ORİJİNAL ARAŞTIRMALAR
ORIGINAL INVESTIGATIONS

Effective Regurgitant Orifice Area of Rheumatic Mitral Insufficiency: Response to Angiotensin Converting Enzyme Inhibitor Treatment

Romatizmal Mitral Yetersizliğinde Efektif Regürjitan Orifisi: Anjiyotensin Konverting Enzim İnhibitörü Tedavisine Cevap

F.Sedef Tunaoğlu, MD, Rana Olguntürk, MD, Serdar Kula, MD, Deniz Oğuz*, MD

Gazi University Medical Faculty, Department of Pediatric Cardiology
Dr. Sami Ulus Children Hospital, Department of Pediatric Cardiology*, *Ankara, Turkey*

Abstract

Objective: This study was designed for quantification of mitral regurgitation by echocardiographic measurements such as regurgitant volume (RV), regurgitant fraction (RF) and effective regurgitant orifice area (EROA), and to assess the effect of angiotensin converting enzyme inhibitor (ACEI) therapy on these measurements.
Methods: Patients with rheumatic mitral insufficiency were divided into two groups: Study group (SG)-10 females, 2 males aged 10-18years, body surface area 1.49±0.05m2, receiving digoxin therapy for at least one year and Control group (CG)-8 females, 4 males, aged 8-17years, body surface area 1.38±0.07m2, with no treatment. Patients in the two groups had no symptoms of cardiac failure. Angiotensin converting enzyme inhibitor therapy was given to SG patients on admission. Echocardiographic examinations were applied on admission and at the 20th day of therapy with ACEI and digoxin.
Results: Study group's left ventricular end-diastolic volume (108.03±41.21 ml/m2), mitral stroke volume (510.37±321.58 ml/m2) and regurgitant volume (423.48±305.00 ml/m2) were significantly higher ($p<0.05$) on admission than in the CG (81.98±21.53 ml/m2, 315.34±207.38mL/m2 and 245.77±179.84mlm2, respectively). Aortic stroke volume at the 20th day of therapy was significantly higher in SG than in the CG. Therapy with ACEI decreased significantly SG's left ventricular diastolic volume.
Conclusion: Angiotensin converting enzyme inhibitors should be started at an early stage of mitral regurgitation. The effective regurgitant orifice area is a feasible and easy method for the outpatient follow-up of mitral regurgitation. *(Anadolu Kardiyol Derg 2004; 4: 3-7)*
Key Words: EROA, mitral insufficiency, ACEI, rheumatic heart disease

Özet

Amaç: Bu çalışma romatizmal mitral yetersizliğini ekokardiyografik ölçümlerle - regürjitan volüm (RV), regürjitan fraksiyon (RF) ve efektif regürjitan orifis alanı (EROA)- derecelendirmek ve anjiyotensin konverting enzim inhibitörü (ACEİ) tedavisinin bu ölçümlere olan etkisini belirlemek amacıyla planlanmıştır.
Yöntem: Romatizmal mitral yetersizliği olan hastalar: Çalışma grubu (ÇG) (en az 1 yıldır digoksin tedavisi alan 10 kadın, 2 erkek, 10-18 yaş, vücut alanı ort:1.49±0.05m2) ve Kontrol grubu (KG) (tedavi almayan 8 kadın, 4 erkek, 8-17 yaş, vucüt alanı 1.38±m2) olmak üzere iki gruba ayrılarak incelenmiştir. Her iki grupta da kalp yetersizliği bulgusu olan hasta bulunmamaktadır. Grupların ekokardiyografik ölçümleri yapıldıktan sonra ÇG'nun tedavisine ACEİ tedavisi eklenmiş ve ACEİ tedavisinin 20. günü ölçümler yinelenmiştir.
Sonuçlar: Çalışma grubunun sol ventrikül diyastolik volumü (108.03±41.21 ml/m2), mitral strok volumü (510.37±321.58 ml/m2) ve regürjitan volumü (423.48±305.00 ml/m2) olup, KG'nun değerlerinden sırasıyla (81.98±21.53 ml/m2, 315.34±207.38mL/m2, 245.77±179.84ml/m2) belirgin olarak yüksek bulunmuş ($p<0.05$), ACEİ tedavisi ile bu fark ortadan kalkmıştır. Çalışma grubunda sol ventrikül diyastolik volumü ACEI tedavisi ile belirgin olarak azalmıştır ve tedavinin 20.gününde aort strok volümü KG'nin değerinden belirgin olarak yüksek bulunmuştur.
Sonuç: Anjiyotensin konverting enzim inhibitörü tedavisi romatizmal mitral yetersizlikli hastaların kalp yetersizliği tedavisine erken evrede eklenmelidir. Mitral yetersizliğinin derecesini ve tedaviye verdiği yanıtı belirlemede ekokardiyografi kolay uygulanan ve etkin bir yöntem olarak kullanılabilir. *(Anadolu Kardiyol Derg 2004; 4: 3-7)*
Anahtar Kelimeler: EROA, mitral yetersizliği, ACEİ, romatizmal kalp hastalığı

Introduction

Mitral regurgitation (MR) induces a change in the loading conditions that could affect the indices of left ventricular function (1). Vasoactive drugs such as angiotensin converting enzyme inhibitors are used in severe MR in addition to digoxin therapy (2). Severe MR often produces minimal symptoms but still results in a high incidence of left ventricular dysfunction that might affect postoperative survival (3). Deter-

Adress for correspondence: F.Sedef Tunaoğlu, MD, Gazi University, Gazi Hospital Department of Pediatric Cardiology, Beşevler 06510 Ankara-Turkey, Fax: 0090 312 212 26 18, e mail: fst@gazi.edu.tr

mination of the severity of MR is of vital importance in the decision of the time and type of surgery. For this purpose new, easier and more feasible methods are developed for the follow-up of MR (4,5).

This prospective study was planned for the quantification of MR by echocardiographic measurements such as regurgitant volume (RV), regurgitant fraction (RF) and effective regurgitant orifice area (EROA), and to assess the effect of ACEI therapy on these measurements.

Material and Methods

This study was performed on 24 patients with rheumatic MR who are followed in the pediatric cardiology outpatient clinic. Patients were divided into two groups. The study group (SG) consisted of 10 females and 2 males, aged 10-18 years, mean: 14.0±0.72 years. Due to symptoms like tachycardia or cardiomegaly on chest X-ray, digoxin therapy was started in them for at least one year ago. The other group was the control group (CG) consisted of 8 females and 4 males, aged 8-17 years, (mean: 13.5±0.91 years). They were asymptomatic patients and followed yearly in the outpatient clinic. They received no therapy. Body surface areas of SG and CG patients were 1.49±0.05 m2 (1.39-1.58) and 1.38±0.07 m2 (0.96-1.76), respectively. Body weights of the DG and CG's patients were 50.79±3.24 kg (45.00-56.00) and 46.16±12.89 kg (26.00-68.00), respectively. All the patients in both groups were asymptomatic during the study, were in sinus rhythm, and none of them had signs of aortic insufficiency.

On admission ACEI therapy (Enapril 0.5 mg/kg, over 30 kgs 10 mg/day, b.i.d, p.o) was given to SG patients. Echocardiographic examinations were applied in the DG and CG patients on admission, and at the 20th day of therapy in SG. Doppler and 2-dimensional echocardiographic examinations were performed by the same echocardiographer, using the RT 6800 General Electric machine, equipped with 2.2MHz and 3.5 MHz transducers. The mitral annulus in diastole was measured at the point of insertion of the leaflets. Continuous wave Doppler echocardiography was recorded with an apical window guided by colour flow imaging to obtain the maximum velocities of the regurgitant jet, and the velocity time integrals (VTI) of the regurgitant jet (Fig.1) and mitral flow VTI (Fig.2) were computed. The aortic annulus in systole was measured at the point of insertion of leaflet, and aortic flow pulse Doppler signals were recorded from apical two-chamber view with further computation of VTI (Fig.3). All measurements were repeated in three consecutive cardiac cycles by the same echocardiographer.

Left ventricular systolic functions were determined by Teicholz method and indexed to body surface area.

Mitral and aortic valve areas were calculated by the πr^2 formula. Mitral and aortic stroke volumes were obtained by multiplying the valve area by the respective VTI determined by pulsed Doppler imaging, then stroke volumes were indexed to body surface area.

Regurgitant volume (RV) was calculated as the difference between forward stroke volumes across the mitral valve and the aortic valve, and indexed to body surface area.

Regurgitant fraction (RF) was calculated as RV divided by the forward stroke volume across the mitral valve.

Effective regurgitant orifice area (EROA) was calculated as RV divided by the VTI of regurgitant jet measured from continuous wave Doppler tracing of mitral valve (6).

Descriptive results were indexed to body surface area, and expressed as mean value±SD (minimum-maximum). Statistical analysis was performed by Student's t test employing SPSS 9.0 (The Statistical Package for the Social Science Program) for Windows statistic package. Statistical difference was represented by a probability value of $p \leq 0.05$.

Results

Left ventricular end-diastolic volume (LVEDV) of the study group was 108.03± 41.21 ml/m2 (55.07-184.18) on admission, and 83.17± 25.25 ml/m2 (48.84-133.33) at the 20th day of therapy with ACEI. The decrease in the SG's LVEDV value was significant ($p<0.05$) (Table 1).

Comparison of SG's LVEDV with CG one, showed that SG's LVEDV (81.98 ± 21.53 ml/m2) was significantly higher than in the CG on admission; but at the 20th day of therapy, there was no significant difference between the two groups (Table 1). Also, other parameters of systolic functions of SG and CG did not show any significant difference.

Annular diameters, VTI and stroke volumes of mitral and aortic valves between the groups are shown in Table 1. There was significant difference in the VTI of mitral valve between the groups on admission. This difference disappeared at the 20th day of therapy ($p>0.05$). Mitral valve VTI values were decreased slightly by ACEI therapy. However, this decrease was not significant.

There was a significant difference in the mitral stroke volumes between the groups on admission. This difference was not found at the 20th day of therapy. Mitral stroke volume of the SG decreased from 510.37±321.58 ml/m^2 (123.03-1116.14) to 475.13±262.94 ml/m^2 (111.81-914.10) by the ACEI therapy ($p>0.05$).

There was no significant difference in the aortic annular diameter between the groups on admission and at the 20th day of therapy.

The VTI of aortic valve of the SG and CG on admission were 26.02±5.97 cm /m^2 (19.30-36.97) and 23.16±3.87 cm /m2 (17.55-32.87), respectively, and there was a significant difference between these values ($p<0.05$). Aortic valve VTI was 26.16±8.42 cm /m^2 (14.27-42.07) at the 20th day of therapy in SG and it was significantly different from the CG`s value. However, no significant difference occured in the SG`s VTI of the aortic valve during the therapy.

Aortic stroke volumes of SG and CG on the admission were 86.89±59.11 ml/ m2 (25.10-215.53) and 82.91±28.29 ml/m2 (36.49-145.24), respectively. Although there was no significant difference between groups on admission, SG`s aortic stroke volume [(94.72±70.11 ml/m2 (32.36-239.28)] at the 20th day of the therapy was significantly higher than in the CG.

Regurgitant jet VTI values of the groups are shown in Table 1. The SG's values were higher than the CG values on the admission, and they decreased by the therapy. However, this decrease was not significant.

Study group regurgitant values were significantly higher when compared to CG on admission but further decreased at the 20th day of therapy, ameliorating significant difference between the SG and CG's values.

There was significant difference between two groups in the DG's and CG's regurgitant fraction values on admission. Further SG`s RF values decreased by the therapy, but this change was not significant.

There were also significant differences in EROA between SG and CG on admission and at the 20th day of therapy. We could not find any significant difference in the SG's values on admission and at the 20th day of therapy.

Discussion

Mitral insuffiency is the most frequent valvular disease caused by rheumatic fever which is one of the most important health problems in the developing countries (7). Determination of the severity of mitral regurgitation is of major importance for the decision of the type and time of the therapy. Mitral valve repair has been suggested as it provides a better outcome than valve replacement for mitral regurgitation (8). The low operative risk of valve repair is an incentive to consider surgery at an early stage in the cour-

Table 1. Echocardiographic and clinial parameters of the patients

	CONTROL GROUP	STUDY GROUP	
		Baseline, (digoxin alone)	At the 20th day of treatment ACE inhibitors + digoxin
LVEDV, (ml/m2)	81.98±21.53[a]	108.03±41.21[c]	83.17±25.25
Mitral anulus, (cm)	4.37±0.66	4.90±0.94	4.94±0.99
Mitral VTI, (cm)	27.78±10.93[a]	36.69±13.88	33.81±8.82
Mitral stroke volume, (ml/m^2)	315.34±207.38[a]	510.37±321.58	475.13±262.94
Aortic annulus, (cm)	2.45±0.35	2.45±0.48	2.50±0.47
Aortic VTI, (cm)	23.16±3.87[ab]	26.02±5.97	26.16±8.42
Aortic stroke volume, (ml/m^2)	82.91±28.29[b]	86.89±59.11	94.72±70.11
Regurgitant VTI, (cm)	65.54±53.60	71.32±45.88	66.76±53.12
Regurgitant volume, (ml/m^2)	245.77±179.94[a]	423.48±305.00	370.38±242.97
Regurgitant fraction, (%)	0.69±0.14[a]	0.78±0.15	0.74±0.22
EROA, (mm^2 /m^2)	10.43±9.62 a[b]	15.5±14.5	15.8±17.7
Heart rate, (bpm)	101.83±3.09	104.33±3.18	105.25±4.69
Systolic blood pressure, (mmHg)	108.50±3.05	114.17±1.93	109.17±2.37 values.

a- significant difference between CG and SG on admission, ($p>0.05$).
b- significant difference between CG and SG at the 20th day of treatment, ($p<0.05$).
c- significant difference between on admission and at the 20th day in SG, ($p>0.05$).

se of the disease before the advent of left ventricular dysfunction. However severe regurgitation often produces minimal symptoms but still results in a high incidence of left ventricular dysfunction that might affect postoperative survival (9). There is a need for the reliable, reproducible, non-invasive method for determination of the accurate quantification of valve regurgitation. As angiocardiography is an invasive method, it is not used routinely in the follow-up clinics (10). Doppler echocardiography has been proved to be the most accurate of current non-invasive techniques for mitral regurgitation quantification (11). Doppler echocardiographic methods are also able to distinguish mild, moderate and severe mitral regurgitation. Enriquez-Sarano et al (12) reported that quantitative Doppler can provide not only the RF (like angiocardiography) but also RV and the EROA. Experimental (13,14) and clinical (15-17) data indicate that the degree of regurgitation is variable with hemodynamic manipulation, EROA is usually less variable , and is not affected by heart rate (18). Enriquez- Sarano et al (12) calculated the EROA by Doppler echocardiography, and compared it with the color-flow mapping, angiography, surgical classification, regurgitant fraction and volume. They have stated that the value of effective regurgitant orifice calculation has confirmed not only the lesion but also the hemodynamic consequences of the valve lesion by a strong correlation.

In our study, although patients were asymptomatic, SG had higher left ventricular end-diastolic volume, mitral stroke volume, regurgitant volume and regurgitant fraction. However aortic stroke volume of the groups were not different. Indicating that although SG`s left ventricle works hard, this volume load is not reflected to the systemic circulation.

This volume load was decreased by the ACEI therapy. Besides this improvement, aortic flow was slightly increased in the SG while mitral stroke volume decreased, which means that cardiac stress has decreased and peripheral circulation has improved. Although ACEI therapy caused some changes in the parameters used to calculate EROA, the actual EROA values did not change. Short observation period of the study may be the reason for this result. In order to observe the more prominent effects of ACEI therapy on EROA, the patients should be followed for a longer period of time during ACEI therapy.

According to the Dujardin et al. study (19) in adult patients, our EROA results are considered to be mild regurgitation. However, our RV and RF measurements are higher than reported by the existing limited studies (20). We need more data for the definition of cut off values of RV, RF and EROA for the determination of mild, moderate and severe mitral regurgitation in children.

According to our results even if patients have digoxin therapy, left ventricular loading conditions may progress silently. Therefore ACEI should be started at an early stage of mitral regurgitation treatment. This will decrease volume overload, and improve left ventricular functions, and the time of surgical therapy might be delayed (21). The effective regurgitant orifice area is an important index of the severity of regurgitation, and a feasible and easy method for the outpatient follow-up clinics.

Study Limitations

Observation of the long-term ACEI therapy may clear up it's effects on EROA.

Body weight of children are greatly variable with their age. Using the body surface can correct this variation. Placement of the sample volume of Doppler is an important issue which is effective on the measurements/calculations.

Eccentricity of the regurgitant jet may affect the VTI measurements. Color guided Doppler study can solve this problem. Small variation in annular diameter results in a large variation in the calculated valve area. This variation can be limited with increased experience, and by using the same echocardiographer in outpatient clinics for the follow up.

References

1. El-Said GM, Refaee MM, Sorour KA, El-Said HG. Rheumatic fever and rheumatic heart disease. In: Garson A, Bricker JT, Fisher DJ, Neish SR, editors. The Science and Practice of Pediatric Cardiology. 2nd ed. Baltimore: William&Wilkins; 1998: p.1691-724.
2. Chatterjee K, Parmley WW, Cohn JN. A comparative multicenter study of captopril in congestive heart failure: hemodynamic effects and long-term response. Am Heart J 1985;110:439-47.
3. Braunwald E. Valvular heart disease. In: Braunwald E, editor. Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, PA: WB Saunders Co; 1992: p.1018-28.
4. Wu YT, Chang AC, Chin AJ. Semiquantitative assessment of mitral regurgitation by Doppler color flow imaging in patients aged < 20 years. Am J Cardiol 1993;71:727-32.
5. Flachskampf F. Recent progresses in quantitative echocardiography. Current Opin Cardiol 1995;10:634-9.
6. Enriquez-Sarano ME, Bailey KR, Seward JB, Tajik AJ, Krohn MJ, Mays JM. Quantitative Doppler assessment

of valvular regurgitation . Circulation 1993;87:841-8.
7. Olguntürk R, Aydın GB, Tunaoğlu FS, Akalın N. Rheumatic heart disease prevalence among school children in Ankara, Turkey. Turk J Pediatr 1999;41:201-6.
8. Enriquez-Sarano ME, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. Circulation 1995;91:1022-8.
9. Enriquez-Sarano ME, Tajik AJ, Hartzell VS, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation 1994;90:830-7.
10. Croft CH, Lipscomb K, Mathis K, et al. Limitations of qualitative angiographic grading in aortic or mitral regurgitation. Am J Cardiol 1984;53:1593-8.
11. Zhang Y, Ihlen H, Myhre E, Levostad K, Nitter-Hauge S. Measurement of mitral regurgitation by Doppler echocardiography. Br Heart J 1985;54:384-91.
12. Enriquez-Sarano M, Seward JB, Bailey KR, Tajik J. Effective regurgitant orifice area : a noninvasive Doppler development of an old hemodynamic concept. J Am Coll Cardiol 1994;23:443-51.
13. Yoran C, Yellin EL, Becker RM, Gabbay S, Frater RWM, Sonnenblick EH. Dynamic aspects of acute mitral regurgitation: effects of ventricular volume, pressure and contractility on the effective regurgitant orifice area. Circulation 1979;60:170-6.
14. Simpson IA, Valdes-Cruz LM, Sahn DJ, Murillo A, Tamura T, Chung KJ. Doppler color flow mapping of simulated in vitro regurgitant jets: evaluation of the effects of orifice size and hemodynamic variables. J Am Coll Cardiol 1989;13: 1195-207.
15. Keren G, Laniado S, Sonnenblick EH, LeJemtel TH. Dynamics of functional mitral regurgitation during dobutamine therapy in patients with severe congestive heart failure: a Doppler echocardiographic study. Am Heart J 1989;118:748-54.
16. Yoran C, Yelkin EL, Becker RM, Gabbay S, Frater RW, Sonnenblick EH. Mechanism of reduction of mitral regurgitation with vasodilator therapy. Am J Cardiol 1979;43:773-7.
17. Sasayama S, Ohyagi A, Lee JD, et al. Effect of vasodilator therapy in regurgitant valvular disease. Jpn Circ J 1982;46:443-51.
18. Yoran C, Yelkin EL, Hori M, et al. Effects of heart rate on experimentally produced mitral regurgitation in dogs. Am J Cardiol 1983;52:1345-9.
19. Dujardin KS, Enriquez-Sarano M, Bailey KR, et al. Dynamic aspects of acute mitral regurgitation: effects of ventricular volume, pressure and contractility on the effective regurgitant orifice area. Circulation 1979; 60:170-6.
20. Calabro R, Pisacane C, Pacileo G, Russo MG. Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation. Am Heart J 1999;138: 955-61.
21. Pisacane C, Pacileo G, Santoro G et al. New insights in the pathophysiology of mitral and aortic regurgitation in pediatric age: role of angiotensin-converting enzyme inhibitor therapy. Ital Heart J 2001;2: 100-6.

Hava Kuvvetleri Hastanesi Film Fotoğraf Ekibi

"Onurumuz modern Türk Kadınının simgesi, Türkiye Cumhuriyeti'nin ilk kadın pilotu ve Dünya'nın ilk kadın savaş pilotu Sabiha Gökçen Hanımefendi (önde, sağdan ikinci) 1998 yılında Eskişehir Hava Hastanesi'nde onuruna yapılan bir merasimde. Fizyolojik Eğitim Merkezi GATA Hava ve Uzay Hekimliği Anabilim Dalı başkanlarıyla birlikte bir anı."