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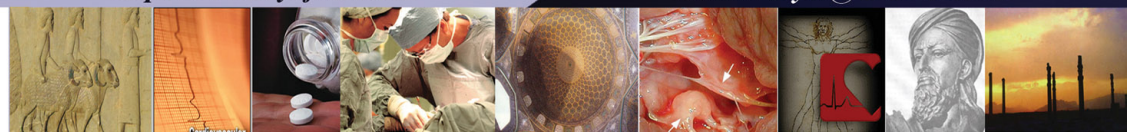

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- **Original Articles** are scientific reports of the results of original clinical research. The text is limited to 3000 words (excluding abstracts and references), with a structured abstract, a maximum of 5 tables and figures (total), and up to 40 references.
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Comparison of cardiovascular risk factors and biochemical profile in patients with cardiac syndrome X and obstructive coronary artery disease: A propensity score-matched study

Ali Vasheghani-Farahani[(1)], Nasrin Nouri[(2)], Soroush Seifirad[(3)], Mahmood Sheikh Fathollahi[(4)], Elham Hakki[(5)], Mohammad Alidoosti[(1)], Gholamreza Davoodi[(1)], Farzad Masoudkabir[(6)], Hamidreza Poorhosseini[(1)]

Original Article

Abstract

BACKGROUND: This study was designed to compare the frequency of conventional cardiovascular disease risk factors and clinical biochemistry profile in patients with cardiac syndrome X (CSX) and obstructive coronary artery disease (CAD).

METHODS: A cross-sectional study was conducted on patients with typical angina and positive exercise tolerance test undergoing coronary angiography in our center. 342 consecutive patients with CSX were enrolled into this study and were matched regarding age and sex with 342 patients with acute coronary syndrome (ACS) and also 342 patients with chronic stable angina (SA). Cardiovascular risk factors as well as biochemistry profile of the patients were recorded.

RESULTS: Mean age of the studied patients was 53.0 years and 41.5% were male. There was no significant difference between the CSX patients and CAD patients regarding body mass index (BMI). Frequency of diabetes mellitus, hyperlipidemia, smoking, family history of premature CAD and hypertension was significantly lower in patients with CSX than ACS and SA patients. Patients with CSX had significantly higher levels of high-density lipoprotein cholesterol (HDL-cholesterol) than comparators while the levels of low-density lipoprotein cholesterol (LDL-cholesterol), total cholesterol, triglyceride and fasting blood sugar (FBS) were significantly lower in patients with CSX than CAD patients.

CONCLUSION: The present study demonstrated that CSX patients had substantially lower frequency of all conventional CVD risk factors than patients with obstructive CAD. This might aid in developing novel scoring systems or appropriateness criteria for angiographic evaluation of patients with typical angina and positive exercise test in order to reduce the rate of negative results.

Keywords: Cardiac Syndrome X, Microvascular Dysfunction, Coronary Artery Disease, Risk Factors

Date of submission: 14 Jan 2013, ***Date of acceptance:*** 08 Jun 2013

Introduction

Cardiac syndrome X (CSX) is defined as typical angina pectoris and normal or near normal coronary arteries at angiography; however, ST segment depression during exercise stress test is also included in the modified definitions of CSX.[1-4] Regardless of low mortality, patients with CSX have high morbidity and health care expenditure comparable to patients with obstructive coronary artery disease (CAD).[5,6] In fact, because of the refractory nature of the chest pain, a significant functional disability may remain in many of these patients, often women, and represents a considerable burden on hospital resources, as these patients continue to use hospital facilities, including emergency and coronary care beds.[5]

CSX is associated with a wide range of clinical characteristics which may reflect differences in etiology and outcome. Several pathophysiologic mechanisms have been suggested for that; inflammation, endothelial dysfunction (ED),

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impaired pain perception, and insulin resistance are among the suggested etiologies of CSX.[7] A major diagnostic challenge for the cardiologist, however, is whether patients with CSX can be distinguished with sufficient validity and reliability from those with obstructive CAD on the basis of a careful assessment of clinical characteristics and non-invasive investigations. This would avoid subjecting the patient to the small but definite risk associated with coronary angiography, which would have favorable effects on healthcare costs and allow better utilization of medical resources.[8] Thus, this study was designed to compare the frequency of conventional CVD risk factors between the patients with angiographically determined obstructive CAD and patients with CSX. The results of this study might be a substrate for clinical differentiation of CSX and CAD and for more comprehensive planning for diagnostic tests.

Materials and Methods

Study Population

A retrospective cross-sectional study was performed in this study. Between May 2009 and May 2010, 373 patients with typical angina and a positive exercise test were enrolled in the study who underwent diagnostic coronary angiography at cardiac catheterization laboratory of Tehran Heart Center (affiliated to Tehran University of Medical Sciences) and found to have normal coronary angiograms. After excluding 41 patients with valvular heart disease, left ventricle hypertrophy, cardiomyopathy, left ventricular ejection fraction (LVEF) ≤ 50%, congestive heart failure and a positive history of coronary spasm, 342 remaining patients were considered for the final analysis. In addition, there were 2031 patients with ACS and 2470 patients with chronic stable angina (SA) who underwent coronary angiography at the same time period who were used as a pool of potential comparators. In fact, as there was evidence that patients with CSX were more likely to be female and to have lower ages and on the other hand conventional risk factors of CVD were more likely to be present in males and older ages, it was decided to eliminate the potential confounding effects of age and gender through matching for more clarification of the difference of the CSX and CAD patients regarding their risk factors. Hence, propensity scores were used to match the 342 CSX patients with 342 ACS and 342 SA matched comparators for age and sex in a 1: 1 fashion.

Study Protocol

Demographic data including sex, age, weight, body mass index (BMI), hypertension, hyperlipidemia, DM, smoking, and family history of CAD, in addition with the results of biochemical examinations including fasting blood glucose and lipid profile were recorded and analyzed. Medication history of the patients in each group was also recorded and compared with together The study protocol was reviewed and accepted by the Ethics Committees of Tehran University of Medical Sciences and Tehran Heart Center (Approval date: 2008-11-08, approval number: 89/210/7962) and verbal informed consent was obtained from all the patients. Investigators guaranteed to use the medical documents of the study participants confidently and not to impose any research-related charge to them.

Laboratory Assays

Peripheral venous blood specimens were collected from an antecubital vein after 10-12 fasting hour of the subjects. Fasting plasma glucose (FPG) was measured by the glucose-oxidation method (Pars Azmoon, Tehran, Iran) and total cholesterol (TC), triglyceride (TG), and low density lipoprotein-cholesterol (LDL-C) were determined by enzyme colorimetric assay (Pars Azmoon, Tehran, Iran) using a Hitachi autoanalyzer (type 717, Hitachi medico, Tokyo, Japan). High density lipoprotein-cholesterol (HDL-C) was measured using precipitation-based method. All measurements were performed in Tehran Heart Center laboratory with adherence to external quality control.

Definitions

Cardiac syndrome X was defined as coexistence of typical angina pectoris, positive exercise stress test (ST segment depression during stress test) and normal coronary angiogram.[4] CAD was defined as ≥ 50% luminal diameter stenosis in one or more major epicardial vessel and included patients with ACS and SA.[9,10] ACS consists of ST elevation myocardial infarction, non ST elevation myocardial infarction and unstable angina. Angina pectoris and associated CAD symptoms precipitated by activity with minimal or non-existent symptoms at rest, were defined as SA.[11]

Risk factors including smoking, DM, hypertension, hyperlipidemia, and family history of premature CAD were defined on the strength of standard definitions.[12-15] Patients who consumed opium by any route (inhalation or oral) were considered as opium-users.[16]

Statistical Analysis and Propensity Score Matching

A propensity score-matching methodology was applied to identify comparator groups who were statistically equivalent based on age and gender.[17]

Using nearest available Mahalanobis metric matching within calipers defined by the propensity score, each CSX patient with an ACS patient and a SA patient whose propensity scores were closest were adjuste.[18] The Kolmogorov-Smirnov test was applied to examine normal distribution. Continuous variables were expressed as mean ± SD and were compared among three groups of patients by analysis of variance (ANOVA) followed by Scheffe's post-hoc test for pairwise comparisons. Categorical variables were compared using a chi-square test or Fischer's exact test as appropriate, and were presented as absolute frequencies with percentages. All P values were two-tailed with significance defined as $p \leq 0.05$. For the statistical analysis, the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) was used.

Results

Clinical characteristics of the patients in three groups are presented in table 1. Mean age of the study subjects was 53 years and 426 of them (41.5%) were male. There was no significant difference between CSX patients and ACS patients and also between CSX and SA patients with respect to BMI. Frequency of diabetes mellitus was significantly smaller in patients with CSX (15.6%) than ACS (37.0%) and SA (32.8%) patients (P for both comparisons < 0.0001). Similar to diabetes mellitus, the prevalence of hyperlipidemia was also significantly lower in CSX group (16.4%) than ACS (36.8%) and SA (32.7%) groups. While patients with SA were more likely to be hypertensive than CSX patients (190 vs. 138, respectively), there was no significant difference between CSX and ACS groups regarding the prevalence of hypertension. ACS and SA groups were also more likely to have a positive family history of premature CAD as compared to CSX group (P for both comparisons < 0.0001). The frequency of current smoking was significantly lower in patients with CSX (36) than ACS (84) and SA groups (58). Although the opium abuse was more frequent in ACS group than CSX group (52 vs. 22, respectively, P = 0.001), the prevalence of opium abuse was similar in CSX and SA groups.

Table 2 demonstrates the plasma biochemistry profile of the participants. Plasma concentrations of HDL-C was significantly higher in patients with CSX compared to ACS and SA groups (P = 0.001 and P = 0.026, respectively). Although the comparison of LDL-C levels did not show a statistically significant difference between ACS and XSC groups (P = 0.076), patients with SA had a significantly higher concentrations of LDL-C than CSX patients (124.6 mg/dl vs. 115.3 mg/dl, respectively; P = 0.009). Serum levels of TC, TG and FPG were also significantly higher in ACS and SA groups compared to CSX group (P for all comparisons < 0.0001).

Table 1. Baseline clinical characteristics of the study subjects

	ACS (n = 342)	SA (n = 342)	CSX (n = 342)	P ACS vs. SA	P CSX vs. SA	P CSX vs. ACS
Age (yr)	53.0 ± 8.5	53.0 ± 8.3	52.9 ± 8.6	0.993	0.817	0.8120
Male sex, n (%)	142 (41.5)	141 (41.2)	143(41.8)	0.999	0.938	0.9990
BMI (Kg/m^2)	28.1 ± 4.9	29.0± 4.7	28.5 ± 4.4	0.010	0.134	0.2490
CV risk factors, n (%)						
Diabetes mellitus	126 (37.0)	112 (32.8)	53(15.6)	0.296	< 0.0001	< 0.0001
Hyperlipidemia	263 (77.8)	268 (78.4)	211 (62.2)	0.926	< 0.0001	< 0.0001
Hypertension	162 (47.4)	190 (55.9)	138 (40.6)	0.027	< 0.0001	0.0770
Family history	136 (41.0)	111 (32.6)	69 (20.4)	0.031	< 0.0001	< 0.0001
Current smoking	84 (24.6)	58 (17.0)	36 (10.6)	0.008	< 0.0001	< 0.0001
Opium abuse	52 (15.2)	26 (7.6)	22 (6.4)	0.006	0.193	0.0010

All plus-minus values are mean ± SD; BMI: Body mass index; CV: Cardiovascular; ACS: Acute coronary syndrome; SA: Chronic stable angina; CSX: Cardiac syndrome X

Table 2. Serum biochemistry profile of the study subjects

	ACS (n = 342)	SA (n = 342)	CSX (n = 342)	P ACS vs. SA	P CSX vs. SA	P CSX vs. ACS
HDL-C (mg/dl)	41.9 ± 10.5	42.90 ± 9.8	44.8 ± 10.3	0.168	0.026	0.001
LDL-C (mg/dl)	121.2 ± 43.3	124.6 ± 47.4	115.3 ± 37.8	0.344	0.009	0.076
Total cholesterol (mg/dl)	206.4 ± 51.7	207.1 ± 53.8	194.5 ± 44.9	0.858	0.002	0.002
Triglycerides (mg/dl)	225.0 ± 142.8	210.6 ± 134.5	175.7 ± 99.6	0.174	< 0.0001	< 0.0001
FPG (mg/dl)	134.9 ± 64.7	128.9 ± 62.5	106.9 ± 34.0	0.219	< 0.0001	< 0.0001

All plus-minus values are mean ± SD; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; FPG: Fasting plasma glucose; ACS: Acute coronary syndrome; SA: Chronic stable angina; CSX: Cardiac syndrome X

Discussion

To our knowledge, our study is the largest study of CSX patients compared to patients with obstructive CAD regarding the clinical and laboratory characteristics.

Our data demonstrated that in CSX group, female to male ratio was 3:2 while some studies reported 2-3:1 ratio and suggested that CSX was a women's disease but our results showed that this claim might not be acceptable.[19]

According to the results of this study, all the conventional cardiovascular risk factors were significantly lower in CSX patients than ACS and SA patients. It has been shown in various studies that approximately 10-30% of patients undergoing diagnostic coronary angiography to evaluate angina-like chest pain have normal coronary angiograms.[20] There are approximately 1,700,000 cardiac catheterizations performed annually in the United States, resulting in 170,000 to 500,000 patients with no clear diagnosis for their chest pain after coronary angiography.[8,20,21] Considering the invasive nature of the cardiac catheterization in addition to its high costs for healthcare systems warrants more efficient selection criteria to reduce the rate of unnecessary normal coronary angiographies and its undesirable complications and costs. The significantly different risk factor profile of CSX patients in comparison to obstructive CAD patients might enable us to develop risk scoring systems in order to more comprehensive enrollment of patients with typical angina and positive exercise test for coronary angiography.

There is consistent evidence that opium abuse is significantly higher in CAD patients (10-22%) than general population (2-2.8%) in Iranian population.[22,23] Moreover, we recently reported that opium abuse is independently associated with the existence, severity and extension of coronary atherosclerosis in diabetic patients with chronic stable angina.[9] In this study, we observed that the frequency of opium abuse among CSX patients was comparable to that in chronic SA patients and seems to be twofold higher than reported prevalence of opium abuse in general population (3%). On the other hand, abnormal pain perception, at least in part, has been suggested for potential pathophysiology of CSX.[8] Several studies have concordantly shown that patients with CSX exhibit enhanced pain perception.[17,24,25] Rosenbaum[17] recently observed that patients with CSX exhibit activation of the right anterior insula cortex during angina and ST changes induced by echocardiographic dobutamine stress test, in the absence of left ventricular wall motion abnormalities. Hyperreactivity of cardiac pain receptors, abnormal transmission and/or modulation of pain signal at subcortical level, or a variable combination of all these abnormalities, might equally account for the abnormal activation of specific pain perception areas in brain.[8,25] As opium users have shown to have abnormal pain perception[26] and patients with CSX are more likely than general population to use opium, it raises this hypothesis that opium abuse might be a risk factor and even an etiologic one in a subgroup of patients with CSX; however, this warrants further evaluation in future studies.

This study had potential limitations that should be mentioned. The main limitation of this study was lack of a healthy age and sex matched group, to compare with CSX patients. Hence, the conclusions about the difference of CSX patients with healthy subjects in some instances was made indirectly through the similarity of the variable of interest in CSX and CAD groups and the consistently known difference of CAD patients with healthy subjects.

In conclusion, our study demonstrated that while CSX is more prevalent in women than men (3:2), it should not be considered as a women's disease. CSX patients have substantially lower frequency of all conventional CVD risk factors than patients with obstructive CAD. This may aid in development of novel scoring systems or enrollment criteria for angiographic evaluation of patients with typical angina and positive exercise test in order to reduce the rate of negative results.

Conflict of Interests

Authors have no conflict of interests.

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Risk of sudden cardiac death

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Original Article

Abstract

BACKGROUND: The aim of this study was to determine characteristics of patients with sudden cardiac arrest (SCA) and/or sudden cardiac death (SCD). We need an effective risk stratification method for SCD in patients without low left ventricular ejection fraction (LVEF).

METHODS: The study population of this cross-sectional study consisted of 241 patients with SCA or SCD who were admitted to an academic hospital, in Tehran, Iran, from 2011 through 2012. SCD was defined as unexpected death from cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute changes in cardiovascular status, or an unobserved death in which the patient was seen and known to be doing well within the previous 24 hours. Survivors of aborted SCD were also included in the study. Clinical and paraclinical characteristics as well as emergency department complications of patients were recorded.

RESULTS: The mean age of population was 66.0 ± 16.5 (17 to 90 years). Among the patients, 166 (68.9 %) were male, 50 (20.7%) were smoker, 77 (32.0%) had hypertension, 47 (19.5%) had diabetes mellitus, 21 (8.7%) had hyperlipidemia, and 32 (13.3%) had renal insufficiency. According to New York Health Association (NYHA) functional class, 31 (12.9%) patients were asymptomatic, 42 (17.4) and 99 (41.1%) subjects were in NYHA I and II, respectively and only 69 (28.6%) patients were in NYHA III or IV. In this study, presenting arrhythmia was pulseless electrical activity or asystole which was observed in 130 (53.9%) subjects. Ventricular tachycardia (VT) or ventricular fibrillation (VF) was seen in 53 (22%) patients. Cardiopulmonary resuscitation in emergency room was successful only in 46 (19.1%) subjects.

CONCLUSION: Low ejection fraction (EF) may be an independent predictor of sudden cardiac death in patients, but it is not enough. While implantable cardioverter defibrillators can save lives, we are lacking effective risk stratification and prevention methods for the majority of patients without low EF who will experience SCD.

Keywords: Death, Sudden Cardiac Arrest, Sudden Cardiac Death

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Introduction

Cardiovascular disease is a leading cause of death in many parts of the world. Despite dramatic advances in diagnosing and treating cardiovascular disease, sudden cardiac death (SCD) still remains a major public health problem. Approximately one-half or more of all cardiac deaths are SCD and also, SCD can be the first manifestation.[1]

Few evidence is available in terms of incidence of sudden cardiac arrest (SCA) and/or sudden cardiac death (SCD) in Iran and in many countries.[2,3] It is necessary to know the true magnitude of this problem for improving risk stratification and prevention methods. As death occurs shortly after the onset of symptoms, there is little time for treatment. Even in the presence of advanced systems for resuscitation of out-of-hospital cardiac arrest, the overall survival was reported in some studies as low as 4.6%.[4] We rely on depressed left ventricular systolic function as the best predictor of SCD and mortality. But ejection fraction (EF) has a low sensitivity to predict SCD and the majority of patients who suffered from SCD have a preserved EF.[5]

Several factors have shown relationship with SCA/SCD like age, sex, smoking, type 2 diabetes

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mellitus, systolic blood pressure, family history of coronary heart disease, family history of SCD, ischemic ST-changes during exercise test, abnormal myocardial perfusion imaging, coronary heart disease, low heart rate recovery, ventricular ectopy during recovery, increased QRS duration, abnormalities in QT interval and QT dispersion, abnormal signal-averaged electrocardiography (ECG), abnormal T-wave alternans, impaired heart rate variability, abnormal heart rate turbulence, low baroreceptor sensitivity, ventricular arrhythmias on Holter monitoring, low cardiorespiratory fitness, depression, and use of antidepressant drugs.[6-8]

To date, there is a lack of evidence with regards to SCD and it is required that pooled data is gathered, as such selection procedures will be performed more accurately, generating more reliable data. The implantable cardioverter defibrillator (ICDs) is very effective in treatment of patients at risk of SCA/SCD; however, the accuracy of available methods to predict SCD on an individual basis is limited.[9]

Materials and Methods

Study population

The study was a single-center, cross-sectional study and included two hundred forty one patients with SCA/SCD who have been admitted to an academic hospital, in Tehran, Iran, from July 1 2011 to July 1 2012. SCD was defined as unexpected, natural death from cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the symptom onset, or an unobserved death in which the patient was seen and known to be doing well within the previous 24 hours. The location of SCA/SCD had to be in an out-of-hospital or emergency department setting. Survivors of aborted SCD were also included in the study. Subjects with known terminal illness (cancer), non-cardiac causes of sudden death (cerebrovascular accident, pulmonary embolism), traumatic, or overdoses related deaths were excluded. Family members were asked for permission to obtain information.

Two internal medicine physicians helped to obtain demographical, clinical, and paraclinical characteristics of selected patients which were recorded at the time of admission. Furthermore, family members reported symptoms of depression and antidepressant medication use were considered as a scale of measuring depression. When available, prior electrocardiograms, echocardiograms, and coronary angiograms were reviewed.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and dichotomous variables as frequencies. Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Differences were examined using Student's t-tests for continuous variables and chi-Square tests for dichotomous variables (or Fisher's exact test as needed). A $P < 0.05$ was considered statistically significant.

Results

The mean age of study population was 66.0 ± 16.5 years (17 to 90 years). Among the patients, 166 (68.9%) were male, 50 (20.7%) were smoker, 29 (12%) were opium user, 10 (4.1%) were amphetamine user, no one was alcohol user, 77 (32.0%) had hypertension, 47 (19.5%) had diabetes mellitus, 21 (8.7%) had hyperlipidemia, 32 (13.3%) had renal insufficiency, and 4(1.7%) had chronic lung disease.

Peripheral vascular disease was presented in 2 (0.8%) patients, cerebrovascular disease in 20 (8.3%), prior coronary artery disease in 48 (19.9.1%), prior congestive heart failure in 24 (10%), prior coronary artery bypass graft in 12 (5%), and prior percutaneous coronary intervention in 3 (1.2%) patients. The distribution of baseline characteristics of enrolled patients is shown in table 1.

Most of the patients were in low or moderate economical situation due to geographic place of the hospital, and 44% of patients had moderate or severe symptoms of depression. According to New York Health Association (NYHA) functional class, 31 (12.9%) patients were asymptomatic, 99 (41.1%) were in NYHA II class of symptoms, and only 69 (28.6%) patients were in NYHA III or IV classes. Clinical characteristics of selected patients are depicted in table 2.

Previous ECG was available in 149 (61.8%) patients with SCA/SCD. They showed normal findings in 25 (10.4%) patients, but pathological Q wave, left ventricular hypertrophia, left bundle branch block (LBBB), right bundle branch block (RBBB), and intraventricular conduction disturbance (IVCD) were observed in 119 (49.4%) patients. Previous echocardiograms were available in 115 (47.7%) subjects. The echocardiograms showed normal findings in 6 (2.5%) patients, and severe left ventricular systolic dysfunction was seen in 50 (20.7%) patients. Previous coronary artery angiograms were available in 32 (13.3%) patients and showed normal findings in 3 (1.2%) (Table 3).

In this study, presenting arrhythmia was pulseless electrical activity or asystole which was

seen in 130 (53.9%) subjects. Ventricular tachycardia (VT) or ventricular fibrillation (VF) was observed in 53 (22%) patients. ECG findings of enrolled patients at admission are shown in table 4.

Table 1. Baseline characteristics of enrolled patients with sudden cardiac arrest/sudden cardiac death

Characteristics	n (%)
Total number	241 (100)
Males	166 (68.9)
Family history of CAD	26 (10.8)
Family history of SCA/SCD	1.0 (0.4)
Smoker	50 (20.7)
Opium use	29 (12.0)
Alcohol use	0.0 (0.0)
Amphetamine	10 (4.1)
Hypertension	77 (32.0)
Hyperlipidemia	21 (8.7)
Diabetes mellitus	47 (19.5)
Renal insufficiency	32 (13.3)
Chronic lung disease	4 (1.7)
Cerebrovascular disease	20 (8.3)
Peripheral vascular disease	2 (0.8)
Prior CAD	48 (19.9)
Prior CHF	24 (10.0)
Prior CABG	12 (5.0)
Prior PCI	3 (1.2)
Economic status	
Low	94 (39.0)
Moderate	145 (60.2)
High	2 (0.8)
Age, years (Mean ± SD)	66.00 ± 16.5

CAD: Coronary artery disease; SCA/SCD: Sudden cardiac arrest/sudden cardiac death; CHF: Congestive heart failure; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention

Table 2. Clinical characteristics of enrolled patients with sudden cardiac arrest/sudden cardiac death

Characteristics	n (%)
NYHA functional class	
No symptoms	31 (12.9)
I	42 (17.4)
II	99 (41.1)
III	56 (23.2)
IV	13 (5.4)
Activity	
Low	110 (45.6)
Moderate	83 (34.4)
High	48 (19.9)
Depression	
Low	135 (56)
Moderate	88 (36.5)
Severe	18 (7.5)
Quality of life	
Low	114 (47.3)
Moderate	124 (51.5)
High	3 (1.2)

NYHA: New York Health Association

Table 3. Prior para clinical characteristics of enrolled patients with sudden cardiac arrest/sudden cardiac death

Characteristics	n (%)
Electrocardiogram	
Available	149 (61.8)
Normal	25 (10.4)
Pathological Q wave	46 (19.1)
LV hypertrophy	25 (10.4)
LBBB	25 (10.4)
RBBB	16 (6.6)
IVCD	7 (2.9)
AF rhythm	5 (2.1)
Echocardiogram	
Available	115 (47.7)
Normal	11 (4.6)
LV systolic dysfunction	27 (11.2)
LV diastolic dysfunction	17 (7.1)
Akinesia in wall motion	28 (11.6)
Pulmonary hypertension	6.0 (2.5)
LV hypertrophy	12 (5.0)
Mitral stenosis/regurgitation	11 (4.6)
Aortic stenosis/regurgitation	2.0 (0.8)
Ejection Fraction in Echocardiogram	
Available	115 (47.7)
EF ≤ 35%	50 (20.7)
EF 36-54%	59 (24.5)
EF ≥ 55%	6 (2.5)
Coronary Artery Angiogram	
Available	32 (13.3)
Normal	3.0 (1.2)

LBBB: Left bundle branch block; RBBB: Right bundle branch block; IVCD: Intraventricular conduction disturbance; LV: Left ventricular; AF: Atrial fibrillation; EF: Ejection fraction

Table 4. Electrocardiograms of Enrolled Patients with sudden cardiac arrest/sudden cardiac death in admission

Electrocardiogram in admission	n (%)
Pulseless electrical activity/asystole	130 (53.9)
ST elevation	31 (12.9)
Ventricular tachycardia	41 (17.0)
Ventricular fibrillation	12 (5.0)
Complete heart block	8 (3.3)
LBBB	6 (2.5)
RBBB	1 (0.4)
AF rhythm	12 (5.0)

LBBB: Left bundle branch block; RBBB: Right bundle branch block; AF: Atrial fibrillation

Cardiopulmonary resuscitation was unsuccessful in 195 (80.9%) patients. Among the groups with successful and unsuccessful CPR there were not statistically significant differences in age, sex, and presence of previous heart disease. The presenting arrhythmia in admission was significantly different between two groups and pulseless electrical

activity/asystole was more common in the group with unsuccessful CPR (Table 5).

Considering study population, 75 (31.1%) patients were female. The mean age was not significantly different between men and women. Moreover, there were no significant sex differences in prevalence of hyperlipidemia, diabetes mellitus, family history of CAD, renal insufficiency, chronic lung disease, cerebrovascular disease, prior coronary artery disease, prior congestive heart failure, or severe left ventricular systolic dysfunction. Women were more likely to have hypertension and men more likely to be smoker. Men were more asymptomatic than women before SCD/SCA event; also they had more physical activity. ECG at admission (pulseless electrical activity/asystole vs. ventricular tachycardia/ ventricular fibrillation) and successfulness of CPR was not significantly different between men and women (Table 6).

Table 5. Relationship between successfulness of cardiopulmonary resuscitation and patients' characteristics

Patients' characteristics	Successful CPR n (%)	Unsuccessful CPR n (%)	P
Total number	46 (19.1)	195 (80.9)	
Males	32 (69.6)	134 (68.7)	1.000
Smoking	9 (19.6)	41 (21.0)	1.000
Hypertension	21 (45.7)	56 (28.7)	0.035
Hyperlipidemia	3 (6.5)	18(9.2)	0.773
Diabetes mellitus	10 (21.7)	37 (19.0)	0.681
Renal insufficiency	8 (17.4)	24 (12.3)	0.343
Chronic lung disease	2 (4.3)	2 (1.0)	0.166
Cerebrovascular disease	1 (2.2)	19 (9.7)	0.136
Peripheral vascular disease	0 (0.0)	2 (1.0)	1.000
Prior coronary artery disease	14 (30.4)	34 (17.4)	0.063
Prior congestive heart failure	4 (8.7)	20 (10.3)	1.000
Left ventricular EF ≤ 35%	8 (17.4)	42 (21.5)	0.330
Electrocardiogram in admission			< 0.001
Pulseless electrical activity/asystole	11 (23.9)	119 (61.0)	
Ventricular tachycardia/fibrillation	11 (23.9)	42 (21.5)	
Other (STEMI, BBB, AF rhythm)	24 (52.2)	34 (17.4)	
Age, years (Mean ± SD)	59.9 ±16.6	63.2 ± 16.9	0.228

CPR: Cardio pulmonary resuscitation; EF: Ejection fraction; BBB: Bundle branch block; AF: Atrial fibrillation, STEMI: ST-elevation myocardial infarction

Table 6. Baseline and cardiac arrest characteristics of men and women with sudden cardiac arrest/sudden cardiac death

Characteristics	Men n (% in sex)	Women n (% in sex)	P
Total number of sex	166	75	-
Family history of CAD	9 (5.4)	17 (22.7)	0.661
Smoking	42 (25.3)	8 (10.7)	0.010
Hypertension	41 (24.7)	36 (48.0)	0.001
Hyperlipidemia	14 (8.4)	7 (9.3)	0.809
Diabetes mellitus	27 (16.3)	20 (26.7)	0.078
Renal insufficiency	23 (13.9)	9 (12.0)	0.838
Chronic lung disease	3 (1.8)	1 (1.3)	1.000
Cerebrovascular disease	10 (6.0)	10(13.3)	0.057
Prior coronary artery disease	35 (21.1)	13 (17.3)	0.602
Prior congestive heart failure	18 (10.8)	6 (8.0)	0.644
No prior symptoms	29 (17.5)	2 (2.7)	0.034
High activity in life	44 (26.5)	4 (5.3)	0.001
Ejection fraction ≤ 35%	33 (19.9)	17 (22.7)	0.570
Electrocardiogram in admission	-	-	0.778
Pulseless electrical activity/asystole	91 (54.8)	39 (52.0)	
Ventricular tachycardia/fibrillation	38 (22.9)	15 (20.0)	
Other (STEMI, BBB, AF rhythm)	37 (22.3)	21 (28.0)	
Unsuccessful CPR	134 (80.7)	61 (81.3)	1.000
Age, years (Mean ± SD)	61.51 ± 16.9	64.95 ± 16.7	0.144

CAD: Coronary artery disease; BBB: Bundle branch block; AF: Atrial fibrillation, STEMI: ST-elevation myocardial infarction; CPR: Cardio pulmonary resuscitation

In study population, 23 (9.5%) patients were under 40 years old (17 to 39 years). Among these group of patients, 19 (82.6%) were male, 5 (21.7%) were smoker, 5 (21.7%) were opium user, 6 (26.1%) were amphetamine user and, and no one was alcohol user. None had any positive history of SCA/SCD, hypertension, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, and/or prior coronary artery disease. The congestive heart failure was detected in 3 (13.0%) patients before the SCD incidence, and one of them was amphetamine user. The NYHA class was two or more in 8 (34.8%) patients. The presenting arrhythmia was predominantly pulseless electrical activity or asystole which was seen in 14 (60.9%) of patients under 40 years old. Two patients had ST-elevated myocardial infarction (STEMI) in first ECG. Long QT syndrome or Brugada pattern was not seen in any patients. Among these 23 young patients with SCA/SCD, only two patients (8.7%) were resuscitated successfully, which one of them had STEMI and the other had asystole in the first ECG.

Discussion

The mean age of affected patients with SCA/SCD in this study was similar to previous reports; in the mid-60s.[10] The prevalence of atherosclerotic risk factors was also similar. Depression has been shown to have a relationship with SCD in some studies. In our results, 44% of patients had moderate or severe depressive mode according to family members idea.

Among the patients, only 19.9% and 10.0% had known coronary artery disease and prior congestive heart failure, respectively. These percentages were lower than similar studies.[11] Severe LV systolic dysfunction was presented in 20.7% of patients. In the majority of cases, SCD was the first manifestation.

In out-of-hospital cardiac arrest, up to 40% of the initial arrhythmias were either VT or VF.[12,13] In some of recent studies, pulseless electrical activity/asystole was found in 52% of patients versus 48% for VT/VF. Pulseless electrical activity cases have been compared with VT/VF cases; they were older, more likely to be female, and importantly less likely to have hospital discharge (6% versus 25%).[11] In this study, presenting arrhythmia was pulseless electrical activity or asystole which was seen in 130 (53.9%) of patients and cardiopulmonary resuscitation was unsuccessful in 195 (80.9%) of patients.

In this study, women were more likely to have hypertension and men more likely to be smoker with no significant sex differences in prevalence of hyperlipidemia, diabetes mellitus, family history of CAD, renal insufficiency, chronic lung disease, cerebrovascular disease, prior coronary artery disease, prior congestive heart failure, or severe left ventricular systolic dysfunction. But in some published studies, women were less likely than men to have a previous diagnosis of coronary artery disease or left ventricular dysfunction. Therefore, they may be less eligible to receive an ICD.[14,15]

Forensic examination of SCD cases is not mandatory in Iran; hence, first relatives may refuse further post-mortem evaluation. But the cause of sudden unexplained death of the young persons before 40 is very important for those who left behind. Arrhythmic death in this age group is often caused by familial disease and every effort should be made to find the probable cause of SCD.[16]

Study limitations

The main limitation was observational nature of this study and the results must be viewed as hypothesis-generating only. The second limitation was the low number of patients that can be recruited in another study.

Conclusion

Unexpected cardiac arrests and/or unexpected cardiac deaths are a major health concern, but the true magnitude of it still remains unknown to the public, and the rate of successful cardiopulmonary resuscitation is low. Reduced EF may be an independent predictor of sudden cardiac death in some patients but it is not enough. Concerning the fact that ICDs can save lives, we are still in need of more effective risk stratification and prevention methods for those vast groups of patients experiencing SCD. As a result, it is recommended that pooled data from large population-based studies of SCD might be useful to find more candidates for ICD implantation.

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Conflict of Interests

Authors have no conflict of interests.

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Preventive effect of cinnamon essential oil on lipid oxidation of vegetable oil

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Original Article

Abstract

BACKGROUND: Lipid oxidation is the main deterioration process that occurs in vegetable oils. This process was effectively prevented by natural antioxidants. *Cinnamomum zeylanicum* (Cinnamon) is rich with antioxidants. The present study was conducted to evaluate the effect of cinnamon on malondialdehyde (MDA) rate production in two high consumption oils in Iranian market.

METHODS: Chemical composition of cinnamon essential oil was analyzed by gas chromatography-mass spectroscopy (GC-MS). 200 µl each oil, 50 µl tween 20, and 2 ml of 40 Mm AAPH solutions were mixed and the prepared solution was divided into four glass vials. Respectively, 50 µl of 500, 1000 and 2000 ppm of cinnamon essential oil were added to three glass vials separately and one of the glass vials was used as the control. All of the glass vials were incubated at 37° C water bath. Rate of MDA production was measured by thiobarbituric acid (TBA) test at the baseline and after the 0.5, 1, 2, 3 and 5 hours.

RESULTS: Compounds of cinnamon essential oil by GC-MS analysis such as cinnamaldehyde (96.8%), alpha-capaene (0.2%), alpha-murolene (0.11%), para-methoxycinnamaldehyde (0.6%) and delta-cadinen (0.4%) were found to be the major compounds. For both oils, maximum rate of MDA production was achieved in 5th hours of heating. Every three concentrations of cinnamon essential oil significantly decreased MDA production ($P < 0.05$) in comparison with the control.

CONCLUSION: Essential oil of cinnamon considerably inhibited MDA production in studied oils and can be used with fresh and heated oils for reduction of lipid peroxidation and adverse free radicals effects on body.

Keywords: Cinnamon, Essential Oil, Lipid Peroxidation, Vegetable Oils

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Introduction

Recently, there has been observed the increased demand for vegetable oil used both, for technical and food purposes.[1] Vegetable fats contain polyunsaturated fatty acids. These fats are prone to oxidation.[2] The free radical activity and the extent of tissue damage are related quantitatively to the amount of lipid peroxide level in the blood.[3] Malondialdehyde (MDA) is one of the end products of lipid peroxidation and extent of lipid peroxidation is measured by estimating MDA levels most frequently.[4] Increased serum level of MDA has been reported in cardiovascular,[5] neurological and other diseases.[6] Oxidation of vegetable oils has a direct influence on consumer acceptance and adversely affects lipids, proteins, carbohydrates, pigments and fat-soluble vitamins, causing development of off-flavor, loss of nutritional value, discoloration and the production of potentially toxic compounds.[7]

A substantial administration of oxidized vegetable oils in diet may lead to aggravation of free

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radical processes. It is believed that such a diet, similar to excessive consumption of products rich in cholesterol, results in development of vascular lesions, leading to atherosclerosis and then to diseases of the cardiovascular system.[2] Furthermore, researches revealed high consumption of antioxidant substances reduces the risk of developing circulatory system diseases.[8] It would seem crucial to find out whether additions of antioxidant substances to food results in reducing the disadvantageous changes caused by the consumption of oxidized vegetable oils.[9,10] In the food industry, lipid oxidation was inhibited by synthetic antioxidants such as butyl hydroxyanisol, butyl hydroxytoluene, terc butyl hidroxiquinona (TBHQ), and Propyl gallate. The use of those compounds has been questioned in many studies in terms of their safety due to risks of causing heart diseases and carcinogenesis. Thus, in the European continent and other countries such as Japan, Canada, and the United States, the use of certain synthetic antioxidants in foods is not permitted.[11-13]

Since lipid oxidation is a critical factor for food quality and prolonged shelf-life of edible oils, many studies have concentrated on prevention of lipid oxidation by natural antioxidants.[14-16]

It has been established that the oils and extracts from *Cinnamomum zeylanicum* L. (Cinnamon) possess a distinct antioxidant activity, which is especially attributed to the presence of phenolic and polyphenolic substances.[17,18] Barks of *cinnamomum* plants are used as spice and herbal medicine. This plant has been employed as a folk remedy to treat several diseases, disorders and ailments.[18-20] Since long time ago, cinnamon and ginger have been used to treat dyspepsia, gastritis, blood circulation disturbance and inflammatory diseases in many countries.[21] Cinnamon is widely been consumed as spices and food preservation. It is added to food products in the form of essential oils and various extracts.[22] In a study by Mancini-Filho,[23] it was reported cinnamon extracts can be used as food antioxidant together with the improvement of food palatability.

Therefore, this experimental study aimed to assess the effect of cinnamon extract on MDA production rate in two high consumption solid oil (A) and liquid oil (B) in Iranian market.

Materials and Methods

Chemicals and Reagents

2,2'-Azobis (2-amidinopropane) dihydrochloride (AAPH) were obtained from Sigma (Sigma Chemical Co., USA). HCl, n-butanol, pyridine, tween-20, thiobarbituric acid (TBA) were purchased from Merk (Merk Chemical Co., Germany).

Vegetable oils

As illustrated in table 1, it is used vegetable oils. For used oils were selected as "A" and "B". In this study, rate of lipid peroxidation in these oils was investigated.

Plant Material and Preparation of Cinnamon Essential Oil

Bark of cinnamon was purchased from a local herbal grocery from the Isfahan, Iran. The bark was washed thoroughly with distilled water (ddH_2O) to remove the dust or any other extraneous material and was dried in the shade and finely was powdered with an electric grinder.

Prepared powder was subjected to steam distillation for 4 hours using a Clevenger-type apparatus to produce the essential oil. After extraction, the essential oil was separated from water using ethyl ether and was dried with anhydrous sodium sulfate.[24]

Chemical composition of the cinnamon was analyzed by GC-MS on a Finnigan MAT Incos-50 instrument mass selective detector coupled with a Hewlett Packard 6890 gas chromatograph, equipped with a DB-5 fused silica capillary column (25 m × 0.25 mm, film thickness 0.25 µm). The GC operating conditions were as follows: carrier gas, helium with a flow rate of 1.5 mL/min; the oven temperature was programmed 5 min isothermal at 60° C and then from 60°-280° C at 4° C/min; injector and detector temperatures, 280° C; volume injected, 0.1 µL of the oil; split ratio, 1:25. The MS operating parameters were as follows: ionization

Table 1. Specification of the used oils

Oil name	Components and characteristic	
A (solid oil)	Sunflower and soybean	
	Total saturated fatty acid	Max. 30%
	Total unsaturated fatty acid	Min. 70%
	Energy (1 g)	9 Kilocalories
B (liquid oil)	Olive oil	
	Total saturated fatty acid	15%
	Total unsaturated fatty acid	85%
	Energy (1 g)	9.1 Kilocalories

potential, 70 eV; ionization current, 2 A; ion source temperatre, 150° C; resolution, 1000.[25]

Preparation of Cinnamon Essential Oil Stocks

One ml essential oil was used for procurement of 100 ml stock. For preparation of 500, 1000 and 2000 ppm of cinnamon essential oil, and 50 µl of stock was added to 25, 100 and 200 ml ddH_2O, respectively.

Preparation of AAPH Stock and Lipid Peroxidation

0.271 g of AAPH powder were added to ddH2O for preparation of 250 ml AAPH stock in 40 mM concentration and it was maintained at 4-5 °C.

Preparation of Oil Emulsion in Water

50 µl tween 20 was mixed to 0.2 ml (200 µl) oil and 2 ml ddH2O and were mixed by vortexing for 5 minutes. Prepared emulsion was stabled at laboratory temperature for 24 h.[26]

Estimation of MDA in TBA Method

MDA, a lipid peroxidation marker (an end product of lipid peroxidation) was measured by the thiobarbituric acid method. MDA reacted with TBA during lipid peroxidation and yielded a reddish color, which peaked at 532 nm. Color rate indicated MDA concentration.[27]

1 n HCl and 0.67% TBA in a ratio of 1:1 were added to each of oil. The sample was vortexed and heated in a 95° C water bath for 15 minutes. After cooling for 10 minutes, 2 mL of n-butanol-pyridine solution was added. The sample was mixed thoroughly, and centrifuged at 2,000 rpm for 15 minutes. The fluorescence of upper layer was measured by a spectrophotometer at 532 nm.

Identification the Effect of Cinnamon Essential Oil on Lipid Oxidation

200 µl each oil, 50 µl tween 20, 2 ml of 40 Mm AAPH solution were mixed by vortexing. Prepared solution was divided into four glass vials. Respectively, 50 µl of 500, 1000, and 2000 ppm of cinnamon essential oil were added to three of the glass vials separately and one of the glass vials was used as the control. All of the glass vials were incubated at 37° C water bath. Rate of MDA production was measured at the baseline and after the 0.5, 1, 2, 3 and 5 hours. Each experiment was performed in six repetitions.[28,29]

Statistical Analysis

Statistical evaluation was conducted using SPSS for Windows 13.0 (SPSS Inc., Chicago, IL, USA). Kruskal-Wallis test was performed for data analysis. Intergroup comparison difference was evaluated using the Dunn's test. Intra-group comparison was carried out by Friedman test. $P < 0.05$ was considered as statistically significant level.

Results

GC-MS analysis of cinnamon chemical composition is illustrated in table 2. Components are as follows: cinnamaldehyde (96.8%), alpha-capaene (0.2%), alpha-murolene (0.11%), para-methoxy-cinnamaldehyde (0.6%), and delta-cadinen (0.4%).

MDA concentration was measured at the baseline and after the 0.5, 1, 2, 3 and 5 hours. Lipid peroxidation was determined based on rate of MDA production in TBA methods in all the samples by the spectrophotometer.

As can be seen in figure 1, maximum rate of MDA concentration obtained in 5th hours of experiment in oil A. Production significantly ($P < 0.05$) reduced with used concentrations of cinnamon essential oil (500, 1000 and 2000 ppm) as compared to the control group in both oils.

As figure 2 illustrates, impact of various concentrations of cinnamon essential oil on changes of MDA rate in oil B were similar to oil A.

Table 3 illustrates intra-group comparison of cinnamon essential oil effects on MDA production in oils A and B. There was no statistically significant difference between the studied groups (control and three case subgroups).

Table 2. GC-MS analysis of chemical composition of *Cinnamomum zeylanicum L.*

Name of compound	Retention time (min)	Ratio of compound in essential oil (%)
Cinnamaldehyde	15.47	96.80
Alpha-capaene	17.90	0.20
Alpha-murolene	21.68	0.11
Para-methoxycinnamaldehyde	22.72	0.60
Delta-cadinen	22.40	0.40

GC-MS: Gas chromatography-mass spectroscopy

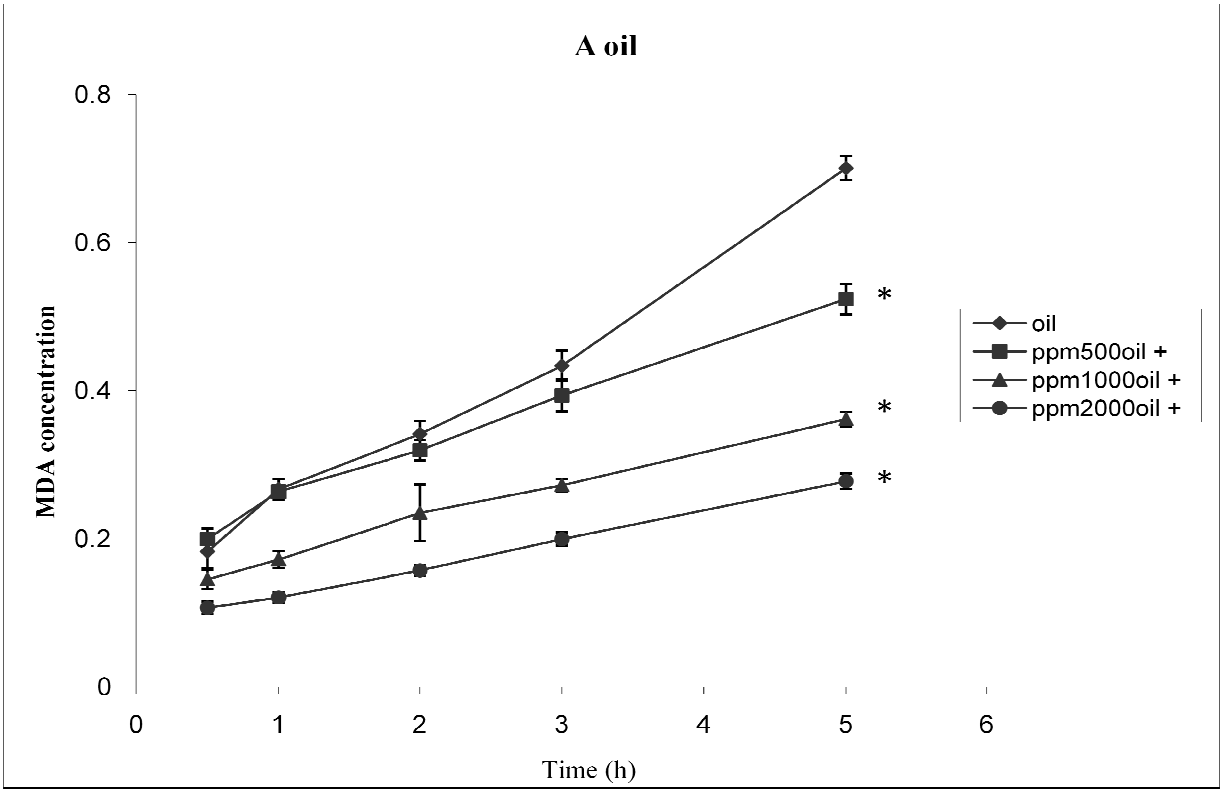

Figure 1. Effect of cinnamon essential oil on malondialdehyde (MDA) production in oil A
*Significant difference between three concentrations of cinnamon essential oil in comparison to the control ($P < 0.05$)

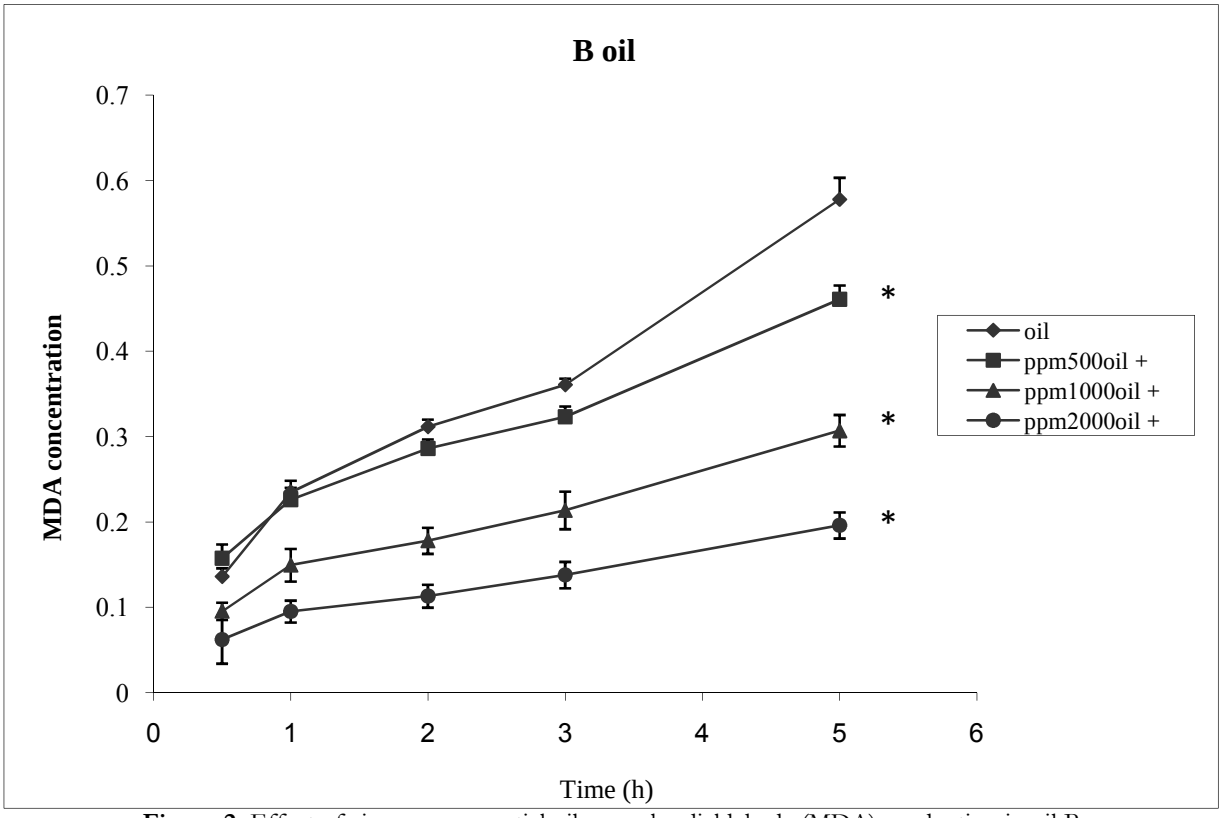

Figure 2. Effect of cinnamon essential oil on malondialdehyde (MDA) production in oil B
*Significant difference between three concentrations of cinnamon essential oil in comparison to the control ($P < 0.05$)

Table 3. Intra-group comparison of cinnamon essential oil effects on malondialdehyde (MDA) production in oils A and B

	Group		Time					P
			0	0.5	1	2	3	5	
Oil A	Control		0.034 (0.030, 0.035)	0.178 (0.164, 0.203)	0.267 (0.252, 0.279)	0.336 (0.326, 0.035)	0.435 (0.418, 0.449)	0.705 (0.684, 0.709)	0.001
	Case (concentration of cinnamon essential oil)	500 ppm	0.085 (0.817, 0.880)	0.199 (0.189, 0.212)	0.262 (0.258, 0.272)	0.318 (0.308, 0.330)	0.394 (0.371, 0.416)	0.522 (0.507, 0.541)	0.001
		1000 ppm	0.062 (0.059, 0.063)	0.145 (0.132, 0.157)	0.172 (0.161, 0.182)	0.229 (0.204, 0.257)	0.273 (0.273, 0.279)	0.364 (0.353, 0.369)	0.001
		2000 ppm	0.050 (0.047, 0.052)	0.105 (0.100, 0.114)	0.119 (0.115, 0.127)	0.161 (0.149, 0.162)	0.196 (0.192, 0.209)	0.276 (0.269, 0.287)	0.001
Oil B	Control		0.065 (0.058, 0.073)	0.133 (0.127, 0.147)	0.237 (0.219, 0.248)	0.313 (0.313, 0.318)	0.361 (0.353, 0.368)	0.579 (0.555, 0.600)	0.001
	Case (concentration of cinnamon essential oil)	500 ppm	0.088 (0.085, 0.092)	0.160 (0.141, 0.168)	0.225 (0.218, 0.237)	0.290 (0.290, 0.294)	0.325 (0.312, 0.333)	0.462 (0.448, 0.475)	0.001
		1000 ppm	0.059 (0.057, 0.063)	0.094 (0.087, 0.104)	0.151 (0.136, 0.163)	0.179 (0.166, 0.190)	0.220 (0.189, 0.230)	0.311 (0.292, 0.319)	0.001
		2000 ppm	0.051 (0.050, 0.053)	0.056 (0.038, 0.093)	0.098 (0.085, 0.103)	0.113 (0.099, 0.126)	0.136 (0.127, 0.152)	0.195 (0.184, 0.207)	0.001

MDA: Malondialdehyde
Data shown based on median (Interquartile range)

Discussion

Studies had demonstrated adverse effect of oxidized dietary fats.[30] Cinnamon is rich in antioxidants. These components are additives that delay the onset of oxidative changes in food.[31] Thus, they contribute to food preservation, prevent changes in flavor, and slow rancidity and discoloration processes.[32]

According to the finding of this study, maximum MDA concentration was obtained in 5th hours and using cinnamon essential oil could be significantly reduced ($P < 0.05$) MDA production and lipid peroxidation.

Cinnamon had strong antioxidant activity.[33] Su et al.[34] stated that 50% acetone extract of cinnamon contained high level of phenolic groups. Scavenging of free radicals is one of the major antioxidation mechanisms to inhibit the chain reaction of lipid peroxidation. Cinnamon essential oil was able to reduce lipid peroxidation in the β-carotene-linoleic acid system.[23] They exhibited a protective capacity against irradiation induced lipid peroxidation in liposomes, and quenched hydroxyl radicals and hydrogen peroxide.[35] Extracts on lard and vegetable oils demonstrated that they could stabilize lard against oxidation and showed antioxidative properties when tested on vegetable oils during storage or frying conditions.[35] Faix et al.[36] revealed, significantly lower lipid peroxidation in plasma and duodenal epithelium of chicks fed the diet supplemented with 0.10% of cinnamon essential oil. Other diets containing 0.05% and 0.025% of essential oil had no effect on lipid peroxidation. In their experiment cinnamon, they had no statistically significant effect on the concentration of MDA in the liver and kidney tissue.[36]

These results suggested that the cinnamon essential oils can be used as a food antioxidant together with the improvement of food palatability. Effect of cinnamon essential oil on MDA production was investigated after the 0, 1, 2, 3 and 5 hours in our study; therefore it seems necessary to study this research in longer intervals. Further studies are needed to identify antioxidant activity of other plants and to investigate effects of synergic association these plants for inhibition of oils lipid peroxidation.

The present study supported that cinnamon extracts supplementation in oils reduce lipid peroxidation. Use of various cinnamon extracts concentrations was lead to determine appropriate concentrations for further studies. However this study was limited in a number of ways which deserve careful attention; first, the time of the study

was short. Second, this experiment can be for more oils in different type such as cooking oils, hydrogenated oils and frying oils and compare MDA formation in these oils in present of cinnamon essential oil.

Conclusion

Findings of the present investigation demonstrated that cinnamon essential oil possesses considerable antioxidant capacity and could readily be implemented as a natural preservative, thus reducing or avoiding losses due to oxidative processes. Thus, it appears that this spice can be used with fresh and heated oils. Further studies will be carried out to determine the types of other oils and other spice or plant rich in antioxidant.

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Conflict of Interests

Authors have no conflict of interests.

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Evaluating the relative frequency and predicting factors of acute renal failure following coronary artery bypass grafting

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Original Article

Abstract

BACKGROUND: Renal dysfunction or acute renal failure in patients undergoing coronary artery bypass grafting (CABG) is an important cause of morbidity and mortality. The great impact of acute renal failure (ARF) in the outcomes of cardiac surgery demands its study in our population, encouraging to the elaboration of this study, which aimed to identify the incidence and risk factors of ARF after CABG.

METHODS: Since March 2010 to 2011, 589 patients were studied who underwent CABG in Sina Hospital (Isfahan, Iran). In this cross-sectional study, patients were divided into two groups based on the occurrence of ARF after CABG and measured variables were compared between the two groups was also statistically significant. P value less than 0.05 was set as a significant level.

RESULTS: A total of 434 men and 155 women were enrolled in the study. The mean age of the study subjects was 57.6 years. ARF was seen in about 22% of patients after CABG. The mean age of ARF group was more than 3 years higher than that in the other group and the difference was significant between the two groups. Serum creatinine level after the surgery was different between the two groups. Moreover, the history of diabetes mellitus was significantly different between the two groups. Pump time comparison also showed was also statistically significant.

CONCLUSION: Our data showed older patients were more prone to affected by ARF. In addition, diabetic patients should be considered as high risk patients and are more likely to deteriorate by ARF. Despite increased prevalence of renal insufficiency in CABG patients, studies show that in most cases, this is not a serious problem and it is easily treatable. A lower proportion of patients (1.0 to 1.7% in different large series) develop ARF severe enough to require dialysis.

Keywords: Coronary Artery Bypass, Acute Kidney Injury, Creatinine

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Introduction

Coronary artery bypass graft (CABG) surgery has been shown to be an effective method for treating angina pectoris and prolonging life in patients with severe coronary artery disease.[1] Each year, 600,000 patients undergo myocardial revascularization with cardiopulmonary bypass and sustain profound physiologic perturbations that precipitate ischemia and infarction in several organ systems.[2] Although the conduct of CABG with cardiopulmonary bypass (CPB) has evolved with continual improvement in morbidity and mortality, cardiopulmonary bypass is known to induce a proinflammatory state with several adverse consequences.[3,4] Clinically, the manifestations of cardiopulmonary bypass associated with morbidity include neurological dysfunction,[5,6] pulmonary dysfunction,[7] renal dysfunction,[8] and possibly infectious-related complications.[9]

Renal dysfunction or acute renal failure in patients undergoing CABG is an important cause of morbidity and mortality.[10] A decrease in cardiac output in the early stage after cardiac surgery is a frequent cause of acute renal failure and a very important risk factor as well.[11] Nonpulsatile blood flow, increased levels of circulating catecholamines and inflammatory mediators, macro embolic and micro embolic insults to kidney, and release of free hemoglobin from traumatized erythrocytes result in numerous pathophysiologic renal responses.[12,13] Many studies have shown that patients who have

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undergone cardiac surgery developed maldistributed renal blood flow, increased renal vascular resistance, and substantive decrease (25% to 75%) in renal blood flow and glomerular filtration rate.[14,15] In a study, the incidence of post-operative renal impairment varied from 3.5% to 31%[16] and the risk of developing a need for dialysis in the post-operative period has varied from 0.5 to 15%.[17-25] The prognosis of ARF in this setting is poor, with mortality rates ranging from 28 to 64%.[18-24] These patients often stayed longer in intensive care units and had higher costs.[2] Survival rate associated with ARF has remained dismal over the past few decades; multiple attempts at therapeutic interventions have failed to demonstrate clear benefits in either amelioration of renal injury or improved survival,[26] possibly because improvements in therapy have been balanced by increasing pre-operative comorbidity.[27] The great impact of ARF in the outcomes of cardiac surgery demand its study in our population, encouraging to the elaboration of this study, which aimed to identify the relative frequency and predicting factors of ARF after myocardial coronary artery bypass surgery.

Materials and Methods

Since March 2010 to 2011, 589 patients were studied who underwent CABG in Sina Hospital in Isfahan, Iran. In this cross-sectional study, patients were divided into two groups based on the occurrence of ARF after CABG and measured variables were compared between the two groups.

The following patients were excluded: Those who had positive history of chronic renal failure (CRF), acute renal failure (ARF), renal stone or serum creatinine > 2.1 mg/dl pre-operatively, patients who had been subjected to off pump CABG or other surgical procedures, those who were receiving renal replacement therapy or who had active endocarditis at the time of operation, patients who required preoperative dialysis, preoperative extracorporeal membrane oxygenation, preoperative tracheostomy or mechanical ventilation, those who underwent procedures for automated implantable cardioverter-defibrillator, left ventricular assist devices or sternal work and finally, patients who passed away within the first 24 hours after the operation (minimum time required for laboratory assessment of renal function).

Acute renal dysfunction was defined based on peak serum creatinine level > 2 mg/dl or more than 2 folds increase in postoperative creatinine level. ARF was defined as deterioration in renal function sufficient to require dialysis within 30 days following surgery. The indications for dialysis included uremia, volume overload or biochemical abnormalities and were measured based on clinical judgment. Creatinine clearance was estimated from serum creatinine, age, weight and gender by the formula of Cockcroft and Gault.

We examined the following variables as possible predictors of ARF: age, gender, body mass index (weight divided by height squared), pre and post operative serum creatinine (mg/dl), pre and post operative hemoglobin, pre and post operative ejection fraction (assessed by preoperative contrast ventriculography, radionucleotide ventriculography or two-dimensional echocardiography), cross-clamp time, CPB time, history of diabetes mellitus (requiring therapy with oral agents or insulin), history of cerebral vascular disease (manifested by previous stroke or transient ischemic attack), history of myocardial infarction (MI which was defined as either a Q-wave or a non-Q-wave infarction. A Q-wave MI was diagnosed centrally by the presence of a new Q wave on each of two postoperative 12-lead electrocardiograms, as defined by Minnesota Code criteria that were scored by a consensus panel of cardiologists. A non-Q-wave myocardial infarction was determined by an elevated creatine kinase-MB level, a new wall-motion abnormality detected by echocardiography or a new perfusion defect on a scintigraphy scan, and history of chronic obstructive pulmonary disease (resulting in functional disability or hospitalization or requiring chronic bronchodilator therapy or $FEV_1 < 75\%$ predicted).

Statistical analyses were carried out with SPSS for Windows 20.0 (SPSS Inc., Chicago, IL, USA), t-test for quantitative variables and chi-square test for qualitative variables were used to find out any association. P value less than 0.05 was set as a significant level.

Results

A total of 434 men and 155 women were enrolled in our study. The mean age of the study subjects was 57.62 years. ARF was observed in about 22% of the patients after CABG. The characteristics of patients with and without postoperative renal dysfunction are listed in table 1.

The mean age of ARF group was more than 3 years higher than that in the other group and the difference was significant between the two groups. About 37.5% patients in non-ARF group and 29% in ARF group were female. The mean changes of serum creatinine level after surgery was statistically

different between the two groups. Moreover, the history of hypertension and the history of diabetes mellitus were significantly different between the two groups. There was a statistically significant difference between the two groups in pump time.

As depicted in table 1, there is no statistically significant association between the gender as well as BMI and occurrence of ARF. Nevertheless, older patients are more prone to affected by ARF. We also compared other cardiac and non-cardiac risk factors between two groups in table 2.

Discussion

Acute renal failure (ARF) is a potential complication of CABG that can arise from a variety of causes including intraoperative hypotension, postoperative cardiac complications that impair renal perfusion, atheroemboli, and exposure to contrast media.[28] One problem with the available data on the incidence of ARF after CABG is the variable definitions used for ARF.[29] The incidence was higher with smaller compared to larger reductions in estimated glomerular filtration rate (e.g. 25% increase in serum creatinine compared to a 100% increase or the requirement for dialysis). In two studies with 843 and 649 patients undergoing cardiac surgery (mostly CABG), the incidence of ARF (defined as a rise in the serum creatinine of only 25%) was 17 and 24%.[30,31]

Other contemporary studies that used a more restrictive definition noted a much lower rate of ARF. The following two studies used the Society of Thoracic Surgeons (STS) definition: either an increase of serum creatinine to > 2 mg/dl (177 μmol/l) with a minimum doubling of the preoperative value, or a new requirement for dialysis. In a review of over 51,000 CABG procedures performed from 1999 to 2002, the incidence of ARF was constant over the four years, ranging from 4 to 5%.[32] In a 2006 data analysis report from the STS, the incidence of ARF was 3.6% after isolated CABG, and 7.5 and 12.9% after CABG combined with aortic or mitral valve replacement, respectively.[16]

Table 1. Baseline characteristics of the patients

Risk Factors		Non-ARF group (n = 458)	ARF group (n = 129)	P
Gender	Female (n)	125	29	ns
	Male (n)	333	100	
Age (mean)		56.90	60.10	0.01
Body mass index (mean)		26.86	27.05	ns

ARF: Acute renal failure; NS: Non significant

Table 2. Compare risk factors between the two groups

Risk Factors		Non-ARF group (n = 458)	ARF group (n = 129)	P
Mean creatinine level (mg/dl)	Preoperative	1.21	1.07	ns
	Postoperative	1.44	2.27	0.001
Postoperative-Preoperative		0.23	1.17	0.020
Mean ejection fraction (%)	Preoperative	49.49	49.29	ns
	Postoperative	47.18	46.18	
Mean cardiac clamp time (minute)		53.77	56.14	ns
Mean pump time (minute)		85.91	91.62	
History of diabetes mellitus	Yes (n)	228	77	0.050
	No (n)	230	52	
History of cerebrovascular accident	Yes (n)	431	126	ns
	No (n)	10	2	
History of MI within recent 30 days	Yes (n)	403	117	ns
	No (n)	42	8	
History of COPD	Yes (n)	19	3	ns
	No (n)	423	123	
Hemoglobin level (g/dl)	Preoperative	14.30	14.32	ns
	Postoperative	10.40	10.48	

ARF: Acute renal failure; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease; NS: Non significant

ARF was observed in about 22% of the patients after CABG in this cross-sectional study. In different studies, the incidence of post-operative renal impairment in cardiac surgery patients varied from 3.5% to 31%.[19] Although, based on the results of the present study, only three important risk factors were associated with the ARF in patients undergoing CABG and no other appreciable differences were found between the two groups (ARF vs. non-ARF), several studies have demonstrated some associations among preoperative, intraoperative and postoperative risk factors with ARF. One important risk factor according to our study was history of hypertension. Cooper et al. also showed that among coronary artery bypass patients, the risk of ARF rose monotonically from 0.6% to 1.6% as preoperative systolic blood pressure rose from < 120 to ≥ 160 mmHg. In addition, they found that body mass index, a measure of obesity, was unrelated to the risk of ARF, similar to our study. In contrast, body surface area, an anthropometric measure estimating overall body size, was inversely correlated with ARF risk.[33] The results of our study also revealed another risk factor that obviously increased the possibility of ARF among patients undergoing CABG and that was history of diabetes mellitus. In the study of Mangano et al. patients, who had previously had a history of type I diabetes mellitus, had a 50% higher risk of postoperative renal dysfunction.[2]

A similar association between ARF requiring dialysis and impaired baseline renal function has been noted in other studies.[17,34] Other important independent risk factors in these reports included New York Heart Association functional class IV valve surgery, peripheral arterial disease, emergency surgery, and the need for preoperative intraaortic balloon pump. These risk factors have permitted the creation of risk scores that can stratify patients into categories of risk ranging from 0.4% to 21.4%.[26]

ARF requiring dialysis has also been associated with increased mortality. In the Veterans Administration study cited above, the 30-day mortality rate in such patients was 63.7% compared to 4.3% in those without ARF requiring dialysis.[34]

It is still controversial whether or not age is important in predisposing to ARF. Although reduced functional capacities of the kidney in the older patients is documented, a number of previous studies failed to demonstrate any statistical association between advanced age and the incidence of renal complications, whereas some others reported it ARF is more likely to develop in older patient.[2] To explain the positive correlation, it has been suggested that older patients may have a reduced ability to cope with a critical circulation or that they more frequently undergo high-risk procedures.[17] In our study, the mean age of ARF patients was higher than that in the other group.

In contrast to our study, other studies demonstrated that factors such as female gender,[26] peripheral artery disease,[19] congestive heart failure (defined by New York Heart Association class III or IV criteria), chronic obstructive pulmonary disease,[26] previous CABG surgery, aortic cross-clamp and total cardiopulmonary bypass lasting at least 2 hours were associated with an increased risk of post-operative renal dysfunction. However, they were not able to reveal low ejection fraction (≤ 0.3) and previous unstable angina as statistically significant risk factors of ARF.[2] In Mangano et al. the use of at least three inotropic drugs was associated with an increased risk of postoperative renal dysfunction. Moreover, the administration of "renal-dose" dopamine did not decrease the likelihood of postoperative renal dysfunction.[2]

This wide variability of the results could be due to different criteria used for diagnosis, the number and characteristics of centers involved in each study, the patients' features, and the size of the sample which hinders data comparison among the several performed studies.[19] Furthermore, the definition chosen for renal dysfunction was arbitrary in each study so the reported incidence of renal dysfunction after cardiac surgery was significantly influenced by the definition used in a given study.[2] We defined postoperative renal dysfunction on the basis of an absolute creatinine value (≥ 2 mg/dl) coupled with a relative change in creatinine level (≥ 2 folds) between the preoperative and the postoperative period. This study showed that the mean changes of creatinine level after surgery could be associated with ARF.

Our study had the limitation of choosing patients from a single center. Therefore, the generalizability of the findings is limited. The model needs to be tested broadly at multiple centers and to be well represented by differences in gender, race, and other risk factors to substantiate its applicability to our society.[26]

Despite the increased prevalence of ARF in the CABG patients, studies showed that in most cases, this is not a serious problem and it is easily treatable. A lower proportion of patients (1.0 to 1.7% in different large series) develops ARF severe enough to require dialysis.[2,35]

Conclusion

Our data showed older patients were more prone to affected by acute renal failure. Diabetic patients should be considered as high risk patients and are more likely to deteriorate by ARF.

Suggestions

1. Performing studies similar this study with larger sample size
2. Sharing our results to other cardiac surgeon for better management
3. And design studies with longer follow-up

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Conflict of Interests

Authors have no conflict of interests.

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A retrospective cohort study on factors associated blood pressure using multilevel modeling

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Original Article

Abstract

BACKGROUND: Hypertension is a health problem in Iran. Given the importance of this subject, we reviewed the factors affecting the blood pressure in this survey.

METHODS: This retrospective cohort study was performed on 3961 male workers employed at Isfahan Polyacryl Corporation (Iran) in health and safety executive between 1996 until 2008. In this study, systolic and diastolic blood pressure (SBP and DBP) were considered as dependent variables; body mass index (BMI), age, type of job, marital status, shift work and educational level were considered as independent variables. MLwiN programmer version 2.1 was used to analyze the data.

RESULTS: BMI, age, shift work, marital status and educational level had statistical significant association with DBP. The result for SBP was similar to DBP except shift work and educational level that had no statistically significant association.

CONCLUSION: The results can be considered in the industry to provide practical solutions to reduce blood pressure.

Keywords: Blood Pressure, Cohort Study, Retrospective Study, Risk Factor, Multilevel Anal

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Introduction

High blood pressure (BP) is a major health issue in both developing and developed countries. It is asymptomatic, common and easily preventable, but despite advances in medical sciences, its hazardous mechanism is still unknown.[1] If untreated, this chronic disease may result in fatal complications.

High blood pressure can lead to hypertension, which is a major risk factor for overall mortality on the global scale.[2] About 1 of 3 United States (US) adults, estimated as 68 million, have high blood pressure,[3] which increases the risk for heart disease and stroke, leading causes of death in the US.[4]

The overall prevalence of hypertension is 17.8% in Iran[5] and its prevalence in the age group of 30-55 years and more than 55 years is 23% and 50%, respectively.[6]

If hypertension is not treated, 50% of the patients will die from coronary artery disease (the most common cause of death in the US) and congestive heart failure, 33% will die from stroke (the third cause of death), and 10-15% will suffer renal complications. Moreover, other organs such as the eye and large vessels are affected by high blood pressure.[7-9]

Hypertension can augment the devastating effect of other cardiovascular risk factors like dyslipidemia, smoking, diabetes and obesity.[10]

According to recent studies, treating hypertension reduces the complications of both types of diabetes. For example, according to an epidemiological study on diabetes, each 10 mmHg decrease in mean arterial pressure reduces diabetic complications by 12%, diabetes-related mortality by 15% and diabetic microvascular complications by 13%.[11] It should also be noted that hypertension accelerates atherosclerosis, leading to its 2- to 3-fold increase.[5]

Studies have showed the association of various

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factors like obesity,[12-14] age,[15] gender,[14,16-18] marital status,[19] quality of married life,[20-22] smoking and being exposed to cigarette smoke,[18-19] loud noise at the work place,[23] workload,[24] stress,[25-26] diet and physical activity,[27] and shift work,[28] with blood pressure.

Considering the importance of blood pressure in health assessment and since the impact of risk factors for high blood pressure may be different in each condition, especially in industrial areas, this survey aimed to longitudinally study of the factors associated with blood pressure using multilevel modeling.

Materials and Methods

This retrospective cohort study was conducted on all male employed workers of Isfahan Polyacryl Corporation (IPC) located in Isfahan, Iran, between 1996 and 2008. A total of 3961 workers participated in this study and 12,986 records of data were derived from their medical records with average reputation of 6 and mean interval of 2 years using the census method.

Study admission criteria included being male and permanent employee with at least 2 years of work experience. Retired employees and those who died during the follow-up period were excluded.

Since workers were legally obligated to attend annual medical examinations, no obligations were implemented by the researchers. Moreover, no incentive or punishment was considered for participation or non-participation. All the participants joined the study willingly and their information kept confidential. In the end, Medical Ethics Committee of Tarbiat Modares University of Medical School approved the study (code number: 5271065).

The blood pressure of both arms was measured in the sitting position after 5 minutes rest, using a calibrated mercury sphygmomanometer. Furthermore, weight and height were measured by a physician using calibrated equipment. Body mass index (BMI) calculated by this formula:

BMI = Weight (kilograms)/[Height (meter)]2

Workers and staffs engaged in three groups: routine rotating shift, weekly rotating shift and day workers. The routine rotating and weekly rotating shifts were scheduled with clockwise rotation plan "2 morning shifts, 2 evening shifts, 2 night shifts and 2 days off" and "3 morning shifts, 3 evening shifts, and 1 day off every two weeks, Fridays always off", respectively.

The morning, evening, and night shifts began at 7 a.m., 3 p.m., and 11 p.m., respectively. Day workers worked from 7 a.m. to 3 p.m. on weekdays, Thursdays and Fridays off.

As we had an extra source of sample dependency, which was related to laborers work area in addition to subject repetition, repeated measure analysis was not able to analyze such data and we had to use multilevel modeling. In this context, regarding the definition of level, in multilevel modeling, repeated measures at different times for each individual was considered as level 1 and each individual was considered as level 2. In addition, belonging of each individual to the aggregate/contextual units (such as work place, factory parts, region and so on) could be considered as the level 3.[29]

Let the random variable Y_{ijk} denote the systolic blood pressure (SBP) or diastolic blood pressure (DBP) measurement at the i^{th} examination for the j^{th} individual in work area k. We then assume that Y_{ijk} satisfies the following general multilevel model:

$Y_{ijk}= \beta_{0+} \beta_1 Age_{ijk} + \beta_2 BMI_{ijk} + \beta_3 Education_{ijk} + \beta_4$ Shift Work $_{ijk} + \beta_5$ Job $Type_{ijk} + \beta_6 Marriage_{ijk} + v_k + u_{jk} + \varepsilon_{ijk}$

where $\varepsilon_{ijk} \sim N(0, \sigma_e^2)$, $u_{jk} \sim N(0, \sigma_u^2)$, $v_k \sim N(0, \sigma_v^2)$ and k = 1..76, j = 1..3961 and I = 1,2,.., n_{ij} (in average $n_{ij}=7$)

$N(\mu, \sigma^2)$ is symbol of normal distribution with mean μ and variance σ^2.

Multilevel models were fitted using MLwiN version 2.1. Parameter estimates were obtained by restricted maximum likelihood estimation (REML). An F-statistic was used to test the significance of the fixed effects with number of degrees of freedom computed using the containment method. The likelihood ratio statistic based on REML likelihoods was used to test the significance of the random effects. The Inter-Class Correlation (ICC) was used to test the proportion of total variance (i.e., cluster plus individual variance) that was attributed to the cluster level. Normality of two latent random effect (v and u) and error term (e) tested using Kolmogorov-Smirnov test (KS-test). Also, the probability value of 0.05 or less ($P \leq 0.05$) was set to know the significance level.

Results

From 1996 to 2008, 3961 male workers who worked at 76 work places underwent the annual health examination. Table 1 represents the frequency distribution of baseline characteristics of the participants at their first health examination. According to this table, most subjects were married, aged over 40 years, had lower than diploma education and were day workers and blue-collar

workers. The percentage of overweight, high DBP and SBP were 49.8%, 2.7% and 4%, respectively.

Table 2 and table 3 show the summary of beta, their standard errors and statistical significance using multilevel modeling for the relationship between predictor variables on SBP and DBP, respectively. According to the results, BMI, age, marital status, shift work and education level had statistical relationship with DBP.

The result for SBP was similar to DBP, except shift work that had no statistical relationship.

In addition, significant parameter of variance model (σ_v^2, σ_u^2) showed that multilevel molding was a convenient model. The ICC was calculated to be 38% and 48% for DBP and SBP, respectively. These percentages represented the proportion of total variance (i.e., cluster plus individual variance) that was attributed to the cluster level observations share. Also, KS-test showed the normality of the two latent random effect of u (P = 0.12), v (P = 0.09) and error term (e) (P = 0.07).

Discussion

Since hypertension is a chronic disease that imposes heavy treatment and care costs,[7] this study was performed to investigate the factors associated with blood pressure.

In this study, the BMI showed a positive relationship with systolic and diastolic blood pressure, indicating that obesity causes systolic and diastolic hypertension. The direction and significance of this relationship were congruent with the findings of previous studies. The direct correlation between obesity and blood pressure has been confirmed in several studies.[12-14] In our study, each 1-unit increase in BMI elevated systolic and diastolic blood pressure by 0.72 and 0.55 mmHg, respectively.

Age also had a direct association with systolic and diastolic blood pressure. Each one-year increase in age elevated systolic and diastolic blood pressure by 0.40 and 0.47 mmHg, respectively. Several cohort and cross sectional studies have confirmed the direct relationship between blood pressure increase and aging in different societies.[15,30]

We found a significant relationship between shift work and diastolic blood pressure; however, no relationship was observed between shift work and systolic blood pressure. In DBP, the results showed a difference in blood pressure between day workers and routine rotating shift workers. Diastolic blood pressure was lower by 0.76 mmHg in routine rotating shift workers when compared to day workers. This finding was similar to some reports[31-32] but incongruent with some others.[33-35]

Table 1. Frequency distribution of baseline characteristics in workers at their first health examination

Variable	Level	n	%
Age (year)	< 25	606	15.3
	25-40	2270	57.3
	40 >	1085	27.4
Marriage	Married	3145	79.4
	Single	816	20.6
Education	Lower Diploma	1588	40.1
	Diploma	1410	35.6
	Associated degree	495	12.5
	Bachelor's degree or upper	467	11.8
Shift work	Weekly rotating shift workers	301	7.6
	Routine rotating shift workers	1731	43.7
	Day workers	1933	48.8
Type of job	Blue-collar workers*	3680	92.9
	White-collar workers**	281	7.1
BMI (kg/m^2)	< 25	1988	50.2
	≥ 25	1973	49.8
DBP (mmHg)	< 90	3854	97.3
	≥ 90	107	2.7
SBP (mmHg)	< 140	3803	96
	≥ 140	158	4

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index

* Person who performs manual labor

** Person who performs works in an office environment and may involve sitting at a computer or desk

Table 2. Multilevel regression results for assessing the effect of predictor variables on systolic blood pressure

Variables	Beta	Se	95% CI		P
			Lower	Upper	
Age (year)	0.40	0.02	0.36	0.44	< 0.001
BMI (kg/m^2)	0.72	0.04	0.64	0.80	< 0.001
Education					< 0.001
Lower diploma	1.94	0.61	0.74	3.14	< 0.001
Diploma	1.95	0.60	0.77	3.13	0.001
Associated degree	2.51	0.74	1.06	3.96	0.001
License or upper	Reference category				
Shift work					0.586
Weekly rotating shift workers	0.42	0.66	-0.87	1.71	0.262
Routine rotating shift workers	0.37	0.39	-0.39	1.13	0.171
Day workers	Reference category				
Type of job					
Blue-collar worker	-1.19	0.73	-2.60	0.22	0.05
White-collar worker	Reference category				
Marriage					
Married	5.55	0.56	4.45	6.65	< 0.001
Single	Reference category				

BMI: Body mass index; Df: Degree of freedom

σ_e^2 = 86.24; σ_u^2 = 77.62; σ_v^2 = 2.40; Intra-class correlation coefficient (ICC) = 48 %

Table 3. Multilevel regression results for assessing the effect of predictor variables on diastolic blood pressure

Variables	Beta	Se	95% CI		P
			Lower	Upper	
Age (year)	0.47	0.01	0.45	0.49	< 0.001
BMI (kg/m^2)	0.55	0.03	0.49	0.61	< 0.001
Education					0.002
Lower diploma	-0.56	0.44	-1.42	0.30	0.102
Diploma	0.39	0.43	-0.45	1.23	0.182
Associated degree	1.13	0.54	0.07	2.19	0.018
License or upper	Reference category				
Shift work					0.026
Weekly rotating shift workers	-0.45	0.47	-1.37	0.47	0.169
Routine rotating shift workers	-0.76	0.28	-1.31	-0.21	0.003
Day workers	Reference category				
Type of job					
Blue-collar worker	-1.01	0.63	-2.24	0.22	0.054
White-collar worker	Reference category				
Marriage					
Married	5.68	0.41	4.88	6.49	< 0.001
Single	Reference category				

BMI: Body Mass Index; Df: Degree of Freedom

σ_e^2 = 60.27; σ_u^2 = 32.89; σ_v^2 = 4.24; Intra-class correlation coefficient (ICC) = 38%

However, it should be mentioned that since the effect of shift work on individuals generally depends on the occupation, personal characteristics, workplace environment and specifications of the shift work,[36,37] this relationship could be due to other reasons such as the variability of the work time, more income, better rest and especially more thinness of the shift workers as compared to day workers.

In our study, being married was showed statistical relationship with systolic and diastolic blood pressure. Married participates had lower blood pressure compared with single participates. This difference was 5.55 mmHg for systolic and 5.68 mmHg for diastolic blood pressure. This may be because of the quality of married-life. Holt-Lunstad et al. reported that marriage itself did not affect blood pressure and stated that the quality of married-life and couple's satisfaction was effective in lowering blood pressure in married individuals.[20] Moreover, Lipowicz et al. found that men who were never married had higher levels of blood pressure when compared to married men. They used psychological indices (more stress and less social support), nutritional status, and economic situations of living a single life to justify this finding.[19]

Our findings showed no relationship between the type of job and diastolic and systolic blood pressure. Education also showed a significant relationship with systolic and diastolic blood pressure.

We found that individuals with higher levels of education had higher levels of DBP and SBP, which could be due to more responsibility and special managerial risks in people with higher education; this relationship is not supported in SBP.

At the end, some of the advantages of this study are its longitudinal design, using multilevel modeling for fitness, adequate sample size and homogeneity of the study population, calculation of BMI and blood pressure indices in the clinic using height and weight and measurement of blood pressure by experts. However, lack of access to the family history of hypertension in close relatives, inability to evaluate the amount of rest and sleep, income, stress, job satisfaction, and smoking habit as confounding factors.

Conclusion

The results of this study demonstrated obesity as a risk factor for high blood pressure. So, an appropriate approach to decrease obesity, as a risk factor of hypertension, is to use incentive policies such as encouraging the staff to use low-fat vegetable-rich diets and increase their physical activity.

Furthermore, considering the effect of marriage on blood pressure, counseling sessions are recommended for married couples in order to enhance the quality of married life. Such counseling sessions can also be held before marriage to help individuals make correct decisions regarding their future life. Moreover, supporting single individuals financially is effective in lowering blood pressure.

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Conflict of Interests

Authors have no conflict of interests.

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Aortic valve streptococcus group B endocarditis post-extracorporeal shock wave lithotripsy

Mohsen Meidani[(1)], Mahboobeh Taghavi[(2)], Morteza Abdar Esfahani[(3)]

Case Report

Abstract

BACKGROUND: Sub-acute left-sided bacterial endocarditis is a serious condition that may present with variable clinical manifestations. Its symptoms include both sterile and infected emboli, and various immunological phenomena.

CASE REPORT: This report presents a 55 year old man with frequency and dysuria after a lithotripsy and several admissions with urosepsis. Due to the suspicion of infective endocarditis echocardiography was done which confirmed streptococcus group B endocarditis.

CONCLUSION: Streptococci group B is one of the rare causes of infective endocarditis, but it was observed after various producers such as lithotripsy.

Keywords: Group B Streptococci, Infective Endocarditis, Lithotripsy

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Introduction

Infective endocarditis is a cardinal disease that can appear in acute and sub-acute pattern. The acute form of this disease is typically caused by staphylococcus aureus and can disturb the valve from a few days to weeks. Moreover, the disease can progress in just a few days. Sub-acute infective endocarditis is usually caused by viridans streptococci, enterococci, coagulase-negative staphylococci, and gram-negative coccobacilli during days to weeks and has less toxin signs.[1] The prevalence of infective endocarditis remained almost constant from 1970 to 2000 and is about 3.6 to 7 cases per 100000 in a year.[1] Some risk factors that can increase infective endocarditis prevalence are rheumatic heart disease, congenital heart disease, IV drug use, cardiac internal devices, and generative diseases.[1] Today, in the general population the most common organisms of native valve endocarditis are staphylococcus aureus and streptococci group B is one of the most rare causes of infective endocarditis.[1,2]

Case Report

A 55 year old man referred with the chief complaint of frequency and dysuria, and urinary tract infection. Examination of the patient showed 4 to 6 mm renal stones in right kidney, 3 small stones in the left kidney, and also a cortical cyst with 5*6 mm width in the right kidney. Extracorporeal shock wave lithotripsy was done for him and fever progress was observed for 4 days. He was treated with ceftriaxone and his general condition improved slightly, but his fever persisted. Kidney sonography was repeated and showed small 3-4 mm stones in both kidneys without abscess and hydronephrosis. Because of continuing fever and hematuria, with urosepsis diagnosis the patient was admitted and started on antibiotics that contain gentamicin, ciprofloxacin and ceftriaxone, but he was referred to our center because he did not respond to treatment. On admission physical examination was normal except temperature = 39.7 °C, HR = 90 min, RR = 26 min, Bp = 135/80 mmHg. Hemodynamic pattern and ECG were normal. Fever workup was done for him. Blood culture was positive for streptococci group B in first and third days after admission. Hematologic and serum chemical laboratory data are shown in table 1.

Although cardiac examination was normal, due to continuing fever and bacteremia echocardiography was done to find the source of infection of urinary system and bacteremia. Echocardiography showed normal ejection fraction

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(60%), mild AI, and vegetation on aortic valve (Figure 1). Antibiotic therapy was started and continued for 4 weeks.

Figure 1. Parasternal long axis view showing vegetation on noncoronary cusp

At the end of the course of medical therapy the patient was well and had shown a good response to antibiotic therapy, and thus did not need cardiac surgery. The patient was discharged when blood culture was negative and the level of ESR was decreased. In 2 years follow-up, he was well without any complications.

Discussion

Streptococci group B is a rare cause of infective endocarditis.[2] However, it involves both normal valves and abnormal valves and is one of the causes leading to high prevalence of embolic morbid native valve endocarditis.[1] Streptococci group B is common in pregnancy, and is one of the causes of neonatal sepsis.[3] It was observed in a few reports about streptococci group B infective endocarditis that in renal transplant patients and submandibular cellulitis the signs of infective endocarditis usually coexist with under lying diseases.[4-6] According to previous research a rare case of infective endocarditis was reported after extracorporeal shock wave lithotripsy and this case had valvular disease.[7]

Our case is one of the very rare presentations of infective endocarditis of streptococci group B that occure after extracorporeal shock wave lithotripsy. The patient after lithotripsy was febrile which continued after antibiotic therapy with urosepsis diagnosis. In order to stop the fever and due to lack of response to antibiotic therapy, although the patient had native valve without any history of cardiac disease, the advanced workup was started. The vegetation on aortic valve was seen in echocardiography.

Conclusion

Although streptococci group B is one of the rare causes of infective endocarditis, it is seen after various procedures such as lithotripsy. Streptococci group B infective endocarditis must be considered in patients who are exposed to lithotripsy and unknown origin of sepsis.

Conflict of Interests

Authors have no conflict of interests.

Table 1. Hematologic and serum chemical laboratory data

Variables	Other hospital	This hospital
Hematocrit (%)	30.3	32.7
Hemoglobin (g/dl)	9.7	11.3
White blood cell count (per mm3)	6000	7000
Differential count (%)		
Neutrophils	66	82.3
Lymphocytes	32	12.3
Eosinophils	2	3.4
Basophils		2
Platelet count (per mm3)	173000	195000
Mean corpuscular volume (m3)	82.6	83
Erythrocyte sedimentation rate (mm/hr)	80	121
Prothrombin time (sec)	15	16
International normalized ratio	1.2	1.3
Sodium (mmol/liter)	126	131
Potassium (mmol/liter)	4.1	3.8
Glucose (mg/dl)	86	90
C-reactive protein	+	++

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A rare anomalous origin of left subclavian artery from the circle of Willis in combination with right sided aortic arch: A case report

Alireza Ahmadi[(1)], Seyed Ali Sonbolestan[(2)]

Case Report

Abstract

BACKGROUND: One of the rare aortic congenital abnormalities is right sided aortic arch which is occurred in approximately 0.1% of the population. The anomalous origin of the subclavian arteries has also been reported.

CASE REPORT: In this study, a case of a right-sided aortic arch with anomalous left subclavian artery origin from the cerebral arteries is presented which was diagnosed in Computed tomography angiogram (CT angiogram) and angiography of a 10-year-old boy referred due to recurrent chest pains during two weeks before admission and pulselessness of his left upper limb and left carotid artery.

CONCLUSION: Many of the congenital vascular anomalies may have no obvious signs or symptoms and therefore the exact history and physical examination could help us in better diagnosis. Besides, some of these anomalies are associated with other abnormalities of other body organs particularly the cardiac system.

Keywords: Congenital Anomaly, Great Arteries, Pediatric

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Introduction

Congenital abnormalities of the aortic arch are sometimes diagnosed in imaging. These abnormalities usually are recognized by accident during imaging for other purposes but it is very important to differentiate the life threatening forms from the other ones.[1] A right sided aortic arch could be diagnosed in about 0.1% of general population and about 50% of these have an aberrant left subclavian artery.[2,3] The aberrant left subclavian artery may happen without any concurrent anomaly however it is the most frequent anomaly which is associated with a right aortic arch.[4,5]

In this study, a case of a right-sided aortic arch with anomalous left subclavian artery origin from cerebral arteries is presented which was diagnosed in computed tomography angiogram (CT angiogram) and angiography of a 10-year-old boy who referred due to recurrent chest pains during two weeks before admission and had pulselessness on left carotid and left upper limb arteries.

Case Report

A 10-year-old boy referred to the pediatric cardiology clinic of Chamran Hospital, Isfahan University of Medical Sciences, Isfahan, Iran on 1-May-2012 with a chief complaint of recurrent chest pain from two weeks ago. He had an atypical chest pain in the 4th and 5th left intercostals areas without any radiation which lasted for several minutes. He had no other symptoms though.

In physical examination, the pulses of left upper limb and left carotid artery were not detected; however, the other pulses were normal. He had no cyanosis or clubbing in his extremities. In heart auscultation, the S1 and S2 sounds were normal and a grade I-II/VI systolic ejection-type murmur was heard on the left sternal border. The other examinations were normal.

No abnormal findings were revealed in electrocardiography.

The cardiothoracic ratio was in upper normal range and the pulmonary vascular markings were normal in chest X-ray (CXR). The right sided aortic arch was observed in figure 1.

The main abnormal findings in echocardiography included mild mitral valve prolapse (MVP) and tricuspid regurgitation (TR) with a pressure gradient of 25 mmHg. Besides, the

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right sided aortic arch was observed.

In CT angiogram, the left carotid artery was significantly narrower than the right one which seemed to be dilated for enough cerebral circulation. Moreover, as a rare anomalous finding, the left subclavian artery aroused from this narrow carotid artery and the left vertebral artery originated from this subclavian artery (Figures 2.A and 2.B).

Figure 1. The patient's chest X-ray

Thereafter, the patient underwent the left heart catheterization. The arterial catheter passed from the femoral artery into descending aorta (DAO), ascending aorta (AAO), and left ventricle (LV), respectively. It entered into the right and left coronary arteries (RCA and LCA) normally.

Systemic sample was saturated. In addition, it entered into the right subclavian and right carotid arteries, but it could not enter into the left brachiocephalic artery.

LV, coronary arteries and aortic root injections revealed no pathologic findings. The right sided aortic arch was observed again. Aortic arch injection in the right anterior oblique view showed normal right subclavian and right carotid arteries and also showed with no connection of the left subclavian artery to the aortic arch.

Selective right carotid artery injection showed opacified left subclavian artery. The left subclavian and left vertebral arteries supplied from the circle of Willis (right vertebral artery). Selective right subclavian artery showed no anomaly (Figures 3.A, 3.B, and 3.C).

Following the whole procedures**,** the patient was discharged and was advised to refer periodically for clinical follow-up.

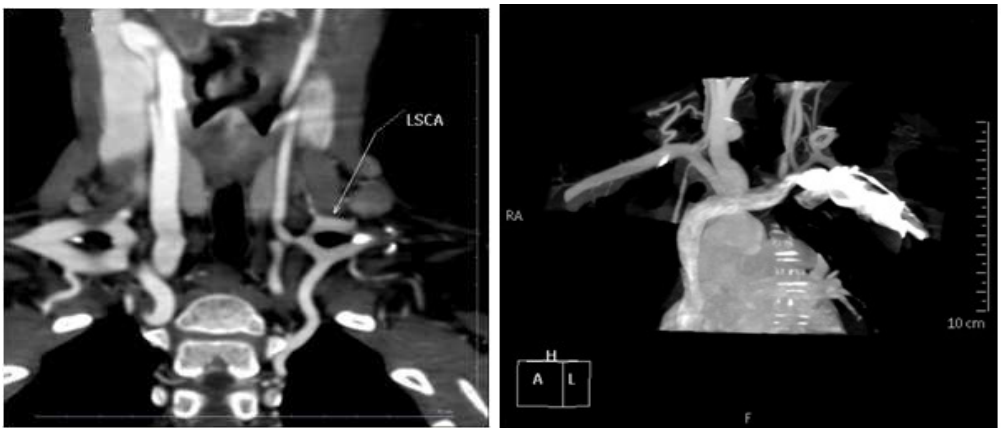

Figure 2. Patient's CT angiogram; (A, left image,) and (B, right image); (A) left carotid artery was significantly narrower than the right one; (B) the left subclavian artery aroused from this narrow carotid artery

Figure 3. The catheterization findings of the patient; (A, left image), (B, middle image), and (C, right image)

Discussion

In this rare case, a child was presented who had no signs and symptoms except an atypical chest pain and the pulselessness of his left upper limb and left carotid arteries, and finally was diagnosed as the right sided aortic arch with isolated left brachiocephalic artery.

The right sided aortic arch is an anomaly which is seen in different types. One of them is its association with an isolated left subclavian artery. In this rare anomaly, the left subclavian artery does not originate from the aortic arch but it is connected to the left vertebral artery and therefore the circle of Willis provides its blood flow and it may cause subclavian steal syndrome in some cases.[6]

According to the embryologic bases, the left subclavian and the left carotid arteries are derived from the left seventh inter segmental artery and the left third aortic arch, respectively.[7] Besides, the right sided aortic arch is the consequence of a breakage in the left fourth arch of primal vascular ring and the isolated subclavian artery is the result of breakage in two places of the left fourth arch.

Due to the amplified blood flow of the vertebral artery in an inverted direction, in this anomaly some degrees of ischemia may happen in vertebrobasilar territory and this ischemia may cause some abnormalities during the fetal development.[8]

On the other hand, increased upper limb activity may result in reduction of cerebral blood flow and cause some steal syndrome symptoms.

In another study, this anomaly was observed in association with patent ductus arteriosus (PDA) and ventricular septal defect (VSD)[6] which were not detected in our patient. In different studies, it was mentioned that it is very rare to have a right sided aortic arch without any concurrent congenital heart anomaly.[9,10]

In this study, the echocardiography, CT angiography and catheterization were used for the diagnosis. One of the other suitable procedures in patients like this is Doppler ultrasound which could show the flow in neck or cranial arteries. Furthermore, findings of CT scan and magnetic resonance imaging (MRI) can show the effects of this anomaly on the brain tissue per se.

In conclusion, many of the congenital vascular anomalies may have no obvious signs or symptoms and therefore -particularly in the field of pediatrics- the exact history and physical examination could help us in better and faster diagnosis. Besides, some of these anomalies are associated with other abnormalities of other body organs particularly the cardiac system. Imaging modalities can be used in these diagnoses.

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

Conflict of Interests

Authors have no conflict of interests.

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Suggested indications of clinical practice guideline for stem cell-therapy in cardiovascular diseases: A stepwise appropriate use criteria for regeneration therapy

Mohaddeseh Behjati[1]

Short Communication

Abstract

Despite astonishing progress concerning cardiovascular diseases, patients are still suffering from complications of acute insults. Due to reverse remodeling and improper myocyte rebuilding, heart failure has become a common problem these days which needs more powerful myocardial reconstructing strategies. Indeed, no option cases afflicted with non-healing peripheral vascular diseases; refractory stable and unstable angina is the other field with paucity of proper treatments. For these cases, stem cell-based therapies became optimistic treatment, but lack of guideline-based indications regarding stem-cell is still a major problem which limits application of these cells for such end-stage cases. Here, an outline of appropriateness criteria for stem cell-based therapy is suggested.

Keywords: Appropriate Use Criteria, Clinical Practice Guideline, Cardiovascular Diseases, Stem Cells

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Introduction

Despite the astonishing progress made in interventional cardiology, cases are still suffering from complications of acute events. Conflicted cases are most often survived from acute insults but deleterious effects of negative remodeling on future outcomes of patients are devastating. Unfortunately in some instances, the vicious cycle of progressive compensatory remodeling cannot be broken by reperfusion strategies and patients ultimately manifest signs and symptoms of poor ventricular function. Thus, myocyte rebuilding and vascular rebuilding seem to be necessarily adjoined.

The field of stem cell therapy for myocardial regeneration began to expand gradually. Since now, several clinical trials of cell transplantation in the setting of acute myocardial infarction (AMI) have been performed. Various stem-cell types and delivery roots have been examined for better efficacy with the goal of perseveration of left ventricular pump function and prevention of developing heart failure. In the case of neglected cell salvage in acute setting, recovery of the failing heart is essential. Much work is needed to be done by stem-cells to re-establish dead myocytes surrounded by fibrous tissue. Stem-cells opened new horizons in the treatment of patients with heart failure irrespective of the etiology. Cellular therapeutic options are also applied for the treatment of refractory angina pectoris. As a matter of fact, stem-cells with high differentiation capacity have the potential to be used for different clinical scenarios, in which peripheral vascular diseases are not exclusion. Disorders related to vascular insufficiency as chronic non-healing wounds have been shown to be improved using cell-based approaches as well.

Despite proved efficacy and safety of cell-based interventions, lack of specific guidelines limit their broad applications especially in acute setting. Indeed, some might not be familiar with the concept of cell-based therapies for acute situations and keep this option just for chronic end-stage cases. Additionally, cellular approaches contain a broad category as pure or modified stem-cells or recruitment and mobilization of stem-cells using chemotactic agents.[1,2] The paucity of constructed guidelines for cell-based approaches in the field of cardiovascular diseases partly backs to ethical issues. Go with guideline (GWG) approaches are not yet paid attention for cell strategies as for other state-of-art medical managements. In any case, availability of guidelines makes both physician and patients confident about the accuracy of the decisions.[3]

Currently, appropriate use criteria (AUC) are generated and updated for various cardiovascular

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diagnostic and therapeutic tests under support of several professional organizations. AUC includes three categories as "appropriate" (acceptable and reasonable), "uncertain" (generally acceptable and may be reasonable) or "inappropriate" (acceptable and is not reasonable).[4] In order to shed more lights on cellular strategies, the need for development of a unified guideline is obvious.

To scheme such an outline published randomized clinical trials (RCTs), non-RCTs and case series articles have been selected and their inclusive, non-inclusive and exclusive criteria have been evaluated. All criteria have been collected and this scheme was approached.

Discussion

An outline of AUC-based indications, uncertainties and contraindications of cell-based interventions for cardiovascular diseases is presented in table 1. However, it is just a scheme and its development needs a technical panel of physicians to review and score vast of clinical scenarios as how likely it would improve outcomes or survival of a patient. This proposed scheme is based on current understanding of technical capabilities and potential benefits of this treatment. Proposed panelist team to give the rate of indications should include interventional cardiologists, non-interventional cardiologists, cardiovascular surgeons, health outcomes researchers, medical officers from a health plan, basic researchers expert in the field of stem cell-based therapies and members of data and safety monitoring board (DSMB). Certainly, these shared evidence-based tips are not intended to replace clinical experience and judgment.

Table 1. A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases

General cardiovascular conditions	AUC category
Age range (18-65 y)	A
Application of good manufacturing practice (GMP) and assessment of cell viability and product sterility	A
Lactating women, pregnant females, women planning to become pregnant or unwanted pregnancy to use appropriate birth control strategies [Intra uterine device (IUD), the pill and etc.] before and two months after cell based treatments	I
Uncorrected anemia (Hb < 8.5 mg/dl)	I
Thrombocytopenia (< 100,000/µl) or platelet counts < 10% above the upper limit of normal (ULN)	I
White blood cell (WBC) count < 2.5 /ul	I
Liver disease [liver enzymes > 2x norm or International normalized ratio (INR) > 1.5]	I
Active infection manifested by fever, WBC > 15000 or < 4000	I
Severe renal failure (serum Cr > 150-250 mmol/l) or hemodialysis	I
Severe chronic obstructive pulmonary disease under continuous use of bronchodilators or steroids	I
Serious co-morbidities with life expectancy < 1 year	I
Patients with poor compliance (unlikely follow-up)	I
Chronic inflammatory diseases	I
Known active or chronic infectious disease [Acquired immunodeficiency syndrome (AIDS), Hepatitis C virus (HCV), Hepatitis B virus (HBV), Treponema pallidum, Cytomegalovirus infection, etc.]	I
Primary bone marrow diseases	I
Patient is unwilling about the performance of cell-based strategies	I
Persistent cardiogenic shock after 72 hours	I
Significant valve disease [Aortic stenosis (AS) with Left ventricle/Aortic valve (LV/AO) gradient < 1.5 cm 3, severe mitral or aortic stenosis and/or mitral regurgitation greater than moderate]	I
Any severe concurrent medical problem as sepsis	I
Acute myocarditis	I
Coagulopathy or bleeding disorders	I
Poorly controlled insulin-dependent diabetes (HbA1C > 7 or presence of proliferative retinopathy)	I
Alcohol consumption and substance abuse	I
Organ transplant recipient	I
Malignancy or use of immune suppressive medications	I
Current smoking unless cessation of smoking at least two weeks before enrollment	I
Left ventricular (LV) thickness of < 7 mm determined by echo in the target areas of cell injection	I
Presence of echocardiography confirmed intracardiac thrombus, left ventricular aneurysm and massive calcification of the aortic valve	I
Hematology disease	I
Multi-organ failure	I

Table 1. A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases (Continue)

General cardiovascular conditions	AUC category
Patients with cognitive or psychiatric problems unable to provide informed consent	I
Sensitivity to Penicillin, Streptomycin, Gentamicin, Amphotericin B, contrast agent or materials used for cell preparation	I
Allergy to Aspirin, Clopidogrel, Heparin	I
Active bleeding including blood on urine dipstick or fecal occult blood	I
Anticipated inability to aspirate patient's bone marrow or draw enough blood volume needed for stem cell isolation and preparation	I
Uncontrolled arrhythmia	I
Constant atrial fibrillation/flutter (unless paced in a regular rhythm)	I
Presence of mechanical aortic or mitral prosthetic valve	I
Stem cell tracking	U
Cardiac imaging after cell delivery in a timely manner	U
In-vitro and in-vivo assessment of cell potency [using cell invasion and migration assays and imaging protocols as Cardiovascular magnetic resonance (CMR), respectively]	U
5000-10,000 IU unfractionated heparin after sheath insertion for percutaneous cell delivery	U
Specific conditions (Non-ischemic cardiomyopathies)	**AUC category**
Ill children with cardiomyopathy due to anti-cancer agents	A
Ejection fraction (EF) less equal or less than 35% with evidence of congestive heart failure	A
Symptomatic patients for more than one year at New York Heart Association (NYHA III-IV) despite optimal pharmacologic therapy for more than 3 months	A
NYHA II have been hospitalized with a dilated cardiomyopathy related condition	A
At least 7% reversibility and viability showed by nuclear study	A
Confirmed diagnosis of non-ischemic cardiomyopathy with normal coronary angiography	A
Serum B-type Natriuretic Peptide (BNP) level > 100 pg/ml.	A
Heart transplantation is contraindicated	A
NYHA I	I
Acute left and/or right sided failure	I
Documented latest ejection fraction > 45%	I
Indication for surgical ventricular reconstruction or mitral valve repair	I
Coronary angiography with significant stenosis amenable to revascularization	I
Recurrent myocardial ischemia or recent acute coronary syndrome (ACS) within last 28 days	I
Known severe pre-existent left ventricular dysfunction (EF < 10%) prior to randomization	I
Cardiomyopathy due to a non-treated reversible cause as thyroid disease, alcohol abuse, etc.	I
Manifest ventricular asynchrony	I
Recent cerebrovascular disease within last 60 days	I
History of syncope during the last year	I
Evidence of life-threatening arrhythmia in the absence of a defibrillator (such as non-sustained ventricular tachycardia in ≥ 20 consecutive beats, sustained ventricular tachycardia lasting 30 seconds or more, complete second or third degree heart block in the absence of a functioning pacemaker) or QTc interval > 550 ms	I
Previous myocardial infarction	I
Congenital heart disease and chromosomal abnormality	I
Weight >140kg	I
Specific conditions (Ischemic cardiomyopathies)	**AUC category**
Symptomatic patients with ischemic cardiomyopathy and HF II-IV NYHA class/stage D, for at least three months despite full medical treatments	A
Severe and persistent HF with EF < 35% and or limiting angina (classes II to IV)	A
Significant coronary heart disease not amenable to revascularization or ineffective coronary revascularization during last 6 months	A
Presence of a defect identified by nuclear imaging	A
History of Q-wave MI with a residual akinetic and nonviable scar	A
Scheduled for surgical revascularization within few days (< 2 weeks) of the initial screening	A
End-stage or uncontrollable congestive heart failure without continues infusion of catecholamine	I
Patient is scheduled for heart transplantation	I
Patients requiring surgical correction of LV aneurism	I

Table 1. A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases (Continue)

General cardiovascular conditions	AUC category
Aortic aneurysm > 5.5 cm (including dissecting aneurysm)	I
Inability to walk on a treadmill except class IV angina patients, who will be evaluated separately	I
Implantable cardioverter-defibrillator shock within 30 days	I
Revascularization within 30 days of consent	I
Specific conditions (Unstable angina)	**AUC category**
Severe refractory chest pain and non-revascularizable coronary disease in diagnosed unstable angina	A
Specific conditions (Chronic stable angina)	**AUC category**
Minimum 7 episodes of chest pain/WK despite of optimal medical therapy for at least 4 weeks, Canadian cardiovascular class (CCS) class II or IV chronic refractory CP with exercise limitation (3-10 min on Bruce) III/IV FC, no candidacy for revascularization, presence of ≥ 1 myocardial segment with ischemia features determined by nuclear imaging, evidence of inducible myocardial ischemia	A
History of successful or partially successful coronary artery bypass surgery (CABG) within 6 months or coronary intervention within last 60 day	I
Specific conditions acute myocardial infarction (AMI)	**AUC category**
AMI with a fixed perfusion defect more than 10% of LV mass on single photon emission computed tomography (SPECT) after 72 hours	A
Still symptomatic patient with extensive AMI after successful reperfusion and culprit artery repair as well as repair of other significant lesions in non-culprit arteries	A
AMI with successful recanalization [Thrombolysis in myocardial infarction (TIMI) 2-3] and impaired reperfusion [myocardial blush 0 or 1 at the end of the procedure and ST segment recovery less than 50% 1 hour after percutaneous coronary intervention (PCI)]	A
Lack of resolution of ST-segment elevations after thrombolysis	A
Still symptomatic patients with AMI after treatment by primary PCI (PPCI) within 6-12 hours of chest pain (CP) or initial treatment with thrombolysis within 2 hours followed by PCI within 24 hours of CP onset	A
Still symptomatic AMI cases with EF < 45-50% and significant regional wall motion abnormality in the territory of infarct related artery (IRA) within 24 hours after PCI of IRA, treated by PPCI within 24 hours of the onset of CP or initial treatment with thrombolysis within 12 hours followed by PCI within 24 hours of the onset of CP, NYHA ≥ 2 and no need for immediate CABG	A
Ungraftable non-viable fibrotic area during mitral valve replacement (MVR) or CABG	A
Verification of coronary blood flow thromolysis in myocardial infarction (TIMI) 3 before application of cell-based therapies	U
Final coronary angiography in order to ascertain vessel patency, absence of embolization and unimpeded flow and TIMI count	U
Evaluation of periprocedular safety measures by checking cardiac enzymes at the day after cell-based therapies	U
AMI with successful reperfusion within 24 hours after symptom	I
Indication for immediate CABG after AMI	I
Mechanical complications of AMI (myocardial rupture of interventricular septum and LV free wall, papillary muscle rupture)	I
IRA with TIMI flow < 3 by the time of cell injection	I
Specific conditions peripheral vascular disease (PVD)	**AUC category**
Ischemic and refractory peripheral vascular disease (PVD) or with rest pain of the index limb (Rutherford category 4) defined as pain requiring analgesia (> two weeks) that occurs at night or at rest or dry gangrene as signs of end stage vascular disease	A
Refractory ambulatory critical limb ischemia (Rutherford score 4/5), ischemic lower extremity non-healing ulcers (Grade II of Wagner's classification) due to infra-inguinal disease present for > 4 weeks	A
Claudication at 100 meters or peak walking time of 1 to 6 minutes on two exercise tests apart by 2 weeks on graded treadmill with Ankle brachial index (ABI) < 1.0, monophasic Doppler waveforms at posterior tibial artery and dorsalis pedis artery with toe pressure < 30 mmHg, ankle pressure < 60 mmHg or toe pressure < 40 mmHg, flat or barely pulsatile pulse on volume recording, toe brachial index ≤ 0.35 or III, TcPO2/TcO2 of ≤ 40 mmHg, reduced TCpO2 (< 30-45 mmHg) at calf muscle	A
Moderate or severe limb-threatening peripheral arterial disease (PAD), defined as ABI < 0.7 in two consecutive examinations at least 1 week apart, peripheral arterial obstructive disease (PAOD) at Fontaine class [IIb, III or IV], distal arterial occlusion of two of the following lower extremity arteries: anterior tibial, posterior tibial, and peroneal	A

Table 1. A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases (Continue)

General cardiovascular conditions	AUC category
No option patients as cases amenable for each kind of vascular reconstruction, defined as cases with prior vascular reconstruction, diffuse multi-segment disease, inability to locate a suitable vein for grafting, or extensive infra-popliteal disease	A
Gangrene (Rutherford 6) or pre-existing major tissue loss	I
Unstable angina, Myocardial infarction (MI), stroke, Congestive heart failure (CHF) (class III or IV) within 6 months of study or presence of conditions that preclude general anesthesia	I
Active infection in the affected leg	I
Eligible patients for traditional endovascular or surgical treatments for PVD	I
Popliteal vascular entrapment syndrome	I
Trans-metatarsal or higher amputations in the affected limb or amputation required within 30 days	I
Gastrointestinal bleeding within last 3 months	I
Surgery or trauma within the last 2 months	I
Successful bypass operation or intervention within the last 3 months	I
Subjects not likely to be benefited with maximal tolerated medical therapy for PVD including stop smoking, control of blood sugar, blood lipids, blood pressure and treatment with aspirin and / or cilostazol (unless medically contraindicated)	I
Stem cell treatment within the past 6 months	I
Patient is unwilling to receive Aspirin and clopidogrel	I
Ischemic ulcers with infectious symptoms (≥ Grade 3 of Wagner classification)	I
Coronary angioplasty within the past 1 year	I
Requiring major amputation (at or above the ankle) within 4 weeks of starting the treatment	I

Conflict of Interests

Authors have no conflict of interests.

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