According to the ruling of the Medical Sciences Publications Commission No. 14313-80/10/1 and 36914-85/2/10 signed by the Minister of Health and Medical Education and the Head of the Medical Sciences Publications Commission of the Islamic Republic of Iran, this journal has been granted accreditation as a scientific-research journal.

This Journal is indexed in the Scientific Information Database (WWW.SID.IR) and IMEMR and Index COPERNICUS, SCOPUS, CINAHL, and Google Scholar.
In the Name of God, the Most Beneficent, the Most Merciful

Dear colleagues and friends,

We are delighted to present to you Volume 16, Number 4 (Winter, 2015) issue of the Iranian Heart Journal (IHJ), which contains some interesting new studies and case reports in the domains of cardiovascular medicine and surgery from our colleagues across Iran. IHJ is indexed in the Scientific Information Database (WWW.SID.IR), IMEMR, Index Copernicus, Scopus, and CINAHL, thereby facilitating access to published literature. There is no doubt, however, that IHJ requires your opinions, ideas, and constructive criticism in order to accomplish its main objective of disseminating cutting-edge medical knowledge. As ever before, we continue to look forward to receiving your latest research and cases.

Yours truly,

A. Hussein Tabatabaie, M.D.
Editor-in-Chief,
Iranian Heart Journal

F. Noohi, M.D.
Chairman,
Iranian Heart Journal
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Original Article

Echocardiographic Evaluation of Patients with Behçet's Disease

Farahnaz Nikdoust, M.D.1, Gelayol Ansari, M.D.1*, Farhad Shahram, M.D.2, Seyed Abdolhussein Tabatabaie, M.D.1

ABSTRACT

Background: Considering the nature of Behçet's disease (BD), which involves multisystem inflammation, we sought to compare the echocardiographic characteristics of BD >5 years’ duration with those of healthy subjects.

Methods: We compared 73 patients with BD with 74 age- and sex-matched healthy controls. The subjects underwent transthoracic echocardiography and tissue Doppler imaging for the measurement of cardiac function and evaluation of the heart valves. The echocardiographic parameters were then compared between the study groups.

Results: Among the echocardiographic parameters, only left ventricular end-diastolic diameter was significantly lower in the patients with BD (47.0±5.2) than that in the control group (50.8±4.7; P<0.001). There was also no relationship between the echocardiographic parameters and the active stage of the disease.

Conclusions: Diastolic dysfunction was significantly more common in the patients with BD >5 years’ duration than in the control group. The other echocardiographic indices were similar in both groups. (Iranian Heart Journal 2015; 16(4): 6-11)

Keywords ■ Behçet's disease ■ Echocardiography ■ Left ventricular end-diastolic diameter ■ Systolic function ■ Diastolic function

Behçet’s disease (BD) is a multisystemic, inflammatory, autoimmune disease with an unknown etiology. Articular, vascular, intestinal, pulmonary, cutaneous, and neurological involvements are common in this disease and its basic pathological process is vasculitis. Mucocutaneous and neurological involvements are the most common manifestations of the disease; however, due
to the systemic inflammatory nature of the disease, the involvement of the other organs and systems is quite common.  

Although cardiac involvement is not a dominant complication in BD, it is observed in some patients. Cardiac involvement in BD is also known as cardiobehçet.  

This condition includes endocarditis, pericarditis, myocarditis, valvular disorders, intracardiac thrombosis, endomyocardial fibrosis, cardiomyopathy, coronary artery lesions, and arrhythmias—particularly ventricular arrhythmias.  

However, data on cardiovascular involvement are limited to case reports and case series. Many aspects of cardiovascular involvement have not been explored yet. Although transthoracic echocardiography has been used to investigate cardiac involvement in previous studies, there is limited evidence regarding the echocardiographic features of patients with BD in the various stages of the disease. Accordingly, we aimed to investigate the echocardiographic characteristics of patients with BD >5 years’ duration referred to our institution in comparison with those of healthy controls. We also compared the echocardiographic characteristics of patients with active disease and those who were in remission to determine whether disease flare-up could influence the cardiac structure and function.

**METHODS**

In this study, we enrolled patients with BD >5 years’ duration referred to the Rheumatology Clinic of Dr. Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. Patients with a history of cardiovascular disease were excluded. Age- and sex-matched healthy controls were selected from the hospital staff. All the participants signed an informed consent before enrolment in the study, and the study protocol was approved by the institutional board of research and Ethics Committee of Tehran University of Medical Sciences.

Following admission, detailed history was obtained from the patients and clinical examination was performed by the physician in charge. Demographic variables comprised age, sex, height, weight, and waist circumference. The patients were also checked for the presence of the classic cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, and family history of premature coronary artery disease. Clinical parameters encompassed heart rate, blood pressure, presenting symptom, history of myocardial infarction or stroke, and congestive cardiac failure. Accordingly, the patients were allocated to 2 groups of with or without the metabolic syndrome.

After collecting baseline demographic and clinical data at the time of admission, the patients were evaluated via transthoracic echocardiography and tissue Doppler imaging, using the GE Vivid 7 Dimensions ultrasound system (GE Healthcare, Milwaukee, WI). All the echocardiographic evaluations were performed by a cardiologist, who was blinded to the study protocol. Left ventricular (LV) size was assessed in terms of end-systolic and end-diastolic diameters in the parasternal long-axis view and end-systolic and end-diastolic volumes in the apical 4-chamber view. LV systolic function and ejection fraction (LVEF) were measured using the Simpson method, M-mode, and eyeball. LV size was evaluated by measuring LV diameter in the apical 4-chamber view. End-systolic and end-diastolic volumes were both measured in apical 4-chamber view. The reference limits of all the echocardiographic parameters were defined according to the guidelines of the American Society of Echocardiography.

**Statistical Analysis**

The continuous variables are shown as means ± standard deviations (SD) and the categorical variables are described as numbers (percentages). The paired t-test was utilized to
compare the continuous variables between the study groups. The chi-square test was used to compare the categorical variables between the groups. All P values <0.05 were considered statistically significant. The statistical analyses were performed using PASW software, version 18 (SPSS Inc., Chicago, Illinois, U.S.A.).

**RESULTS**

In this study, we compared 73 patients with BD >5 years’ duration (mean age= 42.2 y; male gender=48%) with 74 healthy individuals as the control group. The mean duration of disease in the patients with BD was 18.8±6.7 years. Except for body mass index (BMI), both groups were more likely to be similar in the demographic and clinical variables. Prolonged QT interval was identified in 8 patients with BD, while none of the controls had it. However, this was not significantly different. The baseline characteristics of the study groups are compared in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Comparison of the baseline demographic and clinical characteristics between the patients with Behçet’s disease and the healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>BSA, m²</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
</tr>
<tr>
<td>Respiratory rate, /min</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
</tr>
<tr>
<td>Noncardiac disease, n (%)</td>
</tr>
<tr>
<td>ST-T change in ECG, n (%)</td>
</tr>
<tr>
<td>Prolonged QT interval, n (%)</td>
</tr>
<tr>
<td>Heart block, n (%)</td>
</tr>
<tr>
<td>Dysrhythmia, n (%)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, Body mass index; bpm, Beat per minute; BSA, Body surface area; CAD, Coronary artery disease; ECG, Electrocardiogram

In the comparison between the patients with BD and the control group apropos the echocardiographic parameters, there were no significant differences between the groups except regarding end-diastolic diameter, which was more likely to be lower in the patients with BD (P<0.001) (Table 2). Two patients in the BD group had systolic dysfunction, while none of the controls had this condition (P=0.22). Nonetheless, diastolic dysfunction was significantly more common in the patients with BD (17 cases) than in the controls (5 cases) (P<0.001).
Echocardiography in Behçet's Disease

Nikdoust F, et al.

Table 2. Comparison of the echocardiographic characteristics between the patients with Behçet's disease and the healthy controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n=74)</th>
<th>Behçet's Disease (n=73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH, N (%)</td>
<td>5 (6.8)</td>
<td>6 (9.0)</td>
<td>0.64</td>
</tr>
<tr>
<td>MR, N (%)</td>
<td>6 (21.4)</td>
<td>9 (22.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>MVP, N (%)</td>
<td>6 (26.1)</td>
<td>5 (11.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Calcification, n (%)</td>
<td>1 (4.8)</td>
<td>0 (0)</td>
<td>0.16</td>
</tr>
<tr>
<td>TS, N (%)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>TR, N (%)</td>
<td>4 (23.5)</td>
<td>3 (10.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>AS, N (%)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>AR, N (%)</td>
<td>2 (25.0)</td>
<td>2 (9.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>PS, N (%)</td>
<td>0 (0)</td>
<td>1 (2.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>PI, N (%)</td>
<td>4 (40.0)</td>
<td>3 (18.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>TRG</td>
<td>19.6±3.3</td>
<td>18.3±2.4</td>
<td>0.2</td>
</tr>
<tr>
<td>PAP</td>
<td>24.1±3.5</td>
<td>21.2±5.2</td>
<td>0.1</td>
</tr>
<tr>
<td>LA</td>
<td>34.2±4.5</td>
<td>34.6±8.1</td>
<td>0.72</td>
</tr>
<tr>
<td>LVESD</td>
<td>33.5±5.2</td>
<td>32.6±5.5</td>
<td>0.31</td>
</tr>
<tr>
<td>LVEDD</td>
<td>50.8±4.7</td>
<td>47.0±5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWT</td>
<td>7.8±1.1</td>
<td>7.8±1.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Septal thickness</td>
<td>7.7±1.5</td>
<td>7.7±1.9</td>
<td>0.81</td>
</tr>
<tr>
<td>LVEF</td>
<td>57.8±3.8</td>
<td>57.7±3.9</td>
<td>0.81</td>
</tr>
<tr>
<td>M mode</td>
<td>54.2±7.2</td>
<td>57.5±5.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Simpson</td>
<td>56.9±3.0</td>
<td>58.2±4.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Eye ball</td>
<td>57.0±3.3</td>
<td>57.2±3.6</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Abbreviations: AR, Aortic regurgitation; AS, Aortic stenosis; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; PWT, Posterior wall thickness; LVEF, Left ventricular ejection fraction; LVH, Left ventricular hypertrophy; LVESD, Left ventricular end-systolic diameter; PAP, Pulmonary artery pressure; MR, Mitral regurgitation; MVP, Mitral valve prolapse; PI, Pulmonary insufficiency; PS, Pulmonary stenosis; TR, Tricuspid regurgitation; TS, Tricuspid stenosis

DISCUSSION

In the present study, we observed a tendency for diastolic dysfunction in our patients with BD in comparison with our healthy controls. However, there were no other significant echocardiographic findings in this group. The earliest reports of cardiovascular involvement in the context of BD mostly included patients with ventricular thrombi, pericarditis, great artery vasculitis, and valvular involvement.8,10 As cardiac symptoms were uncommon in BD, providing thorough information on cardiovascular conditions in patients with BD was always an issue. So, the frequency and pathophysiology of cardiac lesions in BD are not clear yet and cardiovascular involvement has been reported as 7–46%.11 In a pioneer study on the echocardiographic evaluation of patients with BD, cardiovascular findings included mild-to-moderate asymptomatic pericarditis, slight aortic root dilatation suggesting aortic aneurism, and mitral regurgitation.8 In another study including 35 patients with BD, dilatation of the proximal aorta, interatrial septal aneurysms, and mitral valve prolapse were the common echocardiographic findings among the patients.7 Moreover, sporadic cases of endocarditis, myocarditis, pericarditis, aortic aneurysm, acute myocardial infarction, ventricular thrombosis, congestive cardiomyopathy, and valve dysfunction have been reported.5,12,13 The findings of our study were also similar to previous works. Although none of the valvular conditions were different from the control group, some of the conditions such as tricuspid stenosis, aortic stenosis, and pulmonary stenosis were only observed in the patients with BD. This may be attributable to the involvement of the great arteries inasmuch as the stenosis of the pulmonary arteries in the context of BD-related vasculitis has been
previously reported. Nonetheless, we did not evaluate the presence of vasculitis in patients who had valvular stenosis. We also noticed that LVEDD was significantly lower in the patients with BD, which may be the sign of diastolic dysfunction. This is in line with another study that showed a higher rate of diastolic dysfunction in patients with BD and suggested myocardial fibrosis and coronary ischemia due to vasculitis as the probable causes of this diastolic dysfunction.  

**Study Limitations**  
The first and foremost limitation of this study is the limited number of its participants. BD is not a very common disease; therefore, case selection for clinical studies on BD is challenging. On the other hand, this was a single-center study in a university hospital and the patients received standard care and treatment. Consequently, it is probable that the patients in this study were well-controlled and, thus, had an acceptable clinical condition with minimal complications as compared to patients with BD who live in smaller cities and who may not receive ideal care and, as such, may have more complications including cardiovascular involvement. We, thus, recommend a multicenter study incorporating a larger number of patients with BD in different stages of the disease. Long follow-up of the patients and regular echocardiographic evaluations may help to understand the exact changes of cardiac function and structure in patients with BD.

**CONCLUSIONS**  
Transthoracic and Doppler echocardiography is a useful method for assessing cardiovascular involvement in BD. Our study showed lower LVEDD as a sign of diastolic dysfunction in the patients with BD, although the other echocardiographic parameters were statistically similar to those in the healthy controls. The findings of the present study highlight the necessity for assessing cardiac function in patients with BD. Further investigations are required on the various aspects of cardiac involvement in BD. Indeed, there is a great need for further studies to determine the exact changes in the cardiac function and its exacerbation through time in order to establish preventive and treatment measures.

**Conflict of Interest**  
The authors have no conflict of interests to declare.

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Original Article

Relationship between Late Gadolinium Enhancement Extent in Cardiac Magnetic Resonance Imaging and Severity of Coronary Artery Disease in Old Myocardial Infarction

Mohsen Maadani, M.D. 1, Shabnam Madadi, M.D. 1, Mahmoud Fagheeh M.D. 1*, Sara Adimi, M.Sc. 2, Yaghoob Bagheri, M.D. 1

ABSTRACT

Background: Contrast-enhanced cardiac magnetic resonance imaging (CMR) is an accurate imaging modality for the noninvasive evaluation of myocardial infarction (MI). We sought to assess the relationship between the severity of coronary involvement and the extent and pattern of myocardial scars in CMR of patients with a history of remote MI.

Methods: The CMR of 60 patients with a history of remote ST-elevation or non-ST elevation MI who were candidate for selective coronary angiography and referred for CMR for an evaluation of myocardial viability was reviewed and compared with selective coronary angiographic findings.

Results: Among the 60 patients with a history of old MI, 78.3% were male and the mean (SD) of age was 61.2±11.5 years. There was no association between the severity of coronary stenosis in each territory and the presence of myocardial scar detected by the late gadolinium enhancement of CMR. (P values for all the territories of the 3 vessels were >0.05.) There was a significant association between coronary artery run-off and the presence of late gadolinium enhancement in CMR. (P values for the left anterior descending, left circumflex artery, and right coronary artery were 0.002, <0.001, and <0.001, respectively.) We found a significant relationship between the pattern of the scars in terms of being transmural or non-transmural and the severity of coronary artery stenosis (P<0.001), and the pattern of the scars was not associated with coronary artery run-off (P=0.2).

Conclusions: The results of this study support the hypothesis that the time window for revascularization will be increased in the presence of an antegrade coronary flow in the jeopardized myocardium and that it could limit infarct progression and result in a subsequent lesser extent of myocardial scar. (Iranian Heart Journal 2015; 16(4): 12-18)

Keywords: Magnetic resonance imaging Late gadolinium enhancement Myocardial infarction

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Contrast-enhanced cardiac magnetic resonance imaging (CMR) is an accurate imaging modality for the noninvasive evaluation of coronary artery disease (CAD). The myocardial tissue characteristics can directly be visualized by CMR, and late gadolinium enhancement (LGE) imaging in CMR can detect the presence and extent (degree and pattern) of the myocardial scar tissue in patients with a history of remote or recent myocardial infarction (MI). The extent of the myocardial scar tissue in CMR has a considerable prognostic significance in patients with coronary artery disease and is related to the severity of coronary lesions.

**OBJECTIVES**

In this study, we aimed to investigate the relationship between the severity of coronary involvement and the extent and pattern of myocardial scars in the CMR of patients with a history of remote MI.

**METHODS**

The CMR of 60 patients with a history of remote ST-elevation or non-ST elevation MI who were candidates for selective coronary angiography and were referred for CMR for an evaluation of myocardial viability was reviewed. The presence of MI was confirmed by reviewing the hospital records and considering the guidelines of the American Heart Association (AHA) in the diagnosis of acute MI. Patients with a history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) were excluded.

The study was approved by the institutional research and ethics committee.

**Coronary Angiography Protocol**

The indication for coronary angiography was based on approved guidelines. Selective coronary angiography was performed in all the patients via the femoral approach using the Seldinger technique. The left and right anterior and posterior projections were obtained from the left and right coronary arteries in all the patients. The angiograms were assessed by an expert cardiologist, and the number of the vessels involved, severity of lesions, and run-offs of stenotic coronary arteries were recorded.

**CMR Protocol**

Cardiac MRI with a 1.5 Tesla Avante Siemens device with a gadolinium-based contrast agent (Magnevist) was done. Steady-state free-precession sequences for cine images were done. Consecutive breath-hold short axes of the heart were used to obtain functional assessment. Perfusion MRI was performed at rest using a first-pass technique with fast intravenous injections of a gadolinium-based contrast agent. Myocardial edema in the acute phase of MI was shown as a bright signal on T2-weighted images. LGE images as T1-weighted inversion recovery sequences were acquired 10 minutes after an intravenous administration of gadolinium and the inversion time was chosen to null myocardial signal using the inversion time scout. The pattern of LGE was used to differentiate post-infarction necrosis (subendocardial or transmural LGE) based on ≤50% of wall thickness involvement or ≥50%.

**Statistical Analysis**

IBM SPSS statistics, version 19, for Windows (IBM Corp, Armonk, NY, U.S.A.) was applied for all the statistical analyses. One-sample Kolmogorov–Smirnov test was used to assess normal distribution. The quantitative variables are expressed as means (SD), and the categorical variables are expressed as numbers (percentages). To compare the variables, we employed the chi-square test or the Mann–Whitney test, as appropriate. To assess the sensitivity and specificity of CMR in the prediction of coronary artery involvement, we utilized 2×2 tables. P values <0.05 were considered significant.
**RESULTS**

Among the 60 subjects in the study population, 47 (78.3%) patients were male. The mean (SD) of age was 61.2±11.5 years, between 35 and 86 years. The mean (SD) of left ventricular ejection fraction (LVEF) by echocardiography and CMR was 26.8 (10.3) and 27.6 (11.6), respectively. Table 1 depicts the demographic and angiographic characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristics of the study population (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Values</strong></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
</tr>
<tr>
<td>Sex, number (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>RWMA, number (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Coronary involvement, number (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Table 2 depicts detailed coronary angiographic findings of the study population. The left anterior descending (LAD), left circumflex artery (LCX), and right coronary artery (RCA) were involved in 93.3%, 78.3%, and 83.3% of the subjects, respectively. Severe stenosis and poor run-off were observed in a minority of the patients (Table 2).

<table>
<thead>
<tr>
<th>Severity, number (%)</th>
<th>Coronary Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAD</td>
</tr>
<tr>
<td>Patent</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Mild</td>
<td>34 (56.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

Table 3 depicts the CMR findings of the study population. We found no association between the severity of coronary stenosis in each territory and the presence of myocardial scar detected by LGE in CMR. (P values for all the territories of the 3 vessels were >0.05.) However, there was a significant association between coronary artery run-off and the presence of LGE in CMR. (P values for the LAD, LCX, and RCA were 0.002, <0.001, and <0.001, respectively.) On the other hand, in the patients who showed myocardial scar based on LGE in CMR, there was a significant association between the pattern of the scars in terms of being transmural or non-transmural and the severity of coronary artery stenosis (P<0.001), and the pattern of the scars was not associated with coronary artery run-off (P=0.2).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, mean(SD)</td>
<td>27.6 (11.7)</td>
</tr>
<tr>
<td>LVEDD, mean(SD)</td>
<td>198.5 (65.3)</td>
</tr>
<tr>
<td>LVESD, mean(SD)</td>
<td>139.7 (66.6)</td>
</tr>
<tr>
<td>RWMA, number (%)</td>
<td>Anterior 14 (23.3)</td>
</tr>
<tr>
<td></td>
<td>Posterior 15 (25)</td>
</tr>
<tr>
<td></td>
<td>Anterior and Posterior 31 (51.7)</td>
</tr>
<tr>
<td>LGE, number (%)</td>
<td>LAD territory 51 (85)</td>
</tr>
<tr>
<td></td>
<td>LCX territory 33 (55)</td>
</tr>
<tr>
<td></td>
<td>RCA territory 33 (55)</td>
</tr>
<tr>
<td>Transmural scar, number (%)</td>
<td>LAD territory 35 (58.3)</td>
</tr>
<tr>
<td></td>
<td>LCX territory 17 (28.3)</td>
</tr>
<tr>
<td></td>
<td>RCA territory 17 (28.3)</td>
</tr>
<tr>
<td>Non-transmural scar, number (%)</td>
<td>LAD territory 16 (26.7)</td>
</tr>
<tr>
<td></td>
<td>LCX territory 16 (26.7)</td>
</tr>
<tr>
<td></td>
<td>RCA territory 16 (26.7)</td>
</tr>
<tr>
<td>Scar extent based on LGE</td>
<td>Single-vessel territory 17 (28.3)</td>
</tr>
<tr>
<td></td>
<td>Two-vessel territory 28 (46.7)</td>
</tr>
<tr>
<td></td>
<td>Three-vessel territory 15 (25)</td>
</tr>
</tbody>
</table>

Table 3. Cardiac magnetic resonance findings of the study population (n=60)

Abbreviations: LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; RWMA, Regional wall motion abnormalities; LGE, Late gadolinium enhancement; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery
Diagnostic Accuracy of CMR in the Prediction of Coronary Artery Stenosis

We found specificity of 100% for CMR in the prediction of coronary artery stenosis in all 3 territories. However, the sensitivity of CMR in the prediction of coronary artery stenosis was 91%, 70%, and 66% for the LAD, LCX, and RCA involvement, respectively (Table 4).

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD lesion</td>
<td>91%</td>
<td>100%</td>
<td>85</td>
<td>15</td>
<td>93.2</td>
</tr>
<tr>
<td>LCX lesion</td>
<td>70%</td>
<td>100%</td>
<td>55</td>
<td>45</td>
<td>76.7</td>
</tr>
<tr>
<td>RCA lesion</td>
<td>66%</td>
<td>100%</td>
<td>55</td>
<td>45</td>
<td>71.6</td>
</tr>
</tbody>
</table>

Abbreviations: LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery

Data are presented as percentages.

DISCUSSION

In this study, we found a significant relationship between coronary run-off and the presence of scar detected by LGE in CMR. We also showed an association between the severity of coronary stenosis and the pattern of the scars in terms of being transmural or non-transmural. To our knowledge, this is the first study of its kind to investigate the relationship between the severity of coronary artery disease and myocardial scar in CMR in patients with a history of remote MI.

Among different studies on CMR in MI, 5-7, 9-11, 20-22 Kim et al. investigated the CMR of 24 patients with acute MI to differentiate chronic old myocardial scars from acute infarction and showed that distinctive features of old scars might exist in CMR and that this finding could be used to differentiate between old and acute MI. The authors did not consider the pattern of coronary artery lesions in their study.

Bexell et al. in a similar study examined the relationship between the severity of proximal coronary stenosis, the amount of coronary collaterals, and the myocardial scar extent in patients with a history of chronic coronary artery disease and demonstrated a significant relationship between coronary artery stenosis and the extent of myocardial scar in the absence of MI history. The authors showed that myocardial scarring could be observed even in the presence of nonsignificant coronary lesions and that the extent of coronary collaterals was an important factor in the development of myocardial scar.

In the current study on patients with a history of remote MI, we found that the coronary artery run-off might be more important than the severity of coronary artery stenosis in myocardial scarring. Our results also underscored the importance of coronary stenosis severity in the transmurality of the scar.

Ortiz-Perez et al. examined patients with acute MI treated via primary PCI by CMR and found that TIMI flow and the presence of collaterals were independent predictors of the myocardial salvage index and transmurality. It has been shown in both experimental and clinical studies that an early restoration of the coronary blood flow in the infarct-related artery results in more myocardial salvage and lesser extent of scars. 9, 10, 20, 23-26 Accordingly, it is reasonable to argue that the extent of scarring is related to the coronary artery run-off and the transmurality to the severity of coronary stenosis.

In the present study, we also showed a good specificity (100) for CMR in detecting coronary artery stenosis in our patients with a history of chronic coronary artery disease and demonstrated a significant relationship between coronary artery stenosis and the extent of myocardial scar in the absence of MI history. The authors showed that myocardial scarring could be observed even in the presence of nonsignificant coronary lesions and that the extent of coronary collaterals was an important factor in the development of myocardial scar.

In their study, the specificity of CMR for detecting coronary lesions was between 85 and 87% for different coronary vessels, which is much lower than the specificity we found. On the other hand, the sensitivity of CMR in our
study for detecting stenosis in each coronary vessel was also different from that reported by Bernhardt et al. Additionally, except for the LAD, the sensitivity for the RCA and LCX was higher in their study. Indeed, our study population was chosen from among patients with documented MI who had low ejection fractions and this dissimilarity in the study populations may explain the difference in specificity and sensitivity.

**Study Limitations**
In this study, we had some limitations. First, we did not consider the time of MI occurrence and the type of the event (anterior, inferior, or other types of acute MI). Although we excluded patients with a history of PCI, including primary PCI, the effect of the other types of treatments were not considered in this study. In addition, the presence or absence of coronary collateral as an important predictor of scar extent was not evaluated in this study.

In conclusion, the results of the present study support the hypothesis that the time window for revascularization will be increased in the presence of an antegrade coronary flow in the jeopardized myocardium and results in limiting infarct progression and subsequent lesser extent of myocardial scar. Therefore, the prognosis of patients with early invasive strategies in the treatment of acute MI is better.

CMR is a feasible method in the evaluation of patients with a history of MI and has a good diagnostic accuracy in detecting coronary lesions, particularly in the LAD territory.

**Acknowledgements**
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**Authors’ Contributions**
Mohsen Maadani and Shabnam Madadi developed the original data and protocol and also conducted and supervised the project. Nasim Naderi and Mahmoud Fagheeh cooperated in data analysis and scientific writing of the manuscript. Sara Adimi and Yaghoob Bagheri provided the study material and patients. Sara Adimi provided the study material and patients and collaborated in data collection. Mahmoud Fagheeh approved the final manuscript and carried out the writing of the manuscript.

**Financial Disclosure**
The authors declare that there is no conflict of interests.

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The authors state that there was no financial support.

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Can C-Reactive Protein and Fibrinogen Predict Major Adverse Cardiac Events in Cardiovascular Patients?

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ABSTRACT

Background: We aimed to examine the value of C-reactive protein (CRP) and fibrinogen levels to predict cardiovascular events and compare their predicting power between patients with a history of the acute coronary syndrome, patients with a history of stroke (ischemic type), and healthy individuals.

Methods: This case-control study assessed 79 patients with a history of the acute coronary syndrome and 88 patients with a history of stroke (cerebral ischemia) occurring at least 3 months previously. The patients were selected and followed up from September 2013 to September 2014 for 3 and 6 months after initial assessment to determine 6-month major adverse cardiac events (MACE). The serum levels of CRP and fibrinogen were measured using ELISA kits.

Results: The serum CRP level was significantly higher in the group with the acute coronary syndrome than in the group with a history of stroke and in the healthy group (P=0.045). The Cox regression model showed increased levels of CRP (HR=1.29 [1.01-1.66]; P=0.038) and fibrinogen (HR=1.01 [1.01-1.02]; P<0.001) in the group with a history of the acute coronary syndrome. It also demonstrated increased levels of CRP (HR=1.61 [0.97-2.67]; P=0.065) and fibrinogen (HR=1.02 [1.01-1.04]; P=0.010) in the stroke group and increased levels of CRP (HR= 2.06 [0.71-5.99]; P=0.183) and fibrinogen (HR=1.01 [0.99-1.04]; P=0.294) in the normal group. Consequently, the groups with a history of the acute coronary syndrome and a history of stroke effectively predicted 6-month MACE in the crude and age- and sex-adjusted models.

Conclusions: Our study achieved 2 important findings. First, our results showed that higher values of these biomarkers were able to predict MACE, even after the inclusion of baseline covariates. Increased levels of CRP and fibrinogen, measured after evaluating the acute phase and their related outcome, were able to predict recurrent cardiovascular events in the patients with a history of cerebrovascular ischemia and the acute coronary syndrome. In addition, there were higher levels of both CRP and fibrinogen markers in the patients with a history of the acute coronary syndrome and stroke than in the healthy individuals. (Iranian Heart Journal 2015; 16(4): 19-27)

Keywords: ▪ CRP ▪ Fibrinogen ▪ Cerebrovascular ▪ Cardiovascular ▪ MACE
Atherosclerosis has been fundamentally understood as the chronic inflammatory disease of the cardiovascular system. In this regard, serum and plasma markers of inflammation provide an avenue of insight into the pathophysiology of atherosclerosis and its complications. The presence of inflammatory reactions in atherosclerotic plaques plays a certain role in both plaque rupture and platelet aggregation, leading to acute atherothrombotic events and serious complications. Increasing evidence shows that inflammatory mediators play a major role in determining the degree of plaque inflammation and in contributing to its evaluation from uncomplicated to complex atheroma, which leads to coronary artery disease and stroke. It has been proven that inflammatory reactions in coronary plaques play an important role in the pathogenesis of acute atherothrombotic events; inflammation elsewhere is also associated with both atherogenesis generally and its thrombotic complications. Moreover, with respect to the role of inflammation in cerebrovascular events, it has been shown that increased levels of inflammatory markers such as intracellular and muscular cell adhesion molecules may be related to the development of white matter lesions and lacunar infarcts. In addition, increased levels of inflammatory markers in damaged ischemic neurological tissues may be evidence of the role of inflammation in the development of cerebrovascular ischemic events. Along with the role of C-reactive protein (CRP) as a sensitive marker in inflammatory pathways, the role of fibrinogen as a risk factor for coronary artery disease has also been suggested. It has even been introduced as a risk component for scoring cardiovascular risk. This marker can trigger the coagulation process, which is a major component for the development of atherosclerotic plaques, leading to both cardiovascular and cerebrovascular ischemic events. In this regard, its valuable role in the prediction of further serious morbidities and even mortality has also been suggested. Despite some evidence regarding the role of these 2 inflammatory and coagulative biomarkers in the progression of ischemic events and their valuable role in the prediction of adverse consequences, several recent longitudinal studies have reported that CRP and fibrinogen are not associated with the future risk of ischemic stroke. Nonetheless, others have demonstrated that high-sensitivity CRP (hsCRP) is not associated with ischemic stroke, although it is modestly associated with myocardial infarction and mortality. Currently, there is not sufficient evidence to recommend the measurement of these 2 markers in primary prevention to predict cerebrovascular disease risk because there is insufficient evidence as to whether early detection or intervention based on detection improves health outcomes. Nevertheless, the shared risk of cardiovascular disease indicates that this may be of value. Still, the results of epidemiological studies have demonstrated an association between low-grade inflammation and vascular risk. The application of CRP and fibrinogen testing in clinical practice requires the estimation of risk across a spectrum of
CRP and fibrinogen levels.\textsuperscript{14,15} To the best of our knowledge, there are limited data regarding the role of new biomarkers in stroke, especially in ischemic stroke, as well as in coronary events. Therefore, we designed this study to compare the values of CRP and fibrinogen levels between patients with a history of the acute coronary syndrome, patients with a history of stroke, and healthy individuals. Subsequently, we examined the value of these markers to predict the 6-month outcome of these cardiovascular events.

**METHODS**

**Study Population**

This case-control cohort study recruited 79 patients with a history of the acute coronary syndrome, 88 patients with a history of stroke (ischemic) occurring at least 3 months previously, and also 77 sex- and age-matched healthy individuals (with normal exercise test and neurological assessments), who were referred to general, cardiovascular, or physical medicine clinics in the Iranian cities of Isfahan and Shahrekord from 2013 to 2014. The main inclusion criteria were age >35 years and the occurrence of cardiovascular or cerebrovascular events occurring at least 3 months previously. In this context, those with a previous history of trauma, inflammatory disorders, chronic rheumatismal disorders, acute febrile or infectious disorders (in the previous 3 months), incomplete clinical or laboratory data, and pregnancy were not included. Also excluded were patients who did not use low-dose statin drugs (anti-inflammatory drugs) and those who could not be followed up. Additionally, patients with CRP levels >10 mg/L were excluded since this may reflect acute inflammation. The diagnosis of the acute coronary syndrome was based on the diagnostic criteria of the American College of Cardiology. Data on sex, age, and history of coronary artery disease were obtained by trained nurses. The data collected were either physical and laboratory examinations (anthropometric testing, blood sample laboratory analysis, and blood pressure measurements) or questionnaires. Weight and height were measured with calibrated instruments under the standard protocol. Waist circumference and hip circumference were measured and recorded in centimeters, using the standard methods.\textsuperscript{16} Blood pressure was measured twice from the right hand.\textsuperscript{17} The study protocol was approved by the Research and Ethics Committee of Isfahan University of Medical Sciences. All the baseline information—including demographic characteristics, anthropometric parameters, systolic or diastolic blood pressure values, oral medications, and laboratory parameters—was collected by reviewing the recorded files. All blood and inflammatory indices were tested after a 12-hour fasting period. The serum levels of fasting blood glucose (FBS) and lipid profile were examined using the enzymatic method. The serum levels of CRP and fibrinogen were also measured using ELISA kits.\textsuperscript{13}

**Study End points**

The primary end point was major adverse cardiac events (MACE), comprising fatal and non-fatal Q wave and non-Q wave myocardial infarction, unstable angina, stroke (ischemic), and re-hospitalization due to cardiovascular causes. Cardiovascular death was considered as any death with a cardiovascular cause such as sudden cardiac death. Myocardial infarction was defined by symptoms suggestive of infarction, electrocardiographic changes, and positive cardiac enzymes. Unstable angina was defined as angina pectoris characterized by at least 1 of the following: occurs at rest or minimal exertion and usually lasts <20 minutes (if nitroglycerin is not administered), is severe and is described as flank pain and of new onset (i.e., within 1 month), and occurs with a crescendo pattern (more severe, prolonged, or with increased frequency than previously).\textsuperscript{18,19}
Stroke was defined as the relative sudden occurrence of a focal neurological deficit. Ischemic stroke was classified by the underlying cause of the vascular occlusion and atherosclerosis with superimposed thrombosis affecting large cerebral or extracerebral blood vessels. The patients were assessed 6 months after initial assessment by telephone follow-up or by periodical visiting to determine the occurrence of fatal or non-fatal myocardial infarction, fatal and non-fatal stroke, sudden cardiac death, unstable angina, need to hospitalization, or any changes in medication.

**Statistical Analysis**

The data were analyzed using the statistical software SPSS, version 20, for Windows (SPSS Inc., Chicago IL). The quantitative variables are presented as means ± standard deviations, and the categorical variables are presented by absolute frequencies and percentages. The continuous variables were compared using the ANOVA, and the Tukey test was used as post hoc. The categorical variables were compared using the chi-square test. The Cox regression model was used to determine the value of CRP and fibrinogen increased levels for the prediction of MACE in the group with a history of the acute coronary syndrome and the group with a history of stroke. P values ≤0.05 were considered statistically significant.

**RESULTS**

In total, 244 consecutive patients were assessed: 79 patients with a history of the acute coronary syndrome, 88 patients with a history of stroke occurring at least 3 months previously, and 77 healthy cases as the control. After 5.84±0.62 months of follow-up, 16 subjects had events: 4 patients in the group with a history of stroke, 11 in the group with a history of the acute coronary syndrome, and 1 in the normal group.

The 3 groups were similar in terms of sex and age distribution as well as mean body mass index and traditional risk factors for cardiovascular events (Table 1). Regarding laboratory parameters, the mean levels of FBS and LDL were significantly higher in those with a history of the acute coronary syndrome and the healthy individuals, while the former group had lower serum HDL levels than did the other 2 groups. Using the Tukey post-hoc for ANOVA analysis, the serum CRP level was significantly higher in the group with a history of the acute coronary syndrome than in the group with a history of stroke (P=0.045) and in the healthy group (P<0.001). The mean CRP level was also higher in the patients with a history of stroke than in the normal subjects (P=0.012). Also, the level of serum fibrinogen was significantly higher in the group with a history of stroke than in the normal group (P=0.049), while no difference was observed in the fibrinogen level between the groups with a history of the acute coronary syndrome and stroke (P=0.918).

Regarding 6-month MACE, the rates of the occurrence of the acute coronary syndrome in the healthy group, the group with previous cardiovascular ischemic events, and those with previous stroke were 1.3%, 12.6%, and 1.1%—with a significant difference (P=0.012). Also, the occurrence of stroke was shown in 3.41% of the patients with previous stroke, while it was not observed in the other 2 groups. Also, sudden cardiac death occurred in 1 patient in the cardiovascular disease group, while none of the patients in the other groups had this acute event.
Can C-Reactive Protein and Fibrinogen Predict Major Adverse Cardiac Events in Cardiovascular Patients?  

**Table 1.** Baseline characteristics of the study groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Normal (n=77)</th>
<th>Acute Coronary Syndrome (n=79)</th>
<th>Stroke (Cerebral Ischemia) (n=89)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>43 (55.8)</td>
<td>47 (63.4)</td>
<td>38 (43.5)</td>
<td>0.503</td>
</tr>
<tr>
<td>Age (y)</td>
<td>67.82 ± 10.20</td>
<td>64.70 ± 9.34</td>
<td>66.23 ± 12.40</td>
<td>0.444</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.98 ± 4.11</td>
<td>25.44 ± 3.94</td>
<td>26.56 ± 4.63</td>
<td>0.070</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (22.1)</td>
<td>30 (40.4)</td>
<td>24 (30.4)</td>
<td>0.322</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (7.8)</td>
<td>14 (15.9)</td>
<td>9 (11.4)</td>
<td>0.240</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>19 (24.7)</td>
<td>24 (27.3)</td>
<td>15 (19.0)</td>
<td>0.338</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (6.5)</td>
<td>12 (13.6)</td>
<td>10 (12.7)</td>
<td>0.458</td>
</tr>
<tr>
<td>History of CAD</td>
<td>3 (3.9)</td>
<td>4 (4.5)</td>
<td>5 (5.1)</td>
<td>0.931</td>
</tr>
<tr>
<td>FBS</td>
<td>106.99 ± 26.67</td>
<td>118.49 ± 32.13</td>
<td>104.43 ± 33.62*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TG</td>
<td>156.60 ± 40.04</td>
<td>191.37 ± 47.76*</td>
<td>185.20 ± 63.00*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TC</td>
<td>134.15 ± 47.05</td>
<td>155.04 ± 50.81</td>
<td>146.57 ± 66.14</td>
<td>0.072</td>
</tr>
<tr>
<td>LDL</td>
<td>124.38 ± 30.62</td>
<td>131.95 ± 35.79*</td>
<td>114.31 ± 29.67*</td>
<td>0.004</td>
</tr>
<tr>
<td>HDL</td>
<td>45.76 ± 10.72</td>
<td>41.22 ± 11.14</td>
<td>42.61 ± 9.18</td>
<td>0.027</td>
</tr>
<tr>
<td>CRP</td>
<td>2.92 ± 2.45**</td>
<td>5.02 ± 2.45**</td>
<td>4.01 ± 2.03**</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>276.56 ± 64.41</td>
<td>302.14 ± 93.52</td>
<td>315.07 ± 76.43*</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, Coronary artery disease; FBS, Fasting blood sugar; TC, Total cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; CRP, C-reactive protein

**a:** Chi-square test for the categorical variables  
**b:** ANOVA for the continues variables  
**c:** Turkey test as a post hoc

**Results of the Cox Regression Analysis**

The Cox regression model (Table 2) showed increased levels of CRP (HR=1.29 [1.01-1.66]; P=0.038) and fibrinogen (HR=1.01 [1.01-1.02]; P<0.001) in the group with a history of the acute coronary syndrome. It also demonstrated increased levels of CRP (HR=1.61 [0.97-2.67]; P=0.065) and fibrinogen (HR=1.02 [1.01-1.04]; P=0.010) in the stroke group and increased levels of CRP (HR=2.06 [0.71-5.99]; P=0.183) and fibrinogen (HR=1.01 [0.99-1.04]; P=0.294) in the normal group. Consequently, the groups with a history of the acute coronary syndrome and a history of stroke effectively predicted 6-month MACE in the crude and age- and sex-adjusted models.

**Table 2.** Hazard ratio for the assessment of the amount of CRP and fibrinogen with cardiovascular events in the normal, stroke (cerebral ischemia), and acute coronary crude and age- and sex-adjusted models

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal group</td>
<td>2.06</td>
<td>0.71–5.99</td>
</tr>
<tr>
<td>Stroke group</td>
<td>1.81</td>
<td>0.97–2.67</td>
</tr>
<tr>
<td>ACS group</td>
<td>1.29</td>
<td>1.01–1.66</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal group</td>
<td>2.05</td>
<td>0.15–7.50</td>
</tr>
<tr>
<td>Stroke group</td>
<td>1.57</td>
<td>0.92–2.68</td>
</tr>
<tr>
<td>Past history ACS group</td>
<td>1.30</td>
<td>1.00–1.69</td>
</tr>
</tbody>
</table>

**DISCUSSION**

It is now debated whether increased serum levels of CRP and fibrinogen are considered as prognostic markers of vascular events. A few studies have addressed the relationship between increased levels of these biomarkers and atherosclerosis predisposing patients to vascular events. In the present study, we first showed high levels of both CRP and fibrinogen markers in the patients with a history of the acute coronary syndrome and the patients with a history of stroke compared with the healthy individuals. Notably, in a multiple regression model including baseline fibrinogen and CRP, we showed higher values of both biomarkers to predict the 6-month outcome, after adjusting for sex and age. In
fact, these results suggest that the inclusion of the biomarkers in the initial assessment for patients with a history of ischemic stroke similar to patients with a history of the acute coronary syndrome is necessary and applicable.

Fibrinogen as a coagulation factor and acute-phase reactant can activate hemostasis, blood rheology, and platelet aggregation and it, thus, appears to be a mediator in arterial vessel damage. Furthermore, elevated CRP levels are associated with a profound impairment in systemic endothelial vascular reactivity in patients with coronary artery disease. The blunted systemic endothelial vasodilator function related to elevated plasma CRP levels is independent of classic risk factors for coronary artery disease. CRP as an acute-phase reactant can enhance and stimulate the production of tissue factor and of interleukin-1 (IL-1) and tumor necrosis factor-a (TNF) by monocytes and macrophages. It is well-identified that inflammation has a central role in the beginning and progression of atherosclerotic vascular disease. There is now general agreement that vessel-wall inflammation constitutes a major factor in the development of atherosclerosis, atheroma instability, and plaque disruption followed by local thrombosis. In this regard, we hypothesized that not only could these 2 inflammatory biomarkers predict the presence of ischemic vascular disorders, but also they could strongly predict the adverse outcome of vascular disorders in suspected patients. This predictive role for the 2 biomarkers was successfully confirmed in our survey even after adjusting major risk profiles. Similarly, Coppola et al. reported that the variables independently associated with non-fatal events included fibrinogen and plasma levels of hs-CRP, while fibrinogen independently associated with fatal events. Also, Grau et al. showed that patients with a history of cerebrovascular, cardiovascular, or peripheral arterial disease had higher fibrinogen and CRP than did subjects without vascular risk factors. They also found that subjects under the age of 65 with vascular risk factors but without ischemic diseases had higher fibrinogen and CRP and subjects older than 65 with risk factors had higher CRP than subjects without risk factors or ischemic diseases in the same age group. The treatment of ischemic cardiovascular and cerebrovascular events during the past decade has been improved; however, a substantial risk of death or new vascular events during the first year after the acute episode of these disorders has remained constant. In this regard, identifying new risk markers can facilitate the risk stratification and selection of individuals who might benefit from intensified therapy as well as facilitate the understanding of pathophysiological mechanisms of the diseases and their adverse outcomes. It seems that increased levels of acute-phase proteins, including fibrinogen and CRP, have a major role in predicting adverse clinical consequences of these vascular events.

The present study revealed a relation between elevated CRP and fibrinogens levels and mid-term risk of death or new vascular events following ischemic stroke or ischemic cardiac disorders. Each biomarker seems to have specific pathophysiological pathways to trigger ischemic events. Elevated CRP levels can affect coagulation through the important role of tissue factor expression. High CRP values can also reflect the extent of the ischemic area. Obviously, necrosis triggers a rise in the circulating CRP. Fibrinogen has also 2 major roles in progressing ischemic vascular events as an acute-phase inflammatory and coagulative component. In total, because of the central role of these 2 markers in activating inflammation and coagulation pathways, their role in predicting vascular disorders and their related adverse outcome is expected.

We hypothesized that the biomarkers of inflammation or coagulation might be
associated with the pathogenesis of the recurrence of cardiovascular events and sought to investigate whether these biomarkers could provide prognostic information on the risk of developing stroke and coronary artery disease. In fact, both biomarkers can be used to predict recurrent cardiovascular and cerebrovascular events in patients with a history of cardiovascular events or stroke (cerebral ischemia). We were interested in showing the predictive role of these 2 biomarkers or their ratio alongside traditional risk factors such as smoking, diabetes, hyperlipidemia, and hypertension. Thus, anti-inflammatory therapies can result in favorable outcomes in patients considered high-risk based on elevated levels of these markers.

Acknowledgments
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Can C-Reactive Protein and Fibrinogen Predict Major Adverse Cardiac Events in Cardiovascular Patients?  

Golshahi J, et al.


Original Article

Evaluation of Pentoxifylline in the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Primary Percutaneous Coronary Intervention

Ata Firouzi, M.D.¹, Hossein Shahsavari, M.D.¹, Reza Kiani, M.D.¹, Kamran Aeinfar, M.D.¹, Yousef Shamloo, M.D.¹, Hojjat, Mortezaitan, M.D.¹

ABSTRACT

Background: As percutaneous coronary intervention (PCI) technologies confer increasing patient advantage, the use of iodinated contrast media for diagnostic and interventional procedures is increased. Although contrast media obstacles are transient and mild, contrast-induced nephropathy (CIN) negatively affects long-term patient mortality. PCI creates a high-risk condition for the incidence of CIN even in patients with a normal renal function. Pentoxifylline (PTX) with a variety of mechanisms may prevent CIN. We sought to assess the positive effect of PTX administration at the beginning prior to contrast media use to 24 hours after PCI to prevent CIN in patients with STEMI.

Methods: In this double-blind, single-center, clinical trial, we randomly assigned 296 consecutive patients to the control group (n=148) without PTX and the case group (n=148) with PTX 400 mg/tid at the time of hospitalization to 24 hours after the procedure. Serum creatinine was measured before and 48 hours after the procedure. The occurrence of CIN within 48 hours was our end point. CIN was defined as a 0.5 mg/dL increase or more in serum creatinine or a 25% increase or more above baseline serum creatinine.

Results: A total of 296 patients were enrolled in this trial and were randomly assigned to receive either primary PCI plus PTX or only primary PCI. Out of 148 patients who received PTX, only 12.2% were seen to have CIN incidence (>0.5 mg/dL or a 25% increase in the Cr level); however, the difference between the 2 groups regarding CIN was not significant (P=0.4). Out of the 296 patients, only 20 were found to have chronic kidney disease (CKD) (CKD was defined as baseline Cr>1.5); and of those patients, 3 (15%) showed CIN incidence. Nevertheless, the difference between the 2 groups regarding CIN incidence was not significant (P=0.7). The regression test showed that between all confounding factors in the 2 groups of PTX positive and negative, sex and ejection fraction had positive effects on the rise in the Cr level and, consequently, the incidence of CIN (95% CI: 1.60 to 30.85; P=0.01 and 95% CI: 0.92 to 1; P=0.05).

Conclusions: Administration of oral PTX to patients with increased risk for CIN scheduled for primary PCI may not reduce the Cr level and thus the occurrence of CIN. Given the higher prevalence of hypotension in the patients without PTX, higher prevalence of CKD in the patients without PTX, and absence of significant difference between the 2 groups regarding the incidence of CIN, PTX had no preventive effect on CIN occurrence in STEMI.
Among all factors influencing CIN occurrence, sex and ejection fraction had positive effects on the rise in the Cr level. *(Iranian Heart Journal 2015; 16(4): 28-34)*

**Keywords** ■ Contrast media ■ Primary PCI ■ Contrast-induced nephropathy ■ Pentoxifylline

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Advanced growth in the capacity of computed tomography (CT) images and the efficacy of PCI has developed the utilization of techniques; consequently, the number of the patients who receive contrast media (CM) has increased.\(^1\)^\(^-\)\(^5\) Complications concomitant with CM range from mild symptoms to life-threatening reactions such as hypotension, cardiovascular events, and renal dysfunction. Although most common adverse events are transient, contrast-induced nephropathy (CIN) can have some serious long-term consequences.\(^6\) These possible complications should be considered if renal function is not assessed. The association between complications and CM administration may not be obvious.

CIN is commonly distinct as an acute renal failure occurring within 48 hours of exposure to an intravenous contrast that is not attributable to other causes.\(^7\) CIN, which is either >25% increase in baseline serum creatinine or >0.5 mg/dL increase in serum creatinine above baseline creatinine during 48 hours of exposure, is the most common description.\(^8\)

Pentoxifylline (PTX) is a methylxanthine derivative agent with numerous hematological attributes. It has been recently introduced for CIN prevention inasmuch as it develops oxygen delivery to the ischemic tissue by treating peripheral vascular disease and has anti-inflammatory properties that can reduce nitric oxide deterioration.\(^7\) In septic shock, intravenous PTX has been indicated to reduce the serum level of some inflammatory cytokines.\(^9\) Conversely, the oral absorption of PTX is near complete; the plasma level peaks about 2 to 3 hours after drug absorption and with a variety of mechanisms may prevent CIN.\(^9\) PCI provides a high-risk condition for the incidence of CIN even in patients with normal renal function.\(^9\) In the current study, we hypothesized that the oral administration of PTX at the beginning prior to CM use (usual dose of 400 mg/tid) to 24 hours afterward could help CIN prevention in patients with STEMI.

**METHODS**

**Study Populations**

In the present clinical trial, 296 patients (236 male and 60 female; age >20 y) with STEMI who underwent primary PCI in our tertiary research center between 2013 and 2015 and were considered for emergency coronary angiography and intervention and were candidates for primary PCI were enrolled. A history of taking CM within the previous 10 days and N-acetylcysteine use was considered the exclusion criterion. The patients were divided into 2 groups: those who underwent PCI and did not receive PTX and those who received PTX in addition to their routine drugs. All the patients gave informed written consent before entering the study. The study protocol was approved by the institutional ethics committee. Age, sex, diabetes mellitus, hyperlipidemia, hypertension, hypotension, intravenous contrast volume, use of intra-aortic balloon pump, and chronic kidney disease (CKD) were considered as the study variables.
**Study Protocol**

In this prospective, randomized, double-blind, clinical trial, 296 patients were randomly assigned to the control group (n=148) with routine treatment and no PTX and the study group (n=148) with routine treatment and PTX (400 mg/tid) from the initiation of the study to 24 hours after the procedure; no placebo was administered. Controls were selected randomly out of the patients who came to our hospital and underwent primary PCI and who did not receive PTX, and the cases were selected from the cases that underwent primary PCI and received PTX. The study and control groups had the same routine preparation protocol for angioplasty as hydration before and after angioplasty with normal saline (1-1.5 cc/kg), which was administered at the start of the study to 12 hours after the procedure.

In all the patients, baseline serum creatinine was measured using Beckman Coulter-SYNCHRON CX® PRO Clinical System before angioplasty. One sample serum creatinine was obtained 48 hours after the procedure in all the patients. Measurements were all made in a single center-based laboratory, and the laboratory staff was blinded to the study protocol and serum samples. The choice of the type of CM was left to the interventional cardiologist performing the procedure. The coronary angioplasty procedures were carried out using the iso-osmolar nonionic CM, iodoxanol (Vesipaque 320, GE Healthcare, Cork, Ireland) or iopromide (Ultravist 300, Schering AG, Germany). The primary end point of the study was the occurrence of CIN, which was defined as an increase in serum creatinine level of 0.5 mg/dL or a 25% increase over the baseline creatinine level over a 2-day period after exposure to CM.

**Statistical Analysis**

The continuous data are expressed as means ± standard deviations and they were compared between the 2 groups using the Student t-test. The categorical data are expressed as numbers and percentages and they were compared via the chi-square test. The Mann–Whitney U test was employed to assess the Cr level between the 2 groups. The regression linear test was used to remove the confounding effect of the variables. A P value <0.05 was considered significant. The data were analyzed using SPSS software 13.0 (SPSS Inc. Chicago, Illinois, U.S.A.).

**RESULTS**

A total of 296 patients were enrolled in this trial and were randomly assigned to receive either routine treatment plus PTX (n=148, 117 [79.1%] male; P=0.7) or only routine treatment (n=148). Out of the 148 patients who received PTX, 65 (43.9%) had hypertension (P=0.7), 43 (29.1%) had dyslipidemia (P=0.3), 10 (6.8%) had hypotension (P=0.04), and 49 (33.1%) had diabetes mellitus (P>0.99). All the demographic data and clinical findings are depicted in Table 1 and Table 2.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Pentoxifylline- (n=148)</th>
<th>Pentoxifylline+ (n=148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex Female</td>
<td>58.2±12.5</td>
<td>58.4±10</td>
<td>0.89</td>
</tr>
<tr>
<td>Male</td>
<td>119(80.4%)</td>
<td>117(79.1%)</td>
<td>0.77</td>
</tr>
<tr>
<td>DLP</td>
<td>51(34.5%)</td>
<td>43(29.1%)</td>
<td>0.31</td>
</tr>
<tr>
<td>HTN</td>
<td>68(45.9%)</td>
<td>65(43.92%)</td>
<td>0.04</td>
</tr>
<tr>
<td>FH</td>
<td>20(13.5%)</td>
<td>30(20.3%)</td>
<td>0.12</td>
</tr>
<tr>
<td>DM</td>
<td>49(33.1%)</td>
<td>49(33.1%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Abbreviations: DLP, Dyslipidemia; HTN, Hypertension; FH, Familial history; DM, Diabetes mellitus; CS, Cigarette smoking P<0.05 was considered the level of significance.
Efficacy of Pentoxifyline in the Prevention of CIN in Patients Undergoing PCI

Table 2. Clinical and procedural findings according to pentoxifylline administration

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Pentoxifylline – (n=148)</th>
<th>Pentoxifylline + (n=138)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2(3%)</td>
<td>10 (6.8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>IABP</td>
<td>2(1.4%)</td>
<td>4(2.7%)</td>
<td>0.6</td>
</tr>
<tr>
<td>LVEF&lt;40%</td>
<td>61(41.2%)</td>
<td>65(43.9%)</td>
<td>0.63</td>
</tr>
<tr>
<td>CHF</td>
<td>11(7.4%)</td>
<td>11(7.4%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Anemia</td>
<td>26(17.6%)</td>
<td>23(15.5%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Contrast volume</td>
<td>240±99</td>
<td>240±91</td>
<td>0.31</td>
</tr>
<tr>
<td>CKD</td>
<td>10(6.8%)</td>
<td>3(2%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Abbreviations: IABP, Intra-aortic balloon pump; CHF, Congestive heart failure; LVEF, Left ventricular ejection fraction; CKD, Chronic kidney disease. P<0.05 was considered the level of significance.

Out of the 148 patients who received PTX, only 18 (12.2%) were seen to have CIN incidence (Cr level >0.5 mg/dL or a rise >25%); however, the difference between the 2 groups regarding CIN was not significant. Out of the 148 patients who did not receive PTX, 22 (14.9%) showed CIN incidence (P=0.4) (Table 3).

Table 3. Occurrence of CIN according to the total Cr level (>0.5 mg/dL and a 25% rise)

<table>
<thead>
<tr>
<th>± PTX</th>
<th>CIN+ Total</th>
<th>CIN- Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cr≥0.5 mg/dL</td>
<td>Cr&lt;25%</td>
<td>Cr≥0.5 mg/dL</td>
</tr>
<tr>
<td>Without PTX n=148</td>
<td>22 (14.9%)</td>
<td>126 (85.1%)</td>
<td>0.4</td>
</tr>
<tr>
<td>With PTX n=138</td>
<td>18 (12.2%)</td>
<td>130 (87.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PTX, Pentoxifylline; CIN, Contrast-induced nephropathy. P<0.05 was considered the level of significance.

Out of the 296 patients, 256 (86.5%) showed no CIN incidence, defined as CIN total (0.5≤CIN or 25%≤CIN) and only 40 patients were found with CIN incidence. Out of the 296 patients, only 20 were found to have CKD (CKD were defined as baseline CR >1.5); and of those patients, 3 (15%) showed CIN incidence. The difference, however, between the 2 groups concerning CIN incidence was not significant (P=0.7). Out of the 276 patients who were CKD negative (Cr level <1.5), 239 (86.6%) did not show CIN incidence (Table 4).

Table 4. Occurrence of CKD according to the Cr level (≥1.5)

<table>
<thead>
<tr>
<th>± CKD</th>
<th>CIN+ Total</th>
<th>CIN- Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cr≥0.5 mg/dL</td>
<td>Cr&lt;25%</td>
<td>Cr&lt;0.5 mg/dL</td>
</tr>
<tr>
<td>CKD +</td>
<td>3(15%)</td>
<td>17(85%)</td>
<td>0.8</td>
</tr>
<tr>
<td>CKD -</td>
<td>37(13.4%)</td>
<td>239(86.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CKD, Chronic kidney disease; PTX, Pentoxifylline. P<0.05 was considered the level of significance.

The regression model showed that between all the confounding factors in the 2 groups, sex and ejection fraction had positive effects on the rise in the Cr level and consequently the incidence of CIN (95% CI: 1.60 to 30.85; P=0.01 and 95% CI: 0.92 to 1; P=0.05).

DISCUSSION

PTX can be effective in preventing CIN given its anti-inflammatory, antioxidant, and circulatory properties. There are a few animal studies concerning the renoprotective effect of PTX in contrast nephropathy. A few human studies for the evaluation of the renopreventive effect of PTX in contrast nephropathy have been reported.7,13 Our study is one of the few studies conducted hitherto on the effects of PTX on CIN. A major problem after CM-required procedures is CIN, which is generally characterized as either an absolute increase in serum creatinine (SCr) concentration of 0.5

...
mg/dL (44.2 \text{1 mol/L}) or a relative rise >5% from baseline.\textsuperscript{14,15} CIN typically and clinically manifests within 3 days of CM administration, peaks within 3 to 5 days, and returns to its baseline level within 10 to 21 days.\textsuperscript{16} Nevertheless, in some cases, sustained or permanent nephropathy occurs. It is recommended that SCr measurements be continued for >48 hours after exposure to CM to monitor for CIN.\textsuperscript{17}

In a trial, CKD was defined as SCr>1.5 mg/dL and was also the strongest predictor of all-cause mortality. An analysis of more than 130,000 elderly post-MI patients found that 1-year survival was increasingly reduced as creatinine clearance declined.\textsuperscript{18}

In an investigation, CKD was compared with normal renal function at baseline level in patients with acute myocardial infarction who underwent PCI and was related to an obvious increase in the mortality rate over a 30-day period (7.5\% vs. 0.8\%; P<0.0001) and at 1 year (12.7\% vs. 2.4\%; P<0.0001);\textsuperscript{19} nevertheless, the additional burden of CIN in patients undergoing PCI with previously compromised renal function apparently increases the risk of adverse outcomes.

Patients undergoing PCI with pre-existing renal dysfunction are at increased risk for adverse outcomes in comparison to those with a normal renal function.\textsuperscript{18} The present study showed that the incidence of CIN was 13.5\%, which is almost similar to the rate reported by the previous studies. CIN incidence was reported 1-13\% in elective PCI or 19\% in the Marenzi study.\textsuperscript{20} The incidence of CIN in primary PCI in our study showed that there was no significant increase in CIN after STEMI. We think that this is because of better preventive management in 12-hour hydration in our center, which is a high-volume and referral center for primary PCI with optimal arrangements for primary PCI, which results in the earlier reperfusion of occluded vessels and less hemodynamic burden of myocardial infarction.

The overall incidence of CIN in the control group of a previous study was 13.69\%,\textsuperscript{13} which is comparable to previous reports in an unselected population\textsuperscript{8} and less than the CIN incidence in our study.

In the current study, out of the 148 patients who received PTX, only 10 (6.84\%) had hypotension and there was a significant relationship between the 2 groups apropos hypotension (P=0.04). Nonetheless, due to the small sample size, it was only seen in a small group of our study population. In a study by Firouzi et al.\textsuperscript{13} in patients who underwent angioplasty, it was shown that the oral use of PTX could be recommended for CIN prevention and that it had prophylactic effects, although no statistically significant protective effect was documented. The result of their study was in accordance with our investigation. In the present study, out of the 148 patients who did not receive PTX, only 22 (14.9\%) showed CIN incidence (P=0.4). Therefore, the administration of PTX had no statistically significant effects. Out of the 296 patients, only 40 were found to have CIN incidence. Out of the 296 patients, only 20 were found to have CKD (CKD were defined as baseline Cr >1.5); and of those patients, 3 (15\%) showed CIN incidence (P=0.7).

The regression test revealed that between all the confounding factors in the 2 groups, sex, and ejection fraction had positive effects on the rise in the Cr level and, thus, the incidence of CIN (P=0.01 and P=0.05, respectively). The difference between the present study and the other investigations regarding the beneficial effect of PTX in the prevention of CIN incidence may be due to the different sizes of the study populations. Our results demonstrated that PTX was a useful drug in the prevention of the negative effects of CM and that it had no preventive effects on the alteration in the Cr level and, consequently, CIN incidence.
**Limitations**

The most important limitation of this small and short-term trial study is the lack of sample-size calculation, which resulted in estimating the small sample size on the basis of other similar trials. We suggest that larger studies be conducted on the effect of PTX.

**CONCLUSIONS**

The present clinical trial utilized PTX for CIN prevention and the results suggested that the administration of oral PTX to patients with a high risk of CIN scheduled for angioplasty might not reduce the Cr level and, thus, the occurrence of CIN. Given the higher prevalence of hypotension in the PTX-negative group, higher prevalence of CKD in the patients without PTX, and the absence of a significant difference between the 2 groups regarding the incidence of CIN, PTX had no preventive effects on CIN occurrence in STEMI. Among all the factors influencing CIN occurrence, sex and ejection fraction had positive effects on the rise in the Cr level and, thus, the occurrence of CIN.

**Suggestion**

Measures before, during, and after the use of CM that reduce the incidence of CIN such as discontinuation of nephrotoxic medications, adequate hydration, and use of appropriate volumes and types of CM should be considered in all patients with renal insufficiency or with other risk factors for CIN. Larger trials or studies in higher-risk patients may shed further light on the protective effect of PTX in CIN.

**Acknowledgements**

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**Financial Disclosure**

All the authors declare no conflict of interest. The study complies with the current ethical considerations. Informed consent was obtained from the whole study population.

**Funding/Support**

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Efficacy of Pentoxifylline in the Prevention of CIN in Patients Undergoing PCI

Firouzi A, et al.


Original Article

**QT Interval Parameters: A Screen Test for the Detection of Left Ventricular Hypertrophy**

Arsalan Salari, M.D.¹, Fardin Mirblook, M.D.¹, Zohre Heidarnezhad, M.D.¹, Zahre Atrkar-Roshan, Ph.D.², Fereshteh Saadati, M.D.¹, Fatemeh Moaddab, M.Sc.³*

**ABSTRACT**

**Background:** Electrocardiographic parameters for the detection of left ventricular hypertrophy (LVH) as an independent cardiovascular risk factor and signifier end-organ damage in patients with hypertension are known. The aim of this study was to evaluate the relation between QT interval parameters and LVH in patients with hypertension.

**Methods:** This cross-sectional study recruited 100 patients with primary hypertension who underwent cardiac echocardiography for the evaluation of left ventricular mass (LVM). Standard 12-lead electrocardiography was performed for all the patients, and QT interval parameters (QTmax, QTcmax, QTd [dispersion], and QTdF [difference between maximum and minimum QT intervals]) were calculated. The data were analyzed using SPSS (version 18). The t-test was applied to assess the relationship between QT parameters and left ventricular mass index (LVMI), and the receiver operating characteristic (ROC) curve was drawn to determine the cutoff point for the mentioned electrocardiographic test.

**Results:** The mean age of the patients was 60.52±9.74 years. The mean of QTd, QTmax, and QTcd in the patients with LVH was significantly greater than that of the patients without LVH (P<0.05). ROC curve analyses of QT interval parameters showed that the cutoff points for QTmax, QTd, QTcmax, and QTcd values were 420 (specificity=0.79 and sensitivity=0.40), 50 (specificity=0.58 and sensitivity=0.76), 478 (specificity=0.29 and sensitivity=0.58), and 59 (specificity=0.65 and sensitivity=0.76), respectively.

**Conclusions:** According to our findings, QTcd and QTc would be better tests for the detection of LVH. We recommend further research with larger sample sizes to obtain more generalizable findings. *(Iranian Heart Journal 2015; 16(4): 35-40)*

**Keywords** Electrocardiography, Hypertension, Left ventricular hypertrophy, QT interval

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Hypertension is a major public health concern the world over due to its high prevalence and significant complications such as heart disease and stroke.\(^1\) It is the first and fourth leading cause of death in the United States and in Iran, correspondingly. Hypertension has a rising prevalence in the context of progressive increment in age and body mass index (BMI).\(^2,3\) Indeed, the prevalence of hypertension increases approximately by 0.54% after the age of 20, and the overall prevalence of hypertension in Iran is considerable.\(^2,3\) Hypertension affects the heart and arteries due to various mechanisms such as left ventricular hypertrophy (LVH), increasing the risk for sudden cardiac death and lethal arrhythmias. Arrhythmias occurring in patients with hypertension vary from supraventricular to ventricular tachyarrhythmias, affecting morbidity, mortality, and quality of life.\(^4,5\) Risk indicators for the occurrence of arrhythmias in patients with hypertension include LVH, diminished heart rate variability, QT interval dispersion, and ventricular late potentials.\(^6\) LVH is a strong independent cardiovascular risk factor for sudden death, but the leading cause of this event relevant to LVH is uncertain.\(^7\) In experimental studies, LVH prolongs action potential duration and potentially causes arrhythmogenic ventricular repolarization abnormality. Indeed, LVH increases QT interval and QT dispersion (QT\(_d\)).\(^8,9\) Routinely, surface 12-lead electrocardiography (ECG) has been used for the detection of LVH; it is, however, affected by a large number of extra-cardiac factors that interfere with the relationship between ECG voltage and left ventricular mass (LVM). Nevertheless, measuring QT interval can help detect LVH without any reported evidence of modification by such extra-cardiac factors.\(^10\) In patients with hypertension, QT interval parameters are linked to LVM, but Chapman et al.\(^12\) demonstrated that these parameters were no better than were simple voltage criteria for the detection of LVH.\(^11\) Also, a previous study demonstrated an association between increased left ventricular mass index (LVMI) for body size and QT\(_d\). Salles et al.\(^13\) reported that QT\(_d\) prolongation was associated with LVH but neither QT\(_d\), nor QT interval parameters had sufficient prognostic values for LVH screening. Accordingly, in this study, we investigated the prognostic value of QT interval parameters in relation to LVH.

**METHODS**

This study was a cross-sectional study of 100 consecutive patients recruited from the clinics of Dr. Heshmat Hospital after the consideration of one of the following exclusion criteria and suspected LVH on ECG. The exclusion criteria comprised underlying disorders such as renal failure, renovascular hypertension, diabetes mellitus, thyroid disorder, cancers, hyperaldosteronism, phaeochromocytoma, or coarctation of the aorta. The other factors leading to exclusion from the study were comprised of having no family history of hypertension, having mental disorders, overusing non-antihypertensive drugs, malignant or resistant hypertension, stroke in the previous 6 months, abnormal electrolytes, anemia, cardiopulmonary disease (chronic lung disease and sleep apnea), serum creatinine >140 µmol/L, and taking medications that can increase QT\(_c\) (antiarrhythmic, antibiotics, macrolides, quinolones, and some antipsychotic and antidepressants).\(^14\) Patients with hypertension were those with blood pressure ≥140/90 mm Hg measured 3 times with the same mercury sphygmomanometer with 5-minute intervals in the sitting position.

Standard resting 12-lead ECGs were recorded with the same equipment with response frequencies at 25 mm/s paper speed and 10 mm/mv amplitude (Fukuda M-E Gardisuny). Electrocardiographic voltage criteria for LVH were either Sokolow–Lyon (SV1+RV5 or V6 ≥3.5 mV) or Cornell sex-specific (SV3+
RaVL ≥2 mv in women or 2.8 mv in men). QT interval parameters were measured manually in every ECG lead that was possible, with a minimum of 8 leads and 3 precordial ones being necessary. QT intervals were measured from the beginning of QRS complex to the end of T wave, defined as the visual return to TP baseline or as the nadir between T and U waves. Four QT interval parameters were obtained: maximum QT interval duration (QT_{max}), maximum Bazett formula heart rate corrected QT interval (QT_{cmax}), QT interval dispersion (QT_{dF}: difference between maximum and minimum QT intervals), and rate-corrected QT dispersion (QT_{cdF}: difference between maximum and minimum QTc intervals).

All the subjects underwent transthoracic M-mode, 2-dimensional, and Doppler echocardiography using a MyLab 50 Vision (with a 3.5-MHz transducer) instrument by the same cardiologist. Echocardiography recordings were performed in the parasternal long-axis plane. Measurements including LVM and LVMI were made according to the guidelines stipulated by the American society of Echocardiography (ASE).\textsuperscript{15} LVH was considered present when either one of the following echocardiographic values was obtained: male LVMI ≥115 g/m\textsuperscript{2} and female LVMI ≥95 g/m\textsuperscript{2}.\textsuperscript{16}

Data were collected and analyzed using descriptive statistics (frequencies, percentages, means, and standard deviations) and analytical statistics (Kolmogorov–Smirnov test to determine data normal distribution, chi-square correlation, Fisher exact test, t-test, and ROC curve analyses) in SPSS (version 18) with 95% confidence intervals and test power of 90%. A P value <0.05 was considered significant in all the tests.

This study was approved by the Ethics Committee of the Research Deputyship in Guilan University of Medical Sciences. Written informed consent was obtained from all the subjects at the beginning of the study. All the subjects were informed about the voluntary nature of participation and were assured about the confidentiality of their personal information.

**RESULTS**

One hundred patients with hypertension were included in this survey. Eighty-six (86%) patients had LVH according to the echocardiographic findings. Table 1 shows the baseline characteristics of the study population. The patients with LVH had a greater mean weight, waist measurement, and systolic blood pressure, while the patients without hypertrophy had a greater mean BMI and heart rate. The correlations between QT interval parameters and echocardiographic measurement are shown in Table 2. The 3 dispersion parameters (QT_{d}, QT_{cmax}, and QT_{cd}) had significant associations with LVH (P<0.05), and the ROC curves analyses of QT interval parameters showed that the cutoff points for QT_{max}, QT_{d}, QT_{cmax}, and QT_{cd} values were 420 (specificity=0.79 and sensitivity=0.40), 50 (specificity=0.58 and sensitivity=0.76), 478 (specificity=0.29 and sensitivity=0.58), and 59 (specificity=0.65 and sensitivity=0.76), respectively. These analyses showed that QT_{d} was a better test for the detection of LVH (Figure 1 and Figure 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>With Left Ventricular Hypertrophy (mean±SD)</th>
<th>Without Left Ventricular Hypertrophy (mean±SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.55±9.97</td>
<td>60.28±8.52</td>
<td>0.923</td>
</tr>
<tr>
<td>Weight</td>
<td>71.83±12.99</td>
<td>66.92±11.05</td>
<td>0.185</td>
</tr>
<tr>
<td>Height</td>
<td>157.24±10.83</td>
<td>156.42±7.33</td>
<td>0.787</td>
</tr>
<tr>
<td>Waist measurement</td>
<td>87.16±16.99</td>
<td>76.28±17.35</td>
<td>0.029*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>4.8±29.02</td>
<td>5.61±27.56</td>
<td>0.305</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>173.3±17.47</td>
<td>166.07±25.43</td>
<td>0.186</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>96.86±16.88</td>
<td>96.42±8.41</td>
<td>0.925</td>
</tr>
<tr>
<td>Heart rate</td>
<td>70.08±10.1</td>
<td>75±13.41</td>
<td>0.302</td>
</tr>
</tbody>
</table>

*Significance level was set at P <0.05.
Table 2. Comparison of QT interval parameters in relation to the left ventricular mass index from echocardiographic findings

<table>
<thead>
<tr>
<th>Group</th>
<th>Left Ventricular Hypertrophy</th>
<th>N (%)</th>
<th>Mean±SD</th>
<th>T Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QT&lt;sub&gt;max&lt;/sub&gt;</td>
<td>No</td>
<td>14 (14)</td>
<td>404±20.38</td>
<td>418±20.38</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>86 (86)</td>
<td>412±57.15</td>
<td>426±57.15</td>
<td>4.52</td>
</tr>
<tr>
<td>QT&lt;sub&gt;d&lt;/sub&gt;</td>
<td>No</td>
<td>14 (14)</td>
<td>57±22.82</td>
<td>67±22.82</td>
<td>87±39.08</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>86 (86)</td>
<td>430±21.66</td>
<td>412±21.66</td>
<td>5.59</td>
</tr>
<tr>
<td>QT&lt;sub&gt;cmax&lt;/sub&gt;</td>
<td>No</td>
<td>14 (14)</td>
<td>485±58.99</td>
<td>515±58.99</td>
<td>5.41</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>86 (86)</td>
<td>104±47.37</td>
<td>117±47.37</td>
<td>459±21.66</td>
</tr>
</tbody>
</table>

* Significance level was set at P<0.05.

DISCUSSION

The ECG patterns of LVH are independent cardiovascular risk factors and end-organ damage signs in patients with hypertension. In this regard, ECG has a main role in the detection of LVH. Nonetheless, in some studies, ECG parameters suggesting LVH such as QT<sub>d</sub> did not have sufficient prognostic performance. For instance, a screening method aimed at obtaining prognostic information in patients with arterial hypertension and its value still remains controversial. Thus, we investigated the relation between QT interval parameters and LVH to clarify this issue. We found that the patients suffering from hypertension with LVH had greater QT<sub>d</sub> and QT<sub>cd</sub> means than did those who did not have hypertrophy and QT<sub>d</sub> was a better test for the detection of LVH. Our results chime in with those reported by Izumi et al., who reported that QT<sub>cd</sub> was significantly correlated with VMI and that QT<sub>cd</sub> played a significant role in rising detectability of LVH with other indices. This prospective study was done on 153 unselected Japanese outpatients referring to a clinical physiology test department. Similar to this study, one of our main findings was that the cutoff point of QT<sub>cd</sub> for the detection of LVH varied from that in other studies on Caucasians in Western countries, while our study—similar to the Izumi report—was done on Asians. Also, our findings are concordant with those reported by Dimopoulos et al., who assessed the prognostic value of QT<sub>d</sub> in 108 patients with hypertension in Athens. The authors recognized that QT<sub>d</sub> was an...
CONCLUSIONS

Our ECG findings concerning LVH revealed that QT parameters such as QT_{cd} and QT_{c} would be better tests for the detection of LVH. We would, therefore, suggest that these parameters be employed as a simple, noninvasive, and adjunctive test for the initial evaluation of LVH in the general population.

Acknowledgements

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Conflict of Interest

There is no conflict of interest.

REFERENCES


Original Article

Correlation between Post-Percutaneous Coronary Intervention CKMB Elevation and One-Year Major Adverse Cardiac and Cerebrovascular Events

Farzad Emami, M.D.¹, Shafee Membari, M.D.¹, Behshad Naghshtabrizi, M.D.¹*, Zahra Sohrabi, M.D.¹

ABSTRACT

Background: CKMB elevation after percutaneous coronary intervention (PCI) correlates with major adverse cardiac and cerebrovascular events (MACCE). There is, however, some controversy over this issue, with some studies having reported different conclusions. We assessed the correlation between the CKMB level after PCI and one-year MACCE incidence in these patients.

Methods: We measured the CKMB level before and after PCI in 221 patients with normal baseline CKMB who underwent PCI at Ekbatan University Hospital, Hamedan, Iran, between April 2013 and October 2013, and divided them into 4 groups based on the post-PCI CKMB level. Then, we evaluated one-year MACCE incidence.

Results: CKMB elevation was detected in 81 (37.6%) patients and MACCE occurred in 11 (5%) patients. CKMB elevation after PCI was correlated to MACCE. The predictors of CKMB elevation were hyperlipidemia, number of deployed stents, stent diameter ≥4 mm, and complicated PCI.

Conclusions: CKMB elevation after PCI was detected in 37.6% of the study population and was common in the setting of hyperlipidemia, more than 1 stent deployment, stent diameter ≥4 mm, and complicated PCI. MACCE at 1 year occurred in 5% of the patients and was correlated with the post-PCI CKMB level ≥3 times of normal, history of diabetes mellitus, history of hypertension, and inappropriate use of clopidogrel. (Iranian Heart Journal 2015; 16(4): 41-46)

Keywords: ▪ Percutaneous coronary intervention ▪ CKMB ▪ Major adverse cardiac and cerebrovascular events

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Periprocedural myocardial infarction (MI) is a common complication of percutaneous coronary intervention (PCI) and is defined as CKMB elevation after PCI.\(^1\) Previously, 2 definitions were given for periprocedural MI. The WHO has defined postprocedural MI as a CK level >2 times the normal value with CKMB isoform elevation after PCI. The FDA has defined postprocedural MI as the CKMB level >3 times the normal value after PCI. Depending on local practices and criteria used, 5-30\% of patients who undergo PCI have evidence of periprocedural MI. However, the clinical significance of these events and their management remain a matter of considerable controversy and uncertainty.\(^2,3\) Consequently, numerous publications have demonstrated that CK and CKMB elevations have prognostic implications, even in the absence of pathological Q waves. The cutoff values of CK and/or CKMB used to define periprocedural MI in these studies varied widely. Numerous investigators have used the cutoff value of 3 times the upper limit of normal (ULN) of CK or CKMB (3×ULN) as the defining threshold of periprocedural MI, although it has been traditional to report >1×ULN, >5×ULN, and occasionally >8×ULN values as well.\(^3\)

The current PCI guidelines give a class I recommendation for the measurement of cardiac biomarkers (the MB fraction of creatine kinase [CK-MB], cardiac troponin, or both) in patients who have signs or symptoms suggestive of MI during or after PCI, and for those who have undergone complicated procedures.\(^2,4\) In addition, a class IIa recommendation is given for the routine measurement of cardiac biomarkers, 8 to 12 hours after the procedure. In either case, a new CKMB or troponin I or T rise >5 times ULN would constitute a clinically significant periprocedural MI.\(^1,2,3,4\) Mechanisms corresponding to cardiac events and poor prognoses in these patients are microreentry leading to ventricular arrhythmia, decreased collateral flow, and microvascular dysfunction.\(^2,3,5\) Major adverse cardiac and cerebrovascular events (MACCE) include cardiac mortality, non-fatal MI, target vessel revascularization (TVR), and cerebrovascular accident. The mechanisms of cardiac enzyme elevation after PCI are plaque debris embolization to the distal parts of the vascular field, side branch occlusion, stent thrombosis, vasoactive peptide release, and platelet activation.\(^3\)

**METHODS**

This longitudinal, prospective study was done at Ekbatan University Hospital, Hamedan, Iran. All patients who underwent PCI between April 2013 and October 2013 were considered. Patients with abnormal baseline CKMB levels (checked a day before the procedure) were excluded from the study. The total number of the patients entered in this study was 221. These patients underwent PCI and had a normal preprocedural CKMB level. The patients were followed up over a 12-month period after the procedure for MACCE occurrence with routine visits. The patients who had problems or hospital admissions during this period were visited again. The primary data collected from the patients included age; gender; history of hypertension; history of diabetes mellitus; history of hyperlipidemia; current smoking; preprocedural left ventricular ejection fraction; size, number, and type of deployed stents; target vessel; number of diseased vessels; postprocedural CKMB level; and PCI complications (i.e., side branch occlusion, slow flow, no reflow, coronary dissection, and plaque shift).

After the procedure, blood samples were drawn and electrocardiograms (ECGs) were recorded twice: once on the same day and
thereafter on the next day. If there were no complications or symptoms and no significant CKMB elevation or ECG changes, the patients were discharged a day after the procedure. The patients were divided into 4 groups based on the maximum level of postprocedural CKMB: normal level, 1-3×ULN, 3-5×ULN, and >5×ULN. The types of the stents deployed were the drug-eluting stent (DES) and the bare-metal stent (BMS) based on the operator’s decision and the current guidelines. The length and diameter of the deployed stents were classified as stent length more or less than 20 mm, stent diameter <3 mm, 3-4 mm, and >4 mm. The patients were divided into 2 groups based on their left ventricular ejection fraction: more or less than 40%. All the patients were given ASA (325 mg), clopidogrel (600 mg), and atorvastatin (40 mg) before the procedure, and these medications were prescribed after the procedure as routine.

**Statistical Analysis**
The Pearson chi-square test and the Fisher exact test were carried out to compare the nominal variables between the subgroups. Statistical significance was defined at the level of 0.05 or less. The Kaplan–Meier methods were applied to estimate survival curve. All the analyses were performed using SPSS, version number 20.

**RESULTS**

From the 221 patients, 68.3% were male and 31.7% were female, and the mean age was 59.6 years. The prevalence of diabetes mellitus, hypertension, hyperlipidemia, and cigarette smoking was 20.4%, 43%, 29.4%, and 30.3%, respectively. From these 221 patients, 36.7% had elevated CKMB levels after PCI (Table 1). In addition, 76.9% of the study population had single-vessel disease (SVD), 17.6% 2-vessel disease (2VD), and 5.4% 3-vessel disease (3VD). Target vessels were the left anterior descending (LAD) in 58.8%, right coronary artery (RCA) in 25.8%, left circumflex (LCX) in 16.7%, obtuse marginal (OM) in 9.5%, and diagonal in 3.2%. The incidence of complicated PCI was 7.2%, and the CKMB level in this group was higher than that in the non-complicated group.

<table>
<thead>
<tr>
<th>CKMB Level</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Cumulative Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>63.5</td>
<td>63.3</td>
<td>100</td>
</tr>
<tr>
<td>1-3 times of normal</td>
<td>96.4</td>
<td>33.0</td>
<td>73</td>
</tr>
<tr>
<td>3-5 times of normal</td>
<td>99.5</td>
<td>3.2</td>
<td>7</td>
</tr>
<tr>
<td>&gt;5 times of normal</td>
<td>100</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>221</td>
</tr>
</tbody>
</table>

MACCE occurred in 11 (5%) patients during the 12-month follow-up. Cardiac death occurred in 1.3%, non-fatal MI in 2.3%, TVR in 0.9%, and cerebrovascular accident in 0.9%. During this follow-up period, 95% of the patients used aspirin, 89% clopidogrel, and 93% atorvastatin correctly. There was no in-hospital mortality. Our data analysis showed a correlation between 1-year MACCE and post-PCI CKMB >3×ULN (P=0.01). Also, MACCE was correlated with the incorrect use of clopidogrel (P=0.001), hypertension (P=0.008), and diabetes mellitus (P=0.03) (Table 2). There was no correlation between MACCE and the other factors such as age, gender, target vessel, type of stents, number of stents, length of stents, diameter of stents, number of diseased vessels, incorrect use of aspirin or atorvastatin, and preprocedural ejection fraction. Also, there was no correlation between MACCE and complicated PCI directly, but CKMB elevation was more common in the complicated PCI group. Estimated MACCE-free survival rate of 12 months, using the Kaplan–Meier method, was 95%.

Based on our data collected from this study, elevated post-PCI CKMB levels had correlations with complicated PCI (P<0.0001), stent diameter ≥4 mm (P=0.002),
and hyperlipidemia (P=0.04), whereas there were no correlations with the other factors such as age, gender, target vessel, type of stents, number of stents, length of stents, number of diseased vessels, and preprocedural ejection fraction.

Table 2. Baseline characteristics and their correlations with 1-year major adverse cardiac and cerebrovascular events (MACCE)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Number</th>
<th>MACCE (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151</td>
<td>7 (4.6%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Female</td>
<td>70</td>
<td>4 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>45</td>
<td>5 (11.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>no</td>
<td>176</td>
<td>6 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>95</td>
<td>9 (9.5%)</td>
<td>0.008</td>
</tr>
<tr>
<td>no</td>
<td>126</td>
<td>2 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>67</td>
<td>5 (7.5%)</td>
<td>0.2</td>
</tr>
<tr>
<td>no</td>
<td>154</td>
<td>6 (3.9%)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>65</td>
<td>4 (6.2%)</td>
<td>0.6</td>
</tr>
<tr>
<td>no</td>
<td>156</td>
<td>7 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>CKMB level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 normal &lt;3 normal</td>
<td>213</td>
<td>9 (4.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>≥3 normal</td>
<td>8</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel correct usage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>197</td>
<td>6 (3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>no</td>
<td>24</td>
<td>5 (20%)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin correct usage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>207</td>
<td>9 (4.3%)</td>
<td>0.09</td>
</tr>
<tr>
<td>no</td>
<td>14</td>
<td>2 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>ASA correct usage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>210</td>
<td>11 (5.2%)</td>
<td>0.4</td>
</tr>
<tr>
<td>no</td>
<td>11</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>In-lab complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>16</td>
<td>1 (6.2%)</td>
<td>0.8</td>
</tr>
<tr>
<td>no</td>
<td>205</td>
<td>10 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40%</td>
<td>155</td>
<td>9 (5.8%)</td>
<td>0.2</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>19</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Stent type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>125</td>
<td>6 (4.8%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Bare</td>
<td>106</td>
<td>5 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Number of vessel disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1VD</td>
<td>170</td>
<td>6 (3.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>2VD</td>
<td>39</td>
<td>4 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>3VD</td>
<td>12</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Number of stents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>168</td>
<td>8 (4.8%)</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>2 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>11</td>
<td>1 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Stent length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>139</td>
<td>9 (6.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>≤20 mm</td>
<td>82</td>
<td>2 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>&lt;4 mm</td>
<td>24</td>
<td>1 (4.2%)</td>
<td>0.8</td>
</tr>
<tr>
<td>3-3.5 mm</td>
<td>137</td>
<td>8 (5.8%)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In patients with ischemic heart disease, a slight elevation in cardiac biomarkers is frequently detected after percutaneous coronary revascularization, but their clinical significance is still uncertain. CKMB isoenzyme can be released from myocardial necrosis or severe ischemia. Patients with acute coronary syndromes are more likely to develop periprocedural MI. However, studies examining the incidence of periprocedural MI in this patient population have been limited by certain methodological difficulties. First, it is difficult and more controversial to define periprocedural MI when patients present with elevated markers prior to PCI. Therefore, most of the studies on this topic have excluded these patients from their analysis. Periprocedural MI is a common complication of PCI and is defined as CKMB elevation. Depending on local practices and criteria used, periprocedural MI was seen in 5-30% of the patients who underwent PCI. Although there is much controversy surrounding the definition and prevalence of periprocedural MI with everyday PCI, there is no dispute that significant periprocedural MI is associated with an increased mortality risk. There remains controversy about the pathophysiological mechanisms underlying
this association as well as the definition and the size of periprocedural MI that would confer such increased risk. However, there is convincing evidence that any periprocedural MI is associated with some degree of increased risk of death, particularly with longer follow-up.\(^3\)

The risk of periprocedural MI is significantly increased in patients with evidence of more severe atherosclerotic disease. Multivessel and/or more diffuse coronary artery disease is associated with an approximately 50% increase in the relative risk of developing periprocedural MI.\(^3\)

The predictors of periprocedural MI can be broadly categorized as patient-, lesion-, and procedure-related risk factors. The major risk factors, in terms of both frequency and potency, are complex lesions (e.g., the presence of thrombus, stenosis of a saphenous vein graft, or lesion type), complex procedures (e.g., treatment of multiple lesions or use of rotational atherectomy), and associated complications (e.g., abrupt vessel closure, side branch occlusion, distal embolization, or no reflow). Findings suggest that factors other than the burden of plaque microembolization influence the likelihood of periprocedural MI such as the release of vasoactive factors from the atherosclerotic plaque, platelet activation, and preexisting vulnerability of the myocardium.\(^2\)

The present prospective study showed that in the patients with a normal baseline serum CKMB level, minor elevation (<3 times) occurred in 33% of the patients after PCI, but this minor elevation was not associated with MACCE during a 12-month follow-up. On the other hand, 3.7% of the patients had CKMB elevation ≥3 times, which was correlated with a higher rate of MACCE and reduced event-free survival at 12 months. Numerous investigators have used the cutoff value =3× ULN of CK or CKMB as the defining threshold of periprocedural MI, although it has been traditional to report >1× ULN, >5× ULN, and occasionally >8×ULN values as well.\(^3\) Kavallini et al.\(^7\) showed a linear association between the 2-year mortality rate and the CKMB level, but Kjellvikenes et al.\(^8\) showed that CKMB mass value ≥3 times after elective angioplasty was able to predict reduced long-term event-free survival. However, in another study, Azarnik et al.\(^9\) showed that the mid-term survival of patients with CKMB and/or troponin elevation after PCI was similar to that in individuals with normal enzymes and that stable patients with low-to-medium CKMB and troponin elevation were routinely discharged 2 days after intervention without apparent short-term adverse events.

A contemporary analysis on the prognostic significance of periprocedural MI in patients from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial suggested that periprocedural MI was a marker of baseline risk, atherosclerosis burden, and procedural complexity but in most cases, it did not appear to have an independent prognostic significance.\(^10\) In our study, the most powerful predicting factors for MACCE occurrence after PCI were hypertension, incorrect use of clopidogrel, CKMB elevation ≥3 times, and history of diabetes mellitus. This suggests that the modification of coronary risk factors and correct use of medications such as clopidogrel can reduce MACCE after PCI.

Large periprocedural MIs are usually due to angiographically visible complications; however, this is generally not the case in the vast majority of patients with elevated biomarker levels after PCI. In this study, we also showed the risk factors of post-PCI CKMB elevation. The most powerful risk factors were the occurrence of in-lab complications, number of stents, stent diameter ≥4 mm, and history of hyperlipidemia, respectively. In some studies, risk factors which correlate to CKMB elevation were the occurrence of in-lab complications, multi-vessel intervention, low baseline ejection fraction, peripheral vascular disease, and use of glycoprotein IIb/IIIa inhibitors during intervention.\(^2,11,12,13\)
CONCLUSIONS

CKMB elevation after PCI, which is the definition of periprocedural MI, was detected in 37.6% of the patients and was common in the patients with hyperlipidemia, deployment of more than 1 stent, stent diameter ≥4 mm, and complicated PCI. MACCE at 1 year occurred in 5% of the patients and correlated with the post-PCI CKMB level ≥3×UNL, history of diabetes mellitus or hypertension, and incorrect use of clopidogrel in the 12-month follow-up duration.

Funding Sources and Disclosures
This study was supported by Hamedan Medical University. The authors declare that there was no conflict of interest regarding the publication of this paper.

Acknowledgments
This study was supported by Hamedan University of Medical Sciences. It is a pleasure to acknowledge the many talented collaborators, including the physicians, nurses, paramedics, and others, who contributed to this field and our work. We thank Dr. Hossein Mahjob and Dr. Leily Tapak for the statistical analyses.

REFERENCES


Original Article

Correlation between Angiographic Findings and Pain and Its Palliative Factors in Patients with Chest Pain Referring to Rajaie Cardiovascular, Medical and Research Center

Nafiseh Taraghi Delgarm, M.D.¹, Farshad Shakerian, M.D.¹, Hosein Azarnik, M.D.¹*, Vida Khanlarzade, M.D.¹, Mahdie Mahdinegad, M.D.¹

ABSTRACT

Background: In patients referred for an evaluation of chest pain, the incidence of cardiac disease may be as low as 11–27%. Furthermore, the incidence of normal coronary anatomy in patients investigated invasively varies widely, between 11% and 37%, at different cardiac centers. In this study, we evaluated the correlation between angiographic findings and pain and its palliative factors in patients with chest pain referring to Rajaie Cardiovascular, Medical and Research Center.

Methods: All patients with chest pain who were admitted to the Emergency Department of Rajaie Cardiovascular, Medical and Research Center between September 2013 and March 2014 and needed coronary angiography were enrolled. Demographic data and the results of physical examinations and characteristics of pain and its palliative factors and the chest pain score based on a check list were collected. Thereafter, angiography was performed and correlations between angiographic findings and pain (characteristics and score) and its palliative factors were assessed.

Results: Totally, 194 patients with the average age of 58±10 years were investigated. Of the 194 patients, coronary arteries were normal in 57 (29%) patients. Of these patients, 37 patients were women and 20 patients were men. Single-vessel disease was observed in 53 (40%), 2-vessel disease in 39 (30%), and 3-vessel disease in 40 (30%). Left main stenosis was observed in 1 (0.5%) patient, and 3-vessel disease accompanied with the left main was documented in 4 (2.1%). Also, slow flow was observed in 5 (2.6%) patients. Regarding the localization of the involved vessel, left main involvement was observed in 5 (3.1%) patients, left anterior descending in 82 (24.3%), left circumflex in 62 (32%), and right coronary artery in 54 (27.8%). A pain score of 0 was present in 24 (12%) patients, pain score of 1 in 47 (24%), pain score of 2 in 73 (37%), and pain score of 3 in 50 (25%). The sensitivity value of the pain score in our research was calculated to be 80% by taking advantage of a chest pain score of 0 as the negative predictor of the coronary vessel disease and a chest pain score of 1 to 3 as the positive predictor of coronary vessel disease.

Conclusions: In the present study, there was no relationship between pain characteristics and the results from the involved vessel and the final angiographic results. The pain score is greatly useful in patients with a higher risk of coronary artery disease, whereas in patients with an intermediate pain score, it is important to perform other
Cardiovascular diseases are among the chief reasons for mortality around the world. In developed countries, cardiovascular diseases account for 50% of the death toll or 5 million of 12 million deaths are due to cardiovascular diseases annually.\(^1\) Mortality is also increasing in developing countries, and cardiac diseases are deemed the main cause of 15 to 25% of deaths.\(^2\) Mortality in the time interval from 1990 to 2006 rose from 27 to 37% in Iran. According to the statistics provided by the Health Department, about 39% of all of the referrals to health-treatment centers belong to blood circulation diseases.\(^3\) Also, cardiovascular diseases are the major cause of disabilities around the world. It is estimated that about 81 million Americans are diagnosed with coronary heart diseases.\(^4\)

In Iran as well this disease is an important cause of death in individuals older than 35 years of age.\(^5\) It is estimated that the disease load is over 1.5 million per year.\(^6\) Nonetheless, studies have shown that only 30% of the patients admitted to the coronary care unit (CCU) have had myocardial infarction and 50-60% are known to have had myocardial ischemia. Also, studies have suggested that 16-20% of the population in England and the United States\(^6\) have had a history of chest pain and in most of the cases this has been benign\(^10\) and from among the patients referred to cardiovascular specialists only 11-27% are diagnosed with heart diseases.\(^11,12\) Some studies have indicated that 11 to 37% of the patients who have undergone angiography due to chest pain had normal coronary vessels.\(^13,14\) Therefore, distinguishing cardiac patients from noncardiac patients referring to hospitals with chest pain both reduces unnecessary hospital stays and contributes a great deal to the time of treatment of such patients. Normally, patients with chest pain are screened based on the previous history of heart disease, risk factors, self-report, serial electrocardiography, and measurement of cardiac markers. In patients’ self-reports, pain is classified into typical and atypical, and studies have shown that the interpretation of this classification is individual-specific and yields various results even if it is performed based on standardized questionnaires.\(^15,16\)

In a common survey, patients with chest pain are examined from different aspects such as quality of pain and risk factors and their noninvasive test results such as the treadmill test and scan. Based on the studies performed, a presented pain score enables us to adopt these results for a timely diagnosis and to distinguish cardiac from noncardiac pains in such patients with a view to reducing the number of unnecessary angiography procedures.\(^17\) In the present study, we examined the patients based on this score as well as heart scan and angiographic results and pain characteristics and the factors influencing it. We compared the patients based on the entire test results.

METHODS

Patients with chest pain who were referred to Rajaie Cardiovascular, Medical and Research Center (between
have to stop completely or sit down (rest time index)?
3. How long does the pain last (pain duration index)?

For the first question-index, 10/10 was considered typical pain and the other indices were regarded as atypical. Regarding the second question index, 0/10 and 1/10 were considered typical and the other scores were considered atypical. Concerning the third question, a 5-minute time duration and less was considered typical and the rest of the cases were considered atypical. Eventually, each of the typical variables was assigned a score; therefore, the total score for these 3 questions was a number from 0 to 3. A score of 3 was considered typical chest pain, scores of 1 and 2 were regarded as low intermediate and high intermediate, and 0 was indicative of atypical chest pain.

Patients’ Scan
Heart scan along with simultaneous echocardiography is superior to the treadmill test and is indicative of the localization of coronary stenosis. This test has sensitivity of 88% of the involved vessel. Of course, the treadmill test has sensitivity of 68%. This method provides us with critical information and it can also be performed in patients with abnormal resting electrocardiograms such as bundle branch block or digoxin consumption. Heart scan with pharmacological stress in patients incapable of performing the treadmill test such as old patients, patients with peripheral vessel disease, patients with pulmonary disease, patients with arthritis, and patients with orthopedic disorders is recommended with vasodilators such as adenosine or dipyridamole. This group compromises 40 to 50% of the patients referred for imaging. The diagnostic accuracy of such a method is comparable with that of the scan performed via the treadmill test. The results of the patients’ scan are stratified into 4 sets: negative, positive cases without high risk, positive cases with high risk, and

Clinical Investigations
All the patients were questioned before angiography and were informed of the results via a pre-prepared questionnaire based on the surveyed variables. Also, the pain score was asked from the patients based on 3 questions and the patients’ final score was calculated as follows17:
1. If you walk uphill 10 times, how many times will you experience the same pain for which you have referred to the hospital (repeatability index)?
2. If you experience the pain 10 times along a path, how many times will you
positive cases with intermediate risk.²⁸ If the patients are in the high-risk group, even if they are symptomless, the probability of 3-vessel disease or left main lesion will be high and there is a need for angiography. The group with a negative test result even in the presence of clinical symptoms has an excellent prognosis and this prognosis does not change considerably with angiography. In the current study, the individuals who underwent MPI before angiography were allocated to low-risk, intermediate-risk, and high-risk groups based on the given criteria.²⁸ In the present study, 109 patients were scanned previously and 10 (9%) of these patients had normal scan, 30 (27%) had low-risk scan, 43 (39%) had an intermediate-risk scan, and 26 (24%) had high-risk scan.

**Angiographic Results**

Angiography was performed on all the patients, and the existing stenosis (stenosis ≥50%) in 1 of the epicardial vessels was considered. A stenosis of 30-50% was considered minimal coronary artery disease, and a stenosis <30% was nonsignificant.

**Data Analysis**

The mean and the standard deviation of the variables were calculated, and they were used to evaluate the variables. The chi-square test was utilized to compare the different groups. The Pearson correlation and regression test were used to compare pain characteristics between the different groups. A P value <0.05 was considered significant.

**RESULTS**

Of the 194 patients, coronary arteries were normal in 57 (29%) patients. Of these normal patients, 37 patients were women and 20 patients were men. The average age did not differ considerably between the men and women. Single-vessel disease (SVD) was observed in 42 (21.6%) patients, 2-vessel disease (2VD) in 27 (13.9%), 3-vessel disease (3VD) in 28 (14.4%), left main stenosis in 1 (0.5%), and 3VD accompanied with left main disease in 4 (2.1%). Additionally, slow flow evidence was present in 5 (2.6%) patients. Also, from the perspective of the involved vessel, left main involvement was observed in 5 (3.1%) patients, LAD in 82 (43.3%), LCX in 62 (32%), and RCA in 54 (27.8%). A pain score of 0 was present in 24 (12%) individuals, pain score of 1 in 47 (24%), pain score of 2 in 73 (37%), and pain score of 3 in 50 (25%).

The sensitivity value of the pain score investigated in our research was 20% by taking advantage of a chest pain score of 0 as the negative predictor of coronary vessel disease and a chest pain score of 1 to 3 as the positive predictor.

**Other Factors**

In the current study, the chest pain score in the individuals diagnosed with completely normal coronary vessels on angiography differed considerably from the pain score obtained from the other individuals studied in the study. Other variables which differed considerably between the 2 groups of individuals with normal angiography and the other individuals studied in the current study include the following cases:

- The female gender and the intensification of pain subsequent to stress or excitement (normal angiography cases were greater in the women) and improvement by massage and pain relief by consuming anti-acid or milk were observed more frequently in the individuals with normal angiography, while pain intensification accompanied with activity, lower ejection fraction, pain improvement with TNG, higher risk score, and smoking were observed in the individuals with abnormal angiography.

- From the aspect of chest pain features such as radiation, location, and duration, there were considerable differences between the 2 groups (Table 1). Also, there was no significant relationship between the location of stenosis...
and pain characteristics between the various groups. The regression analysis indicated that gender (P<0.001), the pain score (P=0.01) (Figure 3), scan results (P=0.001) (Figure 2), and the ejection fraction results of the patients (P=0.02) differed independently between the 2 groups. Furthermore, smoking (P=0.01), improvement in pain with rest (P=0.001), pain exacerbation with activity (P=0.001), intensification of pain by consuming food (P=0.001), and improvement in pain by drinking milk (P=0.001) differed considerably between the 2 groups (Figure 4). Contrary to the results of similar studies in this field, there were no significant relationships between age, diabetes prevalence, hypertension, and pain location between the 2 groups (Figure 1).

Figure 1. Prevalence of classic risk factors in NECA and others

Figure 2. Prevalence of the scan results in various risk groups

Figure 3. Prevalence of the pain score between NECA and others

Figure 4. Comparison of the factors that relieved or intensified pain between the 2 groups
Table 1. Relationship between pain characteristics and the scan results and the pain score in the comparison between the 2 groups of normal angiography and with coronary artery disease (other patients)

<table>
<thead>
<tr>
<th></th>
<th>NECA</th>
<th>Other</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper right</td>
<td>0</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Upper middle</td>
<td>6</td>
<td>7</td>
<td>5.1</td>
</tr>
<tr>
<td>Upper left</td>
<td>6</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>Middle right</td>
<td>3</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>Mid external</td>
<td>18</td>
<td>60</td>
<td>43.8</td>
</tr>
<tr>
<td>Left hemithorax</td>
<td>9</td>
<td>16</td>
<td>11.7</td>
</tr>
<tr>
<td>Lower right</td>
<td>1</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Epigastric</td>
<td>8</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Lower left</td>
<td>6</td>
<td>16</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non</td>
<td>24</td>
<td>32</td>
<td>23.4</td>
</tr>
<tr>
<td>Back</td>
<td>14</td>
<td>23</td>
<td>16.8</td>
</tr>
<tr>
<td>Neck</td>
<td>0</td>
<td>25</td>
<td>18.2</td>
</tr>
<tr>
<td>Left arm</td>
<td>9</td>
<td>40</td>
<td>29.2</td>
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<td>Right arm</td>
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<td>7</td>
<td>5.1</td>
</tr>
<tr>
<td>Leg</td>
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<td>0</td>
</tr>
<tr>
<td>Abdomen</td>
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<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Point tenderness</td>
<td>3</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Left to right</td>
<td>0</td>
<td>8</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Pain quality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressing</td>
<td>5</td>
<td>61</td>
<td>44.5</td>
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<tr>
<td>cutting</td>
<td>10</td>
<td>3</td>
<td>2.2</td>
</tr>
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<td>Tingling</td>
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<td>40</td>
<td>29.2</td>
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<td>Feeling heaviness</td>
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<td>33</td>
<td>24.1</td>
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<tr>
<td><strong>Pain duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute</td>
<td>15</td>
<td>98</td>
<td>71.5</td>
</tr>
<tr>
<td>Hour</td>
<td>32</td>
<td>39</td>
<td>28.5</td>
</tr>
<tr>
<td>Day</td>
<td>10</td>
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<td><strong>Pain repetition</strong></td>
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<td></td>
</tr>
<tr>
<td>Daily</td>
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<td>44</td>
<td>3.12</td>
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<td>Weekly</td>
<td>36</td>
<td>84</td>
<td>61.3</td>
</tr>
<tr>
<td>Monthly</td>
<td>10</td>
<td>8</td>
<td>5.8</td>
</tr>
<tr>
<td>Yearly</td>
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<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Pain score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>22 (91.7%)</td>
<td>2 (8.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lower than intermediate</td>
<td>20 (42.6%)</td>
<td>27 (57.4%)</td>
<td></td>
</tr>
<tr>
<td>Higher than intermediate</td>
<td>15 (20.5%)</td>
<td>58 (79.5%)</td>
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</tr>
<tr>
<td>Typical</td>
<td>0</td>
<td>50 (100%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>1 (5.3%)</td>
<td>18 (94.7%)</td>
<td>0.56</td>
</tr>
<tr>
<td>24-29</td>
<td>41 (34.7%)</td>
<td>77 (65.3%)</td>
<td></td>
</tr>
<tr>
<td>30-35</td>
<td>13 (25%)</td>
<td>39 (75.0%)</td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>2 (40%)</td>
<td>3 (60%)</td>
<td></td>
</tr>
<tr>
<td><strong>MPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NI</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low risk</td>
<td>13 (43.3%)</td>
<td>17 (56.7%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>6 (15%)</td>
<td>34 (85%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1 (3.4%)</td>
<td>28 (96.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;30</td>
<td>3 (13.6%)</td>
<td>19 (86.4%)</td>
<td></td>
</tr>
<tr>
<td>30-45</td>
<td>7 (24.1%)</td>
<td>22 (75.9%)</td>
<td></td>
</tr>
<tr>
<td>45-50</td>
<td>4 (15.4%)</td>
<td>22 (84.6%)</td>
<td></td>
</tr>
<tr>
<td>50-55</td>
<td>18 (26.9%)</td>
<td>49 (73.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56.56±9.47</td>
<td>59.2±10.36</td>
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Table 2. Comparison of the number of the involved vessels and pain characteristics between the different groups

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<tr>
<th>CATH</th>
<th>NECA</th>
<th>mCAD</th>
<th>SVD</th>
<th>2VD</th>
<th>( \text{P Value} )</th>
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<td>Pain location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Upper right</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0&lt;br&gt;Upper middle</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>None</td>
<td>24</td>
<td>42.1</td>
<td>10</td>
<td>33.3</td>
<td>7</td>
</tr>
<tr>
<td>Pain quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Pressing</td>
<td>5</td>
<td>8.8</td>
<td>8</td>
<td>26.7</td>
<td>19</td>
</tr>
<tr>
<td>Pain duration</td>
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<td>0.001</td>
</tr>
<tr>
<td>Minute</td>
<td>15</td>
<td>26.3</td>
<td>16</td>
<td>53.3</td>
<td>32</td>
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<td>Pain repetition</td>
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<td>0.21</td>
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<tr>
<td>Daily</td>
<td>11</td>
<td>19.3</td>
<td>6</td>
<td>20</td>
<td>12</td>
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Table 3. Comparison of the number of the involved vessels and pain characteristics between the different groups

<table>
<thead>
<tr>
<th>CATH</th>
<th>3VD</th>
<th>LM</th>
<th>LM-3VD</th>
<th>Slow Flow</th>
<th>( \text{P Value} )</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Upper right</td>
<td>1</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>21.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Pressing</td>
<td>13</td>
<td>46.4</td>
<td>1</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Pain duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Minute</td>
<td>22</td>
<td>78.6</td>
<td>1</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Pain repetition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
</tbody>
</table>
| Daily | 10 | 35.7 | 0 | 0 | 1 | 25 | 2 | 40<br>Weekly | 17 | 60.7 | 1 | 100 | 3 | 75 | 4 | 40<br>Monthly | 1 | 3.6 | 0 | 0 | 0 | 0 | 1 | 20<br>Yearly | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0
Also, no significant relationship was identified between the involved vessel and pain characteristics and its accelerating factors. From the point of view of the number of the involved vessels and the radiation characteristics and quality and duration of pain, there was a significant relationship between the different groups (Table 2 and Table 3). For example, in 42% of the patients with completely normal angiography, the patients’ pain was propagated to no special locality. On the other hand, the radiation of pain to the neck was present in 42% of the individuals with 3VD and in 75% of the individuals with left main/3VD, while this amount was 0% in the individuals with normal angiography and was not a considerable amount in the other groups.

The radiation of pain to the left arm was mostly observed in the individuals with the involvement of 2 or 3 vessels, and the radiation of pain to the leg was observed only in the individuals with normal angiography, while the feeling of pain in the form of a pressing pain or feeling of heaviness in the chest (angina pectoris) was mostly seen in the individuals with the involvement of 2 or 3 vessels as 46% of the patients with 3VD reported pain as a pressing pain, whereas this amount in the individuals with normal angiography was only 8%.

**DISCUSSION**

The present study showed that the pain score could be advantageous in indicating the individuals with a higher probability of coronary artery involvement and that its sensitivity and specificity could be similar to the evaluation by noninvasive studies. This pain score has been evaluated in similar studies. Nevertheless, in order to be able to utilize the pain score clinically at the first visit of the patient, we need to perform further studies. The sensitivity of the test was considerably higher, especially in the patients with a score of 3. These patients can be referred for angiography without completing the supplementary tests. On the other hand, in the patients with a score of 0, the test sensitivity was considerably valuable for rejecting the probability of coronary artery disease and there was no need for more specialized examinations for such patients as 91% of the patients with a pain score of 0 had completely normal vessels on angiography. Moreover, about 70% of the individuals with a pain score of 1 to 2 had coronary artery disease on angiography and, as such, these individuals can be directly referred to angiography without any further investigation.

Among the patients with a pain score of 0 when the scan shows normal results, the possibility of coronary artery disease is very weak and these patients can be excluded from further heart examinations and can be dismissed. Thus, the use of the pain score at the first visit as a consultative examination may reduce the number of referrals to higher levels and the need for unnecessary angiography (anatomically normal vessels). The results of the pain score sensitivity stood low in our study in comparison with that in similar studies, while its specificity was high (40%) in our study in comparison with that in other studies (28%).

**Limitations**

In the current study, we performed visual examination of the percentage of the vessel stenosis to calculate the intensity of coronary artery stenosis and we did not make use of an appropriate quantitative method such as FFR to accurately evaluate the functional intensity stenosis, which may have weakened the study results. However, in contrast to similar studies, we did not determine stenoses <50% as the borderline between the anatomically normal and abnormal coronary artery disease. In the present study, all the studied individuals did not have perfusion scan, which renders a portion of our information
Inaccurate. Also, we evaluated the pain score of the patients with chronic cardiac pain with a duration >1 month. The evaluation of this score is not possible in patients with acute chest pain, which necessitates more serious and faster examinations. The pain score was based on the patients’ self-report, which could have had an influence on their responses because they had been candidate to undergo angiography. This may have led to an overestimation of pain intensity and other factors.

**CONCLUSIONS**

In the present study, there were no relationships between pain characteristics such as location, radiation, quality, and duration and the involved vessel location (LAD, LCX, and RCA). Nonetheless, we found a relationship between a lower ejection fraction, higher pain score, smoking history, and high-risk thallium scan and abnormal angiographic results. Contrary to the previous studies in this field, heart disease risk factors such as diabetes and hypertension did not have a significant relationship with angiographic results, but pain radiation and pain quality had a significant difference between the 2 groups of normal anatomy and abnormal anatomy. Also, the factors accelerating pain, including pain intensification accompanied by activity and food consumption and psychological stress and crying, or the consumption of anti-acid or milk and the improvement in pain with TNG and massage had a significant difference between the 2 groups, which is indicative of the fact that besides pain characteristics, it is necessary to pay more attention to the decreasing and intensifying factors in the examination sessions.

The studied pain score proved greatly useful in the patients with a higher risk of coronary vessel involvement. Be that as it may, in patients with an intermediate pain score, it is important to perform other examinations such as scan or treadmill tests for correct decision-making. In addition, this score can be useful in making decisions to refer the patient to higher therapeutic levels or angiography. For further investigation, it would be desirable to perform similar studies with larger sample volumes. According to our study, the pain score had sensitivity of about 80% and specificity of about 45% for the possibility of coronary artery involvement, which is equal to the sensitivity of the scan, but the specificity of the pain score was lower than that reported in similar studies. Furthermore, it had low specificity in comparison with the treadmill test and MP scan.

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Case Report

Friedreich's Ataxia and Hypertrophic Cardiomyopathy: A Case Report and Review

Hanane Benhalla, M.D.1* , Camelia Sorea, M.D.1

ABSTRACT

Friedreich's ataxia is an autosomal recessive, spinocerebellar, degenerative disease characterized clinically by the ataxia of the limbs and trunk, dysarthria, loss of deep tendon reflexes, sensory abnormalities, skeletal deformities, diabetes mellitus, and cardiac involvement. Friedreich's ataxia is generally associated with concentric hypertrophic cardiomyopathy. Cardiac death occurs primarily in those developing dilated cardiomyopathy. These patients tend to do poorly with rapid progression to end-stage congestive heart failure. (Iranian Heart Journal 2015; 16(4): 57-59)

Keywords Friedreich's ataxia Hypertrophic cardiomyopathy Familial neurodegenerative disease

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Friedreich's ataxia is an autosomal recessive, multisystem disease that leads to a mitochondrial dysfunction affecting the nerve tissue and heart muscle. According to previous studies, cardiac dysfunction, predisposing to congestive heart failure and supraventricular arrhythmias, is the most frequent cause of death.

CASE PRESENTATION

We describe an 19-year-old female with a history of familial neurodegenerative disease, who suffered from a type 1 diabetes mellitus and presented with progressive weakness, vertigo, and loss of lower-limb muscle force of 1 year's duration. The patient had occasional respiratory distress of 6 months' duration, which was exacerbated with activity and improved with rest. She also had atypical chest pain. Physical examination detected truncal ataxia, absent deep tendon reflexes, and dysarthria. The patient's electrocardiographic (ECG) findings were normal sinus rhythm, left axis deviation, heart rate of 94, and left ventricular hypertrophy voltage criteria.

Echocardiography showed left ventricular ejection fraction of 50%, severe left ventricular hypertrophy, no regional wall motion abnormalities at rest, concentric hypertrophy, no aortic or mitral insufficiency, no aortic stenosis, no coarctation of the aorta, and grade 1 diastolic dysfunction (Figure 1).

Figure 1. Echocardiography in the parasternal long-axis view shows the severity of the hypertrophic cardiomyopathy.
Given the patient's neurological findings, familial history of neurodegenerative disease, type 1 diabetes mellitus, cardiac involvement, and echocardiographic findings, Friedreich's ataxia was suggested, which was subsequently confirmed by the neurologist.

**DISCUSSION**

We reported the case of a 19-year-old female, who presented with progressive weakness, vertigo, and loss of lower-limb muscle force of 1 year's duration. In her ECG, there were left ventricular hypertrophy voltage criteria. The most prominent point in her echo was concentric hypertrophic cardiomyopathy. According to her neurological findings, familial history of diabetes mellitus, cardiac involvement, and echocardiographic findings, Friedreich's ataxia was suggested. The neurologist subsequently confirmed the diagnosis.

Friedreich's ataxia is an autosomal, recessive, spinocerebellar, degenerative disease characterized clinically by the ataxia of the limbs and trunk, dysarthria, loss of deep tendon reflexes, sensory abnormalities, skeletal deformities, diabetes mellitus, and cardiac involvement. It is worthy of note that 98% of the patients have an expansion of GAA trinucleotide repeat located within the first intron of the FXN gene. In addition, larger GAA expansions are correlated with earlier age at onset and shorter times to loss of ambulation. Friedreich's ataxia is the most common inherited spinocerebellar degenerative disease, with a prevalence of 1/50000. Neurological symptoms usually manifest around puberty and almost always before the age of 25 years. Progressive loss of neuromuscular function and neurological symptoms precede cardiac symptoms in most but not all cases. Friedreich's ataxia is associated with a high incidence rate of diabetes mellitus. Clinically apparent diabetes is seen in approximately 18% of the affected individuals, while impaired glucose tolerance is present in up to 37% of patients with Friedreich's ataxia.

Friedreich's ataxia is generally associated with concentric hypertrophic cardiomyopathy. Less commonly, asymmetric septal hypertrophy is observed. The presence of a left ventricular outflow gradient associated with septal hypertrophy has been reported. Left ventricular hypertrophy is not always present on the ECG despite echocardiographic evidence. Widespread T-wave inversions are common. The prevalence of hypertrophy varies among studies but increases in prevalence with a younger age at diagnosis and with increasing GAA trinucleotide repeat length. Myocardial fiber disarray is not commonly seen in the hypertrophic cardiomyopathy of Friedreich's ataxia. In most patients with Friedreich's ataxia, progressive neurological dysfunction is the norm, with death from respiratory failure or infection in the fourth or fifth decade. Cardiac death occurs primarily in those developing dilated cardiomyopathy. These patients tend to do poorly with rapid progression to end-stage congestive heart failure. It is unclear whether pharmacological or ICD therapy improves outcomes in Friedreich's ataxia and dilated cardiomyopathy.

**REFERENCES**


Friedreich's Ataxia and Hypertrophic Cardiomyopathy: A Case Report and Review

Benalla H, et al.


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**Forthcoming Meetings**

**The Houston Conference**  
*Thursday, March 3, 2016 to Saturday, March 5, 2016*  
Methodist Institute for Technology, Innovation and Education  
Houston  
United States  
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**Re-Evolution Summit - 7th Annual**  
*Thursday, March 3, 2016 to Saturday, March 5, 2016*  
Houston Methodist Research Institute  
Houston, TX  
United States  
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**12th International Congress of Update in Cardiology and Cardiovascular Surgery**  
*Thursday, March 10, 2016 to Sunday, March 13, 2016*  
Sueno Belek Convention Center  
Antalya  
Turkey  
See map: [Google Maps](#)

**NCVH Hattiesburg 2016**  
*Saturday, March 12, 2016*  
Hattiesburg Lake Terrace Convention Center  
Hattiesburg, MS 39401  
United States  
See map: [Google Maps](#)

**SCTS Annual Meeting & Cardiothoracic Forum 2016**

**Sunday, March 13, 2016 to Tuesday, March 15, 2016**  
International Conference Centre  
Birmingham  
United Kingdom  
See map: [Google Maps](#)

**3rd Annual Conference of South and West Asia Chapter of Extracorporeal Life Support Organization**  
*Wednesday, March 16, 2016 to Saturday, March 19, 2016*  
Beach Rotana Hotel  
Abu Dhabi  
United Arab Emirates  
See map: [Google Maps](#)

**Knowledge Track - 'Antalya Revisited in Istanbul' - A Complete Review of Thoracic Surgery**  
*Wednesday, March 16, 2016 to Sunday, March 20, 2016*  
Elite World Business Hotel  
Istanbul  
Turkey  
See map: [Google Maps](#)

**CATCH-UP 2016: 7th Annual Assist Device Therapy Course**  
*Friday, March 18, 2016 to Saturday, March 19, 2016*  
NewYork-Presbyterian/Columbia University Medical Center  
173 Fort Washington Avenue  
New York 10032  
United States  
See map: [Google Maps](#)

**AATS Focus on Thoracic Surgery: Lung and Esophageal Cancer**  
*Saturday, March 19, 2016 to Sunday, March 20, 2016*  
Hilton Shanghai Hongqiao  
Shanghai
China
See map: Google Maps

**Aortic Asia 2016**
*Thursday, March 31, 2016 to Saturday, April 2, 2016*
Millennium Hilton
Bangkok
Thailand
See map: Google Maps

**24th Annual Meeting of Asian Society for Cardiovascular and Thoracic Surgery (ASCVTS)**
*Wednesday, April 6, 2016 to Sunday, April 10, 2016*
Taipei International Convention Center (TICC)
Taipei
Taiwan
See map: Google Maps

**Miami Robotics Symposium-Fourth Biennial**
*Thursday, April 7, 2016 to Saturday, April 9, 2016*
Eden Roc Hotel
Miami Beach, FL
United States
See map: Google Maps

**4th Asian Single Port VATS Symposium**
*Saturday, April 9, 2016 to Sunday, April 10, 2016*
Taipei International Convention Center
Taipei
Taiwan
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**ESTS Course on Medical Writing**
*Monday, April 11, 2016 to Wednesday, April 13, 2016*
European Surgical Institute
Hamburg
Germany
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**22nd Annual Conference of the Egyptian Society of Cardiothoracic Surgery**

**Wednesday, April 20, 2016 to Friday, April 22, 2016**
Fairmont Helioplis
Cairo
Egypt
See map: Google Maps

**Essential Surgical Skills for Cardiologists**
*Friday, April 29, 2016*
Royal College of Surgeons
London
United Kingdom
See map: Google Maps

**Symposium for Bruno J. Messmer's 80th Birthday**
*Saturday, May 7, 2016*
RWTH Aachen Pauwelsstr.30
Aachen
Germany
See map: Google Maps

**AATS Aortic Symposium 2016**
*Thursday, May 12, 2016 to Friday, May 13, 2016*
Sheraton New York Times Square Hotel
New York, NY
United States
See map: Google Maps

**AATS 96th Annual Meeting**
*Saturday, May 14, 2016 to Wednesday, May 18, 2016*
Baltimore Convention Center
Baltimore, MD
United States
See map: Google Maps

**12th International Conference on Pediatric Mechanical Support Systems & Pediatric Cardiopulmonary Perfusion**
*Wednesday, May 18, 2016 to Saturday, May 21, 2016*
NewYork- Presbyterian/ Columbia University Medical Center
173 Fort Washington Avenue
New York City
United States
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24th European Conference on General Thoracic Surgery  
**Sunday, May 29, 2016 to Wednesday, June 1, 2016**  
Mostra D’Oltremare  
Naples  
Italy  
See map: [Google Maps](#)

The New Orleans Conference: Practices in Cardiac Surgery and Extracorporeal Technologies  
**Wednesday, June 22, 2016 to Saturday, June 25, 2016**  
The Ritz-Carlton  
New Orleans, LA  
United States  
See map: [Google Maps](#)

AATS Patient Safety Course  
**Friday, June 24, 2016 to Saturday, June 25, 2016**  
Renaissance Boston Waterfront Hotel  
Boston, MA  
United States  
See map: [Google Maps](#)

Workshop on Transcervical Approach in Thoracic Surgery - Animal model workshop  
**Friday, June 24, 2016 to Saturday, June 25, 2016**  
Pius Branzeu Center for Laparoscopic Surgery and Microsurgery  
Timisoara  
Romania  
See map: [Google Maps](#)

Complex Cardiovascular Catheter Therapeutics  
**Tuesday, June 28, 2016 to Friday, July 1, 2016**  
Hilton Bonnet Creek Resort/Waldorf Astoria  
Orlando, FL  
United States  
See map: [Google Maps](#)

4th Singapore VALVE 2016  
**Thursday, July 14, 2016 to Saturday, July 16, 2016**  
National Heart Centre Singapore Level 7  
Singapore  
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See map: [Google Maps](#)

Heart Valve-Related Disorders Conference  
**Saturday, July 23, 2016 to Tuesday, July 26, 2016**  
Clare College  
Cambridge  
United Kingdom  
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Endocarditis Symposium  
**Friday, September 2, 2016 to Saturday, September 3, 2016**  
Grand Hilton  
Seoul  
South Korea  
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26th World Society of Cardiothoracic Surgeons 2016 Congress Combined With South African Heart Association Annual Meeting 2016  
**Thursday, September 8, 2016 to Sunday, September 11, 2016**  
Cape Town International Convention Centre  
Cape Town, WC  
South Africa  
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13th Annual Conference CVT Critical Care 2016  
**Thursday, September 15, 2016 to Saturday, September 17, 2016**
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Omni Shoreham Hotel
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Thursday, September 15, 2016 to Saturday, September 17, 2016
Disney's Paradise Pier Hotel
Anaheim, CA
United States
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2016 Duke Masters of Minimally Invasive Thoracic Surgery
Thursday, September 15, 2016 to Saturday, September 17, 2016
Waldorf Astoria Orlando
Orlando, FL
United States
See map: Google Maps

2016 Heart Valve Summit: Medical, Surgical and Interventional Decision Making
Wednesday, October 19, 2016 to Saturday, October 22, 2016
Radisson Blu Aqua Hotel
Chicago, Illinois
United States
See map: Google Maps

AATS Clinical Trials Methods Course
Thursday, October 20, 2016 to Saturday, October 22, 2016
Hyatt Regency O'Hare
Chicago, Illinois
United States
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BelSECT International Symposium on Perfusion
Friday, October 21, 2016 to Saturday, October 22, 2016
Royal Library Meeting Center
Brussels, Belgium
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World Society for Pediatric and Congenital Heart Surgery 5th Scientific Meeting
Thursday, October 27, 2016 to Sunday, October 30, 2016
Abu Dhabi
United Arab Emirates
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AATS Focus on Thoracic Surgery: Current and Future Challenges
Friday, October 28, 2016 to Saturday, October 29, 2016
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