Türk Kardiyol Dern Arş 2002; 30: 233-237

Effects of Dobutamine on Hemodynamic Parameters in Patients with Mitral Stenosis and Determinants of Pulmonary Artery Pressure Responce

Aytül BELGİ, M.D., Umuttan DOĞAN, M.D., Hüseyin YILMAZ, M.D., İbrahim BAŞARICI, M.D., İbrahim DEMİR, M.D., Oktay SANCAKTAR, M.D.
Akdeniz University Medical Faculty, Department of Cardiology, Antalya, Turkey

MİTRAL STENOZLU HASTALARDA DOBUTAMİN'İN HEMODİNAMİK PARAMETRELER ÜZERİNE ETKİSİ ve PULMONER ARTER BASINCI YANITININ BELİRLEYİCİLERİ

ÖZET

Amaç: *Mitral darlığında dobutamin infuzyonuna farklı klinik ve hemodinamik yanıtın mekanizması yeterince anlaşılamamıştır. Bu çalışmanın amacı, mitral darlığında dobutamin infüzyonu sırasında dispne ile ilişkili olarak hemodinamik parametrelerde meydana gelen değişikliği değerlendirmek ve pulmoner arter basıncı yanıtının belirleyicilerini saptamaktır.*

Metod ve Bulgular: *Elliyedi hafif semptomatik veya asemptomatik (51 kadın, 6 erkek; yaş ortalaması 43±7; (yaş aralığı 26-52), New York Kalb Cemiyetine göre sınıf I (9 hasta), sınıf II (48 hasta) mitral darlığı bulunan hasta (ortalama mitral kapak alanı 1.6±0.4 cm²) dobutamin stres ekokardiyografi ile değerlendirildi. Dobutamin infüzyonu ile 18 hastada dispne gelişirken (Grup B), diğer 39 hastada semptom gelişmedi (Grup A). Dispne gelişen grupta, mitral maksimum gradiyent artışı (14±7mmHg'a karşılık, 9± 4 mmHg, p=0.008), ortalama gradiyent artışı (12± 6mmHg'a karşılık, 6±3 mmHg, p<0.0001) ve pulmoner arter basıncı artışı (23±8 mmHg'a karşılık, 16±6 mmHg, p=0.007) dispne gelişmeyen gruba göre anlamlı olarak daha fazlaydı. Ayrıca hemodinamik cevap, kapak patolojisi daha ciddi olan grubu ortaya çıkardı. Klinik ve hemodinamik bulgulara dayanarak 12 hastada tedavi planı değiştirildi (%21): 7 hastaya perkütan mitral balon valvüloplasti, 4 hastaya mitral kapak replasmanı yapıldı ve 1 hastaya yoğun tıbbı tedavi uygulandı. Tüm hastalar dikkate alındığında; pulmoner arter cevabı, pulmoner arter sistolik basıncı (p<0.0001), ortalama mitral gradiyent (p=0.001), mitral kapak alanı (p=0.003) ve mitral kapak hasarının bulgusu olan subvalvular mitral skor (p=0.001) ile ilişkili bulundu.*

Sonuç: *Sonuç olarak, dobutamin infüzyonu sırasında dispne gelişen hastalarda, hemodinamik değişkenlerdeki artış, dispne gelişmeyen hastalara göre daha fazladır. Pulmoner arter basıncı cevabı, bazal pulmoner arter basıncı, ortalama mitral gradiyent, mitral kapak alanı ve subvalvular eko skoru ile ilişkilidir ve bu değişkenler ile tahmin edilebilir.* ***Türk Kardiyol Dern Arş 2002; 30: 233-237***

Anahtar kelimeler: *Mitral darlığı, sinus ritmi, dobutamin, ekokardiyografi*

There are discrepancies between symptoms and hemodynamic parameters at rest in patients with mitral stenosis. The management of patients with mitral stenosis depend on its severity and functional significancy. Resting hemodynamic data may underestimate the severity of mitral obstruction [1-4]. Supine exercise test performed during cardiac catheterization has been used to identify patients with clinically important mitral valve obstruction who may have only mild to moderete transmitral gradient at rest. Some studies in patients with mitral valve stenosis have compared Doppler derived and catheterization measured valve gradient with exercise and have confirmed the accuracy of the noninvasive technique [5,6]. Because of the cumbersome , some patients are unable or unwilling to undergo arm or leg exercise during cardiac catheterization. In addition pressure tracing may be difficult to interpret and echocardiographic examination may not be optimal because of motion artifact and hyperventilation. As an alternative to exercise, dobutamine has been utilized to increase cardiac output by its β1 adrenergic agonist affect. In another study, dobutamine stress echocardiography was compared with cardiac catheterization results and it was suggested as a reliable and feasible noninvasive evaluation method [7]. The present study was designed to assess dobutamine induced changes in hemodynamic parameters and to understand the main determinants of this response in mitral stenosis by using dobutamine stress echocardiography. In addition we investigated the impact of dobutamine stress echocardiography results on patient's management.

Received: 14 November, 2001, revision 28 February 2002
Corrospending Address: Dr. Aytül Belgi, Akdeniz Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, 07070 Antalya
Tlf: (0242) 227 4343/ 55355 Fax: (0242) 227 9911
e-mail: aybel68@hotmail.com

METHOD

Patients: Fifty-seven consecutive patients, whose symptoms and hemodynamics were discordant at rest were evaluated. The study group comprised 6 men and 51 women, with a mean age 43±7 (range 26-52), 9 patients were in Class I, 48 patients were in Class II according to New York Heart Association (NYHA) classification. All patients were in sinus rhythm.

Exclusion criteria: Patients with moderate or severe mitral regurgitation, another valvular lesions, prior valvuloplasty, unstable angina pectoris, severe left ventricular dysfunction, atrial fibrillation were excluded. No patient had a history of coronary artery disease.

Patients were referred for dobutamine echocardiography because a clinic decision (whether to proceed to catheterization, percutaneous mitral balloon valvuloplasty, surgery 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.

Dobutamine Stress 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 with the sample volume positioned below the tip of the mitral valve. 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, calsification 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 (inmobile valve).

Immediately after echocardiographic evaluation at rest, dobutamine was infused in 5 minute increments at 5,10,20,30,40 and 50 µg/k/min until target heart rate was reached which was obtained as "220-age". Heart rate, blood pressure were recorded for each dose. Doppler data were obtained at peak dosage. Test were 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 pulmoner edema, angina pectoris, orthopnea, ventricular tachycardia. One patient developed mild sinusal bradicardia, two patients developed mild tremor during dobutamine infusion.

Statistical Analysis: All values are expressed as a mean value ± SD. Statistical significance was defined as $p< 0.05$.Wilcoxon test was used to compare each variable between baseline and during peak dobutamine infusion in the same group. Comparison of mitral valve characteristics and changes in hemodynamic parameters between the patients groups were performed by a Mann-Whitney U test. The correlation of different variables with change in pulmonary artery pressure was examined by using linear regression analysis.

RESULTS

Dobutamine infusion was terminated because of dyspnea in 18 patients. In the other patients dobutamine was infused until the target heart rate reached. Patients were divided into two groups according to development of dyspnea during dobutamine infusion. Eighteen patients who developed dyspnea consisted of group B, 39 patients who did not dyspnea consisted of group A. The peak dosage of dobutamine ranged from 10 µg/k/min to 50 µg/k/min with a mean of 43±6 µg/k/min. The dyspneic patients reached virtually at the same heart rate as did the patients who were not dyspneic (maximal heart rate 136±4 beats/min in dyspneic patients, 139±4 beats/min in asymptomatic patients). Blood pressure did not show significant change in all patients.

Characteristics of mitral valve at rest; Mitral valve characteristics in both groups are shown in table 1. The mean measured mitral valve area at rest 1.7± 0.3 cm^2 in group A and 1.4±0.2 cm^2 in group B. The mean measured mitral valve area in group B was significantly smaller than in group A (p=0.01).

Hemodynamic response to dobutamine infusion; In group A pulmonary artery systolic pressure, mean and peak mitral gradients increased significantly from 41±13mmHg, 8±3 mmHg, 14±5mmHg, respectively, at rest to 58±17mmHg, 13±6mmHg and 23±8 mmHg with dobutamine infusion ($p<0.0001$, $p<0.0001$, $p<0.0001$, respectively) In group B pul-

Table 1.Mitral valve characteristics in group A and B patients

	Group A (n:39)	Group B (n:18)	p
Mitral valve area (cm^2)	1.7 ± 0.3	1.4 ± 0.2	0.01
Mitral valve echo score	8.4 ± 1.7	8.8 ± 1.5	NS
Subvalvular echo score	2.0 ± 0.5	2.5 ± 0.7	0.04
Leaflet calsification	2.2 ± 0.8	2.1 ± 0.7	NS
Leaflet mobility	2.0 ± 0.5	2.0	NS
Leaflet thickining	2.1 ± 0.5	2.1 ± 0.7	NS

PAP: pulmonary artery pressure
p <0.05 significant

Table 2. Hemodynamic parameters of group A and B patients at rest and during peak dobutamine infusion.

	Group A (n:39)			Group B (n:18)		
	C	PDI	P	C	PDI	P
Mitral peak gradient (mmHg)	14±5	23±8	<0.0001	21±5	35±10	<0.0001
Mitral mean gradient (mmHg)	8±3	13±6	<0.0001	12±5	23±8	<0.0001
PAP (mmHg)	41±13	58±17	<0.0001	48±9	70±14	<0.0001

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

Table 3. The magnitude of change in hemodynamic parameters of group A and B patients between rest and peak dobutamine infusion

	Group A (n:39)	Group B (n:18)	p
Delta PAP (mmHg)	16 ± 6	23 ± 8	0.007
Delta mean gradient (mmHg)	6 ± 3	12 ± 6	<0.0001
Delta peak gradient (mmHg)	9 ± 4	14 ± 7	0.008

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

Table 4. Determinants of the magnitude of change in pulmonary artery pressure

	B	Beta	p	95% CI
Mitral valve area (cm^2)	-9.4	-0.5	0.003	-(15.4-3.2)
Subvalvular echo score	5.3	0.4	0.001	2.1-8.4
Baseline PAP (mmHg)	0.3	0.5	p<0.0001	0.1-0.4
Baseline mean gradient (mmHg)	1.1	0.7	0.001	0.5-1.7

Constant 19.3
PAP: pulmonary artery pressure p<0.05 significant

monary artery systolic pressure, mean and peak mitral gradient increased from 48±9 mmHg, 12±5 mmHg and 21±5 mmHg, respectively, at baseline to 70±14 mmHg, 23±8 mmHg and 35±10 mmHg with dobutamine infusion (p<0.0001, p<0.0001, p<0.0001, respectively) (table 2). Although significant increment in these parameters was measured in both groups, statistical analysis showed a significant difference (p:0.007, p<0.0001, p:0.008, respectively) in favor of a larger increment in pulmonary artery pressure, mean and peak mitral gradient in the patients who developed dyspnea (table 3).

Determinants of the dobutamine induced change in pulmonary artery pressure: The correlation of the magnitude of change in pulmonary artery pressure with different variables was examined by using a linear regression analysis. Mean mitral gradient at rest (p=0.001), baseline pulmonary artery pressure (p<0.0001) and, subvalvular mitral score (p=0.001) showed significant positive linear correlation, measured mitral valve area (p=0.003) showed significant negative linear correlation. The mitral valve area , subvalvular mitral score, mean mitral gradient at rest and baseline pulmonary artery pressure were found to be determinants of the dobutamine induced change in pulmonary artery pressure (Table 4).

DISCUSSION

In mitral stenosis, stress induced changes are not uniform. Dobutamine stress echocardiography provides an objective hemodynamic means to support a rational clinic decision in assessing mitral valve reserve capacity as a noninvasive method. Mitral valve reserve capacity can be determined by the magnitude of change in hemodynamic parameters during dobutamine infusion. Sharon et al. 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 [7]. Another study, using by 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 [11]. In our study, though dobutamine infusion significantly increased pulmonary artery systolic pressure, mean and peak transmitral gradients in all patients, the magnitude of change in these parameters were significantly higher in group who developed dyspnea than the other group who remai-

ned asymptomatic. In above mentioned studies, patients with atrial fibrillation and sinus rhythm were enrolled into study group. We designed our study population with patients in sinus rhythm for the purpose that the influence of rhythm on cardiac output and hemodynamic response could be excluded. Our results confirmed previous studies and showed that the magnitude of changes in all hemodynamic parameters was significantly higher in patients who had dyspnea during the test . The test results demonstrated that dobutamine infusion might provoke dyspnea in patients who had diminished mitral valve reserve capacity.

Although there were some studies on usefulness of stress echocardiography in the assessment of the severity of mitral stenosis, we were unable to find a study assessing the main determinants of hemodynamic response. Dahan et al.[12] using bicycle exercise in 27 patients with a wide range of mitral stenosis (0.50 to 2.25 cm^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. Our study is the first study that subvalvular mitral score was thought as an responsible factor and evaluated in different hemodynamic response during dobutamine infusion. Although total echocardographic mitral score was not different in patients between who had provoked dyspnea and who did not, subvalvular mitral score was significantly higher in patients who had dyspnea. As our study results, resting pulmonary artery pressure, baseline mean mitral gradient, mitral valve area and subvalvular mitral score were found to be correlated with pulmonary artery pressure response. We suggest that the magnitude of change in pulmonary artery pressure can be calculated by these variables before dobutamine infusion.

In this study, the hemodynamic findings significantly impacted the clinical decision making process in 12 patients (21%). In one study, the clinic decision was affected by the test response in %84 of cases [13]. In this study, patients were referred for moderate symptoms of dyspnea, and some patients had additional regurgitant lesions, while our patients had NHYA classes I and II, isolated mitral stenosis.

Limitations

A potential limitation of this study is the lack of invasive correlation with the noninvasive measurements. Several previous studies [14,5,15,16] have shown an extremely high correlation between noninvasive and invasive mitral valve gradient in native and prosthetic valves. In addition, another study have demonstrated invasive evaluation of pulmonary artery pressure at rest and exercise was correlated with noninvasive measurements [17]. Thus, we think that there is adequate prior evidence to validate this method.

In conclusion, patients who had provoked dyspnea during the dobutamine infusion had a greater increase in hemodynamic parameters than patients who did not. We think that pulmonary artery pressure response can be predicted by baseline pulmonary artery pressure, mean gradient, mitral valve area and subvalvular echo score.

REFERENCES

1. Reichec N, Shelburne JC, Perloff JK: Clinical aspects of rheumatic valvular disease. Prog Cardiovasc Dis 1973;15: 461-4

2. Wood P: An apprecition of mitral stenosis. Br Med J 1954;1: 1051-1113

3. Nakhjavan FK, Katz MR, Shedrovilzky H, Maranhao V, Goldberg H: Hemodynamic effects of exercise, catecholamine stimulation and tachycardia in mitral stenosis and sinus rhythm at comparable heart rates. Am J Cardiol 1969;23: 659-64

4. Arani DT, Carleton RA: The deleterious role of tachycardia in mitral stenosis. Circulation 1967;36: 511-5

5. Sagar KB, Wann S, Paulson WJH, Lewis S: Role of exercise Doppler echocardiography in isolated mitral stenosis. Chest 1987; 92: 27-30

6. Tamai J, Nagata S, Akaike M, et al: Improvement in mitral flow dynamics during exercise after percutaneous transvenous mitral commissurotomy: noninvasive evaluation using continuous wave Doppler technique. Circulation 1990; 81: 46-51

7. Hecker SL, Zabalgoitia M, Ashline P, Oneschuk L, O'Rourke RA, Herrera CS: Comparison of exercise and dobutamine stress echocardiography in assessing mitral stenosis. American J Cardiol 1997; 80: 1374-7

8. Hatle L, Angelsen B: Doppler Ultrasound in Cardiolgy: Physical Principles and Clinical Applications. Second ed. Philadelphia, PA: Lea and Febiger, 1995: 110-24

9. Yock PG, Popp RL: Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in pati-

ents with tricuspid regurgitation. Circulation 1984; 70: 657-62

10. Wilkins GT, Weyman Ae, Abascal VM, Block PC, Palacios IF: Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988; 60: 299-308

11. Hwang MH, Pacold I, Piao ZE, Engelmeier R, Scanlon PJ, Loeb HS: The usefulness of dobutamine in the assessment of the severity of mitral stenosis. Am Heart J 1986; 111: 312-15

12. Dahan M, Paillole C, Martin D, Gourgon R: Determinants of stroke volume response to exercise in patients with mitral stenosis: A Doppler echocardiographic study. J Am Coll Cardiol 1993; 21: 384-9

13. Tunick PA, Freedberg RS, Gargiulo A, Krazon I: Exercise Doppler echocardiography as an aid to clinical decision making in mitral valve disease. J Am Soc Echocardiography 1992; 5: 225-30

14. Gonzales MA, Child JS, Krivokapich J: Comparison of two-dimensional and Doppler echocardiography and intracardiac hemodynamic for quantification of mitral stenosis. Am J Cardiol 1987; 60: 327-32

15. Tatineni S, Barner HB, Pearson AC, Halbe D, Woodruff R, Labovitz J: Rest and exercise evaluation of St. Jude Medical and Medtronic Hall prostheses: influence of primary lesion, valvular type, valvular size and left ventricular function. Circulation 1989; 80:16-23

16. Schwartz K, Meltzer RS: Exercise Doppler echocardiography in patients with mitral prosthetic valves. Am Heart J 1989; 118: 755-9

17. Himelman RB, Stulbarg M, Kirchner B, et al: Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. Circulation 1989; 79: 863-71