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Heart rate recovery in exercise test in diabetic patients with and without microalbuminuria

Ali Pourmoghaddas⁽¹⁾, Adrineh Moghaddasian⁽²⁾, Mohammad Garakyaraghi⁽³⁾, Negin Nezarat⁽⁴⁾, Ali Mehrabi⁽⁵⁾

Original Article

Abstract

BACKGROUND: Diabetes mellitus (DM) has a lot of complications such as macrovessel and microvessel disease. Another complication of DM is cardiac autonomic neuropathy (CAN), which have effect on automatic nervous system of heart. Failure in heart rate slowing after exercise is a presentation of this abnormality.

METHODS: We selected diabetic patients and divided them to case and control group based on microalbuminuria. Case group comprised of diabetic patients with microalbuminuria and control group included those without microalbuminuria. Patients in both groups exercised on treadmill using Bruce protocol and heart rate was measured in first and second minutes in the recovery period.

RESULTS: We selected 35 patients with microalbuminuria (case group) and 35 without microalbuminuria (control group) among diabetic patients. No statistically significant difference was seen in sex and age between case and control groups. Heart rate recovery in the first minute of recovery in the case and control groups did not show significant difference; but in the second minute of recovery, it was significantly higher in control group (97 ± 19.4 vs. 101.9 ± 12.4 beat per minute, $P = 0.04$).

CONCLUSION: In this study we evaluated the heart rate recovery or deceleration in diabetic patients with albuminuria and without microalbuminuria in recovery phase after exercise test. We found out that heart rate recovery at the second minute in the case and control groups has statistically significant difference but at the first minute, it did not.

Keywords: Diabetes Mellitus, Exercise Test, Heart Rate Recovery

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Introduction

Diabetes mellitus (DM) is one of the most important causes of morbidity and mortality in the world especially in Middle East, hot spot area for this disease,¹ and diabetic nephropathy is one of the most disabling complications of DM.

About 25% of type 1 diabetic patients will be affected by renal insufficiency, while it is 5% to 10% in type 2. Microalbuminuria is the first sign of progression to kidney disease and proteinuria. 50% of people with type 1 diabetes are affected by microalbuminuria and about 20% by proteinuria;

and progress to the end stage renal failure and diabetic nephropathy in patients with type 2 diabetes is similar to patients with type 1 diabetes.^{2,4}

The risk of cardiovascular disease (CVD) in patients with type 2 diabetes mellitus with microalbuminuria is two or three times more than patients without the albuminuria. However, if a patient has proteinuria, cardiovascular risk increases to 10 times. The survival of type 2 diabetic patients with renal failure is short after the beginning of the dialysis.³ Many of these patients will die with cardiovascular events rather kidney problem.⁵

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The reasons for such close relationships between nephropathy and cardiovascular disease is not definitely determined, but autonomic nervous system disorders that occur more in nephropathic patients can explain this issues.⁶ Cohen et al. showed that fasting blood sugar has independent and strong relationship with abnormal heart rate recovery (HRR) after exercise, even in nondiabetic levels.⁷ The result of Framingham study⁵ has also shown that the low HRR, that means sympathetic and parasympathetic nervous system disorder are seen in diabetic patients. Another studies expressed that the low HRR following the exercise test had an independent relationship with the high prevalence of CVD and all-cause mortality in diabetic men.^{8,9} Therefore, HRR can help the diagnosis and prediction of early stage of CVD and cardiac autonomic neuropathy (CAN) in diabetic patients.¹⁰ We examined HRR, as a sign of cardiac autonomic function, in albuminuric (case group) versus non-albuminuric (control group) diabetic patients.

Materials and Methods

This case-control study was done in diabetic patients in Al-Zahra and Noor University Hospitals, and Isfahan Endocrine, Metabolism and Cardiovascular Research Center in 2011. All patients signed the consent form for participating in the study.

Inclusion criteria were type 1 or 2 diabetic patients without history of angina pectoris, myocardial infarction or stroke in 6 months ago. Exclusion criteria were history of coronary artery bypass graft (CABG) in 3 months before entry to this study, heart failure New York Heart Association (NYHA) class 3 or 4, severe peripheral vessel disease, inability to complete exercise test, history of hospitalization, poor compliance for follow up and serum creatinine more than 3 mg/dl.

Case group included diabetic patients with microalbuminuria and control group consisted of diabetic patients without microalbuminuria. Exercise test was done for both groups by Bruce protocol in Noor Hospital and heart rate was recorded at first and second minute after termination of exercise in recovery period.

Sampling was done by convenience method. The sample size was calculated as 35 subjects in each group in order to compare the two proportionate considering $\alpha = 5\%$, statistical power of 80%, and the 76.6% and 23.4% risk in patients with or without microalbuminuria as mentioned in the literature, respectively.¹¹

Diabetic patients were enrolled and physical examination was done for all patients by a cardiologist who referred them to the laboratory for measurement of urine analyses, microalbuminuria, and urine creatinine after 12 hours fasting. The albumin to urine creatinine ratio (ACR) was calculated and ACR 30-300mg was defined as microalbuminuria.

Based on microalbuminuria, patients were classified to two groups. Then, patients were referred to exercise test department but technician did not know about patient history and laboratory Data. Patients exercised to the maximum expected effort as they can do. All exercise data such as patient's symptoms, heart rate and electrocardiogram were recorded. Recovery period included walking phase with the speed of 1.9km/h and 0% grade of treadmill. Patient's heart rate (HR) was measured and recorded in 2 minutes. Heart rate recovery (HRR) or heart rate deceleration was calculated as below:

Predicated Maximum HR = $220 - \text{age (year)} \pm 10$ beat per minute

HRR = peak HR - HR at 1st min recovery:
Normal > 12 beat per minute

HRR = peak HR -HR at 2nd min recovery:
Normal > 22 beat per minute

Heart rate drop more than 12 and 22 beat per minute (BPM) in the first and second minute, respectively, were considered normal response whereas lower values were considered abnormal. Research data were recorded in a questionnaire sheet and approved by cardiologists and statisticians and were analyzed by SPSS software version 18 (SPSS, Inc., Chicago, IL) using chi-square and Student's t-test.

Results

Among diabetics, we selected 35 patients with microalbuminuria (case group) and 35 without microalbuminuria (control group) with regard to inclusion and exclusion criteria. Among 70 participants, 11 patients excluded (4 in case and 7 in control), due to inability of running enough, or other exclusion criteria. Patient's age was between 16 and 65 years. The average age of patients was 49.9 ± 9.5 years. The average age of microalbuminuric patients was 50 ± 11.5 years and in non-microalbuminuric patients it was 49.9 ± 6.8 years ($P = 0.96$). 35.5% of subjects with microalbuminuria (11 person) and 32.1% subjects (9 of person) without microalbuminuria was male and the rest were female. There was no statistically

significant difference in sex and age between case and control groups.

The average duration of exercise test in all of the patients was 8.5 ± 2.5 minutes, but in two groups (case and control) it was 9.1 ± 2.9 and 7.7 ± 1.5 minutes, respectively (Figure 1), with a statistically significant difference ($P = 0.024$). Average heart rate in peak exercise in the case and control groups was 142.7 ± 25.6 and 157.5 ± 20.6 beat per minute (Figure 2) and the difference between them was statistically significant ($P = 0.02$).

HRR in the first and second minutes was within normal limit in both groups (Table 2) but HRR in the case group was insignificantly lower than the control group in both first minute ($P = 0.051$) and second minute ($P = 0.064$) (Table 1). Average heart rate in the first minute of recovery in the case group was 119.1 ± 24.6 beat per minute and in the control group it was 126.5 ± 15.8 beat per minute without

statistically significant difference ($P = 0.18$).

In the second minute of recovery, the average heart rate in the case and the control groups was 97 ± 19.4 beat per minute and 101.9 ± 12.4 beat per minute, respectively. It showed that the heart rate recovery from peak to 2nd minute of recovery had statistically significant difference between the two groups ($P = 0.04$).

HRR in the first minute of recovery was abnormal in 6 patients (10.2%), among whom 4 patients were in the case group and 2 in the control group (12.9% vs. 7.1%). Based on the Fisher's exact test, there was not any significant difference between them ($P = 0.67$). HRR in the second minute of the recovery in 5 (8.5%) patients was abnormal, which 3 (9.7%) patients were in case group and 2 (7.1%) were in control group without statistically significant difference between the two groups (Fisher's exact test, $P = 0.99$).

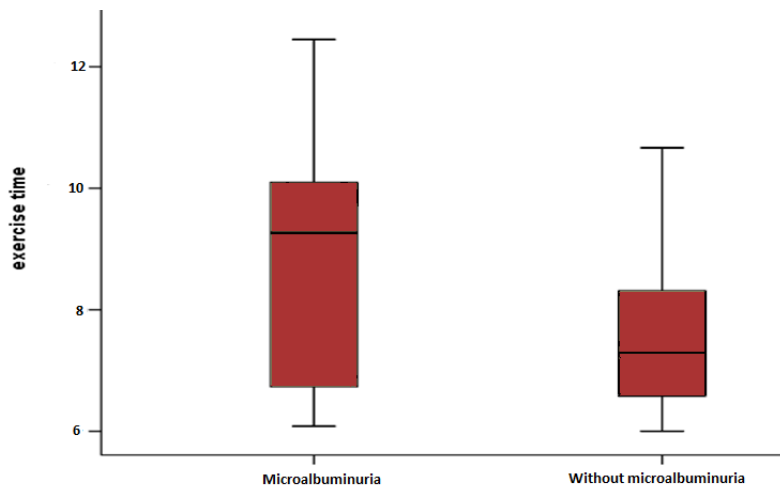


Figure 1. Exercise duration in case (microalbuminuria) and control (without microalbuminuria) groups

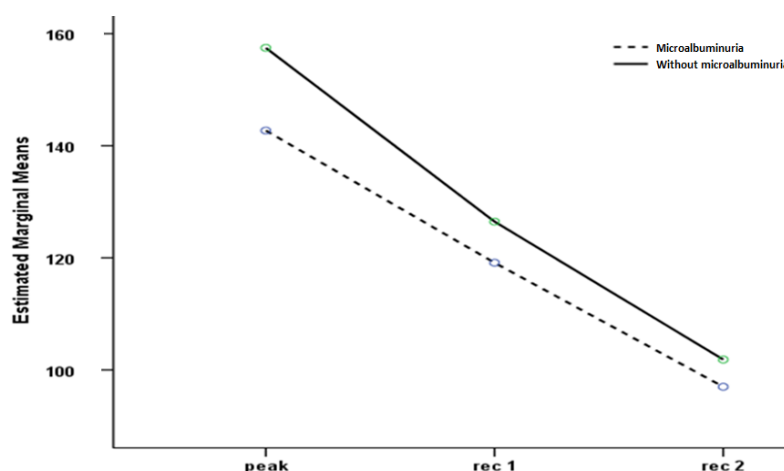


Figure 2. Mean of heart rate (beat per minute) changes from peak to first (rec 1) and second (rec 2) minute recovery time in case and control groups

Table 1. The mean and standard deviation of heart rate in the peak phase and in the first and second minute of recovery

Time	Groups	Heart Rate (BPM)	P
Peak	With microalbuminuria	142.7 ± 25.6	0.020
	Without microalbuminuria	157.5 ± 20.6	
First minute recovery	With microalbuminuria	119.1 ± 24.1	0.180
	Without microalbuminuria	126.5 ± 15.8	
HRR first minute	With microalbuminuria	23.6 ± 13.0	0.051
	Without microalbuminuria	31.0 ± 15.5	
Second minute recovery	With microalbuminuria	97.0 ± 19.4	0.260
	Without microalbuminuria	101.9 ± 12.4	
HRR second minute	With microalbuminuria	45.7 ± 17.1	0.064
	Without microalbuminuria	55.6 ± 23.0	

BPM: Beat per minute; HRR: Heart rate recovery
Data are presented as mean ± standard deviation

Table 2. Heart rate recovery results in nephropathic and non-nephropathic groups

	Group	With microalbuminuria	Without microalbuminuria	P
		n (%)	n (%)	
First minute	Normal	27 (87.1)	26 (92.9)	0.67
	Abnormal	4 (12.9)	2 (7.1)	
Second minute	Normal	28 (90.3)	26 (92.9)	0.99
	Abnormal	3 (9.7)	2 (7.1)	

Discussion

We compared the heart rate recovery following exercise test in diabetic patients with and without microalbuminuria. The mean value of maximum heart rate in the case group was significantly lower than control group but their heart rates recovery to appropriate values was similar to non-microalbuminuric patients.

In our study, heart rate in the case group could not reach the expected target heart rate appropriately ($220 - \text{age} \pm 10$ BPM). Heart rate dramatically decreased in control group and reached to normal values in first and second minutes of recovery time. As shown in table 1, the mean of HRR in case group was lower than values of control group, which is in line with findings of a recent study in Poland.¹²

Diabetes as a complex disease can have variable effects on nervous system. Some presentations of its effects on cardiac system are resting tachycardia, exercise intolerance, orthostatic hypotension, prolonged QT interval, silent ischemia, and sudden cardiac death.¹³ Subclinical diabetic autonomic neuropathy can appear one to two years after abnormality in HRR and the preliminary sign of cardiac autonomic neuropathy (CAN) is the decreased HRR. Although CAN could be presented even one or two year after presence of diabetes, but

it usually develops in patients who have had diabetes for 20 years or more.¹⁴ Therefore, this is not unexpected that we did not find any significant abnormal finding between the two groups.

Conflict of Interests

Authors have no conflict of interests.

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Association between markers of systemic inflammation, oxidative stress, lipid profiles, and insulin resistance in pregnant women

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Original Article

Abstract

BACKGROUND: Increased levels of pro-inflammatory factors, markers of oxidative stress and lipid profiles are known to be associated with several complications. The aim of this study was to determine the association of markers of systemic inflammation, oxidative stress and lipid profiles with insulin resistance in pregnant women in Kashan, Iran.

METHODS: In a cross-sectional study, serum high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF- α), fasting plasma glucose (FPG), serum insulin, 8-oxo-7, 8-dihydroguanine (8-oxo-G), total cholesterol, triglyceride, High density lipoprotein-cholesterol (HDL-cholesterol), and plasma total antioxidant capacity (TAC) were measured among 89 primigravida singleton pregnant women aged 18-30 years at 24-28 weeks of gestation. Pearson's correlation and multiple linear regressions were used to assess their relationships with homeostatic model assessment of insulin resistance (HOMA-IR).

RESULTS: We found that among biochemical indicators of pregnant women, serum hs-CRP and total cholesterol levels were positively correlated with HOMA-IR ($\beta = 0.05$, $P = 0.006$ for hs-CRP and $\beta = 0.006$, $P = 0.006$ for total cholesterol). These associations remained significant even after mutual effect of other biochemical indicators were controlled ($\beta = 0.04$, $P = 0.01$ for hs-CRP and $\beta = 0.007$, $P = 0.02$ for total cholesterol). Further adjustment for body mass index made the association of hs-CRP and HOMA-IR disappeared; however, the relationship for total cholesterol remained statistically significant.

CONCLUSION: Our findings showed that serum total cholesterol is independently correlated with HOMA-IR score. Further studies are needed to confirm our findings.

Keywords: Inflammation, Oxidative Stress, Insulin Resistance, Pregnancy

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Introduction

Insulin resistance is a physiological condition in which cells could not respond to the normal actions of the insulin hormone.¹ The normal compensatory response to insulin resistance is an increase in insulin secretion, which in turn leads to hyperinsulinemia.² Several factors including obesity, storing fat predominantly in the abdomen, sedentary lifestyle,

lack of physical exercise,³ hypertension,⁴ hypertriglyceridemia and low levels of serum HDL-cholesterol⁵ are associated with insulin resistance.

Furthermore, elevated levels of adipocytokines, including tumor necrosis factor-alpha (TNF- α), might accelerate insulin resistance through releasing free fatty acids (FFA) from adipocytes, which in turn block the synthesis of adiponectin.⁶ Increased

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production of pro-inflammatory cytokines can potentially disturb mitochondrial function for mitochondrial DNA damage, the production of reactive oxygen and nitrogen species.⁷ The generation of these reactive species lead to hyperglycemia and hyperlipidemia that will then result in decreased biological efficacy of insulin in target tissues (insulin resistance).⁸ Oxidative stress has also been widely recognized as an important feature of several diseases such as diabetes mellitus, mutagenesis, cancer, rheumatoid arthritis, atherosclerosis and strokes.⁹

Insulin resistance is primarily related to carbohydrate, lipid and protein metabolism disorders in the different tissues especially skeletal muscles, adipose tissue and liver.¹⁰ It can also cause type 2 diabetes (T2D) and gestational diabetes mellitus (GDM).¹⁰ It is reported that T2D can play an active role in the pathogenesis of both microvascular and cardiovascular complications of diabetes,¹¹ oxidative damage of DNA, protein and lipid membranes.^{12,13}

To our knowledge, no reports exist about the association of biomarkers of inflammation, oxidative stress and lipid profiles with insulin resistance during normal pregnancy. Therefore, the aim of current study was to investigate the association between inflammatory biomarkers including serum high sensitivity C-reactive protein (hs-CRP) and TNF- α levels, measures of oxidative stress including serum 8-oxo-7, 8-dihydroguanine (8-oxo-G) and plasma total antioxidant capacity (TAC), and lipid profiles (serum total cholesterol, triglycerides and HDL-cholesterol levels) and insulin resistance during normal pregnancy.

Materials and Methods

Participants: This cross-sectional study was carried out in Kashan, Iran, from October 2010 to March 2011. A total of 89 pregnant women, primigravida, aged 18-30 years old who were carrying singleton pregnancy were recruited in this study. To recruit participants, we applied multi-stage random sampling method in the study; such that we first randomly selected 30 health centers where the pregnant women attended for prenatal care. Then, by the use of proportional-to-size method, we randomly selected pregnant women among those that were visited in these centers, affiliated to Kashan University of Medical Sciences, Kashan, Iran. Individuals with the above-mentioned inclusion criteria were called for participation in the study. Women with multiparity, maternal

hypertension, liver or renal disease and gestational diabetes mellitus (GDM), complete bed rest (CBR), genitalia and systemic infection, history or evidence of rheumatoid arthritis, thyroid and parathyroid or adrenal diseases were not included in the study.¹⁴ Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment. The study was conducted according to the guidelines of Declaration of Helsinki. The ethical committee of Tehran University of Medical Sciences approved the study (No: 20402-89-7-18) and informed written consent was obtained from all participants.

Assessment of anthropometric measures:

Anthropometric measurements were assessed at pre-pregnancy and at week 24-28 of gestation. Body weight was measured in an overnight fasting state, without shoes, with minimal clothing and by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. The pre-pregnancy weight and BMI were taken from the existing records of patients in the clinic.

Biochemical assessment: Fasting blood samples (10 mL) were taken at week 24-28 of gestation at Kashan reference laboratory in an early morning after an overnight fast. Serum samples were analyzed for concentrations of hs-CRP, TNF- α , plasma glucose levels, insulin, 8-oxo-G, and serum total cholesterol, triglycerides, and HDL-cholesterol levels. Serum hs-CRP and TNF- α concentrations were quantified by ELISA. Fasting plasma glucose was measured by glucose oxidase/peroxidase (GOD-POD) method using commercially available kits (Pars Azmun Co, Tehran, Iran). Serum insulin levels were determined by ELISA (Demeditec, Germany). Insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR).¹⁰ Serum 8-oxo-G was assayed by ELISA (Cusabio Biotech Co, China). Serum total cholesterol and triglycerides concentrations were measured enzymatically using Pars Azmoon kits through cholesterol oxidase p-aminophenazon (CHOD-PAP) and glycerol phosphate oxidase-p-aminophenazon (GPO-PAP) methods. HDL-cholesterol levels were also measured enzymatically using commercial kits.¹⁴ The plasma TAC levels was quantified with the FRAP method.¹⁵ The test was performed at 37° C and the 0-4 minute reaction time window was used.

Statistical analysis: To ensure the normal distribution of variables, Histogram and Kolmogorov-Smirnov tests were applied. We used Pearson's correlation and multiple linear regression analysis to assess the relationships. The linear regression analyses were performed in crude and adjusted models which were controlled for mutual effects of other biochemical factors. To reach an independent-of-obesity association, we also added BMI to the regression models. $P < 0.05$ was considered statistically significant. The SPSS version 17 (SPSS, Inc., Chicago, IL) was used for data analysis.

Results

Totally, 89 pregnant women aged 18-30 years who were primigravid participated in the study. Mean maternal age and pre-pregnancy weight was 24.6 ± 3.6 years and 64.1 ± 11.7 kg, respectively. Mean weight at week 24-28 of gestation was 69.2 ± 12.2 kg.

Serum concentrations of hs-CRP, TNF- α , 8-oxo-G, triglycerides, total- and HDL-cholesterol, fasting blood glucose, insulin and plasma TAC at week 24-28 of gestation were 11.53 $\mu\text{g/ml}$, 88.38 pg/ml , 336.62 ng/ml , 247.54, 263.88, 81.01, 97.33 mg/dl , 7.70 $\mu\text{IU/ml}$, and 720.70 mmol/l , respectively (Table 1).

We found that pre-pregnancy weight ($r = 0.463$, $P < 0.001$) and weight at week 24-28 of gestation ($r = 0.451$, $P < 0.001$) was significantly associated with HOMA-IR score. This was also the case for pre-pregnancy BMI ($r = 0.450$, $P < 0.001$) and the BMI at week 24-28 of gestation ($r = 0.428$, $P < 0.001$) (Table 2). Serum hs-CRP and cholesterol levels were also positively correlated with HOMA-IR score ($r = 0.288$, $P = 0.006$ and $r = 0.291$, $P = 0.006$, respectively).

Table 1. Biochemical parameters of pregnant women at weeks 24-28 of gestation

Variables	Mean \pm SD
hs-CRP ($\mu\text{g/mL}$)	11.50 \pm 9.5
TNF- α (pg/mL)	88.40 \pm 51.9
TAC (mmol/L)	720.70 \pm 87.6
8-oxo-G (ng/mL)	336.60 \pm 156.6
Total cholesterol (mg/dL)	263.90 \pm 82.2
Triglycerides (mg/dL)	247.50 \pm 117.1
HDL-cholesterol (mg/dL)	81.00 \pm 22.7
FPG (mg/dL)	97.30 \pm 26.6
Insulin ($\mu\text{IU/mL}$)	7.70 \pm 6.4
HOMA-IR	1.87 \pm 1.7

Hs-CRP: High sensitivity C-reactive protein; TNF- α : Tumor necrosis factor alpha; TAC: Total antioxidant capacity; 8-oxo-G: 8-oxo-7, 8-dihydroguanine; HDL-cholesterol: High density lipoprotein-cholesterol; FPG: Fasting plasma glucose; HOMA-IR: Homeostatic model assessment of insulin resistance

Table 2. Pearson's correlation coefficients of anthropometric and biochemical measures with HOMA-IR in pregnant women

Variables	HOMA-IR	P
Anthropometric factors		
Maternal age (year)	-0.006	0.9500
Pre-pregnancy weight (kg)	0.463	<0.0001
Weight at week 24-28 of gestation (kg)	0.451	<0.0001
Pre-pregnancy BMI (kg/m^2)	0.450	<0.0001
BMI at weeks 24-28 of gestation (kg/m^2)	0.428	<0.0001
Biochemical characteristics		
Hs-CRP ($\mu\text{g/mL}$)	0.288	0.0060
TNF- α (pg/mL)	0.022	0.8300
TAC (mmol/L)	-0.002	0.9800
8-oxo-G (ng/mL)	-0.108	0.3100
Total cholesterol (mg/dL)	0.291	0.0060
Triglycerides (mg/dL)	0.126	0.2300
HDL-cholesterol (mg/dL)	0.095	0.3700

HOMA-IR: Homeostatic model assessment of insulin resistance; BMI: Body mass index; Hs-CRP: High sensitivity C-reactive protein; TNF- α : Tumor necrosis factor alpha; TAC: Total antioxidant capacity; 8-oxo-G: 8-oxo-7, 8-dihydroguanine; HDL-cholesterol: High density lipoprotein-cholesterol

Table 3. Multiple regression analysis between biochemical indicators of pregnant women with HOMA-IR

	HOMA-IR		
	β	95% CI	P
hs-CRP			
Crude	0.050	0.050, 0.090	0.006
Adjusted	0.040	0.008, 0.080	0.010
Adjusted + BMI	0.010	-0.020, 0.040	0.580
TAC			
Crude	-0.002	-0.004, 0.004	0.980
Adjusted	0.001	-0.003, 0.005	0.730
Adjusted + BMI	0.001	-0.004, 0.001	0.310
8-oxo-G			
Crude	-0.001	-0.004, 0.001	0.310
Adjusted	0.000	-0.003, 0.002	0.490
Adjusted + BMI	-0.001	-0.003, 0.001	0.310
Total cholesterol			
Crude	0.006	0.002, 0.010	0.006
Adjusted	0.007	0.001, 0.010	0.020
Adjusted + BMI	0.009	0.030, 0.010	0.002
Triglycerides			
Crude	0.002	-0.001, 0.005	0.230
Adjusted	-0.001	-0.005, 0.002	0.460
Adjusted + BMI	-0.003	-0.007, 0.000	0.070
HDL-cholesterol			
Crude	0.007	-0.009, 0.02	0.370
Adjusted	-0.003	-0.020, 0.01	0.720
Adjusted + BMI	0.000	-0.010, 0.01	0.960

Adjusted: After controlled mutual effect of other biochemical indicators

HOMA-IR: Homeostatic model assessment of insulin resistance; hs-CRP: High sensitivity C-reactive protein; TAC: Total antioxidant capacity; 8-oxo-G: 8-oxo-7, 8-dihydroguanine; HDL-cholesterol: High density lipoprotein-cholesterol

Simple linear regression analysis showed that among biochemical characteristics of pregnant women, serum hs-CRP and total cholesterol levels were positively correlated with HOMA-IR score ($\beta = 0.05$, $P = 0.006$ for hs-CRP and $\beta = 0.006$, $P = 0.006$ for total cholesterol) (Table 3). These associations remained significant even after controlling for other biochemical indicators ($\beta = 0.04$, $P = 0.01$ for hs-CRP and $\beta = 0.007$, $P = 0.02$ for total cholesterol). Further adjustment for BMI made the association of hs-CRP and HOMA-IR disappeared; however, the relationship for total cholesterol levels remained statistically significant ($\beta = 0.009$, $P = 0.002$). Multiple linear regression analysis revealed that there was no association between TAC, 8-oxo-G, triglycerides,

and HDL-cholesterol with HOMA-IR score.

Discussion

Insulin resistance, which is associated with abnormal glucose metabolism and insulin secretion, is a common complication during pregnancy.¹⁰ We found that serum hs-CRP and total cholesterol levels are associated with insulin resistance among pregnant women. Our findings also indicated that pre-pregnancy weight and BMI as well as BMI at weeks 24-28 of gestation are positively correlated with HOMA-IR score.

In line with our study, Stuebe et al. has shown a positive association between maternal fasting insulin levels and gestational weight gain.¹⁶ In addition, it is well documented that several pro-inflammatory

factors are related with obesity.¹⁷ The enlarged adipocytes are probably able to activate macrophages and trigger inflammatory reactions in body.¹⁸ However, this issue has not been fully investigated throughout pregnancy that is associated with expansion of adipose tissue.

In the present study, we failed to find an association between maternal serum TNF- α levels and insulin resistance. In a study by Bo et al. it has been reported that high maternal serum TNF- α levels were associated with insulin resistance.¹⁹ However, this is not the consistent findings in all previous observations. Some investigations have found that high maternal serum TNF- α levels were inversely associated with insulin resistance.^{19,20} Maternal obesity during pregnancy was associated with elevated levels of inflammatory factors.²¹ In the current study, the mean BMI was near the normal ranges. This might help explaining the lack of relationship between serum TNF- α levels and insulin resistance. Clapp and Kiess reported that regular weight-bearing exercise during pregnancy suppressed the usual pregnancy-associated changes in the circulating levels of TNF- α .²² In the current study, most of pregnant women lived in rural areas with high levels of physical activity. Furthermore, increased levels of several hormones including cortisol, catecholamine's and 1, 25 dihydroxy D3 during pregnancy might result in the inhibitory effect of maternal TNF- α production by monocytes and macrophages.²³

We found a positive association between maternal serum hs-CRP levels and insulin resistance. Our findings are in agreement with several previous observations.^{24,25} However, some studies have found that high serum hs-CRP levels during pregnancy were inversely associated with insulin resistance.^{26,27} Existing evidence shows that a chronic inflammatory process represents triggering factor inducing insulin resistance.²⁸ CRP is synthesized by the liver in response to adipocytokines released from adipocytes.²⁹ Some adipocytokines like IL-6 and TNF- α are also produced predominantly by macrophages.²⁹ Elevated CRP levels have also been reported in obesity.³⁰ Taken together, these data suggest a model of obesity-driven systemic inflammation in pregnancy that leads to insulin resistance.

We failed to find a significant correlation between plasma TAC and serum 8-oxo-G levels, as indicators of oxidative stress, and insulin resistance. To our knowledge, this study is the first one examining the association between oxidative stress

parameters and insulin resistance in pregnancy. However, earlier studies have reported the association of oxidative stress parameters and insulin resistance in obese subjects,³¹ type 2 diabetics³² and healthy obese men and women.³³ Kocic et al. showed a positive correlation between serum malondialdehyde (MDA) levels and insulin sensitivity index. However, they failed to find a significant association between total plasma antioxidant capacity, erythrocyte and plasma reduced glutathione levels and insulin resistance.³¹ Tinahones et al. showed a close association between the degree of insulin resistance and biomarkers of oxidative stress in severely obese persons.³⁴ It has been argued that dietary factors are involved in the relationship between oxidative stress parameters and insulin resistance.³⁵ Given the blood sampling in winter and low consumption of fruits and vegetables in this season in the current study, the association between biomarkers of oxidative stress and insulin resistance might be confounded by other environmental factors.

Our study showed that insulin resistance is significantly correlated with serum total cholesterol levels, but we did not find a significant association with serum triglycerides and HDL-cholesterol levels. Our findings were in line with previous study reported high maternal serum total cholesterol levels as a determinant factor of insulin resistance.³⁶ Lampinen et al. showed that the waist-to-hip ratio and serum triglycerides affects the insulin sensitivity in the patients with pre-eclampsia.³⁷ There is a well-known association between triglycerides and insulin sensitivity due to vasodilation resulted from triglycerides.³⁷ Explanations accounting for the different findings include the environmental and genetic factors of our studied subjects that can alter the lipoprotein metabolism, resulting in insulin resistance. Dyslipidemia has frequently been reported in insulin resistance. It seems that several factors including decreased lipoprotein lipase activity (LPL) and peroxisome proliferator-activated receptor gamma (PPAR gamma) as well as increased acetyl-CoA synthetase (ACS) and microsomal triglyceride transfer protein (MTP) might provide some explanations.³⁸

In conclusion, our findings showed that serum total cholesterol levels were independently correlated with HOMA-IR score at weeks 24-28 of gestation. Further studies are needed to confirm our findings.

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Conflict of Interests

Authors have no conflict of interests.

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Effects of a comprehensive cardiac rehabilitation program on quality of life in patients with coronary artery disease

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Original Article

Abstract

BACKGROUND: Health-related quality of life is an important factor to evaluate effects of different interventions in cardiovascular diseases. Improvement in quality of life (QOL) is an important goal for individuals participating in cardiac rehabilitation (CR) programs. The purpose of this study was to assess the impact of comprehensive CR on QOL in patients with cardiovascular disease (CAD).

METHODS: In this quasi-experimental before-after study, the files of 100 patients with CAD who were referred to rehabilitation department of Isfahan Cardiovascular Research Institute were studied using a consecutive sampling method. Data collection was performed from the patient's files including their demographics, ejection fraction, functional capacity, and resting heart rate. All patients participated in a comprehensive CR program and completed the validated questionnaire Short-Form 36 Health Status Survey (SF-36), before and after CR program. Data was analyzed based on sex and age groups (≥ 65 and < 65 years) using independent t-test and paired t-test (to compare variables between groups and before and after CR, respectively).

RESULTS: After CR, scores of all physical domains of the SF-36 including physical function (PF), physical limitation (PL), body pain (BP) and vitality (V) in addition to general health (GH) were significantly improved in all patients ($P < 0.05$) compared to the baseline. Patients with age < 65 years had greater improvements in mental health (MH) and social function (SF) than patients with age ≥ 65 years ($P < 0.05$). Women had greater improvement in PF, V and MH compared to men ($P < 0.05$).

CONCLUSION: These results indicated that CR can improve QOL in cardiac patients especially in women. Elderly patients get benefit the same as other patients in physical domains.

Keywords: Quality of Life, Cardiac Rehabilitation, Cardiovascular Diseases

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Introduction

Cardiac rehabilitation (CR) is an important intervention after myocardial infarction (MI).¹⁻³ Comprehensive CR not only improves physical and physiological status of cardiac patients but also it influences their psychological conditions⁴⁻⁸ and decrease mortality and cardiovascular disease (CAD) risk factors which can improve their life style.^{9,10} Today, quality of life (QOL) is used as important criteria for evaluating the influence of different interventions in different diseases. It indicates personal perception of life in different aspects such as physical and psychosocial function which is in accordance to

the patient's standards and expectations.¹¹ Improving QOL is one of the important goals of patients for participating in CR program.¹²

In traditional CR programs, it was emphasized on improving physiological status and exercise endurance as well as modifying CVD risk factors in state of patients' QOL.¹³ There are many investigations about impact of CR on QOL. Duration and characteristics of these CR programs have been different and there has been considerable diversity in studied populations, resulting in different findings.⁴⁻⁷ Several studies have shown that because of lower exercise capacity in older patients, they have

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more disability, so their cardiovascular status improves more than other patients after CR.^{14,15}

In Iran, there are several studies which have shown improvement of cardiovascular and psychological status of cardiac patients after CR,¹⁶⁻²² but there are little studies about influence of CR on improving QOL.^{23,24} Although a few studies have shown that home exercise and walking program improve QOL in cardiac patients, there is not enough studies on influence of comprehensive CR on QOL. In this study we investigated the impact of 8 weeks comprehensive CR on QOL in cardiac patients.

Materials and Methods

In this semi-experimental before-after study, according to the formula $N = [2(Z_{\alpha} + Z_{\beta})^2 S^2] / d^2$; and $\alpha = 95\%$, $\beta = 20\%$, $d = 0.16$, and $S = 0.4$, a sample size of 98 subjects were calculated. We evaluated the files of 100 cardiac patients who were referred to Isfahan Cardiovascular Research Institute in 2008-2010 using consecutive convenience sampling method. We included patients with history of MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), and CAD. If the files were not complete in terms of duration of cardiac rehabilitation course and any other measurements [ejection fraction (EF), functional capacity, resting heart rate, QOL, and signed consent form], patients were excluded from the study.

Data collection included demographics, past disease history, clinical examination, medications and cardiac history. All patients had participated in an 8 weeks comprehensive CR program. They also received a step II of cardiac diet by a nutritionist. To evaluate the risk of cardiac disease and to determine the exercise intensity, they performed a symptom limited exercise test using a treadmill (Track Master made in US) by Naughton protocol without stopping medication.²⁵ All patients took angiotensin converting enzyme (ACE) inhibitors and beta-blockers. To evaluate EF, echocardiography was performed by a cardiologist. According to American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) 1999 guideline for cardiac rehabilitation,²⁶ risk of cardiac disease was determined. The intensity of exercise was based on 60-80% of maximum heart rate obtained from exercise test.²⁷

CR included 24 sessions (3/week) exercise training; each session consisted of 10-20 minutes warm-up, 20-40 minutes aerobic training using

treadmill, arm ergometer and stationary bicycle, 10 minutes cool-down and 20 minutes relaxation as well as 8 education sessions (weekly) to modify CVD risk factors. CR program was supervised by a team (physician, cardiologist, trained nurse and physiotherapist) and high risk patients were monitored if it was necessary.

Persian version of validated questionnaire Short-Form 36 Health Status Survey (SF-36) was used by a trained person to evaluate QOL before and after CR.^{28,29} This questionnaire consisted of 2 sections, physical and psychological health. Physical section included 4 subsections: Physical function (PF), physical limitation (PL), body pain (BP) and vitality (V). Psychological health subsections included social function (SF), emotional limitation (EL), mental health (MH), and general health (GH). All questions were scored on a scale from 0 to 100, with 100 representing the highest level of possible functioning. Aggregate scores were compiled as a percentage of the total points possible, using the RAND-36 scores. The scores from those questions that addressed each specific area of functional health status were then averaged together, for a final score within each of the 8 dimensions measured.

Data distribution was normal. Therefore, to compare variables before and after CR, paired t-test was used and to compare variables between sex groups and age groups (< 65 years and \geq 65 years), independent t-test was used. Data was analyzed by SPSS version 16 (SPSS, Inc., Chicago, IL) at significant level of $P < 0.05$.

Results

Data of 100 patients was evaluated. There were 31 females (mean age: 60.6 ± 10.9 years) and 69 males (mean age: 58.8 ± 10.8 years). The age groups included 36 patients with age of 65 years and more (mean age: 70.1 ± 4.5 years) and 64 patients with age less than 65 years (mean age: 53.3 ± 8.3 years). Table 1 shows the characteristics of the studied population. All patients showed improvement in PF ($P = 0.002$), PL ($P < 0.001$), V ($P = 0.02$), BP ($P = 0.009$) and GH ($P = 0.009$) (Table 2). In terms of the sex groups, females improved in PF ($P = 0.004$), V ($P = 0.003$), and MH ($P = 0.006$) subsections significantly more than males (Table 3). In age groups, patients with age less than 65 years had more improvements in MH ($P = 0.02$) and SF ($P = 0.002$) subsections than older patients (with age \geq 65 years) (Table 4). Table 5 shows that exercise capacity, EF, and resting heart rate were improved in total population ($P < 0.01$).

Table 1. Characteristics of studied population

	Total (n = 100) Mean ± SD	Male (n = 69) Mean ± SD	Female (n = 31) Mean ± SD
Age (year)	58.9 ± 11.0	58.4 ± 10.9	60.2 ± 11.3
Weight (kg)	74.7 ± 12.1	76.3 ± 10.5	67.8 ± 13.4
Education (%)			
Less than diploma	41.4%	21.7%	86.70%
Diploma	59.6%	44.9%	13.30%
University	23.2%	33.0%	0.0%
Married	96%	72.6%	24.4%
Disease			
CAD	16.0%	22.2%	46.2%
PTCA	36.4%	63.9%	31.6%
CABG	45.5%	77.8%	22.2%
MI	4.0%	5.8%	0.0%
Risk of disease			
Low	75.5%	68.9%	31.3%
Intermediate	13.3%	69.2%	30.8%
High	11.2%	81.8%	18.2%
< 65 years	64%		
≥ 65years	36%		

PTCA: Percutaneous transluminal coronary angioplasty; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; MI: Myocardial infarction

Table 2. Quality of life scores before and after cardiac rehabilitation program in total population

SF-36 subscale	Before Mean ± SD	After Mean ± SD	P
Physical function	61.05 ± 23.3	68.20 ± 22.3	0.002
Physical limitation	33.25 ± 39.1	53.25 ± 38.6	< 0.001
Emotional limitation	55.67 ± 41.8	59.00 ± 42.7	0.480
Vitality	55.15 ± 20.7	60.50 ± 33.2	0.020
Mental health	65.28 ± 21.3	67.04 ± 20.1	0.340
Social function	71.67 ± 22.2	72.67 ± 23.4	0.670
Body pain	65.80 ± 22.7	72.38 ± 23.1	0.009
General health	57.45 ± 18.3	61.92 ± 19.3	0.009

Table 3. Mean percent of changes in quality of life items in males and females

SF-36 subscale	Male Mean ± SD	Female Mean ± SD	P
Physical function	9.62 ± 10.3	42.69 ± 10.1	0.004
Physical limitation	18.08 ± 25.7	61.58 ± 21.3	0.170
Emotional limitation	6.50 ± 3.6	8.73 ± 32.3	0.910
Vitality	8.80 ± 25.8	45.62 ± 30.6	0.003
Mental health	3.42 ± 18.0	42.89 ± 24.9	0.006
Social function	7.46 ± 33.1	18.77 ± 32.7	0.330
Body pain	19.02 ± 63.3	17.70 ± 44.7	0.910
General health	18.24 ± 19.1	12.42 ± 19.5	0.580

Table 4. Comparison of mean percent of changes in quality of life items in patients aged more than 65 years and younger patients

SF-36 subscale	< 65 years (n = 64)		≥ 65 years (n = 36)		P
	Mean ± SD		Mean ± SD		
Physical function	20.78 ± 27.6		17.87 ± 24.2		0.790
Physical limitation	41.66 ± 34.5		-2.60 ± 34.0		0.080
Emotional limitation	16.32 ± 34.1		-9.62 ± 33.7		0.210
Vitality	25.78 ± 26.4		10.31 ± 28.9		0.200
Mental health	25.32 ± 21.8		-1.52 ± 18.2		0.020
Social function	21.31 ± 24.1		-7.43 ± 44.5		0.002
Body pain	21.06 ± 65.0		14.17 ± 44.2		0.530
General health	17.18 ± 18.4		15.24 ± 21.6		0.840

Table 5. Exercise capacity, ejection fraction, and resting heart rate before and after cardiac rehabilitation

		Before		After		P
		Mean ± SD		Mean ± SD		
Exercise capacity	Total	8.55 ± 2.8		10.81 ± 2.9		< 0.001
	Female	6.54 ± 2.1		8.36 ± 2.4		< 0.001
	Male	9.31 ± 2.6		11.74 ± 2.6		< 0.001
Ejection fraction	Total	51.06 ± 11.2		54.78 ± 10.0		< 0.001
	Female	53.62 ± 11.0		56.74 ± 9.9		< 0.001
	Male	50.03 ± 11.1		53.99 ± 10.0		< 0.001
Resting heart rate	Total	81.10 ± 17.1		76.51 ± 14.3		< 0.001
	Female	87.78 ± 15.9		79.74 ± 11.8		0.010
	Male	79.48 ± 17.4		75.16 ± 15.2		< 0.001

Discussion

In this study, QOL was significantly improved in subsections of PF, PL, V, BP, and GH after 8 weeks comprehensive CR. Females were improved more than males in PF, V, and MH subsections. Patients with age less than 65 years were improved more than older patients in MH and SF subsections. Some studies have shown that physical activity influence on QOL so that increasing physical activity improves QOL.³⁰ On the other hand, increasing exercise capacity improves patients' ability for daily living activities, work and leisure activities, which in turn results in improving QOL. In the present study, exercise capacity increased after CR significantly in total population and each sex group. Improving physical status of the patients also influences on their psychological condition and increases ability of return to work and participating in social activities as well as improving well being.

There are a few studies in Iran in this area which are different in their intervention and the studied populations. In a study by Abbasi et al. which evaluated the effect of walking program at home on quality of life and functional ability in patients with heart failure using Minnesota questionnaire.²⁴ Mohammadi and colleagues have shown the effects of home-based cardiac rehabilitation on quality of life in patients with myocardial infarction²³ using

MacNew questionnaire. Both studies compared QOL between case and control groups but at the present study, we compared age and sex groups after a comprehensive CR. Zwisler et al. showed that QOL were improved after CR but anxiety and depression did not significantly change after CR.³¹ The findings of our study were the same as the results of the study by Jegier in 2009 which in both study the duration was 8 weeks.³² Arrigo et al. have shown that a comprehensive CR improves QOL even one year after the program.³³

An investigation by Grace et al. on females showed that QOL and anxiety were improved after CR.³⁴ Although we did not evaluate anxiety and depression, but SF-36 for QOL consists a subsection for mental health. A systematic review article in 2010 indicated that home-based CR and center-based CR both improve QOL.^{35,36} CR can decrease psychological stress of cardiovascular diseases and improve QOL in cardiac patients.³⁶ Izawa et al. pointed out that 12 months CR improves physical index and QOL of cardiac patients.⁶ Mohammadi and colleagues studied impact of 3 months home-based CR on QOL in patients with MI.²³ They reported that CR improved physical and mental aspects of QOL but did not change social aspect of QOL. The results of present study were the same as their findings. Some studies showed that patients with more complex

psychological distress benefited from CR more than others.³⁷ However, there were some investigations with different findings; in Serber et al. study, impact of CR on patients with severe psychological distress was more than others in physical, mental and social aspects of QOL,³⁸ while Hevey et al. showed that QOL was related to primary level of psychological distress of the patients and CR could improve QOL and anxiety just in these group of patients.³⁹

The impact of CR was the same in both age groups in our study. In Marchionni et al. study, CR improved QOL in patients with 65 years or more as well as those with less than 65 years.⁴⁰ At present study, most of patients participated in the program after CABG and PTCA but a few after MI (4%), while in study by Marchionni et al. all the patients had suffered from MI.⁴⁰ Seki et al. showed that elder patients were improved more than others.⁴¹ In our study, QOL was improved in female more than males in mental health, vitality, and physical function, although their age was the same. It can be related to low level of their exercise capacity and QOL in the beginning of the study.^{42,43}

Conclusion

The results of our study showed that CR can improve QOL in PF, PL, BP and V after 8 weeks comprehensive CR. Because this study did not have control group, its results is not strong enough, however, because there are few studies in Iran about impact of CR on QOL in sex and age groups, its results are important. It is recommended to evaluate the impact of different models of CR in different population for example CABG, PTCA, heart failure, etc.

Conflict of Interests

Authors have no conflict of interests.

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Effect of continuous care model on lifestyle of patients with myocardial infarction

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Original Article

Abstract

BACKGROUND: Myocardial infarction (MI) is a life threatening disease that influences the physical, psychological and social dimensions of the individual. Improper lifestyle is one of the causes of this disease. The use of nursing models could be one of the important and fundamental steps in changing the risk factors associated with MI. This study was carried out to evaluate the effect of continuous care model on the lifestyle of patients with MI.

METHODS: This randomized clinical trial was carried out on 70 patients with MI in coronary care units of hospitals affiliated to Shiraz University of Medical Sciences. Enrolled patients were randomly assigned to intervention or control groups using a randomization list (random permuted blocks with length 4). The continuous care model was used for 35 patients in the intervention group for a period of 3 months and in the control group, the usual cares were applied for 35 patients. Data were collected through lifestyle questionnaire before the intervention and 3 months after. The data were analyzed using chi-square, independent t-test and paired t-test.

RESULTS: Patients in the intervention group showed significant improvements in lifestyle (125.6 ± 15.4 vs. 180.1 ± 19.9). Moreover, the lifestyle score of intervention group was significantly better than that of the control group (117.9 ± 22.0 vs. 180.1 ± 19.9 ; $P < 0.001$) after three months.

CONCLUSION: Applying a continuous care model had positive effects on the lifestyle of patients with Myocardial Infarction. In order to reduce the risk factors and improve the lifestyle of patients with MI, nurses could use this model to create an effective change.

Keywords: Myocardial Infarction, Lifestyle, Continuous Care Model

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Introduction

Acute myocardial infarction (MI) or heart attack refers to the ischemic necrosis of cardiac myocytes which occurs due to the lack or reduction of blood supply.¹ This disease is life threatening and influences the physical, psychological and social aspects of the patient's life. The prevalence of this disease is increasing throughout the world.² Cardiovascular diseases are known to be the first mortality cause in Iran and about 138000 deaths occur every year due to this disease (about 40% of the total mortality), half of which being due to MI.³

The incidence of MI in various parts of the world is being affected by demographic characteristics and lifestyle of the individuals.⁴ It is

supposed to be a life threatening disease by patients and they attribute it to their lifestyle.⁵ Behavioral risk factors are often related and closer adherence to a healthier lifestyle might reduce the risk of coronary heart disease.⁶ Several studies indicate that lifestyle change not only prevents but also controls the progress of cardiac diseases and reduces the occurrence of cardiac events in the patients with cardiovascular diseases.^{7,8} Lifestyle modification to prevent the incidence of coronary vascular disorders is among the basic programs of WHO.⁹ Choosing a healthy lifestyle along with a balanced diet reduce the rate of MI and the need to surgery and angioplasty.¹⁰

In spite of the availability of widespread studies regarding the importance of improving the risk

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factors and changing the lifestyle after MI, about half of the patients experience some complications like further MI three years after it¹¹ because changing the lifestyle is difficult. One of the problems of patients with acute MI is making change in their lifestyle during a short period of time. Moreover, patients are not provided with sufficient information in this regard during their hospitalization period¹² or forget the received information gradually and by time lapse.¹³

Evidence shows that no scientific and professional source is available in the Iranian society to help such patients and also their lifestyle is not sufficiently observed by physicians.^{12,14} Experimental studies also have not suggested any proper solution to make behavioral change among patients with MI. Therefore, it seems that a program manageable by nurses (nurse-leader) along with a follow-up using phone could be a successful and practical model.⁵ Using nursing models could be one of the important and basic steps to reach this objective. "Continuous care model" is one of the models planned by Ahmadi for patients suffering from chronic coronary vascular disease.¹⁵ The aim was to establish and maintain a dynamic, flexible, and continuous care relationship between the nurse and the patient for improving the lifestyle of the patients. The continuous care model provides such conditions but this model has not been used for lifestyle change thus far. In view of the importance of improvement in lifestyle of MI patients, this study aimed to investigate the effects of applying a continuous care model on the lifestyle of patients with MI.

Materials and Methods

Patients and setting

This was a randomized controlled trial to examine the effects of applying a continuous care model on the lifestyle of patients with MI. The study was approved by the ethics committee of Shiraz University of Medical Sciences. In this study, 70 patients with MI who were hospitalized at cardiac care unit (CCU) of hospitals affiliated to Shiraz University of Medical Sciences in 2011, and fulfilled the inclusion criteria were selected.

The inclusion criteria were age below 70 years, able to comprehend, MI for the first time, not having a severe and life threatening disease (does not have ejection fraction less than 30%), access to telephone, propensity of participating in the program, possessing insurance booklet, not having uncontrolled diabetes mellitus, hypertension, hyperlipidemia (under treatment), and not being one

of health and treatment personnel or member of their families. In cases of lack of cooperation or the need to coronary artery bypass graft (CABG) during the study, patients were excluded. Patients possessing the inclusion criteria were enrolled in the study after completing the informed consent form, being equally divided into two intervention and control groups using a randomization list (random permuted blocks with length 4).

Intervention and outcome evaluation

Patients were visited daily in CCU of hospitals of Shiraz University of Medical Sciences by the researcher. Data collection was done through questionnaires before the intervention and 3 months after that. One questionnaire was about demographic information like age, sex, education level, marriage status, and occupation. The Walker and Pender's Lifestyle Questionnaire was also employed which included 52 items of lifestyle behaviors consisting of health responsibility (9 items), physical activity (8 items), nutrition (9 items), interpersonal relations (9 items), spiritual growth (9 items), and stress management (8 items). Items were rated on a 4-point Likert-type scale (4 = as usual, 3 = most of times, 2 = sometimes, and 1 = never). Thereafter, the obtained scores from each domain were divided by the number of questions of that domain and the mean score of that domain was calculated for patients of both groups by researcher via interview at the beginning and 3 months after the intervention.

The reliability and content validity of this questionnaire was determined by Safabakhsh with Cronbach's alpha of 0.83.¹⁶ The content validity of the questionnaire was confirmed by 10 faculty members of Shiraz Nursing and Midwifery College. The Cronbach's alpha for each dimension was 0.928 (health responsibility), 0.943 (physical activity), 0.907 (nutrition), 0.849 (spiritual growth), 0.859 (interpersonal relations), and 0.703 (stress management).

The continuous care model was used in the intervention group for a period of 3 months. In the control group, the usual cares were applied. The continuous care was performed in four stages at the time of hospitalization of the patient:

1. Orientation: The first stage of continuous care model consisted of orientation with the aim of making a relationships with the client, attracting his/her collaboration to take part in the research, and creating motivation regarding the necessity of continuous care in the client.

2. Sensitization: The second stage of continuous care model was sensitization which was carried out

simultaneously with orientation, focusing on making the client sensitive to accept his/her health responsibility. In this stage, all educational needs of the patient was also evaluated and the necessary explanations regarding MI disease and its complications, the necessity of continuous care and the importance of improving lifestyle were presented to the patient during 45-60 minutes sessions. The orientation and sensitization was carried out by involving the patient and one of his/her family member. Family members were encouraged and instructed to participate in lifestyle change and to provide support for the rehabilitation practice of the patient. The above two stages took place at the first 3 weeks of the total period of performing the model (12 weeks).

3. Control: In this stage, the survey and continuity of care took place. Nine weeks were allocated to this stage during which the individual and group consultations (in the form of groups of 10 persons) and speech and question-answer sessions (considering the type and nature of needs and problems of patient and his/her family) were carried out at Shiraz Imam Reza clinic. The number of sessions depended upon the rate of knowledge, severity, and the number of similar problems for each of the subjects. On average, 2-4 sessions in the presence of patient and one of his/her family member were held for each group for a period of 1-2 hours. Then continuous care consultations took place daily, weekly and continuously in attendance at clinic or by telephone contacts depending on the type of care requirements. The telephone number of the researcher was given to patients to receive the answers of probable questions.

4. Evaluation: It was the fourth and final stage of the model but this step was considered from the beginning throughout all stages. The objective of this stage was to evaluate the process of care and determine and control the patient's behavior while being followed by researcher and by completing the self-report forms by the patients. The Benson's relaxation training CD and the training booklets regarding the disease were also given to patients of the intervention group.

Statistical analysis

Frequency distributions, mean, and standard deviation (SD) were calculated for the demographic variables. Chi-square analyses were used to assess the differences between groups in demographic variables at baseline. Paired sample t-test was used to test the changes in mean scores of the outcome variables for each group separately. Moreover, an independent sample t-test was applied in order to disclose differences in the mean scores of lifestyle and its related dimensions between the intervention and control groups. Mean differences between groups together with the corresponding 95% confidence Intervals (95% CI) were provided. For statistical analysis, SPSS version 15 (SPSS Inc., Chicago, IL) was used. Results of the tests with $P < 0.05$ were reported as to be statistically significant.

Results

The detailed demographic information about 70 participants is shown in table 1. The results of this study showed that both groups were similar as to the variables of age, sex, education level, marital and occupation status ($P > 0.05$).

Table 1. Baseline characteristics of the patients in control and intervention groups

		Control group	Intervention group	P*
		n (%)	n (%)	
Age group	≤ 50 years	14 (40.0)	15 (42.9)	0.810
	> 50 years	21 (60.0)	20 (57.1)	
Sex	Female	14 (40.0)	12 (34.3)	0.620
	Male	21 (60.0)	23 (65.7)	
Levels of education	Illiterate	13 (37.1)	12 (34.3)	0.170
	Primary	3 (8.6)	6 (17.1)	
	Secondary	5 (14.3)	10 (28.6)	
	Diploma or higher	14 (40.0)	7 (20.0)	
Marital status	Single	1 (2.9)	1 (2.9)	0.690
	Married	32 (91.4)	30 (85.7)	
	Widow	2 (5.7)	4 (11.4)	
Occupation	Employed	2 (5.7)	2 (5.7)	0.600
	Retired	8 (22.9)	4 (11.4)	
	Self-employment	13 (37.1)	17 (48.6)	
	House-keeper	12 (34.3)	12 (34.3)	

*P-value based on chi-square test

Table 2. Comparing dimensions of Life style in the two groups before intervention

Variables	Control group	Intervention group	P
	Mean ± SD	Mean ± SD	
Health responsibility	17.8 ± 3.8	19.2 ± 4.6	0.150
Physical activity	12.5 ± 2.8	13.2 ± 3.4	0.330
Nutrition	19.9 ± 3.6	21.5 ± 3.4	0.070
Spiritual growth	62.2 ± 5.1	27.8 ± 4.8	0.180
Interpersonal relations	24.3 ± 5.1	26.3 ± 4.2	0.070
Stress management	17.7 ± 4.2	17.5 ± 3.6	0.830
Total score	118.5 ± 16.3	125.6 ± 15.4	0.060

Table 3. Differences of mean scores within groups between baseline and three months later

Variables	Control group			Intervention group		
	Baseline	Three months later	P*	Baseline	Three months later	P*
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Health responsibility	17.8 ± 3.8	17.2 ± 4.4	0.39	19.2 ± 4.6	31.5 ± 3.6	< 0.001
Physical activity	12.5 ± 2.8	12.5 ± 4.0	1.00	13.2 ± 3.4	25.9 ± 5.3	< 0.001
Nutrition	19.9 ± 3.6	20.2 ± 4.4	0.73	21.5 ± 3.4	31.9 ± 3.4	< 0.001
Spiritual growth	62.2 ± 5.1	25.9 ± 6.2	0.69	27.8 ± 4.8	32.2 ± 3.4	< 0.001
Interpersonal relations	24.3 ± 5.1	24.3 ± 5.6	0.90	26.3 ± 4.2	31.3 ± 3.8	< 0.001
Stress management	17.7 ± 4.2	17.9 ± 4.4	0.88	17.5 ± 3.6	27.4 ± 7.1	< 0.001
Total score	118.5 ± 16.3	117.9 ± 22.0	0.83	125.6 ± 15.4	180.1 ± 19.9	< 0.001

* Based on paired t-test

Table 4. Difference in mean of lifestyle score and its dimensions between control and intervention group

	Change in control group	Change in intervention group	Difference between control and intervention		
	Mean ± SD	Mean ± SD	Mean difference	95% CI*	P**
Health Responsibility	-0.57 ± 3.8	12.2 ± 6.2	-12.8	(-15.3, -10.3)	< 0.001
Physical activity	0.00 ± 4.2	12.7 ± 6.5	-12.7	(-15.4, -10.1)	< 0.001
Nutrition	0.26 ± 4.4	10.5 ± 4.2	-10.2	(-12.3, -8.14)	< 0.001
Spiritual growth	-0.34 ± 5.0	4.34 ± 5.9	-4.68	(-7.30, -2.07)	0.001
Interpersonal relations	-0.08 ± 3.9	4.91 ± 5.5	-5.00	(-7.26, -2.73)	< 0.001
Stress management	0.11 ± 4.3	9.83 ± 7.1	-12.5	(-12.5, -6.91)	< 0.001
Total score	-0.63 ± 17.1	54.5 ± 25.2	-55.1	(-65.4, -44.9)	< 0.001

* 95% CI: 95% confidence interval

** Based on independent sample Student's t-test

Moreover, the mean scores related to various dimensions and the total score of lifestyle of subjects in intervention and control groups were examined before the intervention (Table 2). The findings based on independent sample t-test showed that both groups were similar before the intervention ($P > 0.05$). The mean scores and SDs for the intervention and control groups at baseline and 3 months of follow-up visits are shown in table 3. The intervention group improved significantly on all related dimensions of lifestyle (health responsibility, physical activity, nutrition, interpersonal relations, spiritual growth and stress management) as well as the total lifestyle score at the three months follow-up visits. However, in the control group the changes in the mean score remained stable over the three months and these changes based on paired sample t-test were not

statistically significant.

Table 4 provides the mean difference and confidence intervals for changes between baseline and three months follow-up in both groups for the total lifestyle score and its dimensions. When comparing the differences between the changes from the baseline to the three month evaluation of the intervention and the control group, independent sample t-test showed a statistically significant increase in the mean scores of lifestyle and its related dimensions in the intervention group ($P < 0.05$).

Discussion

Results of the present study showed that there was a significant difference before and after the intervention in both groups. Therefore, applying continuous care model could have positive effects on the lifestyle of patients with MI. The features of

this study were: 1) Initiating of intervention at the time of hospitalization of the patient when most patients are motivated to change behavior, 2) evaluating all educational needs of the patients and the necessary explanations regarding MI and its complications, 3) follow-up care after discharge and providing essential information, 4) using self-report form and nurse-reinforcement of daily health behaviors, and 5) involving one of his/her family member to participate in lifestyle change and provide support for patients.

Similar to the results of this research, another study indicated that a nurse-led cardiac rehabilitation program can significantly improve the health behaviors and cardiac physiological risk factors in coronary heart disease patients.¹⁷ Based on these findings, it is necessary to consider the role of nurses in a cardiac rehabilitation program.

Some studies showed that participation in cardiac rehabilitation programs had positive changes in various risk factors like blood pressure, total cholesterol, triglyceride, HDL and LDL cholesterol^{17,18} energy expenditure, fat, and stress.¹⁸ Following up the client's behavior at home helped better controlling the heart disease. This reduced the frequency of their rehospitalization, cost of hospitalization and mortality rate.⁹

Gordon et al. also showed a reduction in risk factors of patients with MI, CABG, percutaneous coronary intervention, or angina after participating in traditional cardiac rehabilitation, cardiac rehabilitation with physician supervision, and a community-based exercise program run by exercise physiologists.¹⁹

In addition, several studies showed that continuous care model has positive effects on the quality of life of patients after CABG²⁰ and heart failure, in all physical, emotional and general dimensions.²¹ This model was effective in the reduction of the hospitalization period and chest pain in patients with coronary vascular diseases.⁹ However, the study carried out by Mohammadi et al. aiming to determine the effect of applying cardiac rehabilitation at home on the quality of life of patients with MI showed that the rehabilitation program consisting of training sessions regarding MI disease and its complications, dietary and medicinal regime, risk factors of the disease, etc. at home had no particular effect on various dimensions of the quality of life of this group of patients and there was no significant difference between groups.²² These discrepancies could be related to sample size or follow-up period of patients.

Some evidences showed that education programs and follow-up by telephone have positive effects on knowledge, self-care behaviors, and disease symptoms of patients with cardiac failure.¹³ Patients forget the therapeutic recommendations gradually after discharge from the hospital; therefore, it is necessary to provide such information. On the other hand, the number of healthy undesirable behaviors of patients with MI increases if it is not followed-up at home.²² Since the patients' participation in cardiac rehabilitation programs after an acute MI is low,²³ they require education and follow-up regarding the control of symptoms, medicinal information, and improvement of lifestyle.²⁴

Conclusion

Considering the results of the present study and the available evidence, a management program by the nurses (nurse-leader) accompanying follow-up by telephone could be a successful and practical model for behavior change in patients with MI. Therefore, continuous care model could be applied by nurses as an effective method to reduce risk factors and improve the lifestyle of patients with MI. Rehabilitation centers also could apply this model to follow the patients after MI. Further studies with larger sample size and longer follow-up are recommended to investigate the influence and continuity of the effects of these interventions.

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Conflict of Interests

Authors have no conflict of interests.

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Preconditioning by isoflurane as a volatile anesthetic in elective coronary artery bypass surgery

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Original Article

Abstract

BACKGROUND: Some pharmacological preconditioning approaches are utilized as an effective adjunct to myocardial protection, particularly following cardiac procedures. The current study addressed the potential clinical implications and protective effects of isoflurane as an anesthetic most applicable on postoperative myocardial function measured by cardiac biomarkers.

METHODS: 46 patients were included in the study. In 23 of them, preconditioning was elicited after the onset of cardiopulmonary bypass via a 5-minute exposure to isoflurane (2.5 minimum alveolar concentration), followed by a 10-minute washout before aortic cross clamping and cardioplegic arrest. 23 case-matched control patients underwent an equivalent period (15 minutes) of pre-arrest isoflurane-free bypass. Outcome measurements included creatine phosphokinase (CPK) and creatine kinase–MB (CK-MB) levels until 24 hours after the surgery.

RESULTS: None of the differences in enzyme levels at baseline and 24 hours after surgery between the two groups reached the threshold of statistical significance. The level of CPK was significantly reduced 24 hours after surgery compared with the baseline in the two groups. However, the postoperative release of CPK was consistently smaller in the isoflurane-preconditioned group than in the control group. The release of CK-MB displayed a statistically similar pattern. Multivariate linear regression analysis showed the effect of isoflurane regimen on reducing CPK level within the 24 hours after surgery compared with placebo.

CONCLUSION: Our study supports the cardio protective effect of isoflurane and the role of pharmacological preconditioning of the human heart by this volatile anesthetic during elective coronary artery bypass surgery.

Keywords: Preconditioning, Isoflurane, Volatile Anesthetic, Coronary Artery Bypass Surgery

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Introduction

The increase in cardiac biomarkers appearance following cardiac invasive procedures has been known as accepted indicatives of cell death. Some of these chemical markers, such as creatine phosphokinase (CPK) and creatine kinase-MB (CK-MB), can specifically reflect myocardial necrosis.¹ Therefore, they can predict the outcome of acute coronary syndrome and heart failure, and different cardiac procedures such as bypass surgery

or coronary stenting.²⁻⁶ The use of cardiac protecting strategies can improve the tolerance of the myocardium to myocardial ischemia and necrosis; and therefore, lead to reducing cardiac damages. Some approaches, including pharmacological preconditioning, can be utilized as an effective adjunct to myocardial protection. In this context, volatile anesthetics that are commonly used in general anesthesia for inducing hypnosis, analgesia, amnesia, and mild muscle relaxation are effective

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adjuncts, which provide protection against reperfusion injury.⁷ Some researches on animal models showed an improving post-ischemic recovery at the cellular level in isolated hearts.⁸ In addition, a reduction in the release of cardiac damage biomarkers in those receiving volatile anesthetics as a part of their anesthesia plan has been documented after cardiac surgery, along with reduction in incidences of perioperative myocardial infarction and death.⁹ On the other hand, volatile anesthetics can provide protection against reperfusion injury when administered after myocardial ischemia. However, a few studies have assessed the importance of the myocardial protective effects of these anesthetics when administered before ischemia or during reperfusion. Moreover, a few small randomized controlled studies have yielded conflicting results with respect to the effects of volatile anesthetics on the extent of myocardial damage as assessed by measuring postoperative cardiac biomarker release after cardiac revascularization.

The current study addressed the potential clinical implications and protective effects of isoflurane as a most applicable anesthetic on postoperative myocardial function with the measurement of CPK and CK-MB markers.

Materials and Methods

The current study was a double-blind, placebo-controlled, randomized clinical trial. It was conducted on forty six consecutive patients with two or three diseased coronary arteries confirmed by coronary angiography, and scheduled for isolated elective coronary artery bypass grafting. Patients with active heart failure, previous unusual response to anesthetics, and those who experienced myocardial infarction during the preceding 6 weeks or any cardiac or non-cardiac surgical procedures during current admission were excluded. The other exclusion criteria were the following: concomitant aortic or valvular surgery, elevated CK or CK-MB concentrations within 24 hours before surgery, unstable angina, angina within 24 hours before surgery, haemodynamic instability with the need for medical or mechanical inotropic support, re-intervention, preoperative values of creatinine > 2.0 mg/dl, chronic obstructive pulmonary disease, age of over 70 years, preoperative ejection fraction inferior to 40%, or preoperative hepatopathy. The participants were also excluded if they had used theophylline, sulfonyleureas, allopurinol, or anti-diabetics within the one month before surgery because of their inhibiting effects on

pharmacological preconditioning. Study protocol was performed according to the principles of the Declaration of Helsinki and approved by the ethics committee of the Isfahan University of Medical Sciences, Iran. Written informed consents were obtained from all participants. Baseline characteristics and periprocedural data were collected from the hospital recorded files or via face to face interviewing by a trained, blinded, observer nurse who did not participate in patient care. This information included demographics, general risk factors for coronary artery disease, used drugs, the number of diseased coronary arteries, and left main lesions. Patients were randomly divided into two groups by opening of a sealed envelope the evening before the surgical procedure, and then allocated to receive either isoflurane or placebo. Both groups received general anesthesia (diazepam, fentanyl, pan chromium in a closed circuit). Preconditioning was achieved with a 5-minute exposure to isoflurane (2.5 minimum alveolar concentration), followed by 10 minutes of isoflurane-free bypass before aortic cross-clamping. Isoflurane was added to the gas mixture in the oxygenator. Control patients underwent a time-matched (15-minute) period of isoflurane-free cardiopulmonary bypass and air and oxygen without isoflurane was administered. The type of anesthesia was similar in both groups during cardiopulmonary bypass. The randomization management was delegated to a person unconnected to the clinical experimentation. No operator involved in the care of the patients in every phase had any knowledge of the group to which each single patient belonged; apart from the person who collected the data and the individual who carried out the statistical analysis. No other volatile anesthetics were administered at any time during the study. Blood samples to evaluate CPK and CK-MB chemical parameters were obtained from peripheral venous blood preoperatively and 24 hours after the end of surgery. Blood was collected in plastic tubes with clot activator and was centrifuged before chemical analysis. Myocardial infarction was detected by both enzyme and ECG. In the present study, we tested the hypothesis that the volatile anesthetic isoflurane, given before coronary artery bypass grafting (CABG) will reduce perioperative myocardial damage, as assessed by CPK and CK-MB enzymes, when compared with placebo. Therefore, the main endpoint of the study was the postprocedural release of these two enzymes.

Results were reported as mean \pm standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Mann-Whitney or

Wilcoxon tests for the continuous variables and the chi-squared test (or Fisher's exact test if required) for the categorical variables. Changes in cardiac enzymes were determined primarily by comparing the change between the baseline and final measurements of these enzymes. We also used a multivariate linear regression analysis to evaluate the relationship between cardiac enzyme change and type of treatment schedule with the presence of other variables as cofounders. Beta (β) and standard error for β were calculated. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS for Windows version 16 (SPSS Inc., Chicago, IL) and SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC).

Results

The baseline characteristics and clinical data for the patients are summarized in table 1. The two groups were similar with respect to study parameters,

including demographics, medical history, drug history, the number of involved coronary arteries as well as left main lesion. As presented in table 2, none of the differences in enzyme levels at baseline and 24 hours after surgery between the two groups reached the threshold of statistical significance. The level of CPK was significantly reduced 24 hours after surgery compared with the baseline, however, the postoperative release of CPK was consistently smaller in the isoflurane-preconditioned group than in the control group. The release of CK-MB displayed a statistically similar pattern. Multivariable linear analysis showed the effect of isoflurane regimen on reducing CPK level within the 24 hours after surgery compared with placebo (Table 3).

There were no isoflurane-related side effects. Postoperatively, there were no deaths and no patient had a transmural myocardial infarction. Inotropic support was required in none of the patients of the control and isoflurane-preconditioned groups.

Table 1. Baseline characteristics and clinical data of patients who received isoflurane or placebo

Characteristics	Isoflurane group (n = 23)	Placebo group (n = 23)	P
Gender (male)	18 (87.5)	15 (71.4)	0.454
Age (year)	61.6 \pm 5.4	58.7 \pm 9.1	0.198
Body mass index (kg/m ²)	27.4 \pm 2.9	27.2 \pm 4.3	0.904
Cigarette smoking	3 (13.0)	8 (34.8)	0.084
Opium addiction	3 (13.0)	4 (17.4)	0.678
Myocardial infarction	5 (21.7)	4 (17.4)	0.713
Serum creatinine	0.96 \pm 0.23	0.99 \pm 0.21	0.594
Drug history			
Aspirin	8 (34.8)	6 (26.1)	0.522
Warfarin	0 (0.0)	1 (4.3)	0.315
Beta-blocker	4 (17.4)	3 (13.0)	0.678
Ca-blocker	3 (13.0)	2 (8.7)	0.639
Diuretic	1 (4.3)	2 (8.7)	0.545
ACE inhibitor	3 (13.0)	2 (8.7)	0.639
Digoxin	0 (0.0)	1 (4.3)	0.315
Statins	0 (0.0)	1 (4.3)	0.315
Insulin	2 (8.7)	0 (0.0)	0.198
Diseased vessels			
Two coronaries	2 (8.7)	3 (13.0)	0.998
Three coronaries	21 (91.3)	20 (87.0)	
Left main lesion	6 (26.1)	8 (34.8)	0.522
Ejection fraction	53.6 \pm 11.1	53.1 \pm 10.3	0.964

Data are presented as mean \pm SD or number (%); ACE: Angiotensin converting enzyme

Table 2. Cardiac enzymes concentrations at the baseline and 24 hours after the coronary artery bypass surgery

Characteristics	Isoflurane group median (mean \pm SD) (n = 23)	Placebo group median (mean \pm SD) (n = 23)	P
CPK			
At baseline	410 (487.4 \pm 264.8)	410 (401.7 \pm 182.9)	0.091
24 hours after CABG	277 (267.7 \pm 44.6)	277 (314.9 \pm 184.2)	0.120
P	< 0.001	0.043	
CK-MB			
At baseline	44 (52.4 \pm 34.0)	46 (71.1 \pm 67.0)	0.132
24 hours after CABG	35 (44.3 \pm 23.6)	43.5 (46.3 \pm 19.7)	0.250
P	0.351	0.096	

Data are presented as median (mean \pm SD); CPK: Creatine phosphokinase; CK-MB: creatine kinase-MB; CABG: Coronary artery bypass grafting

Table 3. Multivariate lineae regression analysis of the effect of isoflurane regimen on change in serum CPK level within the 24 hours after coronary artery bypass surgery

Variables	Beta	Standard error	P
Baseline CPK	0.036	0.08	0.665
Isoflurane therapy	-126.5	57.3	0.011
Male gender	15.12	37.9	0.694
Age (year)	3.142	2.5	0.226
Body mass index (kg/m ²)	5.128	4.5	0.268
Diabetes mellitus	2.907	44.3	0.948
Cigarette smoking	70.99	4.9	0.104
Opium addiction	66.95	42.1	0.126
Myocardial infarction	106.91	45.1	0.027
Serum creatinine	51.07	91.9	0.584
Three vessel disease	84.76	69.8	0.237
Left main lesion	58.32	43.5	0.193
Ejection fraction	-3.873	1.40	0.011

R square: 0.510; CPK: Creatine phosphokinase

Discussion

The major finding of the current study is that CPK, as an applicable marker of cardiac damage, reduced significantly more in patients receiving isoflurane according to a preconditioning protocol than the placebo group. Our result was consistent with some other similar studies. In a study by Belhomme et al. a consistently smaller release of troponin I was revealed following administration of isoflurane in comparison with the control group, and the release of creatine kinase-MB followed a similar pattern.¹⁰ In another study by Lee et al. a consistently lower release of troponin I was observed in the isoflurane group compared to the control group, and the mean troponin I level was significantly reduced in the isoflurane group 24 hours after surgery.¹¹ Moreover, Tomai et al. showed that isoflurane could reduce myocardial injury only in patients with impaired left ventricular function undergoing CABG. In their study, when the comparisons were restricted to those patients with preoperative LVEF < 50%, 24 hours after the surgery the isoflurane-treated

patients exhibited a smaller release of troponin I and of CK-MB than controls.¹² However, some studies contrarily could not demonstrate the cardioprotective effect of isoflurane following CABG. In the study by Wang et al. although patients released slightly less CK-MB and troponin I than the controls postoperatively, the difference was not significant.¹³ Some mechanisms of isoflurane in protecting the heart from procedural damages have been considered. Recent studies using animal models of regional ischemia have shown that isoflurane can duplicate the infarct-limiting effects of ischemic preconditioning. On the other hand, this drug causes potassium channel activation, as suggested by the abolishment of its infarct-limiting effects with potassium channel blockers.¹⁴⁻¹⁶ It has also been confirmed that isoflurane increases the probability of potassium channel opening for any given concentration of ATP.¹⁷ This opening could then account for the increase in ecto-5 β -ectosomal activity that has been reported after pharmacological activation of the potassium channels.¹⁷ It was also demonstrated that isoflurane-induced preconditioning

can be dependent on the release of some free radicals such as mercaptopropionyl glycine (MPG) and Mn (III) tetrakis (4-benzoic acid) porphyrin chloride (MnTBAP) that can be markers of infarct size.¹⁸ Recent researches have studied the effect of intravenous and thoracic epidural analgesia after coronary artery bypass graft surgery, and the exact role of inflammatory markers and oxidative stress.¹⁹⁻²²

Because the primary effect of preconditioning is to reduce infarct size, the outcome analysis focused on the sensitive markers of cellular necrosis such as CPK, CK-MB, and troponin I.^{23,24} Although increases in creatine kinase (CK-MB) or troponin levels following CABG are common and are an indicator of myocardial necrosis, it seems that preconditioning with isoflurane and morphine, as general anesthesia drugs, decreased the enzyme level. We could confirm that the postoperative release of CPK enzyme was consistently lower in preconditioned patients than in their control counterparts. This is consistent with the cardio-protective effects of isoflurane. However, the between-group difference in CK-MB level which failed to achieve statistical significance can be explained by the small sample size of our study. Therefore, further studies are recommended to confirm the cardio-protective effect of isoflurane via reducing the release of CK-MB and troponin I using a greater sample size.

Conflict of Interests

Authors have no conflict of interests.

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Lipid profile in antipsychotic drug users: A comparative study

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Original Article

Abstract

BACKGROUND: Schizophrenic patients who receive antipsychotic drugs may be highly prone to metabolic disorders such as weight gain, dyslipidemia, and insulin resistance. The objective of the present study was to compare the effect of atypical and conventional antipsychotics on lipid profile.

METHODS: 128 schizophrenic patients were enrolled into the study. Patients were divided into two groups. One group had received one type of atypical antipsychotic drug, and, the other, one type of conventional antipsychotic drug. They were considered as atypical and conventional groups. Moreover, both groups had not used any other antipsychotic drugs during the past year. Demographic data and food frequency questionnaire were completed by the participants. Serum triglyceride, total cholesterol (TC), high-density lipoprotein and low-density lipoprotein (LDL) cholesterols, and apolipoprotein A and B (Apo B) were tested by blood sample drawing after 12 hours of fasting through the antecubital vein. Student's t-test was used to compare atypical and conventional groups.

RESULTS: There was no significant difference in age, gender, duration of illness, period of drug consumption, and age at onset of illness in the two groups. Patients in the atypical group used clozapine and risperidone (46.9%) more than olanzapine. In the conventional group 81.3% of patients used phenothiazines. Comparison between lipid profile in the conventional and atypical groups showed a significantly higher mean in TC ($P = 0.01$), LDL ($P = 0.03$), and Apo B ($P = 0.01$) in conventional group than the atypical group.

CONCLUSION: In schizophrenic patients, the level of lipid profile had been increased in both atypical and conventional antipsychotic users, especially conventional users, so the effect of antipsychotic drugs should be investigated periodically.

Keywords: Atypical Antipsychotic, Conventional Antipsychotic, Lipid Profile

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Introduction

Antipsychotic agents are mainly used for prevention or treatment of schizophrenia and serious psychotic diseases. There is no suitable monitoring method for the selection of antipsychotic agents, forecast of curative effect, and adjustment of dose. Therefore, to study the curative and toxic effect, and side effects, and to improve the physical health and remote therapy for the prevention and treatment of

mental diseases it has become an issue of international concern.¹

The data generated from studies of schizophrenia patients exposed to conventional antipsychotics illustrate that agents with similar modes of therapeutic action may have significantly different metabolic profiles. Several studies emerged examining the metabolic profiles of this class of antipsychotics. In general, these antipsychotic drugs

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were found to elevate serum triglycerides (TG) and total cholesterol (TC), but with greater effects on TG concentrations. Subsequent studies confirmed the finding that high serum TG seemed to be the primary significant dyslipidemia, but elevated TC could also be found.²

Over the past decade, atypical (or second-generation) antipsychotics have been increasingly used in the treatment of schizophrenia in preference to conventional (first-generation) drugs.³ However, there have been numerous studies that certain atypical antipsychotics have been associated with a greater risk of metabolic abnormalities, including weight gain, hyperlipidemia and new-onset type 2 diabetes mellitus, and elevations of blood cholesterol, triglyceride, and lipid levels.^{4,6}

Due to long term consumption of these drugs in schizophrenic patients, their side effects on metabolic syndrome is notable and should be considered. Thus, in this study, we tried to compare lipoprotein and apolipoprotein serum levels in schizophrenic patients under treatment of conventional or atypical antipsychotic drugs.

Materials and Methods

This case-control study was carried out on 128 schizophrenic patients in 2009. All patients had the criteria for schizophrenia of the fourth edition of Diagnostic and Statistical Manual of Mental disorders (DSM-IV, American Psychiatric Association, 1994); they had received one type of atypical or conventional antipsychotic drug for at least one year before sampling.⁷

Patients, who have received one type of atypical antipsychotic drug and have not received any other antipsychotic drug during the past year, with age range of 21-46 years were considered as atypical group. Patients, who have received one type of conventional antipsychotic drug and have not used any other antipsychotic drug during the past year, with age range of 20-40 years were considered as conventional group.

Inclusion and Exclusion criteria

Patients with an Axis I disorder other than schizophrenia, with an Axis II disorder, or patients at significant suicide risk were excluded via a semistructured psychiatric interview.

Exclusion criteria for the atypical and conventional group included lipid lowering agent and beta blockers consumption and organic diseases such as hypertension, diabetes, cardiovascular, adrenal, hepatic, and thyroid disease documented through physical examination and laboratory tests. In order to

screen organic diseases, laboratory tests including complete blood count, serum electrolyte assay, thyroid function tests, liver function tests, urine analysis, and ECG were performed for all participants.

In addition, informed consents for this study were obtained from participants and their families after complete explanation.

Measurements

All individuals completed a self-administered questionnaire to determine demographic characteristics such as age, gender, duration of illness, the age at onset of illness, duration, and type of drug consumption.

According to their dietary habits, each patient completed a Food Frequency Questionnaire. This instrument was designed according to the WHO's Food Frequency Questionnaire; however, some additions were made. Validity of the questionnaire was confirmed by the Medical Education Development Centre, affiliated to Isfahan University of Medical Sciences, Iran, before being used.⁸

Blood sample was drawn after 12 hours of fasting through the antecubital vein. All the blood sampling procedures were performed in the central laboratory of Isfahan Cardiovascular Research Center, using enzyme-linked method. Serum triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL)-cholesterol, and apolipoprotein A (Apo A) and B (Apo B) were analyzed at sampling date. TC and TG levels were measured within 24 hours by an enzymatic method in Elan2000 autoanalyzer. HDL was assayed with direct method, while LDL was calculated by the Friedewald et al. formula; in cases that TG \geq 400 mg/dl it was measured directly.⁹ Apolipoprotein A and B cases were measured by the Immunturbidometric technique by Pars Azmon-Iran.

Statistical Analysis

Data was analyzed by SPSS for Windows version 15.0 (SPSS, Inc., Chicago, IL). $P \leq 0.05$ was considered significant. All continues variable data were expressed as mean \pm SD and t-test was used for case-control group comparison. Data regarding qualitative variables was expressed as frequency and chi-square was used for the two groups.

Results

There were 128 participants in this study, 96 (75%) male and 32 (25%) female with the mean age of 46.15 ± 12.41 years. They were divided into two equal groups; atypical and conventional groups.

Table 1 shows the characteristics of participants.

In the atypical and conventional groups, there was no significant difference in age, gender, duration of illness, and age at onset of illness. Patients in the atypical group, used olanzapine in 4 (6.3%), clozapine in 30 (46.9%) and risperidone in 30 (46.9%) cases. In the conventional group 56 (81.3%) patients used phenothiazines, 4 (6.3%) thiothixene, and 8 (12.5%) haloperidol.

Table 2 shows drug consumption other than conventional or atypical antipsychotics in the two groups.

Finally, table 3 shows lipid profile in conventional and atypical group. Comparison between the two groups shows a higher mean in TC, LDL, and Apo B in the conventional group than the atypical group, with a significant difference in TC ($P = 0.001$), LDL ($P = 0.001$), and Apo B ($P = 0.001$).

Discussion

The current study is a case-control study of schizophrenia in regard to lipid profile, especially close consideration of serum lipoprotein levels and apolipoproteins A and B, in patients receiving conventional or atypical antipsychotic drugs. In total, we observed that serum lipoprotein levels were high in the two groups. The mean level of HDL and Apo A in the two groups was not significantly different. The mean level of total cholesterol (TC), Apo B, and LDL were statistically higher in the conventional group than the atypical group.

There is no clear evidence to whether atypical antipsychotics are more effective or are better tolerated than conventional antipsychotics.¹⁰

Table 1. Characteristics of patients in the two groups

	Conventional group n = 64	Atypical group n = 64	P
Age (Mean \pm SD) y	47.16 \pm 11.22	45.13 \pm 12.12	0.320
Gender (%)	52.00 (81%)	42.00 (67%)	0.060
Duration of illness (Mean \pm SD) y	17.21 \pm 11.25	18.54 \pm 12.41	0.520
Drug consumption duration (Mean \pm SD) m	15.21 \pm 3.11	17.31 \pm 4.22	0.001
Age onset of illness (Mean \pm SD) y	15.81 \pm 10.78	14.64 \pm 11.83	0.550

Table 2. Consumption of other drugs in the two groups

	Conventional group n = 64	Atypical group n = 64	P
Mood stabilizer	8 (12.5%)	18 (28.1%)	0.028
Tricyclic antidepressant	4 (6.2%)	10 (15.6%)	0.080
Anticholinergic agents	38 (59.4%)	26 (40.6%)	0.030
Selective serotonin reuptake inhibitors	6 (9.4%)	8 (12.5%)	0.570
Benzodiazepines	22 (34.4%)	36 (56.2%)	0.010
Phenobarbital	2 (3.1%)	0 (0.0%)	0.490
Amantadine	0 (0.0%)	2 (0.3%)	0.490

Table 3. Lipid profile and Apo A and B in the two groups

	Conventional group n = 64	Atypical group n = 64	P
Total cholesterol (Mean \pm SD) mg/dl	249.75 \pm 34.44	214.25 \pm 50.32	0.001
Low density lipoprotein (Mean \pm SD) mg/dl	149.96 \pm 24.21	131.93 \pm 36.81	0.001
High density lipoprotein (Mean \pm SD) mg/dl	44.71 \pm 11.81	45.18 \pm 9.42	0.800
Apolipoprotein A (Mean \pm SD) mg/dl	137.12 \pm 23.69	134.05 \pm 22.71	0.450
Apolipoprotein B (Mean \pm SD) mg/dl	122.81 \pm 20.51	104.56 \pm 33.63	0.001

A study was conducted to determine the prevalence of hyperlipidemia in persons who did or did not take antipsychotic drug. High lipid levels were found in persons treated with both atypical and conventional drug. The prevalence of hypercholesterolemia, high LDL cholesterol, and hypertriglyceridemia was high in persons using all types of antipsychotic drugs; this was consistent with our results.¹¹

One study comparing serum TC and TG levels among hospitalized male chronic schizophrenics receiving phenothiazines, or butyrophenones and age and sex-matched controls revealed the negligible effects of butyrophenones on serum lipids. However, it demonstrated significant elevations in serum TG levels for the phenothiazine group compared to the butyrophenone group and controls. There were no significant differences in TC values between the three groups. However, the phenothiazine-treated patients had significant elevations in low-density lipoproteins (LDL-c), and decreased high-density lipoprotein (HDL-c) concentrations.²

A five year naturalistic study on outpatients with schizophrenia or schizoaffective disorder showed that patients treated with clozapine experience significant weight gain and lipid abnormalities.¹² Serum glucose, and lipid were changed during the course of clozapine treatment. There were significant increases in serum triglyceride, total cholesterol, and glucose levels during the treatment. No significant changes were observed in high density lipoprotein (HDL) or low density lipoprotein (LDL).¹³ The effects of olanzapine and risperidone exposure on risk of hyperlipidemia in schizophrenic patients were evaluated in a large health care database. Accordingly, olanzapine use was associated with nearly a 5-fold increase in the odds of developing hyperlipidemia compared with no antipsychotic drug and more than a 3-fold increase compared with those receiving conventional agents. Risperidone was not associated with increased odds of hyperlipidemia compared with no antipsychotic or conventional exposure.⁵ These results are inconsistent with our study.

According to above studies, different atypical or conventional antipsychotic drugs have different effects on lipid profiles, but we did not investigate the effect of atypical and conventional antipsychotic drugs separately. In the conventional group patients used phenothiazines, and in the atypical group patients used clozapine and risperidone more than other types of antipsychotic drugs. Therefore, our results may not be consistent with other studies.

Limitation

The limitation of this study is that the effects of antipsychotic drugs on lipid profiles have been performed exclusively in populations with schizophrenia or schizoaffective disorder. Currently, antipsychotic drugs have widespread use for other psychiatric conditions, including major depression, anxiety disorders, and dementia. The generalizability of these prior studies to other patient populations is unclear. Extending generalizability is particularly important given that schizophrenia may in itself be a risk factor for the development of an adverse metabolic profile. The effect of each drug has not been investigated, so our study results differ from other studies.

Conclusion

In summary, our data suggest that patients treated with antipsychotics are at a higher risk for the development of lipid abnormalities than the general population. In patients who use antipsychotic drugs, lipid profile and metabolic risk factors should be investigated periodically.

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Conflict of Interests

Authors have no conflict of interests.

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Clinical associations between renal dysfunction and vascular events: A literature review

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Review Article

Abstract

Chronic kidney disease affects several other organs of the human body, and causes high levels of morbidity and mortality due to these effects. The cardiovascular system is probably the most vulnerable organ to a decrease in kidney function, and responds very fast to this effect. To the extent that, more kidney disease patients die of cardiovascular events than that of the original renal disease. Moreover, cerebrovascular events have been confirmed to increase, and to have inferior outcomes on the general population. In this review article, we aim to review studies investigating effects of renal disease on vascular events.

Keywords: Renal Disease, Cardiovascular Disorders, Dialysis, Myocardial Infarction, Risk Factor

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Introduction

As more new data is gained through the newly published studies, it has become more evident that kidney diseases can result in vascular disorders and ominous events. In chronic kidney diseases, it has been suggested that mortality more often occurs due to cardiovascular events than the kidney disease itself.¹ Several explanations have been proposed for the observed connections by different authors. In this literature review, we try to summarize the existing data that relates kidney disorders to cardiovascular (CAV) and/or cerebrovascular (CBV) events.

The first part of the present review will, therefore, focus on the epidemiological evidence of links between CAV events and impairment of renal function. The second part will deal with the same relationship between CBV and kidney failure. In the third part we will focus on the newly introduced parameter of renal function, cystatin C, which has been proposed as the most accurate biomarker that shows kidney function irrespective of patients demographic factors including age, sex, muscular property, and etcetera. The fourth part more delicately analyses the associations between different stages of kidney disease, and incidence and outcome of the mentioned vascular events. In the

fifth part we will review data on the treatment of CAV and CBV events in renal disease patients. Finally, in the sixth and last part we make a conclusion of the reviewed articles.

Epidemiology of cardiovascular disorders in kidney dysfunction

Epidemiological evidence for the relationship between renal dysfunction and adverse CAV events is most apparent in the hemodialysis population where the mortality rate associated with cardiovascular events exceeds that of the original renal disease; at least 50% of the mortality in the population has been attributed to the CAV events.² Therefore, it is observed that cardiovascular disorders are very prevalent in the dialysis population. 40% of patients starting dialysis have evidence of coronary artery disease, and 85% of the same patients represent abnormal left ventricular structure and function.³ In peritoneal dialysis patients, it has been reported that 44% have left ventricular hypertrophy (LVH).⁴ In another study, this proportion in pediatric patients on peritoneal dialysis has been reportedly over 48%.⁵ In hemodialysis patients, the condition is even worse and a single center reported that 69% of their hemodialysis patients had LVH compared to 45%

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in their peritoneal dialysis patients.⁶ In pediatric patients, hemodialysis patients have a higher rate of LVH than peritoneal dialysis patients (85% vs. 68%, respectively).⁷ Yet, progressive LVH is supposed to be the strongest predictor of sudden death in dialysis patients.⁸ The rate of LVH has also been attributed to the degree of creatinine clearance; with more severe hypertrophy in lower rates of creatinine clearance.^{9,10}

Prolonged QT interval is also a strong predictor of long term mortality in end-stage renal disease (ESRD) patients.¹¹ It has also been shown that QTc in dialysis patients significantly increases and can be determined in up to 46% of patients.^{12,13} A comparable rate of QTc prolongation has also been observed among peritoneal dialysis patients with a prevalence of 41%.¹⁴

The risk of cardiovascular events in pre-dialysis patients of renal function disorders is also augmented. Data from the hypertension optimal treatment (HOT) study indicates that the adjusted relative risks for total mortality and for major cardiovascular and/or cerebrovascular events were 1.65 and 1.58, respectively, in subjects with glomerular filtration rate or GFR < 60 mL/min compared with those with a GFR > 60 mL/min.¹⁵

Epidemiology of cerebrovascular disorders in kidney dysfunction

The topic of cerebrovascular events occurring in the context of renal disease has recently received high levels of attention. The Northern Manhattan Study (NOMAS) followed 3298 stroke-free subjects of mean follow-up time of 6.5 years for vascular outcomes. This study showed that renal failure patients with GFR levels of between 15 and 59 mL/min are at a high risk for stroke (hazard ratio (HR) 2.65; 95% confidence interval (95% CI) 1.47 to 4.77).¹⁶ Moreover, impaired kidney function has been associated with cerebral microbleeding.¹⁷ The incidence of stroke and associated mortality is also higher in kidney disease patients compared with the general population. Presence of anemia, hypoalbuminemia, malnutrition, uremia, and hyperhomocysteinemia in patients with kidney failure are confirmed factors associated with higher incidence of stroke.¹⁸ Hemodialysis and renal transplant patients are at a higher risk of stroke compared with those who do not require renal replacement therapy. In a large cohort of dialysis patients and people of the general population, after adjustment for age, gender, and race, estimated rates of hospitalized stroke were markedly higher for

dialysis patients compared to the general population. The highest relative risk of stroke was among Caucasian females on dialysis compared to the general population (relative risk or RR: 6.1 [95% CI 5.1-7.1] for Caucasian males, RR: 4.4 [95% CI 3.3-5.5] for African American males, RR: 9.7 [95% CI 8.2-11.2] for Caucasian females, and RR: 6.2 [95% CI 4.8-7.6] for African American females).¹⁹ In a study on the United States Renal Data Systems, the rate of stroke among American dialysis patients was 33/1000 person-years. After adjustment for age and other demographics, high blood pressure (hazard ratio [HR] = 1.11) and markers of malnutrition including serum albumin (per 1 g/dl decrease, HR = 1.43), height-adjusted body weight (per 25% decrease, HR = 1.09), and a subjective assessment of undernourishment (HR = 1.27) were found to be associated with a higher risk of stroke in this population.²⁰ Finally, a recent meta-analysis of 21 studies which included 7863 stroke events suggested that an estimated glomerular filtration rate (EGFR) < 60 mL/min/1.73 m² is associated with the risk of stroke RR 1.43, 95% confidence interval (95% CI) 1.31 to 1.57; P < 0.001), but not an EGFR of 60-90 mL/min/1.73 m² (RR: 1.07, 95% CI: 0.98 to 1.17; P = 0.15).²¹ On the other hand, receiving hemodialysis, alone, worsens the outcome of acute stroke.²² A very interesting population based study in Japan showed that even a minimal kidney function decline is associated with a significantly higher rate of silent lacunar infarctions and white matter lesions.²³

Cystatin C

Cystatin C is a cysteine protease inhibitor excreted by almost all human cells and released into the bloodstream. It is, also, a serum index of renal function which appears to be independent of age, sex, and lean muscle mass, and is reportedly superior to GFR for this estimation. Therefore, it would be a good parameter to investigate the early stages of renal failure and, in this review article, its potential relations to cardiac diseases. This issue has recently attracted much attention. An almost 9 year cohort of 4637 elderly persons in the United States showed that higher cystatin C levels in a dose-response manner were directly associated with a higher risk of death from all causes (Compared to the first quintile, the hazard ratios and 95% confidence intervals (HR [95% CI]) for death were: second quintile: 1.08 [0.86-1.35]; third quintile: 1.23 [1.00-1.53]; fourth quintile: 1.34 [1.09 to 1.66]; quintile 5a: 1.77 [1.34 to 2.26]; 5b: 2.18 [1.72 to

2.78]; and 5c: 2.58 [2.03 to 3.27]). After multivariate analysis, compared with the lowest quintiles with cystatin C levels ≤ 0.99 mg/l, the highest quintile of cystatin C (≥ 1.29 mg per liter) was associated with a significantly elevated risk of death from cardiovascular causes (2.27 [1.73-2.97]), myocardial infarction (1.48 [1.08-2.02]), and stroke (1.47 [1.09-1.96]). The interesting observation of this study is that the fifth quintile of creatinine, as compared with the first quintile, was not independently associated with any of the mentioned outcomes.²⁴ A study by Koenig et al. confirmed these results and declared that multivariate analysis showed that the risk for a secondary CAV event remained significant for the highest quintile of cystatin C level in comparison to the lowest quintile, after adjustments for severity of coronary disease, history of diabetes mellitus, treatment with angiotensin-converting enzyme inhibitors, and C-reactive protein (2.27 [1.05-4.91]).²⁵

In another study in which only elderly patients with normal kidney function (measured by creatinine-based GFR) were enrolled, cystatin C concentrations had strong associations with death (hazard ratio, 1.33 [95% CI, 1.25-1.40]), cardiovascular death (1.42 [1.30-1.54]), noncardiovascular death (1.26 [1.17-1.36]), incident heart failure (1.28 [1.17-1.40]), stroke (1.22 [1.08-1.38]), and myocardial infarction (1.20 [1.06-1.36]) among these participants.²⁶ Again, serum creatinine concentrations had much weaker associations with each outcome and only predicted cardiovascular death. This study showed that even minor alterations in kidney function can augment CAV and CBV events and outcomes. A research studied the relevance of cystatin C for stroke events, and the risk of hemorrhagic and ischemic stroke, as compared with the first (lowest) quintile. This study found that the hazard ratios (and 95% CIs) for stroke were as follows: second quintile, 1.97 (1.07 to 3.64); third quintile, 2.71 (1.50 to 4.90); fourth quintile, 3.79 (2.12 to 6.75); fifth quintile, 6.38 (3.60 to 11.32).²⁷ Follow-up of the patients and controls also showed that high cystatin C levels were associated with high prevalence of cardiovascular events or death from all causes.

Stage of renal disease and risk of vascular events and death

Table 1 shows the stages of the severity of chronic kidney disease. Several authors have investigated whether the stage of kidney disease can predict the incidence and outcome of cardiovascular and cerebrovascular events in renal disease patients.

Unfortunately, not all the studies have reported their data in a comparable manner so that we could be able to summarize them into a table. For example, most studies have merged some stages together to make smaller number of patient groups to compare, or their definition of GFR was not comparable. However, higher stages indicate overall worse kidney function. In a study on an American national survey, Ovbiagele showed that, compared to patients in stages 1 and 2 of kidney disease, renal patients with CKD stage 3 have a higher risk of developing stroke (OR: 2.09 (95% CI: 1.38-3.16)). This risk increases in patients of stages 4 and 5 (2.33 (0.1-5.46)).²⁶ Another study by Tsagalis et al. investigated the risk of developing cardiovascular events and its associated mortality in renal disease patients. They found that, compared to stages 1 and 2 having kidney diseases of stage 3 or stages 4 and 5 are associated with substantial increase both in the risk of development of cardiovascular diseases.²⁸ Both of the above mentioned articles have categorized their patients' kidney disease based on creatinine-based GFR. However, Shlipak et al. in their study of significant methodology, have categorized their patients based on cystatin C, which has been shown to have a more significant correlation to renal disease than creatinine.²⁴

In this study, adjusted risk (Hazard ratio (HR) and 95% CI) of death from cardiovascular events with quintile 1 (cystatin C ≤ 0.89 mg/l) as reference were as follows: quintile 2 (cystatin C: 0.9-0.99 mg/l; HR [95%CI]: 1.33 [0.88–2.00]), quintile 3 (cystatin C: 1-1.1 mg/l; 1.93 [1.33–2.80]), quintile 4 (cystatin C: 1.11-1.28 mg/l; 1.99 [1.38–2.87]), quintile 5a (cystatin C: 1.29-1.39 mg/l; 2.48 [1.63–3.77]), quintile 5b (cystatin C: 1.4-1.59 mg/l; 2.73 [1.81–4.13]), and quintile 5c (cystatin C ≥ 1.6 mg/l; 2.83 [1.85–4.31]). Risk of myocardial infarction was for quintile 2 (0.97 [0.67–1.41]), quintile 3 (1.26 [0.89–1.78]), quintile 4 (1.14 [0.80–1.63]), quintile 5a (1.44 [0.91–2.28]), quintile 5b (1.30 [0.80–2.11]), and for quintile 5c (1.65 [1.03–2.64]). The risk of stroke events for each quintile was as follows: quintile 2 (1.22 [0.87–1.72]), quintile 3 (1.17 [0.83–1.65]), quintile 4 (1.15 [0.82–1.62]), quintile 5a (1.43 [0.92–2.21]), quintile 5b (1.97 [1.31–2.98]), and for quintile 5c (1.80 [1.16–2.79]).²⁴ In another study, Shlipak et al. investigated a similar issue in elderly patients with normal kidney function based on creatinine based calculations.²⁹ All these studies show that, irrespective of the parameter used for the definition of GFR, having higher stages of renal disease is associated with higher rates of CAV and CBV

events, and mortality. This urges us to develop preventive strategies for patients with any stage of renal disease.

Treatment

Treatment of cardiovascular events in renal disease patients has no major alterations than that in the general population.³⁰ Myoglobin is not a reliable biochemical marker in patients with renal failure, but both conventional isoforms of troponin seem safe in the diagnosis of a myocardial infarction.³¹ Management of acute coronary syndromes in renal failure patients is not much different from that in the general population. Moreover, medical and interventional procedures are recommended in these patients; with the suggestion of using more aggressive strategies for the prevention and treatment of acute myocardial infarction in patients on dialysis.³² This is because it has been shown that mortality from myocardial infarction in dialysis patients is three times greater than that in the general population.³³ A large observational study of over 16 thousand ESRD patients with myocardial infarction showed that using reperfusion therapy improves the survival rate of these patients.³⁴ Moreover, it has been shown that dialysis patients respond better to coronary artery bypass grafting (CABG) surgery than percutaneous coronary intervention. Furthermore, stent outcomes were relatively worse than CABG in diabetic patients.³⁵

Management of stroke in kidney disease patients is not suggested to be any different from that in the general population. However, according to the findings of a large prospective cohort study (CHOICE study), outcome after stroke, especially hemorrhagic stroke, was poor with a high case-fatality and low successful recovery rate with one month mortality rate of about 35%.^{36,37} This is quite inferior to the 10-20% adjusted stroke case-fatality in patients of non-dialysis setting.³⁸ The median presentation time of stroke was over 8 hours in the CHOICE study, which is much longer than that

observed in a systematic review.³⁹ However, the mean length of hospital stay, surprisingly, was similar to that in the general population.^{36,40} Several modifiable risk factors have been suggested for renal disease patients developing stroke, which includes hypertension, smoking, diabetes, cardiac disease, and alcohol.⁴¹ The utmost attention must be paid to these factors, due to their substantially higher incidence and the associated inferior outcome of stroke in kidney disease patients.

Kidney transplantation has been proposed as a beneficial method of renal replacement therapy that efficiently halts the progression of cardiovascular disorders in end-stage renal disease patients.⁴² In this study, including over 60 thousand kidney transplant patients, the rates of cardiovascular diseases reached to a peak during the first 3 months post-transplantation and decreased subsequently when data was censored for graft loss. This trend was available for either living or deceased donor transplantations and even in patients whose kidney loss was due to diabetes mellitus. On the other hand, the CVD rates in the ESRD patients on the transplant waiting list substantially increased by time. These data are indicative of the apparent beneficial effects of transplantation on CAV events in ESRD patients.

Immunosuppressive agents used for preventing rejection episodes in renal transplant patients, themselves, are associated with augmented risk for cardiovascular morbidities. Corticosteroids and ciclosporin are the agents with the most negative impact on weight gain, blood pressure, and lipids. Tacrolimus increases the risk of new-onset diabetes mellitus. Sirolimus and everolimus have the most impact on risk factors for post-transplant hyperlipidaemia. Modifications in immunosuppression could improve the cardiovascular profile but there is little evidence regarding the beneficial effects of these changes on patient outcomes.⁴³

Table 1. Stages of chronic kidney disease

Stages	GFR mL/min per 1.73 m ²	Description
1	≥ 90	Albuminuria or structural renal abnormality with normal GFR
2	60-89	Mild GFR decrease
3	30-59	Moderate GFR decrease
4	15-29	Severe GFR decrease
5	< 15 or on renal replacement therapy	Kidney failure

GFR: Glomerular filtration rate

With the dissimilar effects of different immunosuppressant agents on the cardiovascular risk factors in renal recipients, one may assume that knowing this, we can improve patients' outcome with the modification of the patients' drug regimen based on their cardiovascular risk factors. In fact, a recent study has confirmed this presumption showing that conversion from calcineurin inhibitors to sirolimus regresses left ventricular mass thickness regardless of blood pressure changes.⁴⁴ The same observation was also reported when everolimus was used in renal recipients whose cyclosporine dosage administration was diminished.⁴⁵

Conclusion

Even minimal kidney dysfunction is associated with increased rates of cardiovascular and cerebrovascular events. Moreover, the mortality rates associated with these conditions have also been reportedly higher in this patient population. Unfortunately, data on potential strategies which can safely decrease these risks is limited. However, knowing the major factors either in the incidence or outcome of cardiovascular or cerebrovascular disorders in renal disease patients gives us a key point for modification of these factors. Moreover, it urges us to conduct future research on the extent to which these modifications will improve the outcome of renal disease patients regarding vascular events. Nevertheless until we have strong data from large studies, preventive strategies as well as prompt diagnosis and management of the above mentioned disorders seem the best we can do to protect our kidney disease patients.

Conflict of Interests

Authors have no conflict of interests.

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Traumatic right pericardial laceration with tension pneumopericardium associated with hemodynamic instability: A case report

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Case Report

Abstract

BACKGROUND: Pneumopericardium is a rare complication following thoracic trauma, and urgent treatment is rendered necessary when it causes tension pneumopericardium due to cardiac tamponade.

CASE REPORT: The case presented here is a right pericardial laceration with tension pneumopericardium due to falling from a height, presenting to the emergency clinic of our hospital with hemodynamic instability.

CONCLUSION: Pneumopericardium that might develop due to blunt thoracic trauma can easily be diagnosed, may result in cardiac tamponade, and is a potentially fatal pathology without treatment.

Keywords: Pneumopericardium, Trauma, Cardiac Tamponade, Fall

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Introduction

Pneumopericardium is a collection of air in the pericardial cavity that rarely occurs. Penetrating or blunt thoracic trauma, barotrauma caused by respirators, pericardial infection by gas producing bacteria, intra-pericardial perforations of the intra-abdominal organs, and iatrogenic causes have been believed to play a role in the etiology of this disorder.¹ Pericardial laceration or rupture occurs extremely rarely due to blunt trauma; 50-64% of these cases are seen in the left pleuropericardial region, and 9-17% of the cases are seen in the right pleuropericardial region. Small lacerations are asymptomatic and are diagnosed incidentally during emergency thoracotomy.² Pneumopericardium, which is usually with a benign clinical picture, may cause no clinical findings when the volume of the collected air is small, while pericardial lacerations due to serious injury may cause a progressive air collection, cardiac tamponade, and deterioration of hemodynamic measures.³ Auscultation of the cases with pneumopericardium reveals pericardial friction rub, deep heart sounds, metallic heart sounds, and emphysema in transverse sinus, and subcutaneous emphysema can be seen in the chest radiography.¹ Treatment is planned according to the complications of pneumopericardium and the

presence of cardiac compression. No intervention is necessary when the amount of intrapericardial air is small and pneumopericardium is limited with stable hemodynamics. A case of right pericardial laceration and pneumopericardium associated with hemodynamic instability developed secondary to trauma is presented here, since such a clinical picture is extremely rare.

Case Report

An unconscious 44-year-old male patient was brought to the emergency department of our hospital due to falling from a height. The first physical examination revealed a poor general medical condition with a blood pressure of 70/40 mmHg and pulse of 138/minute. Cardiac friction rub and deep cardiac sounds were heard upon the auscultation of the thorax. Computed tomography (CT) of the thorax revealed pneumothorax in the right hemithorax, subcutaneous emphysema (Figure 1), and massive pneumopericardium (Figure 2). The polytraumatized patient underwent an urgent operation since his hemodynamic status was deteriorating. Upon anterolateral thoracotomy through the right sixth intercostal space, a vertical laceration of 10 cm length on the pericardium, close to the superior vena cava and right atrium, and

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anterior to the phrenic nerve, and a 5 cm parenchymal laceration at the right lung medium lobe lateral segment were observed. The pericardial laceration was lengthened through the apex of the heart for cardiac exploration and no cardiac rupture, contusion, hemorrhage, and additional pericardial laceration was identified. Thus, the laceration was repaired with an approximation suture, placing a 32F thorax drain. Parenchymal defect at the medium lobe of the right lung was primarily repaired by a thoracic surgeon. Tissue layers were closed appropriately with placement of a 32F thoracic drain in the right

hemithoracic space, since no bleeding, air leak, or diaphragm pathology was seen. The polytraumatized patient was operated on by orthopedic surgeons for pelvic and right femur neck fractures, and by general surgeons due to intra-abdominal bleeding with intensive blood and blood product transfusion on the same session. Blood pressure was 100/60 mmHg with a pulse rate of 90/min. In the early postoperative period under cardiac supportive therapy, disseminated intravascular coagulopathy (DIC) developed and the patient died, in spite of all supportive therapy, 40 hours after surgery.

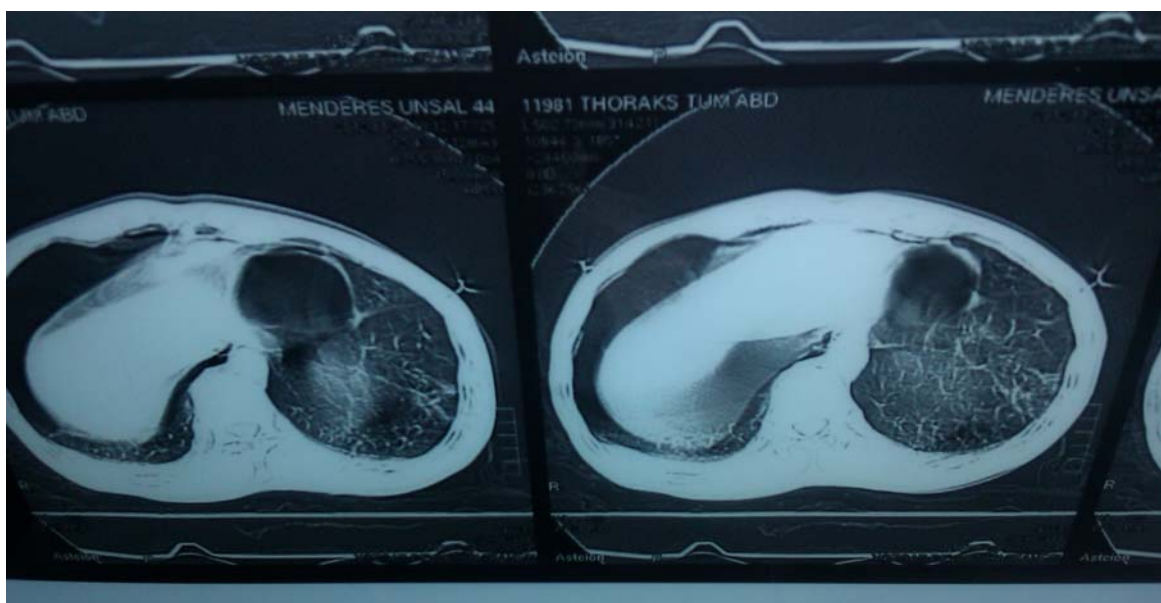


Figure 1. Computed tomography image of pneumopericardium and pneumothorax in the right hemithorax and subcutaneous emphysema of the case

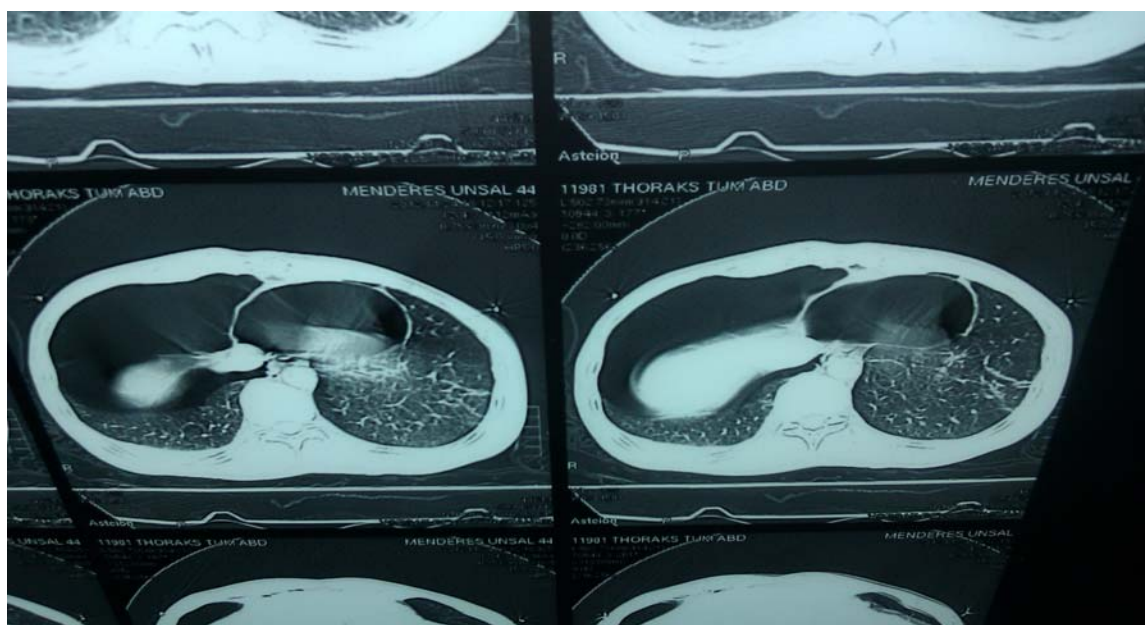


Figure 2. Computed tomography image of massive pneumopericardium of the case

Interpretation

Pericardial laceration with pneumopericardium due to blunt trauma is an extremely rare, clinically important entity, which can easily be diagnosed and might result in cardiac tamponade. Friction rub, deep heart sounds, and metallic sound of 'bruit de moulin' were heard during auscultation of patients with pneumopericardium. Moreover, symptoms such as tachycardia, hypotension, and neck vein engorgement are seen in cases with cardiac tamponade. Pneumopericardium may resolve spontaneously in a small proportion of the adult cases without the need for intervention. The development of tension pneumopericardium, with a mortality of up to 56%, is a sign of a serious chest trauma, which may cause life-threatening complications. Hence, emergent interventional and surgical treatment options should be evaluated in cases with massive pneumopericardium with deteriorating hemodynamic variables.¹

In this case, tension pneumopericardium, which is generally drained through a subxyphoidal window created by open surgery, was together with pneumothorax in the right hemithorax, and other organ injuries. Cardiac exploration and air drainage was performed via a right anterolateral thoracotomy simultaneously with surgical interventions directed to the other organ injuries.

Conclusion

In conclusion, pneumopericardium that might develop due to blunt thoracic trauma can easily be diagnosed, may result in cardiac tamponade, and is a

potentially fatal pathology without treatment. Physicians working in emergency departments should consider this rare pathology, which still has a high rate of mortality in spite of early diagnosis and treatment due to accompanying serious organ injuries, in the differential diagnosis of thoracic trauma associated with shock, and learn the treatment options of this condition.⁴

Conflict of Interests

Authors have no conflict of interests.

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Five chambered heart or large atrial appendage aneurysm: A report of two cases

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Case Report

Abstract

BACKGROUND: Isolated intrapericardial LAA aneurysm is a rare cardiac anomaly which manifests with angina, dyspnea on exertion (DOE), systemic embolization, arrhythmia, and congestive heart failure.

CASE REPORT: A 30-year-old female and a 46-year-old male were referred for evaluation of abnormal cardiac contour on chest radiograph and echocardiographic findings and non-specific symptoms. Transesophageal echocardiography suggested left atrial appendage (LAA) mass filled with clots. The mass had no compression on cardiac chambers and global ejection fraction was within normal limits. The intraoperative diagnosis was isolated congenital LAA aneurysm. After confirmation of the diagnosis, it was resected. She was discharged with uneventful postoperative course. At follow-up she was asymptomatic.

CONCLUSION: These cases demonstrate the role of on-time surgical approaches in the prevention of fatal complication of this rare cardiac anomaly.

Keywords: Left Atrial Appendage, Aneurysm, Clot

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Introduction

Isolated intrapericardial LAA aneurysm is a rare cardiac anomaly which manifests with angina, dyspnea on exertion (DOE), systemic embolization, arrhythmia, and congestive heart failure.^{1,2} Enlarged LAA is associated with an increasing risk of thrombus formation and untreated cases progress to a stroke.^{3,4} Most of the cases present in healthy young patients.⁴ In the current essay, we report two cases of aneurysm of LA appendage which were excised at diagnosis on cardiopulmonary bypass (CPB). Patients have been asymptomatic over the follow-up period.

Case Report

In the current report, we present two of our cases. The first one was a 30-year-old woman who was referred to us for the evaluation of recent easy fatigability and an abnormal chest radiograph. She was previously an asymptomatic healthy person. Physical examination and electrocardiography were normal. Chest radiography (Figure 1) showed enlarged cardiothoracic ratio with enlarged LAA.

Following abnormal trans-thoracic echocardiography (TTE), transesophageal echocardiogram (TEE) was performed, which showed aneurysmal enlargement of LAA, filled with clots and without compression of cardiac chambers (Figure 2). Global ejection fraction was normal (60%). Cardiac CT angiography was performed suggesting aneurysm of LAA.

Our second case was a 46-year-old male with the chief complaint of DOE within the past three months (NYHA Functional class III). He was a cigarette smoker, with the past history of poliomyelitis and stroke (two months ago). His physical examination was normal except for right-sided paralysis. ECG showed left atrial abnormality. TTE demonstrated large pseudoaneurysm of the pericardium with spontaneous echo contrast and filled with clot. This was opened into left atrial chamber with an orifice. The color flow Doppler study demonstrated flow in and out of the aneurysmal chamber. Dilated coronary sinus is also in favor of increased intra-atrial pressure (Video 1).

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Intra-operative diagnosis of both cases confirmed large intrapericardial LAA aneurysm ($5 \times 4 \times 4 \text{ cm}^3$) (Figure 3). In both cases, the LAA aneurysms have been resected on cardiopulmonary



Figure 1. Chest radiograph suggesting increased cardiothoracic ratio and left heart configuration due to large left atrial appendage aneurysm

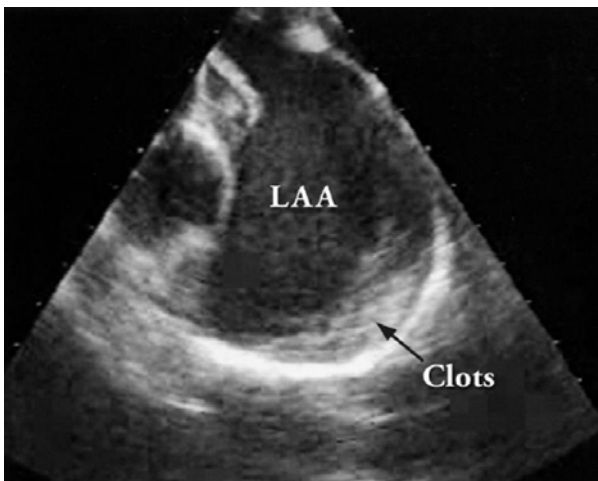


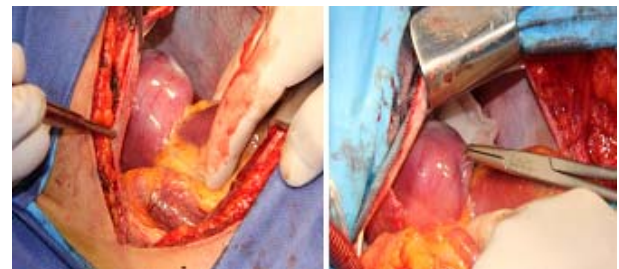
Figure 2. TTE (Trans-thoracic echocardiography) views suggesting large left atrial appendage aneurysm filled partially with clots

Discussion

Isolated aneurismal dilation of LAA is an infrequent non-rheumatic mitral valve disease.⁵ Until now, few cases of this disease have been described in cardiac literatures. Untreated cases develop fatal complications.² We have reported two cases of LAA aneurysm, treated successfully by surgical resection of aneurysm and clot removal. In both cases, with non-specific findings, abnormal cardiac imaging helped in the incidental diagnosis of this rare isolated anomaly. Chest radiographs showed enlarged LAA. Left atrial anomaly was present in

bypass pump and the orifice has been closed. Patients were symptom-free and in sinus rhythm during the post-operative course and on follow-up.

only one case. Gold's diagnostic criteria for LAA aneurysm include: intrapericardial, communication with body of left atrium, and compression of left ventricular (LV) cavity.⁶ In these cases, there was no compression of LV cavity. By resection of the aneurysm, patients became asymptomatic and in sinus rhythm. These cases demonstrate the role of on-time surgical approaches in the prevention of fatal complication of this rare cardiac anomaly.



b)



Figure 3. Intraoperative views taken from large congenital left atrial appendage aneurysm a) from first case, b) from second case

Conflict of Interests

Authors have no conflict of interests.

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