to 66), New York Heart Association (NYHA) class II with mitral stenosis (mean mitral valve area 1.7 ±0.1cm2) were evaluated with dobutamine stress echocardiography. Hemodynamic measurements were obtained at rest and peak dobutamine infusion. LA fractional shortening at rest was used as an index of global LA function. Twelve patients with hemodynamically serious mitral stenosis consisted of Group II (pulmonary artery pressure >60mmHg, transmitral mean gradient >15 mmHg during dobutamine infusion). The remaining 30 patients whose hemodynamic data did not reach the same level formed of group I. LA fractional shortening was significantly lower in group II compared to group I (19 ±3 vs 32 ±5 %, p<0.0001). In addition, left atrial dimension was significantly larger in group II (43 ±5 mm in group I vs. 50 ±2mm in group II, p<0.0001). While baseline hemodynamic parameters and mitral valve characteristics were not different in both groups, an increase in mean transmitral gradient (8 ±3 vs 5 ±2 mmHg, p<0.0001) and pulmonary artery systolic pressure (24 ±3 vs 16 ±8 mmHg, p= 0.007) were significantly greater in group II compared to group I during dobutamine infusion. Left atrial fractional shortening was negatively related to the increase in transmitral mean gradient (r:-0.58, p<0.01).

We that hemodynamic response during dobutamine stress echocardiography correlated with LA fractional shortening in patients with mitral stenosis. In some patients with mitral stenosis patients, manifest elevation in hemodynamic parameters may depend on impaired left atrial function accompanying left atrial enlargement.
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Key Words: *Dobutamine stress echocardiography, left atrial function, mitral stenosis*

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Özet

Mitral Darlığı Olgularının Hemodinamik Yanıtında Sol Atriyum Mekanik Fonksiyonun Önemi: Dobutamin Stres Ekokardiyografi Çalışması

Mitral darlığı olgularında, dobutamin infuzyonuna farklı klinik ve hemodinamik yanıtın mekanizması tam olarak açıklanamamıştır. Bu çalışmanın amacı, mitral darlığı olgularında, dobutamin infüzyonu sırasında meydana gelen hemodinamik yanıt ile sol atriyum mekanik fonksiyonu arasındaki ilişkiyi incelemek ve hemodinamik cevabı bu parametre ile açıklayabilmek idi.

Orta derecede semptomatik 42 mitral darlığı olgusu (33 kadın, 9 erkek; yaş ortalaması 46 ±9, 26-66), NYHA'a göre class II (ortalama kapak alanı 1.7 ±0.1cm2) dobutamin stres ekokardiyografi ile değerlendirildi. Hemodinamik ölçümler istirahat ve pik dobutamin infüzyonu sırasında alındı. Sol atriyal fraksiyonel kısalma, global sol atriyum fonksiyon indeksi olarak kullanıldı. Oniki hemodinamik olarak ciddi mitral darlığı olgusu grup II'yi (dobutamin infüzyonu sırasında pulmoner arter basıncı >60mmHg, ortalama transmitral gradient >15mmHg) oluşturdu. Hemodinamik bulguları aynı değerlere ulaşmayan 30 olgu grup I'i oluşturdu. Sol atriyal fraksiyonel kısalma grup II'de grup I'e göre anlamlı olarak daha düşük idi (%19 ±3, 32 ±5, p<0.0001). Ayrıca, sol atriyum çapı anlamlı olarak grup II'de grup I'e göre daha geniş idi (grup I'de 43 ±5mm, grup II'de 50 ±2mm, p<0.0001). Basal hemodinamik ölçümler ve mitral kapak özellikleri farklı olmamasına rağmen, ortalama transmitral gradient (8 ±3 mmHg, 5 ±2 mmHg, p<0.0001) ve pulmoner arter basıncı artışı (24 ±3, 16 ±8 mmHg, p<0.007) grup II'de grup I'e göre anlamlı olarak daha fazla idi. Sol atriyal fraksiyonel kısalma ile ortalama transmitral gradient artışı arasında anlamlı negatif korelasyon vardı (r:-0.58, p<0.01).

Sonuç olarak bu çalışmada, mitral darlığı olgularında dobutamin infüzyonuna verilen hemodinamik cevabın, sol atriyal fraksiyonel kısalma ile korele olduğu izlendi. Bazı mitral darlığı olgularında, hemodinamik parametrelerde belirgin artışın nedeni, sol atriyum dilatasyonuna eşlik eden bozulmuş sol atriyum fonksiyonu olabilir. ***(Türk Kardiyol Dern Arş 2003;31: 400-8)***

Anahtar Kelimeler: *Dobutamin stres ekokardiyografi, mitral darlığı, sol atriyal fonksiyon*

A subset of patients have significant limiting symptoms yet resting hemodynamics that do not indicate moderate to severe mitral stenosis (MS) [1-4]. If there is a discrepancy between symptoms and hemodynamic data, formal exercise testing or dobutamine stress echocardiography (DSE) may be useful to differentiate symptoms due to MS from other causes of symptoms. Significant increase in pulmonary artery pressure and mean transmitral gradient shows hemodynamicly significant mitral stenosis and indicates necessity for further intervention[5].

Mitral stenosis alters physiology and influences left atrial (LA) function[6,7]. In severe mitral stenosis, both resistance and atrial afterload are increased significantly at the mitral valve level due to obstruction of blood flow during active emptying force, which may account for the left atrial dilatation and impairment of the LA pump function. Despite hemodynamic data and mitral valve area do not indicate moderate to severe MS at rest, some patients may have left atrial enlargement and decreased left atrial function. In these patients, advanced structural alterations and fibrosis in the left atrium due to rheumatic insult and repated exertion-related increase in left atrial pressure may explain these undesirable changes.

Although, in previous studies, it was suggested that

the exercise response is roughly dependent on the degree of mitral stenosis, the exact mechanism of the different hemodynamic responses to stress is still unknown[5]. We have hypothesized that left atrial function at rest may predict hemodynamic response to dobutamine infusion. To test this hypothesis the relation between the LA fractional shortening as an index of LA function and hemodynamic response was investigated in patients with mitral stenosis during dobutamine stress echocardiography. In addition, the impact of dobutamine stress echocardiography on patient management was evaluated.

METHODS

Patient Population

Fourty two consecutive patients who have moderate symptoms and mild mitral stenosis were evaluated with dobutamine stress echocardiography (mean mitral valve area 1.7 ±0.1cm^2). The study group comprised 9 men and 33 women, with a mean age 46 ±9 (range 26-66). All patients were in Class II according to New York Heart Association (NYHA) classification and in sinus rhythm.

Exclusion criterias

Patients with mitral regurgitation of greater severity than mild, another valvular lesions, prior valvuloplasty, unstable angina, left ventricular systolic dysfunction (EF>40%), atrial fibrillation were excluded. No patient had a history of coronary artery disease.

Patients were referred for dobutamine echocardiography because a clinical decision (whether to proceed to catheterization, percutaneous mitral balloon valvuloplasty or medical treatment) could not be made on the basis of the clinical and echocardiographic data at rest. The study protocols were approved by the Institutional Review Board, and written informed consent obtained from all patients.

Echocardiography

All patients underwent standart rest two-dimensional echocardiography in the left lateral decubitus position. Parasternal long and short-axis, apical two and four chamber views were obtained with 2.5 mHz transducer interfaced to Vingmed System Five equipment. The mitral valve area was the average of the values obtained by the pressure half-time formula[8] and planimetry on a two dimensional short-axis view. Continuous wave Doppler examination of mitral inflow was performed in the apical four-chamber view. Color flow imaging was used to help orient the Doppler beam parallel to mitral inflow.The mean mitral valve gradient was obtained by planimetry of the Doppler velocity signal, the systolic pulmonary artery pressure by the Bernoulli principle of the tricuspid regurgitan jet, plus right atrial pressure[9]. Each measurement represented the average of five beats. Mobility, thickening, calcifications of the mitral leaflets and thickening of the subvalvular aparatus were evaluated for each patient, as previously described[10]. It ranged from 0 (entirely normal valve) to 16 (immobile valve).

Maximal LA dimension was determined using M-mode echocardiography according to the recommendation of the American Society of echocardiography[11]. Minimal LA dimension was measured from the same M-mode echocardiogram at the onset of QRS complex of the EKG[12]. LA fractional shortening was estimated as follows:maximal LA dimension-minimal LA dimension/ maximal LA dimension-100[13].

Dobutamine stress echocardiography

Immediately after echocardiographic evaluation at rest, dobutamine was infused in 5 minute increments at 5,10,20,30,40 and 50 g/k/min until target heart rate was reached which was obtained as "220-age"(1 mg atropin was added in inadequate response). Heart rate, blood pressure were recorded for each dose. Doppler data were obtained at peak dosage. Test was discontinued if the following end points were met: 1) frequent ventricular ectopy 2) serious bradycardia and hypotension 3) progresive dyspnea and chest pain. No patient developed pulmonary edema, angina, orthopnea, ventricular tachycardia. One patient developed mild sinus bradycardia, two patients developed mild tremors during dobutamine infusion. Hemodynamically serious mitral stenosis (pulmonary artery pressure >60mmHg,transmitral mean gradient >15 mmHg during dobutamine infusion) was interpreted according to the recommendation of ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease[14].

Statistics

All values are expressed as a mean value ± SD. Wilcoxon test was used to compare each variable between baseline and during peak dobutamine infusion in the same group. Comparisons of mitral valve characteristics and changes in hemodynamic parameters between the patient groups were performed by a Mann-Whitney U test. Correlations between LA fractional shortening and hemodynamic and echocardiographic variables were determined by the Pearson correlation. A value of $p< 0.05$ was considered statistically significant.

RESULTS

Dobutamine infusion was terminated because of dyspnea in 8 patients. In the other patients, dobutamine was infused until the target heart rate was reached. Patients were divided into two groups according to hemodynamic response during dobutamine infusion. Twelve patients who have a significant elevation in pulmonary artery pressure (>60mmHg), mean transmitral gradient (>15mmHg) during dobutamine stress echocardiography were considered for hemodynamically serious mitral stenosis (Group II), 30 patients who did not reach at the same level consisted of group I. The peak dosage of dobutamine ranged from 35 g/k/min to 50 g/k/min with a mean of 43 ±5 g/k/min. In both groups, heart rate increased to the same extent during dobutamine infusion (maximal heart rate 136 ±3 beats/min in group II, 138 ±3 beats/min in group I). Blood pressure did not show significant difference in all patients.

Baseline characteristics

Baseline echocardiographic measurements in both groups are shown in (Table 1). There was no significant difference in both groups with respect to mitral valvea area, total mitral echo score, mean mitral gradient and pulmonary artey pressure. LA fractional shortening was significantly lower in Group II than in group I (19 ±3 vs 35 ±5, $p<0.001$, respectively). Furthermore, LA maximal dimension was significantly greater in Group II than in group I (50 ±2 vs 43 ±5 mm, $p<0.001$, respectively).

Table 1: *Mitral valve characteristics in group I and II patiens*

	Group 1 (n:30)	Group 11 (n:12)	P
Mitral valve area (cm^2)	1.7 ±0.1	1.8 ±0.1	NS
Mitral valve echo score	8.0 ±1.4	9 ±1.6	NS
LA maximum diameter (mm)	43 ±5	50 ±2	<0.0001
LA FS (%)	32 ±5	19 ±3	<0.0001
LV EF (%)	60 ±4	59 ±3	

LA FS: left atrial fractional shortening, LV EF: left ventricle ejection fraction p <0.05 significant NS: not significant

Hemodynamic response to dobutamine infusion

In group I pulmonary artery systolic pressure and mean mitral gradient increased significantly from 31 ±8mmHg and 6 ±2 mmHg, respectively, at rest to 47 ±7 mmHg and 11 ± 3mmHg with dobutamine infusion ($p<0.0001$, $p<0.0001$, respectively) In group II pulmonary artery systolic pressure, mean mitral gradient increased from 45 ±6 mmHg and 9 ±5 mmHg, respectively, at baseline to 69 ± 6 mmHg and 15 ±8mmHg with dobutamine infusion ($p=0.002$, $p=0.002$, respectively) (Table 2). Although significant increase in these parameters was measured in both groups, statistical analysis showed a significant difference in favor of a larger increase in pulmonary artery pressure and mean mitral gradient in group II ($p<0.0001$, $p= 0.007$, respectively) (Table 3).

Relation between LA function and hemodynamic parameters

There was a correlation between LA fractional shortening and the magnitude of change in hemodynamic data during dobutamine infusion. LA fractional shortening was significantly but weakly correlated with the increase in pulmonary artery pressure (r:-0.33, $p=0.03$) and the LA maximal dimension (r:-0.39, $p= 0.01$) . LA fractional shortening and increase in mitral mean gradient were significantly correlated (r:-0.58, $p<0.01$). But relation between LA fractional shortening and mitral valve area was not found (Figure 1).

Table 2: *Hemodynamic parameters of group I and II patients at rest and during peak dobutamine infusion*

	GROUP I (n:30)			GROUP II (n:12)		
	C	PDI	P	C	PDI	P
Mitral- mean gradient(mmHg)	6±2	11 ±3	<0.0001	9 ±5	15 ±8	0.002
PAP(mmHg)	31 ±8	47 ±7	<0.0001	45 ±6	69 ±6	0.002

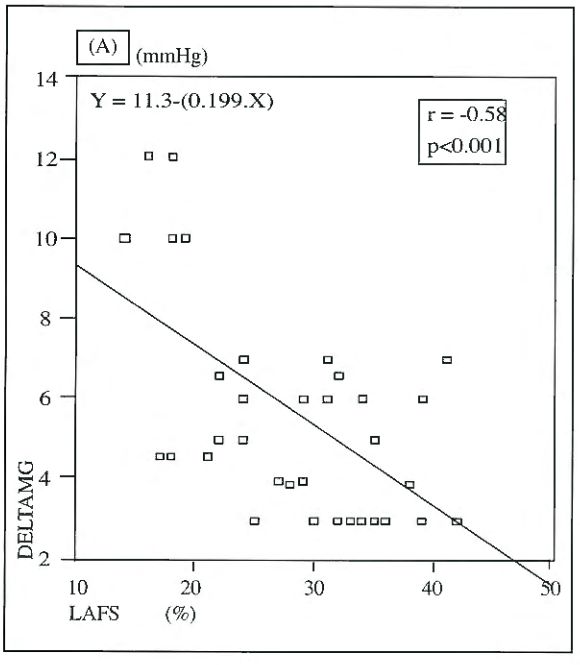
C: rest values; PDI: following peak dobutamine infusion; PAP: pulmonary artery presure, p<0.05 significant

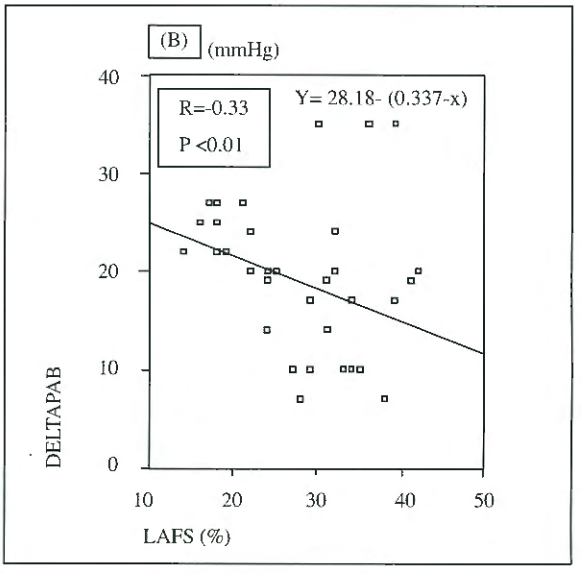
Table 3: *The magnitude of change in hemodynamic parameters of grop I and II patients between rest and peak dobutamine infusion*

	GROUP I (n:30)	GROUP II (n:12)	P
Delta PAP (mmHg)	16 ±8	24 ±3	<0.0001
Delta mean gradient (mmHg)	5 ±2	8 ±3	0.007

Deltavalues: Peak dobutamine values-baseline values, PAP: pulmonary artery pressure, p<0.05 significant

Figure 1: *Relations between LA fractional shortening (LA FS) and change in mean gradient at rest to peak dobutamine (DELTA MG) (A), pulmonary artery pressure at rest to dobutamine (DELTA PAB) (B). The regression lines are shown*





DISSCUSSION

In patients with mitral stenosis and unexplained symptoms, DSE is suggested as a reliable and feasible noninvasive evaluation method[15]. It provides an objective hemodynamic means to support a rational clinical decision in assessing mitral valve reserve capacity. Although there were some studies evaluating the value of stress echocardiography in the assessment of the severity of mitral stenosis, there were only few studies assessing the factors which determine the hemodynamic response during stress echocardiography[5,15]. To our knowledge, this is the first study investigating importance of left atrial function on hemodynamic response during DSE. A previous study, using bicycle exercise, demonstrated that mitral valve gradient increased

significantly in severe mitral stenosis and in nonsignificant mitral stenosis, but pulmonary artery pressure increased significantly only in severe mitral stenosis[5]. Sharon et al.[15] demonstrated that dyspnea might be provoked by dobutamine infusion and a greater increase in the mean gradient was noted among patients who developed dyspnea when compared with those who remained asymptomatic. Dahan et al.[16] using bicycle exercise in 27 patients with a wide range of mitral stenosis(0.50 to 2.25cm^2) demonstrated that an increase in stroke volume and mitral valve area was noted in patients with pliable valve leaflets, whereas there was no significant change or even decrease in these parameters in patients with unpliable leaflets. In our study, morphology of the mitral valve aparatus was not found different in patients who had a significant elevation in hemodynamic data than who did not.

Normal left atrial function consists of reservoir, conduit and pump function[12,17] . Mitral stenosis alters physiology and leads to diminished LA function. The obstruction to blood flow during the active emptying force by the stenotic mitral valve increases the LA afterload[6]. LA stiffness is increased in patients with mitral stenosis, which leads to an increase in LA pressure that is partially compansated for by increased maximal LA dimension[18]. These factors may account for the decreased LA active emptying phase and LA dilatation in patients with mitral stenosis. In most instances, increase in left atrial diameter, and impairment in left atrial function are correlated with the severity of mitral valve disease, but in our clinical practise, a discordance may be encountered in some patients. In this study although there was no significant difference between the groups with respect to mitral valve area, left atrial function was lower and left atrium was larger in patients who had a significant elevation in hemodynamic data. Fibrosis resulting from rheumatic process may effect left atrial function negatively. In addition, in moderate MS, exercise can cause sudden marked increase in pulmonary artery pressure from the increase in heart rate and cardiac output, at times accompanying elevated left atrial pressure. In a long-term repeated exertion-related increase in left atrial pressure may lead to the left atrial enlargement and impairment of the left atrial function. Our findings about the discordance between mitral valve area and LA dimension as well as mitral valve area and LA function could be explained by these mechanisms. In mitral stenosis, stress induced changes are not uniform. Although there was no difference in patients with respect to mitral valve area, hemodynamic response to stress was more pronounced in some patients. The present study demonstrated that hemodynamic response to dobutamine might closely associated with LA fractional shortening at rest. We observed that hemodynamically serious mitral stenosis patients had a lower LA function (low fractional shortening) at rest and a manifest elevation with respect to mean gradient, peak gradient and pulmonary artery pressure during stress echocardiography.

The administration of dobutamine generally results in a substantial increase in systolic blood pressure. In this study, dobutamine-induced increase in the systolic blood pressure was seen in most patients. But, it induced moderate hypotension in some patients (dobutamine induced side effect due to stimulation of peripheral beta 2 receptors). Therefore, change in systolic blood pressure as a response to dobutamine was not found statistically different compared to baseline mesaruments in all patients.

It is known that patients with MS are prone to developing atrial arrhythmias, particularly atrial fibrillation and atrial flutter. In most instances, the risk of atrial fibrillation is related to left atrial size, but a discordance may be encountered in some patients. Atrial fibrillation may be seen in some patients with moderate left atrial enlargement and sinus rhythm may be encountered in some patients with marked

left atrial dilatation in clinical practice. In this study, our patients with left atrial dilatation and impaired left atrial function were in sinus rhythm (We only included patients with mitral stenosis in sinus rhythm in this study). We thought that these patients have a high risk for the development of atrial fibrillation in the future. In addition, it was seen that patients consisting the hemodynamically insignificant mitral stenosis group have a functional tricuspid insufficiency. Mild pulmonary hypertension (determined by resting systolic pulmonary artery pressure average as 31 ±8 mmHg) was thought as a reason for functional tricuspid insufficiency in this group.

In this study, the clinical decision was affected by the test results in 12 patients (28%): 5 underwent percutaneous mitral balloon commissurotomy and 7 received intensive medical treatment. In one series, the clinic decision was affected by the test response in %84 of cases[19]. In that study, patients were referred for moderate symptoms of dyspnea, and some patients had additional regurgitant lesions , while our patients had NHYA class II, isolated mitral stenosis. All patients were in class I through the 1-year follow-up period. In patients undergone percutaneous mitral balloon commissurotomy, decrease in gradient and increase in the calculated mitral valve area resulted in a clear improvement in clinical symptomatology.

Limitations

A potential limitation of this study is the lack of invasive correlation with the noninvasive measurements. Several previous studies[20,21,22,23] have shown an extremely high correlation between noninvasive and invasive mitral valve gradient in native and prosthetic valves. In addition, another study has demonstrated invasive evaluation of pulmonary artery pressure at rest and exercise was correlated with noninvasive measurements [24]. Thus, we think that there is sufficient prior evidence to validate this method. In addition, there is often overestimation of the transmitral gradient when catheterization is performed with pulmonary artery wedge pressure as a substitute for left atrial pressure, even after correction for phase delay. Thus, the transmitral gradient derived by Doppler echocardiography may be more accurate than that obtained by cardiac catheterization with pulmonary artery wedge pressure[25].

The other limitation should be mentioned is that the left atrium is a three-dimensional structure, but we calculated left atrial fractional shortening using one dimension. A previous report demonstrated that there was an excellent correlation between the posterior aortic wall motion of M-mode echocardiography and the change in the left atrial angiographic area[26,27]. Therefore, LA fractional shortening obtained by M-mode echocardography can reflect the left atrial volume change. It should be mentioned that these results could not be generalized to other conditions with mitral stenosis and concurrent atrial fibrillation, left ventricular dysfunction or other valvular heart diseases.

Conslusion

Although mitral valve charasterictics were not different in patients, some patients had a significant elevation in mean transmitral gradient and pulmonary artery pressure during DSE. Hemodynamically serious mitral stenosis patients according to the test results had worse LA function and larger left atrium. In some mitral stenosis patients, manifest elevation in hemodynamic parameters may depend on impaired left atrial function accompaning left atrial enlargement.

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