

Elevated mean pulmonary artery pressure in patients with mild-to-moderate mitral stenosis: a useful predictor of worsening renal functions?

Hafif ve orta derecede mitral darlığı bulunan hastalarda artmış ortalama pulmoner arter basıncı bozulan böbrek fonksiyonlarını göstermede yararlı bir belirteç olabilir mi?

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ABSTRACT

Objective: Renal dysfunction commonly accompanies the course of cardiac disorders and strongly associates with increased morbidity and mortality. Elevated central venous pressure is related to worsening renal function in patients with heart failure. However, predictors of worsening renal function in mitral stenosis-whose pathophysiologic process is similar to heart failure with regard to right heart dysfunction-are unknown. This study aimed to evaluate whether clinical and echocardiographic parameters might predict worsening renal function in patients with mild-to-moderate mitral stenosis.

Methods: The current study has a prospective cohort design. Sixty consecutive patients (9 male, 51 female, mean age 50±13 years) with mild-to-moderate mitral stenosis were followed up for 34±13 months (range 1-60) and their renal functions were monitored. Worsening renal function was defined as a decline in glomerular filtration rate of ≥ 20% on follow-up. In order to presence or absence of worsening renal functions, study patients divided into two groups. Statistical analysis was performed using the Chi-square, Independent samples t / Mann-Whitney U tests, univariate and multivariate Cox proportional hazards analyses, receiver operating characteristic (ROC) and Kaplan-Meier curve analyses.

Results: Worsening renal function was observed in 14 patients (23%). In univariate analysis, male gender, mean pulmonary artery pressure (mPAP), peak tricuspid regurgitation velocity, systolic pulmonary artery pressure, digitalis and antiplatelet usage, right atrial size, and TEI index were determined to be predictors of worsening renal function. In a multivariate Cox proportional hazards model, mPAP (HR=1.136, 95% CI: 1.058-1.220, p<0.001) and male gender (HR=4.110, 95% CI: 1.812-9.322, p=0.001) were associated with increased risk of worsening renal function during the follow-up period. In ROC curve analysis, the optimal cut-off value of mPAP to predict worsening renal function was measured as more than 21 mmHg, with 78.6% sensitivity and 58.7% specificity (AUC 0.725, 95% CI 0.595-0.838). According to the Kaplan-Meier curve, a significant difference was found between those who had mPAP of >21 mmHg, and those who did not have, in terms of worsening renal function (p=0.006), and the difference between the groups increased after 30 months of follow-up.

Conclusion: Elevated mean pulmonary artery pressure at the time of initial evaluation, in patients with mild-to-moderate mitral stenosis, might help to predict worsening renal function. (*Anadolu Kardiyol Derg 2013; 13: 457-64*)

Key words: Mean pulmonary artery pressure, mitral stenosis, worsening renal function, Cox proportional regression analysis, survival

ÖZET

Amaç: Böbrek fonksiyon bozukluğu, sıklıkla kalp hastalıklarına eşlik eder ve yüksek mortalite ve morbiditeye sahiptir. Kalp yetersizliği bulunan hastalarda santral venöz basınç yüksekliği de böbrek fonksiyonlarında bozulmayla ilgilidir. Bununla birlikte; sağ kalbe ait fonksiyon bozukluğu ile kalp yetersizliği bulunan hastalarla benzer patofizyolojik özelliklere sahip mitral darlığı bulunan hastalarda böbrek fonksiyonlarında bozulmayı gösteren belirteçlerin neler olduğu bilinmemektedir. Bu çalışmada, hafif ve orta mitral darlığı bulunan hastalarda klinik ve ekokardiyografik parametrelerin bozulan böbrek fonksiyonlarını göstermedeki yerinin araştırılması hedeflenmiştir.

Yöntemler: Bu çalışma prospektif kohort bir dizayna sahiptir. Hafif ve orta derecede mitral darlığı bulunan, ortalama yaşları 50±13 yıl olan, 9'u erkek 51'i kadın 60 hastada böbrek fonksiyonları ortalama 34±13 ay (1-60 ay) takip edilmiştir. Takip boyunca, glomerüler filtrasyon oranında %20'den fazla azalma görülmesi böbrek fonksiyonlarında bozulma olarak kabul edilmiştir. Hastalar böbrek fonksiyonlarında bozulma gelişip gelişmemesine göre iki gruba ayrıldı. İstatistiksel analiz olarak Ki-kare, bağımsız gruplarda t/Mann-Whitney U testleri, tek ve çok değişkenli Cox orantısız risk analizleri, ROC ve Kaplan-Meier eğrisi analizleri kullanıldı.

Bulgular: Çalışmaya alınan 14 hastada (%23) böbrek fonksiyonlarında bozulma tespit edilmiştir. Yapılan tek değişkenli analizlerde; erkek cinsiyet, ortalama pulmoner arter basıncı, pik triküspit regürjitasyon akımı, sistolik pulmoner arter basıncı, dijital ve antitrombotiklerin kullanımı, sağ

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atriyum boyutları ve TEI indeksi'nin böbrek bozukluklarında bozulmayı gösterdiği saptanmıştır. Çok değişkenli orantısız Cox risk modeli analizleri de, takip döneminde erkek cinsiyet ve ortalama pulmoner arter basıncının böbrek fonksiyonlarında bozulma riskindeki artış ile ilişkili olduğunu göstermiştir. ROC analizinde, mPAP için kötüleşen böbrek fonksiyonunu gösteren optimal cut-off değeri % 78,6 duyarlılık ve %58,7 özgüllük ile (AUC 0,725, %95 CI 0,595-0,838) >21 mmHg olarak ölçüldü. Kaplan-Meier eğrisi ile değerlendirmelerde, mPAP > 21 mmHg olanlar ve olmayanlar arasında renal fonksiyonlarda kötüleşme açısından görülen fark anlamlıydı (p=0,006). Gruplar arasındaki bu fark 30 aylık takip sonrasında daha da arttı.

Sonuç: Hafif ve orta derecede mitral darlığı bulunan hastalarda, ilk değerlendirmede ölçülen artmış ortalama pulmoner arter basıncı, bozulan böbrek fonksiyonlarını göstermede yararlı olabilir. (*Anadolu Kardiyol Derg 2013; 13: 457-64*)

Anahtar kelimeler: Ortalama pulmoner arter basıncı, mitral darlığı, böbrek fonksiyon bozukluğu, Cox orantısız hazard regresyon analizi, sağ kalım

Introduction

The incidence of acute rheumatic fever, and consequently of rheumatic valvular heart diseases, in developed countries has declined over the past decade. Although the occurrence of rheumatic heart diseases, including rheumatic mitral stenosis (MS), has declined in developed countries, it has remained a significant public health problem in developing ones (1). Symptoms of MS usually occur after a latent period following an initial acute rheumatic fever episode. This period might take more than 15 years. During this asymptomatic period, mitral valve area (MVA) reduces gradually. Clinical symptoms suggestive of MS occur when MVA of less than 2 cm², and the appearance of the diastolic pressure gradient between the left atrium and left ventricle, have resulted in a transmitral peak velocity of greater than 1 m/sec. Rates of 5-, 10- and 15-year survival with sole medical therapy (without surgery) were 44%, 32%, and 19%, respectively (2).

It is well known that renal dysfunction frequently accompanies the course of cardiac disorders and is strongly associated with morbidity and mortality (3-6). Worsening renal function (WRF) most commonly occurs in heart failure (HF) as a result of a complex interaction between the heart and kidneys. Recently published studies in HF have clarified its pathophysiology and underlined the importance of venous congestion, which can also be observed in MS due to increased right heart afterload (7-9). The relation between venous congestion and renal dysfunction has been shown in experimental studies (10, 11). These studies suggest that iatrogenically induced hypervolemia, and increase in renal vein pressure, lead directly to renal insufficiency independent of cardiac output or renal blood flow. This has also been shown to be a reversible phenomenon because lowering of renal vein pressure immediately improves urine output and glomerular filtration rate (GFR) (10, 11). Experimental studies have also indicated that temporary renal vein compression results in reduced sodium excretion, reduced GFR, and reduced renal blood flow (12-14). Increased venous congestion also causes an increase in renal interstitial pressure, which might lead to a hypoxic state of the renal parenchyma (15-18). Prolonged increases in plasma volume also attenuate several vascular reflexes, leading to an impaired arterial responsiveness, thereby further impairing the effective renal blood flow (19-22).

However, the prognostic significance of WRF and its clinical and echocardiographic determinants in MS are still unknown. In

this study, we aimed to evaluate the clinical and echocardiographic parameters which might predict WRF in mild-to-moderate MS.

Methods

Study design

This study has a prospective cohort design.

Study population

Eighty consecutive patients with mild-to-moderate rheumatic MS, who were enrolled as part of another study, were prospectively considered in three participating centers between January 2006-January 2011 (23). Twenty patients (with similar age and gender distribution) from the original cohort declined to participate during the follow-up period. Patients with another severe accompanying valvular disorder, history of coronary artery disease, depressed ejection fraction, history of cardiac surgery, previous diagnosis of pulmonary disease, or previous diagnosis of chronic renal failure, were excluded from the study. Patients with a mitral valve area of < 1cm² were also excluded, because these patients required surgical treatment at the time of evaluation. Patients with severe MS who declined surgery were also excluded because these patients already had low cardiac output (authors of this manuscript were considered that this might influence renal functions earlier than expected and could obscure other parameters' significance in determining worsening renal function). Therefore, 60 consecutive patients were enrolled. Patients were evaluated at every 6 months, unless any clinical deterioration and increase in symptoms were observed. The GFR of each participant was followed up at each visit.

The study protocol had been approved by the institutional ethics committee, and written informed consents were taken from all participants of this prospective observational cohort.

GFR assessment

The GFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula (86.3 x sCr^{-1.154} x age^{-0.203}, female: MDRDx0.742, black or non-white: MDRDx1.212). Worsening of renal function was defined as a decline in GFR of ≥ 20% on follow-up.

Clinical examinations

Clinical parameters including age, gender, height, weight, body surface area, body mass index, and presence and dura-

tions of comorbid disorders such as hypertension, diabetes mellitus, hyperlipidemia, smoking, characteristics of cardiac rhythm, and applied treatment as antiplatelets, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors / angiotensin receptor blockers (ARB), diuretics, calcium channel blockers, digitalis, and warfarin were carefully evaluated and recorded.

Echocardiography

Echocardiographic examinations were performed with a cardiac ultrasound system (Vivid 7, GE Healthcare, Wauwatosa, WI, US) to evaluate chamber quantification with a defined protocol (11, 24) by a physician who was unaware of patients' renal function. Resting heart rate was 55-85 bpm in all patients during echocardiographic examination. All echocardiograms were recorded and coded by echocardiographers without identities to eliminate interobserver variability. Recorded and coded data were put into random order by computer assistance and evaluated off-line by an expert echocardiographer. MVA was calculated by the two-dimensional planimetry method, and if the image quality was not sufficient, the Doppler pressure half time method was used (25). Transmitral gradients were calculated by the modified Bernoulli equation (26). Accompanying valvular regurgitations were quantified according to recent guidelines and categorized as mild-moderate (27). The modified Bernoulli equation derived from the tricuspid regurgitation jet velocity and estimated right atrial pressure from inferior vena cava collapsibility was used in determining systolic pulmonary artery pressure (sPAP) (28). Mean pulmonary artery pressure (mPAP) was calculated by the Masuyama method (29). Tricuspid annulus velocities (via tissue Doppler), right ventricular outflow time-velocity integral, Tei index, ejection times, intervals, and tricuspid annular plane systolic excursion were measured accordingly in all patients (30-33). Echocardiographic parameters at the time of initial evaluation were used in statistical analysis, as predictors of WRF during follow-up.

Statistical analysis

All statistical procedures were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean±standard deviation or median (interquartile range) in the presence of abnormal distribution, categorical variables as percentages. Comparisons between groups of patients were made by use of a Chi-square test for categorical variables, an independent samples t-test for normally distributed continuous variables, and the Mann-Whitney U test when the distribution was skewed. Univariate Cox proportional hazards analysis was used to quantify the association of variables with worsening renal function. Variables found to be significant at the $p < 0.1$ level in univariate analysis were used in a multivariate Cox proportional hazards model with a forward stepwise method in order to determine the independent predictors of WRF. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of mPAP (at which sensitivity and

specificity would be maximal) for the prediction of WRF. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC by use of the Z test. Kaplan-Meier curves were used to show the development of WRF in two patient subgroups, defined as having no increased (≤ 21 mmHg) or increased (> 21 mmHg) mPAP based on a cut off value. A p-value of 0.05 was considered as statistically significant.

Results

Baseline clinical characteristics and echocardiographic parameters

Sixty mild-to-moderate MS patients were followed up for a mean period of 34 ± 13 months (range 1-60). The mean age of the study population was 50 ± 13 years (85% females, 15% males). The mean MVA and mean transmitral gradient of the study population were 1.6 ± 0.2 cm² and 6.4 ± 2.9 mmHg, respectively. Comparison of patients' baseline clinical characteristics and echocardiographic parameters, according to the presence of WRF, has been shown in Table 1 and Table 2. Worsening renal function on follow-up was more frequent in patients of male gender, or with a history of digitalis use ($p=0.025$ and $p=0.044$, respectively). Maximum tricuspid regurgitation velocity (TR max velocity), sPAP and mPAP were higher in patients with worsening renal function ($p < 0.05$). Other baseline clinical and echocardiographic parameters were similar between groups (Table 1 and 2).

Regression analyses for the development of worsening renal function

Results of the univariate and multivariate Cox proportional hazards analyses have been shown in Table 3. Male gender, mPAP, TR max velocity, sPAP, digitalis and antiplatelet agent usage, right atrial diameter, and Tei index were found to be univariate predictors of WRF. In the multivariate Cox proportional hazards model, mPAP (HR=1.136, 95% CI: 1.058-1.220, $p < 0.001$) and male gender (HR=4.110, 95% CI: 1.812-9.322, $p=0.001$) were associated with an increased risk of WRF during follow-up.

ROC curve for mPAP to predict worsening renal function

According to the ROC curve analysis, the optimal cut-off value of mPAP to predict WRF was measured as more than 21 mmHg, with 78.6% sensitivity and 58.7% specificity (AUC 0.725, 95% CI 0.595-0.838, Fig. 1). On the other hand, mPAP of > 36.21 mmHg was found to have 100% specificity for WRF on follow-up, though sensitivity was low (14.3%).

Survival analysis

According to the Kaplan-Meier curve, a significant difference was found between those who had mPAP of > 21 mmHg, and those who did not, in terms of worsening renal function ($p=0.006$), and the difference between the groups became bigger after 30 months of follow-up (Fig. 2).

Table 1. Baseline characteristics and differences between patients who did and did not develop worsening renal function during follow-up

Variables	Patients without worsening renal function on follow up (n=46)	Patients with worsening renal function on follow up (n=14)	*p
Mean age, years	49±12	52±16	0.486
Male gender, n (%)	4 (9)	5 (36)	0.025
Height, cm	158±5	161±10	0.387
Weight, kg	73±14	70±15	0.471
BSA, m ²	1.8±0.1	1.7±0.2	0.598
BMI, kg/m ²	29±6	27±6	0.245
Follow-up time, months	34±14	36±10	0.592
Presence of hypertension	18(39)	8(57)	0.235
Baseline GFR, mL/min/m ²	107±34	100±50	0.570
Final GFR, mL/min/m ²	112±35	57±33	< 0.001
Change of GFR, %	0 (-12.5/25)	-40 (-57/-31)	< 0.001
Presence of diabetes mellitus	6 (13)	1 (7)	1.000
Duration of diabetes mellitus, years	3±6	4±10	0.804
Hyperlipidemia, n (%)	11 (24)	3 (21)	1.000
Duration of hyperlipidemia, years	1.5±2	1±1	0.678
Smoking, n (%)	5 (11)	2(14)	0.660
Duration of smoking, years	5±10	12±20	0.759
Atrial fibrillation, n (%)	18 (39)	5 (36)	0.817
Antiplatelet agents, n (%)	34 (74)	7 (50)	0.111
Beta blockers, n (%)	27 (59)	8 (57)	0.918
ACE inhibitors/ ARB, n (%)	16 (35)	5 (36)	1.000
Diuretics, n (%)	11(24)	2 (14)	0.713
Calcium canal blockers, n (%)	13 (28)	3 (21)	0.740
Digitalis, n (%)	5 (11)	5 (36)	0.044
Warfarin, n (%)	21 (46)	5 (36)	0.508

Data are presented as number (percentage) and mean±SD or median (interquartile range) values
 *Independent samples t-test, Mann-Whitney U test, and Chi-square test
 ACEI - angiotensin - converting enzyme inhibitor, ARB - angiotensin receptor blocker, BMI - body mass index, BSA - body surface area

Discussion

In this study, we aimed to evaluate whether clinical and echocardiographic parameters might predict WRF in patients with mild-to-moderate mitral stenosis. Male gender, mPAP, TRmax velocity, sPAP, digitalis and antiplatelet agent usage, right atrial diameter and TEI index were found to be univariate predictors of worsening renal function. However, even after controlling these parameters, we demonstrated that only mPAP and male gender were independently associated with an increased risk of WRF during follow-up in patients with mild-to-moderate mitral stenosis.

The kidney and the heart are two closely interrelated organs. It is well known that any disorder affecting one of the two deteriorates the other's functional status. Deterioration of this close interrelation between these two organ systems is known as "cardio-renal syndrome," and studies in HF have clarified the

pathophysiological mechanisms behind this syndrome. It has been thought that renal dysfunction in HF is attributable to low cardiac output, which consequently causes reduction in blood flow and renal perfusion pressure (9, 34). Decreased cardiac output also activates the renin-angiotensin-aldosterone system and the sympathetic nervous system, which in turn causes congestion and constriction in afferent arterioles. These results in further decreases in renal perfusion pressure (34). Theoretically, the above-mentioned pathophysiological mechanism is valid; however, recent studies suggest different mechanisms. Heywood et al., (35) have shown that renal dysfunction is similar in patients with systolic and diastolic dysfunction; this result suggests mechanisms other than low cardiac output. Recently published HF studies have explained the role of venous congestion in renal dysfunction (7-9, 36, 37). Some other studies have suggested right atrial and central venous pressure, rather than

Table 2. Comparison of the echocardiographic parameters between patients who did and did not develop worsening renal function during follow-up

Variables	Patients without worsening renal function on follow up (n=46)	Patients with worsening renal function on follow up (n=14)	*p
E velocity, m/sec	1.3±0.7	1.4±0.5	0.882
A velocity, m/sec	1.5±0.5	1.4±0.3	0.593
E/A ratio	0.8±0.4	0.9±0.3	0.648
Ejection fraction, %	55±7	56±8	0.647
LV diastolic volume, mL	92±24	96±39	0.685
LV systolic volume, mL	41±14	39±14	0.602
Left atrial diameter 4C1, cm	4.7±0.8	4.6±0.8	0.667
Left atrial diameter 4C2, cm	6.8±1.0	6.7±0.9	0.915
Area of left atrium, cm ²	34±47	28±9	0.610
Right atrial diameter 4C1, cm	3.7±0.9	4.3±0.8	0.058
Right atrial diameter 4C2, cm	5.3±0.9	5.5±1.0	0.364
Area of right atrium, cm ²	19±7	23±8	0.101
RV diameter D2, cm	3.1±0.6	3.4±0.5	0.266
E' velocity, m/sec	0.15±0.04	0.16±0.04	0.566
A' velocity, m/sec	0.20±0.2	0.16±0.06	0.565
S velocity, m/sec	0.15±0.15	0.13±0.04	0.664
RV Ejection time, msec	287±41	291±47	0.798
IVCT, msec	74±20	71±11	0.624
IVRT, msec	77±19	73±19	0.479
TEI index	0.52±0.13	0.46±0.17	0.189
RV fractional area change, %	16±4	18±4	0.174
TR max velocity, m/sec	2.7±0.3	3.1±0.5	0.007
RVOT TVI, cm	18±5	17±4	0.590
PVmax, m/sec	0.8±0.1	0.8±0.1	0.591
PacT, msec	112±25	97±25	0.051
TAPSE, cm	2.2±0.6	2.1±0.5	0.541
Aortic regurgitation, mild/moderate	28/18	7/7	0.680
Mitral regurgitation, mild/moderate	25/21	8/6	1.000
Area of mitral regurgitation, cm ²	4.8±2.8	4.9±3.8	0.881
Tricuspid regurgitation, mild/moderate	33/13	8/6	0.338
Area of tricuspid regurgitation, cm ²	4.2±3.6	4.3±2.2	0.919
MVA planimetric, cm ²	1.6±0.2	1.5±0.2	0.525
MVA PHT, cm ²	1.6±0.3	1.5±0.3	0.522
Maximum MV gradient, mmHg	13.7±5.1	15.0±6.0	0.434
Mean MV gradient, mmHg	6.2±2.8	6.9±3.6	0.460
Systolic PA pressure, mmHg	30.6±7.9	39±13.9	0.048
Mean PA pressure, mmHg	20.7±5.3	26.4±8.1	0.003

Data are presented as number (percentage) and mean±SD values.

* Independent samples t-test, Mann-Whitney U test, and Chi-square test

A - peak late diastolic mitral inflow velocity, A' - annular late diastolic wave, E - peak early diastolic mitral inflow velocity, E' - annular early diastolic wave, IVCT - isovolumic contraction time, IVRT - isovolumic relaxation time, LV - left ventricle, 4C1 - measurement taken in a plane perpendicular to the long-axis of the atrium and extends from the lateral border to the interatrial septum in apical four chamber view at end-systole, MV - mitral valve, MVA - mitral valve area, 4C2 - measurement from the back wall to the line across the hinge points of the mitral or tricuspid valve in apical four chamber view at end-systole, PA - pulmonary artery, PacT - pulmonary acceleration time, PHT - pressure half-time, Pymax - pulmonary maximal velocity, RV - right ventricle, RVOT TVI - right ventricular outflow time-velocity integral, S - systolic annular myocardial velocity, TAPSE - tricuspid annular plane systolic excursion, TR - tricuspid regurgitation

Table 3. Univariate and multivariate predictors of worsening renal function

Variables	HR	95% CI	p	HR	95% CI	*p
Male gender	2.697	1.446-5.028	0.002	4.110	1.812-9.322	0.001
Mean PA pressure, mmHg	1.084	1.025-1.147	0.005	1.136	1.058-1.220	<0.001
TR max velocity, m/sec	3.580	1.457-8.798	0.005			
Systolic PA pressure, mmHg	1.047	1.013-1.183	0.007			
Digitalis usage	3.591	1.192-10.816	0.023			
Right atrial diameter, cm	1.666	0.990-2.802	0.054			
Antiplatelet agents	2.743	0.945-7.963	0.064			
Tei index	0.037	0.001-1.727	0.093			

*Multivariate cox proportional hazard analysis with forward stepwise method
 Dependent variable - worsening renal function, independent variables: male gender, mean PA pressure, TR max velocity, systolic PA pressure, digitalis usage, right atrial diameter, antiplatelet agents, Tei index.
 All the variables from Table 1 and 2 were examined and only those significant at p<0.1 level are shown.
 Multivariate cox proportional hazard model including all univariate predictors.
 CI - confidence interval, HR - hazard ratio, PA - pulmonary artery, TR - tricuspid regurgitation

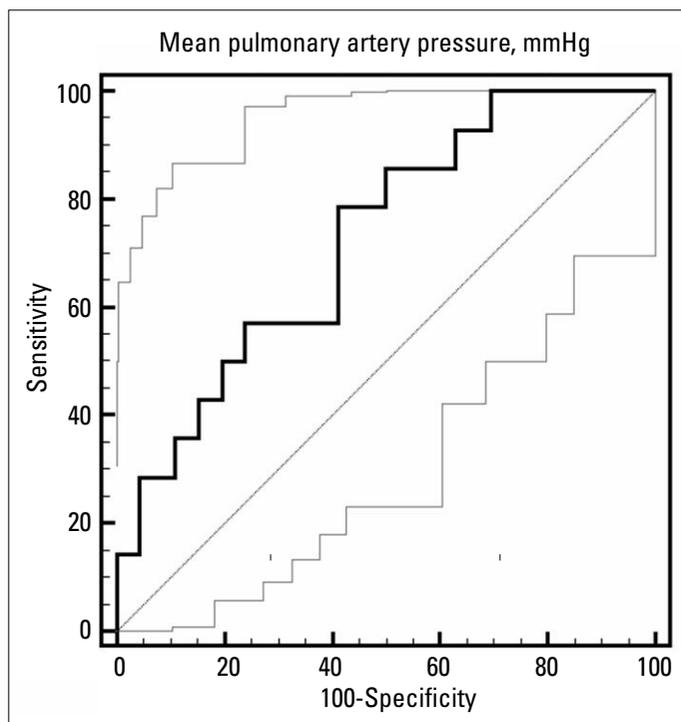


Figure 1. ROC Curve for mean pulmonary artery pressure to predict worsening renal function (AUC-0.725, 95%CI 0.595-0.838)

cardiac index, as the main predictors of worsening renal function (37, 38). Increased oxidative stress and inflammation in the tubule-interstitium developed after venous congestion may also have a role in renal dysfunction (39).

Renal dysfunction may also potentially complicate the course of rheumatic MS. Just like in HF, right ventricular dysfunction secondary to increased right heart afterload, and venous congestion, are also common findings of MS. However, the potential role of echocardiography in predicting WRF in MS is unknown. In this study, we investigated clinical and echocardiographic indices of WRF in MS. In our study, mPAP was found to be an independent

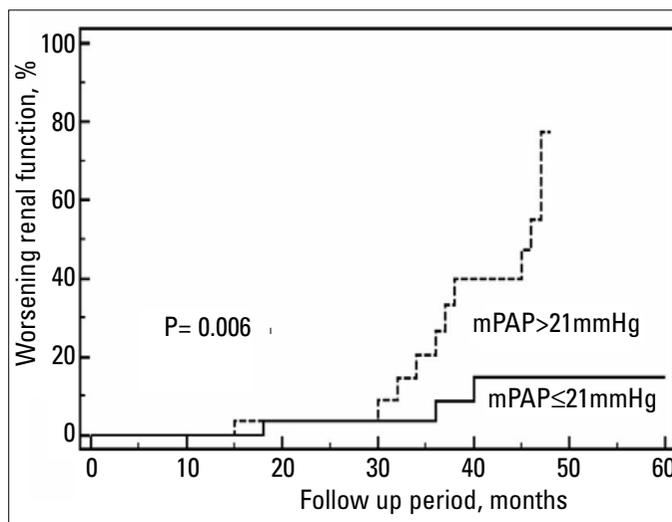


Figure 2. Ratio of those with worsening renal function on follow-up
 mPAP - mean pulmonary artery pressure

predictor of WRF. Systolic PAP and TR max velocity were other predictors in univariate analysis, though they lost their significance after multivariate analysis. On the other hand, in this study, echocardiographic indices of MS severity including transmitral gradients and valve area, as well as left atrial diameters, had no influence in predicting WRF. These findings were consistent with the above-mentioned data derived from HF studies, which proved the role of venous congestion and right ventricular dysfunction in WRF. It is notable that cardiac output may have a potential role in worsening renal function; however, we excluded patients with severe MS since these patients needed intervention at the time of evaluation. In our study, right ventricular diameter was within normal range and did not differ between groups. This was also true for TAPSE and Tei indices. These findings suggest that right ventricular systolic function was relatively preserved at the time of evaluation; however, an afterload mismatch of the right ventri-

cle, in the form of increased pulmonary pressure, was already there. This increased afterload seemed to bring about right ventricular diastolic dysfunction, which in turn increased right atrial pressures and caused venous congestion. Increased transverse right atrial diameter, observed in this study, supports this hypothesis (Table 2). The right atrial area was also increased in patients with WRF, though it could not reach statistical significance ($p=0.101$). We think invasive measurement of right atrial pressure might clarify this hypothesis.

Study limitations

Although a lack of invasive measurements was the major limitation of our study, we did not consider invasive assessment, since it might cause ethical problems if performed in cases of mild-to-moderate MS. Central venous pressure and inferior vena cava diameters, which remain other important study limitations, were also not recorded in our study. Because right ventricular systolic function was preserved, this issue was overlooked. Male gender was also found to be a predictor of WRF; however, it is better not to generalize about this, since there were relatively few male patients in the cohort, which is another limitation of this study. The number of patients enrolled in this study was another limitation; therefore, our findings should not be generalized. These findings should be supported by further studies conducted with a sufficient number of patients.

Conclusion

Increased mPAP at the time of evaluation, in patients with mild-to-moderate MS, seems to predict WRF during follow-up; hence, we think close monitoring of these patients, particularly those with mPAP of > 36.2 mmHg-which as a rule designates very high specificity in test results-may be useful in terms of renal function.

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