Pulmonary Functions in Patients with Mitral Stenosis in Various Stages of Disease: Effects of inhaled corticosteroid on pulmonary functions in mitral stenosis

ÇEŞİTLİ EVRELERDEKİ MİTRAL STENOZLU HASTALARDA SOLUNUM FONKSİYONLARI: İNHALE KORTİKOSTEROİDLERİN ETKİSİ

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Summary-

Objective: The aim of the study was to assess pulmonary function in patients with mitral stenosis at different stages and whether treatment with inhaled budesonide improves pulmonary dysfunction seen in mitral stenosis or not.

Materials and Methods: The study group consisted of 43 patients with mitral stenosis. 35 age-matched, healthy subjects were selected as a control group. Each patient was assessed by echocardiographic examination, pulmonary function test and CO diffusion test. Second phase of the study was randomised, double blind and placebo controlled. In this phase, among 43 mitral stenosis, 20 patients, who have a pulmonary dysfunction, were selected. These patients received placebo or inhaled budesonide (400 microg/day) for four weeks. Then, pulmonary function tests were repeated.

Results: The mean predicted values for FVC%, FEV_1%, FEV_1/FVC and $FEF_{25-75\%}$ in the patients with mitral stenosis were significantly lower than those in healthy control subjects ($p<0.05$), whereas DLCO/VA did not significantly differ among the two groups. Correlation analysis showed that there were significant positive correlation between mitral valve area (MVA) and FVC% ($r=0.52$, $p<0.001$), MVA and FEV_1% ($r=0.59$, pO.OOl), MVA and FEV_1/FVC ($r=0.46$, pO.OOl), MVA and FEF_{25-75}% ($r=0.57$, pO.001). After four weeks of treatment, only $FEF_{25-75\%}$ increased significantly in inhaled budesonide group compared to placebo group ($p<0.01$).

Conclusion: Pulmonary dysfunction might occur in patients with mitral stenosis especially in severe cases, and inhaled budesonide did not seem to improve pulmonary functions in these patients.

Key Words: Mitral stenosis, Pulmonary function tests, Carbon monoxide (DLCO) diffusion test, Inhaled budesonide. Inhaled corticosteroid

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Ozet

Amaç: Bu çalışmada çeşitli evrelerdeki mitral stcnozlu hastalarda solunum fonksiyonlarını değerlendirmek ve bu hastalardaki solunum fonksiyon bozukluğuna inhale budesonidin etkisini araştırmak amaçlandı.

Materyal ve Metod: Çalışma grubu 43 mitral stenozlu hastadan oluşuyordu. Yaş ve cins karşılaştırması yapılmış 35 sağlıklı kişi kontrol grubu olarak seçildi. Her hastaya ekokardiografık inceleme, solunum fonksiyon testleri ve CO difıizyon testi yapıldı. Çalışmanın ikinci bölümü çift kör, random ve plasebo kontrollü idi. Bu bölümde, 43 mitral stenozlu hastadan solunum fonksiyon bozukluğu saptanan 20 hasta dört hafta süreyle inhale budesonide (400 microgram/gün) ya da inhale plasebo kullandı. Bu hastaların dört hafta sonra solunum fonksiyonları tekrarlandı.

Bulgular: Mitral stenozlularda FEV_1, FVC, FEV_1/FVC ve $FEF_{.5-75\%}$ parametreleri kontrol grubuna göre anlamlı derecede düşük bulunurken ($p<0.05$), DLCO/VA'da anlamlı bir farklılık bulunmadı. Mitral kapak alanı (MVA) ile FVC% ($r=0.52$, $p<0.001$), MVA ile FEV_1% ($r=0.59$, pO.OOl), MVA ile FEV_1/FVC ($r=0.46$, pO.OOl) ve MVA ile $FEF_{.5-75\%}$ ($r=0.57$, pO.OOl) arasında pozitif korelasyon bulundu. Dört haftalık inhaler tedavi sonrasında inhale budesonide grubunda sadece $FEF_{.5-75\%}$ parametresinde istatistiksel olarak anlamlı artış saptandı (pO.01).

Sonuç: Mitral stenozlu hastalarda, özellikle de ağır derecede olanlarında daha fazla olmak üzere solunum fonksiyon bozukluğu görülebilmekte olup, bu hastalardaki solunum fonksiyon bozukluğuna inhale budesonidin önemli derecede düzeltici bir etkisi bulunmamıştır.

Anahtar Kelimeler: Mitral stenoz, Solunum fonksiyon testi, CO difüzyon testi, İnhale budesonide, İnhale kortikosteroid

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Disorders of the heart frequently cause pulmonary dysfunction because of the close structural and functional association of the heart and lungs (1,2). Various studies showed that pulmonary func-

tions are adversely affected by mitral stenosis (3-18). The major disturbances of pulmonary function that have been reported in such patients with mitral stenosis are increase of total airway resistance (5,16), peripheral airway obstruction (4,9,12), large airway obstruction (5,14), bronchial hyperreactivity (4-8), increase of diurnal variation of PEF rate (7), restrictive ventilatory impairment (16), alterations in lung pressure-volume curve with a reduction in expiratory compliance (16), regional ventilation/perfusion mismatching (17) and diminishment in pulmonary diffusing capacity (3,9,15). It has been reported that pulmonary dysfunction generally seen in patients with mitral stenosis were partially ameliorated after correction of mitral valve by mitral surgery (10,11), PTMC (3) or PBMV (6,9). But it is still not clear whether treatment with inhaled steroid can improve pulmonary dysfunction seen in mitral stenosis or not.

In the present study, we aimed to assess pulmonary functions in patients with mitral stenosis at different stages and whether treatment with inhaled budesonide ameliorates pulmonary dysfunction seen in mitral stenosis or not.

Materials and Methods

We studied on 43 patients (38 females and 5 males, age range= 17-70) with mitral stenosis who were admitted to the Department of Cardiology at Mersin University. 35 age-matched, healthy subjects were included as a control group. Patients with known pulmonary diseases (e.g. bronchial asthma, chronic obstructive pulmonary disease), history of atopy, uncontrolled hypertension, aortic or tricuspid valve diseases, ischemic left heart damage, recent (within 8 weeks) airway infection, cigarette smoking within the preceding 10 years were excluded.

Each of the patients was assessed by clinical, electrocardiographic, echocardiographic examination, chest X-ray, pulmonary function tests and carbon monoxide (DLCO) diffusion test. Second phase of the study was randomised, double blind, and placebo controlled. After evaluation of pulmonary function test, among 43 patients with mitral stenosis, 20 patients, who have a pulmonary dysfunction, were selected. These patients randomly received placebo (10 patients) or inhaled budesonide (400 microgram/day) (10 patients) for four weeks. After four weeks of the treatment we repeated pulmonary function test of these patients. Throughout the study period, the same doses of medicines (diuretics, calcium antagonists, and angiotensin converting enzyme inhibitors) were given all the patients with mitral stenosis.

Doppler Echocardiographic Evaluation: M-Mode, two-dimensional echocardiography, and continuous-wave Doppler studies were obtained with Wingmed system five echocardiography units. Using established methods, we measured left atrium dimensions (LA) and fractional shortening (FS) of left ventricle as on systolic index. Short axis views of two-dimensional echocardiography were used primarily to quantitate the mitral valve area (MVA). Pulmonary artery pressures (PAP) and mitral valve pressure gradients (MVG) were measured according to a modified Bernoulli equation (gradient = peak velocity^2 x 4), with gradient in millimeters of mercury. A11 measurements represent the average of at least three cardiac cycles.

Pulmonary function tests: Pulmonary function tests were measured with a computer assisted spirometry (Vmax22D, SensorMedics, California, USA). Several tests were employed to measure pulmonary function. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEVi), FEVVFVC, maximal expiratory flow at 25-75 percent of VC (FEF_{25-75} %), peak expiratory flow (PEF) and diffusion capacity for carbon monoxide per unit volume (DLCO/VA) were obtained. Carbon monoxide diffusing capacity (DLCO) was measured by the single-breath method.

Statistical Analysis: Data analyses were performed with the statistical package for the social science 9.05 (SPSS 9.05). Results are presented as mean values + SD. Independent t test was used to compare the differences of two means and one-way ANOVA analysis was used when there is more than two groups. Paired t test was used to compare the differences of a variable between

before and after treatment in a same group. Correlation analyses were performed to assess relation between pulmonary functions and echocardiographic parameters. A value of $p < 0.05$ was considered statistically significant.

Results

The mean age of 43 patients of mitral stenosis (38 female and 5 male) and of 35 control subjects (30 female and 5 male) were 48.1 ± 13.6 and 44.1 ± 13.1 respectively. 29.6% of patients with mitral stenosis were ex-smoker and 70.4% non-smoker. On the other hand 28.5% of control subjects were ex-smoker and 71.5% non-smoker. There were no significant differences in age, sex or smoking status between patients and control subjects.

In whole of patients with mitral stenosis, 24 (55.8%) patients had minimal degree of mitral regurgitation.

The results of echocardiographic evaluation and pulmonary function tests are presented in Table 1.

Echocardiographic evaluation revealed that 28 patients had mild mitral stenosis (MVA> 1.5 cm^2), 10 patients had moderate (MVA< 1.5 cm^2 and > 1 cm^2), and 5 patients had severe mitral stenosis (MVA< 1 cm^2).

FVC%, FEV, %, FEV,/ FVC, FEF $_{25}$-$_{75}$ % and DLCO/VA were found lower in moderate-severe mitral stenosis than the mild cases, but there were not significant differences among the mild, moderate and severe cases in the one-way ANOVA analysis.

Correlation analysis between MVA and pulmonary function parameters showed that there were significant positive correlation between MVA and FVC% (r=0.52, p< 0.001), MVA and FEV,% (r= 0.59, pO.OOl), MVA and FEV1/FVC (r=0.46, pO.OOl), MVA and FEF$_{25-75}$% (r=0.57, pO.OOl). There was no significant correlation between MVA and DLCO/VA.

Changes in the MVG correlated negatively with the changes in FVC% (r= -0.43, p< 0.001), in FEV,% (r= -0.49, pO.OOl), in FEV,/ FVC (r=-0.35, p<0.005), in FEF$_{25}$-$_{75}$% (r= - 0.47, pO.OOl).

Table 1. The means of cardiopulmonary variables of groups

	MITRAL STENOSIS	CONTROL	P
FEV,% predicted	78 ±20.9	102.4 ± 15.8	<0.001'
FEV, (Lt)	2 ± 0.5	3 ±0.5	0.001'
FVC% predicted	87.2 ± 18.6	105.3 ± 16	<0.001*
FVC (Lt)	2.6 ±0.6	3.6 ±0.7	<0.001'
FEV,/FVC predicted	75.2 ±7.8	82.7 ± 6.2	0.001'
FEF25.75 % predicted	53.1 ±21.4	84.1 ± 19.8	<0.001'
FEF$_{25}$% predicted	69.4 ± 26.9	80 ± 18.5	<0.05'
FEF$_{50}$% predicted	58.7 ±25.8	94.5 ± 17.7	0.001"
DLCO/VA predicted	90.7 ± 22.9	94.8 ±4.1	>0.05
MVA	1.95 ± 0.6	5 ±0.8	O.01
Maximum MVG	15 ±6.7	4 ± 0.59	O.01
Mean MVG	6.6 ±3.7	2.2 ±0.6	O.01
PAP	38.8 ± 12	20.6 ± 1.9	O.01
FS	32.1 ±5.7	34.7 ± 0.9	0.01
LA	5.3 ± 1.3	3.6 ±0.1	0.01

Abbreviations: VC=Vital capacity, FVC=forced vital capacity, FEV|=forced expiratory volume in one second, FEF25.75 %=maximal expiratory flow at 25-75 percent of VC, PEF=peak expiratory flow, DLCO/VA=dilTusion capacity for carbon monoxide per unit volume, MVA= mitral valve area, MVG=milral valve gradient, PAP=Pulmonary arter pressure, FS=fraxionel shortening, LA=left atrium

Table 2. The means of cardiopulmonary variables of groups

	Placebo	Inh. budesonid group	P
Age	49.6 ± 11.9	46.2 ± 8.7	>0.05
FEV, (Lt)	1.9 ±0.6	1.6 ±0.4	>0.05
FEV1% predicted	66.4 ± 16.1	61.4 ± 15.8	>0.05
FVC (Lt)	2.6 ±0.8	2.2 ±0.6	>0.05
FVC% predicted	78 ± 14.3	74.3 ± 16.9	>0.05
FEV 1/FVC predicted	71.9 ± 8.9	69.5 ± 5.5	>0.05
FEF 25.75% predicted	43.2 ± 14.4	33.3 ± 11.4	>0.05
DLCO/VA predicted	88.3 ± 25.6	85.7 ± 10.1	>0.05
MVA	1.91 ± 0.4	1.9 ± 0.7	**>0.05**
Mean MVG	7.6 ±3.87	7.7 ±4.2	**>0.05**
PAP	35 ±3.2	40.4 ±7.5	**>0.05**

FVC%, FEV, %, FEV,/ FVC, and FEF 25-75% were closely correlated with PAP (r= -0.53, pO.OOl; r= -0.60, pO.OOl; r= -0.46, pO.OOl, and r= -0.56, pO.OOl, respectively), but there was no significant correlation between DLCO/VA and PAP.

There were no significant differences between placebo and inhaled budesonide groups in respect

Table 3. The baseline and after treatment means of pulmonary functions in patients with received inhaled budesonide

	Before treatment	After inh. budesonide	P
FEV, (Lt)	1.6 ±0.4	1.7 ±0.6	>0.05
FEV 1% predicted	61.4 ± 15.8	61.5 ± 15.3	>0.05
FVC (Lt)	2.2 ± 0.6	2.3 ±0.7	>0.05
FVC% predicted	74.3 ± 16.9	74.3 ± 16.2	>0.05
FEV)/FVC predicted	69.5 ± 5.5	69.8 ±5.2	>0.05
FEF $_{25-75\%}$ predicted	33.3 ± 11.4	36.2 ±11.2	0.009

Table 4. The baseline and after treatment means of pulmonary functions in patients with received placebo

	Before placebo	After placebo	P
FEV, (Lt)	1.9 ±0.6	1.95 ±0.5	>0.05
FEV 1% predicted	66.4 ± 16.1	66.6 ± 15.2	>0.05
FVC (Lt)	2.6 ±0.8	2.6 ± 0.9	>0.05
FVC% predicted	78 ± 14.3	78.3 ±14.1	>0.05
FEV1/FVC predicted	71.9 ±8.9	72 ± 8.7	>0.05
FEF $_{25.75\%}$ predicted	43.2 ± 14.4	46.2 ± 12.1	>0.05

of baseline means of MVA, MVG and PAP, FVC%, FEV,%, FEV,/FVC, FEF $_{25-75}$% and DLCO/VA (p>0.05), (Table 2). After four weeks of treatment, FEF $_{25-75\%}$ increased significantly in inhaled budesonide group (p<0.01), whereas FVC%, FEV, %, FEV,/ FVC did not show any significant changes in both of two groups. Before and after treatment of pulmonary functions in patients with placebo and inhaled budesonide groups are shown in Table 3 and Table 4.

Discussion

In this study, we demonstrated that FVC%, FEV, %, FEV,/ FVC and FEF $_{25-75\%}$ in the patients with mitral stenosis were significantly lower than those in healthy control subjects, whereas DLCO/VA did not significantly differ among the two groups. Pulmonary functions were closely correlated with MVA, MVG and PAP, suggesting that the decreases of pulmonary functions are significantly associated with the severity of mitral stenosis. In addition, we found that FEF25-75 increased significantly after inhaled budesonide treatment.

Various studies showed that pulmonary functions are adversely affected by mitral stenosis (3-18). Rolla et al evaluated bronchial responsiveness and diurnal peak expiratory flow (PEF) rate in patients with moderate mitral stenosis, and they reported airway responsiveness of patients with mitral stenosis seems to be more similar to that reported in bronchitic than in asthmatic patients. Additionally, they found decreased FEV1 and FEV1/FVC and MEF50 in patients with mitral stenosis (7). Nishimura et al reported that patients with long term mitral valve disease (MVD) have marked bronchial hyperreactivity (BHR) and that BHR in long term MVD is related to peripheral airway narrowing with organic remodelling, which was not ameliorated with mitral valve replacement procedure, in addition to pulmonary congestion (4). Nour et al studied lung function in patients with advanced mitral stenosis and revealed an obstructive ventilatory pattern (decreased FEV1, FEV1/FVC, PEF and, Vmax50). Additionally they found that this obstructive impairment improves with the salbutamol inhalation (12).

Chronic left-sided congestive heart failure seen in mitral stenosis can cause secondary changes in the pulmonary vasculature (1,2,14,17). Pulmonary hypertension and increased pulmonary vascular resistance can causes reflex bronchoconstriction. Bronchial mucosal swelling may also contribute. Chronic left heart failure is characterised by interstitial oedema at the level of the alveolar and bronchial capillary beds. Airway narrowing by nonreflex mechanism definitely occurs. The results are measurable restrictions in the static volumes, and in particular of the obstruction parameters that involves especially the small airways (1,2,14).

FEV1 and FEV1/FVC were found significantly decreased when compared to the healthy controls in this study. These parameters showed that there is an obstruction in the large airways. Additionally, we found that FEF25-75 % was significantly lower than the controls and peripheral air-

way obstruction increased while the degree of mitral stenosis increased. These results consistent with previous results that there is peripheral airway obstruction in mitral stenosis. While the mechanisms underlying the airway narrowing in patients with mitral stenosis are complex and not completely understood, several mechanisms such as bronchial oedema, pulmonary vascular dilatation, stimulation of J receptors and C fibers may be considered (5,13,14,18). In contrast to bronchial asthma, there is little evidence for mediator involvement in the development of increased bronchial reactivity in patients with mitral valve stenosis (19).

The size of transmitral gradient is important in the evaluation of functional or/and structural changes in the blood vessels of pulmonary circulation. It has been reported that noninvasive echocardiography method is valid in the evaluation of stenotic mitral valve area, transmitral gradient and severity of mitral stenosis (20,21).

Ota et al reported that there were significant relationships between delta FEV1 (delta: postoperative value-preoperative value) and delta PAP (11). Gulec et al showed that severity of bronchial responsiveness is significantly correlated with the severity of mitral stenosis (6).

In this study, pulmonary functions were closely correlated with MVA, MVG and PAP, suggesting that the decreases of pulmonary functions are significantly associated with the severity of mitral stenosis. These results may suggest that testing pulmonary function parameter help to evaluate left heart function and diagnose early pulmonary oedema.

Progressive pulmonary hypertension, as is exemplified for mitral stenosis, leads to measurable restrictive (16) and obstructive impairment of lung function (12,14), and as also over the long term, to a diminishment in membrane diffusion capacity (15). In the passive pulmonary hypertension phase, diffusion capacity increases firstly; in the further course of the disease, with development of interstitial and alveolar oedema, it decreases again It has been reported that low values of the diffusing capacity were more frequently found in moderate to severe mitral stenosis, subnormal values were seen in mild cases. The greater part of the decrease in the diffusing capacity in mitral stenosis might be due to irreversible changes in the membrane factors, such as interstitial or alveolar fibrosis. (1-3,15). Messner-Pelenc et al reported that diffusing capacity and DLCO/VA were not different at rest between tight mitral stenosis and controls, but during peak exercise DLCO didn't increase in patients (differed from control) (22).

We could not find a significant difference in DLCO/VA between mitral stenosis and controls. We thought that the reason of this result was that the most of patients with mitral stenosis who were included in our study were consisted of mild cases. On the other hand DLCO/VA in moderate-severe mitral stenosis was lower than the mild cases, but there were not significant differences among the mild, moderate and severe cases.

Unlike congenital heart disease, severe grades of pulmonary arterial damage are not seen in left heart failure from mitral stenosis and consequently with surgical correction pulmonary hypertension reverses (1). It is suggested that pulmonary dysfunction in patients with mild mitral stenosis is mainly due to an obstructive ventilatory defect without damaging the pulmonary vasculature, because pulmonary dysfunction generally seen in patients with mitral stenosis were partially ameliorated after correction of mitral valve by mitral surgery (10, 11), PTMC (3) or PBMV (6,9).

It is still not clear whether treatment with inhaled steroid can improve pulmonary dysfunction seen in mitral stenosis or not. Cieclewicz et al reported that six weeks of treatment with inhaled budesonide significantly decreased bronchial reactivity and improves symptoms in patients with mitral valve stenosis (13). We could not find any report except Cieclewicz's about treatment with inhaled corticosteroid in patients with mitral stenosis. We could not find any significant changes in FEV, , FVC and FEV,/FVC after four weeks of treatment with inhaled budesonide. On the other

hand, FEF25.75 % shows a little increase after inhaled budesonide treatment, but difference was found to be statistically significant. Our results were partly consistent with the Cieclewicz's results. In this study none of the patients had a history of atopy or other lung disease, therefore, the improvement in FEF_{25-75}% following treatment with budesonide was not likely due to treatment of an underlying lung disorder, and it seems unlikely that decreases in pulmonary congestion were responsible for the improvement in FEF25-75 as they continued receiving the same doses of other medications during the four week study. We thought that this improvement might result from possible effect of glucocorticoids on altering mucus secretion and vascular permeability (23). It was demonstrated that circulating prostaglandin I_2 and E_2 levels elevated in patients with chronic hearth failure (19). These prostaglandins may cause bronchconstriction and inhaled steroids may decrease their synthesis through inhibition of phospholipase A_2 (23).

In summary, our study demonstrated that pulmonary dysfunction might be occur in patients with mitral stenosis, especially in severe cases. However, inhaled budesonide did not seem to improve pulmonary functions in these patients. Based on these results we can not conclude which is the major cause of the pulmonary dysfunction, organic change of pulmonary tissue or functional hemodynamic effects. We thought that follow-up studies of longer duration must be earned out to clarify these questions.

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