

Manuscript type: Original Article

DOI: 10.5152/EurJTher.2019.19063

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

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Received: 13.06.2019

Accepted: 16.06.2019

Cite this article as: Kaplan M, Yavuz F, Davutoğlu V, Yüce M, Dönmez Y, Özcan Abacıoğlu Ö. The Relationship between Mitral Chordae Rupture and Inflammation Level and Oxidative Stress. Eur J Ther 2019; DOI: 10.5152/EurJTher.2019.19063

Abstract

Background and aim: There are many factors associated with chorda tendinea rupture. The present study aims to investigate the role of Interleukin-6 (IL-6), total antioxidant activity (TAA), total oxidant activity (TOA) and tumor necrosis factor alpha (TNF- α) levels on the development of the mitral valve chordae tendinea rupture.

Methods: Our study consisted of 30 patients with mitral chordae rupture, 30 patients with severe rheumatic mitral regurgitation, and 20 healthy participants who were admitted to our polyclinic unit. The participants do not have a previously known comorbid disease. After transthoracic echocardiography, their diagnoses were confirmed by the transesophageal echocardiography. Plasma IL-6, TAA-TOA and TNF- α level of all patients were measured and their oxidative stress index (OSI) was calculated.

Results: Compared to the rheumatic severe mitral insufficiency patients and control group, TOA-OSI levels in the chordae rupture group were significantly higher ($p=0.038$ and $p=0.019$, respectively). The TNF- α levels in the rheumatic severe mitral insufficiency group were determined as statistically and significantly higher than the chordae rupture group ($p=0.028$).

Conclusion: We have put forth that there is a significant relationship between the chordae rupture levels and oxidative stress levels (TOA-OSI) for the first time in our study. According to the results of our study, high oxidative stress might be accepted as a risk factor for chordae rupture. In addition, it has been observed that the TNF- α level in the rheumatic severe mitral insufficiency group have been higher than those in the chordae rupture group. It seems, these data support the role of inflammation in the rheumatic severe mitral insufficiency development.

Keywords: Mitral valve, chordae rupture, oxidative stress, IL-6, TNF- α

Introduction

Chordae tendinea rupture (CTR) is increasingly reported as an important cause of mitral regurgitation (1). Mitral valve prolapse (MVP), rheumatic valve disease, calcific-degenerative valve disease and infective endocarditis (IE) have been reported as leading causes of chorda tendinea rupture (2). The underlying causes of chordae tendinea rupture and their frequencies vary.

Today more than a hundred diseases are associated with free oxygen radicals. Total oxidant activity (TOA) is a parameter which represents the total amount of all oxidants in a sample. Total antioxidant activity (TAA) is a parameter indicating the total amount of all antioxidants in a similar way. The oxidative stress index value is calculated by dividing these values to each other (3).

IL-6 is pleiotropic cytokine produced by T cells, lymphocytes, fibroblasts, adipocytes, macrophages and endothelial cells (4). IL-6 has both endocrine and paracrine effects, and stimulates platelet aggregation along with tissue factor, CRP and the expression of fibrinogen (5). Several studies showed that the inflammatory component in atherosclerosis may contribute to increased risk for cardiovascular disease (CVD). IL-6 and TNF- α assumed as key pro-inflammatory and immune-stimulatory cytokines for CVD and the metabolic syndrome. TNF- α has also been implicated in the

pathogenesis of a number of cardiovascular diseases, including atherosclerosis, myocardial infarction, heart failure, myocarditis and cardiac allograft rejection.(6).

TAA, TOA, IL6 and TNF- α are thought to increase the tissue damage. In this study, we planned to seek the relationship between IL-6, TNF- α , TAA, TOA and mitral valve chordae rupture.

Methods

30 patients having mitral chordae rupture (group 1), 30 patients 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 1 June 2014 and 31 January 2015 included to this study. The participants do not have a previously known comorbid disease. The study was approved by the Gaziantep University Medicine Faculty Ethics Committee. All patients and participants provided written informed consent.

Exclusion criteria were previous acute coronary syndrome, coronary artery disease, dilated cardiomyopathy, smoking, autoimmune diseases, pregnancy, diabetes mellitus, rheumatologic diseases, ejection fraction less than 50%, chronic renal or liver disease, active malignancy, vitamin or antioxidant replacement therapy, and known chronic diseases.

Age, sex, body mass index, drug therapy, hematological and biochemical results were recorded. Blood samples were obtained to measure IL-6, TNF-, TAA, TOA and OSI. The OSI was defined as the ratio of the TOA level to TAA level.

All patients underwent echocardiography to assess left ventricular systolic, diastolic functions and dimensions. Ejection fraction by Simpson method, volumes, tissue Doppler parameters (S, e, a), mitral valve PW parameters (E, A) were recorded, grading of mitral insufficiency was assessed by PISA method, vena contracta size and jet area/left atrial area (7).

Laboratory methods

All blood samples were collected to measure IL-6, TNF- α , TAA, TOA and OSI during 1 June 2014-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. TAS - TOS reagents were charged to spectrophotometry (Tokyo Boeki Medical System, Japan). After controlling the calibration device to the examples given device. After operation of the sample results were printed. Patients and controls TNF-alpha and IL-6 serum levels were measured using a human ELISA kit (Shanghai YeHua Biological Technology). This double antibody kit to measure serum levels of TNF- alpha is to use the sandwich ELISA technique. Serum TNF-alpha and IL-6 levels in patients and controls were analyzed by standard graphics.

Statistical analysis

All statistical tests were carried out using SPSS 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous data are expressed as mean \pm standard deviation and categorical data are expressed as percentages. Kolmogorov-Smirnov test was used to test the distribution type. Normal distributed variables were compared with One Way ANOVA test and appropriate post-hoc analysis. Not normal distributed variables were compared with Kruskal–Wallis test. Mann Whitey U test was used for the post-hoc analysis. The χ^2 -test was used to assess differences in categorical variables between groups. The relationship between quantitative variables was tested with the Spearman rank correlation coefficient. The results are expressed as relative risk and 95% confidence interval (CI). A p-value less than 0.05 considered statistically significant.

Results

First, these subjects were divided into three groups: chordae rupture group (n = 30), rheumatic mitral regurgitation group (n = 30) and control group (n=20). The demographic characteristics of the patients are shown in Table 1. Statistically, there was no significant difference between the groups in age, gender and systolic and diastolic blood pressure.

Statistically, there was no significant difference between all groups (group 1, 2 and 3) in laboratory parameters ($p>0,05$). These results of the patients are shown in Table 2.

Compared with the rheumatic severe mitral insufficiency patients, the TOA and OSI levels in the chordae rupture group (group 1) have been found to be significantly high in terms of statistics ($p=0.038$, $p=0.026$ respectively). Compared with the control group (group 3), the TOA and OSI levels in the chordae rupture group have been found to be significantly high in terms of statistics (respectively $p=0.019$ and $p=0.023$). Group 1 and group 3 patients serum IL-6, TNF- α , TAA, TOA and OSI values shown in table 3. Statistically there was no significant difference between both groups (group 1 and 3) regarding TAA, IL-6 and TNF- α ($p>0,05$).

The TNF- α levels in the (group 2) have been determined as statistically and significantly higher than the levels in the chordae rupture group ($p=0.028$). Group 2 and group 3 patients serum IL-6, TNF- α , TAA, TOA and OSI values shown in table 3. Statistically there was no significant difference between both groups (group 2 and 3) regarding TAA, TOA, OSI, IL-6 and TNF- α (respectively $p=0,169$, $p=0,566$, $p=0,714$, $p=0,488$ and $p=0,303$).

All groups' echocardiographic values were shown in Table 4. Statistically, there was no significant difference between groups regarding ejection fraction. But compared with the control group, 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 have been found to be significantly high in terms of statistics ($p < 0.001$). The comparisons of echocardiographic parameters are shown in table 4.

Discussion

Reactive oxygen species (ROS) are produced in metabolic and physiological processes, and harmful oxidative reactions may occur in organisms. These harmful products removed by enzymatic and non-enzymatic antioxidative mechanisms. Antioxidant systems normally work in unity; they protect the cells from the toxic oxygen free radicals damage. Antioxidant molecules generated in the body prevents harmful substances by inhibiting them. Under certain conditions, the increase in oxidants and decrease in antioxidants cannot be prevented, and the oxidative/antioxidative balance shifts towards the oxidative status. Consequently, oxidative stress, which has been implicated in over 100 disorders, develops (3).

In recent years, many diseases (cancer, coronary artery disease, chronic inflammatory diseases) are stated to be linked with increased free radical activity. Because of that oxidant / antioxidant balance is very important.

The mitral valve (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. There are many factors associated with chorda tendinea rupture. Mitral valve prolapse (MVP), rheumatic valve disease, calcific-degenerative valve disease, connective tissue diseases, cardiac trauma, hypertrophic cardiomyopathy, ischemic heart diseases and infective endocarditis (IE) have been reported as the causes of chorda tendinea rupture. Also pregnancy, hypertension and thalassemia have been reported as predisposing factors. (2)

Juang et al. analyzed 494 patients with ruptured chorda tendinea. Most of the patients (71%) were idiopathic, while remaining 29% had secondary causes. Of these 143 patients; 50 patients had subacute bacterial endocarditis, 35 patients had rheumatic heart disease, 61 patients had MVP, while 3 patients had other reasons (8). In our study; most of the cases of chordae tendinea rupture developed on rheumatic ground. Sixteen (53.3%) cases of chorda tendinea rupture occurred in the rheumatic mitral valve, 7 (23.3%) in degenerative valves and 7 (23.3%) in MVP.

In literature, oxidative stress is associated with cardiovascular risk factors including hypertension, endothelial dysfunction, increased systemic arterial stiffness, increased carotid wall thickness(9). As

a result of recent studies, inflammation and oxidative stress may be a predisposing factor in the development of the chorda tendinea rupture (10).

Niao et al. reported that new evidence of increased oxidative stress in human severe mitral regurgitation, probably contributing to atrial enlargement. The serum oxidative stress index was significantly higher in the mitral regurgitation AF group and sinus group than in the lone AF group and healthy subjects ($p < 0.0001$). Left atrial size was significantly larger in the mitral regurgitation AF group and sinus group than in the lone AF group and healthy subjects ($p < 0.0001$). The oxidative stress index significantly and positively correlated with left atrial size in the overall study population ($p = 0.0008$) (11).

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

Previous studies have widely addressed the problem of oxidative stress in atherosclerosis and coronary artery disease, suggesting that oxidative stress might even be considered as a unifying mechanism for many cardiovascular risk factors. That 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). A recent pilot study assessing a limited number of patients suggested a possible link between serum oxidative stress index, left atrial enlargement and atrial fibrillation (14). All these results suggest that the oxidative stress may play a role in heart-valve pathogenesis.

Serum paraoxonase-1 activity is reduced in patients with heart valve diseases, caused by elevated 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 oxidative stress markers are potential ancillary tests to evaluate the state of the disease (15).

Also in other studies, oxidative stress has been regarded as one of the most important contributors to the progression of rheumatic and degenerative valve diseases (16, 17). Aydemir et al. reported that there were positive significant correlations between midkine, and reduced glutathione and selenium levels in patients with chorda tendinea rupture. According to their data in which selenium, zinc, midkine, and reduced glutathione decreased in chorda tendinea rupture patients, inflammatory response, oxidative stress, and trace element levels may contribute to etiopathogenesis of mitral

regurgitation and/or ruptured chordae tendineae (10). Oxidative stress leads to vascular damage and participates in the pathomechanisms of aortic dissection and aneurysm formation. This study suggests that increased oxidative stress may play an important role in the thoracic aorta dissection (18).

In our study, oxidative/antioxidative balance is evaluated in all groups. Compared with the other groups, the TOA and OSI levels in the chordae rupture (group 1) have been found to be significantly high in terms of statistics. According to the results of our study, high oxidative stress might be accepted as a risk factor for chordae rupture.

Inflammation is an important contributor to the pathogenesis of rheumatic heart disease (RHD). It 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. Cytokines are known to play an important role in regulating immunological and inflammatory reactions. The cytokines TNF- α and IL-6 have an active role in the pathogenesis of many diseases. In the literature, cytokines play role in developing rheumatic valve disease, hypertension, coronary artery disease, heart failure and pulmonary hypertension (19,20,21).

TNF- α is a cytokine that has an active role in the pathogenesis of rheumatic diseases. Increased TNF- α levels have been shown when the heart is infiltrated by inflammatory cells (22). Davutoğlu et al. reported that plasma levels of IL-6, Interleukin-8(IL-8) , IL-2 receptor (IL-2R), TNF- α and high-sensitive C-reactive protein (hs-CRP) were significantly higher in patients with RVD than in controls ($p < 0.001$). The chronic phase of RVD is associated with ongoing serum inflammatory mediators which 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 (23).

Mohamed et al. reported that TNF- α level was significantly higher in patients with rheumatic valvular involvement (24). Similar findings were found in the study by Rehman et al (25). Our findings were consistent with these two studies. TNF- α levels may be an indicator of increased inflammation in rheumatic mitral valve disease. This data supports that inflammation may be an important factor in the development of rheumatic valve diseases.

Conclusion

We showed that there is a significant relationship between chordae rupture and oxidative stress markers (TOA-OSI) in our study. High oxidative stress might be accepted as a risk factor for chordae rupture. In addition, TNF- α levels in the rheumatic severe mitral insufficiency group were higher

than the chordae rupture group. These data support the role of inflammation in the developing of rheumatic severe mitral insufficiency.

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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

Abbreviations: 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

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

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

Abbreviations: 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

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

Abbreviations: 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**