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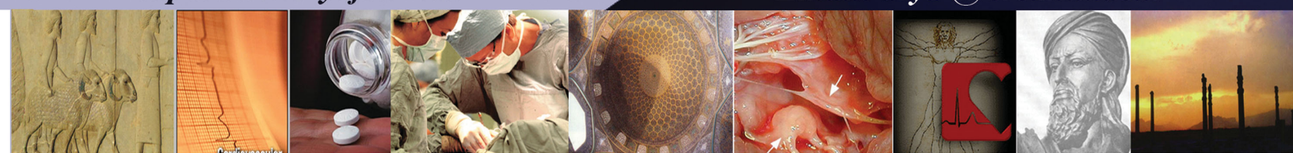

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Probiotic soy milk and anthropometric measures: Is probiotic soy milk beyond soy milk?

Fahimeh Haghighatdoost[(1)], Leila Azadbakht[(2)]

Editorial

Date of submission: 15 May 2015, ***Date of acceptance:*** 18 Aug 2015

Introduction

During last years, probiotic products have attracted great interest in treating various health complications, including chronic kidney diseases, metabolic abnormalities such as dyslipidemia, chronic inflammation, and hyperglycemia as well as obesity.[1-5] It has been suggested that because of the significant contribution of gut microbiota to energy metabolism, consuming probiotic products may be useful in weight control.[6] Consistently, the beneficiary impacts of functional foods like soy products have been reported in previous investigations.[7-10] It is possible that combining probiotics with functional foods intensify the helpful outcomes of each component.

In this supplement issue of the ARYA Atherosclerosis journal, Hariri et al. have shown that consuming probiotic soy milk leads to similar reductions in weight, body mass index (BMI) and waist to hip ratio, compared with soy milk, in type II diabetic patients.[11] However, the reductive effects of probiotic soy milk on systolic and diastolic blood pressures were significantly greater than soy milk.

The non-significant difference in anthropometric measures between intervention and control groups might be attributable to the polyphenols content of soy products.[12] Indeed it is possible that favorable effects of these components to be stronger than the effects of probiotics on the growth of gut microbiota, and in a short time intervention, as 8 weeks, could better impose their effects. In the support of this hypothesis, another clinical trial indicated that soy milk consumption for 4 weeks could reduce waist circumference greater than cow's milk.[8] However, it needs to be examined in future studies that if polyphenols are more effective than probiotics in anthropometric changes or not. In addition, their effects on blood pressure might be different and probiotics to be stronger than polyphenols. These question needs to be answered in longer and larger studies. In the current study, adherence to dietary intervention was assessed by using 1-day recall,[11] whilst monitoring returned soy milk bottles might be more precise method. Baseline soy consumption and BMI of participants must be taken into account, since these variables might have prominent role in the effects of polyphenols and probiotic soy milk. Despite these limitations, this study has some strength, which are worth nothing. This study was conducted in free-living type II diabetic patients and indicates that this intervention could clinically be practical. Moreover, both sexes were included in this study, and their findings could be generalized to both sexes.

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None.

Conflict of Interests

Authors have no conflict of interests.

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Interleukin-1 beta, interferon-gamma, and tumor necrosis factor-alpha gene expression in peripheral blood mononuclear cells of patients with coronary artery disease

Samaneh Enayati[(1)], Soroush Seifirad[(2)], Parvin Amiri[(1)], Milad Abolhalaj[(1)], Mahsa Mohammad-Amoli[(1)]

Original Article

Abstract

BACKGROUND: Several inflammatory mediators have been proposed to contribute to the pathogenesis of atherosclerosis. The aim of this study was to evaluate the quantitative expression of pro-inflammatory cytokines in un-stimulated peripheral blood mononuclear cell of patients with coronary artery disease (CAD).

METHODS: Interleukin-1 beta (IL-1β), tumor necrosis factor-alpha, and interferon-gamma (IFN-γ) gene expression were evaluated in angiography confirmed patients with and without CAD in a case-control study using quantitative real-time polymerase chain reaction.

RESULTS: A significant increase (P = 0.030) in IL-1β gene expression was found in patients with CAD [median interquartile range (IQR) = 4.890 (6.084)] compared to patients without CAD [median (IQR) = 1.792 (3.172)]. Despite the increase in IFN-γ gene expression in patients with CAD [median (IQR) = 1.298 (3.896)] versus patients without CAD [median (IQR) = 0.841 (2.79)], there was not statistically significant difference (P = 0.990).

CONCLUSION: Our results provide evidence for possible association between IL-1β and development of atherosclerosis as a crucial cytokine that induce a network of signaling pathways. This finding if proved in future would suggest IL-1β as a potent therapeutic target in CAD.

Keywords: Coronary Artery Disease, Interleukin-1 Beta, Tumor Necrosis Factor-alpha, Interferon-gamma, Gene Expression

Date of submission: 26 Feb 2015, ***Date of acceptance:*** 15 Aug 2015

Introduction

Several lines of evidence have previously confirmed the contribution of chronic inflammatory process in atherosclerosis.[1-3] The Immune responses to accumulation of oxidized lipoproteins in the vessels lead to mobilization of macrophages, dendritic cells, and lymphocytes in areas of disturbed blood flow and secretion of pro-inflammatory, chemokines, and matrix metalloproteinases.[4,5] Activation of pro-inflammatory cytokines including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) and initiation of an immune mediated response from the site of plaque formation in arterial wall making a complex of reactions with a number of immune component being involved in atherosclerosis.[6]

Innate immune responses beside adaptive immunity have major role in the initiation of atherosclerosis.[5] Infiltrating monocytes and macrophages play major role in pro-inflammatory cytokine productions in atherosclerosis in particular expression of IL-1. IL-1 is a pro-inflammatory cytokine which is shown to have important effects on atherosclerotic lesions cellular constitution.[7-10]

T helper-1 (Th1) cells are the most abundant T cells observed in atherosclerotic plaque.[11] Th1 cytokines with interferon-γ (INF-γ) as the prototype of this group are widely accepted as a key regulator of immune mechanisms in atherogenesis.[12] Studies have shown that INF-γ reduces vascular smooth muscle proliferation and collagen production. IL-1 and INF-γ upregulate the matrix metalloproteinases expression at the site of plaque formation; result in atherosclerotic plaque instability.[12-15]

TNF-α is another pro-inflammatory cytokine

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which is also reported as a potent risk factor for cardiovascular diseases.[12,15] Association between atherosclerosis and augmented risk of thromboembolic complications has also been attributed to several factors related to TNF-α expression. TNF-α is known as an ultimate mediator of the acute phase response and is involved in production of other inflammatory mediators including chemokines with important role in recruitment of leucocytes to the site of inflammation.[16]

In this study to further examine the role of IL-1 β, IFN-γ, and TNF-α in pathophysiology of coronary artery diseases (CAD), we compared the expression profile of these cytokines in un-stimulated peripheral blood lymphocytes (PBMCs) of patients with CAD (CAD+) versus their age, sex matched patients without CAD (CAD−).

Materials and Methods

Study subjects have been recruited from individuals who had a history of chest- pain and anginal symptoms that underwent coronary artery angiography at Cath Lab Center of Dr. Shariati Hospital, Tehran, Iran, from February 2008 to March 2010. Trained cardiologists performed the whole procedures of angiography. Study power was been set as 80%. The study group comprised of 25 patients with more than 50% stenosis in all three main coronary arteries (right coronary artery, left anterior descending artery, and the left circumflex coronary artery) were known as CAD+ and 25 sex, age, and smoking habits matched subjects with smooth angiography were categorized as CAD−. Patients with history of percutaneous coronary intervention, arteriovenous graft, familial hypercholesterolemia and congenital defects of the heart valves were excluded. Written informed consent was obtained from all individuals attending the study. Study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. We also completed personal questioner for all the participants and recorded history of diabetes mellitus (DM) (fasting plasma glucose ≥ 126 mg/dl or 2 hours plasma glucose ≥ 200 mg/dl)[17] hypertension (HTN) (an average blood pressure of ≥ 140/90 mmHg or history of taking medication for HTN),[18] hyperlipidemia [low-density lipoprotein (LDL) ≥ 130 and/or high-density lipoprotein < 40)],[19] smoking status (current smoking and/or history of smoking more than one pack/year was defined as smoker) and family history of other cardiovascular disorders such as premature CAD [presence of first elective or emergency coronary artery bypass graft (CABG), first elective or emergency percutaneous transluminal coronary angioplasty (PTCA), acute myocardial infarction without previous CABG and PTCA in the first degree relative men under 55, and women under 65][20] or myocardial infarction (MI) in first degree relatives.

Five ml peripheral blood was collected from each individual in heparin-containing tubes and was processed for Lymphocytes isolation by Lympholyte-H (Cedarlane Laboratories). RNA was extracted from PBMCs as described by Tripure reagents (Roche) manufacturer's instructions. RNA pellets were stored at -80 °C after solving into DEPC treated water. RNA solution has been qualified by measuring ratio of optical density (OD) 260/280 on a Nano Drop spectrophotometer (NanoDrop Thermo Scientific 2000), and the solution with OD260/280 ratio < 1.6 was discarded. RNA was reverse transcribed by First Strand cDNA Synthesis Kit (Thermo Science) as the manufacturer recommends.

Quantitative real-time polymerase chain reaction (PCR) was performed using SYBR Green PCR Master Mix (Amplicon), primer pairs (Table 1) and an ABI stepOne™ (Applied Biosystems) Real Time PCR machine. Gene expression data were normalized against hypoxanthine-guanine phosphoribosyltransferase as a reference gene. Data analysis was performed using Livak formula, $2^{-\Delta\Delta CT}$ method.[21]

Table 1. Primer sequences for real-time polymerase chain reaction (PCR) quantification

Gene	Primer pair sequences	Amplicon size
HPRT F	5'-CCTGGCGTCGTGATTAGTGAT-3'	131 bp
HPRT R	5'-AGACGTTCAGTCCTGTCCATAA-3'	
TNF-α F	5´-CCCAGGCAGTCAGATCATCTTC-3´	85 bp
TNF-α R	5´-AGCTGCCCCTCAGCTTGA-3´	
IL-1β F	5'-ATGGCTTATTACAGTGGCAATGAG-3'	138 bp
IL-1β R	5'-GTAGTGGTGG TCGGAGATTCG-3'	
INF-γ F	5'-AGCGGATAATGGAACTCTTTTCTTAG-3'	103 bp
INF-γ R	5'-AAGTTTGAAGTAAAAGGAGACAATTTGG-3'	

HPRT: Hypoxanthine-guanine phosphoribosyltransferase; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1 beta; IFN-γ: Interferon-gamma

Test of normality for distribution of variables was performed using Kolmogorov–Smirnov test. Qualitative variables were analysis by chi-square test. Quantitative variables were compared using t-test. Since variables of genes expression levels were not normally distributed, these variables were expressed as well as medians with 25th and 75th percentiles and interquartile range, and comparisons were performed using the Mann–Whitney U-test.

Statistical analyses were performed using SPSS software for Windows (version 15, SPSS Inc. Chicago, IL, USA) and $P < 0.050$ was considered as statistically significant difference.

Results

The means of stenosis in CAD+ was 55% (range 50-90%) and in CAD− was 25% (range 20-45%). Characteristics of cases (range 50-90%) and controls, including age, sex, lipid profiles, and risk factors (e.g. DM, dyslipidemia, HTN, and smoking) are presented in table 2. DM and HTN were more frequent in CAD+ patients ($P = 0.050$, $P = 0.001$ respectively). The history of MI which were significantly higher in CAD+ patients compared to their CAD− counter group ($P < 0.001$), as well as CAD+ patients had higher serum levels of triglyceride ($P = 0.044$).

Medians of genes expression was shown in table 3. A significant increase in expression of IL-1β gene was observed ($P = 0.037$) in the patients with CAD (CAD+) compared to the patients without CAD (CAD−).

The level of INF-γ gene expression was higher in CAD+ compared to the CAD- patients; however it was not a significant difference ($P = 0.930$). We found no significant differences in quantitative expression of TNF-α gene in patients with and without CAD ($P = 0.980$).

Figures 1a-f, shows melt curve and amplification plot for quantitative analysis of IL-1 IFN and TNF gene expression respectively, using real time PCR analysis (Figure 1a-f).

Discussion

In this study, we found a significant increase in IL-1 gene expression in un-stimulated PBMCs of patients with angiography confirmed CAD compared to patients without CAD. However, the results were not significantly different for INF-γ and TNF-α gene expression between these groups. To the best of our knowledge, this is the first study which evaluates the quantitative expression of IL-1, IFN-γ, and TNF-a gene in un-stimulated PBMCs of patients with CAD. Compelling data suggested that IL-1β, INF-γ, and TNF-α play an important role in the development of atherosclerosis.[22]

Table 2. Baseline characteristics in subjects with and without coronary artery disease (CAD)

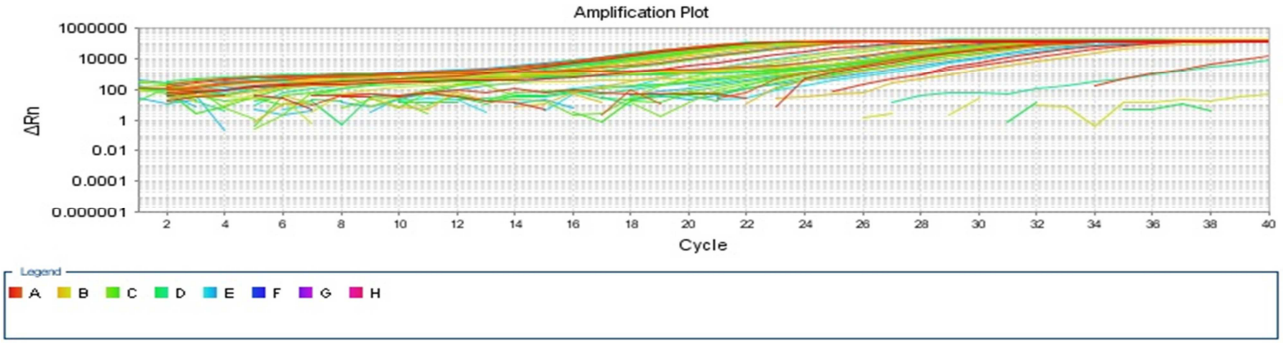
Variable	CAD+ (n = 25)	CAD− (n = 25)	P
Sex* (male) [n (%)]	18 (71)	17 (68)	0.500
Current smokers* [n (%)]	4 (16)	2 (8)	0.384
HTN* [n (%)]	19 (76)	11 (44)	0.050
DM* [n (%)]	14 (56)	2 (8)	0.001
Dyslipidemia	9 (36)	4 (16)	0.070
Past MI* [n (%)]	15 (60)	0 (0)	< 0.001
TChol£	183.40 ± 42.70	184.73 ± 44.24	0.914
TG£	185.43 ± 77.04	148.15 ± 47.10	0.044
LDL£	108.50 ± 36.75	129.27 ± 42.47	0.068
HDL£	40.88 ± 10.86	41.00 ± 8.88	0.623
Age£ (year)	60.19 ± 8.55	59.68 ± 11.01	0.855

CAD: Coronary artery disease; HTN: Hypertension; DM: Diabetes mellitus; Past MI: Past history of myocardial infarction; TChol: Total cholesterol; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; * Comparisons were performed using chi-square analysis; £ Variables are described based mean ± standard deviation

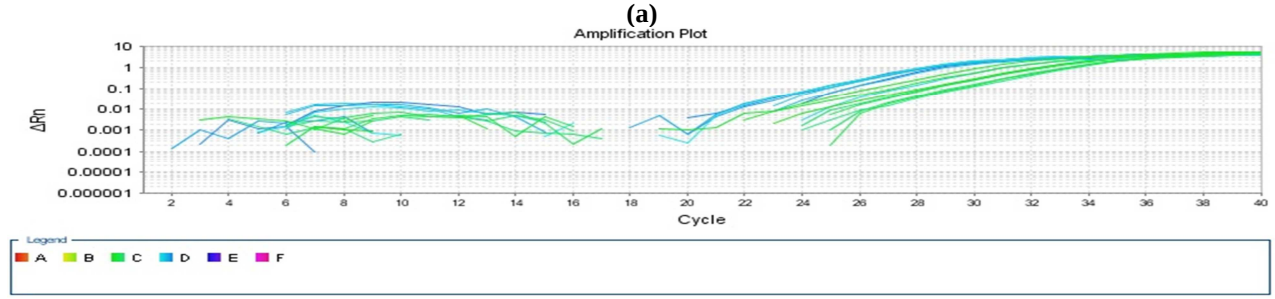
Table 3. IL-1β, TNF-α and IFN-γ gene expression median (IQR) in CAD+ versus CAD− individuals

Variable	CAD−* (n = 25)	CAD+* (n = 25)	P
IL-1β gene expression**	1.792 (3.172)	4.890 (6.084)	0.037
TNF-α gene expression**	0.841 (2.790)	1.298 (3.896)	0.930
IFN-γ gene expression**	0.946 (1.089)	0.986 (1.121)	0.991

Comparisons were performed using Mann–Whitney U-test; * CAD+: Patients with CAD; CAD−: Patients without CAD; ** Variables are described based median (IQR); CAD: Coronary artery disease; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor-alpha; IFN-γ: Interferon-gamma



(a)



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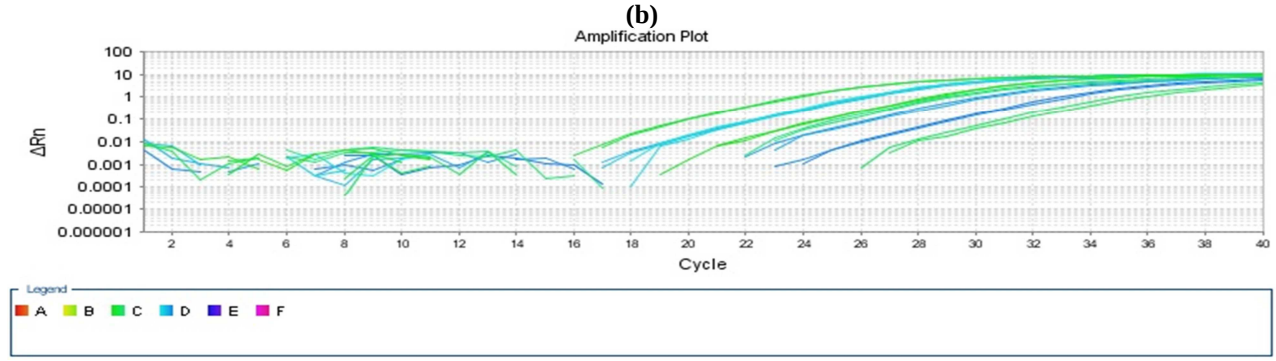

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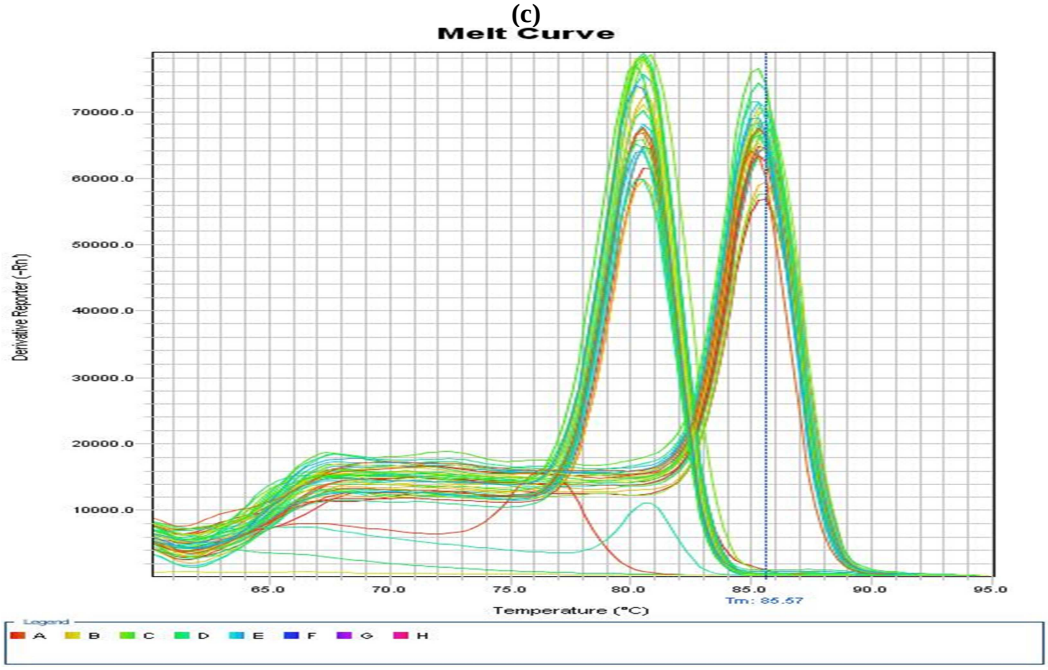
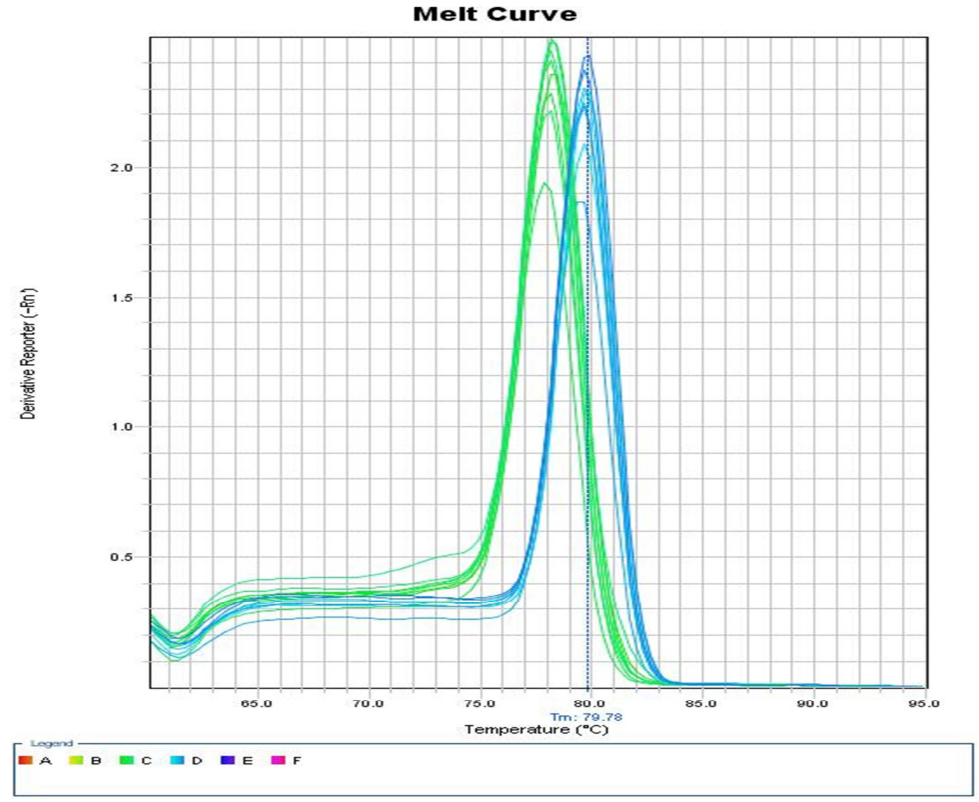
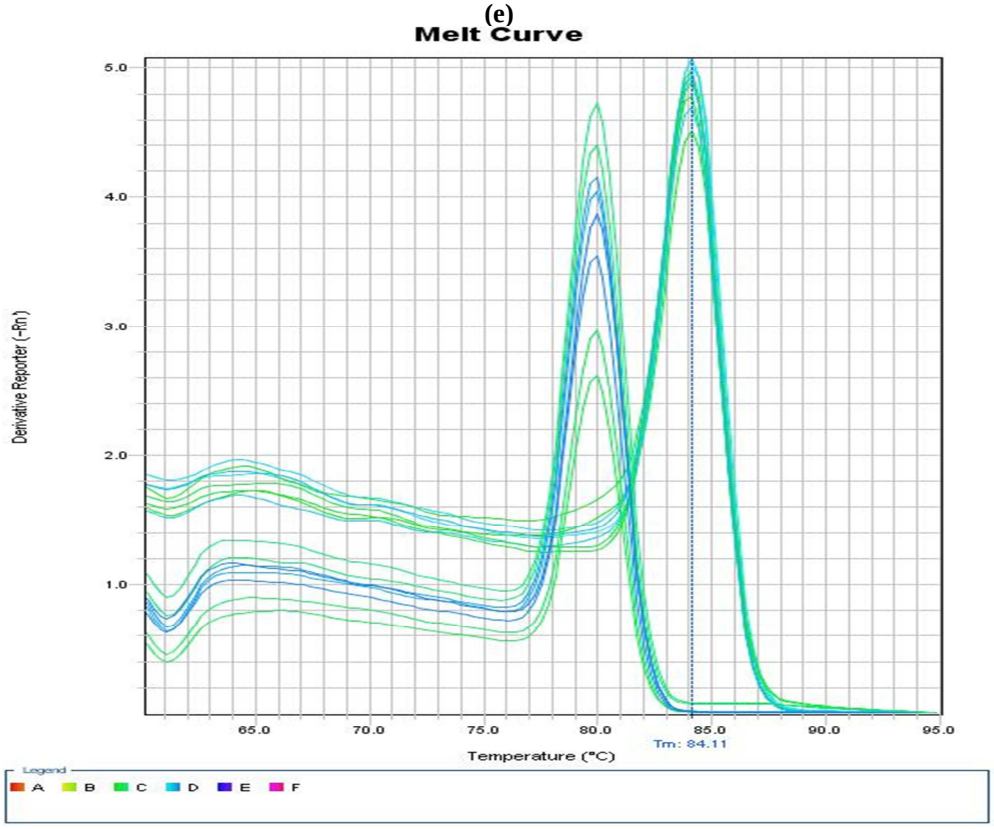


(d)

Figure 1. (a-f) Melt curve and amplification plot for quantitative analysis of interleukin-1 interferon and tumor necrosis factor gene expression, respectively, using real time polymerase chain reaction analysis



(e)



(f)

Figure 1. (a-f) Melt curve and amplification plot for quantitative analysis of interleukin-1 interferon and tumor necrosis factor gene expression, respectively, using real time polymerase chain reaction analysis (Continue)

The involvements of these cytokines are supported by their increased expression in human atherosclerotic plaques.[23-27] IL-1β is a pro-inflammatory cytokine which has been previously proposed as a pro-atherogenic element.[28,29] The increased expression of IL-1β observed in our study is in line with previous reports supporting the role of IL-1β in acceleration of atherosclerosis.[30-38] Recent studies on animal models have shown a significant decrease in the severity of atherosclerosis in IL-1β/ apolipoprotein E (APOE) double knockout mice.[39]

We did not find a significant difference for expression of TNF-α gene between our groups. Although increased serum levels of TNF-α has been suggested to be associated with increased risk of recurrent MI and age related atherosclerosis,[16] however this might not certainly reflect the expression of TNF-α at the mRNA level which has been examined in our study.

We also did not find any significant difference in IFN-γ gene expression in PBMCs of patients with CAD compared to patients without CAD. IFN-γ is a proinflammatory cytokine with pleiotropic biological effects which is reported to be highly expressed by various cell types including macrophages and Th1-cells in atherosclerotic plaques. IFN-γ is proposed to be rather directly or indirectly implicated during atherogenesis. Several animal experiments using APOE-/-mice for modeling atherosclerosis suggested that daily injection of IFN-γ in APOE-/- mice is associated with significant increase in lesion size and number of T-cells within lesion. Furthermore, it has been shown that development of atherosclerotic lesion and severity of the phenotype in female and male LDLR-/- mice with IFN-γ deficiencies are significantly decreased.[40-42] As our gene expression study was carried out on PBMCs of patients not from the cells obtained from the site of atherosclerotic plaque, therefore, the discrepancies in our finding compared to previous reports might be due to the fact that IFN-γ is produced and initiates its effect at the site of inflammation and might not have a significant role in immune milieu of subjects with atherosclerosis.

The results of this study might indicate the significant role of IL-1β as an atherogenic cytokine in pathogenesis of CAD, and if proved in future study it would be a potential target for treatment of atherosclerosis. Our data shows that IL-1 might be involved in atherosclerosis in a distinct manner compared to INF-γ and TNF-α. However regarding the limitations in our study the data needs to be interpreted with cautious. Previous reports indicate the crucial role of IL-1 receptor antagonist in development of atherosclerosis emphasizing the IL-1/IL-1Ra ratio as an important factor in the process of atherogenesis.[43] It has been reported that IL-1Ra-/- knock-out mice are unable to produce cholesterol 7α-hydroxylase enzyme resulting in increased plasma cholesterol levels compared to the normal mice.[44] It is known that Pro IL-1β maturation to IL-β is through caspase-1 pathway.[45] This process is activated by NALP3-inflammasome.[46] A recent study support the fact that cholesterol crystals and oxidized LDL as a ligand might induce NALP3-inflammasome by CD36 cell surface marker, leading to the production of IL-1β consequently. In support of this notion, Sheedy et al. reported decrease of IL-1β serum concentrations after targeting CD36 in atherosclerotic mice.[47]

Future studies on larger number of samples are required to further clarify the role of pro-inflammatory cytokines particularly IL-1β in pathogenesis of CAD.

Since controls of this study recruited from patients with chest pain and normal angiography, they could assign as cardiac syndrome X.[48] It has been shown that degrees of increased inflammation in these patients is responsible for their symptoms, hence loss of significant difference in pro-inflammatory cytokines might be due to probable mild increased inflammation in our controls. In addition, our controls are not matched for DM, TG, and HTN which could have an effect on the cytokines release. Studies on age, sex, and other CAD risk factors matched symptomatic healthy controls (subclinical atherosclerosis should be rolled out) are suggested and could further enhance our findings. Our findings constitute a significant increased IL-1 gene expression in CAD patients which confirms the previously described role of IL-1 in atherosclerosis. This finding in addition to some prognostic implications could be utilized in therapeutic strategies focusing on modulation of inflammatory pathways involved in CAD.

Conclusion

In conclusion, our data reinforce the potential role of the IL-1β as a critical atherosclerotic marker.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Obstructive sleep apnea, diagnosed by the Berlin questionnaire and association with coronary artery disease severity

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Original Article

Abstract

BACKGROUND: Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep-related disorder that is associated with increased risk of hypertension (HTN) and coronary heart disease. This study aimed to evaluate the correlation between the OSAS and coronary artery disease (CAD) severity.

METHODS: The cross-sectional study was conducted from September 2012 to December 2013. We enrolled 127 patients with chronic stable angina who were referred for coronary angiographic studies in Shahid Chamran and Nour Hospitals in Isfahan, Iran. The Berlin questionnaire (BQ) was used for estimate the probability of OSAS in patients as a low or high probability. Demographic characteristics and metabolic risk factors including diabetes mellitus, HTN, obesity, and smoking also were recorded. The severity of CAD was assessed and compared based on the Gensini score with Mann–Whitney U statistical test. Independent t-test for continuous variables and chi-square test for categorical variables were used.

RESULTS: Totally, 65.4% of subjects were considered as high and 34.6% as low probability for OSAS, which 81.1% of them had CAD. There was a significant difference between body mass index, systolic blood pressure, diastolic blood pressure, and ischemic heart disease drug consumption with OSAS probability ($P < 0.0500$). CAD was accompanied by OSAS significantly ($P = 0.0260$). The Gensini score was significantly higher in patients with high OSAS probability (100.4 ± 69.1 vs. 65.3 ± 68.9; $P = 0.0030$). OSAS also increase odds of CAD based on regression analysis (odds ratio, 95% confidence interval = 2.7).

CONCLUSION: This study indicates that more severe CAD is associated with high OSAS probability identified by BQ.

Keywords: Coronary Artery Disease, Obstructive Sleep Apnea Syndrome, Berlin Questionnaire

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Introduction

Cardiovascular diseases (CVD) are of the most important causes of morbidity and mortality in both developed and developing countries with a rising pattern of occurrence all over the world.[1] Over 17 million people die annually from CVD related disorders of which most of them occurs in countries with low to intermediate income, thus there is the world-wide concern to find suitable ways of controlling and management of CVD disorders.[2,3] Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep-related disorder characterized by repeated partial or complete closure of the pharynx, gasping episodes, sleep fragmentation, and daytime sleepiness that affect 5% of the adult population.[4-6]

This syndrome is associated with increased risk of hypertension (HTN), coronary heart disease, atrial and ventricular arrhythmias, and ultimately increases the mortality rates due to cardiovascular disorders.[7-9] The effects of OSAS on cardiovascular system have been established as a multi factorial phenomenon by the American College of Cardiology and American Heart Association.[10-12]

OSAS is under-diagnosed most of the times,

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especially by primary care physicians who regularly visit the patients; and only about 75% of even severe OSAS patients are diagnosed.[13,14] Polysomnography is the golden standard method for sleep apnea diagnosis.[15] The use of validated questionnaires like Berlin questionnaire (BQ) can be simpler and inexpensive alternative methods;[16,17] which it has acceptable sensitivity and specificity among the instruments for OSAS diagnosis.[18] The BQ indicates the presence of sleep apnea by addressing the presence and frequency of snoring behavior, wake time sleepiness or fatigue, and history of obesity or HTN.[16] The evaluation of specificity and sensitivity of the BQ in Iran is currently underway in Isfahan, Iran, by Amra et al.[19]

The aim of the present study was to explore the correlation between the OSAS (diagnose by BQ) and coronary artery disease (CAD) severity with the application of coronary artery angiography, Gensini scoring evaluation system.

Materials and Methods

The present analytical cross sectional study was conducted from September 2012 to December 2013. We enrolled 127 patients with chronic stable angina who were referred for coronary catheterization studies to our university hospitals including Nour and Shahid Chamran hospitals, Isfahan, Iran. Chronic stable angina is defined as a chest pain or discomfort that most often occurs with activity or stress. Angina is due to poor blood flow through the blood vessels in the heart.[20] Inclusion criteria were all male and female presented with chronic stable angina and candidate for coronary catheterization. People who do not consent to participate in the study and catheterization, patients with heart failure, cardiomyopathy, severe valvular heart diseases, congenital heart disease, chronic obstructive pulmonary disease, history of ischemic heart disease (IHD), or acute coronary syndrome during the last month, patients with recent cerebral hypoxia and recently had oxygen therapy and patients with body mass index (BMI) more than 40 kg/m^2 were defined as exclusion criteria. The design of the study was approved by research and ethical committees of Isfahan University of Medical Sciences, Isfahan, Iran. Informed consents also were taken from the patients for their approval of involvement in the study. Cases were selected using a simple non-random sampling model.

After taking medical history and physical examination, the patients evaluated for OSAS. BQ filled out for each patient to estimate the probability of OSAS. According to the questionnaire, patients were divided into two groups; high and low probability.[16] The BQ consists 10 questions in three categories that having two positive categories define as high probability situation. The first category consists of five questions on snoring. Being symptomatic for more than 3-4 times a week in 2 questions or more, renders this category positive. The second category consists of three item on daytime somnolence that are considered positive if in 2 or more questions the patient is symptomatic for 3-4 times a week. The third category has two questions on the history of HTN and/or BMI > 30 kg/m^2 and will be considered positive with each of these questions being positive. Illiterate and low-educated patients filled out the questionnaire with the assistance of an investigator.

Coronary angiography usually was performed using the left and right Judkins catheters through common femoral artery. Coronary catheterization and the severity of coronary disorder were recorded by the same cardiologist based on the Gensini score.[21] Calculation of Gensini score was carried as previously reported.[18] Severity score depending on the degree of stenosis [25% (1 score), 50% (2 score), 75% (4 score), 90% (8 score), 99% (16 score), and 100% (32 score) stenosis] and its location score (proximal, middle, or distal tract) along the target vessel and the type of coronary vessel involved (left anterior descending, left circumflex artery, or right coronary artery) (Figure 1). The mean of Gensini score for each participant was recorded.

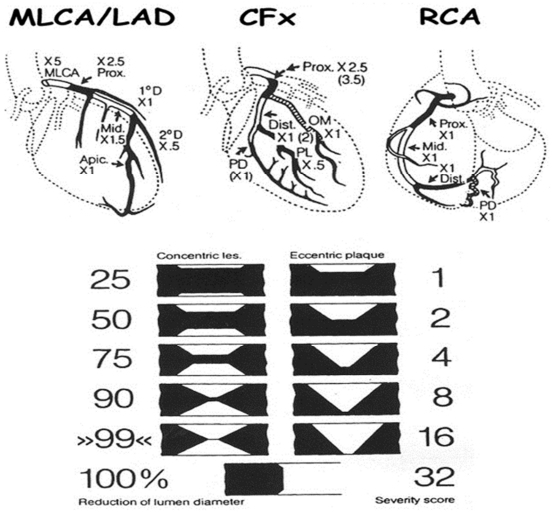

Figure 1. Gensini score calculation
RCA: Right coronary artery; CFx: Circumflex; LAD: Left anterior descending artery; MLCA: Main left coronary artery

Demographic characteristics and metabolic risk factors including diabetes mellitus, HTN, obesity, smoking, and IHD drugs consumption including antiplatelet, beta adrenergic receptor blocker, statins and angiotensin converting enzyme inhibitors or angiotensin receptor blocker also were recorded.

Continuous variables were expressed as mean ± standard deviation and were compared by independent sample t-test for normal variables and Mann–Whitney test for non-normal variables. Categorical variables were compared using a chi-square test and presented as frequencies with percentages. Simple and multiple logistic regression analysis were used to assess the crud and adjust effect of OSAS on CAD. The effect was hierarchically first adjusted by age and sex (Model 1), and then adjusted by BMI, HTN, diabetes mellitus, smoking, and drug consumption (Model 2). For all analyses, statistical package SPSS (version 15.0, SPSS Inc., Chicago, IL, USA) was used. All P values were 2-tailed with significance defined as $P < 0.0500$.

Results

The participant's mean of age was 59.00 ± 9.01 years. The youngest and the oldest participants had 32 and 82 years old, respectively. Of the participants, 74 (58.3%) were male. The mean BMI of participants was 26.67 ± 4.59. Totally, 65.4% of subjects were considered as high and 34.6% as low probability for OSAS, which 81.10% of them had CAD. There was significant difference between BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), HTN and IHD drug consumption with OSAS probability ($P < 0.0500$) (Table 1). 72 (86.7%) cases of high probable OSAS subjects had CAD; while it was 31 (70.5%) cases in low probable OSAS subjects ($P = 0.0260$). The Gensini score was also significantly higher in patients with high probability of OSAS comparing subjects with low probability (100.4 ± 69.1 vs. 65.3± 68.9; $P = 0.0030$) (Table 1).

Simple and multiple logistic regression analysis were used to assess the crud and adjust effect of OSAS on CAD. The effect was adjusted with age and sex in model 1 and with age, sex and other metabolic risk factors (is described) in model 2. As it shown for all models, OSAS had significant effect on CAD incidence by increases odds of CAD based on regression analysis (Table 2).

Discussion

Our finding demonstrated that OSAS identified by the BQ was associated with a significant risk of incidence and severity of CAD. The association between OSAS and CAD has been reported in previous studies.[22-26]

Table 1. Sleep apnea obstructive syndrome probability and demographic and risk factor characteristics, Gensini score and coronary artery disease (CAD) cases [mean ± standard deviation or frequency (%)]

Variables	Sleep apnea obstructive syndrome		P
	High (n = 83)	Low (n = 44)	
Demographic characteristics			
Age	59.30 ± 9.20	57.54 ± 8.70	0.2980
BMI	27.32 ± 4.90	25.44 ± 3.70	0.0160
SBP	142.60 ± 17.20	126.23 ± 19.30	0.0040
DBP	93.80 ± 14.50	79.70 ± 13.10	0.0020
Sex (male) (%)	46 (55.4)	28 (63.6)	0.3720
Risk factors (%)			
HTN	60 (72.3)	14 (31.8)	< 0.0001
Diabetic	24 (28.9)	10 (22.7)	0.4540
Obesity	38 (45.8)	14 (31.8)	0.1280
Smoker	28 (33.7)	12 (27.3)	0.4560
IHD drug consumption (%)			
Use	66 (86.8)	24 (57.1)	< 0.0001
Gensini score	100.4 ± 69.1	65.3 ± 68.9	0.0030*
CAD (%)			
Positive	72 (86.7)	31 (70.5)	0.0260
Negative	11 (13.3)	13 (29.5)	

Use independent t-test for continuous variables and chi-square test for categorical variables; * Use Mann–Whitney U-test; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HTN: Hypertension; IHD: Ischemic heart disease; CAD: Coronary artery disease

Table 2. Odds ratio (OR) confidence interval (95% CI) of obstructive sleep apnea syndrome (OSAS) effect on coronary artery disease (CAD) with and without controlling other variables using logistic regression

CAD existence	Model	OR (95% CI)	P
CAD	Crud	2.75 (1.11, 6.79)	0.0290
	Model 1	2.80 (1.08, 7.27)	0.0340
	Model 2	4.74 (1.29, 17.29)	0.0180

Model 1: Adjust age, sex; Model 2: Adjust age, sex, BMI, HTN, diabetes mellitus, smoking and IHD drug consumption; OR: Odds ratio; CI: Confidence interval; CAD: Coronary artery disease; BMI: Body mass index; HTN: Hypertension; IHD: Ischemic heart disease

Martinez et al.[27] and Massierer et al.[28] reported that OSAS diagnosis based on BQ greatly increases the risks of CAD in patients having significant coronary artery lesions according to coronary angiography particularly in younger women. Although, at older ages, other risk factors especially metabolic risk factors play a more important role in CAD and IHD incidence. Lu et al.[29] indicated that higher Gensini score was in moderate to severe OSAS patients significantly. This results also reported by Hayashi et al.,[30] about revealed a positive correlation between Gensini score and the severity of sleep apnea. Our results was similar to research by Massierer et al.[28] which revealed there was an association between BMI, SBP, DBP and risk factors such as HTN and OSAS. BMI values were observed to increase significantly incidence of OSAS in our study which is in agreement with previous studies.[31] Furthermore, Gus et al.[17] demonstrated high risk for OSAS assessed by the BQ was highly prevalent and associated with resistant HTN and using antihypertensive drugs. This event can be justified by theory that breathing disorders during sleep can result in high SPB.[32] Our findings also showed OSAS increases odds ratio (OR) for the presence of CAD [OR, 95% confidence interval (CI) = 4.7] like Martinez et al.[27] study that presented OR (95% CI) 4.5 for CAD with same risk factor adjustments.

Our study had some limitations. This study was simple non-random sampling model because we enrolled just patients with chronic stable angina and did not enrolled patient with other type of angina like acute coronary syndrome or prinzmetal angina. In addition, the study method was analytical cross-sectional study. Evaluation of acute coronary events and OSAS is recommended for future studies.

Conclusion

This study indicates that more severe CAD is associated with high OSAS probability identified by BQ. Moreover, this study confirmed the association between OSAS and CAD again.

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Conflict of Interests

Authors have no conflict of interests.

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Cardiovascular patients' experiences of living with pacemaker: Qualitative study

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Original Article

Abstract

BACKGROUND: A pacemaker implantation is considered major life event for cardiovascular patients, so they will probably have very interesting experiences of living with this device. The aim of this study was to explore the experiences of cardiovascular patients living with the pacemaker.

METHODS: In this qualitative study, 27 patients were chosen through purposive sampling to achieve data saturation, and their experiences were examined using semi-structured interviews. The patients' statements were recorded with their consent and analyzed using content analysis method.

RESULTS: Participants' experiences included three main themes: "Problems and limitations," "feeling and dealing with pacemaker", and "sources of comfort" and 10 sub-themes including: physical problems, financial problems, social problems, the first encounter, the feeling of living with the pacemaker, how to cope with pacemaker, satisfaction with pacemaker, good family support, hospital and hospital staff performance, and role of religious beliefs.

CONCLUSION: Planning to solve social problems, identifying and changing feelings of patients using pacemakers, reinforcing the resources of comfort especially family support seem to be necessary steps for improving quality of life and impact of using pacemaker.

Keywords: Cardio-Vascular Disease, Pacemaker, Experiences

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Introduction

Cardiovascular diseases are among the most common causes of disease-associated mortality.[1-4] Due to rapid increase in urbanization, industrialized lifestyle, lack of sufficient physical activity, and socio-economic conditions, the morbidity and mortality caused by these diseases is still rising so that today,[5] about 30% of all deaths are because of cardiovascular diseases.[6,7] In the United States, about 12 million people suffer from coronary artery disease, and annually about 1.5 million people suffer from heart attack and nearly 600 thousand people die due to coronary artery disease.[8,9] In Iran also, cardiovascular diseases are considered to be the most common cause of mortality.[10,11]

One of the most important advances in providing care and service to cardiovascular patients is using pacemaker in patients suffering from acute cardiac problems.[12] Pacemaker is a device that continuously monitors the status of the body and regulates heartbeats based on the body need.[13] About 3 million people worldwide have a pacemaker and about 600 thousand pacemakers are implanted annually.[14] Implantation of pacemaker may lead to changes in one's mental expectations of this device, and can result in problems relating to psycho-social compatibility and quality of life, and can trigger emotional disorders.[15] So, these people will probably have very diverse and interesting experiences of living with this device. Since quantitative studies have certain limitations in exploring such issues,[16] the present study has been designed and conducted as a qualitative study with the aim of examining and determining the experiences of people living with a pacemaker.

Materials and Methods

This qualitative study was conducted in 2014 at Tabriz University of Medical Sciences, Iran, (TUMS). The rationale for choosing the method of qualitative

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studies was because of the capability of these studies in accessing the experiences and the unknown knowledge within the participants and their ability to pull them out.[16,17] Among different approaches of qualitative studies, the phenomenological approach was chosen due to its ability of reviewing human experiences and believing that in the life experiences and phenomena, there are essences that can be fathomed and studied.[18,19] The participants were selected from among cardiovascular patients, who had the history of using pacemaker, and had referred to subspecialty Heart clinics in TUMS for care and follow-up. Some patients did not participate in the study because of some physical problems and lack of time. These people were selected due to having great experiences of living with pacemaker. Inclusion criteria included: At least 6 months experience of using pacemaker and having the desire and ability to participate in the study. Purposive sampling was used for selection of participants (In this method, people who have the greatest and richest information and could appropriately provide the researchers with their information are selected as the participants[17,20] and was continued until data saturation, i.e., to the point that the researchers feel that they cannot get new information by continuing the sampling.[21] This stage was fulfilled with 21 participants in the present study but for obtaining more confidence, the researchers continued the sampling up to 27 patients. Semi-structure interviews were used for data collection. During the interviews, guided questions designed using the literature review and the opinions of experts in this field were used (Appendix 1). Duration of each interview ranged from 30 to 60 minutes. The interviews were recorded with the participants' consent, and also the interviewers took notes for recording information. Soon after each interview, the record was assessed several times by the researchers and implemented. Content-analysis, which is a method for identifying, analyzing and reporting themes within a text and applicable in the analysis of qualitative data, was used for data analysis.[22,23] Responded validity was used for data rigor so that at the end of the meeting, the participants' statements were summarized and retold to give the chance to the participants to confirm the accuracy of the notes and perceptions of researchers. Peer check and immersed in data which are methods for creating rigor were used as well. Considering the ethics, informed consent was obtained from participants, and they could withdraw and leave the study at any time they would like to. Besides, the objectives of the study were explained to the participants at the beginning. To conduct the present study, ethical approval was obtained from the Regional Committee of ethics in research at TUMS.

Results

In this study, the experiences of 27 cardiovascular patients with a history of using pacemakers were extracted. 14 patients (52%) were female. 11 patients (40%) were illiterate. The mean duration of pacemaker use was about 43 months.

Some demographic characteristics of participants are shown in table 1.

The results of the analysis and coding of the participants' experiences were three main themes and 10 subthemes shown in figure 1.

Problems and restrictions

Physical problems

Many participants complained about health problems after pacemaker implantation. The most common of these were neurological problems; the participants noted that they were bored and bad tempered after pacemaker implant. Participant number 6 stated that, "… I have become impatient; I get angry quickly …." Another common problem that patients complained about were pain.

Participant number 15 mentioned that, "… When I'm walking, it aches (the heart) … when I want to work, it aches (the heart) …" Other health problems that participants were suffering from included dyspnea, fatigue, and sleeping problems.

Financial problems

Some participants complained about high costs of the pacemaker and said that financial problem was their main concern about the pacemaker implant surgery. Participant number 2 stated that, "… It costed too much…" and participant number 6 said that, "… I was upset both in terms of operation and its costs (pacemaker implant) …" Some other participants were also upset about the high cost of surgery and pacemaker implant.

Socialization problems

Most of the participants mentioned the limitation of their social relationships and activities after pacemaker implant. Participant number 4 said that, "… my heart has become like a broken dish since I had the battery in (the pacemaker), just like a broken dish if it is hit, it'll break. I go out with fear." Or participant number 7 said that, "… I cannot go out a lot anymore …" And participant number 20 said that, "having tour and going out cannot be the way it used to be (before pacemaker implant)."

Table 1. Some demographic characteristics of participants

Number	Sex/age	Job	Education	History of pacemaker implant (month)
1	M 71	Carpenter	Illiterate	4
2	M 66	Farmer	Elementary	11
3	F 73	Housewife	Illiterate	21
4	F 68	Housewife	Illiterate	20
5	F 81	Housewife	Illiterate	60
6	F 77	Housewife	Illiterate	72
7	M 82	Army officer	Elementary	18
8	F 61	Housewife	Elementary	96
9	F 46	Housewife	Elementary	72
10	F 53	Housewife	Elementary	36
11	F 60	Housewife	Elementary	48
12	M 73	Carpet maker	Illiterate	72
13	M 87	Medicine man	Elementary	60
14	M 67	Clerk	Illiterate	30
15	F 58	Housewife	Illiterate	6
16	F 35	Housewife	Elementary	60
17	F 76	Housewife	Illiterate	120
18	M 52	Unemployed	Illiterate	84
19	F 75	Housewife	Elementary	72
20	M 79	Clerk	Illiterate	8
21	M 53	Tailor	Elementary	3
22	M 69	Clerk	Elementary	12
23	F 51	Housewife	Diploma	108
24	M 65	Repairman	Diploma	14
25	M 82	Army officer	Elementary	18
26	M 77	Teacher	Bachelor's degree	8
27	F 56	Faculty member	Bachelor's degree	24

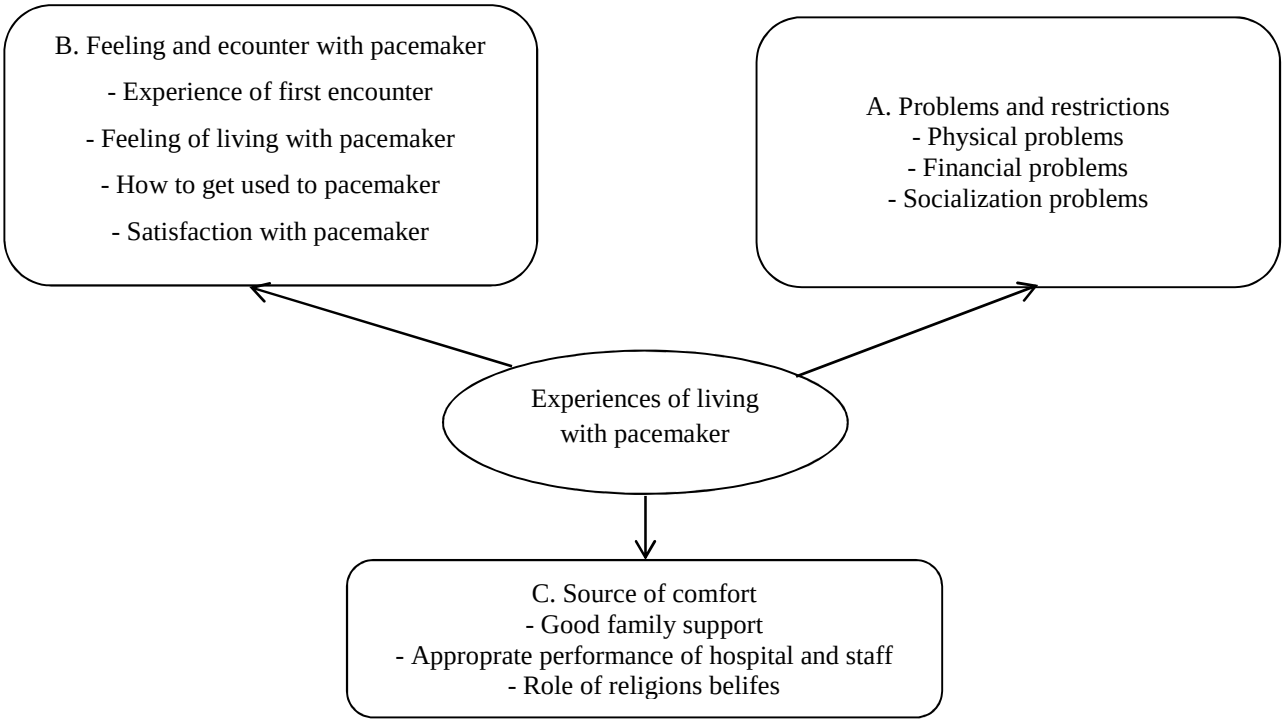

Figure 1. Main themes and subthemes extracted from participants' experiences of living with pacemaker

Feeling and dealing with pacemaker

The experience of first encounter

Feelings of fear, sickness and getting shocked were the most common feelings and experiences among the participants when they had first heard that they needed the pacemaker. Participant number 3 said that, "The first time I heard, I was a little scared …." Participant number 7 said: "… I felt I was ill…I got a little upset …" and participant number 16 also said that, "… It was a shock to me, I cried all night …"

What it is like to live with the pacemaker

Some participants despite satisfaction of the pacemaker did not feel comfortable living with it. Feelings of absurdity, worthlessness and weakness in life were the most common types of these unpleasant feelings. Participant number 7 said: "… At that time (prior to pacemaker implant) I was like a king but now I'm like a worthless paper … I have home, I have money … but I am not pleased with anything …" Or participant number 12 said: "… I feel I am retarded, I feel like a chipped dish and people think that if they touch me, I will break."

Coping with pacemaker

Most participants pointed to a spontaneous process and others to a compulsory one as the ways to get used to living with pacemaker. For example, when the interviewer asked the participants how they coped with the pacemaker, participant number 2 answered, "… spontaneously, little by little …" or participant number 7 said, "Gradually I got used to it …" and participants number 5 and 18 replied, "… I had no choice…"

Satisfaction with pacemaker

As mentioned in the discussion of the feeling of living with pacemakers, most participants were satisfied with the performance and implanting of pacemaker and were happy with it. Here are some views of the participants:

Number 3: "… I have been comfortable since the battery was implanted…"

Number 13: "… Battery is a good thing … it is like a help … reassures you…"

Number 9: "Battery is good, not bad."

As a general view, the participants were satisfied with the performance of pacemakers.

Resources of comfort

Good family support

Most participants were happy and satisfied with the good support and help of family and friends and considered it as an effective factor to tolerate and improve the life with pacemaker. Participant number 3 said: "… they care a lot (i.e., spouse and children) … they are very nice …," or participant number 16 who was satisfied with help and affection of relatives said: "My husband is so nice to me … my mom, my sister, my sister-in-law and my mother-in-law help me a lot …" and participant number 26 stated that "I get along with my family and relatives really well and I have great relationships with them…"

Good performance of hospital and its staff

Almost all participants were well-satisfied with the performance of the hospital and doctors. Participant number 11 said that, "I had a good time at the hospital … I was not annoyed at all …" and participant number 18 said: "… I did not know how it passed (having a good time in the hospital) … I was satisfied with them (doctors and nurses)…"

Constructive role of religious beliefs

High religious faith made some of the participants get along well with the pacemaker and not be afraid of its consequences particularly death. Some ideas of the participants were as follows:

Participant number 2: "Man is born once and dies once…"

Participant number 4: "I said to myself I will either die or live; ultimately everybody will meet death…"

Participant number 11: "… I didn't think of anything … I just trusted in God…".

Discussion

In this study, physical problem was one of the main problems and complaints of patients using pacemaker. In the study conducted by Afrasiabifar et al.[24] on the experiences of the elderly having had heart attack and in the study of Sadat et al.[25] on the experiences of the patients with multiple sclerosis, physical problems was one of the main problems and complaints of the participants. Furthermore, this was the case with the studies of Hildingh et al.[26] and Kerr and Fothergill-Bourbonnais.[27] Thus, regarding the results of this study and other similar studies, physical problems are among the major problems of the cardiovascular patients specially those using pacemakers, who indicates the need for serious consideration of the patients' problems, that must be reduced and eliminated using medical techniques, rehabilitation, and other supportive programs.

Some patients complained about financial problems during and after pacemaker implant in the present study. In the study of Rybarczyk et al.[28] financial problems and unemployment are referred to as major problems of the participants unlike the

present study. This could be justified by two factors, the first could be high cost of pacemaker implant and lack of appropriate insurance coverage for these costs and the second might be due to the fact that the majority of participants in this study were from rural areas and did not have good financial status.

One of the major limitations and problems of patients using pacemaker was limitation in social interaction and relationships with others. In a way that most of the participants noted a limitation in their social relationships and interactions after pacemaker implantation. In most of similar studies conducted in other categories of cardiovascular patients, these problems and limitations were also regarded as the main problem. Among the most important of these studies are the study of Abedi et al.[29] in which the psychological experiences of patients receiving heart transplants were examined, and the study of Jones et al.[30] reviewing the experiences of fatigue in patients with congestive heart failure. Other studies have also demonstrated these limitations and problems.[12,31,32]

Although the participants in this study stated that their social relationships and communication have been limited, they referred to the good support of family members, relatives, neighbors, and others along with them. Despite this encouraging culture, providing the conditions and supportive programs for the patients' collaboration and social activities seems to be inevitable.

In this study, the feelings of sickness, absurdity and depression were the most common emotions and experiences when the participants found out they needed pacemaker for the first time and were feelings of living with. In some other studies also similar feelings have been expressed by the participants.[33,34] So, considering the effect of the feelings and attitudes of patients in their recovery and treatment process,[33] providing supportive and consulting programs aiming at improving the feelings of these patients seems to be necessary.

Most participants in our study pointed out to a spontaneous and compulsory process of getting used to pacemaker. Yet in most studies conducted in other countries, the participants regarded the lifestyle changes and increasing awareness of their condition as strategies for coping with their disease situation.[35,36] The reason could be due to the illiteracy and low awareness of the participants in this study. This indicates the need for increasing the awareness and helping to change lifestyle in the patients using pacemakers.

Good family support, proper performance of the hospital and the hospital staff and the constructive role of religious beliefs were relaxing factors for the patients using pacemaker. In the study conducted by Shafipour et al.,[37] patients with a history of cardiac surgery noted the proper relationship with nurses, being placed in a safe and suitable environment for patients and good family support as the resources of comfort. The results of many other studies confirm these results.[38-40] So, considering the constructive outcomes of the mentioned factors inpatients' recovery, endeavors must be done for increasing the good family and relative support, improving the quality of hospital care, and reinforcing the religious beliefs to help the patients recover and feel comfortable.

The fear of pacemaker implantation and its impacts on life was also very common among study participants; an issue that was observed in Campbell et al's.[33] study too. Regarding the effect of feelings and attitudes of patients toward their treatment process,[33] providing supportive and consulted programs to change and improve these patients' feelings seems to be an important and necessary action.

The illiteracy or low education of many participants could be a limitation of the present study which caused most of the participants not to be able to give better and richer information about their experiences to the researchers in spite of the purposive selection. To compensate this problem, researchers continued sampling after saturation (21 patients) up to 27 participants by participants who were more educated to get more detailed and richer information than the previous interviews. Another limitation that could be pointed out as well was the lack of similar studies on the pacemaker patients' experiences in literature review which caused us not to be capable of comparing the results of this study with the results of other studies. Therefore, it is suggested that similar studies on pacemaker and its various aspects be designed and carried out. The results of this study could not be generalized to various conditions and patients like other studies' results. However, the method of this study can be used in other studies.

Conclusion

The study results showed that patients show different feelings about living with pacemaker ranging from fear and being shocked to spontaneous or compulsive adaptation to living with the pacemaker. It also showed that patients face different problems such as financial, physical and social problems after pacemaker implantation and to reduce or eliminate

these problems they rely on care provided by relatives, appropriate medical care and religious beliefs. Due to the increasing rate of cardiovascular patients using pacemaker and the lack of studies conducted in this field, the need to study the effects, patients' experiences and other aspects can be felt more than ever. The present study examined the experiences of pacemaker patients using qualitative research methods whose results can be used in providing high quality care, finding the best way to interact with patients, identifying and solving problems arising from pacemaker implantation, identifying and taking advantage of the experiences and feelings of patients and finally helping the patients using pacemakers.

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Conflict of Interests

Authors have no conflict of interests.

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Appendix 1: Interviews guides

1. When for the first time you realized that you have to live the rest of your life with a cardiovascular device how did it feel like?

2. What feelings or experiences do you have about this situation (living with a device) regarding your familial relationships and the role you play in your family?

3. What feelings or experiences do you have about this situation (living with a device) regarding the society and your role in it?

4. What feelings or experiences do you have about this situation (living with a device) regarding hospitals or other healthcare providing centers and the care they have brought to you since?

5. How have you adapted to this situation (living with a device) and come along with it?

6. What are the most important barriers and obstacles for you regarding this situation (living with a device) and how do you feel about them?

7. Eventually what general experiences or feelings do you have regarding this situation (living with the pacemaker)?

E101K and M123V alpha-cardiac actin gene mutations are not associated with cardiomyopathy in Iranian population

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Original Article

Abstract

BACKGROUND: Cardiomyopathies are myocardial disorders in which the heart muscle is structurally and functionally abnormal. Several mutations in sarcomere protein coding genes are responsible for different types of cardiomyopathies. ACTC1 is one of the main sarcomere components in heart muscle. Two mutations of E101K and M123V in this gene are shown to be associated with cardiomyopathies.

METHODS: In this case and control study, a sample of contains 30 hypertrophic cardiomyopathy and 100 dilated cardiomyopathy patients, as well as 130 healthy individuals were screened for two mutations of E101K and M123V. The genotypes of samples were determined in whole blood genomic DNA by restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) and mismatched-PCR-RLFP techniques.

RESULTS: All patients and healthy peoples had wild type genotype for both locations and even no heterozygous was detected.

CONCLUSION: Despite previous reports, no association was observed between both mutations with cardiomyopathy. Our results indicated that two mutations of E101K and M123V of ACTC1 gene may are not associated with cardiomyopathy in Iranian population.

Keywords: ACTC1, Cardiomyopathy, Mutation, E101K, M123V

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Introduction

Cardiovascular diseases (CVDs) are the main causes of death worldwide, accounting for over 16 million deaths each year. CVDs include conditions such as coronary heart disease (angina and heart attack) and stroke. The common types of CVD are cardiomyopathies.[1-4]

Cardiomyopathy defines as a myocardial disorder in which the structure and function of heart muscle is abnormal. Although several mechanisms reported to be involved in the development and progression of cardiomyopathies, their molecular pathophysiology is not fully understood.[5] Cardiomyopathies are classified into the different groups. Hypertrophic cardiomyopathy (HCM), which is one of the most common inherited cardiac diseases, occurring about 1 in 500 people[6,7] and is the main cause of sudden cardiac death in young people.[8] It is characterized by thickening of the left ventricle that more common affects the septum.[9,10] Common symptoms include angina, dyspnea, palpitation, syncope, and exercise limitation, which is inherited as an autosomal dominant trait.[7,8]

Dilated cardiomyopathy (DCM) occurs in 5-8 per 100 000 and is defined by the left ventricular dilatation and disturbed systolic function.[5,9,11] The most common form of its inheritance is autosomal dominant; however, recessive, X-linked, and mitochondrial inheritances have also been reported.[7,12,13] Ischemic cardiomyopathy (ICM) is the most common type of DCM. ICM is the term used to describe patients whose heart can no longer pump enough blood to the rest of their bodies.[14]

More than 50 genes are identified that are associated with the different types of cardiomyopathies[10,15] among them; more than 200 mutations are reported to be in sarcomeric protein genes.[8,16] These genes encode cardiac sarcomere proteins, components of thick and thin filaments with contractile, structural or regulatory functions (Table 1).[7]

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Table 1. Some prevalent genes, which their deficiencies are reported to be associated with cardiomyopathies

Genes	Ref
TNNT2 (troponin T)	[11]
MYL3 (essential myosin light chain)	[15]
MYBPC3 (myosin binding protein C)	[11]
MYL2 (regulatory myosin light chain)	[15]
MYH7 (β-myosin heavy chain)	[15]
TPM1 (α-tropomyosin)	[12]
TNNI3 (troponin I)	[14]
ACTC (α-cardiac actin)	[11]

It has been suggested that the α-cardiac actin gene (ACTC) deficiency plays a destructive role in cardiac function and identified to cause both HCM and DCM.[7,9,16] ACTC1 gene spans about 7.7 K bp and contains 7 exons encoding a protein with 377 amino acids, located on 15q14 chromosome. Several point mutations in this gene seem to be associated with different types of cardiomyopathies (Table 2).[5,7,8,10,15,17-19]

Table 2. Common ACTC1 point mutations, reported to be associated with cardiomyopathy

Mutations	Ref
Met 305 Leu	[10]
Tyr 166 Cys	[10]
Ala 295 Ser	[10]
Pro 164 Ala	[16]
Ala 331 Pro	[16]
Glu 99 Lys	[16,10]
Met 123 Val	[12]
Glu 101 Lys	[11,15]

Recently, some studies have reported that Glu 101 Lys (E101K) mutation of ACTC1 leads to HCM, DCM and left ventricular non-compaction. Furthermore, both of the E101K and Met 123 Val (M123V) mutations cause atrial septal defects (ASD) distinguished by incomplete closure of the ostium secundum that enables blood flow between the left and right atria via the interatrial septum.[18,19] Here, we investigated the association of M123V and E101K mutations with cardiomyopathy in a sample of Iranian patients and healthy individuals.

Materials and Methods

A total of 130 healthy individuals and 130 patients (30 HCM and 100 dilated cardiomyopathy) were participated in this study. All the patients and healthy controls were diagnosed based on echocardiography examination by a heart specialist. All the patients and controls were selected from Tehran Heart Center outpatient clinic from 2009 to 2011. The Medical Ethics Committee of Tarbiat Modares University, Tehran, Iran, approved the study. Written informed consents were obtained from all subjects in accordance with the declaration of Helsinki and prior to sampling. Table 3 summarizes the demographic characteristics of the patient and control individuals.

Table 3. Demographic and clinical characteristics of patient and control individuals

Characteristic	Patients	Controls
Numbers (HCM/DCM)	130 (100/30)	130
Age (mean ± SD)	54 ± 5.1	44 ± 4.6
Sex (M/F)	98/34	104/26
Abnormal ECG (%)	61	0
Family history (%)	30	0

HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; ECG: Electrocardiogram; SD: Standard deviation

Genomic DNA was extracted from blood samples using a DNP™ Kit (Cinnagen, Iran). Briefly, lysis solution was used to lyse blood cells and then genomic DNA from white blood cells selectively precipitated by isopropanol. The precipitated DNA was washed and desalted by ethanol and dissolved in TE buffer and stored in −20 °C. The quantity and quality of extracted DNA were examined spectrophotometrically or visually by electrophoresis of samples on 1% agarose gel.

The value of 100 ng of purified genomic DNA used for genotyping. The genotypes for mutations of E101K and M123V were determined by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) and a mismatch PCR-RLFP method, respectively. Specific primer pairs for genotype determination of each mutation was designed by Gene Runner software (version 5, University of Wisconsin, Madison, WI, USA) and confirmed by Amplify software (Table 4). Since there was no restriction site in the M123V site, the forward primer was designed as a mismatch primer to introduce a Bcl I restriction site. E101K and M123V mutations abolish the recognition site for Ava I (Takara, Japan) and Bcl I (Fermentas, Canada) restriction enzymes, respectively. A gradient PCR used to find the best annealing temperature of 58 °C for primers in DNA amplification. The genotyping PCR was performed through following instruction: an initial denaturation at 95 °C for 5 minutes, followed by 40 cycles of denaturation at 95 °C for 30 seconds, and annealing at 58 °C for 45 seconds, extension at 72 °C for 75 seconds and a final extension of 5 minutes at 72 °C.

Table 4. Designed primers used for genotyping of selected ACTC1 mutations. The genotype for E101K mutation was examined by a PCR-RFLP technique, while the M123V mutation was determined by a mismatch PCR-RLFP. The mismatch base has been shown in bold. The primers were designed using Gene Runner Software

Mutation	Primer	Sequence	GC%	Mw (g/mol)	The length of amplicon
E101K	Forward	5'-AATTATACATCTTTGGGGGAGTGG-3'	41.7	7462.7	708 bp
	Reverse	5'-TAATTGTGCTCCGAAACTAACCTC-3'	41.7	7271.6	
M123V	Forward	5'-AGGCCAACCGGGAGAAGATGACTC**T**GATC-3'	55.2	8960.7	290 bp
	Reverse	5'-TAATTGTGCTCCGAAACTAACCTC-3'	41.7	7271.6	

PCR-RFLP: Polymerase chain reaction Restriction fragment length polymorphism

PCR products were digested with Ava I or Bcl I restriction enzymes in a total volume of 20 µl at 37° C or 55 °C in overnight according to manufacturer's instructions, respectively. The resulted products of digestion for E101K and M123V were analyzed by electrophoresis on a 1.2% agarose gel or 12.5 % polyacrylamide gel respectively, following ethidium bromide staining. The authenticity of used techniques was investigated by sequencing the 30% randomly selected samples of both cases and control samples for each mutation.

The Chi-square test was performed by SPSS software (version 16, SPSS Inc., Chicago, IL, USA) to analysis the Hardy Weinberg equilibrium and the difference of mutation frequency between patients and healthy individuals. A conventional $P \leq 0.05$ was considered significant.

Results

E101K and M123V mutations were not detected in case and control samples

We included 130 patients and 130 matched healthy individuals as controls in this study. In wild type genotype, Ava I enzyme cuts 708 base pair fragment into two fragments of 331 bp and 373 bp. While in the presence of E101K mutation, a change from G to A, abolishes the recognition site and the enzyme cannot cut the 708 bp fragment. In our study, the 708 bp fragments of all control and patient samples were cut into two fragments, thus, genotypes of all patients were GG (Figure 1). Table 5 shows the genotype of all control and patient samples for E101K mutation. No statistical difference was observed between the genotype and allelic frequency in patient and control groups.

In screening of genomic DNA for detection of M123V, a mismatch primer was used to introduce a Bcl I restriction enzyme including mutation nucleotide. Therefore in the case of wild type genotype, this enzyme can cut the 290 base pair amplicon to two fragments with the length of 261 bp and 25 bp (Figure 2). M123V mutation cause a change of A to G that abolishes the recognition site of efnzyme and the amplicon of 290 bp remain intact (Figure 2).

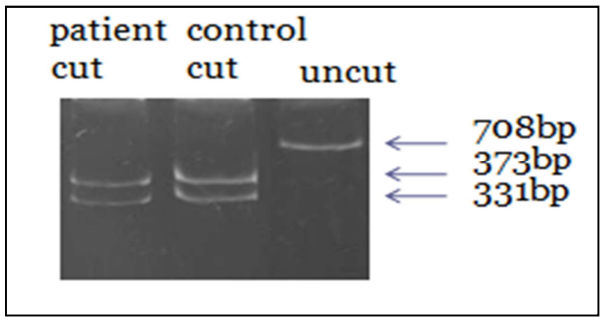

Figure 1. The results of digestion of polymerase chain reaction (PCR) product for detection of E101K mutation in ACTC1 gene. A PCR-restriction fragment length polymorphism technique was used for the genotyping. In the case of wild type genotype Ava I enzyme cuts the 708 bp PCR product into two fragments with 331 bp and 373 bp length

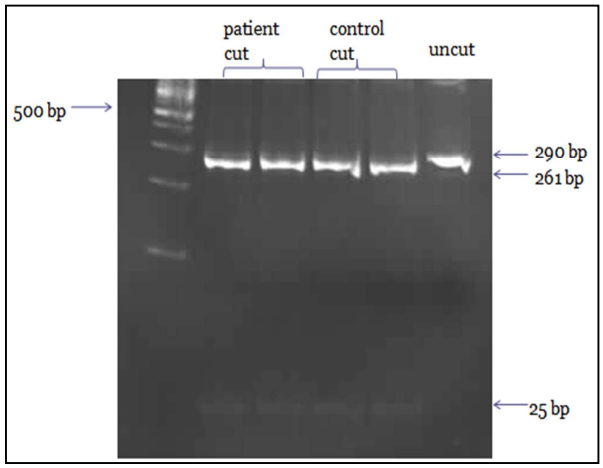

Figure 2. The results of digestion of polymerase chain reaction (PCR) product for screening of amplicon for M123V mutation. A mismatch PCR-restriction fragment length polymorphism technique was used for genotyping of ACTC1 gene for this mutation. In presence of wild type genotype the restriction enzyme of Bcl I cuts the amplicon with 290 bp into two fragments of 261 bp and 25 bp in the length

Table 5. The genotyping screening results of patients and healthy individuals for E101K (a) and M123V (b) mutations in ACTC1 gene. All samples had wild type homozygote genotypes for both mutations

Category	Genotype		
a			
E101K	AA	AG	GG
Healthy	130	0	0
Patients	130	0	0
b			
M123V	AA	AG	GG
Healthy	130	0	0
Patients	130	0	0

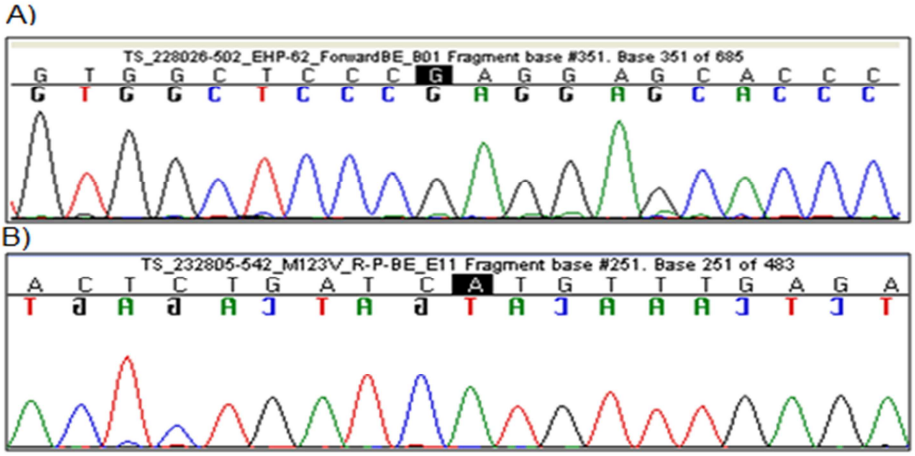

Figure 3. The sequencing result of the polymerase chain reaction (PCR) products that contain two studied mutations in ACTC1 gene. The results of DNA sequencing were consistent with determined genotypes by PCR-restriction fragment length polymorphism and mismatch PCR-RLFP techniques and no mutations were detected in all of case and control samples. (A) Chromatogram of sequencing of E101K. (B) Chromatogram of sequencing of M123V

Our results showed that all of control and patient samples were cut with Bcl I and had a wild type genotype. Thus, no significant difference was observed in genotype and allelic frequencies between the patients and healthy individuals for M123 V mutation.

Sequencing confirms the molecular analysis results

To validate the obtained results of genotyping by molecular techniques, the DNA sequences of amplicons for 30% of randomly selected of PCR products in the patients and controls groups was determined in two directions (Macrogen, Korea). The result of sequencing was compatible with obtained results from other molecular techniques (Figure 3).

Discussion

In this research, we could not detect any mutations of E101K and M123V in cardiomyopathy patients. Actions are extremely conserved proteins with 90% similarity in their amino acid sequence and constitute 10-20% of cellular proteins. The important roles of actions in cellular processes consist of muscle contraction, gene transcription, chromosome morphology, cell cycle control, modulation of a variety of membrane responses, translation of several mRNA species, and cellular apoptosis.[17,20,21] In higher vertebrates, six main isoforms of actin have been identified. The main isoform in adult heart is ACTC1.[17,19-21]

ACTC1 is the prevalent form of actions in early muscle development in most cultured cell lines and in the late grades of fetal development. Mice lacking cardiac actin do not survive more than 2 weeks and knockdown of ACTC1 in chick embryos causes ASD.[17,19] Furthermore, the genetic damage in ACTC1 that only express in cardiomyocyte induces CVD phenotypes.[17] Several microsatellite markers,

polymorphic repeats, and mutation were reported to affect ACTC1 function.[18,19] Therefore in the present study, we investigated the association of two ACTC1 mutations (E101K and M123V) with cardiomyopathy.

Some previous studies shown that E101K mutation in ACTC1 gene is associated with apical HCM, left ventricular non-compaction and septal defects. Monserrat et al. didn't find any mutant carrier without pathological manifestation due to high frequency of this mutation. The E101K mutation is associated with a typical ventricular morphology with some variation in the degree of wall thickening and trabeculation.[18]

The second functional mutation of Glu101Lys in α-cardiac actin filament locates adjacent to the myosin head and establishes a weak actomyosin-binding site. The result of this event is slower motility, reduced mediocre force, and a weak interaction with cardiac myosin in the presence of ATP. These defects at the molecular level are sufficient to trigger the disease phenotype.[15,18] This mutation is usually benign, and sudden death is an exception that occurs in patients with more severe wall thickening and/or systolic dysfunction.[18]

Previous studies[17,19] have reported that M123V, a missense mutation in exon 2 of ACTC1 (change from A to G at cDNA position 373) have been observed in secundum ASD patients.[17,19] It seems M123V mutation also prevents the assembly of actin monomers into a filamentous polymer that can support the movement by myosin. Therefore M123V actin has a reduced affinity for myosin in the presence of ATP. The M123V is located in close proximity to the Glu-101, so it seems the two polymorphisms influence similarly actin interaction with myosin.[19,22] Despite previous reports for the role of two mutations E101K and M123V in pathogenesis of cardiomyopathies,[15,16,18,19] we could not detect any of these in our HCM or DCM patients even in heterozygous form.

To our knowledge, this is the first study to investigate the possibility involvement of genetic variations in ACTC1 gene in pathogenesis of cardiomyopathy in Iranian population. However, according to pivotal function of actin in cardiac muscle, it's possible that other polymorphisms or genetic changes in ACTC1 are associated with cardiomyopathy in the Iranian population.

This study suffers from some limitations such as focusing on only two mutations of E101K and M123V and low number in the case and control groups. So, further studies with higher number of samples should be performed to verify the biological role of ACTC1 deficiency in the pathogenesis of cardiomyopathy in our population.

Conclusion

ACTC1 is one of the main components of the sarcomeric thin filaments and is necessary for normal heart morphogenesis and cardiac muscle contraction. Although previous studies documented that genetic mutations of E101K and M123V in ACTC1 are associated with different types of cardiomyopathies, still to but our study no mutations were found in the patients with defined symptoms. Therefore, this result suggests that there is no possible association between the investigated mutations of ACTC1 with cardiomyopathy in the Iranian population. Altogether, despite limitations of this study, it is necessary to investigate for the other mutations and functional polymorphisms of ACTC1 gene in pathogenesis of heart muscle diseases in our population with larger sample size. Also, examination of genetic changes in other sarcomere protein coding genes to find the genetic basis of these genes in pathogenesis of cardiomyopathy in Iranian patients would be interesting.

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Conflict of Interests

Authors have no conflict of interests.

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Antidepressants and cardiovascular adverse events: A narrative review

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Review Article

Abstract

BACKGROUND: Major depression or deterioration of previous mood disorders is a common adverse consequence of coronary heart disease, heart failure, and cardiac revascularization procedures. Therefore, treatment of depression is expected to result in improvement of mood condition in these patients. Despite demonstrated effects of anti-depressive treatment in heart disease patients, the use of some antidepressants have shown to be associated with some adverse cardiac and non-cardiac events. In this narrative review, the authors aimed to first assess the findings of published studies on beneficial and also harmful effects of different types of antidepressants used in patients with heart diseases. Finally, a new categorization for selecting antidepressants according to their cardiovascular effects was described.

METHODS: Using PubMed, Web of Science, SCOPUS, Index Copernicus, CINAHL, and Cochrane Database, we identified studies designed to evaluate the effects of depression and also using antidepressants on cardiovascular outcome. A 40 studies were finally assessed systematically. Among those eligible studies, 14 were cohort or historical cohort studies, 15 were randomized clinical trial, 4 were retrospective were case-control studies, 3 were meta-analyses and 2 animal studies, and 2 case studies.

RESULTS: According to the current review, we recommend to divide antidepressants into three categories based on the severity of cardiovascular adverse consequences including (1) the safest drugs including those drugs with cardio-protective effects on ventricular function, as well as cardiac conductive system including selective serotonin reuptake inhibitors, (2) neutralized drugs with no evidenced effects on cardiovascular system including serotonin–norepinephrine reuptake inhibitors, and (3) harmful drugs with adverse effects on cardiac function, hemodynamic stability, and heart rate variability including tricyclic antidepressants, serotonin antagonist and reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants.

CONCLUSION: The presented categorization of antidepressants can be clinically helpful to have the best selection for antidepressants to minimizing their cardiovascular harmful effects.

Keywords: Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressant, Antidepressants, Review

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Introduction

Major depression or deterioration of previous mood disorders is a common adverse consequence of coronary heart disease (CHD), heart failure, and cardiac revascularization procedures.[1-3] Therefore, treatment of depression is expected to result in improvement of mood condition in these patients. Despite demonstrated effects of anti-depressive treatment in heart disease patients, the use of some antidepressants have shown to be associated with some adverse cardiac and non-cardiac events that may even lead to high mortality and morbidity as well as to lower patients' survival.[4-6] Especially focusing newer antidepressants generations shows some notable adverse events (AEs) emphasizing individualize therapy to minimize these AEs.[7]

Unfortunately, in the current industrialized world, the prevalence of mood disorders has an upward trend because of economic problems, the lack of social security insurance after cardiac surgeries and also significant physical and social disabilities following disease progression. In recent published meta-analyses,

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the overall prevalence of major depression in coronary artery disease patients has been estimated 18.7% in women and 12.0% in men.[8] In patients who suffer acute myocardial infarction (MI), the prevalence of major depression ranges from 15% to 20%.[9] Those with heart failure experience higher rate of depression with a range 36%.[10] Although affected heart disease patients may remain undiagnosed with regard to the presence of depression, but most of these subjects treated with a variety of antidepressants and thus appearing side effects of these drugs is expectable in undertreated patients.

In this narrative review, the authors aimed to assess the findings of published studies on beneficial and also harmful effects of different types of antidepressants used in patients with heart diseases. Finally, a new categorization for selecting antidepressants according to their cardiovascular effects was described.

Materials and Methods

Using PubMed, Web of Science, SCOPUS, Index Copernicus, CINAHL, and Cochrane Database, we identified studies designed to evaluate the effects of depression and also using antidepressants on cardiovascular outcome (Figure 1). The study criteria for inclusion in the review were: a randomized controlled trial, cohort study, retrospective case-control study, case studies, animal experimental studies, or a meta-analysis published in a peer-reviewed journal, inclusion of patients with different types of cardiovascular disorders, and comparison of the effects of different antidepressants. The search strategy was based on the search terms "antidepressant" and "cardiovascular event." The searches were performed up to December 2014. All available English abstracts and full texts were reviewed. In initial reviewing, 275 papers met our inclusion criteria. By considering the exclusion criteria of no full-text availability, review without meta-analysis, and non-English language texts, and review articles without meta-analysis, 40 studies were finally assessed systematically. Among those eligible studies (Table 1), 14 were cohort or historical cohort studies, 15 were randomized clinical trial, 4 were retrospective were case-control studies, 3 were meta-analyses and 2 animal studies, and 2 case studies. According to drug groups evaluated, 5 groups of antidepressant medications were assessed including (1) selective serotonin reuptake inhibitors (SSRIs) (escitalopram, sertraline, citalopram, fluoxetine, paroxetine); (2) tricyclic antidepressants (TCAs) (amitriptyline, imipramine, dezipramine.); (3) serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine, sibutramine); (4) serotonin antagonist and reuptake inhibitors (SARIs) (trazodone); and (5) noradrenergic and specific serotonergic antidepressants (NaSSAs) (mirtazapine). Furthermore, the considered cardiovascular outcome included cardiac or non-cardiac related death, heart rate variability, ischemic events (MI), brain stroke, and hemodynamic instability. The data were abstracted, and differences were finally resolved by consensus.

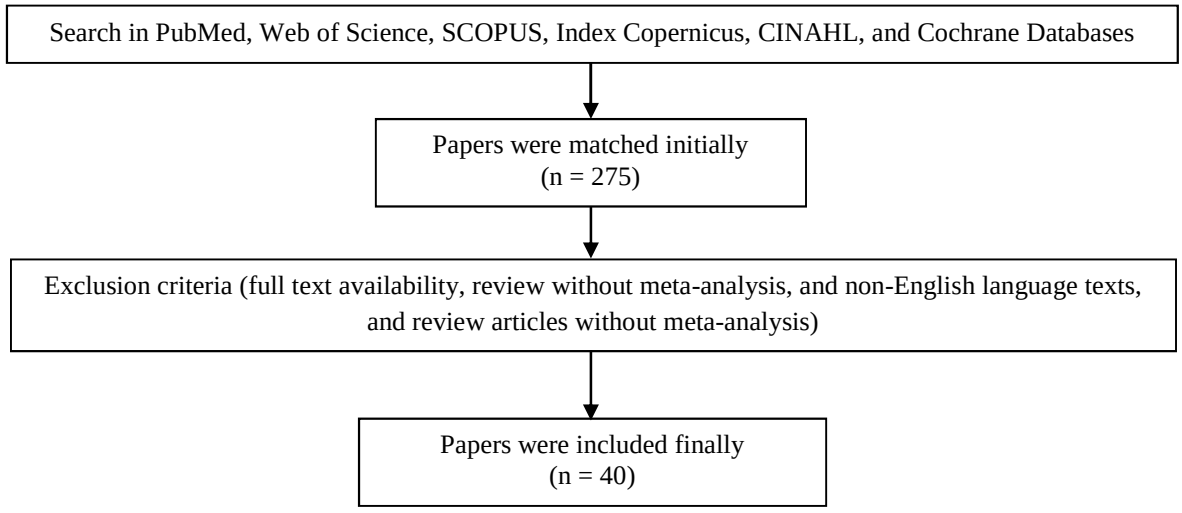

Figure 1. Process for selecting final studies

Table 1. Review of the studies on the effects of antidepressants on cardiovascular system

Author	Country	Study	Participants	End point	Finding
Rutledge et al.[10]	USA	Retrospective cohort	936 women	Depression, dietary habits, and cardiovascular events	Mechanisms linking depression to CVD is related to dietary habit
Thase et al.[11]	USA	Clinical trial	3298 on escitalopram	Cardiovascular safety profile of escitalopram	escitalopram, like other SSRIs, has a statistically significant effect on heart rate and on ECG values
Hanash et al.[12]	Denmark	Clinical trial	240 patients with CAD	Cardiovascular safety profile of escitalopram	One-year escitalopram treatment was safe and well tolerated in patients with recent ACS
Santangelo et al.[13]	Italy	Cohort study	110 the elderly	Sertraline or Citalopram and cardiovascular risk in the elderly	After 4, 6 and 12 months of treatment, we observed a reduction of the cardiovascular events
Glassman et al.[14]	USA	Clinical trial	369 patients with depression	Sertraline treatment of major depression in patients with acute MI or unstable angina	Sertraline is a safe and effective treatment for recurrent depression in patients with recent MI or unstable angina
Wilens et al.[15]	USA	Clinical trial	187 children and adolescents	Cardiovascular adverse effects of sertraline in children and adolescents	Cardiovascular safety of sertraline at doses up to 200 mg in children and adolescents
Weeke et al.[16]	Denmark	Case-control	19,110 patients with out-of-hospital cardiac arrest	Antidepressant use and risk of out-of-hospital cardiac arrest	An association between cardiac arrest and antidepressant use was documented in both the SSRI and TCA classes of drugs
Roose et al.[17]	USA	Clinical trial	27 depressed patients with CHD	Cardiovascular effects of fluoxetine	Fluoxetine treatment was not associated with the cardiovascular effects
Yeragani et al.[18]	USA	Clinical trial	Depressed cardiac patients	effects of paroxetine and nortriptyline on long-term heart rate variability measures	nortriptyline has stronger vagolytic effects on cardiac autonomic function compared with paroxetine
Acharya et al.[19]	USA	Retrospective, cross-sectional	664 on antidepressant 472 control	Antidepressant and cardiovascular events	Favor treatment of depression with SSRIs among patients at increased cardiovascular risk
Pequignot et al.[20]	France	Cohort study	7,308 ones with no history of CAD	Antidepressants heart disease and stroke events	Depressive symptoms are associated with first fatal CHD or stroke events
Zuidersma et al.[21]	Netherland	Clinical trial	331 depressed MI-patients	Depression treatment and cardiovascular events	Receiving depression treatment increased survival
Jerrell and McIntyre[22]	USA	Retrospective cohort	14,171 children and adolescents	Cardiovascular and neurological events with antidepressant	patients were at a significantly higher risk for incident cardiovascular events when exposed to selective serotonin reuptake inhibitors and weight-inducing antidepressants
Grace et al.[23]	USA	Cohort study	661 ACS inpatients	Correlates of antidepressant use in ACS patients	Antidepressant users were more likely to be anxious and have more comorbidity, and were less likely to work full-time, whereas number of medications, age, and marital status were not related
Swenson et al.[24]	Canada	Meta-analysis	6,588 individuals with cardiovascular events	Cardiovascular events in antidepressant trials	Did not determine whether SSRIs are associated with a greater or lesser risk of cardiovascular AEs
Taylor et al.[25]	USA	Retrospective cohort	2481 depressed and/or socially isolated patients	Antidepressant medication on morbidity and mortality after MI	Use of selective serotonin reuptake inhibitors in depressed patients who experience an acute MI might reduce subsequent cardiovascular morbidity and mortality
Roose et al.[26]	USA	Clinical trial	81 depressed patients with CHD	paroxetine and nortriptyline in depressed patients with CHD	Nortriptyline treatment was associated with a significantly higher rate of serious adverse cardiac events compared with paroxetine
Jeon et al.[27]	Korea	Animal study	4 animal sample	Nortriptyline and QT prolongation	Nortriptyline affects the ventricular repolarization process
Bar et al. [28]	Germany	Clinical trial	52 depressed subjects	cardio-respiratory coupling after treatment with nortriptyline	decreases of non-linear measures of heart rate variability in the nortriptyline group

Table 1. Review of the studies on the effects of antidepressants on cardiovascular system (Continue)

Author	Country	Study	Participants	End point	Finding
Kiev et al.[29]	USA	Clinical trial	58 depressed patients	Cardiovascular effects of nortriptyline in depressed outpatients	Slowing of cardiac conduction and possibly of rate-corrected repolarization
Thayssen et al.[30]	Germany	Clinical trial	21 elderly depressed patients	Cardiovascular effect of imipramine and nortriptyline in the elderly	Neither imipramine nor nortriptyline induced changes in cardiac conduction time measurements or arrhythmias
Giardina et al.[31]	USA	Clinical trial	Non-depressed cardiac patients	Imipramine and nortriptyline on left ventricular function and blood pressure	Neither drug significantly changed mean ejection fraction or peak systolic pressure end-systolic volume ratio
Hamer et al.[32]	UK	Cohort study	14,784 without CAD	Antidepressant use and future CVD	The use of TCAs was associated with elevated risk of CVD The use of SSRIs was not associated with CVD Neither class of drug was associated with all-cause mortality risk
Robinson et al.[33]	UK	Clinical trial	Depressed outpatients	Cardiovascular effects of phenelzine and amitriptyline	Amitriptyline significantly increased heart rate, while phenelzine produced slowing
Waslick et al.[34]	USA	Clinical trial	22 subjects	Cardiovascular effects of desipramine in children and adults during exercise testing	DMI has only minor effects on the cardiovascular response to exercise, and these effects do not appear age-related
Ho et al.[35]	Canada	Retrospective cohort	48,876 on venlafaxine 41,238 on sertraline	Adverse cardiac events of venlafaxine	Low to moderate dose venlafaxine is not associated with an increased risk of adverse cardiac events
Xue et al.[36]	USA	cohort study	64,000 cases	Duloxetine and cardiovascular events	The incidence of cardiovascular events did not differ among duloxetine initiators relative to other antidepressant but was higher than those without depression
Wernicke et al.[37]	USA	Meta-analysis	8504 depressed subjects	Cardiovascular safety profile of duloxetine	Use of duloxetine does not appear to be associated with significant cardiovascular risks
Scheen[38]	Belgium	cohort study	10 742 overweight/obese subjects	Cardiovascular risk-benefit profile of sibutramine	Drug should not be prescribed for overweight/obese patients with a high cardiovascular risk profile
James et al.[39]	UK	cohort study	10,744 overweight or obese subjects	Cardiovascular risk-benefit profile of sibutramine	Long-term sibutramine treatment had an increased risk of nonfatal MI and nonfatal stroke but not of cardiovascular death
Harrison-Woolrych et al.[40]	New Zealand	cohort study	15 686 overweight or obese subjects	Cardiovascular risk-benefit profile of sibutramine	Risk of death from a cardiovascular event in this general population of patients prescribed sibutramine was lower than has been reported in other overweight/obese populations
Maggioni et al.[41]	Italy	Cohort study	10,742 cases with CAD	Cardiovascular risk-benefit profile of sibutramine	overall mortality rate was low and sibutramine was well tolerated
Gaciong and Placha[42]	Poland	Cohort study	2225 overweight and obese subjects	Cardiovascular risk-benefit profile of sibutramine	Treatment with sibutramine resulted in clinically significant weight loss during short-term therapy in obese adults
Service and Waring[43]	UK	Case study	A depressed woman	QT prolongation and delayed atrioventricular conduction by ingestion of trazodone	The possibility of cardiotoxic effects after trazodone overdose
Krahn et al.[44]	USA	Retrospective	100 patients who received ECT	Cardiovascular complications in patients taking trazodone	Administering low-dose trazodone for insomnia in conjunction with ECT does not appear to increase cardiovascular complications
Boschmans et al.[45]	South Africa	Animal study	Heart rats	Coronary vascular responses after trazodone	Trazodone elicited a marked elevation in coronary flow over the dose range of 2.5-250 µM
Tulen et al.[46]	Netherlands	Clinical trial	10 depressed ones	Cardiovascular variability due to mirtazapine	Increase in heart rate and decrease in heart rate variability

SSRIs: Selective serotonin re-uptake inhibitors; ECG: Electrocardiogram; CAD: Coronary artery disease; ACS: Acute coronary syndrome; MI: Myocardial infarction; CHD: Coronary heart disease; AEs: Adverse events; TCAs: Tricyclic antidepressants; CVD: Cardiovascular disease; ECT: Electroconvulsive therapy; DMI: Desipramine

Results

First antidepressants group (SSRIs)

Most studies on cardiovascular effects of different types of SSRIs have emphasized neutralized or even beneficial cardioprotective effects of SSRIs especially newer generations on cardiovascular system. In a clinical trial study by Thase et al.[11] on 3298 depressed patients, escitalopram was used at doses between 5 and 20 mg/day for two acute (8-12 weeks) and long-term (24 weeks) phases to assess cardiovascular outcome including heart rate, blood pressure (BP), treatment-emergent AEs, and electrocardiograms (ECGs). The study showed no significant difference in BP, ECG, or cardiovascular AEs, but a slight decrease in heart rate without clinical consequences. In a similar study by Hanash et al.,[12] 240 patients were randomized to escitalopram 10 mg daily or matching placebo for 1-year and finally biochemical markers, as well as ECG and echocardiography patterns were assessed between study intervention groups. They could show similar findings between intervention and placebo groups in the incidence of ventricular arrhythmia and episodes of ST-segment depression, length of QTc, and systolic and diastolic echocardiographic measures as well as 1-year AEs including death, recurrent acute coronary syndrome, or need to repeating revascularization. Regarding the effects of sertraline and citalopram as other new types of SSRIs, Santangelo et al.,[13] 110 patients were treated with citalopram, 20-40 mg/day, or sertraline 50-100 mg/day leading considerable reduction in cardiovascular events in a 1-year follow-up time demonstrating cardioprotective effects of these two types of antidepressants on cardiovascular system in depressed patients. Glassman et al.[14] also assessed the effects of sertraline in patients with acute MI or unstable angina. In their study, depressed patients were randomly assigned to receive sertraline in flexible dosages of 50-200 mg/d or placebo for a treatment period of 6 months indicating no inter-group differences in the left ventricular function, ventricular arrhythmias, ECG patterns, and cardiovascular major AEs. The cardiovascular effects of sertraline have been also studies in children and young adolescents. In a study by Wilens et al.[15] on 107 children and 80 adolescents who suffered obsessive-compulsive disorder, cardiovascular effects of sertraline with the doses of < or = 200 mg/day for 12 weeks were assessed showing no clinically significant cardiovascular AEs in any of the subjects enrolled in the study assessed by ECG pattern and hemodynamic indices. Only, in a study by Weeke et al.,[16] increased risk for cardiac arrest was reported by administrating citalopram so that in a case-control study including 19,110 patients with the history of out-of-hospital cardiac arrest, the risk for cardiac arrest increased following use of citalopram with an odds ratio 1.29. The effects of first generations of SSRIs were assessed in the earlier studies. In a study Roose et al.[17] in 1998, 27 depressed patients were participated in an open medication trial of fluoxetine, up to 60 mg/day, for 7 weeks. The authors revealed a slight reduce in heart rate, a slight increase in systolic BP, and a slight increase in ejection fraction with no effect on cardiac conduction, ventricular arrhythmia, or orthostatic BP that all changes were reported to be tolerable. In another study by Yeragani et al.,[18] the administration of paroxetine was suggested to be cardio-protective especially with regard to sleeping, and awake heart period variability measures. In this regard, no adverse cardiovascular events was also reported by other authors such as Acharya et al.,[19] Pequignot et al.,[20] Zuidersma et al.,[21] Jerrell and McIntyre,[22] Grace et al.,[23] Swenson et al.,[24] and Taylor et al.[25] (Table 1) following the use of SSRIs.

Second antidepressants group (TCAs)

The cardiovascular effects of TCAs group of drugs have been into categories of their effects on left ventricular function and also on cardiac conduction system and ECG pattern. In a clinical trial by Roose et al.,[26] the use of nortriptyline with the dose of 50-150 ng/ml for 6 weeks led to a sustained increase in heart rate and also a reduction in heart rate variability. In an animal study by Jeon et al.,[27] the use of nortriptyline resulted in change of ventricular repolarization process indicated by the increase in QTc indicating the effect of nortriptyline on QT prolongation. In a study by Bar et al.,[28] 26 depressed subjects were treated with nortriptyline leading a decrease of non-linear measures of heart rate variability in addition to reduced cardio-respiratory coupling in the patients. In an earlier clinical trial study by Kiev et al.,[29] a treatment regimen including nortriptyline 75-150 mg/day led to adverse consequences such as a slowing of cardiac conduction. Contrarily, Thayssen et al.[30] in a clinical trial including elderly depressed patients who treated with imipramine or nortriptyline could not show significant changes in cardiac conduction time measurements or arrhythmias. With regard to the effects of TCAs on left ventricular functional status, Giardina et al.[31] conducted a clinical trial study on 20 non-depressed cardiac patients treated for ventricular premature depolarization. The patients

were administered 1 mg/kg/day imipramine or 0.5 mg/kg/day nortriptyline and finally showed that neither drug significantly changed mean left ventricular ejection fraction or peak systolic pressure end-systolic volume indicating the safety of those two drugs even in patients with impaired systolic function. Hamer et al.[32] in a cohort study could show no significant association between TCAs use and CHD events or all-cause mortality risk.

Regarding cardiovascular changes following the use of amitriptyline, amitriptyline usage is associated with significant prolongation of QRS and QTc as well as increased in heart rate while little overall change can be revealed in BP.[33] Furthermore, desipramine may be led to release serum norepinephrine may results in increase the risk of exercise-associated arrhythmias.[34]

Third antidepressants group (SNRIs)

With respect to the effects of SNRIs group on cardiovascular system, a limited number of studies have been conducted. In a recent retrospective study by Ho et al.[35] by reviewing the records of 48,876 an elder patients, who receiving venlafaxine, not only low to moderate doses of this drug had no adverse cardiovascular events, but also the lower risk of heart failure in comparison with other drugs such as sertraline was also shown. Regarding the effects of another type of drug in this group, duloxetine, Xue et al.[36] prospectively assessed the cardiovascular events in 17,386 depressed patients receiving duloxetine and showed no difference in the rate of AEs between depressed patients treated with duloxetine and untreated ones emphasizing occurrence of cardiovascular events by depression itself, not by duloxetine. In a meta-analysis by Wernicke et al.,[37] 42 placebo-controlled clinical trials of 8504 patients who were treated with duloxetine were systematically reviewed. They showed slight bit not significant decreases from baseline in RR, QRS, and QT intervals, as well as no increased risk of sustained BP elevation with duloxetine treatment. More attentions have focused the cardiovascular consequences of using sibutramine as a drug in the SNRIs group. In a study by Scheen,[38] the efficacy/safety ratio of sibutramine in overweight/obese high-risk subjects was prospectively assessed. In this cohort study, sibutramine 10 mg/day was administered for 6 weeks. Long-term follow-up of patients showed the increased risk for nonfatal MI and nonfatal stroke and thus it should not be recommended in obese subjects with previous history of cardiovascular disorders. In another cohort study by James et al.,[39] 10,744 overweight or obese older subjects, with preexisting cardiovascular disease, type 2 diabetes mellitus, or both that received sibutramine were followed and similarly showed higher risk for nonfatal MI and nonfatal stroke in these patients. In another cohort study by Harrison-Woolrych et al.,[40] the studied cohort experienced significant AEs of hypertension, palpitations, hypotensive events and tachycardia, but with a low risk for cardiac death. Maggioni et al.[41] also indicated that only 3.1% of patients treated with sibutramine discontinued their regimen because of some slight complications including drug intolerance, headache, insomnia, nausea, dry mouth, and constipation-, tachycardia-, and hypertension and thus the drug was well tolerated. Gaciong and Placha[42] also showed that the patients received sibutramine in single daily doses of 10 and/or 15 mg experienced a tolerable decrease in systolic and diastolic BP and heart rate about 12 weeks of drug use.

Forth antidepressants group (SARIs)

In this group, trazodone has been more studied regarding its effects on cardiovascular system. According to the case-control study by Weeke et al.,[16] there was no association between the use of SARIs drugs such as trazodone and cardiac-related death. In a case study by Service and Waring[43] that described a woman who overdosed by acute ingestion of trazodone, significant QT prolongation and delayed atrioventricular nodal conduction was developed after injecting trazodone. In a retrospective study by Krahn et al.,[44] 100 patients who received electroconvulsive therapy with concurrent trazodone, except for orthostatic hypotension that was more observed in patients taking trazodone, no difference was revealed between these patients and the controls and thus using low-dose trazodone does not appear to increase cardiovascular AEs. In an animal study by Boschmans et al.[45] on hearts of the rats, trazodone could elicit a significant elevation in coronary flow over the dose range of 2.5-250 μM.

Fifth antidepressants group (NaSSAs)

Most studies performed on the cardiovascular effects of NaSSAs have mainly focused their effects on heart rate variability. However, the studies have reached contradictory results. In a meta-analysis study by Kemp et al.,[47] mirtazapine had no significant impact on heart rate variability. In a case study by Rajpurohit et al.[48] in 2014, subsequent to

the first dose of mirtazapine the patient experienced bradycardia and prolonged QRS as well as QTc intervals on ECG pattern. In a study by Terhardt et al.,[49] 21 moderately depressed patients being treated with mirtazapine that finally experienced increased heart rate and reduced heart rate variability compared with the non-depressed controls. In another trial study by Tulen et al.,[46] it was shown that although using mirtazapine had no effect on BP or BP variability, but early after use of this drug, increase in heart rate and decrease in heart rate variability could be observed might be due to the anticholinergic properties of this drug.

Discussion

According to the current review, we recommend to divide antidepressants into three categories based on the severity of cardiovascular adverse consequences including (1) the safest drugs including those drugs with cardio-protective effects on ventricular function as well as cardiac conductive system (SSRIs), (2) neutralized drugs with no evidenced effects on cardiovascular system (SNRIs), and (3) harmful drugs with adverse effects on cardiac function, hemodynamic stability, and heart rate variability (TCAs, SARIs, and NaSSAs). In fact, the cardiovascular effects of the variety of these drugs can referred to the chemical nature of the drug and its effect mechanism. Regarding the harmful cardiovascular effects of TCAs, it has been well demonstrated that blocking the reuptake of norepinephrine and serotonin at nerve terminals is responsible for their effects on cardiac arrhythmias and thus appearing heart conduction impairment. On the other hand, following sodium channel blockade induced by TCAs, prolonged intraventricular conduction in expected. In overdose of TCAs, this conductive prolongation may be also life-threatening because of tending increase in premature ventricular contractions and ventricular tachycardia.[31,50-53] Furthermore, the overdose of this drugs can result in suppressing potassium channels in myocytes leading QT interval prolongation and also appearing the pattern of torsades de pointes.[54,55]

In respect to the harmful effects of SARIs such as trazodone, although this group of drugs is structurally different from the TCAs, but because these drugs can selectively blocks the reuptake of serotonin describing their effects on decreasing BP. Furthermore, in some cases, the risk for premature ventricular contractions (PVCs) may be increased following the use of trazodone, however this group is suggested to be very safer than TCAs and thus can be a proper alternative for TCAs.[56,57] Along with safety of SARIs, the use of NaSSAs is not recommended in those with cardiovascular abnormalities because of their potential harmful effects on heart rate variability.

Different mechanisms have been identified regarding effects of SSRIs on cardiovascular system. These types of drugs can inhibit the reuptake of serotonin at presynaptic terminals, resulting in increased serotonergic activity in the interneuron space. In this regards, some protective effects of SSRIs may be related to their effects on vasculature, conduction system. One of the main beneficial effects of SSRIs in depressed patients is their effects on platelet activities. It has been shown that the depressed patients have elevated level of platelet adhesion and aggregation leading increased risk for cardiovascular events.[56,57] In fact, the use of SSRIs may prevent developing atherosclerotic plaques and also arterial thrombosis.[58-60] Along with their related beneficial effects, the harmful effects of SSRIs on cardiovascular system were only reported in less than 0.0003%[61] that can be only observed in drugs overdoses.

Conclusion

In conclusion, it seems that considering the new presented categorization of antidepressants can be clinically helpful to have the best selection for antidepressants to minimizing their cardiovascular harmful effects. However, the completeness of this categorization should be more assessed in further studies.

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None.

Conflict of Interests

Authors have no conflict of interests.

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Percutaneous trans-ulnar artery approach for coronary angiography and angioplasty; A case series study

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Case Series

Abstract

BACKGROUND: Coronary angiography is the gold standard method for diagnosis of coronary heart disease and usually performed by femoral approach that has several complications. To reduce these complications, upper extremity approach is increasingly used and is becoming preferred access site by many interventionists. Although radial approach is relatively well studied, safety, feasibility and risk of applying ulnar approach in not clearly known yet.

METHODS: We followed 97 patients (man = 56%, mean ± standard deviation of age = 57 ± 18) who had undergone coronary angiography or angioplasty via ulnar approach for 6-10 months and recorded their outcomes.

RESULTS: In 97 patients out of 105 ones (92.38%), procedure through ulnar access were successfully done. Unsuccessful puncture (3 patients), wiring (2 patients), passing of sheet (2 patients), and anatomically unsuitable ulnar artery (1 patient) were the reasons of failure. In 94 patients (89.52%), the angiography and angioplasty was done without any complications. Five patients (5.1%) hematoma and 11 patients (11%) experienced low-grade pain that resolved with painkiller. No infection, amputation or need for surgery was reported.

CONCLUSION: This study demonstrated that ulnar access in our patients was a safe and practical approach for coronary angiography or angioplasty, without any major complication. Bearing in mind its high success rate, it can be utilized when a radial artery is not useful for the catheterization and in cases such as prior harvesting of the radial artery (in prior coronary artery bypass grafting).

Keywords: Outcome of Arterial Access, Coronary Angiography, Coronary Angioplasty

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Introduction

Coronary angiography (CAG) is the gold standard for detection of arterial narrowing related to atherosclerotic coronary artery disease (CAD). This procedure provides the most reliable information for determining the effectiveness of medical therapy as well as interventional procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in patients with CAD.[1]

Coronary angiography is performed through percutaneous approach to arteries; therefore, selecting the best vascular access is one of the first decisions for any percutaneous cardiovascular procedure. For the first time this approach was applied in 1953,[2] and brachial artery was the first access to use.[3] Then cardiovascular interventionists began to use of femoral access for CAG and PCI due to some complications of brachial access in 1967.[4] However, this new access site has shown to have several complications as well.[5-9] During 1989 till 1999 percutaneous radial artery approach started to be applied by cardiology interventionists.[10] There is already a considerable amount of articles that discuss about the conversion to predominantly radial access and its results.[11] Moreover recently, an interest for upper limb approach has been emerged in some patients as it has been shown to result in significantly less clinical complications.[12]

Trashima and his colleagues were the first who reported the feasibility of trans-ulnar approach for diagnostic catheterization of coronary arteries more

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than one decade ago[13] and their study was followed by limited numbers of investigations later.[14] A number of studies has revealed that this method is safe and feasible and has some advantages over trans-radial approach.[15] However, while the transradial approach has been proven to be useful and is established as an accepted alternative to femoral approach,[16,17] trans-ulnar artery approach, and its potential risks need to be more investigated. In this article, we will discuss this approach based on 6-10 months follow-up of 97 patients undergone CAG or PCI through ulnar access.

Materials and Methods

We examined 97 patients that have been under CAG or PCI through ulnar approach from June 2013 till February 2014.We followed all of the patients that were under ulnar approach.

The patients were from two hospitals of Isfahan University of Medical Sciences, Iran, (Chamran Heart Center and Noor Hospital).

Clinical diagnosis of 78 patients was chronic CAD, while acute coronary syndrome (ACS) and acute myocardial infarction (AMI) were the indications of the intervention in 15 and 4 patients respectively (risk factors for need to intervention is presented in table 1).

CAG was performed in 81 patients and 16 patients underwent PCI. We used right hand ulnar artery in 86 patients and left one in 11 cases.

Assessment of the deep palmar arch (Allen's test) was done for all of the patients.

For the procedure, after injection of 1.5 cc lidocaine (2%) by 2 cc syringe at the puncture site (usually about 2 cm from the head of ulnar bone) the ulnar artery was punctured with fine needle. A short guide wire was inserted and then a 5-6 French radial hydrophilic sheets was placed over the wire.

After injecting 5 cc of cocktail (consist of nitroglycerine 250 μg, verapamil 2.5 mg and normal saline diluted heparin 2500 units), 0.035" wire was passed through ulnar artery into brachial artery and entered coronary arteries via ascending artery.

6" tiger, right judkins and left judkins catheters were used for CAG and 6" Icari, extra back-up and right judkins guiding catheters for PCI. Using ulnar approach was canceled in four cases due to the severe tortuosity of their ulnar arteries.

The patients were followed by observation and examination at the post catheters laboratory (right after procedure), at coronary care unit (CCU) or ward and every other month for at least 6 months and up to 10 months at the clinical office.

We used a data gathering form to record patients' related information including demographic data, diagnosis, complications (major complications such as pulselessness, site ischemia, ulnar nerve damage, surgery or need to consult with surgeon, need to blood transfusion or hand amputation, myocardial infarction or pseudoaneurysm, AV fistula and ulnar artery occlusion), (minor complications such as low grade hematoma (Grade 1 hematoma: under 5 cm subcutaneous hematoma or Grade 2: under 10 cm), pain, irritation of ulnar nerve, and methods for resolving the complications and patients outcomes. Risk factors of complications in ulnar approach were emergent procedure, severe tortuosity of ulnar artery, narrowing of ulnar artery and lack of good and new wire.

Results

Totally, 54 patients (55.67%) were males and the age range of patients was from 37 to 84 years (mean ± standard deviation: 57 ± 18). Table 1 showed the frequency of major cardiovascular risk factors in both sexes. In total, 78 (80%), 15 (16%), and 4 (4%) suffer from CAD, ACS, and AMI, respectively. among the patient 81 (83%) and 16 (17%) underwent CABG and PCI, respectively. Angiography procedures performed 86 (88%) by the right hand and 11 (12%) by the left hand.

Table 1. Frequency of major cardiovascular risk factors based on sex

Risk factor	Men n (%)	Women n (%)
Smoking (ever smoked)	20 (37)	1 (2)
Diabetes (FBS ≥ 26 mg/dl)	15 (33)	19 (44)
Hypertension (SBP ≥ 140, DBP ≥ 90 mmHg)	17 (31)	15 (35)
History of myocardial infarction	11 (20)	4 (9)
Hyperlipidemia (Chol ≥ 200 mg/dl)	23 (42)	25 (58)
Family history of coronary artery disease	11 (20)	13 (30)

FBS: Fasting blood sugar; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

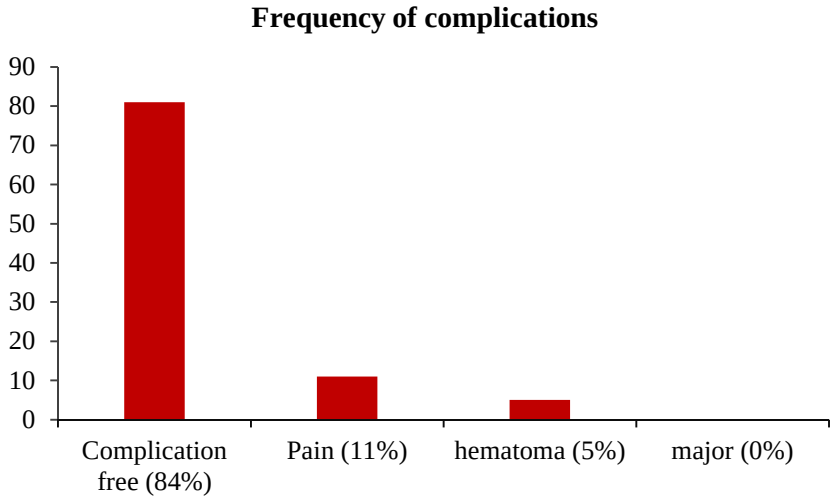

Figure 1. Frequency of trans-ulnar approach complications

Considering major complications, none of our patients showed any of them. Regarding minor complications, 5 patients in PCI group experienced Grade 1 hematoma in ulnar region (5.1%), which was healed by local compression, bandage and oral analgesics. All of these 5 patients discharged one day after the procedure. Furthermore, 11 patients (11.3%) had a low grade pain in their hand and irritation of ulnar nerve that were resolved by administration of dexamethasone (0/5 mg) + non-steroidal anti-inflammatory drugs (200 mg ibuprofen) + gabapentin (100 mg) (oral). In 8 cases of 105 patients, this approach was not successful. Unsuccessful puncture (3 patients), unsuccessful wiring (2 patients), unsuccessful passing of sheet (2 patients) and anatomically unsuitable ulnar artery (1 patient) were the reasons of failures. Figure 1 shows the frequency of trans-ulnar approach complications among our study population.

Discussion

This study showed that ulnar approach for CAG or PCI in our patients could be consider as a safe and practical method with only minor and easily resolvable complications. Our patients showed very limited minor complications that relieved easily and quickly. In line with this, two studies had been designed to evaluate safety and feasibility of this approach. In the first study 13 patients had been followed for 30 days and in the second study 28 patients were followed for 1 week.[15,18] In both studies they didn't find any major complication due to this access and have concluded that ulnar artery is a safe and feasible approach for cardiac CABG and PCI. Furthermore in a recent study on 410 patients, access site related complications were reported only in 3.9% of patients without any incidence of major complications.[19] De Andrade et al.[19] have listed their reasons for using ulnar approach and a wider and easily palpable pulse of the ulnar artery compared to the radial, was reported as the first reason which accounts for 73.2% of the cases. According to this article, this approach results in decreasing the incidence of vasospasm and consequently procedure failure and leads to more patient satisfaction.

Success rate of using this approach in our study was 92%. The reported success rates in some other studies have been 100% (20), 98.5% (19) and 88%.[13] Besides, results of an investigation done to compare two upper limb accesses for arterial cannulation, showed that arterial cannulation success rate is equivalent in radial and ulnar (with strong pulse) approache.[20]

Ulnar artery is usually larger than radial which may make it less disposed to catheter-induced vasospasm compared to the radial artery. Furthermore, this can lead to taking advantage of larger arterial sheaths. Moreover, ulnar nerve trauma is a potential complication of this method, which has not been reported in some studies. It is believed that applying a proper size needle and careful placement of it would be helpful to avoid the occurrence of this complication.[15,21-23]

Furthermore, we recommend performance of Doppler sonography of upper limb in patients with persistent signs or weak end pulses. Furthermore, coronary angiography via femoral artery access should be considered in the case of severe hand

ischemia, although we didn't need to use any of these procedures.

In summary, in our patients, trans-ulnar approach for PCI and CAG was safe an alternative to the trans-femoral and trans-radial approaches that can be safely applied when those accesses are at high risk of complications or failure and even potentially may be considered as the preferred primary access site.

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Conflict of Interests

Authors have no conflict of interests.

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Survival after left ventricular free wall rupture due to acute myocardial infarction

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Case Report

Abstract

BACKGROUND: Left ventricular free wall rupture is a frequent catastrophic complication of acute myocardial infarction (AMI) and occurs in 1-3% of patients with acute myocardial infarction; it is the third most common cause of death caused by acute myocardial infarction, too.

CASE REPORT: We describe acute left ventricular free wall rupture due to acute myocardial infarction in a 60-year-old man. He was survived after urgent surgical intervention.

CONCLUSION: The long-term survivors of free wall rupture repair have not been extensively reported; early diagnosis is very critical and immediate surgical repair is the treatment of choice.

Keywords: Myocardial Infarction, Free Wall Rupture, Left Ventricle

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Introduction

Left ventricular free wall rupture (LVFWR) is a frequent catastrophic complication, and the third most common cause of death after acute myocardial infarction (AMI). This most severe mechanical complication of the AMI occurs in 1-3% of patients and often remains undiagnosed.[1,2]

Case Report

We describe 60-year-old man with acute left ventricular free wall rupture due to AMI. He was admitted in emergency department with severe retrosternal chest pain, dyspnea, and sweating. A presumed diagnosis of anterior wall AMI with ST segment elevation was made. Treatment with streptokinase was started. Retrosternal chest pain was relieved, but the ST segment elevations did not resolve. The patient was transferred to a cardiac care unit.

The coronary angiography demonstrated a three-vessel disease with proximal significant stenosis of the left anterior descending (LAD) and right coronary (RCA) arteries and totally occluded left circumflex artery (LCX) filling via collaterals (Figure 1).

The patient was discharged after 7 days and candidate for elective coronary artery bypass graft (CABG). Six hours after discharge, he was brought back to emergency department in a state of hemodynamic collapse. His blood pressure was 60/45 mmHg; his heart rate was 130 beats/minute; and an electrocardiogram showed sinus tachycardia. Signs of systemic hypoperfusion and cardiogenic shock were noted, and intra-aortic balloon pump (IABP) support was started immediately. Further electrocardiography revealed sinus tachycardia, low-voltage QRS complexes with diffuse ST segment elevation, and no electrical changes. Echocardiography revealed a moderate pericardial effusion and manifestations of early cardiac tamponade [right atrium (RA) and right ventricle (RV) diastolic collapse] but no signs of myocardial tear, mitral regurgitation, or ventricular septal defect.

The patient was transported to the operating room, and midsternotomy was done. Later, 300 ml of blood and clot was drained from the pericardium, and cardiopulmonary bypass (CPB) was established. Rupture of anterolateral wall of LV was repaired via Gore-Tex and Dacron patch, and CABG was done (Figures 2-4).

The patient recovered quickly and after 12 days, he was discharged from the hospital.

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At the 18-month follow-up, the patient was taking statins, diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and warfarin. Follow-up echocardiography revealed a left ventricular ejection fraction of 35% to 40%, mild enlargement of the left ventricle, and mild mitral valve regurgitation.

Discussion

In 1647, William Harvey reported the first clinical case of post-infarction left ventricular wall rupture.[3] Left ventricular free wall usually occurs between 3 to 6 days following AMI, and the survival is associated with emergency operation.[4] Previous studies report that the anterior wall is more often susceptible to rupture, and the more recent studies indicate that the rupture is more common on the lateral or posterior wall.[2] In a review of cases, the segmental distribution of free-wall rupture location was posterior wall (43%), lateral wall (28%), and then apical wall (24%) followed by other segments at equal frequency.[5] In our patient, the anterolateral wall was involved.

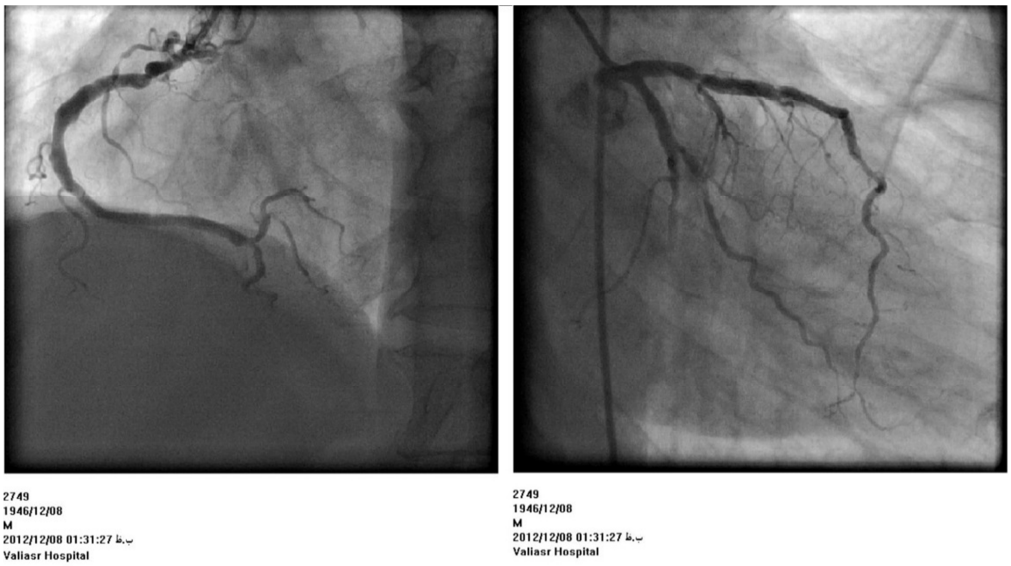

Figure 1. The coronary angioghrphy views

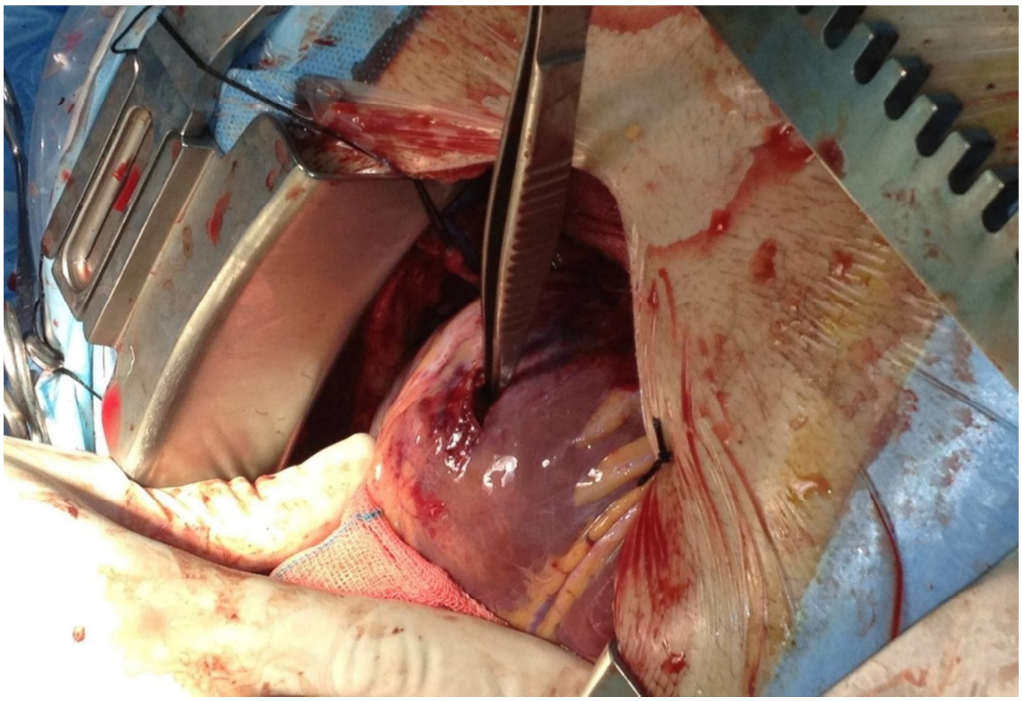

Figure 2. Left ventricular free wall rupture after acute myocardial infarction (AMI)

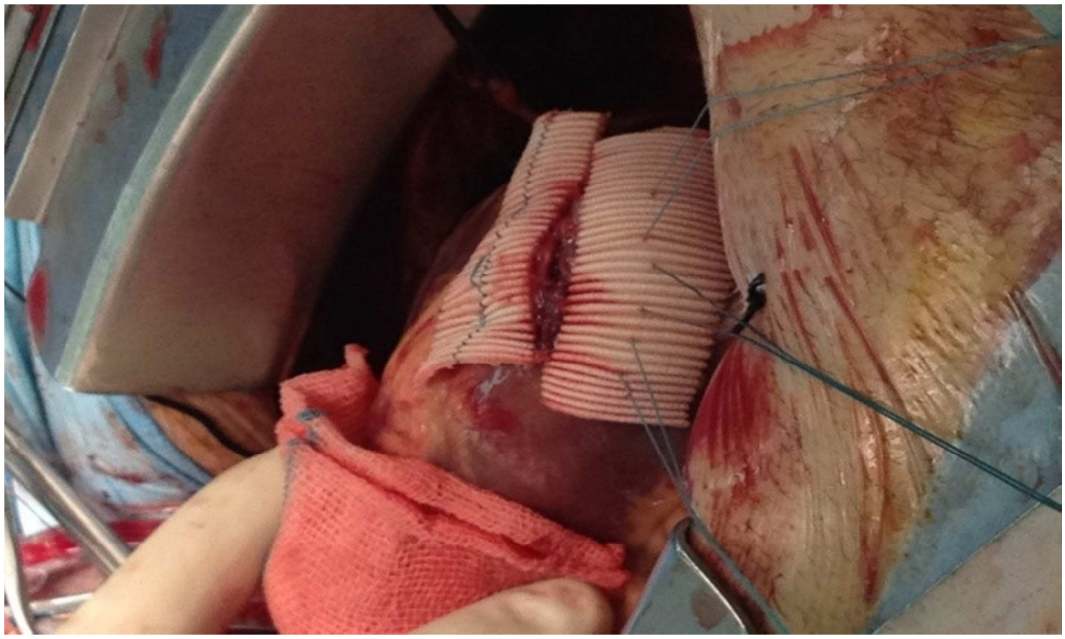

Figure 3. Repair of left ventricular rupture with Dacron patch

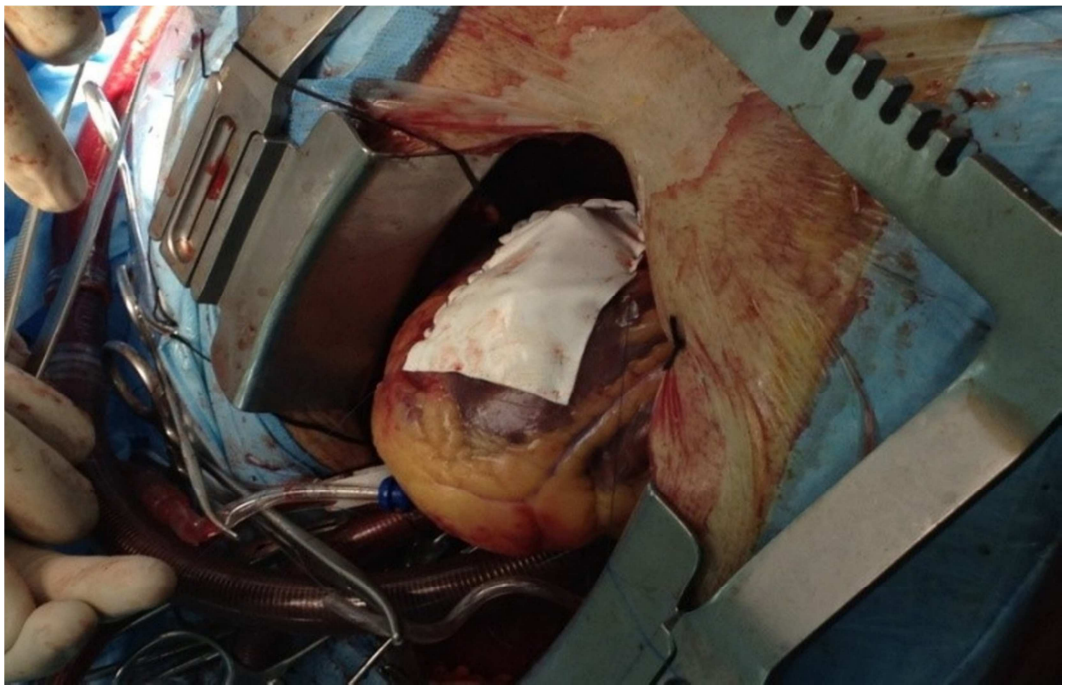

Figure 4. Reinforcement of left ventricular rupture after repair with Gore-Tex patch

Rupture of the ventricular free wall and cardiogenic shock are the major causes of death following AMI, contributing to 66% of deaths due to first AMI.[6]

The evolution of the events in acute free wall rupture rarely provides the adequate time to treat the patient surgically.[7] Patients usually die within a few minutes. This most fetal complication of the AMI often remains undiagnosed and constitutes a necropsy finding.[7] Surgical treatment of myocardial free wall rupture has been achieved with different degrees of success.[8]

However, when there is strong suspicion of cardiac rupture, biological glue can be administered intrapericardially following pericardiocentesis, ensuring valuable time until the patient is led to the operating room. The goals of surgery include avoiding cardiac tamponade and performing closure of the ventricular deficit.

In our case, since there was no delay in surgical

treatment, we used an IABP counter-pulsation. Placement of IABP was very useful in the patient who brought in the emergency room with evidence of cardiogenic shock following AMI.[9]

Localized pericardial effusion is the most frequent echocardiographic finding in the case of left ventricular free wall rupture. Thus, echocardiography can aid in early diagnosis of cardiac rupture. In our case study, echocardiography and IABP played a prominent role for management of AMI complication.

Comment

This case demonstrates that left ventricular free wall rupture is not always fatal. Early diagnosis and institution of intra-aortic balloon pump support in such patients can allow successful bridging to definitive emergency surgical therapy.

Acknowledgments

None

Conflict of Interests

Authors have no conflict of interests.

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