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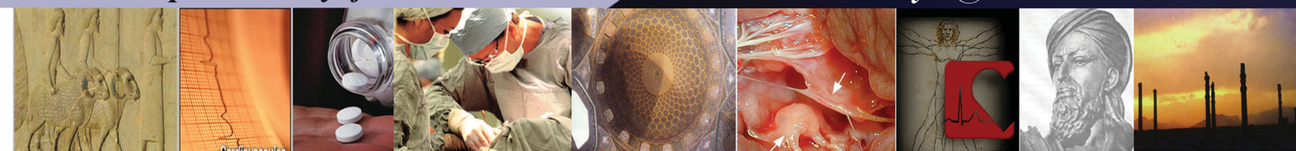

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Evaluation of haptoglobin genotypes in patients with metabolic syndrome: A preliminary report

Alireza Nakhaee[(1)], Mohammad Hashemi[(2)], Alireza Rezaeifar[(3)], Mahmoud Ali Kaykhaei[(4)]

Original Article

Abstract

BACKGROUND: Haptoglobin (Hp) polymorphisms have been suggested to be associated with many pathological conditions, including cardiovascular diseases, infectious diseases, and type 2 diabetes. For the first time, we aimed to investigate the possible association between Hp genotypes and metabolic syndrome (MES) in a sample of Iranian subjects.

METHODS: In this study, 291 patients with MES according to National Cholesterol Education Program-Adult Treatment Panel III criteria, and 284 healthy individuals have been studied. We determined Hp genotype by polymerase chain reaction.

RESULTS: The frequency of three genotype (Hp1-1, Hp2-1, and Hp2-2) in healthy individuals and patients were 7.74, 39.7, 52.46, and 7.9, 31.61, 60.48 percent, respectively. There was no significant difference between the groups regarding Hp genotypes. The Hp2 allele was the predominant allele in MES (76.29%) and normal subjects (72.54%).

CONCLUSION: Hp polymorphisms are not risk factor for predisposition to MES in a sample of the Iranian population. Further studies with different ethnicities are required to validate our findings.

Keywords: Haptoglobin, Phenotype, Metabolic Syndrome

Date of submission: 20 Oct 2014, ***Date of acceptance:*** 06 Feb 2015

Introduction

Metabolic syndrome (MES) is a collection of cardiovascular risk factors including central obesity, hypertension, hyperglycemia, and dyslipidemia.[1] Human haptoglobin (Hp), an acute phase protein, encoded by two major co-dominant alleles, Hp1 and Hp2, results in three functionally distinct phenotypes, Hp1-1, Hp1-2 and Hp2-2. Hp is a tetramer composed of two beta (or heavy) and two alpha (or light) chains connected by disulfide bonds. Hp is biologically the most effective hemoglobin (Hb)-binding protein and its main function are to clear tissues and circulation from this strong oxidant.[2] Hp is a potent antioxidant playing a scavenging role for the toxic free Hb, which accumulates during acute-phase inflammatory reaction. Hp also exerts a direct angiogenic, anti-inflammatory and immunomodulatory function in extravascular tissues and body fluids. In fact in response to various stimuli, HP is able to migrate through vessel walls and is expressed in different tissues.[3] Furthermore, Hp can be released from neutrophil granulocytes at sites of injury or inflammation and locally dampens tissue damage.[4] Hp receptors include CD163 expressed on the monocyte-macrophage system and CD11b (CR3) found on granulocytes, natural killer cells, and in small lymphocyte sub-populations.[5] Hp has also been shown to bind to the majority of CD4+ and CD8+ T lymphocytes, directly inhibiting their proliferation and modifying the T-helper (Th) Th1/Th2 balance.[6] The Hp1-1 protein is the most effective in binding free Hb and suppressing inflammatory responses, Hp2-2 is the least active, and Hp2-1 is moderately active.[7] The major difference among alleles Hp1 and Hp2 is the presence of a duplicated ~1.7 Kb DNA segment within Hp2, but not Hp1.[8]

As functional differences in the antioxidant, scavenging, and immune-regulatory properties of Hp arise as a function of its polymorphism, the Hp genotypes has important biological and clinical

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consequences and have been reported as risk factor for several diseases such as infections, cardiovascular, diabetes mellitus, neurological disorders, preeclampsia, and malignancies.[9-15] To the best of our knowledge, there is not any report regarding the association between Hp genotypes and MES. Thus, this study was aimed to evaluate the possible association between Hp genotypes and MES in a sample of the Iranian population.

Materials and Methods

This cross-sectional study was performed on 291 MES and 284 normal subjects in Zahedan, Iran, from January 2010 to February 2011. Local Ethical Committee of Zahedan University of Medical Sciences, Iran, approved the project and informed consents were obtained from all subjects (Ethics No. 89-2053). The MES was determined as the presence of three or more of five components according to the National Cholesterol Education Program Adult Treatment Panel III[16] as described previously.[1,17] Whole blood were used for genomic DNA extraction as described previously.[18] Sera were used for biochemical analysis.[17]

Hp genotyping was performed using polymerase chain reaction (PCR) method described by Koch et al.[19] The primers used were A (5-GAGGGGAGCTTGCCTTTCCATTG-3) and B (5-GAGATTTTTGAGCCCTGGCTGGT-3) for amplification of a 1757-bp specific sequence of Hp1 allele and a 3481-bp Hp2 allele-specific sequence. 349-bp Hp2 allele-specific sequence was amplified using primers C (5-CCTGCCTCGTATTAACTGCACCAT-3) and D (5-CCGAGTGCTCCACATAGCCATGT-3).

Target sequences were amplified in a volume of 50 µl, containing 5 µl of ×10 buffer (Mg_2+plus) (Qiagen), 250 nM each of primers, 200 µM each of dNTP, about 0.1-10 ng genomic DNA and 2U Taq DNA polymerase. PCR condition for Hp1 and Hp2 allele-specific sequence with primers of A and B was 95 °C for 5 min, followed by 30 cycles of denaturing at 95 °C for 1 min, annealing at 69 °C for 1 min, extension at 72 °C for 2 min with a final extension cycle at 72 °C for 10 min. The temperature profile for 349-bp Hp2 allele-specific sequence with primers of C and D was 95 °C for 4 min, followed by 35 cycles of denaturing at 95 °C for 1 min, annealing at 69 °C for 1 min, extension at 72 °C for 30 s and final extension cycle at 72 °C for 10 min.

The statistical analysis of the data was performed using the SPSS for Windows (version 17, SPSS Inc., Chicago, IL, USA). Demographics and biochemical parameters between the groups were analyses by independent sample t-test for continuous data and χ^2 test for categorical data. The associations between genotypes of Hp gene and MES were estimated by computing the odds ratio (OR) and 95% confidence intervals (95% CI) from logistic regression analyses. $P < 0.050$ was considered statistically significant.

Results

This study consisted of 291 subjects with MES (87 males and 197 females; age 43.91 ± 14.71) and 284 normal subjects (127 males and 156 females; age 33.69 ± 13.25). The demographic and clinical characteristics of the groups are presented in table 1.

Table 1. Biochemical parameters in metabolic syndrome (MES) and normal subjects

Parameters	MES	Normal	P
	n = 291	n = 284	
Sex (male/female)	87/197	127/156	
Age (year)	43.91 ± 14.71	33.69 ± 13.25	
FBG (mg/dl)	109.30 ± 44.97	86.14 ± 14.08	
Waist circumference (cm)	99.50 ± 11.61	82.14 ± 15.04	
Triglyceride (mg/dl)	183.72 ± 77.15	112.46 ± 48.41	< 0.001
Total cholesterol (mg/dl)	210.48 ± 45.10	173.34 ± 39.35	
HDL-C (mg/dl)	41.76 ± 6.97	45.45 ± 7.22	
LDL-C (mg/dl)	124.57 ± 40.72	102.49 ± 33.22	
BMI (kg/m^2)	28.84 ± 4.65	23.49 ± 4.68	
Blood pressure			
Systolic (mmHg)	126.42 ± 21.40	114.34 ± 14.41	< 0.001
Diastolic (mmHg)	80.56 ± 14.35	73.21 ± 10.80	

MES: Metabolic syndrome; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; BMI: Body mass index

Table 2. Genotypes and alleles frequency of haptoglobin (Hp) gene between metabolic syndrome (MES) and normal subjects

Variable	MES [n (%)]	Normal [n (%)]	OR (95%CI)	P	OR (95% CI)*	P
Genotypes						
Hp1-1	23 (7.90)	22 (7.74)	Ref.		Ref.	-
Hp2-1	92 (31.61)	113 (39.70)	0.78 (0.41-1.49)	0.448	0.66 (0.33-1.33)	0.243
Hp2-2	176 (60.48)	149 (52.46)	1.13 (0.61-2.11)	0.701	0.96 (0.49-1.89)	0.907
Alleles						
Hp1	138 (23.71)	157 (27.46)	Ref.		Ref.	-
Hp2	444 (76.29)	411 (72.54)	1.23 (0.09-1.60)	0.137	1.23 (0.09-1.60)	0.137

* Adjusted for age and sex; Hp: Haptoglobin; MES: Metabolic syndrome; OR: Odd ratio; CI: Confidence interval

Table 3. Clinical and biochemical parameters of all subjects according to their haptoglobin (Hp) genotypes

Parameters	Hp1-1	Hp2-1	Hp2-2	P
	n = 45	n = 201	n = 321	
BMI (kg/m^2)	25.5 ± 4.9	26.2 ± 5.3	26.3 ± 5.5	0.701
Waist circumference (cm)	91.1 ± 12.8	90.1 ± 16.9	91.3 ± 15.8	0.711
FBG (mg/dl)	96.6 ± 27.5	95.7 ± 32.6	99.2 ± 37.8	0.539
Triglyceride (mg/dl)	141.6 ± 66.7	145.6 ± 74.8	150.7 ± 73.7	0.612
HDL-C (mg/dl)	43.9 ± 7.4	44.0 ±7.5	43.3 ± 7.3	0.611
Blood pressure				
Systolic (mmHg)	120.8 ± 16.2	122.6 ± 20.6	118.9 ± 18.6	0.253
Diastolic (mmHg)	79.3 ± 13.7	78.1 ± 12.7	75.8 ± 13.4	0.059

Hp: Haptoglobin; BMI: Body mass index; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol

The genotypes and allele frequencies distribution of the Hp polymorphisms were compared among MES and normal subjects (Table 2). There were no significant differences regarding Hp polymorphism among MES and normal subjects (χ^2 = 4.33, P = 0.115). The results showed that 23.71% of MES and 27.41% of normal subjects have Hp1 allele. No significant difference was found among the groups concerning Hp alleles (OR = 1.229, 95% CI = 0.0943-1.602, P = 0.137).

In addition, we calculated clinical and biochemical parameters of all subjects according to their Hp genotypes (Table 3). The results showed that there were no significant differences between genotypes and clinical/biochemical parameters (P > 0.050).

Discussion

This study is the first report indicates that Hp polymorphisms are not risk factor for the development of MES. Several studies have related Hp polymorphism to susceptibility and outcome in important diseases, such as cardiovascular, hematologic and neurologic disorders, infectious diseases, malignant neoplasms and diabetes mellitus.[7]

It is thought that genetic and environmental factors are involved in susceptibility to MES.[20] Several candidate genes polymorphism, including FTO,[21] paraoxonase,[22] tumor necrosis factor-alpha,[23] cell death-inducing DNA fragmentation factor alpha-like effector A,[24] CD36[25] and angiotensin-1-converting enzyme[26] have been shown to be involved in MES.

Human plasma Hp, which is determined by two alleles Hp1 and Hp2, is classified into three common phenotypes. Hp1-1 is a molecule of homodimer or $(\alpha\beta)_2$, whereas Hp2-1 is comprised of multiple forms including homodimer, trimer, tetramer and other linear polymers. Hp2-2, on the other hand, consists of the trimer, tetramer, and other cyclic polymers.

Hp polymorphism has been suggested as a candidate genetic marker in essential hypertension and Hp1 allele a risk factor for essential hypertension.[27,28] It has been reported that Hp2-1 phenotype predicts rapid growth of abdominal aortic aneurysms.[29] Hp2-2 phenotype is a risk factor for type 2 diabetes.[30] Among subjects with diabetes, Hp2-2 is associated with an elevated risk to develop cardiovascular disease (CVD).[31] Diabetic patients with Hp2-2 had impaired endothelial function compared with healthy controls and diabetic patients with Hp1-1.[32] The Hp2-2 genotype has been associated with a higher incidence of CVD during 6-year follow-up in American Indians with diabetes[33] as well as higher incidence of coronary artery disease during 18 years follow-up of subjects with type-1 diabetes.[34] The Hp genotype apparently plays no role in the development or worsening of

proliferative retinopathy in diabetes mellitus 2 (DM2).[35]

Individuals with both DM and the Hp 2-2 genotype are at increased risk of CVD. Strategy of screening DM individuals for the Hp genotype and treating those with Hp2-2 with vitamin E appears to be highly clinically effective and significantly improves the quality of high-density lipoprotein (HDL) in Hp2-2 diabetic individuals.[36,37] Reverse cholesterol transport is decreased in Hp2-2 DM. This may explain in part the increased atherosclerotic burden found in Hp2-2 DM individuals.[38]

No effect of the different Hp subtypes was found on total serum cholesterol, triglycerides or HDL cholesterol.[39] Hp polymorphism, at least in the Korean population, does not predispose to the occurrence of CVD.[40]

The gene frequencies of the Hp1 and Hp2 alleles differ geographically.[9] In West Africa, East Africa and South America, the Hp1 allele is predominant while North America, Europe, Asia and Australia have a predominant Hp2 allele. It has been proposed that the Hp2 have derived from the Hp1 allele in India and has a selective advantage.[9] We found that Hp2 allele was predominant in our population. The limitation of this study is relatively low sample sizes. The results, therefore, need to be interpreted with caution.

Conclusion

The lack of an association between MES and polymorphisms of the Hp gene indicates that Hp genotypes cannot be genetic markers of predisposition to MES in a sample of the Iranian population. Further studies with different ethnicities are required to validate our findings.

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Conflict of Interests

Authors have no conflict of interests.

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A study of the efficacy of furosemide as a prophylaxis of acute renal failure in coronary artery bypass grafting patients: A clinical trial

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Original Article

Abstract

BACKGROUND: Renal failure is a frequent event after coronary artery bypass grafting (CABG). Hemodynamic alterations during surgery as well as the underlying disease are the predisposing factors. We aimed to study intermittent furosemide therapy in the prevention of renal failure in patients undergoing CABG.

METHODS: In a single-blind randomized controlled trial, 123 elective CABG patients, 18-75 years, entered the study. Clearance of creatinine, urea and water were measured. Patients were randomly assigned into three groups: furosemide in prime (0.3-0.4 mg/kg); intermittent furosemide during CABG (0.2 mg/kg, if there was a decrease in urinary excretion) and control (no furosemide).

RESULTS: There was a significant change in serum urea, sodium and fluid balance in "intermittent furosemide" group; other variables did not change significantly before or after the operation. Post-operative fluid balance was significantly higher in "intermittent furosemide" group (2573 ± 205 ml) compared to control (1574.0 ± 155.0 ml) ($P < 0.010$); also, fluid balance was higher in "intermittent furosemide" group (2573 ± 205 ml) compared to "furosemide in prime" group (1935.0 ± 169.00 ml) ($P < 0.010$).

CONCLUSION: The study demonstrated no benefit from intermittent furosemide in elective CABG compared to furosemide in prime volume or even placebo.

Keywords: Renal Failure, Coronary Artery Bypass Grafting, Furosemide

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Introduction

Acute renal failure (ARF) is a complex disorder, which is commonly seen in the perioperative period and in the intensive care unit (ICU). This phenomenon occurs in a variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.[1,2] It would be associated with a prolonged hospital stay and high morbidity and mortality.[3] ARF after coronary artery bypass grafting (CABG) is an important and independent risk factor of mortality and morbidity.[4,5] As a result, the implications of acute kidney injury after cardiac surgery are very well-known to cardiac anesthesiologists and intensivists.[6-8]

Recent studies have focused on the preventive strategies; which could be used for the high risk subsets for ARF.[9] Moreover, it has been demonstrated that in high-risk cardiac surgical patients, post-operative furosemide infusion could not improve the clinical outcome of the patients in preventing the occurrence of ARF.[10] Here, we aimed to study the possible role of early furosemide administration (as two different modes) compared with control, in the prevention of renal failure in patients undergoing elective CABG. Hence, there are some controversial issues regarding the need for more sophisticated studies to come to a final decision to define which therapeutic option is more effective.

Materials and Methods

This study was a single-blinded, randomized controlled trial; which was performed from January 2009 to November 2010, in a tertiary level, referral

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university hospital which is only a cardiovascular center. After institutional review board (IRB) approval, Tehran University of Medical Science, Iran, regarding ethical considerations and also, after taking informed written consent, among a total of 250 patients, after considering inclusion and exclusion criteria, 126 patients aged 40-75 entered the study; but among them, 123 could finish the study.

Inclusion criteria were:

- Age 40-75
- Elective CABG with cardiopulmonary bypass (CPB)
- Constant surgeon
- Informed written consent.

Exclusion criteria were:

- Old age (> 75 years)
- Emergency and high-risk surgery
- Ischemic heart disease
- Diabetes mellitus
- Diabetic ketoacidosis
- Non-kenotic hyperosmolar diabetic coma
- ARF
- Chronic kidney disease causing serum Cr > 2 mg/dl
- Glomerulonephritis
- Hepatic failure causing liver function test failure (> 3 times than normal)
- Off-pump CABG
- Any unwanted complication in the operation period
- Re-starting CPB after weaning from bypass
- Pulmonary artery pressure > 30 before operation
- Ejection fraction < 30 (%)
- Re-operation in the post-operative period
- Congestive heart failure
- Thyroid disorders
- Acute infections
- Stroke
- Pregnancy
- Hospital admission in the recent 3 months.

Sample size calculation is discussed below. Our sampling strategy was a randomized single blind clinical trial; neither the patients nor the directly involved physicians knew who will belong to which group. For randomization of the patients, first, we prepared 126 small sized papers and divided them into three groups: 42 in each; A, B, or C; accordingly; Group A, Group B, or Group C.

All the patients were scheduled for elective CABG. The diagnosis of acute coronary syndrome was confirmed according to the criteria of American College of Cardiology.[11] Renal function was assessed by calculating the clearance of creatinine, urea and water.

The patients were fully blinded regarding the study group in which they were allocated; also, they were randomly assigned into three groups (Figure 1).

1. The first group (Group A): Intra-prime furosemide therapy was performed; i.e., these patients received 0.3-0.4 mg/kg furosemide in the prime solution; it means that furosemide was added to the CPB reservoir and when the bypass was initiated, it was mixed with patients' blood
2. The second group (Group B): Intermittent furosemide therapy was done; i.e., patients received 0.2 mg/kg furosemide during CABG only in the case of decreased urinary excretion rate; the method of monitoring intra operation decrease in urinary output was exact control of hourly urinary flow by urine flow meter; if urine flow was < 1 ml/kg/h, it was considered as decreased urinary flow
3. The third group (Group C): i.e., the control group, the patients did not receive furosemide or any other drug as renal failure prophylaxis.

All the other therapeutic protocols were adjusted the same in the three groups. Also, we hold the diuretics before surgery.

Furthermore, those patients with the previous furosemide administration were excluded since patients who receive pre-operative furosemide may have a different response to diuretic during CABG.

The study variables were measured using one of the three following approaches:

- Clinical observation (for pre-operative, intraoperative and post-operative clinical findings)
- Laboratory measurements (for measuring the results of blood levels of hemoglobin and hematocrit, serum electrolytes, and serum metabolites)
- Patients' clinical files for assessing and registering their demographic and clinical data.

All the measurements for variables were done by the same person; she was blind to the patients' group.

Blood samples were collected after almost 12 ho of fasting and, serum creatinine, lactate, blood urea nitrogen (BUN), sodium (Na) and potassium (K) were measured for all the patients before and after CABG. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula; which estimated the creatinine clearance rate.[12] The patients did not receive any other diuretics except for furosemide during the operation. Although Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

(RIFLE) criteria have been proposed as useful criteria for staging of patients with acute kidney injuries; this criteria focuses mainly on GFR. However, the current study has used many other factors, including GFR and other criteria, including a number of electrolytes, hemoglobin, and fluid balance.

Inside the operating theater, demographic and anthropometric data including age, sex, presence of diabetes and blood pressure in sitting position were recorded. Blood pressure was measured twice after 5 min on average. Also, body mass index was calculated as kg/m^2.

All patients underwent catheterization using standard Judkins or Sones techniques. Angiographic scoring was performed by 2 cardiologists. Coronary angiographies were interpreted visually and were always analyzed in 2 orthogonal views. Stenosis of > 50% in any of the main epicardial vessels reflected a significant coronary artery disease. CABG was performed according to the guidelines of American College of Cardiology.[13]

Sample size was determined after a power analysis (power = 0.8, $\beta = 0.2$, $\alpha = 0.02$); using the power analysis and sample size software: PASS 2005 (NCSS Statistical Software, Utah, USA). The clinical criterion for sample size determination was the observed frequency of "per hour urinary output needing medical intervention;" so, we required 35 patients in each group; equals a total of 105; however, to compensate for possible dropouts, we added 20% to the calculated sample size to have a final sample of 126 (42 in each group).

The statistical package SPSS software for Windows (version 16, SPSS Inc., Chicago, IL, USA), was used for analysis. Quantitative variables were presented as mean ± standard deviation. Qualitative variables were presented as number and percentage. Paired sample t-test was employed for the comparison of the pre-operative and post-operative variables in each group. T-test and ANOVA were used for the comparison of the studied variables between groups.

This study has been registered in www.irct.ir, under the number: 201502122804N8.

Results

Of 126, 123 patients could finally finish the trial. Among the study population (123 patients) the majority were men: 87 (70.7%) men versus 35 (28.4%) women. The mean age of the patients was 58 ± 1.2 years. There were 39 (31.7%) patients in intra-prime furosemide group; 42 (34.1%) in intermittent furosemide therapy group and 42 (34.1%) in the control group. Basic demographic data of the participants are presented in table 1. There was no significant difference between the three groups regarding basic variables; including age (years), gender, duration of operation, ejection fraction, pre-operative serum levels of "creatinine, sodium (Na), potassium (K), lactate, GFR, BUN, hemoglobin" and also, pre-operative fluid balance (Table 1). Also, the CPB and aortic cross-clamp times were similar between the three study groups.

During the post-operative period, the patients were transferred to the cardiac ICU; meanwhile, significant changes in fluid balance, serum levels of BUN and serum levels of sodium (Na) were seen in Group A (P value for ANOVA < 0.010); while there was no significant difference regarding other variables before and after the operation. However, there was a significant positive fluid balance during the early post-operative period in Group B (2573 ± 205 ml) compared to Group C (1574.0 ± 155.0) and Group A (1935.0 ± 169.00); (P value for ANOVA < 0.010).

Also, after performing ANOVA test, we performed the Tukey post-hoc test; this test was done to assess, which group was different from the others in between the three groups; the group, which was different from the two others was indicated with a asterix (*) in table 2; i.e., the group differed significantly from the two other groups (P < 0.050).

Table 1. Basic variables of the study groups

Variables	Intra-prime furosemide (Group A) (n = 42)	Intermittent furosemide therapy (Group B) (n = 42)	Control (Group C) (n = 42)	P (for ANOVA)
Age (year)	61.0 ± 1.4	62.0 ± 1.8	57.0 ± 2.3	0.147
BUN	21.4 ± 2.1	24.2 ± 3.3	19.6 ± 2.5	0.151
Creatinine	1.5 ± 0.4	1.4 ± 0.3	1.6 ± 0.5	0.382
Hemoglobin	15.5 ± 3.1	15.6 ± 3.3	16.3 ± 3.3	0.307
Sodium	142.0 ± 1.4	140.0 ± 1.3	140.0 ± 1.2	0.391
Lactate	1.8 ± 0.2	2.1 ± 0.1	2.1 ± 0.2	0.223
Fluid balance (intra-operative)	1833.0 ± 405.0	1379.0 ± 292.0	1411.0 ± 117.0	0.141
Potassium	4.2 ± 1.0	4.1 ± 1.0	4.1 ± 1.0	0.092
GFR (ml/min)	71.0 ± 8.3	58.0 ± 3.2	63.0 ± 3.9	0.079

Data are presented as mean ± SD; One-way ANOVA test was used for data analysis; SD: Standard deviation; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate

Table 2. Pre-operative and post-operative findings in three study groups

Data variables	Intra-prime furosemide (Group A) (n = 42)	Intermittent furosemide therapy (Group B) (n = 42)	Control (Group C) (n = 42)	P for ANOVA
Pre-operative blood urea nitrogen	19.4 ± 3.02	19.2 ± 3.3	19.6 ± 2.9	0.311
Post-operative blood urea nitrogen	16.1 ± 1.00	25.7 ± 3.3*	15.8 ± 1.2	0.002
1st day post-operative blood urea nitrogen	18.9 ± 1.35	19.9 ± 1.5	18.1 ± 1.1	0.271
2nd day post-operative blood urea nitrogen	20.1 ± 1.50	28.3 ± 3.6*	19.3 ± 1.4	0.001
Pre-operative creatinine	1.5 ± 0.40	1.4 ± 0.4	1.7 ± 0.5	0.132
Post-operative creatinine	1.2 ± 0.10	1.3 ± 0.1	1.2 ± 0.1	0.320
1st day post-operative creatinine	1.2 ± 0.10	1.4 ± 0.1	1.3 ± 0.1	0.211
2nd day post-operative creatinine	1.2 ± 0.10	1.5 ± 0.1	1.2 ± 0.1	0.103
Pre-operative hemoglobin	14.5 ± 1.20	14.9 ± 1.4	14.3 ± 1.3	0.111
Post-operative hemoglobin	10.3 ± 1.30	9.8 ± 1.2	9.9 ± 1.2	0.101
1st day post-operative hemoglobin	9.1 ± 1.10	9.4 ± 1.2	9.1 ± 1.1	0.171
2nd day post-operative hemoglobin	9.3 ± 1.20	9.7 ± 1.1	9.7 ± 1.3	0.262
Pre-operative sodium	142.0 ± 1.50	140.0 ± 1.6	140.0 ± 1.6	0.251
Post-operative sodium	136.0 ± 1.40	148.0 ± 3.2*	139.0 ± 1.1	0.004
1st day post-operative sodium	140.0 ± 1.00	148.0 ± 0.8*	141.0 ± 1.0	0.002
2nd day post-operative sodium	142.0 ± 1.90	148.0 ± 1.4*	139.0 ± 1.0	0.001
Pre-operative lactate level	1.9 ± 1.150	2.0 ± 1.1	2.1 ± 1.2	0.320
Intra-operative lactate	4.0 ± 1.40	3.9 ± 0.3	3.8 ± 0.8	0.162
Pre-operative fluid balance	1333.0 ± 405.00	1379.0 ± 392.0	1411.0 ± 417.0	0.120
Postoperative fluid balance	1908.0 ± 381.00	2514.0 ± 662.0*	1717.0 ± 295.0	0.003
Post-operative fluid balance in first day of ICU	2798.0 ± 194.00	2849.0 ± 171.0	2717.0 ± 150.0	0.114
Post-operative fluid balance in second day of ICU	1935.0 ± 169.00	2573.0 ± 205.0*	1574.0 ± 155.0	0.005
Intra-operative urine output	543.0 ± 280.00	583.0 ± 246.0	550.0 ± 296.0	0.211
Post-operative urine output	298.0 ± 23.00	280.0 ± 29.0	298.0 ± 27.0	0.130
Preoperative glomerular filtration rate	71.5 ± 4.30	58.0 ± 3.8	63.0 ± 3.9	0.120
Post-operative glomerular filtration rate	70.6 ± 3.70	59.5 ± 4.1	65.6 ± 3.9	0.121
Preoperative potassium	4.2 ± 1.00	4.1 ± 1.0	4.1 ± 1.0	0.222
Postoperative potassium	4.4 ± 1.00	4.2 ± 1.0	4.3 ± 1.0	0.271
First day post op potassium	4.2 ± 1.00	4.4 ± 1.0	4.2 ± 1.0	0.232
Second day post-operative potassium	4.2 ± 1.00	4.4 ± 1.0	4.2 ± 1.0	0.221

Data are presented as mean ± SD; There was no difference within the two other groups, one-way ANOVA test was used for data analysis; * The results of this test demonstrated that the group indicated by asterix (*****) differed significantly from the two other groups ($P < 0.050$); SD: Standard deviation; ICU: Intensive care unit

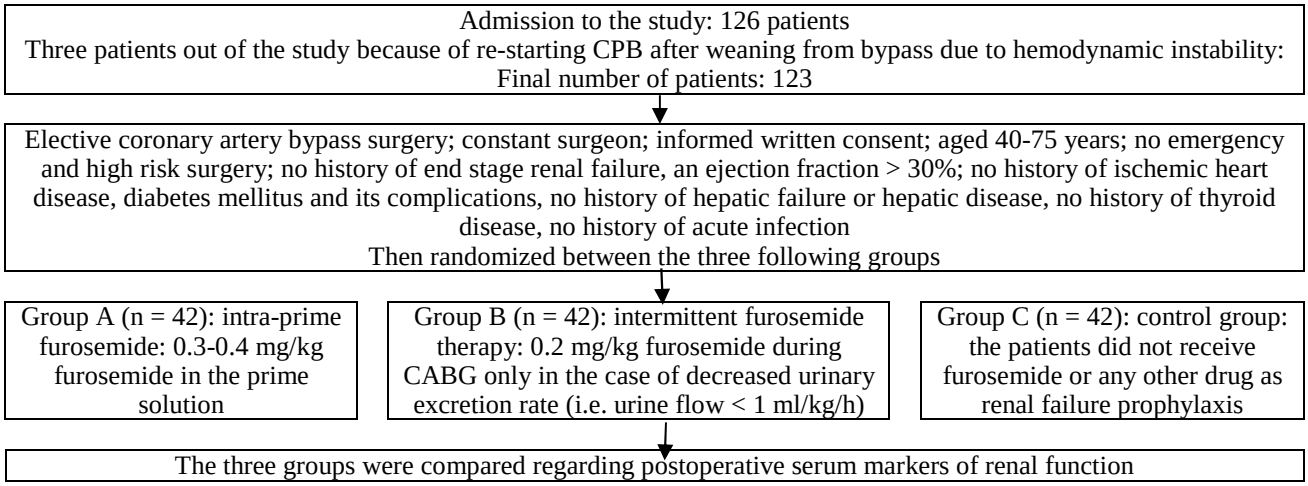

Figure 1. Study flowchart

CPB: Cardiopulmonary bypass; CABG: Coronary artery bypass grafting

Discussion

This study demonstrated that intermittent furosemide therapy does not significantly improve the renal outcome of the patients undergoing elective CABG compared with the patients receiving either an intra-prime dose or the patients in the control group.

However, the findings indicated that patients receiving intermittent furosemide therapy had the greatest positive fluid balance (i.e., extra fluid remaining in the body) compared to the other patient groups. The question here is why patients with positive fluid balance had decreased urine production during the operation; this finding could possibly be due to hypotension during the operation.

Besides, the patients receiving intra prime furosemide had significantly improved serum levels of BUN and Na, and also, improved fluid balance status.

Based on other studies, renal function is an important determinant of post-operative clinical outcome.[14] also, ARF after cardiac surgery is a significant predictor of hospital mortality.[15]

On the other hand, some studies have demonstrated different independent risk factors, including old age, previous renal failure, emergency and high risk surgery, ischemic heart disease, congestive heart disease, and the need for inotropic drugs for ARF in CABG patients.[6-8] ARF is also independently associated with early mortality following cardiac surgery, even after adjustment for comorbidities and post-operative complications.[16]

These findings are of great clinical importance. Inconsistent with our findings, many other studies have questioned the role of intermittent furosemide therapy in the prevention of ARF.[17] In a recent randomized clinical trial by Mahesh et al.,[10] and Faritous et al.[18] furosemide-infusion did not showed any benefit in high-risk cardiac surgical patients and despite an increase in urinary output with furosemide, there was no decrease in renal injury, and no decrease in incidence of renal dysfunction. It could be concluded that the intermittent furosemide therapy, only increases urinary output and is not effective in the prevention of ARF. Moreover, we showed that in some parameters, intermittent furosemide therapy might deteriorate some of the renal function test indices in patients undergoing CABG with CPB.

Could we conclude that intermittent furosemide therapy is not effective in the prevention of ARF? We are not reaching to this final conclusion in this research; however, there are studies demonstrating that in cardiac surgery patients, perioperative furosemide administration could not reduce the patients' need for renal replacement therapy.[19,20] Hence, other studies have failed to demonstrate any benefit from administration of perioperative furosemide in patients undergoing cardiac surgery; our study demonstrated that perioperative furosemide in cardiac surgery patients has no superiority even compared with placebo.

Finally, this study demonstrated that in patients undergoing CABG with CPB, intermittent furosemide administration has no documented benefit regarding kidney protection; even, adding furosemide to the intra-prime volume or intermittent doses of furosemide administered during CPB should be regarded cautiously, especially in patients with decreased urinary output; this finding which is a novel finding from the current study may be controversial with some of the routine practice that anesthesiologists do during daily CABG cases.

Limitations

The main limitation of this study is its short term follow up. However we took advantage of a relatively large sample size and the close similarity between groups in most of the potentially confounding variables. Also, we did not perform post-hoc analysis for ANOVA; so we had limitations regarding the completion of ANOVA analysis.

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Conflict of Interests

Authors have no conflict of interests.

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Applying the Framingham risk score for prediction of metabolic syndrome: The Kerman Coronary Artery Disease Risk Study, Iran

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Original Article

Abstract

BACKGROUND: There has been a few studies about the predictability of metabolic syndrome (MetS) based on the Framingham risk score (FRS) as a tool for predicting the risk of 10-years cardiovascular diseases (CVD) in Iranian population. The aim of this study was to compare the risk stratification obtained with the FRS and MetS in a cohort of the Iranian population.

METHODS: In this population-based study Kerman Coronary Artery Disease Risk study, Iran, MetS was diagnosed as defined by the revised National Cholesterol Education Program definition criteria (ATPIII) and the FRS was calculated using a computer program, previously reported algorithm.

RESULTS: Overall, the prevalence 10-years risk of CVD for patients with MetS was significantly different with those without MetS (74.3 vs. 86.4% for low-risk patients, 18.1 vs. 12.3% for intermediate-risk people, and 7.6 vs. 1.3% for high-risk individuals) ($P < 0.001$). The frequency of intermediate-risk and high-risk for 10-year CVD in men with MetS (39.5 and 18.3%, respectively) was considerably higher than women with MetS (3.2 and 0.1%, respectively). Using multiple logistic regression, the odds ratio of MetS in intermediate-risk and high-risk FRS group was 1.7 and 6.7, respectively ($P < 0.001$).

CONCLUSION: Significant association between the presence of MetS and high risk for CVD based on FRS was revealed in both men and women indicating a good concordance between MetS and FRS in predicting the risk of CVDs. However, the odds ratio of the development of risk of cardiovascular events among women was higher than men with MetS.

Keywords: Metabolic Syndrome, Framingham Risk Score, Cardiovascular Disease, Ischemic Heart Disease

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Introduction

The Framingham risk score (FRS) is a simplified and common clinical tool for assessment of the risk level of coronary artery disease (CAD) as well as for identifying individuals who were candidate for risk factors modification.[1] This tool consists of various coronary risk components including gender, age, smoking, systolic blood pressure, and lipid profile state. FRS is the most applicable method for predicting a person's chance of developing cardiovascular disease (CVD) in long-term.[2,3] Because this risk score give an indication of the likely benefits of prevention, it can be effectively useful for both the patient and for the clinicians in deciding whether lifestyle modification and preventive medical treatment,[4,5] and for patient education, by identifying men and women at increased risk for future cardiovascular events.[6] However, despite the applicability of this tool, it is powerless to evaluate some key factors, which influenced by dietary and metabolic patterns modification. Proverbially, it remained unknown whether the FRS is a good predictor of metabolic disturbances underlying ischemic heart disease.[7] Moreover, the FRS has been shown to overestimate coronary disease risk in Europeans and thus its recalibration in special populations is recommended.[8]

Because of metabolic syndrome (MetS) defined as a complete cluster of cardiovascular metabolic risk factors even diabetes mellitus, insulin resistance, and abdominal obesity, it may offer a better view of the prediction of coronary heart disease in suspected individuals.[7,9-11] However, findings of

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previous studies on comparing the predictive value of FRS versus MetS have been varied widely. Although the MetS score with age included has been identified to be a valid tool for predicting CVD and its predictive ability was as good as the FRS,[12] some others have emphasized inferiority of MetS toward the FRS.[13-16]

There has been no study about the predictability of MetS according to FRS in Iranian population. The aim of this study was to compare the risk stratification obtained with the FRS between individuals with and without MetS in a cohort of the Iranian population.

Materials and Methods

This population-based study is a great part of The Kerman, Iran, CAD Risk study that scheduled for a cohort of 5874 individuals aged 15-75 years and residence in Kerman city addressing the information of the risk profile of CAD including serum lipids, physical activity, alcohol and drugs addiction, mental disorders like stress and depression, hypertension as well as dietary regimens. The study was approved by the research and ethics committees of the Kerman University of Medical Sciences, Iran, and informed consent was obtained from all participants.

In this survey, a detailed interview regarding social demographics and risk profile was administered and all subjects underwent a clinical examination that included measurement of body composition, systolic and diastolic blood pressure, serum blood sugar and serum lipids. We examined weight and standing height expressed as a body mass index (weight in kilograms divided by height in meters squared). The waist circumference (WC) was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Blood pressure was recorded using an automatic oscillometric blood pressure recorder after at least 5 min of rest in a chair and arm supported at heart level. Systolic blood pressure was measured at the point where the first of two or more sounds was heard (Phase 1), and diastolic blood pressure before the disappearance of sounds (Phase 5). For biochemical analysis, blood samples of 5 ml were drawn after 12 h overnight fasting for measuring lipid profile, fasting blood sugar, and hemoglobin A1c. Plasma glucose was measured using the glucose oxidase-peroxidase method. The level of serum lipid profile was also determined by standard enzymatic procedures.

MetS was diagnosed as three or more of the following five factors as defined by the revised National Cholesterol Education Program definition criteria for Asian population: (1) fasting triglycerides > 150 mg/dl or lipid medications; (2) systolic blood pressure > 130 mmHg, diastolic blood pressure > 85 mmHg, or antihypertensive medications; (3) fasting plasma glucose > 5.6 g/dl or diabetes medications; (4) high-density lipoprotein (HDL) cholesterol < 40 mg/dl (men) or < 50 mg/dl (women); and (5) WC > 102 cm (men) or > 88 cm (women).[17]

The FRS was calculated using a computer program[18] and based on using a previously reported algorithm,[2] which takes into account age, sex, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, smoking and the presence of diabetes. The participants were then classified into groups according to cardiovascular risk consistent with the obtained score that individuals with low risk had 10% or less coronary disease risk at 10 years, with intermediate-risk 10-20%, and with high risk 20% or more.[19]

Results were presented as mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of < 5 were observed. Quantitative variables were also compared using t-test. Statistical significance was determined as a $P < 0.050$. All statistical analysis was performed using SPSS software for Windows (version 20, SPSS Inc., Chicago, IL, USA).

Results

The mean age for the entire cohort was 44.34 ± 16.32 years (range 10.87 years). Among, MetS was diagnosed in 2346 subjects (39.7%). The baseline demographics comparing subjects with and without MetS are shown in table 1. Compared to non-MetS group, those with MetS were older, were more female, had higher systolic and diastolic blood pressure, had higher fasting blood sugar, and also had different lipid profile status as higher serum total cholesterol, serum triglyceride, and lower HDL.

Overall, 74.3% patients with MetS were low-risk, 18.1% were intermediate-risk, and 7.6% were high-risk for 10-year CVD. Besides, the 10-year risk for cardiovascular disorders according to FRS scoring was significantly lower in those without MetS that 86.4% were low-risk, 12.3% were intermediate-risk, and only 1.3% of them were high-risk for cardiovascular disorders (Table 2). This

significant association between the presence of MetS and high risk for CVD based on FRS was revealed in both men and women indicating a good concordance between MetS and FRS in predicting the risk of CVD s. However, the prevalence intermediate- and high-risk for 10-years risk of CVD in men (39.5 and 18.3%, respectively) was significantly much more compared with those in women (3.2 and 0.1%, respectively) ($P < 0.001$) (Table 2). In other words, the frequency of low-risk category in women was significantly high than men (96.8 vs. 42.1%, respectively).

As shown in table 3, using multiple logistic regression modeling and considering low-risk group as the reference, the odds ratio of risk for MetS was 1.7 in intermediate-risk FRS group and was 6.7 in high-risk FRS group ($P < 0.001$). The odds ratios of intermediate-risk and high-risk among men respectively were 2.63 and 11.4 ($P < 0.001$) and among women were 12.02 and 22.01 ($P < 0.001$). The 10-year increased risk for CVDs according to FRS risk categories was significantly associated with the number of MetS definitional components (Figure 1) that 10-year high risk of cardiovascular disorders was predict in 0.6% of patients with one MetS component, 2.6% in two MetS components group, 7.1% in three MetS components group, 8% in individuals with four or five components group ($P < 0.050$).

Discussion

Our study performed on a great sample of the Iranian population revealed a prevalence of 39.7% for MetS that is nearly consistent with the previous reports. In a recent report, the overall prevalence of MetS in different Iran areas ranged between 30% and 45%[20-23] that is nearly in the range that reported in neighbor country of Iran including Saudi (39.3%)[24] and Turkish (33%) populations.[25] However, the global prevalence of this phenomenon varies widely so that the published reports from western countries and from southeastern nations documented MetS prevalence of 24.0 and 14.2%, respectively.[26,27] The observed discrepancy might be due to the different in used MetS definitional criteria and also to the differences in genetic predisposition, various lifestyle patterns as well as different nutritional behaviors leading variance in the prevalence of MetS for different communities and ethnic groups.

Table 1. Baseline characteristics in individuals with and without metabolic syndrome (MetS)

Characteristics	Group with MetS (n = 2346)	Group without MetS (n = 3528)	P
Female gender (%)	1392 (58.9)	1846 (52.2)	
Age (year)	53.14 ± 13.16	38.48 ± 15.57	
Systolic blood pressure (mmHg)	128.85 ± 20.40	109.97 ± 20.14	
Diastolic blood pressure (mmHg)	82.07 ± 10.54	74.22 ± 9.01	
WC (cm)	93.06 ± 10.99	79.61 ± 10.90	< 0.001
Fasting blood sugar (mg/dl)	121.59 ± 48.96	91.23 ± 22.53	
Serum triglyceride (mg/dl)	198.43 ± 113.34	113.07 ± 75.35	
Serum total cholesterol (mg/dl)	208.47 ± 45.73	181.84 ± 40.50	
Serum HDL (mg/dl)	35.01 ± 8.54	40.58 ± 10.91	

MetS: Metabolic syndrome; WC: Waist circumference; HDL: High-density lipoprotein

Table 2. The comparison of 10-year risk for cardiovascular disorders [according to Framingham risk score (FRS) scoring] between two groups of with and without MetS (results reported for the whole population and gender subgroups)

Characteristics	Group with MetS (n = 2346)	Group without MetS (n = 3528)	P
Total			
Low-risk	1756 (74.3)	3056 (86.4)	
Intermediate-risk	428 (18.1)	435 (12.3)	
High-risk	179 (7.6)	46 (1.3)	
Men			
Low-risk	409 (42.1)	1215 (71.9)	< 0.001
Intermediate-risk	384 (39.5)	430 (25.4)	
High-risk	178 (18.3)	46 (2.7)	
Women			
Low-risk	1347 (96.8)	1841 (99.7)	
Intermediate-risk	44 (3.2)	5 (0.3)	
High-risk	1 (0.1)	0 (0.0)	

MetS: Metabolic syndrome

Table 3. Multiple logistic regression models for assessing the odds ratio of metabolic syndrome (MetS) in the levels of Framingham risk score (FRS) risk scores

FRS risk categories	Odds ratio	95% CI	P
Total			
Low-risk (ref)	1	-	-
Intermediate-risk	1.712	1.480-1.981	< 0.001
High-risk	6.772	4.872-9.413	
Men			
Low-risk (ref)	1	-	-
Intermediate-risk	2.653	2.222-3.168	< 0.001
High-risk	11.495	8.157-16.199	
Women			
Low-risk (ref)	1	-	-
Intermediate-risk	12.027	4.757-30.412	< 0.001
High-risk	22.009	10.151-46.790	

CI: Confidence interval; FRS: Framingham risk score

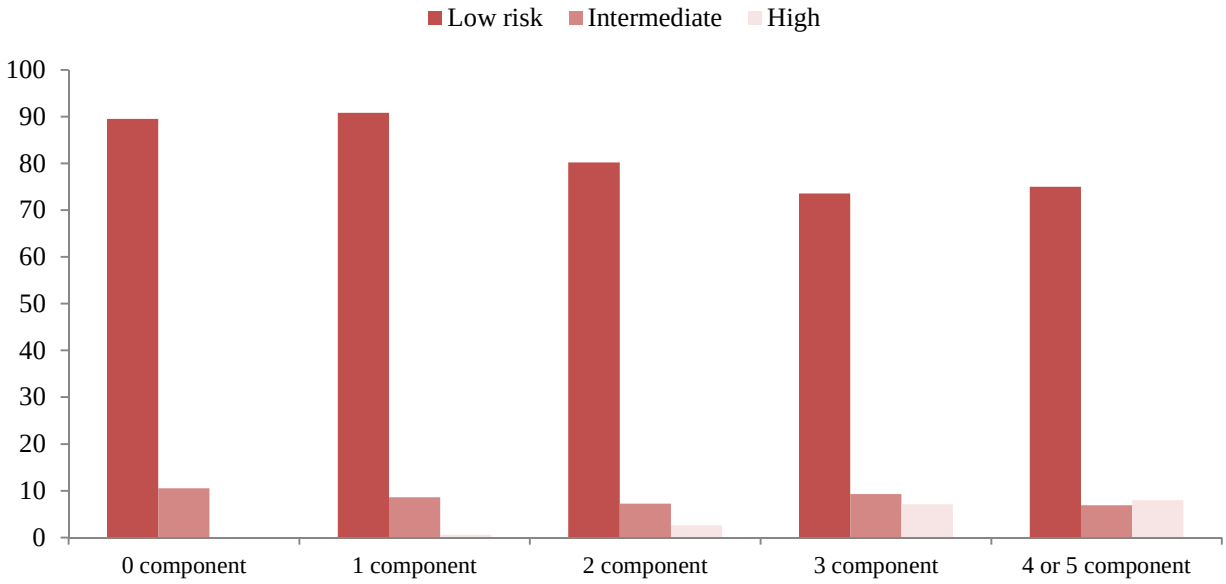

Figure 1. Association between Framingham risk score risk categories and number of metabolic syndrome components

Several studies have been conducted in past to assess the relative merits of MetS and FRS for prediction of cardiovascular risk, but have shown inconsistent results.[9,13,16] Furthermore, numerous studies attempted to evaluate the concordance between these two predicting tools confirming the superiority of one method over the other. Our study showed a strong correlation between these tools so that higher-risk FRS status has been expressed to be associated with the presence of MetS and its numbers of components. On the other hand, both MetS and FRS can be effectively used for predicting the long-term appearance of cardiovascular events. However because of some potential limitations of FRS such as heavy dependent on age factor and underestimation of cardiovascular disorders in the young,[28,29] and lack of coverage several prominent features of MetS such as obesity, hyper-triglyceridemia and elevated high sensitivity-C reactive protein levels,[17] the use of MetS is more preferred to predict occurrence of CVDs. Yu et al. showed that MetS score, including age appeared greater association with CVD than FRS on the same exposed subjects and thus can have more validation than FRS and, therefore, its predictive ability can be higher than the latter tool.[12] In contrast, because of short-term modification of some life-style-related risk factors such as blood sugar state or obesity, MetS may be an independent determinant of significant CAD only among those individuals at low 10-year risk for future coronary events.[30] Moreover, MetS was found to be less effective at

predicting heart disease than the FRS according the two recent US reports showing the syndrome to be less predictive of CVD then the FRS.[13,14] Meanwhile, the combined use of these two tools did not result in more benefits. In the recent report of the National Heart, Lung, and Blood Institute and American Heart Association conference proceedings, analysis of the Framingham data indicated that no advantage is gained in risk assessment by adding the components of MetS to the FRS.[9] Thus, it still remains to be determined whether FRS or MetS is a better risk assessment tool in young individuals.

This study had some potential limitations. First, its cross-sectional nature and the lack of patients with the angiographically established CVD did not allow us to evaluate whether MetS is a better marker of cardiovascular risk than FRS in our individuals. It was preferred to assess this concordance considering both CVD and healthy subgroups. In addition, our study only covered a local population in eastern Iran and did not include a great sample from all regions of the country. Therefore, results are not generalized to all parts of the country.

In the present study, we found that in spite of increasing frequency of moderate- and high-risk for 10-year cardiovascular events in men, but the odds ratio of development of MetS among women in both moderate- and high-risk groups compared with low-risk group as reference group was remarkably higher in men. The present findings seem to be consistent with other research in the literature review, which found somehow the similar results. In a meta-analysis, patients with the MetS had approximately 60% increased risk of CVD than those without the MetS and that the MetS could be a stronger risk factor for CVD in women compared to men.[31] In another study among a group of people with low prevalence of coronary heart disease (CHD), stroke, and diabetes, the probability to develop CHD after controlling other serious risk factors, among women with the MetsS (2 times) was greater than that in men (1.5 times).[14] There have found an association between the MetS and an increased number of CVD events.[32,33] The MetS worsens the development of some main non-communicable diseases like diabetes, CAD, myocardial infarction, stroke, and heart failure. It has indicated that the MetS can be a stronger predictor of CVD events even than diabetes. The studies have shown the discrepancies between men and women concerning the role of the MetS on the development of diseases events. The MetS was related to an increased prevalence of coronary heart disease.[34-37] In Marroquin et al.'s study, which conducted only in women, the MetS deteriorated the prognosis of CVD. The hazard ratio of the impact of the MetS on the prognosis of cardiovascular events was 4.93, almost 5 times higher than that in women without CAD, which was 1.41.[38] There was a strong association between the MetS and CVD mortality among women compared with men (more than twice) based on the data from the San Antonio Heart Study.[39] Dekker et al.[40] also suggested that associations of MetS with non-fatal CVD generally were stronger in women than in men. Although the recent study concluded that the FRS can underestimate absolute coronary heart disease risk in older adults, especially among women by 51% compared to 8% in men.[41]

Conclusion

In conclusion, both MetS and FRS predicting tools can serve as simple clinical approaches to identifying cardiovascular vulnerable and at-risk patients in order to its acceptable concordance. However, because of covering some important metabolic components, including obesity, blood sugar changes as well as pro-inflammatory status, the use of MetS for predicting CVDs is preferable.

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Conflict of Interests

Authors have no conflict of interests.

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Effects of single antegrade hot shot in comparison with no hot shot administration during coronary artery bypass grafting

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Original Article

Abstract

BACKGROUND: Superior results will be achieved from cardiac surgery by minimizing the effect of ischemia/reperfusion injury during cross-clamping of the aorta. Different cardioplegia solutions have been introduced, but the optimum one is still ambiguous. The aim of this study is to determine the effect of single antegrade hot shot terminal warm blood cardioplegia (TWBC) on patients who had undergone coronary artery bypass grafting (CABG).

METHODS: In total, 2488 patients who had CABG surgery in Sina Hospital, Isfahan, Iran, from 2003 to 2011 were enrolled in this case-control study. They were divided into two groups, those who received cold cardioplegia only and those who received a hot shot following cold cardioplegia. Demographics, and clinical data, such as; premature atrial contraction (PAC) arrhythmia, diabetes treatment, and left ventricular ejection fraction (EF), were collected and logistic regression analysis was used to analyze the data.

RESULTS: There were significant differences found between subjects receiving antegrade hot shot based on direct current (DC) shocks, with regard to; female, EF levels, diabetes treatment ($P < 0.050$). Those who did not receive the hot shot and were not diabetic received more DC shock ($P = 0.019$). The prevalence of subjects who did no need DC shock was significantly higher among male subjects who had good EF and acceptable diabetic treatment. Multiple logistic regression showed that PAC arrhythmia did not have a significant effect on receiving DC shock during CAGB [0.84 (0.25, 2.85), ($P = 0.780$)]. Having poor EF increased the risk of receiving DC shock among subjects by 2.81 [(1.69, 4.69), ($P \leq 0.001$)] ($P < 0.001$). Among the diabetic subjects, receiving insulin decreased the risk of receiving DC shock by 0.54 (0.29, 0.98) ($P = 0.042$).

CONCLUSION: It was concluded that single antegrade hot shot following cold cardioplegia was not particularly effective in the CABG group. TWBC will decrease the need for DC shock.

Keywords: Coronary Artery Bypass, Heart Arrest, Induced, Stroke, Mortality, Oxidative Stress, Reperfusion Injury

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Introduction

Since the coronary artery bypass grafting (CABG) procedure was introduced, ischemia/reperfusion (I/R) injury has become one of the most challenging problems in modern cardiac surgery. Hence, numerous solutions and techniques have been introduced to preserve the myocardium during this type of surgery.[1-4]

Cold cardioplegia reduces the oxygen demands of myocardial cells by keeping the heart in an arrested state.[5] As a consequence, the saved energy results in greater preservation of the heart and less reperfusion injury.[6] Terminal warm blood cardioplegia (TWBC) has proved to be effective in reducing I/R injury.[5-7] The mechanisms which are responsible for myocardial protection using (TWBC) remain uncertain.[8] In addition, TWBC has a significant impact in decreasing the incidence of I/R injuries, especially during coronary artery bypass surgery.[9] There have been a number of studies conducted on patients undergoing coronary artery bypass graft using widely differing cardioplegia techniques, but there are fewer studies that have focused on hot shot administration during CABG and its clinical impact.[8,10,11]

The aim of this study was to compare the effect

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of intermittent antegrade cold blood cardioplegia with or without TWBC (hot shot) on different clinical indictors in patients undergoing CABG.

Materials and Methods

A total of 2488 patients who underwent cardiac surgery in Sina Hospital, Isfahan, Iran, between 2003 and 2011, were enrolled in this study. Those patients who received warm blood cardioplegia or underwent reoperation were excluded. Patients were divided into two groups, those who only received intermittent cold blood cardioplegia (Group A, 925 patients) and those who were given intermittent cold blood cardioplegia, plus TWBC (hot shot) (Group B, 1563 patients). The research protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences. All participants gave their written informed consent.

All of the surgeries were carried out by one surgeon, using the same surgical technique and devices. All of the patients were operated on with a median sternotomy. The left internal mammary artery (LIMA), saphenous vein, and radial artery were harvested simultaneously. Next, heparin 3 mg/kg was administered, and subsequently, cardiopulmonary bypass was established. The core body temperature was reduced to 34 °C (mild hypothermia). During the next stage, cardiac arrest was induced with antegrade cardioplegia through the ascending aorta via an inserted cannula. The radial artery was anastomosed to the arteries with more than 90% stenosis, in order to prevent competitive flow, which can compromise graft flow through the radial artery. Next, a saphenous vein graft was applied to the arteries based on angiographic findings. Then, the LIMA was anastomosed to the left anterior descending artery. After each distal anastomosis, 200-300 cc antegrade warm blood cardioplegia (hot shot) was administered randomly.

All of the patients received intermittent cold cardioplegia (1:8).

Data were gathered from Sina's Hospital electronic database, which is based on European Association of Cardiothoracic Surgeons' database. The technique of the surgeries and devices, which were used during cardiac surgery to all of the patients were the same. All statistics were carried out by SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Data were shown as frequency (%) (or mean ± standard deviation where appropriate). For comparing qualitative variables between groups chi-square test (or Fisher exact test where appropriate) and for comparing quantitative variables independent sample t-test used. Multiple logistic regressions were used to determine multiple effects. $P < 0.050$ considered to be statistically significant. Variables included: sex, intra-aortic balloon pump post-operative, arrhythmia of premature atrial contraction (PAC), diabetes treatment, and hospital stay. Ejection fraction (EF) category defined as good (> 50%), fair (30-50%) and poor (< 30%).[12] The arrhythmias that recorded in this study are after weaning of cardiopulmonary bypass.

Results

In this study, a total of 2488 patients were selected (693 males and 1795 females). Mean length of the patients' hospital stay for those who received direct current (DC) shock was 7.81 ± 3.20 and for those who did not (7.92 ± 4.77). Overall, 1.1% had PAC arrhythmia. In total, 62.8% of the patients received antegrade hot shot). Table 1 shows the demographic characteristics of subjects who received an antegrade hot shot in compared with no DC shock.

There were significant differences between receiving DC shock based on hot shot with regard to: sex, EF category, diabetes treatment ($P < 0.050$). The non-diabetic patients who received hot shot got less DC shock ($P = 0.019$). In Group B, female subjects and diabetic patients with oral agents got less DC shock. Subjects with good EF level received less DC shock in Group B ($P = 0.003$) (Table 1). Table 2 shows the effect of antegrade hotshot on dc shock within group of peri and post-CABG complications. In Group B, those who experienced PAC and atrial fibrillation the need for DC shock cardioversion were less. Multiple logistic regression showed that receiving a hot shot in subjects who had PAC arrhythmia had no significant effect on DC shock during CAGB [0.84 (0.25-2.85) $P = 0.780$]. Prevalence of other arrhythmias was few in cases. Multiple logistic regression showed that having poor EF level increased the risk of receiving DC shock among subjects by 2.81 (1.69, 4.69) ($P < 0.001$) (Table 3). In this regard, using antegrade hotshot decreased the chance of getting DC shock by 0.65 (0.51, 0.84) ($P = 0.001$). Among the diabetic subjects, receiving insulin decreased the risk of DC shock by 0.54 (0.29, 0.98) ($P = 0.042$). In Group B the mean length of hospital stay in those who received DC shock was not statistically significant (0.775).

Table 1. Effect of antegrade hot shot on direct current (DC) shock within group of different demographic characteristics

Characteristics	Ante grade hot shot	DC-shock	P
Sex			
Male	Yes	32 (9.1)	0.491
	No	27 (10.8)	
Female	Yes	128 (11)	0.001
	No	104 (16.4)	
EF category			
Poor	Yes	15 (22.4)	0.460
	No	8 (29.6)	
Fair	Yes	79 (11.6)	0.198
	No	58 (14.3)	
Good	Yes	69 (8.5)	0.003
	No	67 (13.6)	
Diabetes treat			
Oral alone	Yes	29 (7.5)	0.048
	No	28 (12.3)	
Diet	Yes	10 (16.7)	0.717
	No	5 (13.9)	
Insulin	Yes	9 (7.1)	0.975
	No	4 (7.3)	
None	Yes	116 (11.7)	0.019
	No	96 (15.9)	

EF: Ejection fraction; DC: Direct current

Table 2. Effect of antegrade hot shot on direct current (DC) shock within group of peri and post coronary artery bypass grafting (CABG) complications

Arrhythmia	Ante grade hot shot	DC-shock	P
PAC arrhythmia			
No	Have	55 (10.0)	0.002
	Not have	150 (15.6)	
Yes	Have	1 (25.0)	> 0.999
	Not have	3 (17.6)	
AF arrhythmia			
No	Have	52 (10.3)	0.009
	Not have	131 (15.2)	
Yes	Have	4 (8.7)	0.117
	Not have	22(18.6)	

DC: Direct current; PAC: Paroxysmal atrial contracture; AF: Atrial fibrillation

Table 3. Multiple logistic regressions for effect of characteristics on no need to direct current (DC) shock

Characteristics	OR (95.0% CI)	P
Sex (female)	1.21 (0.89, 1.66)	0.226
PAC arrhythmia (yes)	0.84 (0.25, 2.85)	0.780
EF category		
Poor	2.81 (1.69, 4.69)	< 0.001
Fair	1.22 (0.94, 1.58)	0.136
Good (ref)	1	-
Diabetes treat		
Oral alone	0.69 (0.51, 0.96)	0.026
Diet	1.24 (0.69, 2.21)	0.465
Insulin	0.54 (0.29, 0.98)	0.042
None (ref)	1	-
Hospital stay	1.21 (0.89, 1.66)	0.226
Ante grade hot shot	0.65 (0.51, 0.84)	0.001

Values are multiple adjusted by each other; PAC: Paroxysmal atrial contracture; OR: Odd ratio; CI: Confidence interval; EF: Ejection fraction

Discussion

Our results showed that a single antegrade hot shot following cold cardioplegia is not significantly effective in the CABG group. TWBC will decrease the chance of receiving Dc shock by 0.35 [0.65 (0.51, 0.84), P = 0.001]. Good EF (> 50%) shows that the heart muscle is strong. Obviously those patients with good EF required less DC shock. Undoubtedly those with pre-operative sinus rhythm will need less DC shock. Diabetic subjects who controlled their diabetes mellitus (DM) with oral agents received 0.69 times more TWBC, however, in patients using other methods this was not the case. Diabetic patients who controlled their blood glucose with oral drugs alone, required less defibrillator during their surgery, this may be because of the lower levels of free radicals and better control of DM in these patients. Single hot shot does not seem to have an effect on the different types of arrhythmia. The length of hospital stay and spontaneous rhythm time from declamping were not statistically significant. As discussed above, the effect of single antegrade hot shot on defibrillator usage during cardiac surgery is still a matter of debate. In our literature review, the studies that examined the positive effects of hot shot in reducing DC shock defibrillator were rare. In contrast to our findings, Goncu et al. showed that antegrade hot shot does not affect DC shock usage. They concluded that combined antegrade cardioplegic infusion via the aortic root, with additional cardioplegia from a vein or free arterial grafts after each distal anastomosis, will result in decreased DC shock usage.[13] Contrary to our findings, Ghazy et al. showed that single shot cardioplegia does not change the incidence of arrhythmia.[3] Moreover, Akowuah et al. showed that retrograde cardioplegia does not have an effect on ventricular tachycardia/ventricular fibrillation arrhythmia during surgery.[8] In addition, Falcoz et al. reported there was no difference in the number of electroshocks administered between two groups of cold crystalloid cardioplegia, followed by warm and cold crystalloid cardioplegia. Falcoz et al. compared electroshock usage only in heart valve surgery, and the sample size was 70 patients. The content of the cardioplegia solution was also different from ours.[14] It is concluded that single antegrade hot shot can have an effect on DC shock usage during cardiac surgery. It can lower defibrillator usage 1.55-fold in contrast to not administering hot shot.

It is assumed that the constituents of the hot shot are also effective in preserving myocardial function because of the lower damage, but more biochemical studies are required in order to evaluate the exact effect of this solution. The limitation of our study is that we did not evaluate the biomarkers in the two groups of patients, and the post-operative parameters are few in number. More studies favorably randomized clinical trials are needed in future in order to find the best contents for a hot shot and cold cardioplegia.

Assurances

- The research protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences. All participants gave their written informed consent
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- Financial disclosure: N/A.

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Conflict of Interests

Authors have no conflict of interests.

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Adiponectin inhibits oxidized low density lipoprotein-induced increase in matrix metalloproteinase 9 expression in vascular smooth muscle cells

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Original Article

Abstract

BACKGROUND: High expression of matrix metalloproteinase 9 (MMP9) during vascular injury and inflammation plays an important role in atherosclerotic plaque formation and rupture. In the process of atherosclerosis, oxidized low-density lipoprotein (oxLDL) upregulates MMP9 in human aortic vascular smooth muscle cells (HA/VSMCs). Adiponectin is an adipose tissue-derived hormone that has been shown to exert anti-atherogenic and anti-inflammatory effects. The aim of this study was to investigate the effect of adiponectin on MMP9 expression under pathogenic condition created by oxLDL in HA/VSMCs.

METHODS: In this experimental study, HA/VSMC were stimulated with oxLDL alone and in the presence of adiponectin for 24 and 48 h. The expression of MMP9 gene was determined by real-time polymerase chain reaction method. The protein level of this gene was investigated by western blotting technique.

RESULTS: An oxLDL increased MMP9 expression 2.16 ± 0.24- and 3.32 ± 0.25-fold after 24 and 48 h, respectively and adiponectin decreased oxLDL-induced MMP9 expression in a time-dependent manner.

CONCLUSION: These results show that adiponectin changes extracellular matrix by reducing MMP9 mRNA and protein, therefore, may stabilize lesions and reduce atheroma rupture.

Keywords: Matrix Metalloproteinase 9, Adiponectin, Oxidized Low Density Lipoprotein

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Introduction

Atherosclerosis is a multifactorial disease that remains one of the leading causes of mortality worldwide.[1] Obesity and its dependence on the pathogenesis of cardiovascular disease have evoked great interest in understanding the impact of adipokine secreted from adipose tissue on atherosclerosis.[2] It has been well established that adipose tissue constitutes a versatile endocrine gland in the body and is actively involved in the regulation of many biological processes.[3] Some adipose tissue-derived factors have proinflammatory activity and, in contrast, some factors like adiponectin inhibit inflammatory processes.[4] Fluctuation in adipokines is a key mechanism that connects obesity to increased risk of vascular complications.[5] Adiponectin has attracted special attention of investigators because of its ability to impact cardiovascular disease.[6] According to clinical studies, high molecular weight form of adiponectin is more clinically relevant[7] because it exerts the protective effects on vascular diseases.[8]

Matrix metalloproteinases (MMP) are a family of zinc-dependent proteolytic enzymes, which are collectively capable of degrading various components of the extracellular matrix.[9]

Human epidemiological and genetic studies show that (MMP9) is the strongest candidate for inducing plaque rupture.[10,11] These studies confirmed that MMP9 played a basic role in progression of arterial lesions because it regulated vascular smooth muscle cells (VSMCs) proliferation and migration into the intima.[12] Several studies have indicated that oxidized low-density lipoprotein (oxLDL) induced MMP9 gene expression in smooth muscle cells and macrophages.[13-15] It is well

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known that oxLDL is involved in the induction and also in the progression of atherosclerosis.[16] Furthermore, it is responsible for destabilizing plaques through increased expression of metalloproteinases.[17] However, the functions of adiponectin in atherosclerosis have not yet been fully understood. Further research regarding the mechanism of adiponectin action will lead to better understanding of the pathogenesis of atherosclerosis. Due to importance role of oxLDL and MMP9 in atheroma formation and progression, it seems that atheroma progression can be reduced by using adiponectin. The purpose of this study was to investigate the effect of adiponectin on MMP9 expression under pathogenic condition created by oxLDL in human aortic VSMCs (HA/VSMCs).

Materials and Methods

In this experimental study, HA/VSMCs prepared from Pasteur Institute of Iran were maintained in F12K medium. F12 media contained 0.05 mg/ml ascorbic acid, 0.01 mg/ml insulin, 0.01 mg/ml transferrin, 10 ng/ml sodium selenite, 0.03 mg/ml endothelial cell growth supplement, 2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid (HEPES) to a final concentration of 10 mm, TES to a final concentration of 10 mm, 100 U/ml penicillin, 100 µg/ml streptomycin, and 0.01% amphotericin B. HA/VSMCs between passages 3 and 7 were used in this experiment. For treatment, we seed HA/VSMCs into 12-well plate at a density of 15×10^3 cells/well and incubated them at 37 °C in 5% CO_2. Cells achieving 80% confluence were treated by oxLDL.[18] We treated cells with oxLDL (100 µg/ml)[17] alone and in combination with adiponectin (5 µg/ml)[19] for 24 and 48 h. The cells without any treatment were used as the control.

The treated cells were washed with cold phosphate-buffered saline (PBS). Total RNA was extracted with Biozol reagent (BioFlux-China), according to the manufacturer's instructions. Total RNA concentration and quality were evaluated by NanoDrop spectrophotometer (Thermo-USA). The single stranded cDNA was synthesized using cDNA Synthesis Kit (Thermo, Canada) with 1 µg total RNA. The cDNA was amplified by real time-polymerase chain reaction (PCR) using SYBR® Green PCR Master Mix (Qiagen, Germany). Gene expression was detected by Rotor-Gene 3000 (Corbett, Australia). Results were normalized against the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA.

Primers for MMP9 were as follows: Forward: 5'-GCTCACCTTCACTCGCGTGTA-3', reverse: 5'-TCCGTGCTCCGCGACA-3', and primers for GAPDH; forward: 5'-ACACCCACTCCTCCACCTTTG -3', reverse: 5'-TCCACCACCCTGTTGCTGTAG -3'. The temperature profile for the reaction was an initial stage of 95 °C for 5 min then 40 cycles of 95 °C for 15 s, 59 °C for 20 s, and 72 °C for 30 s. Results were normalized against the housekeeping gene GAPDH mRNA. Data analysis was performed on the basis of the comparative delta CT method with the formula $2^{-\Delta\Delta CT}$ to perform relative quantification of target genes (gene expression).

To determine MMP9 expression at the protein level, cells were washed with PBS and lysed with radioimmunoprecipitation assay (RIPA) buffer containing protease inhibitor cocktail. The lysates were centrifuged at 10,000 g for 10 min at 4 °C. To equalize the concentrations, protein concentrations were determined by NanoDrop spectrophotometer. Protein lysates with an equal volume of Lameli buffer (0.125 M Tris-HCl 4%, sodium dodecyl sulfate (SDS) 20%, glycine 10%, and 2-mercaptoethanol) were mixed and boiled for 5 min. To separate based on the size equal amounts of protein (300 µg) per lane were loaded onto 10% SDS-polyacrylamide gel electrophoresis. The proteins were blotted onto polyvinylidene difluoride (PVDF) membranes (Roche-Germany) at 120 V for 2 h in transfer buffer (25 mM Tris, 192 mM glycine, and 20% methanol). PVDF membranes were blocked overnight at 4 °C with 5% skim milk in Tris-buffered saline containing 0.1% Tween 20 (TBST). After being washed 3 times with TBST buffer, the blots were incubated with antibodies against MMP9 (1:3000 dilution; Abcam, Cambridge, UK) and antie dies against MMP9 (1:300Abcam, Cambridge, UK) as an internal control in blocking buffer (skim milk and TBST) and were shaken for 2 h. We washed membranes again and incubated them with goat polyclonal secondary antibody to rabbit IgG (1:5000 dilution; Abcam, Cambridge, UK) for 90 min. Finally, bands were visualized using BM blue-POD substrate (Roche-Germany).

All experiments were done in triplicate. Statistical analysis was done using by nonparametric Kruskal–Wallis test and pairwise comparisons among groups were performed by Mann–Whitney test. All statistical analyses were performed with Graph Pad Prism for Windows (version 5, Graph Pad, Software Inc., San Diego, CA, 2005). Graphs were represented as a mean ± standard error of mean, and $P < 0.05$ was considered as the level of significance.

Results

To determine the role of adiponectin protein in MMP9 expression in HA/VSMCs in the presence of oxLDL, the cells were stimulated with oxLDL alone and in the presence of adiponectin for 24 and 48 h.

Our results show that oxLDL increased MMP9 expression 2.16 ± 0.24- and 3.32 ± 0.25-fold after 24 and 48 h, respectively ($P < 0.05$). An oxLDL-induced MMP9 expression was markedly inhibited by adiponectin. Adiponectin decreased oxLDL-induced MMP9 expression 34 and 61% after 24 and 48 h, respectively ($P < 0.05$) (Figure 1a).

Melting curves confirmed that the desired fragments were specifically amplified. In a parallel experiment, western blot analysis confirmed the changes observed at mRNA level (Figure 1b).

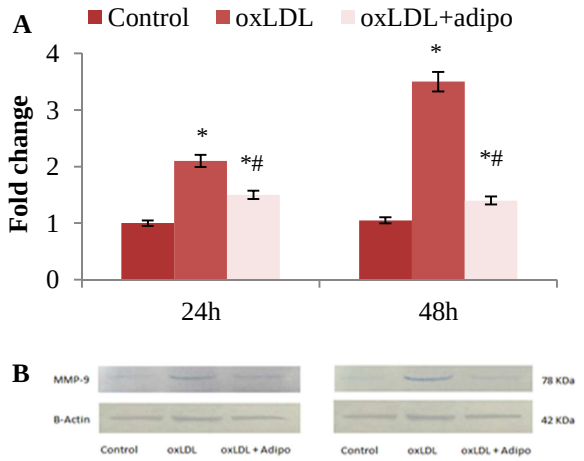

Figure 1. The effect of adiponectin on oxLDL-induced MMP9 expression after 24 and 48 h; (A) Real time PCR analysis of MMP9 mRNA expression levels in HA/VSMCs in the presence of oxLDL with or without adiponectin after 24 and 48 h. Values are expressed as mean ± SE from two independent experiments performed in triplicate. Differences between groups were determined as significant at $P < 0.05$; (B) MMP9 protein expression levels by western blotting for 24 and 48 h. β-actin was used as internal control

* Means $P < 0.05$ compared to the control VSMCs; # Means $P < 0.05$ compared to the oxLDL-exposed VSMCs; oxLDL: Oxidized low-density lipoprotein; VSMCs: human aortic vascular smooth muscle cells; MMP9: matrix metalloproteinase 9; PCR: Polymerase chain reaction

Discussion

Our findings indicate that adiponectin reduces gene expression and protein mass of MMP9 in a time-dependent manner. According to the anti-inflammatory properties of adiponectin and inflammatory role of MMP9, reduction of MMP9 mRNA observed by the adiponectin in this study was not unexpected. Adiponectin exerts protective effects on vascular diseases through its direct actions on vascular component cells including endothelial cells, macrophages, and smooth muscle cells.[8,20,21] In vitro studies on VSMCs have shown that adiponectin can inhibit proliferation and migration of VSMCs induced by several atherogenic growth factors through inhibition of extracellular signal-regulated kinase activation.[22] The results of the present study are consistent with previous results, and indicate that adiponectin through reducing MMP9 can be effective in reducing the risk of cardiovascular disease.[22] Animal studies results have indicated a key role for adiponectin in the progression of atherosclerosis.[22] Considering the fact that, the progression and stability of atherosclerotic lesions are associated with concentrations of metalloproteinases and their inhibitors,[23] the effect of adiponectin on atheroma lesions in these experiments may be due to changes occurring in the extracellular matrix. The present study has shown that changes in the extracellular matrix occurred as the changes in MMP9 concentration happened. Our study has shown that reduction in MMP9 protein concentration is due to decrease in gene expression following adiponectin treatment. Experiment on macrophage shows that adiponectin augmented tissue inhibitor of metalloproteinases-1 (TIMP-1) expression without affecting the mRNA, protein levels, and activities of MMP-9.[24] These results together with the fact that adiponectin with MMP9/TIMP-1 ratio has an inverse relationship in patients with acute coronary syndrome, suggest that adiponectin through the balancing of this ratio modulates plaque stability.[25] The general conclusion from these studies that indicate adiponectin has protective properties is consistent with our findings. Studies performed on macrophages have shown that adiponectin has no effect on MMP9 expression,[24] whereas our study shows that adiponectin has a direct effect on the mRNA and protein levels of MMP9. It could be concluded that the beneficial effect of adiponectin is more intense under pathogenic conditions that we have established in the presence of oxLDL. This demonstrates the value of clinical use of adiponectin. In general, adiponectin through reducing gene expression of MMP9 might contribute to change in the extracellular matrix, hence leading to its vasculoprotective activity through stabilization of atheroma lesions and

reducing rupture of atheroma. It is hoped that these findings will lead to better understanding of the pathology of atherosclerosis and its treatment.

Conclusion

In summary, our findings in this experimental study indicate that adiponectin decreased oxLDL-induced MMP9 expression. These results suggest that adiponectin protects smooth muscle in the vessel wall from the damaging effect of oxLDL in pathologic condition.

Conflict of Interests

Authors have no conflict of interests.

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Effects of citalopram on heart rate variability in women with generalized anxiety disorder

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Original Article

Abstract

BACKGROUND: Heart rate variability (HRV) is defined as variations in R-R interval with time. Dysautonomia is common in patients with psychiatric disorders such as depression and anxiety. Using HRV analysis, recent studies showed that in anxiety disorders, the vagal cardiac function decreases, and sympathetic function increases. This study aimed at investigating citalopram effects on HRV.

METHODS: This before and after study was conducted in 25 generalized anxiety disorder (GAD) patients. GAD was diagnosed based on clinical interview according to diagnostic and statistical manual of mental disorders IV-Text revised (DSM-IV-TR) criteria using Structured Clinical Interview for DSM Disorders-I questionnaire. A cardiologist studied 24 h ambulatory monitoring of the electrocardiogram (Holter) on all patients before the treatment. A volume of 20 mg of citalopram was administered to the subjects on a daily basis. Then, they were studied by Holter monitoring again after 1-month of administration of citalopram.

RESULTS: The average age of participants was 35.32 ± 8.7. The average Holter monitoring time was 23.29 ± 1.14 h before treatment and 23.81 ± 0.68 after it. The 3 h low frequency/high frequency ratio was significantly different between 3 h segments of time before treatment ($P < 0.001$). This difference was even higher after treatment ($P = 0.001$). Data showed an increase in parasympathetic tone during sleep both before and after treatment.

CONCLUSION: These patients showed some impairments of HRV indices that did not improve by citalopram in future, the clinical importance of such disturbances should be evaluated in details with prolonged follow-up and greater sample size.

Keywords: Anxiety Disorders, Heart Rate, Ambulatory Electrocardiography

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Introduction

Heart rate variability (HRV) is defined as variations in R-R interval with time. HRV is actually heartbeat variations from one beat to another, which is used for evaluation of sympathetic and vagus nerve effects on the Sinoatrial node, and consequently on the heartbeat.[1,2]

Apart from body mass index and elevated blood glucose or blood pressure, mental status, and related processes can significantly affect cardiac autonomic control.[3] Stressors increase cardiac sympathetic control and decrease cardiac parasympathetic control, which consequently result in an increase in low frequency (LF) HRV and a decrease in high frequency (HF) HRV.[4] Dysautonomia is common in patients with psychiatric disorders such as depression and anxiety. This is diagnosed via HRV.[5] Anxiety disorders are highly associated with dysautonomia, which increases cardiovascular mortality. Patients with panic disorder or phobia are prone to cardiovascular diseases.[6-8] Using HRV analysis, recent studies showed that in anxiety disorders, the vagal cardiac function decreases, and sympathetic function increases.[9,10] Miu et al. showed a correlation between characteristic anxiety and dysautonomia using HRV analysis.[11]

Generalized anxiety disorder (GAD) is characterized by a pattern of frequent, persistent

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worry, and anxiety that is disproportionate to the impact of the events or circumstances on which the worry focuses.[12] An acute episode of anxiety is defined as an increase in heart rate, decrease in HRV, and respiratory sinus arrhythmia. Anxiety disorders are highly associated with an increased risk of mortality and cardiovascular complications.[13,14] One of the hypotheses raised on this issue is impaired regulation of cardiac autonomic control due to the correlation of the cardiac autonomic control system with cardiovascular diseases and mortality.[15]

The selective serotonin reuptake inhibitors (SSRIs) do have cardiac effects, the best demonstrated of those being a mild bradycardia observed during chronic treatment with fluoxetine, fluvoxamin, and paroxetine. Moreover, there are increasing the number of case reports on dysrhythmia and syncope associated with fluoxetine and another SSRIs treatment and overdose. A multicenter case-control study has shown that in the elderly the consumption of fluoxetine was significantly associated with an excess risk of syncope and orthostatic hypotension.[16] This study aimed to investigate effects of citalopram on HRV.

Materials and Methods

This before and after study aimed to investigate the effects of citalopram on HRV in patients with GAD. GAD was diagnosed based on clinical interview, according to diagnostic and statistical manual of mental disorders IV–Text revised criteria using Structured Clinical Interview for DSM Disorders-I questionnaire.[12] Due to shortage in studies that could provide valid data to estimate the sample size appropriately, we were not able to make a sample size calculation and started the study as a pilot exploratory design with minimum sample size (30 patients). Because of a higher prevalence of GAD in women, all of the participants were selected by using convenience sampling from female patients. Patients from Razi Hospital, Tabriz, Iran, outpatient clinic voluntarily entered the study after being diagnosed with GAD and considering inclusion and exclusion criteria from August to December in 2013. After explaining the safety of Holter monitoring to patients, providing them with the full information required for participation in interventional studies and letting them know that no cost will be imposed on them, subjects entered the study. In addition, all of them could withdraw from the study at any point. They were also ensured that all of their personal and medical information would remain confidential.

A cardiologist performed 24 h ambulatory monitoring of the electrocardiogram (Holter–Norav version 2.978) on all patients before the treatment. A volume of 20 mg of citalopram was administered to the subjects on a daily basis. Then, they were studied by Holter monitoring again after 1-month of administration of citalopram. Usually, the patients with GAD show a response to treatment in 4 weeks.

Techniques for measures calculating HRV in regard of equipment, condition, and preparation met the criteria mentioned in another article on HRV.[17]

Holter monitoring calculates two indicator categories HRV: Time domain and frequency domain parameters. Frequency domain analysis is measured in 2-5 min intervals. HRV indicators are presented in table 1. The 24 h monitoring of HRV are divided into 4 periods of 3 h recordings by the device (16-19, 20-23, 02-05 and 11-14). Each parameter of time domain and frequency domain measured again. Inclusion criteria were female gender, diagnosed with GAD and informed consent to participate in the study. Exclusion criteria were pregnant and lactating women, menopausal age, having an underlying heart disease, medical conditions affecting the heart rhythm including thyroid disease, diabetes mellitus, neuropathy, and tetraplegia concurrent use of drugs affecting heart rhythm and existence of atrial fibrillation; and significant rhythm disorders of heart like as frequent extra stimuli. Demographic variables that were assessed in the study were: Age, education level, and occupation. GAD diagnosis was given if at least three symptoms were present.

Descriptive methodologies (frequency, percentage, mean ± standard deviation) were used to perform statistical analysis. Kolmogorov–Smirnov test was used for normality assessment. In variables that had non-normal distribution, we used non-parametric tests (Wilcoxon test) to perform comparisons between before and after HRV indices in variables with normal distribution, paired t-test was used. Used repeated measure analysis of variance for evaluates, the effect of 3 h segments of time (within subjects) and groups (between subjects). Mauchly's sphericity test was used to validate it. If sphericity is violated, the Greenhouse-Geisser correction was used. All statistical analyses were conducted via SPSS software for Windows (version 16, SPSS Inc., Chicago, IL, USA). Significance level was considered as $P < 0.050$. Trends for time domain measures in 24 hour electrocardiography monitoring are shown in figure 1.

Results

The average age of participants was 35.32 ± 8.7, with the minimum and maximum age of 25 and 59, respectively. Five patients dropped out of the study (because of unwillingness to do after treatment Holter monitoring), so 25 were studied. Four patients (16%) were single, and 21 of them (84%) were married. In addition, 6 (24%), 11 (44%), and 8 (32%) held undergraduate, graduated, and higher education degrees, respectively. Seven (28%) and 18 (72%) were employed and housekeepers, respectively. The average Holter monitoring time was 23.29 ± 1.14 h before treatment and 23.81 ± 0.68 after it table 2 shows the variation of HRV indices in 24 h.

The data showed that 7 individuals suffered from ventricular arrhythmia before the administration of citalopram. Moreover, 3, 2, and 2 patients suffered from premature ventricular contraction (PVC), bigeminy and trigeminy, respectively. In follow-up, Holter monitoring, which was done 1-month after the administration of citalopram, ventricular arrhythmia, PVC, bigeminy, and trigeminy were observed in 5, 2, 2, and 3 individuals, respectively. One of the three patients suffering from PVC prior to the treatment had no symptoms. The frequency of PVCs in the other 2 participants reduced from 818 to 618 in the first and from 1050 to 625 beats in the second patient, during 24 h, respectively. During the initial monitoring, supraventricular arrhythmia (SVT) [premature atrial contraction (PAC)] was observed in 4 cases and SVT in one case, while during the follow-up monitoring, PAC was observed in 3 cases. The frequency of PACs increased in one case after treatment, but none of the subjects had SVT.

The 3 h LF/HF ratio was significantly different between 3 h segments of time before treatment ($P < 0.001$). This difference was higher after treatment ($P = 0.001$) (Figure 2). Figure 2 shows a significant increase in parasympathetic tone during sleep both before and after treatment. Table 3 shows no significant different between variables before and after using citalopram.

Table 1. Heart rate variability (HRV) parameters: Definition and normal ranges

Variables	Definition	Normal values (mean ± SD)
Time domain		
SDNN (ms)	Standard deviation of NN intervals (24 h)	141.0 ± 39.0
SDANN (ms)	Standard deviation of average (5 min duration) of NN interval	127.0 ± 35.0
RMSSD (ms)	Square root of mean squared difference of successive NN intervals	27.0 ± 12.0
HRV triangle (ms)	Heart rate variability	37.0 ± 15.0
Frequency domain		
ULF(ms^2)	Ultra low frequency	1170.0 ± 416.0
VLF (ms^2)	Very low frequency	975.0 ± 203.0
LF (nu)	Low frequency	54.0 ± 4.0
HF (nu)	High frequency	29.0 ± 3.0
LF/HF ratio		1.5 ± 2.0

SD: Standard deviation; SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability; ULF: Ultra low frequency; VLF: Very low frequency; LF: Low frequency, HF: High frequency

Table 2. Heart rate variability (HRV) in 24 h Holter monitoring before and after citalopram

HRV	Parameters		
	Before	After	P
Time domain			
SDNN	252.0 ± 207.0	317.0 ± 378.0	0.354*
SDANN	121.0 ± 88.0	118.0 ± 78.0	0.664
RMSSD	248.0 ± 314.0	316.0 ± 496.0	0.440*
HRV triangle	36.5 ± 9.2	37.5 ± 9.2	0.821
Frequency domain			
ULF	90.0± 300.0	93.0 ± 33.0	0.543
VLF	261.0± 68.0	254.0 ± 64.0	0.876
LF	154.0 ± 29.0	151.0 ± 21.0	0.305
HF	137.0 ± 33.0	136.0 ± 33.0	0.848
LF/HF	1.2 ± 0.5	1.2 ± 0.4	0.582

* Wilcoxon test; Other variables: paired t-test; SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability; ULF: Ultra low frequency; LF: Low frequency, HF: High frequency; VLF: Very low frequency

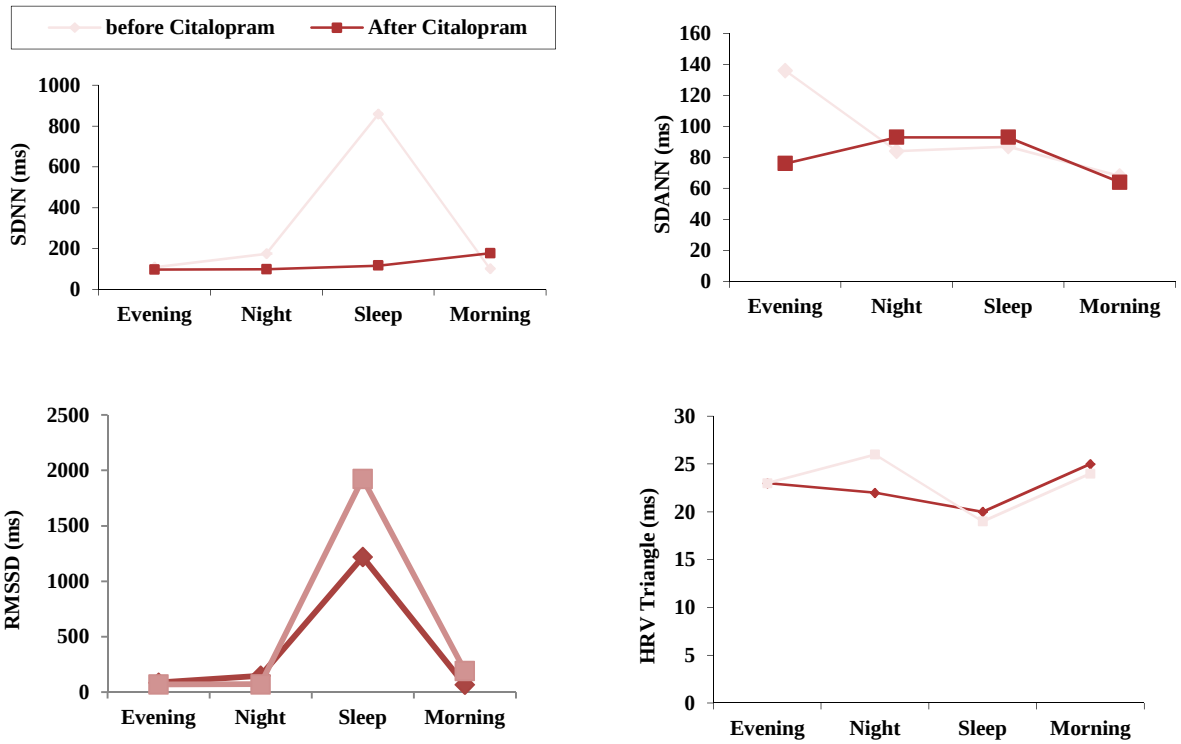

Figure 1. Trends of time domain measures in 24 h electrocardiogram monitoring
SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability

In frequency domain analysis, LF/HF ratio variations, which is a sign of sympathetic and parasympathetic balance, were compared during 3-h periods before the treatment, and indicated a significant difference (P = 0.010). This index showed that sympathetic and parasympathetic balance differences during different periods of the day were different between time periods, but this difference was higher after treatment (P = 0.003). These findings mean that the flat and narrow difference of balance between sympathetic and parasympathetic activation becomes wider after therapy. While the sympathetic tone of patients decreased after treatment but the parasympathetic tone was not increased significantly after treatment. Sleep is the time that increasing in parasympathetic tone should be increased but both before and after treatment this increase was not high enough to improve the LF/HF ratio.

Discussion

HRV triangle is the estimate for total HR variability. This index was 36.52 before treatment, which increased to 37.55 after treatment. Although this difference was not different statistically, but the difference between time segments of HRV before treatment was significant (P = 0.010). This difference was not significant after treatment, which indicates some kind of autonomic stability after therapy with citalopram.

The standard deviation of NN intervals (SDNN) is an estimate for total HRV parameters. The total value of this parameter was 252 and the normal value 141. The average is better than normal but when comparing 3 h periods, the privilege of this parameter occurred during sleep. In other words, when the patient was awake this parameter was lower than normal. Furthermore, van Zyl et al. showed that SSRIs decrease heart rate and also cause a possible increase in SDNN.[18]

The disturbances in autonomic function were high when the patient was awake. It is notable that standard deviation of average of NN interval (SDANN) before treatment was very high when Holter monitoring started during evening and soon reached its average state during night time. This finding did not occur during follow-up. This finding may be related to the extra anxiety of patients who were attached to leads and device for the first time.

SDANN, which is a long-term estimate of HRV, may be a better estimation for HRV because it removes short-term effects of HRV components. This parameter was always lower in patients before and after treatment. Patients with anxiety disorders had autonomic disorders, which did not improve by gitolpram administration despite the improvement in their clinical status.

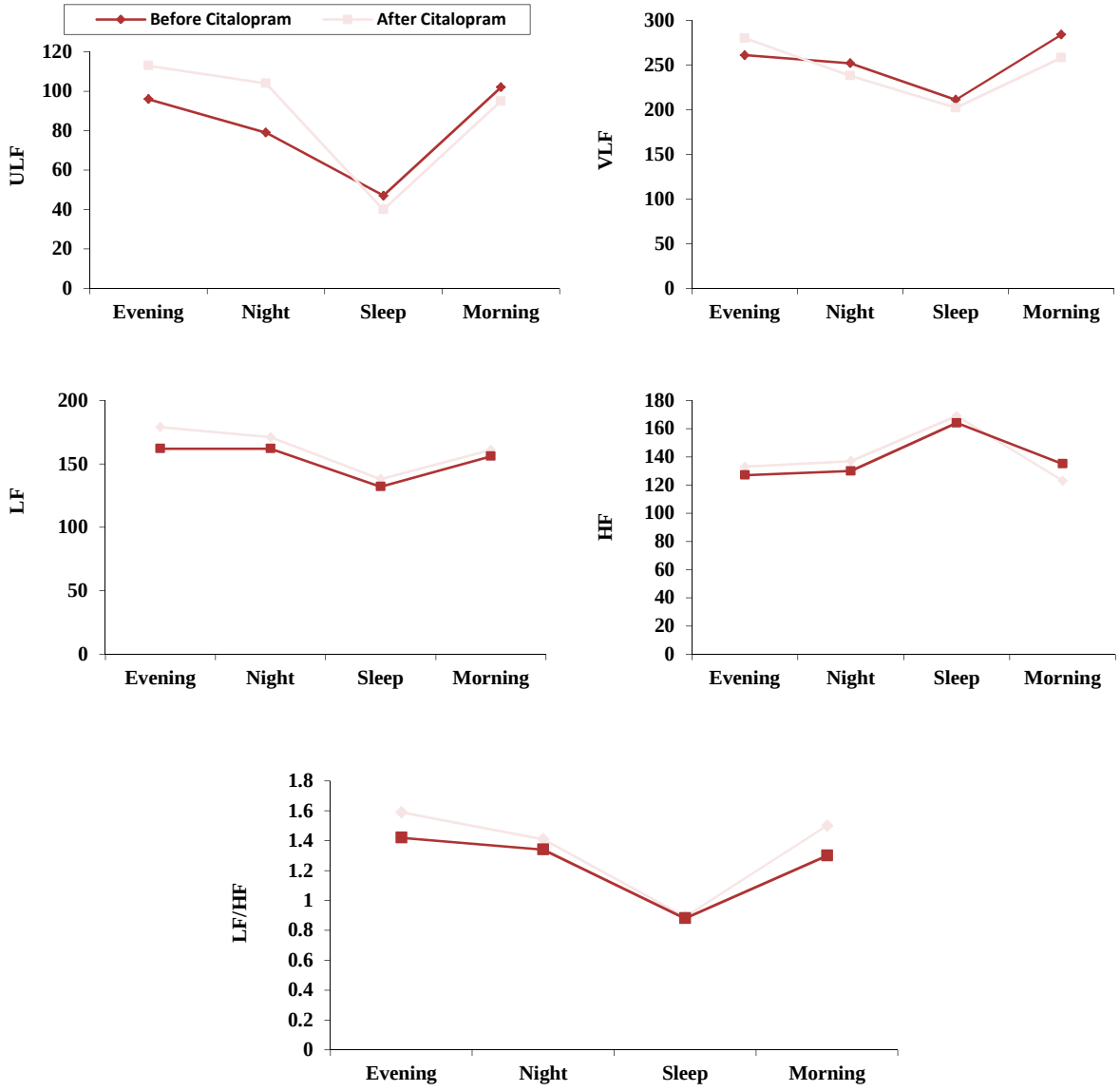

Figure 2. Trends of frequency domain measures in 24 h electrocardiogram monitoring
ULF: Ultra low frequency; VLF: Very low frequency; LF: Low frequency, HF: High frequency

Root mean square of the successive differences is an estimate of short-term variation of autonomic balance. This parameter was always higher than normal value, which indicates a high level of fluctuation and variation in the autonomic drive of patients. The clinical importance of this finding should be evaluated further.

The value of LF and HF in the frequency domain analysis was lower than normal before and after therapy. The ratio of LF/HF was higher than normal values except during sleep. This finding is not a correct finding and is could not be interpreted as a sign of improvement in HRV. The values of LF and HF were less than normal. Their ratio can be normal but based on components of this ratio, the LF/HF ration cannot be interpreted as a sign of improvement in HRV. Actually, this finding shows our patients had blunted autonomic status before and after therapy for anxiety disorders.

The above mentioned results are comparable with other findings. McFarlane et al. showed that the HRV improvement indices in depressed patients with myocardial infarction, who received sertraline for 6 months was more than those of the control group, and this increase in HRV was equal to non-depressed patients.[19] In a randomized clinical trial study, Brunoni et al. demonstrates that HRV did not change after treatment with 50 mg sertraline for 6 weeks, neither was an increased HRV observed in the clinical response.[20]

Table 3. Heart rate variability (HRV) in four periods of 3 h before and after citalopram

HRV	Before citalopram					After citalopram					P*
	Evening	Night	Sleep	Mid-day	P	Evening	Night	Sleep	Mid-day	P	
Time domain											
SDNN	108 ± 49	174.0 ± 356.0	858.0 ± 3303.0	100.0 ± 30.0	0.352	96 ± 28	98.0 ± 29.0	116.0 ± 78.0	176.0 ± 354.0	0.326	0.337
SDANN	136 ± 133	84.0 ± 91.0	87.0 ± 72.0	68.0 ± 82.0	0.150	76 ± 88	93.0 ± 81.0	93.0 ± 104.0	64.0 ± 53.0	0.298	0.505
RMSSD	86 ± 79	148.0 ± 364.0	1219.0 ± 4920.0	67.0 ± 39.0	0.335	70 ± 45	71.0 ± 39.0	1926.0 ± 6998.0	193.0 ± 526.0	0.261	0.730
HRV triangle	23 ± 7	22.4 ± 5.6	20.3 ± 5.2	25.8 ± 9.3	0.032	23 ± 6	25.9 ± 7.6	19.4 ± 9.1	24.1 ± 5.5	0.777	0.767
Frequency domain											
ULF	96 ± 50	76.0± 42.0	47.0 ± 26.0	102.0 ± 44.0	0.840	113 ± 48	104.0 ± 43.0	40.0 ± 22.0	95.0 ± 50.0	0.026	0.213
VLF	261 ± 95	252.0 ± 86.0	211.0 ± 75.0	284.0 ± 85.0	0.515	280 ± 76	238.0 ± 77.0	202.0 ± 29.0	258.0 ± 87.0	0.132	0.548
LF	179 ± 54	171.0 ± 44.0	138.0 ± 31.0	161.0 ± 43.0	0.015	162 ± 47	162.0 ± 35.0	132.0 ± 29.0	156.0 ± 32.0	0.009	0.124
HF	133 ± 47	137.0 ± 41.0	169.0 ± 43.0	123.0 ± 46.0	0.959	127 ± 42	130.0 ± 37.0	164.0 ± 42.0	135.0 ± 43.0	< 0.001	0.859

Use repeated measure analysis of variance; * Significant between the average of variable before and after using citalopram; SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability; ULF: Ultra low frequency; LF: Low frequency; HF: High frequency; VLF: Very low frequency

In their clinical trial study, Chappell et al. stated that duloxetine and escitalopram did not have a significant effect on HRV.[21] Penttila et al. reported that the cardiac effect of citalopram on heart rate was the same as a placebo.[22] In the Netherlands Study of Depression and Anxiety, Licht et al. showed that patients with anxiety had lower SDNN compared to the control group.[23] Kemp et al. in a meta-analysis showed that tricyclic medication decreased HRV, although serotonin reuptake inhibitors, mirtazapine, and nefazodone had no significant impact on HRV despite patients' response to treatment.[24] Although tricyclic antidepressants reduce HRV, at least one study has suggested that, in patients with panic disorder, treatment with the SSRI paroxetine normalizes HRV.[25]

Conclusion

Our patients showed some impairment of HRV indices that did not improve significantly after therapy with citalopram in future; the clinical importance of such disturbances should be evaluated in details with prolonged follow-up and greater sample size.

Limitation

- We had not a control group
- We studied only the female patients.

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Conflict of Interests

Authors have no conflict of interests.

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Percutaneous aortic valve implantation in bicuspid aortic valve: A case report

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Case Report

Abstract

BACKGROUND: Transcatheter aortic valve implantation (TAVI) was known as an alternative technique for treatment of severe aortic stenosis (AS). This technique is controversial in bicuspid aortic valve (BAV). Here, we report TAVI for severe AS in a BAV setting in a patient with serious lung disease.

CASE REPORT: A 68-year-old woman with a history of coronary artery bypass graft, BAV and severe AS, asthma, who had repeatedly denied any suggestion for open heart surgery, was our volunteer candidate for TAVI. The peak and mean pressure gradient decreased from 53 and 43 mm Hg to 13and 6 mm Hg respectively.

CONCLUSION: TAVI could be a viable option for highly selected patients with AS and BAV who have a prohibitive risk for open heart surgery.

Keywords: Transcatheter Aortic Valve Implantation, Aortic Stenosis, Bicuspid Aortic Valve

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Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart disease[1] with a potential to progress finally to aortic stenosis (AS). In patients over 80 years of age, BAV is the cause of 30-50% of the cases with severe AS, necessitating invasive treatment.[1,2]

There is a limited experience with transcatheter aortic valve implantation (TAVI) in the setting of a bicuspid valve. Incomplete valve expansion or malposition are the most frequent problems in this setting. There is, therefore, a concern over scheduling these patients for TAVI due to the bulky and asymmetric leaflets in a BAV, which may result in hemodynamic disturbances, reduced durability, paravalvular leaks, or embolization. Another complication that may occur in these patients is the occlusion of the left main artery by the bulky valve.

Many authors believe that congenital BAV is a contraindication for TAVI[1,3-5] however, successful cases of TAVI in patients with severe symptomatic AS who were very high risk for open heart surgery have recently been published.[1,3,4]

Here we introduce a patient with severe AS due to BAV who was not a candidate for open heart surgery and was finally treated with TAVI.

Case Report

A 68-year-old woman with a history of coronary artery disease and coronary artery bypass graft surgery in 2001, presented with dyspnea (The Canadian Cardiovascular Society Functional Class IV) and chest pain. The echocardiography (ECG) findings included normal sinus rhythm, normal axis, heart rate of 72 beats/min, ST depression, and T inversion in leads I, AVL, and V_1-V_6. Echocardiography revealed BAV with severe AS and moderate thickening and calcification and trivial aortic insufficiency. In addition, the ascending aorta was mildly dilated to 3.9 cm with mild left ventricular (LV) hypertrophy, diastolic LV dysfunction, good LV size and systolic function, and good right ventricular size and function. The aortic annular diameter and aortic valve area were about 2.3 cm and 0.6 cm respectively (Figure 1).

On her coronary angiography in December 2011, the left anterior descending artery had significant stenosis in the proximal portion with a

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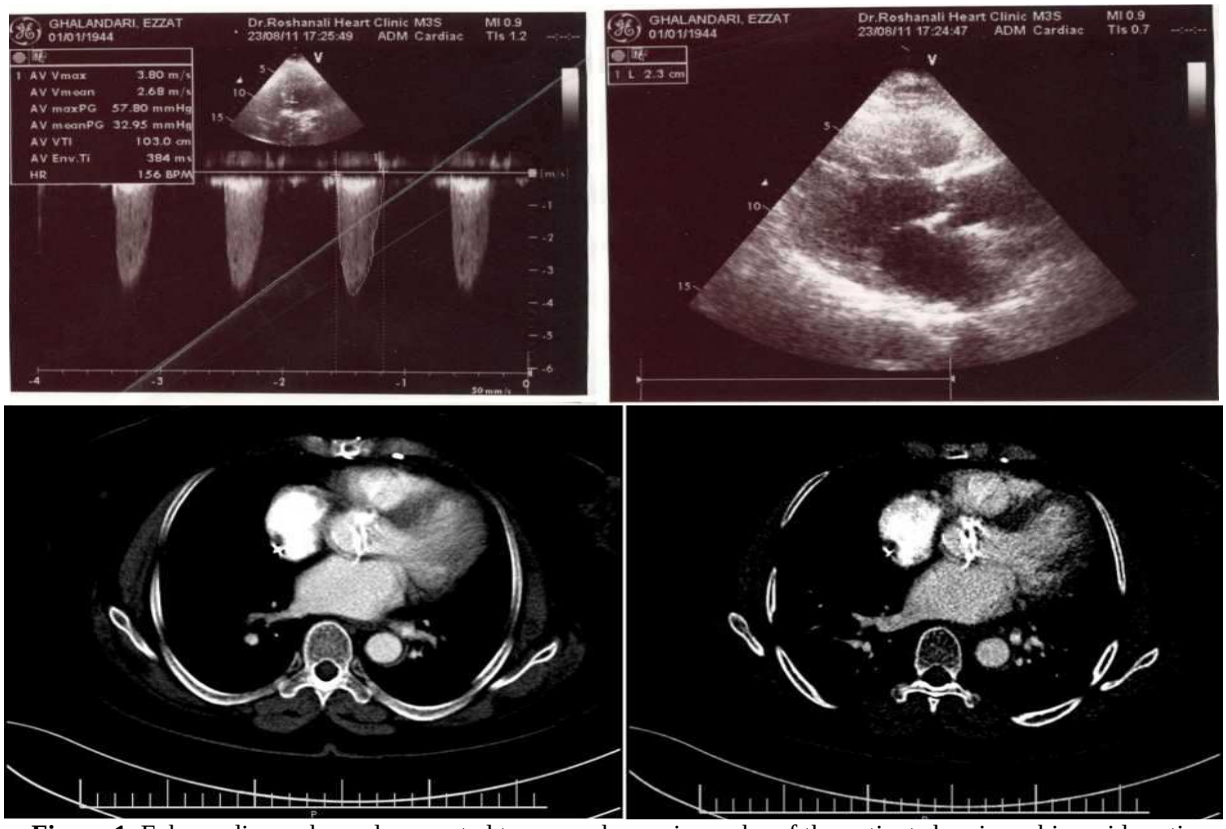

Figure 1. Echocardiography and computed tomography angiography of the patient showing a bicuspid aortic valve with a peak pressure gradient of 57.8 mm Hg

good competitive flow from the left internal mammary artery. The left circumflex artery was cut-off at its distal portion, and the right coronary artery was diffusely diseased. The saphenous vein graft on the posterior descending artery was patent, and so was the left internal mammary artery on the left anterior descending artery. The saphenous vein graft on the obtuse marginal was occluded based on its stump on aortography. Multi-slice computed tomography angiography showed the left internal mammary artery graft was exactly behind the sternum suggesting a possible risk of compromising the left internal mammary artery during surgery.

The patient had moderate asthma, for which she had been on corticosteroids for quite a long period of time. She had repeatedly denied any suggestion for open heart surgery during the previous years. Considering the patient's past medical history and her clinical conditions, our cardiac surgeons refused to perform open-heart surgery, and she was referred for TAVI.

The details of the TAVI procedure, especially drawbacks of this technique for patients with BAV were described for the patient and her family, followed by written consents from them. General anesthesia, transesophageal echocardiography, pre-implantation balloon aortic valvuloplasty, and rapid ventricular pacing were carried out as a routine standard protocol. Arteriotomy was performed to obtain an appropriate femoral access. An 18 French 26 mm Nova flex Edwards-Sapien XT valve (Edwards Lifesciences, Inc., Irvine, California) was selected and all the stages of implantation were evaluated via intra-procedural transesophageal echocardiography (Figures 2 and 3).

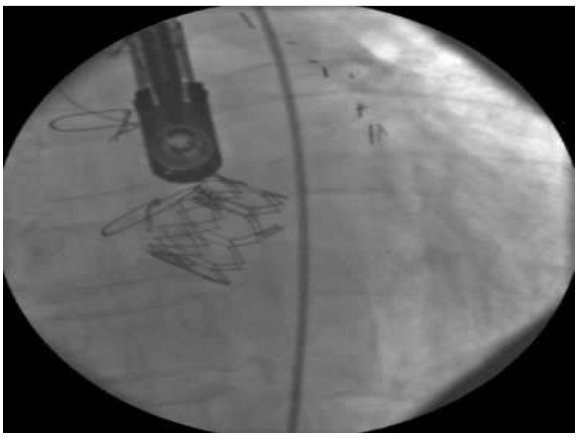

Figure 2. The implanted prosthetic aortic valve

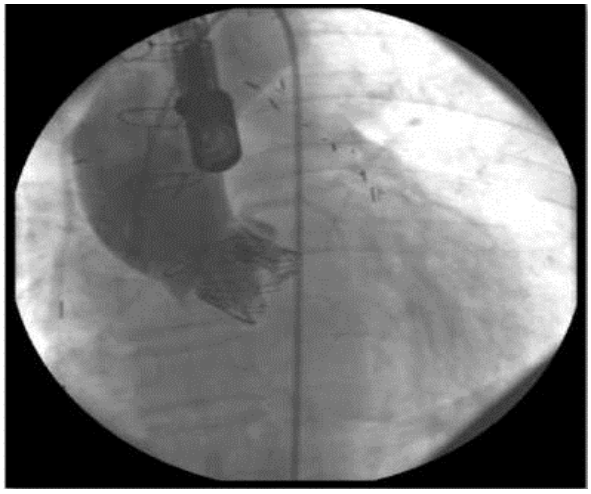

Figure 3. Aortography after transcatheter aortic valve implantation, showing no obvious aortic insufficiency

Pre-implantation balloon valvuloplasty was done with a 20-40 balloon, and full balloon expansion could be achieved. The above-mentioned valve was thereafter successfully implanted. The peak pressure gradients (PPG) and mean pressure gradients (MPG) by echocardiography decreased from 57 mm Hg to 13 mm Hg and from 43 mm Hg to 6 mm Hg, respectively. No obvious aortic insufficiency was detected. A 30 day follow-up showed significant improvement in clinical and hemodynamic findings in that the patient had milder dyspnea (The Canadian Cardiovascular Society functional Class II), prosthetic aortic valve PPG of 13.1 mm Hg, MPG of 6.5 mm Hg, mild tricuspid regurgitation, and systolic pulmonary artery pressure of 35 mm Hg (Figure 4).

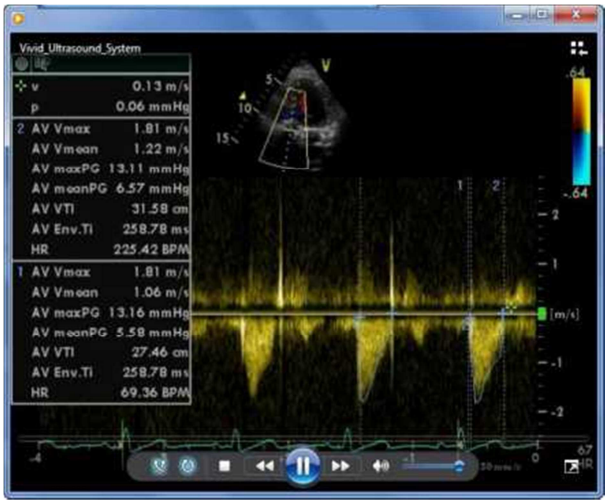

Figure 4. Doppler echocardiography after transcatheter aortic valve implantation showed peak pressure gradient: 13.1 mean pressure gradients: 6.5 mmHg

Discussion

Up to one-third of patients who require life-saving surgical aortic valve replacement are denied surgery due to high co-morbidities resulting in a higher operative mortality rate.[6] In the past, such patients could only be treated with medical therapy or percutaneous aortic valvuloplasty. Neither of those approaches was demonstrated to improve the survival. With advances in interventional cardiology, transcatheter methods have been developed for aortic valve replacement with an aim of offering a therapeutic solution for patients unfit for surgical therapy.[6]

Transcatheter stent-valve implantation in stenotic congenital BAV is under debate. Heavily calcified elliptic bicuspid valves represent a contraindication to catheter-based valve therapies because of concerns over the risks for stent-valve displacement, distortion, or malfunctioning after implantation.[5] Some previous studies have advised against TAVI in heavily calcified aortic valves because of the very high possibility of congenital malformation (BAV or unicuspid aortic valve) in those valves.[7] Given that most of those concerns about poor results of TAVI in BAV originated from the experimental studies done by self-expandable stents,[1] the recommendations against TAVI in patients with BAV are not based on well-designed clinical studies. Indeed, there have recently been a few reports of successful TAVI in patients with BAV,[1,3,5,8] consequently, TAVI seems promising in the treatment of the severe stenosis of BAV, especially in high-risk patients.

In our case, significant clinical improvement (The Canadian Cardiovascular Society functional Class IV to II) was achieved, and PPG and MPG decreased from 57 mm Hg to 43 mm Hg to 13 mm Hg to 6 mm Hg, respectively.

Wijesinghe et al.[1] published their experience on 11 patients and reported significant symptomatic and hemodynamic improvement in 91% of their patients. In their study, MPG decreased from 41 ± 22.4 mm Hg to 13.4 ± 5.7 mm Hg. Baralis et al.[3] and Ferrari et al.[5] reported successful TAVI in a BAV setting in two separate cases with significant improvement in clinical situation. Himbert et al. reported the largest series (15 cases) of TAVI in BAV:[9] the MPG decreased from 60 ± 19 mm Hg to 11 ± 4 mm HG and significant clinical improvement was achieved in 80% of the patients and after 7-8 months follow-up, one patient had died due to aortic dissection and two patients had

hospitalization because of dyspnea (functional class higher than II).

In our patient, there was no obvious paravalvular leakage on intraoperative transesophageal echocardiography and on transthoracic echocardiography in 1-month follow-up. In contrast, in the Himbert et al.'s study, periprosthetic leaks (< 1+) were observed in 13 of 15 patients.[9] Wijesinghe et al. reported 2 out of 11 patients with moderate paravalvular leaks.[1]

Conclusion

Contrary to concerns raised in recent studies, our experience of TAVI in a patient with BAV shows that this modality could be a viable option for patients with prohibitive risk for open heart surgery. This technique should, however, be performed cautiously, paying sufficient heed to preoperative and intraoperative valve imaging, in meticulously selected patients.

Acknowledgments

We would like to thank the patient for her participation in the present study.

Conflict of Interests

Authors have no conflict of interests.

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Surgical embolectomy in the management of massive and sub-massive pulmonary embolism: The results of 30 consecutive ill patients

Ali Azari[(1)], Leila Bigdelu[(2)], Zahra Moravvej[(3)]

Short Communication

Abstract

BACKGROUND: Despite the improvement in the diagnosis and treatment of acute pulmonary embolism, it is yet a common clinical problem. The actual role of open embolectomy has not been well understood. The present report aimed to extrapolate the outcome of early open pulmonary embolectomy in a number of patients with acute (sub) massive pulmonary embolism (AMPE/ASMPE).

METHODS: A prospective study was performed on 30 patients who underwent emergency embolectomy at Ghaem Hospital, Mashhad, Iran during January 2005 to November 2012. All patients with an indication for pulmonary embolectomy according to recent American Heart Association guideline were enrolled in this study. Echocardiographic features, pulmonary artery pressure, and right ventricular (RV) diameter were recorded. The patients were followed up monthly by two cardiologists.

RESULTS: Indications for operation in descending order consisted of contraindication for fibrinolytic therapy (30%), failure to respond to fibrinolysis (26.66%), cardiopulmonary arrest (20%), patent foramen ovale (20%), right atrium clot (10%), and cardiogenic shock (10%). Mean pulmonary artery pressures were 52.26 ± 6.54 and 29.43 ± 2.87 mmHg before and after the operation, respectively ($P < 0.0001$). RV function and diameter improved significantly after surgery ($P < 0.0001$ and < 0.0001, respectively). Complete follow-up was performed in all surviving patients. All patients survived the operation, except one who died 2 days after surgery due to profound hypotension.

CONCLUSION: Short and long-term outcomes of early open embolectomy seemed to be satisfactory in high-risk patients presenting high clot burden in central pulmonary arteries. This study demonstrated that pulmonary embolectomy may play a promising role in the management of AMPE and ASMPE and recommended for future clinical trials.

Keywords: Echocardiography, Fibrinolysis, Embolectomy, Thromboembolism, Pulmonary, Treatment Outcome

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Introduction

Acute massive pulmonary embolism (AMPE) is an acute and disastrous process with high mortality rates in spite of recent diagnosis and therapy advances. The main criteria in categorizing AMPE are widespread thrombosis, affecting at least half of the pulmonary artery bed. Patients with AMPE may develop cardiogenic shock, systemic hypotension and multi-organ failure. Patients with acute sub massive pulmonary embolism (ASMPE) present with increase in troponin, pro-brain natriuretic peptide (pro-BNP), or BNP levels as well as moderate to severe right ventricular (RV) dysfunction and enlargement. More than one-third of the pulmonary vascular bed is usually obstructed in ASMPE. If there is no previous history of cardiopulmonary diseases, patients may be hemodynamically stable.[1]

The management strategy in AMPE and ASMPE depend upon the conditions of the patients

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and has been controversial in some situations. Therapeutic methods include: thrombolytic agents, catheter-based thrombus fragmentation or aspiration and surgical embolectomy. The two former procedures may fail to resolve thrombotic materials adequately causing persistent pulmonary hypertension. In addition, fibrinolytic agents increase the risk of bleeding and catheter embolectomy procedure is limited due to mechanical hemolysis and micro or macro emboli.[1-3]

Due to building up experiences of surgeons and improvement of surgical and anesthetic techniques, surgical embolectomy with cardiopulmonary bypass has reemerged as an effective therapy. The present report aimed to provide an extrapolation of the outcome of early open pulmonary embolectomy in a number of patients with AMPE and ASMPE over an 8-year period in Ghaem Hospital, Mashhad, Iran.

Materials and Methods

A prospective study was performed on 30 consecutive patients with AMPE and ASMPE who underwent emergency pulmonary embolectomy at Ghaem Hospital during January 2005-November 2012. The hospital is considered as a referral and specialized educational hospital where the patients are referred from around cities for surgical embolectomy. Written informed consent was obtained from each patient. The patients were followed with routine monthly visits to the cardiologist.

Patients with AMPE and ASMPE who satisfied the indications for surgical embolectomy were included in this study. According to recent American Heart Association (AHA) guideline indications for surgical embolectomy included a central or para-central (sub) massive embolism with one of the following situations: cardio-respiratory arrest, thrombus in the right heart, large patent foramen ovale (PFO), failure to respond to thrombolytic therapy, and absolute contraindications for thrombolytic therapy.[4,5]

Based on local hospital policies and low costs, streptokinase was chosen as the thrombolytic agent. Thrombolytic therapy failure was defined as: sustained systolic blood pressure below 90 mmHg, refractory shock, RV dysfunction which persisted for more than 36 h, and residual pulmonary vascular obstruction > 30% at the 10th days after thrombolysis on right heart catheterization or multidetector computed tomographic (CT) pulmonary angiography.[6] In the case of failure to thrombolytic therapy, surgical embolectomy was performed within 72 h of the initial thrombolysis.

Absolute contraindications to thrombolytic therapy included the following: (1) prior intra cranial hemorrhage, (2) ischemic stroke (between 3 h and 3 months), (3) aortic dissection, (4) intracranial disease e.g. neoplasm, arteriovenous malformations, etc. (5) head injury < 3 months ago, (6) bleeding disorder.

Based on recent AHA guideline, indications for fibrinolytic therapy in acute pulmonary embolism were regarded as follows: (1) patients with acute (< 14 days) massive pulmonary embolism and acceptable risk of bleeding complications (Class IIa), (2) in some situation it may be considered for patients with ASMPE judged to have high risk condition such as new hemodynamic instability, presence of major myocardial necrosis, which was defined with elevated serum troponin level, high level of N-terminal pro-BNP or BNP, or presence of severe RV enlargement on echocardiography/CT scan and low risk of bleeding complications (Class IIb).[4]

Based on the mentioned criteria the patients enrolled in the study and their demographic information, initial presentation and symptoms, risk factors, methods of diagnosis, localization of thrombotic material, indication for operation, mortality, and morbidity were recorded and analyzed. The exclusion criteria included the patients with severe co-morbidities, and those who did not consent to surgery or did not refer for follow-up.

The main diagnostic tool was CT pulmonary angiography. Echocardiography was also performed by one cardiologist, but patients were followed by two cardiologists. Standard two-dimensional (2D) and Doppler transthoracic echocardiographic (TTE) studies were performed using the Vivid 3 and Vivid 7 with a 3.2 MHz transducer in left lateral position. RV diameter was measured on 2D and pulmonary systolic pressure was estimated by adding a trans-tricuspid gradient to the right atrial (RA) pressure. The RA pressure was also estimated by the respiratory motion of the inferior vena cava seen on 2D echocardiogram. The presence or absence of PFO was evaluated by contrast echocardiography. The proximal parts of the inferior and superior vena cava were searched for thrombus using echocardiogram. Bed side transesophageal echocardiography (TEE) was the initial diagnostic tool in 11 patients. Troponin levels were evaluated, and color Doppler ultrasonography was also performed in all patients.

Depending on the patient's condition surgical embolectomy was performed in the 1st h up to 72 h after diagnosis. Each patient was operated with a unique technique. Depending on patient's situation, general anesthesia was induced with ketamine or etomidate and patients were intubated. After connecting appropriate monitoring devices and placing electrocardiographic electrodes, a vertical median sternotomy was performed, and cannulae were inserted into the ascending aorta and both vena cava. The cannulae inserted into the ascending aorta was used to deliver antegrade cardioplegia and for later air aspiration. Cardiopulmonary bypass was established, and cooling was initiated. The aorta was clamped, and the cold cardioplegic solution was infused through the aortic root. After cardiac arrest, longitudinal arteriotomy of the main pulmonary artery was performed; the incision was extended onto the left and right branches and the clots were removed by forceps and assisting suction. To avoid additional damage to the lung parenchyma, lung massage was not performed. In seven patients, RA was incised, and the PFO was repaired in 6, and RA clot was removed in 3 patients. After removing the thrombotic materials, the pulmonary arteriotomy site and RA incision were sutured with continuous No.5-0 polypropylene sutures. Coronary artery bypass grafting (CABG) was required in 2 patients. After rewarming and evacuating air from cardiac chambers, patients were weaned off cardiopulmonary bypass.

We aimed to evaluate early mortality, systolic pulmonary artery pressure (SPAP), RV dysfunction and bleeding complications during hospitalization and to compare echocardiographic data before and after surgery. Late mortality, new presentation of symptoms and warfarin therapy complications were also recorded.

Absolute number and percentage were computed to describe non-numeric data. Data were expressed as mean ± standard deviation for continuous variables. The echocardiographic parameters had a normal distribution, and paired-sample t-test was used to test for significant difference between these parameters before and after surgery. Data analyses were performed using SPSS software for Windows (version 11.5, SPSS Inc., Chicago, IL, USA). $P < 0.0500$ was considered significant for all data analyses.

Results

Thirty patients who underwent surgical embolectomy for AMPE and ASMPE enrolled in our study from January 2005 to November 2012. This study included 13 men and 17 women whose mean age was 56.1 years (range, 23-83 years). Baseline patients' characteristics are summarized in table 1. One patient underwent cardiopulmonary resuscitation twice, one in the emergency room and another in the operating room. The indications for operation are summarized in table 1 (some patients had more than one indication for operation). One patient was an 83-year-old man who had a large clot in his RA, which slightly passed through the PFO to the left atrium.

The mean cardiopulmonary bypass time was 43 min (range, 20-64 min), and the mean aortic cross clamp time was 32 min (range, 15-60 min). All patients survived the operation. Heparin therapy was started 4 h after operation and warfarin therapy was initiated on the 2nd day post operation. Target international normalization ratio was between 2.0 and 3.0. The median length of stay was 7 days (range, 5-10 days). 29 patients were discharged and placed on long term anticoagulation therapy with warfarin.

One patient was a 73-year-old man who died 2 days after surgery; he had undergone CABG 2 months before admission for acute pulmonary emboli. He had pulmonary hypertension and RV dysfunction before his CABG and had presented with dyspnea and mild hemoptysis 7 weeks after CABG. He was treated with fibrinolysis; however, open embolectomy was performed due to unstable hemodynamic conditions. Two days after surgery, he was complicated by profound hypotension which was unresponsive to medical treatment.

Post operation echocardiography was performed in all patients. Mean SPAP and RV diameter reduced significantly after surgery and RV function also improved ($P < 0.0001$). Pre- and post-operational echocardiographic data are presented in table 2. The median and mean follow-up duration was 45 and 42 months respectively (range, 3-94 months). In patients' follow-up, 10 cases (33.33%) with warfarin toxicity, 2 cases (6.66%) with gastrointestinal bleeding, and 5 cases (16.66) with pneumonia were diagnosed, all of which improved with medical treatment. No recurrent embolus was observed. Two patients (6.66%) died later due to cancer metastasis. There were not new patients' symptoms.

Discussion

Despite improvement in the diagnosis and treatment of acute pulmonary embolism, it is yet a common clinical problem. If obstruction of the pulmonary artery vascular bed is > 50%, estimated

Table 1. Patient characteristics and indications for operation

Patient characteristics	n (%)
Sign and symptom	
Dyspnea	30 (100.0)
Cardiac arrest	6 (20.0)
Hypotension	6 (20.0)
Syncope	4 (13.3)
Faintness	5 (16.6)
Hemoptysis	1 (3.3)
Localizations of thrombi	
Main pulmonary artery	10 (33.3)
Left pulmonary artery	18 (60.0)
Right pulmonary artery	16 (53.3)
RA	3 (10.0)
Inferior vena cava	4 (13.3)
Indications for operation	
Cardiopulmonary arrest	6 (20.0)
Failure to respond to fibrinolysis	
Sustained systolic blood pressure below 90 mmHg	4 (13.3)
Residual pulmonary vascular obstruction > 30%	3 (10.0)
Persistent RV dysfunction and pulmonary hypertension	1 (3.3)
Contraindication for fibrinolysis	
Prior brain surgery	4 (13.3)
Recent orthopedic surgery	4 (13.3)
Recent ischemic stroke	1 (3.3)
Right atrium clot	
ASMPE with huge RA clot	2 (6.7)
ASMPE with a large clot in RA passing through the PFO	1 (3.3)
PFO	
Large PFO with RA clot	3 (10.0)
Prior brain surgery with PFO	1 (3.3)
Cardiopulmonary arrest with PFO	1 (3.3)
Only large PFO	1 (3.3)
Cardiogenic shock with maximum inotropic agent	3 (10.0)

ASMPE: Acute sub-massive pulmonary embolism; PFO: Patent foramen ovale; RA: Right atrium, RV: Right ventricular

Table 2. Comparison between the echocardiographic parameters (mean ± SD) before and after operation

Parameter	Time		P*
	Preoperational (mean ± SD)	Post operational (mean ± SD)	
RV diameter (mm)	39.83 ± 4.42	33.70 ± 2.33	
TAPSE (mm)	12.20 ± 2.60	18.93 ± 1.41	< 0.0001
SPAP (mmHg)	52.26 ± 6.54	29.43 ± 2.87	

* Paired-sample t-test; RV: Right ventricular; TAPSE; Tricuspid annular plane systolic excursion; SPAP: Systolic pulmonary artery pressure; SD: Standard deviation

mortality rate of patients approaches 50% and if the patient requires vasopressor therapy, the mortality rate increases to 70%. If hemodynamic deterioration continues, mortality rate approaches 100%.[1] In acute pulmonary embolism, pulmonary vascular resistance and RV after load suddenly increase, resulting in RV dilation and strain and subsequent difficulty in contraction. Ventricular pressure overload shifts the interventricular septum leftward, with resultant under-filling of the left ventricle, declining cardiac output and systolic arterial pressure, and consequently decreases coronary blood flow. The combination of high RV wall tension and myocardial O_2 demand with coronary hypoperfusion cause RV ischemia and further RV dysfunction. Perpetuation of this vicious cycle leads to circulatory collapse, and death. Interruption of this cycle by immediate and complete removal of clots is the only option for good prognosis.

According to recent guidelines, fibrinolytic therapy is strongly recommended in high-risk patients presenting with cardiogenic shock or hypotension, unless major contraindications exist. However, some

studies reported that it did not reduce mortality rates.[1,7] Due to major bleeding risk, thrombolytic therapy remain controversial in normotensive high-risk patients. Women also have a 27% risk of major bleeding compared to 15% in men.[7]

Other options for acute pulmonary emboli treatment is catheter based techniques. It is applied when there are contraindications for fibrinolysis and surgery is impossible or not available. However this technique has some adverse effects including: pericardial effusion and tamponade, pulmonary hemorrhage, dissection of aorta, and distal embolization. After hemodynamic improvement, the procedure should be stopped, regardless of angiographic result. In some situations thrombolytic therapy and catheter embolectomy fail to resolve thrombi adequately. The clots may then undergo organization and incomplete recanalization and incorporate into the vascular bed. This process leads to persistent pulmonary hypertension and RV dysfunction, which appears to be a significant contributor to poor prognosis. Open pulmonary embolectomy is a definitive treatment; in which clot-debulking is usually complete and rapid improvement of the pulmonary artery pressure and RV function is achieved. The true role of open embolectomy has not been well established.[8,9] In the past, surgical embolectomy was the last therapeutic option and only performed on patients with cardiopulmonary arrest, failure to respond to fibrinolysis, or contraindication for fibrinolysis. Ahmed et al.[10] indicated that surgical outcome was significantly improved with early surgery (< 24 h from presentation) compared to delayed surgery (> 24 h). Hence the approach to massive and submassive embolism has been recently modified and open embolectomy is performed in many centers with little adverse outcome. The mortality rates of this procedure have decreased from 57% in 1960 to 6% in 2005.[11,12]

Few available studies have compared surgical versus medical management. In a non-randomized comparison of medical and surgical treatment, the medically treated patients had a higher mortality rate.[1] Our study demonstrated that early surgical intervention in patients presenting with high clot burden in central pulmonary arteries and with evidence of RV enlargement/dysfunction showed satisfactory short and long-term results. These findings were also compatible with other studies.[2,10,11,13-15] The patients had a significant decrease in pulmonary artery pressure and an improvement in RV function.

It is advised that indications for open embolectomy should be extended so that high-risk patients with severe RV dysfunction or hypotension and high centrally located clot burden, be considered for surgery before cardiac arrest and severe RV failure. It seems that TTE and TEE are non-invasive and available diagnostic tools suitable for risk stratification and the diagnosis of RV dysfunction or enlargement, and severe pulmonary hypertension. These disorders might be considered as prodromes of cardiac arrest.

In our study, one patient died after surgery. It was assumed that this early death was largely attributed to previous pulmonary hypertension, severe RV dysfunction and delayed surgery. The degree of hemodynamic compromise and pervious cardiopulmonary disease are probably the most powerful predictors of in-hospital death.

Conclusion

Integrated approach to acute pulmonary embolism and rapid diagnosis followed by early intervention, are essential. The present study suggests the short and long term outcomes of early open embolectomy be satisfactory in high-risk patients presenting high clot burden in central pulmonary arteries. However, a randomized study comparing surgical embolectomy and fibrinolytic therapy might confirm the role of embolectomy in such patients. This study demonstrated that pulmonary embolectomy may play a promising role in the management of AMPE and ASMPE and is recommended for future clinical trials.

Limitations

It was acknowledged that the number of patients was limited and no control group (non-surgical management) was available for comparison. The limitation was due to the nature of the study and the relatively rare cases of AMPE and ASMPE.

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Conflict of Interests

Authors have no conflict of interests.

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