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Original Research

The Relationship between Mitral Chordae Rupture and Inflammation Level and Oxidative Stress

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ABSTRACT

Objective: Several factors have been reported to be associated with chordae tendineae rupture. The present study aimed at investigating the role of Interleukin-6 (IL-6), total antioxidant activity (TAA), total oxidant activity (TOA), and tumor necrosis factor alpha (TNFα) levels in the development of the mitral valve chordae tendinea rupture.

Methods: In this comparative study, 30 patients with mitral chordae rupture, 30 with severe rheumatic mitral regurgitation, and 20 healthy participants who were admitted to the Gaziantep University Medicine Faculty Cardiology Polyclinic were included. None of the participants had a previously known comorbid disease, and their diagnoses were confirmed by transthoracic echocardiography, followed by transesophageal echocardiography. Plasma levels of IL-6, TAA–TOA, and TNFα in all patients were measured and their oxidative stress index (OSI) was calculated.

Results: While the TOA–OSI levels in the chordae rupture group were significantly higher than the levels in patients with severe rheumatic mitral insufficiency and the control group (p=0.038 and p=0.019, respectively), the TNFα levels in the severe rheumatic mitral insufficiency group were statistically and significantly higher than the chordae rupture group (p=0.028).

Conclusion: Our study reports for the first time the significant relationship between the chordae rupture and oxidative stress levels (TOA-OSI). The results of this study show that high oxidative stress can be accepted as a risk factor for chordae rupture. In addition, it has also been observed that the TNFα level in the severe rheumatic mitral insufficiency group was higher than in the chordae rupture group. These data support the role of inflammation in the development of severe rheumatic mitral insufficiency.

Keywords: Chordae rupture, IL-6, Mitral valve, oxidative stress, TNFα

INTRODUCTION

Chordae tendinea rupture (CTR) has been increasingly reported as an important cause of mitral regurgitation (1). Although, mitral valve prolapse (MVP), rheumatic heart disease, calcific-degenerative valve disease, and infective endocarditis (IE) have been reported as the leading causes of CTR (2), its underlying causes and their frequencies vary.

Today, more than a hundred diseases are associated with free oxygen radicals. The oxidative stress index (OSI) is calculated as the ratio percentage of the total oxidant activity (TOA). Total antioxidant activity (TAA) is an analyte frequently used to assess the antioxidant status of biological samples and can evaluate the antioxidant response against the free radicals produced in a given disease.

Interleukin-6 (IL-6) is a pleiotropic cytokine produced by various cells including T-cells, lymphocytes, fibroblasts, adipocytes, macrophages, and endothelial cells (4). With its endocrine and paracrine effects, IL-6 stimulates platelet aggregation along with tissue factor, CRP, and the expression of fibrinogen (5). While the inflammatory component in atherosclerosis has been reported to contribute to the increased risk for cardiovascular disease (CVD) in several studies, IL-6 and TNFα are considered as the key pro-inflammatory and immune-stimulatory cytokines for CVD and the metabolic syndrome. TNFα has also been implicated in the pathogenesis of a number of CVDs, including atherosclerosis, myocardial infarction, heart failure, myocarditis, and cardiac allograft rejection (6).

It is believed that TAA, TOA, IL6, and TNFα increase tissue damage. This study seeks to find the relationship between IL-6, TNFα, TAA, TOA levels, and mitral valve (MV) chordae rupture.

METHODS

This comparative study included 30 patients with mitral chordae rupture (group 1), 30 with severe rheumatic mitral regurgitation (group 2), and 20 healthy participants (group 3) admitted to the Gaziantep University Medicine Faculty Cardiology Polyclinic for various reasons between June 1, 2014 and January 31, 2015.

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None of the participants had a previously known comorbid disease. The study was approved by the Gaziantep University Medicine Faculty Ethics Committee, and a written informed consent was given by all participants prior to the study.

On the contrary, the exclusion criteria for the study were: previous acute coronary syndrome, coronary artery disease, dilated cardiomyopathy, smoking, autoimmune diseases, pregnancy, diabetes mellitus, rheumatologic diseases, ejection fraction <50%, chronic renal or liver disease, active malignancy, vitamin or antioxidant replacement therapy, and known chronic diseases.

While the age, sex, body mass index, drug therapy, hematological, and biochemical results of all participants were recorded, blood samples were also obtained to measure the IL-6, TNFα, TAA, TOA, and OSI. The OSI is defined as the ratio of the TOA level to the TAA level.

The left ventricular systolic and diastolic functions and dimensions were assessed for all patients using echocardiography. Ejection fraction by Simpson method, volumes, tissue Doppler parameters (S, e, a), MV PW parameters (E, A) were recorded, and grading of mitral insufficiency was assessed by Proximal Isovelocity Surface Area (PISA) method, vena conracta width, and ratio of jet area to the left atrial area (7).

Laboratory Methods

To measure the IL-6, TNFα, TAA, and TOA levels and OSI in all participants, blood samples were drawn between June 1, 2014 and February 2015. Serum was separated and stored at -70°C within 30 min of collection. The reagents and serum samples were allowed to come to room temperature and were measured using a spectrophotometer (Tokyo Boeki Medical System, Japan). The serum levels of TNFα and IL-6 in both patients and controls were measured using a human Enzyme-linked immuno sorbent assay (ELISA) kit (Shanghai YeHua Biological Technology). The double-antibody sandwich ELISA kit was used to measure serum level of TNFα. Standard graphics were used to analyze the serum levels of TNFα and IL-6 in both patients and controls groups.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences software for Windows (IBM Corp., Armonk, NY, USA) version 22.0. Continuous data were expressed as mean ± standard deviation and categorical data as percentages. The Kolmogorov–Smirnov test was used to test the distribution type.

Main Points:

- Our study reports for the first time the significant relationship between the chordae rupture and oxidative stress levels (TOA-OSI).
- The results of this study show that high oxidative stress can be accepted as a risk factor for chordae rupture.
- TNFα level in the severe rheumatic mitral insufficiency group was statistically higher. These data support the role of inflammation in the development of severe rheumatic mitral insufficiency.

While the normally distributed variables were compared using the One-way Analysis of Variance (ANOVA) ANOVA test and appropriate post-hoc analysis, the not normally distributed variables were compared using the Kruskal–Wallis test, followed by a post-hoc analysis using the Mann–Whitey U-test. Further, the Chi-square test was used to assess the differences in the categorical variables between groups and the relationship between quantitative variables was tested using the Spearman rank correlation coefficient. The results were expressed as relative risk and 95% confidence interval. A $p<0.05$ was considered as statistically significant.

RESULTS

First, as mentioned earlier, the subjects in this study were divided into three groups: chordae rupture group (group 1; n=30), rheumatic mitral regurgitation group (group 2; n=30), and control group (group 3; n=20). Table 1 shows the demographic characteristics of the patients and that no statistically significant difference was observed between the groups in terms of age, gender, and systolic and diastolic blood pressure.

Table 1. Demographic assessment of patients

	Chordae rupture (n=30)	Rheumatic MR (n=30)	Control (n=20)	p
Age (years)	51.1±19.8	45.2±15.6	43.8±12.4	0.362
BMI (kg/m^2)	26.5±3.1	25.5±3.2	24.5±3.9	0.726
Systolic blood pressure (mm Hg)	124.0±10.2	118.6±9.8	120.6±8.8	0.782
Diastolic blood pressure (mm Hg)	78.0±7.1	70.9±9.7	74.9±7.7	0.564

BMI: Body mass index, MR: Mitral regurgitation

Table 2. Comparison of laboratory parameters

	Chordae rupture (n=30)	Rheumatic MR (n=30)	Control (n=20)	p
Hemoglobin (g/dL)	13.2±1.7	13.6±1.9	13.9±2.1	0.742
Hematocrit (%)	38.2±5.4	40.0±6.2	42.1±4.2	0.550
Platelet (/μ)	242.2±94.4	267.9±84.7	288.7±64.7	0.480
MCV (fL)	86.6±7.9	83.9±5.9	84.9±5.5	0.562
WBC (/μ)	8.6±3.0	7.8±2.4	8.8±2.1	0.724
Triglyceride (mg/dL)	159.4±72.1	156.4±102.2	162.4±62.1	0.664
Creatinine (mg/dL)	0.70±0.3	0.68±0.4	0.72±0.4	0.840
LDL (mg/dL)	104.0±29.2	118.1±35.3	108.1±34.9	0.736
HDL (mg/dL)	43.2±11.7	43.7±8.2	44.7±6.2	0.852

WBC: White blood cell, MCV: Mean cell volume, LDL: Low density lipoprotein, HDL: High density lipoprotein, MR: Mitral regurgitation

Similarly, as shown in Table 2, no statistically significant difference with respect to laboratory parameters (p>0.05) was observed between the three groups. The TOA and OSI levels in group 1 were found to be statistically higher than group 2 (p=0.038, p=0.026, respectively). Also TOA and OSI levels in group 1 were statistically higher than group 3 (p=0.019 and p=0.023, respectively). However no statistically significant difference with respect to the TAA, IL-6, and TNFα levels was observed between groups 1 and 3 (p>0.05). These datas are shown in Table 3.

On the contrary, the TNFα levels in group 2 were found to be statistically and significantly higher than the levels in group 1 (p=0.028). However, as shown in Table 3, no statistically significant difference with respect to TAA, TOA, OSI, IL-6, and TNFα levels (p=0.169, p=0.566, p=0.714, p=0.488, and p=0.303, respectively) was observed between groups 2 and 3.

Table 4 presents the comparison of the echocardiographic values of all groups and shows that there was no significant difference between the groups with respect to ejection fraction. The left ventricle (LV) end-diastolic volume, LV end-systolic volume, LV end-diastolic diameter, left atrium (LA) diastolic volume, LA systolic volume, LA end-diastolic diameter, and pulmonary artery systolic pressure were found to be statistically higher in groups 1 and 2 than group 3 (p<0.001).

Table 3. Comparison of inflammatory parameters

	Chordae rupture (n=30) (group 1)	Rheumatic MR (n=30) (group 2)	Control (n=20) (group 3)	p
TAA	2.19±0.27	2.21±0.36	2.09±0.18	0.370
TOA	11.73±15.83*,#	6.95±5.71	5.68±3.10	0.032
OSI	0.50±0.61*,#	0.31±0.24	0.27±0.15	0.029
IL–6	96.87±109.18	101.89±82.69	64.42±23.20	0.428
TNF–α	104.25±107.27	125.89±95.99#	81.25±32.10	0.049

TAA: Total antioxidant activity, TOA: Total oxidant activity, OSI: Oxidative stress index, IL–6: Interleukin–6, TNF– ALFA: Tumor necrosis factor alpha, MR: Mitral regurgitation
* p<0.05 for chorda rupture vs control group
# p<0.05 for chorda rupture vs rheumatic MR group

DISCUSSION

Reactive oxygen species are formed as normal products of metabolic and physiological processes and may cause harmful oxidative reactions in organisms. These harmful products can be removed by enzymatic and non-enzymatic antioxidative mechanisms. Antioxidant systems normally work in unity; they neutralize and inhibit the toxic oxygen free radicals, preventing cell damage caused by them. However, there are certain conditions under which the increase in oxidants and decrease in antioxidants cannot be prevented, and the oxidative/antioxidative balance shifts toward the oxidative status. Consequently, the oxidative stress, which has been implicated in more than 100 disorders, develops (3).

In recent years, many diseases (cancer, coronary artery disease, chronic inflammatory diseases) have been reported to be linked with increased free radical activity, establishing the importance of maintaining the oxidant/antioxidant balance.

The MV is a highly complex cardiac valve consisting of an annulus, anterior and posterior leaflets, chordae tendinea (chords), and two papillary muscles. The chordae tendinea mechanics play a pivotal role in proper MV function. Many factors including mitral valve prolapse (MVP), rheumatic valve disease, calcific-degenerative valve disease, connective tissue diseases, cardiac trauma, hypertrophic cardiomyopathy, ischemic heart diseases, and IE have been reported to be associated with CTR. Also, pregnancy, hypertension, and thalassemia have been reported as predisposing factors (2).

In a study by Juang et al. (8), 494 patients with ruptured chordae tendinea were analyzed, and 71% of them were found to be idiopathic, while 29% had secondary causes. Of the 143 patients with secondary causes, 50 had subacute bacterial endocarditis, 35 had rheumatic heart disease (RHD), 61 had MVP, while 3 re-

Table 4. Comparison of echocardiographic parameters

	Chordae rupture (n=30)	Rheumatic MR (n=30)	Control (n=20)	p
Ejection fraction (%)	56.76±7.69	56.80±7.77	61.25±6.67	0.076
Left ventricle end–diastolic volume (ml)	94.43±21.89 *,#	110.00±25.96**	69.85±12.21	<0.001
Left ventricle end–systolic volume (ml)	40.20±13.28*	47.26±13.71**	27.45±7.30	<0.001
Left ventricle end–diastolic diameter (mm)	54.40±4.93*	54.76±4.71**	45.85±1.49	<0.001
Left atrium diastolic volume (ml)	73.73±27.69*	79.06±36.59**	32.40±6.73	<0.001
Left atrium systolic volume (ml)	39.66±23.48*	51.76±35.41**	15.30±3.82	<0.001
Left atrium end–diastolic diameter (mm)	45.00±6.07*	46.76±6.85**	33.10±2.04	<0.001
Pulmonary artery systolic pressure (mmHg)	38.00±10.27*	40.66±17.31**	20.60±2.06	<0.001

MR: Mitral regurgitation
* p<0.05 for chorda rupture vs control group
# p<0.05 for chorda rupture vs rheumatic MR group
** p<0.05 for rheumatic MR vs control group

ported other reasons. Interestingly, in our study, most CTR cases developed on rheumatic ground, of which 16 (53.3%) occurred in the rheumatic MV, 7 (23.3%) in degenerative valves, and 7 (23.3%) in MVP.

Besides, based on the literature, oxidative stress has been reported to be associated with several cardiovascular risk factors such as hypertension, endothelial dysfunction, increased systemic arterial stiffness, and increased carotid wall thickness (9). However, owing to the results of recent studies, oxidative stress and inflammation may also be a predisposing factor in the development of CTR (10).

Moreover, Niao et al. (11), in their study reported new evidence of increased oxidative stress in patients with severe mitral regurgitation, probably contributing to atrial enlargement. In their study, the serum OSI was significantly higher in the mitral regurgitation AF and sinus groups than in the lone AF and healthy subjects groups ($p<0.0001$). Similarly, the left atrial size was also significantly larger in the mitral regurgitation AF and sinus groups than in the lone AF and healthy subjects groups ($p<0.0001$). In addition, in the overall study population, the OSI significantly and positively correlated with the left atrial size ($p=0.0008$).

Another study by Lloyd et al. (12) reported that myofibrillar degeneration can occur as a result of increased oxidative stress and can be responsible for the increase in the heart failure.

Overall, many previous studies have addressed the problem of oxidative stress in atherosclerosis and coronary artery disease, suggesting it as a possible unifying mechanism for many cardiovascular risk factors. This vicious circle between oxidative stress and inflammation can occur not only in the diseased arterial wall-where it also causes loss of antioxidant protection and cell death (13)-but, as suggested in a recent pilot study, there could also be a possible link between the serum OSI, left atrial enlargement, and atrial fibrillation (14). These results suggest that the oxidative stress may play a role in heart-valve pathogenesis.

In patients with heart-valve diseases, the serum paraoxonase-1 activity is reportedly reduced due to the elevated levels of oxidative stress and disturbances of heart-valve metabolism. The findings from this novel detailed approach implicate an inflammatory/oxidative stress process in the pathogenesis of the valve's presentation associated with the heart-valve disease. The strength of the significance in differences encourage us to propose that the role of oxidative stress in heart-valve disease pathogenesis is very prominent, and that the oxidative stress markers are potential ancillary tests to evaluate the state of the disease (15).

Many studies have reported oxidative stress as one of the most important contributors to the progression of rheumatic and degenerative valve diseases (16, 17). Aydemir et al. (10) reported positive significant correlations between midkine and reduced glutathione and selenium levels in patients with CTR. According to their data in which selenium, zinc, midkine, and reduced glutathione decreased in CTR patients, the inflammatory response, oxidative stress, and trace element levels may contribute to the etiopathogenesis of mitral regurgitation and/or ruptured chordae tendinea. Oxidative stress has also been reported to lead to vascular damage and participate in the pathomechanisms of aortic dissection and aneurysm formation. Another study suggests that increased oxidative stress may play an important role in the thoracic aorta dissection (18).

Nevertheless, in our study, the oxidative/antioxidative balance was evaluated in all groups. Compared with the other two groups, the TOA and OSI levels in the chordae rupture (group 1) were found to be significantly and statistically higher. Based on the results of this study, we report that high oxidative stress can be accepted as a risk factor for chordae rupture.

Inflammation is an important contributor to the pathogenesis of RHD. An RHD is a disorder of heart valves caused by a combination of immune, genetic, and environmental factors. Cytokines are important mediators of inflammatory and immune responses. They are known to play an important role in regulating immunological and inflammatory reactions. According to the literature, cytokines play a role in developing rheumatic valve disease, hypertension, coronary artery disease, heart failure, and pulmonary hypertension (19-21).

The cytokines TNFα and IL-6 play a pivotal role in the pathogenesis of many diseases, and TNFα, in particular, plays an active role in the pathogenesis of rheumatic diseases. Increased TNFα levels are generally reported when the heart is infiltrated by inflammatory cells (22). Davutoğlu et al. (23) reported in their study that plasma levels of IL-6, Interleukin-8 (IL-8), IL-2 receptor (IL-2R), TNFα, and high-sensitive C-reactive protein (hs-CRP) were significantly higher in patients with RVD than the controls ($p<0.001$). The chronic phase of RVD is associated with ongoing serum inflammatory mediators that correlate strongly with the severity of valve involvement, valve scarring, subsequent valve calcification, and decreasing functional status. Future research in this area should focus on whether anti-inflammatory drugs might reduce progression, morbidity, and mortality in patients with chronic RVD.

In another study by Mohamed et al. (24), the TNFα level was reported to be significantly higher in patients with rheumatic valvular involvement. Similar findings were found in the study by Rehman et al. (25). Our findings are therefore consistent with these two studies. The TNFα levels may be an indicator of increased inflammation in rheumatic MV disease and should be considered as an important factor in the development of rheumatic valve diseases.

CONCLUSION

This study shows that there is a significant relationship between chordae rupture and oxidative stress markers (TOA–OSI) and that high oxidative stress can be accepted as a risk factor for chordae rupture. In addition, TNFα levels in the rheumatic severe mitral insufficiency group were found to be higher than the chordae rupture group, which supports the role of inflammation in the development of rheumatic severe mitral insufficiency.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School of Medicine (1185- 02.02.2015).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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