In the name of God

The Journal of Tehran University Heart Center

The Quarterly Official Journal of the Cardiovascular Research Center of the Tehran University of Medical Sciences

Editor – in – Chief
Abbasali Karimi, MD
Associate Professor of Cardiac Surgery
Tehran University of Medical Sciences

Managing Editor
Seyed Hesameddin Abbasi, MD
Tehran Heart Center

Editorial Board
Ahmadi. H                   Boroumand. M. A
Akhondzadeh. S             Dehpour. A. R
Karimi. A. A                Kazemi Saleh. D
Maleki. M                   Marzban. M
Nematipour. E               Mohebi. A
Moghbadam. M                Mirhoseini. M
Moradmand. S                Namazi. M. H
Sadehjian. S
Salarifar. M
Sarraf –Zadegan. N

International Editors
Al-halees ZY.               Marco J.
Bolooki H.                  Massumi A.
Dodge Y.                   Mestres CA.
Dodge –Khatami A.          Numan MT.
Gandjbakhch I.             Salehi Omran A.
Işık O.                    Rezaee M.
Kabbani S.                 Wann L. S.
Kamalvand K.               USA
UK

Advisory Editors
Abbasi. K                   Kazemi Saeed. A
Abdi. S                    Majid Ardekani. J
Aldoost. M                 Mazdak Pour. E
Aslanabadi. N              Mirbolook. F
Amirzadegan. A. R          Najafi. M
Darabian. S                Nozari. Y
Davoodi. S                 Saadat. H
Firooz. I
Hoseini. S. K
Kassanian. S. E
Feroozannia. S. Kh
Ghaemian. A
Ghasemi Movahedi. N
Ghasi. A
Hashemi. M

Statistical Consultant
Mahmood Sheikhatollahi

Technical Editors
Fatemeh Talebian
Pedram Amouzadeh

Shima Sadeghi

Journal of Tehran University Heart Center is indexed in Cochrane, Index Copernicus, Index Medicus for the WHO Eastern Mediterranean Region (IMEMR) and SID

Address
North Kargar Street, Tehran Heart Center, Tehran, Iran 1411713138. Tel: +98-21-88029702. Fax: +98-21-88029702. Web Site: http://jthc.tums.ac.ir. E-mail: jthc@tums.ac.ir.
Spring, Iranian Flowers-IRAN
Content

Volume: 2    Number: 2    Spring 2007

The Journal of Tehran University Heart Center

Editorial

THC Registers with the Cochrane Handsearching Program
Hamad Aljufairi, Mona Nasser ................................................................. 67

Review Article

Apical Ballooning Syndrome or Tako-tsubo Cardiomyopathy: What We Know about It
Mohammad Alasti, Amir Ali Mehrabanfar, Mohammad Hassan Adel, Ahmad Reza Assareh ................................................................. 69

Original Articles

Randomized, Blinded Trial Comparing Enoxaparin with Unfractionated Heparin in Patients Undergoing Contemporary Percutaneous Coronary Intervention
Hosein Vakili, Ali Mir, Mohammad Hassan Namazi, Habibollahie Saadat, Morteza Safi, Mohammad Reza Motamedi, Roxana Sadeghi .......... 77

Short-term Outcomes and Mid-term Follow-up After Coronary Angioplasty in Patients Younger Than 40 Years of Age
Seyed Ebrahim Kasaian, Mohammad Alidoosti, Mojtaba Salarifar, Alimohammad Haji Zeinali, Ebrahim Nematipour, Saeed Sadeghian, Hamidreza Poorhosseini, Leila Pirzadeh, Hamidreza Goodarzynejad, Ahmad Sharafi ................................................................. 81

Overexpression of Protein Tyrosine Phosphatase 1B in HepG2 Cells Ameliorates Insulin-mediated Suppression of Apolipoprotein B mRNA Translation Via Its Untranslated Regions
Parvin Pasalar, Wei Qiu, Rita Kohan Avramoglu, Gus Sidiropoulos, Khosrow Adeli ...................................................................................... 87

Early Outcome of Coronary Artery Bypass Grafting in Patients Less Than 40 Years Old Comparing with Elderly Patients
Abbasali Karimi, Seyed Hosein Ahmadi, Saeed Davoodi, Mehrab Marzban, Namvar Movahhedi, Kyomars Abbasi, Abbas Salehi Omran, Mahmood Shirzad, Mehrdad Sheikhvatan, Seyed Hesameddin Abbasi ................................................................. 95

Non Invasive Assessment of Myocardial Perfusion After First Myocardial Infarction with Transthoracic Echocardiography
Mehrnoush Toufan, Jahanbakhsh Samadikah, Azin Alizadeh Asl, Rasoul Azarfarin, Seyed Hadi Hakim ................................................................. 101

Clinical and Angiographic Characteristics of Myocardial Bridges: a Descriptive Report of 19 Cases and Follow-up Outcomes
Sirus Darabian, Alireza Amirzadegan, Hakimeh Sadeghian, Saeed Sadeghian, Maria Raissi Dehkordi, Hamidreza Goodarzynejad .............. 105

Brief Communication

Free Wall Rupture and Ventricular Septal Defect Post Acute Anterior Myocardial Infarction
Hakimeh Sadeghian, Kyomars Abbasi, Naghneh Mostaghi, Mahmood Shirzad, Shahla Majidi, Seyed Hesameddin Abbasi, Maryam Semnani, Ali Mohammad Haji Zeinali, Mohammad Sahebjam, Seyed Ebrahim Kasaian ................................................................. 111

Case Reports

Coronary Artery Fistula with Double Outlet Right Ventricle: a Case Report
Yaser Jenab, Ali Kazemi Khaledi, Hassan Ranjbarnejad, Arezu Zoroufian, Mahmood Shahzadi ................................................................. 115

A Large Mobile Aortic Arch Mass
Mehrnoush Toufan, Farzad Sefahi, Saba Asghari, Arminosein Fathi .............................................................................................................. 117
“The Journal of Tehran University Heart Center”

Has Been Approved as a Scientific & Research Journal by the
Iranian Commission for Medical Publications
The Cochrane Collaboration is an international non-profit and independent organization, driven by a world-wide effort, and dedicated to ensuring the availability of up-to-date and accurate information about the effects of healthcare. It synthesizes and disseminates systematic reviews, of healthcare interventions, which have been assembled from a comprehensive search for evidence in the form of clinical trials and other studies.

Cochrane Reviews are systematic assessments of evidence of the effects of healthcare interventions intended to help people make informed decisions about healthcare, their own or someone else’s. They are needed to help ensure that healthcare decisions throughout the world can be informed by high quality and timely research evidence. At present The Cochrane Library includes over 3197 full text completed systematic reviews and nearly 1744 protocols (reviews in progress) covering a wide range of healthcare interventions and specialties.

Cochrane Reviews synthesize results from randomized controlled trials (RCTs) of the highest methodological quality. The global handsearching program, one of the Collaboration’s most important activities, serves as a major way of identifying reports of randomized controlled trials which may have otherwise not been found. The identified trials are then classified as either randomized (RCT) or quasi-randomized (CCT) according to Cochrane eligibility criteria. The eligible trials are then posted in the Cochrane Central Register of Controlled Trials (CENTRAL), where they are readily accessible to the global research community.

Hundreds of journals have been or are being hand searched by members of The Cochrane Collaboration. An estimated 1,000 searchers are contributing to this effort, by searching for and cataloguing trials.

With the more recent upsurge of interest in the work of the Cochrane Collaboration in Iran it is most probably time for those colleagues with similar interests to meet formally and to seek closer working relationships to increase their cooperation with the Cochrane Collaboration. Not only will this help authors to develop Cochrane systematic reviews which are relevant to the specific health problems in Iran, but it will also bring together existing research through the handsearching of our journals which will help guide the direction of future research.

The Journal of the Tehran University Heart Center has recently been registered on the Cochrane Collaborations Master list of journals being handsearched and arrangements are being made to ensure that each issue will be searched comprehensively and that any reports of randomized controlled trials that are identified are forwarded to the Bahrain Branch of the UK Cochrane Centre for forward transmission to CENTRAL. This work is currently being coordinated by Mona Nasser and Hamad Aljufairi.
Apical Ballooning Syndrome or Tako-tsubo Cardiomyopathy: What We Know About It

Mohammad Alasti, MD*, Amir Ali Mehrabanfar, MD, Mohammad Hassan Adel, MD, Ahmad Reza Assareh, MD

Department of Cardiology, Jondi Shapour University of Medical Sciences, Ahwaz, Iran.

Abstract

Apical ballooning syndrome (ABS) is a reversible cardiomyopathy with presentation mimicking an acute coronary syndrome. So in clinical practice, it is essential to consider it in the differential diagnosis of patients presenting with chest pain, especially in postmenopausal women. Coronary angiography is usually indicated to achieve a proper diagnosis. Typically, patients do not have significant coronary artery lesions. Left ventriculography and echocardiography reveal a regional systolic dysfunction with akinesis of the midventricle, apex and compensatory hyperkinesis of the basal ventricular segments. Occurrence of an emotionally or physically stressful event is a feature of ABS but its absence does not exclude this diagnosis. Several pathophysiologic mechanisms had been proposed. The prognosis of ABS is good. In this review, we highlight the clinical manifestations, pathophysiology and management of this syndrome.

Keywords: Apical ballooning syndrome • Tako-tsubo cardiomyopathy • Stress cardiomyopathy

Introduction

Apical ballooning syndrome (ABS) is a recognized form of heart disease that has been categorized as an acquired primary cardiomyopathy.1

It was described for the first time in the Japanese population in 1991 and called Tako-tsubo cardiomyopathy [Tako-tsubo is a pot with a round bottom and narrow neck used for trapping octopus in Japan] and characterized as resting ischemic chest pain, ST elevation on ECG and absence of obstructive coronary artery disease. Other names used to describe this syndrome include broken heart syndrome, stress cardiomyopathy, amphora cardiomyopathy or ampulla cardiomyopathy.2

It is often misdiagnosed as an acute coronary syndrome (ACS) related to occluded epicardial coronary arteries. Its incidence is 1 to 2% of patients who present with ACS. This syndrome has been reported in European, American and Asian populations.2

Diagnosis

Proposed criteria for the clinical diagnosis of ABS include:
1. Transient akinesis or dyskinesis of the left ventricular apical and midventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution,
2. Absence of obstructive coronary disease or angiographic
Evidence of acute plaque rupture,
3. New electrocardiographic abnormalities
4. Absence of Recent significant head trauma, Intracranial bleeding, Pheochromocytoma, Obstructive epicardial coronary artery disease, Myocarditis, Hypertrophic cardiomyopathy. Patients typically do not have obstructive coronary disease but cases of ABS with severe coronary artery disease have been reported.

Occurrence of an emotionally or physically stressful event is a feature of ABS but its absence does not exclude the diagnosis. Events such as exhausting work, death of relatives, catastrophic medical diagnosis, devastating financial loss, asthma attack, gastric endoscopy, prolonged electrophysiology study and ablation, permanent pacemaker implantation, surgical operations, meningitis, induction of general anaesthesia, frequent epinephrine medication in management of refractory asthmatic attack, opioid withdrawal, alcohol withdrawal, lightening strike, hypoglycemic attack, neuroleptic malignant syndrome, plasmapheresis for treatment of myasthenic crisis, acute pancreatitis, earthquake, treadmill exercise tolerance test, scorpion bites, adrenalectomy for Pheochromocytoma, high dose dobutamine infusion during pharmacological stress myocardial perfusion imaging and thyrotoxicosis have been reported. ABS can occur in critically ill patients admitted to intensive care units.

Clinical features

Most patients present with chest pain at rest. Some patients present with dyspnea and rarely present with syncope or sudden cardiac death (SCD). ABS often occurs in postmenopausal women but it may occur in young women and men. The majority of ABS cases manifest at night and in the cold seasons. These women usually have a short stature (less than 1.58 cm) and a small body surface area (less than 1.62 m²). The majority of ABS patients also have other cardiovascular risk factors (overweight, hypertension, insulin resistance, dyslipidemia, tobacco). The mean age of presentation ranges from 58 to 75 years old.

In physical examination, left ventricular apical bulge is palpable in 80% of patients. A MR murmur can be heard in 5% of patients. Tachycardia is always present, and 70% of patients have an arrhythmic pulse. Most patients present with chest pain at rest. Some patients present with dyspnea and rarely present with syncope or sudden cardiac death (SCD). ABS often occurs in postmenopausal women but it may occur in young women and men. The majority of ABS cases manifest at night and in the cold seasons. These women usually have a short stature (less than 1.58 cm) and a small body surface area (less than 1.62 m²). The majority of ABS patients also have other cardiovascular risk factors (overweight, hypertension, insulin resistance, dyslipidemia, tobacco). The mean age of presentation ranges from 58 to 75 years old.

In physical examination, left ventricular apical bulge is palpable in 80% of patients. A MR murmur can be heard in 5% of patients. Tachycardia is always present, and 70% of patients have an arrhythmic pulse. Most patients present with chest pain at rest. Some patients present with dyspnea and rarely present with syncope or sudden cardiac death (SCD). ABS often occurs in postmenopausal women but it may occur in young women and men. The majority of ABS cases manifest at night and in the cold seasons. These women usually have a short stature (less than 1.58 cm) and a small body surface area (less than 1.62 m²). The majority of ABS patients also have other cardiovascular risk factors (overweight, hypertension, insulin resistance, dyslipidemia, tobacco). The mean age of presentation ranges from 58 to 75 years old.

In physical examination, left ventricular apical bulge is palpable in 80% of patients. A MR murmur can be heard in 5% of patients. Tachycardia is always present, and 70% of patients have an arrhythmic pulse. Most patients present with chest pain at rest. Some patients present with dyspnea and rarely present with syncope or sudden cardiac death (SCD). ABS often occurs in postmenopausal women but it may occur in young women and men. The majority of ABS cases manifest at night and in the cold seasons. These women usually have a short stature (less than 1.58 cm) and a small body surface area (less than 1.62 m²). The majority of ABS patients also have other cardiovascular risk factors (overweight, hypertension, insulin resistance, dyslipidemia, tobacco). The mean age of presentation ranges from 58 to 75 years old.

Cardiac biomarkers

Most of patients have a small increase in cardiac biomarkers. In a study, troponin was positive in 86.2% and CK-MB was positive in 73.9% of cases. In a study, the consecutively performed measurements after admission showed a continuous decline in a short time period indicating immediate recovery of myocardial function. Serum levels of creatine kinase (CK), CK-MB and troponin T were initially increased but returned to normal values within two days. Most patients have findings of mild to moderate congestive heart failure so many of them have elevated level of BNP.

Electrocardiography

ECG can be normal but ST elevation is the most frequent finding on ECG, often in left precordial leads. Other abnormalities can be nonspecific T wave abnormality or ST elevation in limb leads. 20% of ABS cases have an ST depression in three or more leads. Occasionally, pathologic Q wave may be seen. Prolongation of corrected QT interval is a frequent finding. A prolonged PR interval or new bundle branch block are less common than above mentioned changes. In one study, ST elevation was present in 76 to 86% of patients. T wave abnormalities were seen in 58 to 70% and Q wave in 26 to 38% of patients. There was a prolonged PR interval in 24% of cases, mostly with a first-degree AV-block, supraventricular beats in 45% of cases and a left or right bundle branch in less than 5% of cases; 37% of cases had pathological Q waves in three or more leads (mostly V1–3); 33% of cases had ventricular premature beats and 23% of cases had a ventricular tachycardia. Evolutionary changes include resolution of the ST elevation and diffuse and deep T wave inversion. Giant negative T waves are seen in 86% of cases, especially on the 3rd day and, rather characteristic for ABS, again after 2–3 weeks. In 20% of cases, the T changes may be seen years later. The ECG is not a useful tool to distinguish a definite diagnosis. However, the T wave inversion is deeper and the QT interval is more prolonged in stress-induced cardiomyopathy at 3 days or later. The direction of the ST segment deviation on the surface ECG usually does not accurately localize an involved region. Indeed, the ECG indicates many lesions, and the ST elevations are typically in non-contiguous leads. The T-wave changes are not parallel to the ST deviation.

In a study, the absence of reciprocal changes, absence of abnormal Q waves, and the ratio of ST-segment elevation in leads V (4-6) to V (1-3) all showed a high sensitivity and specificity for diagnosing ABS. The combination of ventricular arrhythmias and prolonged QT intervals may favor the occurrence of torsades de pointes and this arrhythmia may be lethal. Most Q waves disappear within 6–12 months, but in 3% of cases they are permanent (expressing a myocardial scar). Most ST changes disappear within 1 year.

Echocardiography

A pattern of regional wall motion abnormality extending the distribution of a single epicardial coronary artery is common in ABS. Regional left ventricular ejection fraction (LVEF) is markedly reduced (up to 35%) in the mid-portion and severely reduced (up to 20%) in the apex region. The right ventricle is involved in 1/3 of patients. Patients with
ABS had significantly greater RV free wall and LV lateral wall dysfunction as compared with patients with ACS.\textsuperscript{39}

Mean ejection fraction ranges from 20 to 49\% which improves to normal at varying ranges from a few days to a few weeks. A significant change in LV wall thickness and reversible valve insufficiencies are other characteristics of ABS.

As mentioned, during acute phase, all patients have moderate to severe mid-ventricular dysfunction and apical akinesia or dyskinesia with preserved or hypercontractility of basal portion, but the regional wall motion abnormalities are transient. So assessment of LVEF should be performed at 4 to 6 weeks after discharge from hospital.\textsuperscript{2}

\textbf{Angiography}

Patients with ABS typically do not have obstructive coronary artery disease.

In most patients with ABS, the coronary arteries are smaller and shorter than usual and in 40\% of cases there is an anomaly, with hypoplastic branching in the apical region.\textsuperscript{31}

Spontaneous multivessel epicardial spasm is uncommon and after ergonovine or acetylcholine infusion, it was observed only in 30\% of patients.

The left ventriculography shows characteristic wall motion abnormality of mid and apical segments. There is hypercontractility of basal segment.

\textbf{Atypical forms}

A “typical” apical wall motion abnormality is only seen in 60\% of patients.\textsuperscript{40} Hurst et al described a variant of ABS in which only the midventricular is affected with hypercontractility of apical and basal segments.\textsuperscript{31}

Mazzarotto et al reported a case of ABS with anterior location of wall motion abnormalities.\textsuperscript{42}

\textbf{Magnetic resonance imaging}

Contrast-enhanced cardiovascular magnetic resonance (CMR) is a useful adjunct in the diagnostic work up of patients with ABS. It may be helpful in excluding myocardial infarction, because delayed gadolinium hyperenhancement is not a feature of ABS.\textsuperscript{7}

Delayed hyperenhancement on gadolinium-enhanced CMR, which is indicative of active inflammation (e.g. myocarditis) or myocardial fibrosis (e.g. myocardial infarction), is usually absent in patients with ABS.\textsuperscript{45}

\textbf{Cardiac scintigraphy}

An abnormal subendocardial perfusion is present in 90\% of patients. A reverse distribution phenomenon is detected in more than 80\% of patients.\textsuperscript{33}

In a study, technetium-99m tetrofosmin tomographic imaging revealed decreased uptake at the apex of the left ventricle in 85\% of patients that later returned to uniform.\textsuperscript{44} 123I-MIBG is a radiolabelled analogue of noradrenaline and depicts the distribution of cardiac sympathetic innervation. Pessoa et al observation showed that ABS is associated with a cardiac sympathetic innervation deficit characterized by a reduced global 123I-MIBG uptake and an apical uptake defect. The lack of 62Ga uptake in the acute phase of this syndrome indicates that ABS is probably not associated with an inflammatory process.\textsuperscript{45} In another study, initial 123I-MIBG myocardial scintigraphy in patients with ABS, depicted a unique pattern of ventricular asynchrony and indicated the existence of cardiac sympathetic hyperactivity, although coronary blood flow was maintained. The mismatch between perfusion and innervation reinforces the hypothesis of a primary neurogenic disorder.\textsuperscript{46}

\textbf{Pathophysiology}

The precise etiology and pathophysiology of this syndrome remain unknown. Several mechanisms have been proposed including multivessel epicardial spasm, catecholamine induced myocardial stunning, coronary microvascular dysfunction and myocarditis.

A genetic etiology was postulated in two sisters with ABS.\textsuperscript{47} Also, there is some evidence that viruses can have a role in pathophysiology of ABS.\textsuperscript{48-49}

Dote and associates suggested coronary vasospasm as the pathogenic mechanism; however, induction of coronary vasospasm by acetylcholine or ergonovine has yielded mixed results. In some series, vasospasm in at least one epicardial coronary artery was present in most patients, whereas Akashi and colleagues did not observe any coronary vasospasm in patients who underwent an acetylcholine challenge.\textsuperscript{50}

Akashi et al found that the standard deviation of the mean cycle length of normal-normal R-R (NN) intervals over 24 h (SDNN), and the 24-h standard deviation of the mean value of the difference between the NN intervals for each 5-min segment (SDANN) improved significantly during three month follow up. These results support the hypothesis that acute autonomic dysfunction can cause neurogenic stunning of the myocardium.\textsuperscript{51}

In a study using positron emission tomography with 13N-ammonia and 18F-fluorodeoxy glucose within 72 hours of presentation with ABS, all patients exhibited reduced glucose uptake in the mid-LV and apical myocardial segments, which was out of proportion with perfusion abnormalities in half of the cases.\textsuperscript{48} In another study, Feola et al observed severe degree and transient pattern of the impairment of tissue metabolism in the dysfunctioning left ventricle with nearly preserved myocardial blood flow at rest. This pattern is known as inverse metabolic/ perfusion mismatch. The severe
reduction of glucose metabolism in dyskinetic myocardium without electrocardiographic signs of necrosis, as well as only minor cardiac-specific enzymatic release, suggests that apical ballooning represents a transient metabolic disorder on the cellular level, rather than a structural contractile disease of the myocardium.52

It is possible that an impaired or differential sympathetic activation is responsible for the inhomogeneous contractile response to adrenergic stimulation (stress or physical effort) between the basal and periapical regions. This condition, in turn, results in transient left ventricle outflow tract (LVOT) obstruction.

In myocardial segments with abnormal functional innervation, as detected by MIBG myocardial scintigraphy, dobutamine stress echocardiography elicits functional abnormalities comparable to those observed in the acute phase of the disease, linking abnormal regional beta-adrenergic stimulation with abnormal cardiac presynaptic innervation.53

Impaired myocardial perfusion due to abnormal microvascular blood flow is frequently present in patients with ABS and correlates with the extent of myocardial injury. So microvascular dysfunction may play a pivotal role in the pathogenesis of myocardial stunning in ABS.54

In a study, TIMI frame counts were abnormal in all patients and often abnormal in all 3 major coronary vessels, suggesting that the diffuse impairment of coronary microcirculatory function may play a role in the pathogenesis of the syndrome.55

In these patients, a catecholamine-mediated endothelial injury might be responsible of microvascular coronary dysfunction.56

Serial non-invasive measurements of coronary blood flow in a case suggested transient impairment of the coronary microcirculation during the acute phase of the syndrome. The improvement of the microcirculation parallels the regression of the wall motion abnormalities.

There is some evidence suggesting that the apical myocardium may be more responsive to sympathetic stimulation and may be more vulnerable to sudden catecholamine surges.57 A longitudinal, base-to-apex decline in LV myocardial perfusion has also been proposed as a possible alternative explanation.51 Data of a study suggested that myocardial bridging possibly enhanced by catecholamines during stress may contribute, in association with left ventricular hypertrophy, to the preferential apical localization of ABS.58

The reason for the much more common occurrence in post-menopausal women is unclear. Several explanations have been proposed. Sex hormones may exert important influences on the sympathetic neurohormonal axis and on coronary vasoreactivity.

Women appear also to be more vulnerable to sympathetically mediated myocardial stunning. Post-menopausal alteration of endothelial function in response to reduced estrogen levels has been advocated as a possible alternative explanation.56

**Pathology**

Endomyocardial biopsy data from five patients have been published. Four had interstitial infiltrates consisting primarily of mononuclear lymphocytes, macrophages, and contraction bands without myocyte necrosis. The other patient had an extensive lymphocytic infiltrate and multiple foci of contraction-band myocyte necrosis (a sign of catecholamine cardiotoxicity).59

**Prognosis and complications**

The prognosis of patients experiencing this syndrome is generally favorable.

In-hospital mortality is less than 2%. LVEF recovers slowly: after 6 months of follow-up, the apical ventricular ejection is often 40% or less. LVEF is usually normalized within 12 months.

In many patients, reduced stroke volume and dynamic LVOT obstruction can produce hypotension and even cardiogenic shock.

Other complications include cardiogenic shock due to LV dysfunction, ventricular septum perforation, 60 left free wall rupture, 61 left ventricle apical rupture, 62 embolic stroke, 63 torsade de pointes, 64 and acute pericarditis.57

Nef et al reported a case of ABS complicated by a prolonged third-degree atrioventricular block requiring the implantation of a pacemaker.65

Chandrasegaram et al reported a case of ABS with acute pulmonary edema, severe mitral regurgitation and systolic anterior motion of the mitral valve with significant left ventricular outflow tract obstruction. The left ventricular outflow tract obstruction and mitral regurgitation were corrected by mechanical mitral valve replacement.66

RV involvement is common in ABS and seems to be associated with a more severe impairment in LV systolic function. It may be suspected by the presence of pleural effusion.67

The recurrence rate of ABS is no more than 10%. Blessing et al described a case where repeated emotional stress caused recurrent ventricular dysfunction in varying regions of the left ventricle.68

**Management**

The optimal management of ABS has not been established. Beta blockers are useful. Inappropriate administration of fibrinolytic to patients with ABS may be harmful and it would be appropriate to transfer the patients for emergent coronary angiography. Diuretics may be useful for treatment of CHF. Anticoagulants should be considered to prevent thromboembolism until recovery of wall motion abnormality.
If there is considerable dynamic LVOT obstruction in patients who are hemodynamically unstable, a cautious trial of beta blockers may be helpful. In this condition, using inotropes is contraindicated but infusion of phenylephrine can be effective because it increases afterload and ventricular cavity size. Cardiogenic shock should be treated with inotropes and intraaortic balloon pump.

Levosimendan has been suggested as the inotrope of choice in cardiogenic shock secondary to ABS. Once the diagnosis of ABS has been made, ASA can be discontinued unless there is coexisting coronary atherosclerosis. Some recommend chronic beta-blocker therapy. Such course of action may be useful in reducing the likelihood of a recurrent episode.

Ueyama et al suggested that estrogen supplementation partially prevented emotional stress-induced cardiovascular responses both by indirect action on the nervous system and by direct action on the heart.69

**Conclusion**

ABS is a recognized reversible cardiomyopathy. Clinicians should consider this syndrome in the differential diagnosis of patients presenting with chest pain, especially in postmenopausal women with a recent history of emotional or physical stress.

**References**


58. Bybee KA, Prasad A, Barssens GW, Lerman A, Jaffe AS, Murphy JG, Wright RS, Rihal CS. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. Am J Cardiol 2004;19;343-346.
Randomized, Blinded Trial Comparing Enoxaparin with Unfractionated Heparin in Patients Undergoing Contemporary Percutaneous Coronary Intervention

Hosein Vakili, MD*, Ali Mir, MD, Mohammad Hasan Namazi, MD, Habibollahe Saadat, MD, Morteza Safi, MD, Mohammad Reza Motamedi, MD, Roxana Sadeghi, MD

Cardiovascular Research Center, Modarres Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

Received 13 March 2006; Accepted 19 April 2007

Abstract

Background: This study was designed to examine a unique and low dose use of intravenous enoxaparin in elective percutaneous coronary intervention (PCI) that would be applicable to an unselected population regardless of age, weight, and renal function. There is limited experience in anticoagulation using intravenous low-molecular-weight heparin in PCI.

Methods: A total of 100 consecutive patients undergoing elective PCI were treated with a single IV bolus of enoxaparin (0.5mg/kg) in group A of patients (n=50) or with unfractionated heparin in group B of patients (n=50). Sheaths were removed immediately after the procedure in patients treated with enoxaparin and some hours later in those treated with unfractionated heparin.

Results: In group A, ACT was 124.6±9.3 before PCI and 149.2±17.1 after that (P<0.05). In group B, one patient (2.9%) developed groin hematoma. No deaths, MI, or urgent target vessel revascularization were reported.

Conclusion: Low- dose (0.5 mg/kg) IV enoxaparin allows a target level of anticoagulation in patients undergoing PCI, appears to be safe and effective, allows immediate sheath removal, and does not require dose adjustment.

J Teh Univ Heart Ctr 2 (2007) 77-80

Keywords: Percutaneous coronary intervention • Low molecular weight heparin • Enoxaparin • Unfractionated heparin

Introduction

Unfractionated heparin (UFH) has traditionally been used to prevent complications in patients undergoing percutaneous coronary intervention (PCI). UFH exerts its anticoagulant effect by catalyzing the inhibition of thrombin and factor...
Xa by antithrombin. UFH has several important limitations, including its unpredictable anticoagulant effect necessitating careful laboratory monitoring, high protein binding, and inactivation by platelet factor 4. To overcome some of these limitations, newer agents with more predictable anticoagulant effects and with greater anti-factor Xa activity are being evaluated. Factor Xa occupies a pivotal role in the clotting cascade because it is the final common pathway linking the intrinsic and extrinsic systems leading to the generation of thrombin.

Low molecular weight heparins (LMWHs) are rapidly emerging as an alternation form of anticoagulant therapy to the standard unfractionated heparin (UFH). They are formed by controlled enzymatic or chemical depolymerization of UFH producing monosaccharide chains of varying lengths (3 to 7 kD) but with a mean molecular weight of ~5 kD. Similar to UFH, LMWHs exert their anticoagulant activity by activating AT III. The principal difference between LMWHs and UFH lies in their relative abilities to catalyze the inactivation of factor-Xa and factor-IIa, which is dependent upon the relative composition of molecules with high affinity to AT III, called high-affinity molecules. They exist in two functionally different forms; below critical length molecules (BCLM) (5-17 monosaccharide units<5.4 kD), which catalyze factor-Xa inactivation but not factor-IIa, and above critical length molecules (ACLM) (>18 monosaccharide units >5.4 kD), which catalyze the inactivation of both factor-Xa and thrombin and inhibit thrombin generation. UFH is mostly composed of ACLM, whereas less than half of the chains of LMWHs contain ACLM.

LMWHs have greater activity against factor-Xa, are less bound to plasma proteins, endothelial cells and platelets, are resistant to inactivation by PF4, and are efficient inhibitors of thrombin generation.

In addition, LMWHs also have a reduced potential to cause bleeding compared with UFH because they are less likely to increase microvascular permeability or interfere with platelet-vessel wall interaction.

There are significant differences among LMWHs with respect to the ratio of anti-Xa to anti-IIa activity. An LMWH with the highest percentage of BCLM and the lowest percentage of ACLM is likely to exhibit superior pharmacologic efficacy. Currently, among LMWHs enoxaparin has the highest percentage of BCLM. Enoxaparin has shown to provide the fastest peak of anti-Xa activity (3 to 4 h), the highest bioavailability, and the longest duration of anti-Xa activity (~12 h) after a subcutaneous injection compared with dalteparin and nadroparin.

The key question whether these pharmacologic differences translate into differences in clinical outcomes remains largely unresolved. The logistic ease of administration without the need for monitoring anticoagulation appears to be the major advantage over UFH.

Methods

Patient population

A total of 100 consecutive patients admitted for elective PCI were enrolled in the study. All the patients were>18 years old and were referred for elective PCI of a native vessel stenosis>60%. Exclusion criteria were primary PCI for ST-elevation MI, thrombolytic therapy for STEMI in the previous 24 hours (rescue PCI), LMWHs or UFH within the last 48 hours before PCI, or a GP IIb-IIIa antagonist within the previous two weeks. The study was approved by the Ethical Committee of the Cardiovascular Research Center, and informed consent was obtained from all the patients.

Study Medications

The patients were randomized to receive either enoxaparin in group A (0.5 mg/kg) or UFH in group B (100U/kg). Near-patient ACT monitoring was used for all the patients before and after the procedure. The patients received aspirin with a daily dose of 80 or 325mg. Clopidogrel (300mg) was administered immediately after coronary angiography except to patients who had previously received clopidogrel and then 75mg per day was administered. GP IIb-IIIa inhibitors were not used in this study. The use of any other medications was left to the discretion of the investigator in accordance with the ACC guidelines.

Procedures for PCI

PCI was performed later after a coronary angiogram using standard techniques, the femoral approach, and 6F or 7F guiding catheter in all the patients. Vascular access site sheaths were removed with manual compression immediately after PCI if enoxaparin was administered and were removed several hours later if PCI was performed with UFH when PTT measurement reached below 60 seconds. The patients were allowed to walk the next morning (bed-rest time>12 hours), and they left the hospital on the next day.

Clinical follow-up

In-hospital follow-up was based on physical examination, electrocardiogram (ECG), and CK and CK-MB levels. ECG and markers of periprocedural myonecrosis were determined systematically in all the patients before PCI and 6 to 8 hours and 12 to 14 hours after PCI. All the patients in this study were followed up at one month by written questionnaires or telephone interviews. The information obtained was relative to living status, rehospitalization, reinfarction, subsequent cardiac catheterization or revascularization, and any form of

78
bleeding. The outcome end point was defined as a composite of death, myocardial infarction (MI), and urgent target vessel revascularization. Myocardial infarction was defined as recurrent chest pain and/or ECG changes with at least one of the following: Troponin-I positive, with levels of CK>2 times the upper limit of normal and an increase of >50% of the previous value, or the appearance of a new left bundle branch block or new Q waves. Urgent revascularization was defined as urgent PCI or coronary artery bypass grafting necessitated by the recurrent ischaemia of the target vessel. Bleeding definition was adapted from the Thrombolysis In Myocardial Infarction (TIMI) criteria. Major hemorrhage corresponded to: 1) bleeding resulting in death or requiring surgery; 2) bleeding in an intracranial or intraocular location; and 3) a drop in the serum concentration of hemoglobin ≥5g/dl (or >15% of the hematocrit value). Minor bleeding was any clinically important bleeding that did not qualify as major or that was not clinically identified but associated with a drop in the serum hemoglobin concentration >4 g/dl or >12% of the hematocrit level.

Statistical Analysis

Continuous variables are expressed as mean±SD, and dichotomous variables as frequencies. Categorical variables were compared using the chi-square test and continuous variables by using the Student’s t-test. P values<0.05 were considered statistically significant.

Results

A total of 100 consecutive patients, who underwent elective PCI to treat 115 coronary lesions, were enrolled in this study. Table 1 shows the patients’ baseline and angiographic characteristics.

Mean age was 55.94±8.1 years in group A (enoxaparin) and 55.51±9.3 in group B (UFH) (P<0.02). There was no significant difference between group A and B for coronary risk factors (P<0.05). Also, there was no significant difference between two groups for target vessel involvement. Multiple vessels angioplasty was performed in 15 patients (15%). A stent was implanted in 115 of the 115 de novo lesions (100%).

In group A, ACT was 124.6±9.3 before PCI and 149±17.1 after that (P=0.05).

In group B, one patient (2.9%) developed groin hematoma. This patient’s ACT was 90 before PCI and 330 at the end of the procedure.

Vascular access site sheath was removed 6 hours later with an acceptable PTT (below 60 seconds).

Follow-up was obtained in all the patients. No deaths, MI, or urgent target vessel revascularization were reported.

Table 1. Baseline Clinical Characteristics of Enrolled Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>55.6±7.8</td>
<td></td>
</tr>
<tr>
<td>Age&gt;75 yrs, n (%)</td>
<td>6 (6%)</td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>73 (73%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction*, %</td>
<td>55±8%</td>
<td></td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>30 (30%)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>59 (59%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (45%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (32%)</td>
<td></td>
</tr>
<tr>
<td>Previous MI (&gt;1month)</td>
<td>33 (33%)</td>
<td></td>
</tr>
<tr>
<td>Recent MI (&lt;1 month)</td>
<td>8 (8%)</td>
<td></td>
</tr>
<tr>
<td>Previous coronary angioplasty</td>
<td>10 (10%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15 (15%)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Target vessel of PCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>47 (40%)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>30 (27%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>38 (33%)</td>
<td></td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean±SD

Discussion

The purpose of this study was to assess the feasibility of using enoxaparin during PCI and to explore the risk (either bleeding or periprocedural clinical complication). We acknowledge that smaller differences between the groups are detectable given the modest sample size.

Our data suggest that a single IV bolus of 0.5 mg/kg enoxaparin is feasible in elective PCI. This reduced dose allows reaching the prespecified level of anticoagulation without dose adjustment or coagulation monitoring, which simplifies anticoagulation management during the procedure, allows immediate sheath removal when PCI is performed with enoxaparin alone, and provides similar anticoagulation and safety in patients, irrespective of advanced age, renal dysfunction, or being overweight.10

Unfractionated heparin has been the primary anticoagulant therapy for PCI for more than 20 years, but the optimal dose and the ideal target activated clotting time (ACT) remains uncertain and controversial.8,11 The low bioavailability, unpredictable anticoagulant response, activation of platelets, unsatisfactory correlation between measurements of ACT and PTT, device-to-device variations in ACT measurements, and the lack of net prospective evaluations to correlate ACT measurements to clinical outcomes associated with UFH have led to empirical recommendations for both UFH doses and ACT target values.11,12

Although LMWH dose not have the same disadvantages as UFH, the ideal regimen for its use in PCI has yet to be determined. However, the predictable anticoagulant response
following a single IV dose of LMWH suggests that neither dose adjustment nor on-site coagulation monitoring is necessary. The risk of overdose with a single IV dose is not related to the degree of subcutaneous resorption and should be much less dependent on renal function.

The reduced dose of enoxaparin used here allowed safe immediate sheath withdrawal with manual compression favoring expeditive care for these elective cases. Clearly, our study is not sized or designed to draw any definite conclusion on the use of this low dose of enoxaparin. Be that as it may, our study provides the first evaluation of a low dose of IV enoxaparin in nonselected patients in a research center in Iran. These data may aid the design of future randomized trials comparing LMWH with UFH in PCI.

Conclusion

Low-dose (0.5 mg/kg) IV enoxaparin allows a target level of anticoagulation in patients undergoing PCI, appears to be safe and effective, allows immediate sheath removal and does not require dose adjustment.

Acknowledgments

This study was supported by Shaheed Beheshti University of Medical Sciences. The study protocol was approved by the Ethics Committee of Cardiovascular Research Center of Shaheed Beheshti University.

References

Short-Term Outcomes and Mid-term Follow-up After Coronary Angioplasty in Patients Younger Than 40 Years of Age

Seyed Ebrahim Kassaian, MD, Mohammad Alidoosti, MD, Mojtaba Salarifar, MD*, Alimohammad Haji Zeinali, MD, Ebrahim Nematipour, MD, Saeed Sadeghian, MD, Hamidreza Poorhosseini, MD, Leila Pirzadeh, MD, Hamidreza Goodarzynejad, MD, Ahmad Sharafi, MD

Tehran Heart Center, Medical Sciences / University of Tehran, Tehran, Iran

Received 7 December 2006; Accepted 24 February 2007

Abstract

Background: Stenting is currently the standard of care in percutaneous coronary intervention (PCI). Whether young patients remain at increased risk after PCI in the present stent era has not been investigated widely. We evaluated angiographic characteristics and short- and mid-term outcomes in patients younger than 40 years of age who underwent PCI.

Methods: From April 2003 to March 2005, prospective data were collected in 118 consecutive patients, who were less than 40 years of age and underwent PCI at our referral center. The PCI outcomes in these patients were compared to those in 354 patients, randomly selected from 2493 patients older than 40 years of age in our database. Follow-up was scheduled at 1 month, 5 months, and 9 months through clinic visits, telephone interviews, and reviewing hospital records.

Results: Patients <40 years of age were more often male (91.5% vs. 71.8%, P<0.001), current smokers (33.9% vs. 15.2%, P<0.001), and had more family history of coronary artery disease (38.1% vs. 21.8%, P<0.001) and myocardial infarction (44.1 vs. 31.1, p=0.01), while diabetes mellitus (6.8% vs. 22.1%, P<0.001), hypertension (13.6% vs. 35.3%, P<0.001), and hyperlipidemia (34.7% vs. 44.8%, P=0.055) were less common in these patients. There were no significant differences between the two groups regarding vessel involvement, reference vessel diameter, stenosis rate (before and after procedure), and lesion characteristics, with an exception that angulated lesions were more common in the patients ≤ 40 years of age (P<0.05). The young patients, who underwent PCI, presented more frequently with single-vessel disease (61% vs. 46%, P=0.01). The vessel and lesion sites of PCI and clinical success rates were similar in these age groups. Usage of stent was high and similar, and drug-eluting stent use was not significantly different between the two groups. With a high procedural success (94.9% vs. 91.8%), intra-hospital and late complications were very low and similar in both groups.

Conclusion: Percutaneous coronary intervention is a safe and effective procedure for young patients, and major adverse cardiac events are similar in young and older patients.

J Teh Univ Heart Ctr 2 (2007) 81-86

Keywords: Percutaneous coronary intervention • Young patients • Major adverse cardiac events

Introduction

Specific characteristics of the natural history and presentation of coronary artery disease (CAD) in young patients make the choice of effective therapy particularly challenging.1,2 Many young patients present with myocardial infarction without previous angina,3 and in some there may be a prothrombic tendency.4,5 Moreover, the natural progression
angioplasty from the first randomized clinical trials. Suboptimal results have been reported for the treatment of CAD in patients younger than 40 years of age showing poor long-term results, with a high rate of new coronary surgery and myocardial infarction in patients who had previous saphenous vein bypass graft implantation. Several studies have shown that percutaneous transluminal coronary angioplasty (PTCA) in young patients with CAD could be a safe and successful alternative to medical or surgical therapy. However, most of these studies date back to mid 1990s. The introduction and refinement of techniques for the implantation of coronary stents coupled with ongoing developments in stent, balloon, and catheter technology resulted in dramatic changes in practice during the mid-1990s. Coronary stenting is well known to have contributed to the decrease in the rate of restenosis and improvement of early and late outcome of percutaneous angioplasty from the first randomized clinical trials. There is limited published data regarding the results of percutaneous coronary intervention (PCI) in patients younger than 40 years of age in the stent era. The aim of this study was first to determine whether there were age-related differences in early and late outcomes in patients undergoing PCI in the current stent era; and, second, because to our knowledge there were no published data on the epidemiology of Iranian patients with premature atherosclerosis who underwent PCI, we sought to investigate the likely epidemiologic differences among our study population with premature (<40 years of age) CAD undergoing PCI as a representative of the Iranian population.

**Methods**

**Patient population**

The study population comprised 118 consecutive patients younger than 40 years of age who underwent elective or urgent PCI at our institution between April 2003 and March 2005. During this period, angioplasty procedures were performed in the patients. The age cut off of 40 years was used to identify young adult patients based on formerly accepted nomenclature. The outcome of young patients was compared to that of 354 randomly selected patients out of 2493 patients aged 40 or more. Informed consent was obtained from all the patients.

**Procedure and data collection**

Baseline data were obtained from a computerized database of prospectively recorded clinical and procedural information during the in-hospital period and at follow-up on standardized forms. Hypercholesterolemia was defined as a total cholesterol level > 200 mg/dl, a low density lipoprotein cholesterol level > 130 mg/dl, or receiving cholesterol lowering treatment by the patient at present or past history. Procedural success was defined as < 30% residual diameter stenosis, and clinical success was defined as procedural success without hospital complications (death, Q wave myocardial infarction, or target vessel revascularization). Target vessel revascularization was defined as the revascularization of the vessel formerly treated by PCI during the index hospitalization by a repeat percutaneous intervention or bypass surgery. Emergency coronary artery bypass grafting (CABG) was defined as CABG performed within 24 hours after the index percutaneous procedure. For all the patients, 12-lead electrocardiography was obtained prior and following intervention to detect procedure-related ischemic changes and or the appearance of a new pathologic Q wave on the surface electrocardiogram. After the procedure, all the patients were checked for creatine kinase MB enzyme sampling at 8 and 16 hours (normal values to 35 IU/L). The diagnosis of non Q wave MI was considered as creatine kinase MB elevation > 3 times normal values in the absence of new pathologic Q waves on electrocardiograms following intervention.

**Patient follow-up**

Follow-up response rate at 9 months was 83% for the young (n = 98) and ≥ 40 years of age patients (n = 294). Data of the early outcomes and occurrence of death, new non-fatal MI, need for CABG, subsequent need for repeat PCI, and occurrence of angina in both groups were recorded. Follow-up was scheduled at 1 month, 5 months, and 9 months through clinic visits or, if patients were unable to come to the clinics, through telephone interviews, mailing, and reviewing hospital records.

**Statistical analysis**

Early outcomes (in-hospital period) after PCI, including procedural success, occurrence of death and non-fatal MI, and emergency CABG were compared between the two groups. Mid-term outcomes at 9 months after PCI, including mortality, stroke, ischemia-driven TVR, non-fatal MI, and recurrence of angina were also compared between the groups. Statistical analyses were performed with SPSS soft ware version 11.5 statistical package. Continuous variables were expressed as mean±1SD and categorical data as percentage. Statistical analyses were completed on the categorical variables using a chi-square, and comparisons of the continuous variables between the two groups were performed with t-tests. A p value of < 0.05 was judged significant.
Results

Baseline characteristics

The baseline characteristics of the patients are listed in Table 1. PCI was performed in 118 patients younger than 40 years of age (108 men and 10 women), with a mean age of 35.21±3.7 years (range, 21 to 39 years). The young patients were more likely to be current smokers and to have a positive family history for CAD while there a significantly higher incidence of hypertension, diabetes and hyperlipidemia in the older group. There were no significant differences between the two groups in terms of the presenting symptom. Mean left ventricular ejection fraction in the patients<40 years of age was 50.39±8.55 vs. 53.09±9.01 in patients≥40 years of age (P<0.02).

Procedural characteristics

The procedural characteristics are presented in Table 2. As age increased, the number of patients with 2- and 3-vessel disease rose and the number with single vessel disease decreased (P=0.03). The analysis involved the treatment of 606 lesions (465 in older and 141 in younger patients) in 472 patients. The left anterior descending artery was dilated in about 65% of the patients in both groups. Stent usage was high and around 90% in both groups. Various stent types were used in both patient populations; however, the number of stents per patient, stent diameter after inflation, stent length, and pre and post stenting diameter stenosis were similar between the two age groups.

Table 1. Baseline clinical characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Age&lt;40 years</th>
<th>Age≥40 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yr)</td>
<td>35±4</td>
<td>56±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>91.5</td>
<td>71.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>50±9</td>
<td>53±9</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF&lt;40%</td>
<td>11.8</td>
<td>6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Prior bypass surgery</td>
<td>0.9</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>2.6</td>
<td>6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>44.1</td>
<td>31.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Multi vessel disease</td>
<td>39.4</td>
<td>54.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>21.3</td>
<td>23.3</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13.6</td>
<td>35.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.8</td>
<td>22.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>34.7</td>
<td>44.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Current smoking</td>
<td>33.9</td>
<td>15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>38.1</td>
<td>21.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD or percentages

Table 2. Qualitative angiographic lesion characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Age&lt;40 years</th>
<th>Age≥40 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of stent</td>
<td>92.9</td>
<td>87.5</td>
<td>NS</td>
</tr>
<tr>
<td>DES stent</td>
<td>16.3</td>
<td>11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Artery treated</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left main</td>
<td>67.8</td>
<td>60.7</td>
<td>NS</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>20.3</td>
<td>27.1</td>
<td>NS</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>19.5</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lesion characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ostial</td>
<td>2.5</td>
<td>5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal</td>
<td>35.6</td>
<td>39.3</td>
<td>NS</td>
</tr>
<tr>
<td>Long</td>
<td>54.2</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Diffuse (Length&gt;20mm)</td>
<td>22.9</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>10.2</td>
<td>7.6</td>
<td>NS</td>
</tr>
<tr>
<td>Eccentric</td>
<td>13.9</td>
<td>22.1</td>
<td>NS</td>
</tr>
<tr>
<td>Angulated</td>
<td>17.1</td>
<td>11.1</td>
<td>NS</td>
</tr>
<tr>
<td>Evidence of thrombus</td>
<td>2.5</td>
<td>2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>13.6</td>
<td>13.8</td>
<td>NS</td>
</tr>
<tr>
<td>AHA/ACC type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>18.2</td>
<td>25.6</td>
<td>NS</td>
</tr>
<tr>
<td>C</td>
<td>38.2</td>
<td>32.7</td>
<td>NS</td>
</tr>
<tr>
<td>Procedure type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>3.8</td>
<td>3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Adhoc</td>
<td>2.1</td>
<td>13.5</td>
<td>NS</td>
</tr>
<tr>
<td>Elective</td>
<td>84.4</td>
<td>88.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data are presented as percentages

DES, Drug-eluting stent; AHA/ACC, American heart association/ American college of cardiology

Major adverse cardiac events (MACE) outcomes

Procedural successes as well as in-hospital and 9-month follow-up MACE are shown in Table 3. Procedural success was high and nearly equal in both age groups. In-hospital mortality was similar in the young and older patients (0% vs. 0.3%, P=0.56). At mid-term follow-up, there was a higher incidence of younger patients needing CABG after PCI (4.1% vs. 1.4%, P=0.09), but it did not reach statistical significance. Incidence of death, non-fatal MI, and ischemic-driven TVR at 9 months was not statistically different between the two age groups. Combined MACE rate at 9 months was low and similar in both age groups (5.1% vs. 6.5%).

Revascularization and angina recurrence

Ischemia-driven TVR and recurrence of angina at 9 months’ follow-up can be seen in Table 4. Multivariable analysis was performed to identify independent predictors of the composite of MACE at 9 months. Variables entered were sex, stent usage, diabetes mellitus, smoking, prior MI, and lesion treated. There was no statistically significant difference noted with any variable.
Table 3. In-hospital outcomes*

<table>
<thead>
<tr>
<th></th>
<th>Age&lt;40 years</th>
<th>Age ≥40 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=118)</td>
<td>(n=354)</td>
<td></td>
</tr>
<tr>
<td>Procedural success</td>
<td>112 (94.9)</td>
<td>325 (91.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Procedural complications</td>
<td>8 (6.8)</td>
<td>25 (7.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Elastic recoil</td>
<td>1 (0.8)</td>
<td>2 (0.6)</td>
<td>0.073</td>
</tr>
<tr>
<td>Side branch occlusion</td>
<td>1 (0.8)</td>
<td>7 (2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Dissection</td>
<td>6 (5.1)</td>
<td>13 (3.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Access site complications</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Clinical success</td>
<td>109 (92.4)</td>
<td>313 (88.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Q Wave MI</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Non Q wave MI</td>
<td>0</td>
<td>3 (1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>0</td>
<td>6 (1.7)</td>
<td>0.344</td>
</tr>
</tbody>
</table>

*Data are presented as n (%)

MI, Myocardial infarction; CABG, Coronary artery bypass graft; MACE, Major adverse cardiac events; NS, Non-significant

Table 4. Clinical outcomes at follow-up*

<table>
<thead>
<tr>
<th></th>
<th>Age&lt;40 years</th>
<th>Age ≥40 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=98)</td>
<td>(n=294)</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>10.09±3.89</td>
<td>10.10±3.69</td>
<td>0.99</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>6 (2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1 (1)</td>
<td>4 (1.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (4.1)</td>
<td>4 (1.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ischemia driven TVR</td>
<td>4 (4.1)</td>
<td>9 (3.1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Recurrence of angina</td>
<td>2 (2)</td>
<td>5 (1.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>MACE</td>
<td>5 (5.1)</td>
<td>19 (6.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Target lesion angioplasty</td>
<td>0</td>
<td>5 (1.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Re PCI</td>
<td>0</td>
<td>4 (1.4)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Data are presented as n (%) or mean±SD

MI, Myocardial infarction; CABG, Coronary artery bypass grafting; TVR, Target vessel revascularization; MACE, Major adverse cardiac events; PCI, Percutaneous coronary intervention

Discussion

We studied a consecutive series of young patients (<40 years of age) to estimate the impact of age on the early- and mid-term outcomes after PCI in the current stent era. As the practice of PCI has evolved over the last decade, outcomes of patients undergoing PCI have improved and advanced age has been shown to be an independent predictive factor for mortality. Most of these data predate stent usage. In our study, the patients≥40 years old showed a non-significant trend toward slight increase in intra-hospital mortality and the procedural success was high and comparable in the young and older patients. These results may indicate that the practice of interventional cardiology has been altered. Coronary stents are widely used, and catheters and techniques have been improved. Alternative devices for lesion-specific treatment and new adjunctive medical therapy are available. In line with previously published studies of young patients with coronary artery disease, our results show a greater incidence of history of previous myocardial infarction, high prevalence of single vessel disease, and a frequent incidence of coronary risk factors such as cigarette smoking and family history of coronary artery disease. As is depicted in Table 5, our immediate results are in concordance with those of previous reports and confirm the high success rate (>94%) and low major complication rates (0%) of PCI in young adults. Interestingly, in our study, a non-significant trend towards increased need for CABG following PCI in patients<40 years of age was observed.

Table 5. Outcomes of formerly published data regarding coronary angioplasty in young patients

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>No of patients</th>
<th>Primary success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone et al. [5]</td>
<td>&lt;35</td>
<td>71</td>
<td>95</td>
</tr>
<tr>
<td>Simpfendorfer et al. [15]</td>
<td>&lt;35</td>
<td>33</td>
<td>94</td>
</tr>
<tr>
<td>Glazier et al. [16]</td>
<td>&lt;35</td>
<td>23</td>
<td>91</td>
</tr>
<tr>
<td>Colasante et al. [18]</td>
<td>&lt;35</td>
<td>57</td>
<td>81</td>
</tr>
<tr>
<td>Kofflard et al. [19]</td>
<td>&lt;35</td>
<td>57</td>
<td>92</td>
</tr>
<tr>
<td>Webb et al. [17]</td>
<td>&lt;40</td>
<td>148</td>
<td>90</td>
</tr>
<tr>
<td>Buffet et al. [20]</td>
<td>&lt;40</td>
<td>140</td>
<td>86</td>
</tr>
<tr>
<td>Ellis et al. [21]</td>
<td>&lt;40</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>Hara et al. [22]</td>
<td>&lt;40</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>Araujo et al. [23]</td>
<td>&lt;40</td>
<td>66</td>
<td>96</td>
</tr>
<tr>
<td>Mehan et al. [24]</td>
<td>&lt;40</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Palomo villada et al. [25]</td>
<td>&lt;40</td>
<td>30</td>
<td>93.75</td>
</tr>
<tr>
<td>Singhaviranon et al. [26]</td>
<td>&lt;40</td>
<td>30</td>
<td>89</td>
</tr>
</tbody>
</table>

* Numbers in [ ] are reference numbers

The reason why the young patients had an increased incidence of CABG may be due to the fact that they had high risk factor profiles and more aggressive coronary artery disease. Diabetes and smoking have been shown to be particularly associated with a heightened cardiovascular mortality and morbidity in young patients. There are several limitations to our study. We report a single center experience, possibly limiting generality of our results despite the fact that our institution is a referral center. The study group is relatively small to make the definitive conclusions, and the sample size may limit mortality data to reach Statistical significance. However, the characteristics of patients and rate of stenting are comparable to other reports. As the majority of our patients were elective procedures, this low risk subset of patients may justify low mortality rates. Finally as with any observational study, uncontrolled confounding factors could have affected our analysis of differences in outcomes.

Conclusion

In the current stent era, PCI in young adults has a high likelihood of success, with low morbidity and very low
mortality rates. Mid term survival is very satisfactory. However, young patients should not be dismissed at low risk on the basis of age alone, and emphasis should be focused on early detection and screening of risk factors in this group. In addition, more studies are needed to investigate long-term outcomes of PCI in young patients in the current stenting era.

Acknowledgements

This research project has been supported by Medical Sciences / University of Tehran. We thank Dr Mahmoud Sheikhfatollahi for the statistical analysis provided. Our thanks are also due to Miss Leila Ghassabi for typing the manuscript.

References

29. Schöning N, Neumann FJ, Kastrati A, Schühlen H, Blasini


Overexpression of Protein Tyrosine Phosphatase 1B in HepG2 Cells Ameliorates Insulin-mediated Suppression of Apolipoprotein B mRNA Translation Via its Untranslated Regions

Parvin Pasalar, PhD1,2*, Wei Qiu, PhD2, Rita Kohen Avramoglu, PhD2, Gus Sidiropoulos2, Khosrow Adeli, PhD2

1Biochemistry Department, Faculty of Medicine, Medical Sciences / University of Tehran, Tehran, Iran.
2Department of Laboratory Medicine & Pathobiology, Hospital for Sick Children, University of Toronto, Toronto, Canada.

Received 26 January 2007; Accepted 3 April 2007

Abstract

Background: The hepatic secretion of apolipoprotein B (apoB), containing lipoproteins, is known to be regulated by insulin, and the overproduction of these atherogenic lipoproteins occurs in insulin-resistant states. Protein tyrosine phosphatase 1B (PTP-1B) is a key regulator of hepatic insulin signaling and is also upregulated in insulin resistance. We aimed to investigate the role of PTP-1B in regulating apoB mRNA translational efficiency mediated by 5'/3' untranslated regions (UTRs) under conditions of insulin stimulation.

Methods: Human hepatoma HepG2 cells were transfected with a vector carrying the firefly luciferase reporter gene and either a chimeric apoB mRNA encoding the 5'/3' untranslated region (5'LUC3'-pGL3) or a null sequence of length equivalent to apoB 5' UTR (LUC-pGL3). The transfected cells were then infected with adenovirus carrying the mouse PTP-1B gene (AdPTP1B) in the absence or presence of insulin, and the cellular luciferase activity was determined. The RNA extracts from cells were transfected with constructs carrying 5'/3' apoB UTR, or a null sequence was also translated in vitro in a rabbit reticulocyte translation system.

Results: The luciferase activity of the cells transfected with constructs containing the apoB UTR sequences (5'LUC3') was significantly higher than that of the control constructs carrying a null sequence (p<0.01, n=12). Similar results were observed following in vitro translation studies showing a significantly higher expression of the 5'/3’ UTR constructs (p<0.001, n=6). Treatment with 100 nM insulin led to a significant reduction in the luciferase activity of the constructs carrying apoB 5'/3' UTR (p<0.0001, n=12). The down regulation of the apoB mRNA translation mediated by insulin was mediated by the apoB 5'/3' UTR sequences since insulin did not affect the control constructs containing a null sequence. The infection of HepG2 cells expressing 5'LUC3' or control constructs with AdPTP-1B attenuated the inhibitory effect of insulin and led to higher levels of luciferase activity compared to the Adß-gal infected control cells (p<0.05, n=12). However, the activity was lower than that in the control cells infected with 5'LUC3'-pGL3 but not treated with insulin (p<0.05, n=12).

Conclusion: Our data suggest that PTP-1B can potentially modulate apoB synthesis by blocking insulin-mediated inhibition of the apoB mRNA translation via its 5'/3’ UTR sequences. We hypothesize that the PTP-1B-mediated attenuation of the insulin action can lead to the upregulation of the apoB mRNA translation and contribute to a lipoprotein overproduction in conditions such as insulin resistance.

Keywords: Apolipoprotein B • Protein tyrosine phosphatase 1B • Untranslated region • In vitro translation assay

*Corresponding Author: Parvin Pasalar, Associate Professor of Biochemistry, Department of biochemistry, Faculty of Medicine, Medical Sciences/University of Tehran, Tehran, Iran. P.O.Box: 14155. Tel: +98 21 66649204. Fax: +98 21 66418588. Email: pasalar@tums.ac.ir.
**Introduction**

Apolipoprotein B (apoB) is the major structural protein associated with very low density lipoprotein (VLDL) and low density lipoprotein (LDL) and, as such, is an important risk factor for the development of coronary artery disease. The overproduction of atherogenic apoB is thought to be a common underlying factor in many dyslipidemic conditions including those associated with insulin resistance and the metabolic syndrome.\(^8\) The complex, interdependent processes that regulate the apoB lipoprotein assembly involve numerous proteins and co-factors that facilitate translation, lipidation, folding, and quality control. The inhibition of a number of these co-factors in HepG2 cells leads to posttranslational degradation of apoB via the ubiquitin-proteasome pathway, as well as other non-proteasomal pathways.\(^7\)

Although the regulation of apoB biogenesis is thought to occur largely posttranslationally, there is also evidence that regulation may begin at the translational level.\(^8,9\) Insulin, thyroid hormone, and the microsomal triglyceride transfer protein (MTP) have all been reported to be involved in the translational control of apoB.\(^10-13\) The effect of insulin is occurs largely posttranslationally, there is also evidence that apoB secretion through an increased post-translational degradation as well as a decreased synthetic rate.\(^6\) Despite these observations, the precise molecular mechanisms mediating the translational control of apoB remain incompletely understood.

Recent evidence based on both experimental data and thermodynamic modeling suggests that the translational control of apoB mRNA may be governed by the structural properties of the 3' and 5' UTR regions.\(^15\) ApoB mRNA is 14121 nucleotides long, and its 5' and 3' UTRs are composed of 76% GC r-nucleotides that possess a high potential for forming a stable secondary structure.\(^10\) An investigation into the 5' and 3' UTR sequences of apoB mRNA revealed RNA elements with the potential to form a stable secondary structure which in turn may mediate the translational control of apoB mRNA.\(^15\) The present study investigated the role of the UTR in the regulation of the apoB mRNA translation first by analyzing the apoB UTR sequences using Mfold, a program used to predict the RNA secondary structure. The Mfold analysis revealed hairpin-like elements within the 5' and 3' UTRs of apoB mRNA with the potential to form a stable secondary structure. Chimeric mRNAs, containing the 5' and/or 3' apoB UTRs linked to an LUC reporter gene or the apoB15 sequence, were employed to investigate the biological activity of these UTR motifs.\(^15\) The data suggested that the potential cis-trans interactions of these motifs with putative RNA binding proteins/translational factors are likely to govern the apoB mRNA translation and protein synthesis and may play an important role in the dysregulation of the atherogenic lipoprotein production in dyslipidemic states.

Protein tyrosine phosphatase 1B (PTP-1B) is a phosphatase involved in the dephosphorylation of the key components of the insulin signaling cascade including the insulin receptor and IRS family of proteins.\(^16-20\) The overexpression of this protein is believed to play a role in insulin resistance,\(^21,22\) and PTP-1B gene polymorphisms have been linked to the development of type 2 diabetes.\(^23\) Interestingly, in PTP-1B knockout mice, there was a decrease in the plasma triglyceride levels as well as resistance to fat-induced insulin resistance. More recently, our laboratory has reported a direct correlation between PTP-1B expression and hepatic apoB production.\(^24\) PTP-1B knockout mice were found to be resistant to a high-fructose diet, demonstrating significantly lower plasma triglyceride and apoB levels. The adenosiviral-mediated overexpression of PTP-1B led to a significant increase in the apoB secretion in the cultured hepatocytes. Overall, the available data suggest a potential role for PTP-1B in the regulation of the hepatic apoB production.

In light of these observations, we investigated the possible role of PTP-1B in regulating the translational control of apoB mRNA. We employed the adenosiviral-mediated overexpression of PTP-1B in HepG2 cells to determine whether PTP-1B could exert an effect on the translation of chimeric luciferase reporter constructs containing 5' and 3' UTR sequences under insulin stimulated conditions.

**Methods**

Cell culture HepG2 cells (American Type Culture Collection, ATCC8065) were maintained in an alpha-modification of Eagle’s minimum essential medium (α-MEM) with 10% fetal bovine serum and 1% penicillin/streptomycin at 37 °C in 5% CO2.

DNA constructs The 5'/3' UTRs were generated by PCR using apoB100 cDNA as template (kindly provided by Dr. Zemin Yao, University of Ottawa Heart Institute). The UTRs were cloned into the eukaryotic vector pGL3 (Promega, Madison, WI), containing SV40 promoter and enhancer sequences and the entire sequence encoding the firefly luciferase (FF-LUC) reporter gene. The 5' UTR and 3' UTR were cloned upstream and downstream of the LUC coding sequence, respectively. A control construct was made by using a null sequence of equivalent length to the apoB 5' UTR (128 base pairs) and was cloned upstream of the LUC gene into pGL3 vector to ensure that the observed effects were due to the presence of the specific apoB UTR sequence. The transfection efficiency was monitored by using a pRL-TK vector (Promega). This vector contains the Renilla luciferase gene (R-LUC) with the HSV-thymidine kinase and is suitable to use as control because it provides neutral constitutive expression of the renilla luciferase control vector.

In vitro translation assay – Cell lysates were prepared from HepG2 cells transfected with either 5' LUC3'-pGL3 or LUC-
pGL3 and treated for 18 hours with 100 nM insulin 48 hours following transfection. The Flexirabbit reticulocyte lysate kit (Promega) was used according to the manufacturers’ instructions for in vitro translation.

Transfection of DNA constructs and viral transduction. The PTP-1B adenovirus (AdPTP1Bm) was constructed as described.24 × 106 cells per well were seeded onto collagen-coated 6-well plates. The cells were allowed to attach to the plate overnight, and the transfection experiments were carried out at 70-80% confluence. 0.4 μg per well of each DNA construct was transfected using the Lipofectamine Plus Kit (Life Technologies, Bethesda, MD) for 4 hours. To normalize the transfection efficiency, the cells were co-transfected with 0.4 μg/well of the pRL-TK vector (Promega), which contained the renilla luciferase gene and the HSV-thymidine kinase promoter under the same conditions. The promoter is suitable to use as it provides the neutral constitutive expression of the renilla luciferase control vector. Following transfection, the media was replaced with complete α-MEM, and the cells were maintained for 48 hours. The cells were then harvested, cell extracts prepared, and luciferase assay was carried out by using the Dual-Luciferase Reporter Assay System (Promega). A ratio of firefly to renilla luciferase activity was calculated for each sample to normalize differences in the cell number and transfection efficiency. All the experiments, including DNA transfection and enzyme assays, were performed at least in triplicate.

**Results**

Effect of insulin on the expression of chimeric luciferase reporter constructs containing the 5’/3’ untranslated regions of apoB mRNA

Figure 1 shows a schematic diagram of the constructs used in this study. The first construct encodes the fire fly luciferase gene (FF-LUC gene) flanked by the 5’ and 3’ UTR regions of the apoB gene (Figure 1A). A null sequence of equivalent length to the apoB 5’ UTR was cloned upstream of the FF-LUC gene and was used as a negative control (Figure 1B). Transfection efficiency was monitored using the renilla luciferase coding region (R-LUC gene) encoding the HSV thymidine kinase promoter (Figure 1C).

We first determined whether insulin could affect the luciferase activity in HepG2 cells transfected with the 5’/3’ UTR apoB-luciferase by performing an insulin dose-response experiment (0-300 nM insulin). Figure 2A shows that the luciferase activity of 5’LUC3’apoB-pGL3 luciferase was reduced in a dose-dependent manner and was inhibited in the presence of 25 nM insulin (p<0.05) and up to 300 nM insulin (p<0.05). Under basal conditions (no insulin), the luciferase activity of the cells transfected with constructs containing the 5’/3’ UTR of apoB (5’LUC3’-pGL3) was considerably higher than that in the cells transfected with control constructs containing no UTR sequences (LUC-pGL3) (~4.5 fold higher, p<0.001, n=12) (Figure 2B). In the presence of 100 nM insulin, the luciferase activity of the cells transfected with constructs containing the 5’/3’UTR of apoB (5’LUC3’-pGL3) was significantly decreased by over 50% (p<0.05) compared to that in the absence of insulin (Figure 2B). No changes in the luciferase activity was observed in the control cells transfected with the control LUC-pGL3 when treated with insulin (data not shown), suggesting that the effect of insulin on the inhibition of the luciferase activity of the 5’LUC3’-pGL3 apoB-luciferase was specific to the constructs carrying the 5’/3’ UTR sequences.

In vitro translation experiments in a rabbit reticulocyte translation system were also performed by using the RNA extracts from the cells transfected with 5’LUC3’-pGL3 apoB-luciferase or control LUC-pGL3 carrying a null UTR sequence. A significantly increased luciferase activity was observed with 5’LUC3’-pGL3 (~4.2 fold, p<0.01, n=12) compared to that of the null-LUC-pGL3 (Figure 2C). Interestingly, the in vitro translation of the RNA isolated from the insulin-treated HepG2 cells transfected with 5’LUC3’-pGL3 showed a significantly lower luciferase activity compared to the activity of the RNA isolated from the same cells but in the absence of insulin (~40%, p<0.01, n=12) (Figure 2C).

Insulin did not have any significant inhibitory effect on the translation of RNA isolated from the cells transfected with the LUC-pGL3 control construct (data not shown). Overexpression of protein tyrosine phosphatase 1B (PTP-1B) partially reversed the negative effect of insulin on 5’/3’ UTR of apoB. We also investigated the effect of PTP-1B on the translation of chimeric luciferase reporter constructs carrying the 5’/3’ UTR of apoB mRNA. An adenovirus carrying the mouse PTP1B gene (AdPTP1Bm) as well as a control adenovirus (Adβ-gal, control adenovirus, in which the ß-galactosidase gene had been cloned) was employed.
Figure 2. Effect of insulin on the expression of chimeric luciferase reporter constructs containing the 5'/3' untranslated regions of apoB mRNA. Panel A) LUC activity of 5'/3' UTR apoB constructs is suppressed by insulin in a dose-dependent manner. The suppression effect of increasing dose of insulin on the apoB5'/3'UTR-luciferase constructs in HepG2 cells. Each experiment was performed in triplicate, results are represented as mean ± S.E., n=6. Panel B) LUC activity of 5'/3' UTR apoB constructs is suppressed by insulin. The suppression effect of 100 nM of insulin on the apoB5'/3'UTR-luciferase constructs was examined in HepG2 cells. Each experiment was performed in triplicate, results are represented as mean ± S.E., n=12. Panel C) In vitro translation of apoB5'/3' UTR from HepG2 cell lysate. RNA isolated from HepG2 cells transfected with either the 5'LUC3'-pGL3 apoB-luciferase construct or LUC-pGL3 control construct and treated overnight with 100 nM insulin 48 hours following transfection were incubated with rabbit reticulocyte in vitro translation system. Results are means ± S.E., n=6

The construction of these adenoviruses has been previously described. HepG2 cells were infected with AdPTP1B or Adß-gal viruses 30 minutes after being transfected with 5'LUC3'-pGL3 apoB-luciferase or LUC-pGL3 control. As shown in Figure 3A, the infection of HepG2 cells with AdPTP1B led to a significantly higher protein mass of PTP-1B (5.4 fold±0.45, p<0.01) based on an immunoblot analysis of the HepG2 cells compared with that in the control cells infected with Adß-gal encoding the β-galactosidase gene.

Once the overexpression of PTP-1B was confirmed under these conditions, the HepG2 cells were transfected with 5'LUC3'-pGL3 apoB-luciferase or LUC-pGL3 control construct and then infected with either AdPTP1B or Adß-gal adenovirus. The cells were also treated with or without 100 nM insulin for 16 hours. As shown in Figure 3B, in the absence of insulin, no changes in the luciferase activity were observed in cells transfected with 5'LUC3'-pGL3 and infected with either AdPTP-1B or Adß-gal. Interestingly, when the HepG2 cells transfected with 5'LUC3'-pGL3 and infected with the AdPTP-1B were treated with insulin, there was a significant increase in the level of the luciferase activity (Figure 3B) (an increase of ~35%, p<0.05, n=12, compared to that of the control cells infected with Adß-gal).

Figure 3. Overexpression of protein tyrosine phosphatase 1B (PTP-1B) partially reversed the negative effect of insulin on 5'/3' UTR of apoB. Panel A) Adenovirus-mediated overexpression of PTP1B in HepG2 cells. Immunoblot analysis of HepG2 cells transfected with empty vector, control adenovirus encoding ß-galactosidase (Adβ-gal), or adenovirus encoding the mouse PTP1B mRNA (AdPTP1Bm). Results are means ± S.E., n=3. Panel B) PTP-1B overexpression impeded the inhibitory effect of insulin luciferase activity of apoB 5'/3' UTR HepG2 cells transfected with 5'LUC3'-pGL3 apoB-luciferase construct or LUC-pGL3 control construct were infected with PTP-1B adenovirus. Results are means ± SE, n=12.
This suggests that the overexpression of PTP-1B can block the negative effect of insulin on the expression of constructs carrying the apoB-5′/3′UTR. Importantly, the luciferase activity of cells transfected with both 5′LUC3′-pGL3 and AdPTP-1B was still significantly lower than that in the cells under basal conditions (not treated with insulin) (p<0.05, n=12), suggesting that the overexpression of PTP-1B only partially reversed the negative effect of insulin on the expression of 5′LUC3′-pGL3. The presence or absence of insulin had no effect on the luciferase activity in cells transfected with the control construct under the same conditions. Finally, the luciferase activity in the cells transfected with 5′LUC3′-pGL3 and infected with either AdPTP-1B or Adβ-gal was tested in the absence and presence of insulin in order to ensure the luciferase activity observed was not an artifact of the transfection itself. No significant increase in the luciferase activity was observed under any of these conditions (Figure 4).

Discussion

It has previously been reported that insulin has a suppressive effect on the hepatic apoB assembly and secretion; however, the precise mechanism of regulation remains incompletely understood. Recent evidence implicates sequence and structural elements within the UTR sequences of apoB mRNA in the translational control and apoB synthesis. In a previous study, 5′ and 3′ apoB UTR sequences were cloned into a eukaryotic expression vector pGL3 upstream and downstream of the firefly luciferase reporter gene. The UTR sequences, and particularly the 5′ UTR, had a significant stimulatory effect on the expression and in vitro translation of the reporter construct. In the present study, we demonstrate that the UTR-stimulated increase in the translational efficiency can be significantly ameliorated following the insulin treatment of HepG2 cells. The insulin-mediated down regulation of the reporter expression appeared to be mediated by the 5′/3′ UTR sequences since the cells expressing the control constructs lacking the UTR sequences were unresponsive to insulin exposure. In vitro translation experiments using a reticulocyte lysate system confirmed that the effects observed in the cell transfection studies were translational in nature. Interestingly, this down regulation was observed despite a global increase in total mRNA and protein abundance due to the widely-recognized anabolic effect of insulin (data not shown).

Our results show the importance of the apoB-UTR sequences in the mRNA translation by comparison with several other studies; furthermore, our findings suggest that the secondary structure and sequence of the 5′ and 3′ UTRs of mRNA are critical to the translational control. The UTRs within pre-proinsulin mRNA play crucial roles in regulating the insulin production and, therefore, glucose homeostasis by regulating the translation and the stability of the preproinsulin mRNA. The 3′ UTR of the PTP-1B gene is associated with several features of insulin resistance. Studies have generally shown that highly structured 5′ UTR sequences tend to inhibit efficient translation. Within the 5′ UTR, there are several other studies; furthermore, our findings suggest that the effects observed in the cell transfection studies were mediated by the 5′/3′ UTR sequences since the cells expressing the control constructs lacking the UTR sequences were unresponsive to insulin exposure. In vitro translation experiments using a reticulocyte lysate system confirmed that the effects observed in the cell transfection studies were translational in nature. Interestingly, this down regulation was observed despite a global increase in total mRNA and protein abundance due to the widely-recognized anabolic effect of insulin (data not shown).

Our results show the importance of the apoB-UTR sequences in the mRNA translation by comparison with several other studies; furthermore, our findings suggest that the secondary structure and sequence of the 5′ and 3′ UTRs of mRNA are critical to the translational control. The UTRs within pre-proinsulin mRNA play crucial roles in regulating the insulin production and, therefore, glucose homeostasis by regulating the translation and the stability of the preproinsulin mRNA. The 3′ UTR of the PTP-1B gene is associated with several features of insulin resistance. Studies have generally shown that highly structured 5′ UTR sequences tend to inhibit efficient translation. Within the 5′ UTR, there are several other studies; furthermore, our findings suggest that the effects observed in the cell transfection studies were mediated by the 5′/3′ UTR sequences since the cells expressing the control constructs lacking the UTR sequences were unresponsive to insulin exposure. In vitro translation experiments using a reticulocyte lysate system confirmed that the effects observed in the cell transfection studies were translational in nature. Interestingly, this down regulation was observed despite a global increase in total mRNA and protein abundance due to the widely-recognized anabolic effect of insulin (data not shown).

Our results show the importance of the apoB-UTR sequences in the mRNA translation by comparison with several other studies; furthermore, our findings suggest that the secondary structure and sequence of the 5′ and 3′ UTRs of mRNA are critical to the translational control. The UTRs within pre-proinsulin mRNA play crucial roles in regulating the insulin production and, therefore, glucose homeostasis by regulating the translation and the stability of the preproinsulin mRNA. The 3′ UTR of the PTP-1B gene is associated with several features of insulin resistance. Studies have generally shown that highly structured 5′ UTR sequences tend to inhibit efficient translation. Within the 5′ UTR, there are several other studies; furthermore, our findings suggest that the effects observed in the cell transfection studies were mediated by the 5′/3′ UTR sequences since the cells expressing the control constructs lacking the UTR sequences were unresponsive to insulin exposure. In vitro translation experiments using a reticulocyte lysate system confirmed that the effects observed in the cell transfection studies were translational in nature. Interestingly, this down regulation was observed despite a global increase in total mRNA and protein abundance due to the widely-recognized anabolic effect of insulin (data not shown).

The structure of a eukaryotic mRNA showing different types of UTR-specific regulatory elements involved in the posttranscriptional regulation of gene expression has been shown. Unlike DNA-mediated regulatory signals, whose activity is essentially mediated by their primary structure, the biological activity of regulatory patterns acting at the RNA level relies on a combination of primary and secondary structure elements assembled in a consensus structure generally recognized by specific RNA-binding proteins. Several studies suggest that the secondary structure and sequence of the 5′ and 3′ UTR mediate the translational control. These structural features may be a potential binding site for RNA-binding proteins; the interaction of cis-elements...
with trans-acting factors may modulate the translation or alter the stability of the message. An analysis of the apoB UTR sequences using the Mfold, a program used to predict the RNA secondary structure, revealed hairpin-like elements with the potential to form a stable secondary structure within the 5' and 3' UTR regions of apoB mRNA. Chimeric mRNAs containing the 5'and/or 3'apoB UTRs linked to a LUC reporter gene or the apoB15 sequence were employed to investigate the biological activity of these UTR motifs. The data suggest that the putative 5' UTR motifs are important for an optimal translation of the apoB message, whereas the presence of the 3' UTR appears to attenuate a wild-type expression. The potential cis/trans interactions of these motifs with the putative RNA binding proteins/translational factors are likely to govern the apoB mRNA translation and protein synthesis and may play an important role in the dysregulation of the atherogenic lipoprotein production in dyslipidemic states. More recently, we have identified a 110-kDa insulin-sensitive factor that binds to the 5' UTR and regulates the apoB mRNA translation. Insulin-mediated alterations in the binding of this factor to the 5'UTR include the modulation of the apoB mRNA translation and protein synthesis. This appears to be direct evidence for the potential cis/trans interactions at the 5'UTR and lead to alterations in the rate of the apoB synthesis (data not shown).

Early studies in the 1990s suggested the translational control of apoB mRNA by insulin and thyroid hormone in HepG2 cells. Studies in primary rat hepatocytes have also shown that insulin suppresses the apoB secretion in part by stimulating the degradation of freshly translated apoB and also by reducing the apoB synthesis. It has been suggested that a reduced apoB synthesis is a result of a decreased translational efficiency. Additional studies in streptozotocin-induced diabetic rats have provided further evidence of the apoB mRNA translational control. A decreased apoB synthesis observed in primary hepatocyte cultures derived from these diabetic rats was believed to be due to a reduced translational efficiency. This was found to be a result of impaired or slowed translation rates as determined by ribosome transit studies. Studies in cultured human fetal intestinal cells have also suggested that the insulin-mediated suppression of the apoB secretion may be mediated by co- and posttranslational modulation including mRNA translation. A more recent study in HepG2 cells found that the apoB synthesis decreased in response to treatment with CP-10447, an inhibitor of microsomal triglyceride transfer protein (MTP). The decrease was attributed to a translational effect as the apoB mRNA levels remained unchanged in response to the MTP inhibitor. The authors postulated that the decrease in the apoB translation was due to delayed polypeptide elongation rates as determined by synchronization studies with puromycin and by ribosome transit studies. Overall, these studies suggest that the apoB synthesis may be regulated at the level of translation by insulin. However, the molecular mechanisms or factors which mediate the translational control of apoB mRNA by insulin have not been elucidated.

Insulin signaling can be attenuated by the activity of protein tyrosine phosphatases (PTPases) which dephosphorylate the insulin receptor, IRS-1, IRS-2, and the docking protein, Shc, leading to the modulation of insulin action. Among these, PTP-1B is widely expressed in insulin sensitive tissues (liver, fat, and muscle), can efficiently dephosphorylate the insulin receptor in vitro, and induce the down regulation of IRS-1 and PI-3 kinase activity. Increased PTP-1B has been associated with insulin resistance induced by an exposure to high glucose levels, and such insulin resistance can be reversed by the normalization of the PTP-1B level and activity. PTP-1B knockout mice exhibit improved insulin sensitivity on a high fat diet and increased insulin-induced insulin receptor and IRS-1 tyrosine phosphorylation. Interestingly, PTP-1B knockout mice were resistant to diet-induced obesity and did not develop hyperglycemia on a high fat diet. In addition, a single nucleotide polymorphism within the PTP-1B gene in humans has been shown to correlate with protection from type 2 diabetes. Overall, there is strong evidence suggesting that PTP-1B can modulate insulin signaling, and may thus play an important role in the pathogenesis of insulin resistance and possibly metabolic dyslipidemia.

It was of interest, therefore, to study the potential effect of PTP-1B on the suppression of the apoB mRNA translation by insulin. To study the effect of PTP-1B on the translation efficacy of insulin-treated HepG2 cells transfected with the apoB 5'/3'UTR construct, we used recombinant adenoviruses that overexpress the mouse PTP-1B gene (AdPTP1B). An adenovirus in which the β-galactosidase gene had been cloned (Adβ-gal) was also used as negative control. The overexpression of PTP-1B has recently been shown to lead to the down regulation of insulin signaling in HepG2 cells and induce the apoB100 overproduction. In the present report, we provide evidence that a PTP-1B overexpression could partially block the insulin-mediated suppression of the expression of luciferase reporter constructs carrying 5'/3'UTR sequences. This appears to be direct evidence for an effect of PTP-1B on the translational control of mRNA translation via the 5'/3'UTR sequences. The PTP-1B overexpression was, however, unable to completely restore the translational efficiency of apoB mRNA in the presence of insulin.

Conclusion

We postulate that the PTP-1B overexpression attenuates insulin signaling transduction and thus leads to at least a partial block in the insulin-mediated suppression of the apoB mRNA translation. It is important to note, however, that our conclusions are based on the use of reporter constructs and not in the context of a complete apoB mRNA coding sequence and will need further confirmation in future studies.
**Acknowledgment**

This work was supported by an operating grant from NSERC to Khosrow Adeli. Rita Kohen Avramoglou is a recipient of a Heart and Stroke Foundation of Canada postdoctoral fellowship.

**References**


33. Goldstein BJ, Li PM, Ding W, Ahmad F, Zhang WR. Regulation of insulin action by protein tyrosine phosphatases. Vitam Horm
Early Outcome of Coronary Artery Bypass Grafting in Patients Less Than 40 Years Old Comparing with Elderly Patients

Abbasali Karimi, MD*, Sayed Hosein Ahmadi, MD, Saeed Davoodi, MD, Mehrab Marzban, MD, Namvar Movahhedi, MD, Kyomars Abbasi, MD, Abbas Salehi Omran, MD, Mahmood Shirzad, MD, Mehrdad Sheikvatan, MD, Seyed Hesameddin Abbasi, MD

Tehran Heart Center, Medical Sciences / University of Tehran, Tehran, Iran

Received 21 January 2007; Accepted 27 March 2007

Abstract

Background: Age is one of the most important factors that have consistently emerged as the most potent predictors of mortality and morbidity after coronary artery bypass graft (CABG) surgery. However, early results of CABG in young patients in comparison with elderly ones have been different in previous surveys. The aim of this study was to compare short-term mortality and morbidity in young versus older patients and evaluate the presence of risk factors and their influence on outcome in both groups.

Methods: We conducted a retrospective database review of 13222 patients divided into two age groups: patients less than 40 years old (411 patients) and those older (12811 patients), who underwent CABG at Tehran Heart Center between January 2002 and January 2007. We also compared preoperative, operative, and postoperative characteristics between them and assessed the influence of the variables on the length of stay in hospital (LOS) in the two groups.

Results: Among postoperative complications, only atrial fibrillation (P<0.001) was more prevalent in the elderly group and other complications were similar. The thirty-day mortality rate was higher in the elderly group (1.1% vs. 0%, P=0.023). Also, prolonged LOS (P<0.001) and ICU stay (P<0.001) were found more prevalent in the elderly group. Among the preoperative and postoperative variables, emergency surgery, diabetes mellitus, and previous myocardial infarction influenced the prolonged LOS in the young patients.

Conclusion: Early mortality rate and prolonged length of stay in ICU and hospital were higher in the elderly than those in the young patients; however, other postoperative early complications were similar between the two groups.

Keywords: Coronary artery bypass grafting • Age • Outcome

Introduction

During the past two decades, the mean age of patients selected for coronary artery bypass graft (CABG) surgery has increased.1 Despite the fact that improved myocardial preservation, anesthesia, surgical techniques, and postoperative care have improved the outcome of surgery, older age still causes increased morbidity and longer hospital stays.1 Thus, age is one of the most important factors that have consistently emerged as the most potent predictors of mortality and morbidity after CABG. Elderly patients being considered for CABG has a higher average risk for mortality.
and morbidity in a direct relation to age. However, early results of CABG in young patients in comparison with elderly ones have been different in previous surveys. In some studies, the prognosis for young patients was worse with decreasing age of the first coronary episode; and in some others, the outcome for young patients was better than that for older patients. Also, coronary artery disease (CAD) carries a significant morbidity, psychological effects, and financial constraints for the person and the family when it occurs at a young age. Furthermore, the prevalence of risk factors is on the rise in young adults and children. This will result in an increased disease burden in the near future.

According to the different results of CABG in young versus elderly patients and the increase of risk factors for CAD in young groups, we compared short-term mortality and morbidity in young patients and evaluated the presence of risk factors and their influence on early outcome in this group versus elderly patients.

**Methods**

Preoperative, intraoperative, and postoperative characteristics were collected and entered into a computerized database from 13222 patients undergoing isolated CABG at Tehran Heart Center from January 2002 to January 2007. In this study, CAD was considered significant if there was a 75% or greater stenosis in the luminal diameter of coronary arteries in any view. A stenosis of 50% or more in the left main coronary artery was considered significant. The following data were included for analyzing the preoperative variables: 1) general characteristics: age, gender, and body mass index (BMI); 2) preoperative risk factors: current smoking history (patient regularly smokes a tobacco product/products one or more times per day or has smoked in the 30 days prior to admission), hypercholesterolemia (total cholesterol≥220 mg/dl, HDL-cholesterol≤35 mg/dl, LDL-cholesterol≥160 mg/dl), family history of CAD (first-degree relatives before the age of 55 in men and 65 years in women), hypertension (systolic blood pressure>140 mmHg and/or diastolic>90 mmHg and/or on anti-hypertensive treatment), diabetes mellitus (symptoms of diabetes plus plasma glucose concentration>200 mg/dl or fasting plasma glucose>126 mg/dl or 2-hp>200 mg/dl), renal failure (creatinine>4.0 mg/dl with a rise of >44 units or urine output below 0.3 ml/kg for 24 h), cerebrovascular disease, and chronic lung disease; 3) preoperative cardiac status: previous myocardial infarction (an acute event with abnormal creatine phosphokinase and troponin levels), New York Heart Association (NYHA) score, Euroscore, and arrhythmia; and 4) preoperative hemodynamic status: number of defected coronary vessels, left main disease>50%, and left ventricular ejection fraction.

The operative data included type of surgery (elective or emergency), the number of distal anastomoses with vein grafts, and the use of internal mammary artery (IMA) as grafts.

We considered four criteria for postoperative short-term outcome:

1) In-hospital postoperative complications (existence of at least one of these complications): cardiac complications (heart block, cardiac arrest, tamponade, and atrial fibrillation) and non-cardiac complications (brain stroke, renal failure, pulmonary emboli, acute limb ischemia, multi-system failure, continuous coma>24 hours, and prolonged ventilation>10 hours); 2) prolonged length of stay in ICU; 3) prolonged hospital stay; and 4) 30-day mortality rate (sometimes termed as operative mortality) defined as death within 30 days of operation.

Numerical variables were presented as the mean±SD, while categorized variables were summarized by percentages. Continuous variables were compared using the Student’s t test or nonparametric Mann-Whitney U test whenever the data did not appear to have normal distributions, and categorical variables were compared using the chi-square or Fisher’s exact test.

Power analysis showed that there was about 90% chance of detecting a significant difference using a two-sided test with significance level=0.05.

Multivariate stepwise logistic regression model for risk factors predicting prolonged LOS was constructed separately for young and elderly patients. Variables were included into the multivariate model if the p value was found to be less than or equal to 0.15 in the univariate analysis. The associations of independent predictors with prolonged LOS in the final model were expressed as odds ratios (OR) with 95% Confidence Intervals (CIs). Model discrimination was measured using the c statistic, which is equal to the area under the ROC (Receiver Operating Characteristic) curve. Model calibration was estimated using the Hosmer Lemeshow (HL) goodness-of-fit statistic (higher P values imply that the model fit the observed data better). For the statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were used. All p values were 2-tailed, with statistical significance defined by p<0.05.

**Results**

There were 411 and 12811 CABG operations performed on patients≤40 years old and elderly patients, respectively. The main preoperative characteristics are summarized in Table 1. Among CAD risk factors, family history of CAD (P<0.001), previous myocardial infarction (P=0.001), and cigarette smoking (P=0.001) were higher in groups≤40 years old, whereas history of hypertension (P<0.001), diabetes mellitus (P<0.001), peripheral vascular disease...
Early Outcome of Coronary Artery Bypass Grafting in Patients Less Than 40 Years Old

(P=0.044), and arrhythmia (P=0.011) were more prevalent in the elderly group. Also, the mean of Euroscore in the young patients was less than that in the elderly group (P<0.001). No significant differences in other risk factors between the two groups were found. Preoperative ejection fraction and the mean of NYHA score were also similar between the two groups. There was a significant difference in the number of defected vessels between the two groups (P<0.001). Also, left main disease>50% was more prevalent in group>40 years old (P<0.001).

The main postoperative complications are summarized in Table 3. Among postoperative complications, only atrial fibrillation (P<0.001) was more prevalent in the elderly patients, and the other studied complications were similar between the two groups. The thirty-day mortality rate in group≤40 years old was significantly less than that in the other group. Also, prolonged length of stay in hospital (LOS) (P<0.001) and total ICU stay (P=0.001) were more prevalent in the elderly patients.

A multivariate stepwise logistic regression analysis showed that several preoperative and postoperative characteristics influenced the prolonged LOS in the elderly patients (Table 4). However, only three factors of emergency versus elective surgery (P=0.0003), history of diabetes mellitus (P=0.0047), and pre-CABG myocardial infarction (P=0.0038) were main predictors for prolonged LOS in hospital in young patients (table 5).

The operative cardiac indices are shown in Table 2. Arterial grafts were used more in group≤40 years old (P=0.031), whereas the use of vein grafts was found more in the other group (P<0.001).
Table 5. Predictors for prolonged LOS in young patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate P value</th>
<th>Multivariate P value</th>
<th>Odds Ratio 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency surgery</td>
<td>&lt;0.0001</td>
<td>0.0003</td>
<td>0.244 0.113-0.526</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.002</td>
<td>0.0038</td>
<td>1.904 1.239-2.925</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.002</td>
<td>0.0047</td>
<td>2.253 1.289-3.939</td>
</tr>
</tbody>
</table>

LOS, Length of stay in hospital; MI, Myocardial infarction
Hosmer-Lemeshow statistic: $\chi^2 = 0.51$, $P=0.776$
Area under the ROC curve c=0.636

**Discussion**

CABG surgery has been shown to be an effective method for treating angina pectoris and prolonging life in patients with severe coronary artery disease. Be that as it may, it has not yet been determined whether younger patients benefit from this procedure to the same extent as elderly patients. The present study compares three preoperative, operative, and postoperative characteristics of patients≤40 years old who underwent CABG with elder patients in this center between 2002 and 2006.

In this study, frequency of CABG procedures in men ≤40 years old and elderly men were 87.6% and 74.1%, respectively. In line with our study, French et al. reported the frequency of 84% for men≤40 years old who underwent CABG procedures. Furthermore, in the Keskimaki et al. study, in relation to hospitalization due to CAD, women received proportionally less surgery than men.

The average age of patients≤40 years old in our study was 36.7 years old. In the Kelly study, the average age of these patients was reported to be 35 years. In our study, history of cigarette smoking and family history of CAD in the young patients were more frequent than those in the patients>40 years old. We also found that history of hypertension and diabetes mellitus in patients≤40 years old was seen less than that in the elderly patients. Kelly and Rohrer-Gubler et al. found similar results in their studies. In marked contrast to their studies, however, we found no significant difference between history of hypercholesterolemia in the young patients and patients>40 years old that underwent CABG procedure. In the Kelly and Rohrer studies, patients less than 40 years were more likely to have elevated cholesterol levels. In the French et al. study, the prevalence of cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, and family history of CAD was strikingly less than that in our study.

In our study, previous myocardial infarction was more prevalent in the elderly group. Rohrer et al. found that the group≤40 years old had more preoperative myocardial infarction. Casas et al. found that the younger patients appeared to carry the same risks for myocardial infarction and death as an elderly patient. In their study, a total of 61% of young patients had a recent history of a myocardial infarction and 60% had NYHA Class IV just prior to operation, whereas we found the prevalence of recent myocardial infarction in 45.8% of younger patients and NYHA Class≥3 only in 20.3% of our patients. Results of several studies have suggested that CABG is becoming safer to perform in very old persons; and although older patients are referred for CABG at a significantly lower functional level, the functional improvement after CABG is not significantly different among age groups.

Among postoperative criteria, atrial fibrillation was more frequent in patients>40 years old. Atrial fibrillation after CABG is the most common sustained arrhythmia. Its pathophysiology is unclear, and its prevention and management remain suboptimal. Post-CABG atrial fibrillation seems to require a well-defined anatomical and electrical substrate that is generated by increased left atrial dimensions, a greater extension of coronary lesions, and a possible electrical remodeling consequent to prior repetitive episodes of paroxysmal atrial fibrillation.

In our study, the 30-day mortality rate was more in the elderly group. In the Kelly et al. study, the percentage of death was much higher for younger patients. In the Peterson et al. study, age was a significant predictor of the 30-day mortality. For example, an 85-year-old patient undergoing bypass surgery would have nearly 40% higher odds for mortality at 30 days than a similar patient of age 80 years. Also, measures of acute coronary disease, such as acute myocardial infarction before bypass surgery and congestive heart failure, and comorbid illnesses such as peripheral vascular disease and chronic renal disease were highly predictive of 30-day mortality.

We also found that the length of hospital stay in the elderly patients was higher than the other group. Results of other studies indicated that elderly patients were much more likely to be discharged to extended-care facilities. In our study, the female gender was an important predictor for prolonged length of stay in hospital, which chimes in with the results of the Borzak study. In several studies, the female sex is reported to be an independent predictor of length of stay in hospital. Vaccarino et al. reported that women undergoing CABG had higher rates of hospital readmission than men at 6 weeks. It seems that the most common causes of prolonged lengths of stay in hospital in females are a higher incidence of preoperative risk factors and postoperative complications of CABG in females than in males. Therefore, it is important to control these risk factors in female patients before operation.

**Conclusion**

Finally, it can be concluded that early mortality rates and prolonged lengths of stay in ICU and hospital are higher in elderly patients by comparison with young ones. However, other postoperative complications are similar between the two groups.
In view of our findings, additional investigations are needed to compare long-term mortality rates of young with elderly patients who undergo CABG and study the effects of operative and postoperative indices on late CABG outcome in younger patients.

Acknowledgement

This research project was supported by Medical Sciences/University of Tehran. We are indebted to Dr. Shahin Akhoundzadeh and Dr. Soheil Saadat, for technical assistance and Dr. Mahmood Sheikh fathollahi for statistical analysis.

References

Non Invasive Assessment of Myocardial Perfusion after First Myocardial Infarction with Transthoracic Echocardiography

Mehrnoush Toufan, MD, Jahanbakhsh Samadikah, MD, Azin Alizadeh Asl, MD*, Rasoul Azarfarin, MD, Seyed Hadi Hakim, MD

Cardiovascular Research Center, Madani Heart Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

Received 26 November 2006; Accepted 6 February 2007

Abstract

Background: Standard methods for the measurement of myocardial perfusion are invasive and require cardiac catheterization or the use of radioisotope dyes. The coronary sinus blood flow (CSBF) is an appropriate criterion for the efficacy of myocardial perfusion. This study sought to measure CSBF via transthoracic echocardiography (TTE) in patients with acute myocardial infarction (AMI) and to assess its relation with left ventricular ejection fraction (LVEF), wall motion scoring index (WMSI), and in-hospital mortality.

Methods: This case-control study evaluated 20 patients (pts) with anterior AMI and 20 healthy individuals as controls over a 6-month period (in 2005) in Madani Heart Center in Tabriz (Iran). All the patients received the same drugs for AMI treatment (e.g. fibrinolytic). CSBF and WMSI, having been obtained via TTE, were compared between the two groups.

Results: Baseline variables were similar between the two groups (P>0.05). CSBF in the AMI group was 287.8±128 ml/min and in the control group was 415±127 ml/min (P=0.001). There was a significant correlation between CSBF and LVEF (r=0.52, P=0.01), between CSBF and WMSI (r=-0.77, P=0.0001), and between CSBF and in-hospital mortality (r=0.58, P=0.03).

Conclusion: Our study demonstrated a good correlation between CSBF measured with 2D-doppler TTE and LVEF, WMSI, and in-hospital mortality.

Keywords: Myocardial perfusion • Coronary sinus blood flow • Transthoracic echocardiography • Wall motion scoring index • Acute myocardial infarction

Introduction

The coronary sinus blood flow (CSBF) is often utilized as a measure of cardiac perfusion. However, the standard techniques for the measurement of cardiac perfusion are invasive and require cardiac catheterization (intravascular Doppler flow wire, thermodilution catheter, or digital coronary angiography) or the use of radioisotope dyes (argon technique or xenon scintigraphy). Pervious studies have described the use of transesophageal echocardiography...
(TEE) in the measurement of CSBF and coronary flow reserve and demonstrated the feasibility and reproducibility of TEE in measuring CSBF. In contrast to TEE, transthoracic echocardiography (TTE) with Doppler flow measurement provides a non-invasive means of measuring CSBF. Daniel Wing Chong Ng et al.,1 having applied this non-invasive method, succeeded in demonstrating a statistically significant increase in the coronary artery flow after revascularization procedures, a finding previously established by invasive studies.

The aim of this study was to measure CSBF via TTE in patients with acute myocardial infarction (AMI) and to assess its relation with left ventricular ejection fraction (LVEF), wall motion scoring index (WMSI), and in-hospital mortality.

**Methods**

The study was approved by the Ethics Committee of our institution, and written informed consent was obtained from all the patients. In this case control study, 20 patients with anterior MI and 20 healthy individuals as controls were studied over a 6-month period (in 2005) in Madani Heart Center in Tabriz (Iran). Acute anterior myocardial infarction was defined as the presence of typical chest pain lasting for more than 30 minutes, ST-segment elevation of more than 0.1 mV in the adjacent V1-4 leads, and a serum creatine kinase concentration that was more than twice the upper limit of the normal range. Standard 12-lead and right precordial electrocardiograms were obtained immediately after admission. The twenty healthy individuals were selected from the hospital staff and the patients' adult relatives with no history of cardiovascular diseases. All the patients received the same drugs for AMI treatment (e.g. streptokinase). We did not receive funds for the study from any other party other than our own institution.

CSBF and WMSI data were obtained via TTE 48 hours after admission and compared between the two groups. Echocardiographic studies were performed by a single expert cardiologist. A 2.5-MHZ transducer of commercially available echocardiography equipment (VIVID7, GE, USA) was used. The coronary sinus diameter was measured in the posterior angulated four-chamber view, and its flow was obtained in the right ventricular (RV) inflow view with optimized zooming and the placement of the pulse wave sample volume (PWSV) in its orifice to record the blood flow. CSBF was identified through systolic and diastolic signals with very little respiratory variation. The coronary sinus velocity time integral (CSVTI) was measured by outlining the flow velocity signal and using a computer algorithm in the ultrasound machine. The coronary sinus was then imaged in the apical four-chamber view of the coronary sinus, with posterior tilting of the transducer.

The diameters of the coronary sinus were taken at five equally spaced segments in the cardiac cycle over three cardiac cycles before they were averaged and used as the major diameter of the coronary sinus. Assuming that the cross section of the coronary sinus is an ellipse and that the major diameter is double the length of the minor diameter, the cross-sectional area of the CS was calculated as: \[0.39 \times \text{major diameter}^2\]. CSBF was then calculated as: \[(\text{CSVTI}) \times \text{(cross-sectional area of the CS)} \times \text{(heart rate)}\].

Collected variables between the two groups were analyzed using SPSS vs.13.0 (SPSS Inc. Chicago, IL) statistical package. Continuous parameters are expressed as mean and standard deviation. Comparisons between the continuous variables recorded from the control and AMI groups were made by an independent samples t-test. Categorical variables between the two groups were analyzed with a Chi-square or Fisher’s exact test as appropriate. Statistical significance was accepted when \(P \leq 0.05\).

**Results**

Baseline variables (age, sex, history of diabetes mellitus, hypertension, hyperlipidemia, smoking, and body mass index) were similar between the two study groups. Also, heart rate and coronary sinus diameter were similar between the two groups (Table 1). The coronary sinus was visualized in all the 20 AMI patients and 20 control participants with adequate samples of coronary sinus flow velocity. All the patients were in sinus rhythm. Two patients in the AMI group died during hospital stay, but there was no mortality in the control group.

CSBF in the AMI group was 287.8±128 ml/min, while in the control group it was 415±127 ml/min (\(P=0.001\)). Figure 1 shows the correlations between CSBF and LVEF (\(r=0.52, P=0.01\)), between CSBF and WMSI (\(r=-0.77, P=0.0001\)), and between CSBF and in-hospital mortality (\(n=2\), \(r=0.58, P=0.03\)).

![Figure 1. Linear regression between coronary sinus (CS) blood flow and left ventricular ejection fraction (LVEF; plot A), and wall motion scoring index (WMSI; plot B) in patients with acute myocardial infarction.](image-url)
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute MI group (n=20)</th>
<th>Control Group (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53.8±12.4</td>
<td>47.9±12.3</td>
<td>0.0136</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/5</td>
<td>14/6</td>
<td>1.000</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168±10</td>
<td>167±9</td>
<td>0.784</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77±15</td>
<td>72±12</td>
<td>0.272</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1±3.9</td>
<td>25.8±3.6</td>
<td>0.284</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.39±7%</td>
<td>0.58±4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>8(40%)</td>
<td>4(20%)</td>
<td>0.271</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>9(45%)</td>
<td>7(35%)</td>
<td>0.748</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9(45%)</td>
<td>4(20%)</td>
<td>0.177</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3(15%)</td>
<td>2(10%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary sinus diameter (cm)</td>
<td>0.88±0.15</td>
<td>0.83±0.17</td>
<td>0.120</td>
</tr>
<tr>
<td>Heart rate (per minute)</td>
<td>80±10</td>
<td>73±12</td>
<td>0.100</td>
</tr>
</tbody>
</table>

*Values are shown as mean±SD
MI, Myocardial infarction; BMI, Body mass index; LVEF, Left ventricular ejection fraction

**Discussion**

Several studies have demonstrated that AMI produces a remarkable decrease in CSBF. Be that as it may, an objective measurement of CSBF has traditionally required invasive studies. Terekhov VN assessed CSBF in 42 patients using a continuous thermodilution technique in the presence of thrombolytic treatment. The coronary venous flow was shown to have increased by 20% and more in 17 patients, more than 30% in 15, and more than 40% in 10 after treatment with streptokinase.

Inferior wall MI was associated with a significant increase in the blood flow rate in the coronary sinus as well as in other cardiac veins, while anterior MI was associated with a flow rate increase in the coronary sinus only. Bogatyrev IV by continuous coronary sinus thermodilution showed that patients with anterior MI had a significantly less blood flow in the vena cordis magna than did those with posterolateral infarction. However, continuous coronary sinus thermodilution cannot be used for an indirect identification of the site of myocardial infarction.

Other techniques employed for the measurement of CSBF are CS myocardial clearance technique (Fick), positron emission tomography, MRI, radionuclide imaging, and recently TEE. It is noteworthy that all of these techniques are invasive or expensive.

The koskenvuo JW study demonstrated that the global myocardial blood flow and global flow reserve measurements via MRI and PET were comparable.

Bates et al., having used a digital radiographic technique during cardiac catheterization to measure the coronary flow before and after revascularization, demonstrate an elevated homodynamic state, which implied an increased coronary blood flow.

Toyota S and Amaki V were able to measure the CS flow velocity using pulse-Doppler TEE during coronary artery bypass graft (CABG) surgery. The peak velocity and VTI of CSBF in the post–cardiopulmonary bypass period increased significantly compared with those in the pre-cardiopulmonary bypass period. The results of this preliminary study showed the feasibility of a clinical evaluation of CABG intraoperatively. Siostrzonek P showed a strong association between CSBF measured with TEE and coronary sinus catheterism.

Using xenon-133 scintigraphy, Goldman et al. measured the blood flow before and after bypass surgery involving the left anterior descending vessels and found that the blood flow normalized after CABG, with the blood flow at rest in the bypassed arteries being very similar to that measured in normal coronary vessels. Chatterjee K et al. showed that, in patients with aortocoronary bypass surgery, CSBF was higher after surgery than it was before surgery. More recently, Crone-Munzebrocke et al. conducted thallium-201 scintigraphic studies of myocardial perfusion scanning before and after CABG. They found that thallium-201 uptake and washout in thallium-201 scintigraphy improved after CABG and that CSBF during pacing improved after CABG. By using the non-invasive method of measuring CSBF via TTE, Daniel Wing Chong et al. were able to show a
statistically significant increase in the coronary artery flow after revascularization procedures, a finding previously established by invasive studies.

There is no information in the existing medical literature on the use of TTE for the measurement of CSBF in AMI patients. The present study, having utilized this non-invasive method, found a statistically significant decrease in the coronary artery flow after AMI, a finding that has thus far been observed only through invasive studies. Our data showed a decrease in CSBF in the AMI group. In general, the decrease in CSBF was not related to the initial flow and was within the range of 100 to 200 ml/min.

Moreover, CSBF had a good correlation with LVEF, WMSI, and in-hospital mortality.

The limitation of this study was the inability to compare the measured data with those of an invasive technique. Nonetheless, our results correlated well with those invasive studies by demonstrating a decrease in CSBF after AMI.

**Conclusion**

The findings of the present study revealed that TTE can be used to measure CSBF in AMI patients. This clinically important finding, in accordance with previous invasive studies, suggests that TTE can be applied as a non-invasive modality to monitor changes in CSBF and to determine coronary perfusion in MI patients.

**Acknowledgement**

This study was supported by the Research Deputy of Tabriz University of Medical Sciences. Thanks are due to the research authorities of the university and Mrs. Nikbakht for her help with typing and editing this article. This study was approved by the institutional review board of Tabriz University of Medical Sciences.

**Reference**

Clinical and Angiographic Characteristics of Myocardial Bridges: a Descriptive Report of 19 Cases and Follow-up Outcomes

Sirus Darabian, MD*, Alireza Amirzadegan, MD, Hakimeh Sadeghian, MD, Saeed Sadeghian, MD, Maria Raissi Dehkordi, MD, Hamidreza Goodarzynejad, MD

Tehran Heart Center, Medical Sciences / University of Tehran, Tehran, Iran

Received 16 December 2006; Accepted 13 March 2007

Abstract

**Background:** Muscle fibers overlying the intramyocardial segment of an epicardial coronary artery are termed myocardial bridge (MB). The aim of this study was to analyze the mid-term outcome of MB and to examine its possible association with angiographic findings and concomitant cardiac pathologies such as hypertrophic cardiomyopathy (HCM).

**Methods:** From a total of 3218 patients admitted for coronary angiography during 9 consecutive months, 28 (0.9%) were diagnosed with MBs with stenoses≥50%. Of these, 19 referred for follow-up with a median duration of 18 months.

**Results:** HCM was present in 5 patients (26.3%), of whom 4 had MB as the sole finding in angiography. Of the 19 patients, 14 had diastolic dysfunction. In follow-up, 2 patients were treated with revascularization strategies due to the concomitant coronary artery disease and in 2, syncope occurred. For two patients, an intra-cardiac device and a permanent pacemaker were implanted. Three patients with MB as the sole finding in angiography were readmitted because of chest pain.

**Conclusion:** Diastolic dysfunction may contribute to the presentation of symptoms of muscle bridging. Also, myocardial bridging as the only finding in coronary angiography is highly associated with hypertrophic cardiomyopathy and may help to detect this group of patients. The mid-term outcome of myocardial bridges is favorable.

Keywords: Myocardial infarction • Coronary artery disease • Hypertrophic cardiomyopathy

Introduction

Muscle overlying the intramyocardial segment of an epicardial coronary artery, first mentioned in 1737 and described angiographically in 1960 is termed a myocardial bridge (MB). This situation is characterized by the decrease in the coronary blood flow during systole due to the compression of the myocardial fibrils surrounding the epicardial coronary artery in a certain segment. Autopsy studies have found a frequency of 15 to 85 percent, while angiographic studies have noted a lower incidence of myocardial bridging ranging from 0.5 to 33 percent. It has been suggested that bridging rarely causes myocardial ischemia and this could partly explain such discrepancies. On the other hand, the wide variability in the incidence of different anatomicopathological series seems to depend on the skill of the operators performing the
Several diseases have been reported concomitantly with myocardial bridges. For instance, previous literature has shown the incidence of myocardial bridging to be 28 to 40 percent in children with hypertrophic cardiomyopathy (HCM).\textsuperscript{11,12} The presence of MB has also been known as an important cause of myocardial ischemia in HCM.\textsuperscript{13,14}

This study was designed to analyze the mid-term outcomes of patients with myocardial bridges in a series of 19 cases and to describe the possible association between myocardial bridge, demographic and angiographic findings, and concomitant diseases like hypertrophic cardiomyopathy.

Methods

The study population was selected from among a total of 3218 patients with suspected coronary artery disease (CAD) admitted to Tehran Heart Center for coronary angiography between July 2004 and February 2005. Coronary compression was defined as a maximum systolic compression $\geq$50%. In this population, 28 patients had systolic compression $\geq$50%, from whom only 19 referred for follow-up. The remaining 9 patients were missed because of geographic diversity and/or residential change, and inaccessibility of their new addresses. Hence, this study population included 19 patients. All angiograms were assessed by two independent reviewers unaware of the patients’ clinical status. In cases of controversy, the opinion of a third cardiologist was sought. Left ventricular ejection fraction (LVEF) was measured by the quantitative two dimensional (biplane Simpson) method. Patients were defined as having systolic dysfunction if their LVEF was 50%. Patients with an LVEF$>$50% were further examined for diastolic dysfunction. Each of these patients underwent pulsed wave Doppler examination of mitral inflow before and during the Valsalva maneuver. Diastolic dysfunction was categorized according to the progression of diastolic dysfunction as normal; mild (grade 1), defined as impaired relaxation without evidence of increased filling pressures; moderate (grade 2), defined as impaired relaxation associated with moderately increased filling pressures or pseudonormal filling; and severe (grades 3 and 4), defined as reversible restrictive or fixed restrictive patterns.\textsuperscript{15} The HCM cases were confirmed by two cardiologists according to the clinical, electrocardiographic, and echocardiographic evidence, and reconfirmed by a third cardiologist in controversial cases. A cardiologist performed repeated echocardiography and completed the follow-up questionnaires in the 18-month follow-up duration. Results of exercise thallium scintigraphy were evaluated when available, and images were analyzed qualitatively in the anterior, apical, inferior, septal, and lateral regions. Holter recordings were analyzed for the detection of ventricular tachycardia. Problems in follow-up included readmission, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), syncope, and death. Informed consent was obtained from all the patients before enrollment into this study. The procedures followed were in accordance with ethical standards of the Tehran Heart Center Ethics Committee.

Results

Demographic findings

Selective demographic and clinical characteristics are shown in Tables 1 and 2. Of the 19 patients with angiograms judged adequate for the diagnosis of myocardial bridging, 18 were male and 1 was female. The mean age$\pm$standard deviation was 52.6$\pm$12.7 years (range: 28-72 years). As shown in Table 1, two patients had diabetes mellitus, 7 had systemic hypertension, 9 had hyperlipidemia, 3 had family history of sudden cardiac death, and 5 were active smokers at the time when coronary angiography was performed. Symptoms at presentation included stable angina in 7, unstable angina in 6, 2 anterior and 1 inferior myocardial infarction (MI) in 3, palpitation in 1, and syncope in 2. The indications for coronary angiography were: positive exercise tolerance test in 6, MI in 2, positive perfusion scans in 3, syncope in 2, and high clinical suspicion for CAD in the remaining 6. In 5 of these cases (26.3%), HCM was present. From among 11 patients who had myocardial bridging as the sole finding in coronary angiography (without HCM or significant CAD), 5 had presented with stable angina, 5 with unstable angina, and 1 with anterior MI. In this population, no one had presented with syncope or palpitation.

Echocardiographic, scintigraphic, and angiographic findings

All the myocardial bridges were detected in the mid portion of the LAD. Table 2 shows that out of the 19 patients, 8 had left ventricular hypertrophy and 14 had diastolic dysfunction. Myocardial perfusion scan was performed for 3 patients, which showed inferior ischemia in all of them. No reverse redistribution was detected. Two of these patients had presented with chest pain and one with syncope. In all of these patients, myocardial bridge was the only angiographic finding. All of these patients had diastolic dysfunction, and the length of MB fragment in them was 20-25 mm. The lengths of myocardial bridges in the total population were less than 10 mm in one, 10-20 mm in 13, and above 20 mm in the remaining 5 patients. The severity of systolic compression was about 50% in 9, over 50% to 70% in 6, 70%-90% in 3 patients, and over 90% in 1 patient. One of the patients had left main tract involvement. In 3 patients, the left circumflex artery was dominant. In one case, there was co-dominance; and in the remaining cases, the right coronary artery was
dominant. In all of the cases with myocardial bridge, the mid-portion of LAD was affected.

Table 1. Demographic characteristics (n=19)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52.6±12.7</td>
</tr>
<tr>
<td>Male</td>
<td>18 (94.7%)</td>
</tr>
<tr>
<td>Hypertension (mm Hg)</td>
<td>9 (47.4%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (36.8%)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Family history of sudden cardiac death</td>
<td>3 (15.8%)</td>
</tr>
</tbody>
</table>

*Mean±standard deviation

Table 2. Clinical and angiographic characteristics (n=19)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular hypertrophy</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>14 (73.7%)</td>
</tr>
<tr>
<td>Dominancy</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>15 (78.9%)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Vessel involvement</td>
<td></td>
</tr>
<tr>
<td>Myocardial bridge</td>
<td>14 (73.7%)</td>
</tr>
<tr>
<td>Myocardial bridge + 1-vessel disease</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Myocardial bridge + 2-vessel disease</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>60±2±5.9</td>
</tr>
<tr>
<td>Severity of MB stenosis (%)</td>
<td>60±14.5</td>
</tr>
<tr>
<td>Length of MB (mm)</td>
<td>19.6±4.9</td>
</tr>
</tbody>
</table>

*Mean±standard deviation

MB, Myocardial bridging

**Follow-up data**

The median follow-up duration was 18 months (range: 12-23 months). In the follow-up period, one patient underwent CABG, another one was treated with PCI based on angiographic results, and in 2 patients syncope occurred. The causes for syncope were transient complete heart block and ventricular tachycardia with underlying hypertrophic cardiomyopathy. Four patients were readmitted because of chest pain. In two patients, an implantable cardioverter defibrillator (ICD) and permanent pacemaker (PPM) were implanted. All the patients received beta-blockers, and some patients took diltiazem as well. All of the 11 cases without HCM or CAD were followed by medical therapy.

**Discussion**

Our study is a descriptive report of baseline and angiographic characteristics in a series of 19 patients who had been diagnosed with myocardial bridging. The angiographic appearance of myocardial bridges depends on several factors, including the length of myocardial bridge.16 The use of provocation tests may enhance systolic myocardial compression and thereby reveal myocardial bridges in 40% of cases.17 In this study, the lengths of myocardial bridges were between 10 and 25 mm, which were within the typical range.16 Moreover, like the Lozano’s study,18 intracoronary nitroglycerine was not administered systematically, except when a possible reduction in the vessel diameter was detected at some point in the coronary tree. On the other hand, we only included myocardial bridges with at least 50% stenosis. These factors may account for the relatively low prevalence of myocardial bridging in our study population (0.9%) compared to other studies.

In our study, the segment that was affected was only the mid-portion of the LAD, although some cases have been found in other coronary segments.19,20 It has been reported that the compressed segment is frequently spared from atherosclerotic changes.2,3 Interestingly, we found atherosclerotic plaques neither in the territory of the bridge nor in the distal LAD.

The latter finding is consistent with a previous report.21 One of the striking results was that diastolic dysfunction presented in as much as 73.7% of our study population. Normally, only 15% of the coronary blood flow occurs during systole, and because myocardial bridging is a systolic event on angiography, its clinical significance and relevance have been questioned.22 It has been proposed that although arterial compression takes place during systole, there is also inadequate coronary flow in the first third of diastole, probably leading to a decreased reserve of coronary flow and lower-than-normal ischemia threshold.23 However, this flow reserve is sufficient in baseline situations and ischemia is only manifested in situations like increased oxygen demand.24,25 Our finding may be of particular importance, suggesting that in addition to these high-oxygen demanding situations, diastolic dysfunction may also play a role in making the patients symptomatic. Diastolic dysfunction may predispose patients to symptomatic myocardial bridging through the following mechanisms: First, if relaxation is excessively slow, it can elevate not only early but also late diastolic pressures, particularly at faster heart rates such as during exercise;26 as left ventricular pressure increases in diastolic dysfunction, the myocardial perfusion pressure drops. Second, because of the delay in myocardial relaxation, a part of the compression produced in the early diastole persists through the whole diastole27 and causes further reduction in the blood flow to the myocardium; Furthermore, after a vessel is compressed during systole, it is refilled with blood during diastole, and the intra-luminal volume of the vessel is increased. This refilling causes a delay in the blood flow during diastole; hence myocardial perfusion further decreases. The longer the duration of decompression during diastole is, the clearer the effect of this delay will be. This may be a reason why myocardial bridging, albeit a congenital condition, becomes symptomatic in adults. This is contrary to the fact that in
lower ages, the heart beats faster than the adults, and the time that the heart remains in systole is longer. According to some authors, the presence of tachycardia could unmask the ischemic effect of a myocardial bridge by decreasing the diastolic filling time and coronary flow reserve and increasing the importance of systolic blood flow. For all these reasons, it is hypothesized that some additional factors such as diastolic dysfunction may contribute to the adverse outcomes of systolic compression.

The relationship between the degree of systolic compression and the clinical symptoms has been debated in many previous studies, either showing the presence of an association or no association. In our study, the degree of systolic compression was between 50 and 90 percent. We did not find any correlation between the degree of vessel compression and the presenting symptoms. However, this may be partly due to the small sample size.

In our study, out of the 11 patients who had only myocardial bridging in coronary angiography, 5 had stable angina, 5 had unstable angina, and 1 presented with MI. Other studies have reported stable or unstable angina as frequent, and myocardial infarction, ventricular tachyarrhythmia, and cardiac death as infrequent clinical presentations. Be that as it may, considering the prevalence of myocardial bridging, these complications are rare.

Therapy in symptomatic patients, may improve quality of life, although hard evidence for a favorable effect on morbidity and mortality is missing. Three treatment strategies have been explored: (1) negative inotropic and/or negative chronotropic agents, like beta-blockers and calcium antagonists; (2) surgical myotomy and/or CABG and (3) stenting of the tunneled segment. In our study, all the patients were medically treated with beta-blockers, and in some cases, with diltiazem. Only one of our patients, who had concomitant coronary artery disease, underwent surgical un-roofing. This patient had severe systolic compression with signs refractory to medical treatment, which is an indication for surgical intervention, according to some previous Reports. Some authors have shown improved prognosis with the surgical division of the bridge with low operative risks and excellent mid-term results.

Conflicting observations have been reported on the prognosis of myocardial bridges. Some reports have shown an excellent long-term prognosis with angiographically detected, isolated bridges. Overall, long-term prognosis in patients with isolated myocardial bridging is generally good. In two studies on the long-term outcomes, no myocardial bridge-related MI or death was reported in patients with otherwise normal coronary arteries. In the latter study, among 21 patients monitored for 3.4 years, two patients with coexistent CAD experienced MI infarction and underwent CABG. All the other patients, including 7 with HCM and 8 with normal coronaries remained event-free. In our study, CABG and PCI were performed for 2 patients, as recommended by coronary angiography and the established coronary artery disease. Two patients experienced syncope at follow-up, and 4 of them were readmitted, of whom, one had HCM. Two other patients with HCM developed syncope at follow-up, for whom ICD and PPM were implanted. We observed that three patients with myocardial bridging as the only finding were readmitted to the hospital. This could show that the events at follow-up could be more correlated with the severity of concomitant vessel involvement and/or HCM rather than the presence of myocardial bridge, suggesting that myocardial bridges may have excellent mid-term outcomes.

Myocardial bridging is most often considered to be a congenital anomaly, and concomitant cardiac pathologies, such as hypertrophic cardiomyopathy, have also been reported. In our study population, 5 patients (26.4%) had HCM with an age range of 44-55 years old. In 4 of them, we found myocardial bridging as the sole underlying coronary finding. Indeed, myocardial ischemia is an important aspect of the pathophysiology for HCM patients, but significant coronary artery stenosis is rarely noted. This may be an important finding, as it has been shown that adverse cardiac events such as sudden death, ventricular tachycardia, and impaired exercise test may occur as a result of myocardial bridging in cases with HCM. HCM in many instances is present as a genetic mutation, and may remain clinically undiagnosed. A study on the genetic mutations in myocardial bridging may lead to the identification of genotypes of HCM.

The results of this study need to be confirmed by further studies with larger study populations. Moreover, as this study was performed retrospectively, it was not possible to match the patients in the angiographic performance and medical options. This problem can influence the identification and selection of patients and also the results of follow-up. Finally, we did not use intravenous nitroglycerine. This may have caused us to miss possible, but infrequent, cases of myocardial bridges in the distal parts.

**Conclusion**

In our setting, the frequency of myocardial bridging, although low, was within the general range. We detected a high percentage of cases of diastolic dysfunction in these patients, and hypothesized that this factor may contribute to the presentation of symptoms in this condition. Also, the possibility of a high correlation between myocardial bridging and presentation of symptoms in hypertrophic cardiomyopathy is suggested.

**Acknowledgement**

This study was supported by Tehran Heart Center, Tehran University of Medical Sciences. The authors declare that
they do not have any conflicts of interests.

References

43. Harikrishnan S, Sunder KR, Tharakan J, Titus T, Bhat A, Sivasankaran S, Bimal F. Clinical and angiographic profile and

Abstract

Myocardial free wall rupture is a catastrophic complication of acute myocardial infarction, and prognosis will depend on the prompt diagnosis by echocardiography, extension of infarct size, and prompt surgical treatment. Free wall rupture concomitant with ventricular septal defect (VSD) may be more complicated for management. A case of a 69-year-old man with myocardial free wall rupture and VSD following acute anterior myocardial infarction is presented.

Keywords: Ventricular septal defect • Myocardial free wall rupture • Myocardial infarction

Introduction

Myocardial free wall rupture is the second most common cause of in-hospital mortality among patients with an acute myocardial infarction; and based upon several large studies, it accounts for 7-17% of all deaths.12 Free wall rupture may present with a constellation of symptoms that, if recognized early and diagnosed accurately, may allow for emergent successful treatment. These include chest pain, hypotension, nausea, vomiting, agitation, and signs of increased adrenergic drive. Autopsy studies suggest that a subset of free wall ruptures, up to 40%, follow a sub acute course.3 Numerous pathologic observations have confirmed that rupture is an ongoing stuttering process characterized by progressive tears and hemorrhage into the pericardial space, which may seal itself with an overlying clot or with the formation of a pseudoaneurysm.4 Ventricular septal defect (VSD) is a rare and serious complication. The incidence is 1-2% of all myocardial infarctions.5

Case report

A 69-year-old man with a history of hypertension, diabetes mellitus, and acute renal failure with creatinine=3.1 mg/dl was admitted in our hospital with an acute anterior myocardial infarction. His electrocardiogram showed Q wave, elevation of ST segments, terminal T invert in the leads V1 through V6, and a rise in serum levels of the myocardial specific isoenzyme of creatine kinase and of troponine.

Transthoracic echocardiography (TTE) suggested: normal left ventricular (LV) size; concentric left ventricular hypertrophy (LVH); evidence of myocardial infarction in 6 segments in the left anterior descending artery (LAD) territory: relatively thin with akinesia of apical segments, anteroseptal mid portion, and septal mid portion with aneurismal formation in septal apical and inferoapical; large immobile LV apical clot; global left ventricular ejection fraction (LVEF) about 30%; a large ventricular septal defect (VSD) (Figure 1) in septal apical with peak systolic gradient.
about 52 mmHg; and severe pericardial effusion up to 30 mm around right ventricular (RV) and up to 15 mm around left ventricular (LV) with right atrium (RA) and right ventricular (RV) collapse. Color Doppler showed evidence of active flow into the pericardium and rupture of septal apical into the pericardium. Flow within the pericardium was non turbulent (Figure 2), but in the site of rupture of septal apical to pericardium, there was a turbulent flow (Figure 3).

Also, there was mild tricuspid valve regurgitation (TR), estimated pulmonary artery pressure (PAP)=42 mmHg, and mild RV enlargement with mild RV systolic dysfunction. Cardiac catheterization showed three-vessel coronary artery disease with an ejection fraction of 30%.

Because of hemodynamical instability, intra-aortic balloon pump (IABP) was used before surgery. The patient underwent surgery for repair of VSD and myocardial free wall rupture concomitant with coronary artery bypass grafting (CABG). At surgery, blood was present in the pericardium, and a localized rupture site in the anterolateral wall of LV was conceded. When the rupture of LV was opened, large apical and mid septal VSD was seen, and necrosis had progressed close to the base of the heart. The surgical procedure included ventriculotomy throughout necrotic and ruptured LV, debridement of necrotic free wall and septum, extensive septal patch with cortex 0.6, and closure of LV by Teflon felt and prolene. Because of the necrosis of the LAD artery, we did not use the left internal mammary artery (LIMA) for grafting. CABG with two saphenous vein bypass grafts was performed. Postoperative echocardiography findings were: LVEF=35%, no myocardial rupture or VSD, mild pericardial effusion, and mild TR and PAP= 24 mmHg.

About 4 weeks after surgery, the patient was discharged uneventfully.

Discussion

Free wall rupture complicates 4-6% of all infarctions. It is the most common cause of hemopericardium, exceeding even that of aortic dissection.3,7 With advances in echocardiography, it is possible to diagnose free wall rupture prior to the development of tamponade and hemodynamic collapse. The absence of pulse and heart sounds despite normal rhythm on the electrocardiogram suggests that cardiac rupture after acute myocardial infarction produces tamponade and electromechanical dissociation. Two-dimensional echocardiography is the most sensitive and expeditious test for the diagnosis of cardiac rupture, as demonstrated from numerous studies. The most common findings of rupture on echocardiography are that of a pericardial effusion and layered echogenic pericardial thrombus.8,9 Finding regional dilatation and an abnormally thin myocardium with akinesis, which may indicate infarct expansion, increases the specificity.

Lopez-Seadan et al. prospectively looked at the sensitivity and specificity of echocardiography and found that echocardiograms were 100% sensitive, as all patients with rupture had at least a 5-mm pericardial effusion during diastole and 97% had evidence of an intrapericardial thrombus.10

The incidence of ventricular septal rupture following a myocardial infarct is approximately 1%.11 Clinical features associated with an increased risk of rupture of the interventricular septum include lack of development of a
collateral network, advanced age, hypertension, anterior location of infarction, and possibly Thrombolysis. The timing of the rupture varies between several hours and several weeks following the infarct. The site of rupture depends on the coronary anatomy and the infracted vessel. Two large studies have reported that concomitant CABG is beneficial. First, Muehrcke et al. found that patients who had coronary artery disease outside of the infracted region of myocardium fared significantly better, long term, if they were grafted. Cox et al. reported similar findings.

Management of hemodynamically unstable patients with a large septal rupture consists of inotropic support, left ventricular afterload reduction by medical therapy, as well as placement of an intra-aortic balloon pump. Urgent surgical closure of such VSDs is recommended. We presented one case of anterior MI complicated by both VSD and free wall rupture in which transthoracic echocardiography clearly assisted in the correct diagnosis.

Conclusion

Our patient had VSD concomitant with myocardial rupture post acute anterior MI. Echocardiography, which has already been proven to be the most effective diagnostic tool in the acute setting, led to the correct and immediate diagnosis of both lesions.

References

Coronary Artery Fistula with Double Outlet Right Ventricle: a Case Report

Yaser Jenab, MD1*, Ali Kazemi Khaledi, MD1, Hassan Ranjbarnejad, MD1, Arezu Zoroufian, MD2, Mahmood Shahzadi, MD1

1Imam Khomeini Hospital, Medical Sciences / University of Tehran, Tehran, Iran.
2Tehran Heart Center, Medical Sciences / University of Tehran, Tehran, Iran.

Received 15 November 2006; Accepted 10 March 2007

Abstract

The majority of coronary artery fistulas (CAFs) are congenital. The anomaly accounts for 0.4% of congenital heart defects and approximately 50% of pediatric coronary vasculature anomalies. Twenty percent of people with congenital CAFs have other concomitant cardiac anomalies, most frequently aortic and pulmonary atresia and patent ductus arteriosus. It is worthy of note that CAF with the tetralogy of Fallot has also been reported. Here we describe a patient with a double outlet right ventricle in association with a coronary artery fistula.

Keywords: Double outlet right ventricle • Coronary artery fistula • Tetralogy of Fallot

Introduction

Coronary artery fistula (CAF) is a rare, usually solitary, anomaly that accounts for approximately 0.4% of congenital heart defects. The majority of cases in the pediatric population are congenital in nature, while acquired fistulas are often iatrogenic as a result of coronary insult.1 There are some reported cases of congenital CAF in association with the tetralogy of Fallot (TOF)2-5 and some iatrogenic cases detected postoperatively in patients with TOF.

Case report

A 14-year-old girl was referred for cardiac surgery with a diagnosis of TOF. She had had central cyanosis and exertional dyspnea since birth and had not been able to walk since she was two years old. On examination, she was underdeveloped with central cyanosis, clubbing of fingers, and a squatting position. A right ventricular impulse and systolic thrill were palpable along the left sternal border. The second heart sound was single. Arterial oxygen saturation was about 55% on admission.

Transthoracic echocardiography showed a double outlet right ventricle (about 75% overriding of the aorta toward the right ventricle, lack of fibrous continuity between the posterior aortic valve leaflet and anterior mitral valve leaflet, and side-by-side position of aorta and pulmonary artery); large perimembranous ventricular septal defect; hypoplastic right ventricular outflow tract, pulmonary artery, and pulmonary artery branches; thickened pulmonary valve; small atrial septal defect; severe right ventricular enlargement.
and hypertrophy; and continuous flow and turbulancy in the ascending aorta toward the main pulmonary artery, which could be a fistular connection or aortopulmonary window. There was also a continuous flow and turbulancy between the descending aorta and left pulmonary artery, which could be a small patent ductus arteriosus or a collateral vessel. Catheterization showed atrial septal defect, large ventricular septal defect, severe subvalvular pulmonary stenosis in oximetric and pressure studies, and simultaneous opacification of both aorta and pulmonary artery in right ventricular injection. In addition, no patent ductus arteriosus was detected in aortography. In selective coronary angiography, a large fistula from the proximal left anterior descending to pulmonary artery was apparent (Figure 1).

Figure 1. Selective coronary angiography demonstrated ectatic coronary arteries and a large fistula from proximal of left anterior descending artery (LAD) to pulmonary artery

Discussion

CAF is a rare, usually solitary, anomaly that accounts for approximately 0.4% of congenital heart defects. The majority of cases in the pediatric population are congenital in nature, possibly arising from the persistence of sinusoidal–coronary arterial connection, while acquired fistulas are often iatrogenic because of coronary insult or the patient’s having undergone endomyocardial biopsies. Congenital fistulas most frequently arise from the right coronary artery system, and the great majority (~90%) exit into the right heart structures, including the vena cava, coronary sinus, or pulmonary arteries. \(^1\) Twenty percent of people with congenital CAF have other concomitant cardiac anomalies, most frequently aortic and pulmonary atresia and patent ductus arteriosus. \(^6\)

In this patient with a diagnosis of a double outlet right ventricle with a subaortic ventricular septal defect and subpulmonary stenosis, the clinical scenario and management algorithm were similar or identical to those of TOF. Coronary artery anomalies are encountered in up to 12% of patients with TOF. The most common variants include the left anterior descending arising form the right coronary artery or separately from the right sinus of Valsalva. Many of these variants result in a major coronary artery coursing anterior to the pulmonary outflow tract, which in turn complicates the ultimate surgical repair.

The recently acquired ability to repair TOF early in life, regardless of the coronary artery anatomy, has largely been the reason for many academic centers to no longer perform routine coronary artery angiography prior to surgery. \(^1\)

Catheterization and coronary angiography were performed in this patient to clarify the suspicious flow and turbulancy in the ascending aorta toward the pulmonary artery and the descending aorta toward the left pulmonary artery. Coronary angiography showed a CAF between the left anterior descending and pulmonary artery, which helped the patient by providing a left to right shunt.

In the existing literature, there are some reported cases of congenital CAFs with TOF, \(^2-5\) but no cases with a double outlet right ventricle have been reported. Therefore, this patient is the first reported case of CAF with a double outlet right ventricle. Surgery was performed with central shunting from the ascending aorta to the pulmonary artery because a corrective surgery was impossible due to the patient’s hypoplastic pulmonary artery branches. The oxygen saturation increased from 55% to 78% after surgery.

Conclusion

This case was interesting because of association of double outlet right ventricle and coronary artery fistula. As in this case we should consider coronary artery fistula especially in patients with tetralogy of fallot or double outlet right ventricle both in echocardiography and catheterization.

References

Case Report

A Large Mobile Aortic Arch Mass

Mehrnoush Toufan, MD*, Farnaz Sepasi, MSc, Saba Asghari, MSc, Amirhosein Fathi, MSc

Tabriz Heart Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Received 20 December 2006; Accepted 26 February 2007

Abstract

Mobile luminal mass of aortic arch is an unusual finding in patients with peripheral embolization. To search the source of these emboli, aortic arch mass should be considered. To our knowledge, transesophageal echocardiography (TEE) can be a useful modality to demonstrate the nature and exact location of the mass. This report is illustrative of a large mobile aortic arch mass, histologically thrombus, found by TEE in a 48-year-old woman with embolic symptoms.

Keywords: Aortic arch mass • Thrombus • Transesophageal echocardiography

Introduction

Mobile luminal mass of aortic arch is an unusual finding in patients with peripheral embolization, as in this case, emboli to liver, spleen, kidney and lower extremities. Herein we report a mobile aortic arch mass found by transesophageal echocardiography (TEE) in a 48-year-old woman with embolic symptoms. A pathologic examination of the specimen after surgery revealed thrombus.

Case Report

A 48-year-old woman was referred from the rheumatology ward to our heart center. Her Chief Complaint was: claudication and lower extremity pain that had become worse during the past 3 weeks.

On physical examination, lungs and heart were normal. There were no palpable lymph nodes in the neck. No organomegally was found. There were no skin lesions, but discoloration of the lower extremity skin in favour of arterial ischemia was detected. All radial, brachial, femoral, popliteal, dorsalis pedis, and tibiialis posterior pulses were diminished. Radial and brachial pulses were normally palpated after heparinization.

Lab tests revealed: ESR=93, CRP=2+, and Creatinine=2.1 mg/dl. Protein C, Protein S, and Anti thrombin III were not checked. Liver function test had increased. Other lab findings are shown in Table 1.

Table 1. Laboratory results

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR 1st hour</td>
<td>93</td>
<td>0-20 mm/hr</td>
</tr>
<tr>
<td>ESR 2nd hour</td>
<td>120</td>
<td>0-30 mm/hr</td>
</tr>
<tr>
<td>CRP</td>
<td>2+</td>
<td>Neg</td>
</tr>
<tr>
<td>Ct</td>
<td>2.1</td>
<td>0.6-1.3 mg/dl</td>
</tr>
<tr>
<td>ALT</td>
<td>98</td>
<td>5-40 mg/dl</td>
</tr>
<tr>
<td>AST</td>
<td>183</td>
<td>5-40 mg/dl</td>
</tr>
<tr>
<td>BUN</td>
<td>40</td>
<td>7-20 mg/dl</td>
</tr>
<tr>
<td>ANA</td>
<td>Neg</td>
<td>Neg&lt;1:40</td>
</tr>
<tr>
<td>RF</td>
<td>Neg</td>
<td>Neg&lt;1:80 or 60 u/ml</td>
</tr>
</tbody>
</table>

ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; Ct, Creatinine, ALT, Alanine aminotransferase, AST, Asparate aminotransferase, BUN, Blood urea nitrogen; ANA, Anti nuclear antibody; RF, Rheumatoid factor

*Corresponding Author: Mehrnoush Toufan, Assistant Professor of Cardiology, Heart Research Center, Tabriz University of Medical Sciences. Golgasht St. Attar Neishaboori Ave, Tabriz, Iran. Tel: +98 914 311 12 84. Fax: +98 411 669 52 04. E-mail: m_toufan@yahoo.com.
Chest X-ray showed normal heart and lungs. Doppler ultrasonography studies showed 70% occlusion of the Tibioproneal artery with filling defect, and decreased flow of anterior and posterior tibioproneal in both lower extremities. Over the next few days, the patient underwent a CT angiography, which identified the occlusion of the aortic arch. CT angiogram also demonstrated emboli in the liver, spleen, left kidney, and extremities.

To search for a possible embolic source a TEE was done. The echogram showed no evidence of valvular vegetations, with normal chamber size. Ejection fraction (EF) was 45-50%. TEE revealed a large mobile irregular nonhemogeneous mass attached to the wall of the intraluminal aortic arch with a narrow stalk (attachment site: lesser curve of aortic arch), and no intimal thickening, no flap, no arteritis, and no plaque were found (Figure 1).

Surgical removal of the mass was considered urgently, so the patient was taken to the operating room for direct surgical mass removal. The resected mass from the aortic arch was 7 cm in length and 1.5 cm in width. Postoperative TEE showed no mobile mass in the ascending aorta and aortic arch, while EF was the same. The patient responded positively to receiving systemic heparinization. Histologically, sections from the received specimen disclosed only blood clot.

After this procedure, the patient continued to improve and was discharged home on warfarin therapy.

**Discussion**

Use of TEE has greatly improved the visualization of lesions involving the thoracic aorta and aortic arch. Choukroum et al. reported 9 cases with embolic thoracic aorta thrombi diagnosed by TEE. Klocker et al. suggested the association of mobile thoracic aorta debris and blue toe syndrome. These studies suggest a definite risk of peripheral embolization associated with mobile aortic thrombi. It seems that TEE is the most reliable method for the detection of mobile aortic thrombi.

Correlations of TEE and pathologic findings of operative specimens confirm that mobile aortic debris is formed by thrombus with associated atherosclerotic plaques. But in the present study, no intimal thickening, no arteritis, and no plaque were found. The appearance of the mass was atypical from what has previously described as atherosclerotic plaque. It was a highly mobile mass in front of the blood jet.

**Conclusion**

We should pay attention to the cases with multiple peripheral embolic symptoms. Aortic thrombus with embolic potential should be considered. To our knowledge, TEE can be a useful and valuable diagnostic modality, to demonstrate the nature and exact location of the mass.

We reported a case where an aortic mass was without mural atherosclerotic plaque diagnosed by TEE. The mass could be a source for embolization. Microscopic study of the resected mass revealed a blood clot.

**References**

# International Cardiovascular Surgery Meetings Calendar (2007-2008)

<table>
<thead>
<tr>
<th>Congress</th>
<th>Time-Location</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore LIVE 2007 (16th Annual Live Interventions in Vascular Endotherapy)</td>
<td>January 22-24, 2007, Singapore</td>
<td>Email: <a href="mailto:contact@singlivecourse.com">contact@singlivecourse.com</a> Website: <a href="http://www.singlivecourse.com/">http://www.singlivecourse.com/</a></td>
</tr>
<tr>
<td>43rd Annual Meeting of The Society of Thoracic Surgeons (STS)</td>
<td>January 29 – 31, 2007, San Diego, California, USA</td>
<td>Email: <a href="mailto:sts@sts.org">sts@sts.org</a> Website: <a href="http://www.sts.org/">http://www.sts.org/</a></td>
</tr>
<tr>
<td>7th Indian Society of Extra-Corporeal Technology (ISECT CON 2007)</td>
<td>February 9 – 10, 2007, Jaipur, Rajasthan, India</td>
<td>Tel: 91 0935 135 2897 Email: <a href="mailto:info@ctcon2007.com">info@ctcon2007.com</a></td>
</tr>
<tr>
<td>37th Annual Meeting of the Japanese Society for Cardiovascular Surgery (JSCVS)</td>
<td>February 21 – 23, 2007, Tokyo, Japan</td>
<td>Email: <a href="mailto:JSCVS37@hij.twmu.ac.jp">JSCVS37@hij.twmu.ac.jp</a> Website: jscvs37.umin.jp</td>
</tr>
<tr>
<td>25th International Cardiovascular Surgical Symposium Annual Meeting</td>
<td>March 3–10, 2007, Zürs, Arlberg, Austria</td>
<td>Email: <a href="mailto:congress@herzchirurgie.at">congress@herzchirurgie.at</a> Website: <a href="http://www.asian-annals.org/">http://www.asian-annals.org/</a> general/www.surgery-zur.at</td>
</tr>
<tr>
<td>71st Annual Scientific Meeting of the Japanese Circulation Society</td>
<td>March 15 – 17, 2007, Kobe, Japan</td>
<td>Email: <a href="mailto:71junkan@congre.co.jp">71junkan@congre.co.jp</a> Website: <a href="http://www.congre.co.jp/jcs71">www.congre.co.jp/jcs71</a></td>
</tr>
<tr>
<td>CREF 27 - The San Diego Cardiothoracic Surgery Symposium: Science and Techniques of Perfusion</td>
<td>March 15 – 18, 2007, San Diego, California, USA</td>
<td>Email: <a href="mailto:info2007@amainc.com">info2007@amainc.com</a> Website: <a href="http://www.amainc.com/">http://www.amainc.com/</a></td>
</tr>
<tr>
<td>Congress</td>
<td>Time-Location</td>
<td>Address</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>----------------------------------------------</td>
</tr>
</tbody>
</table>
| First Annual Florida Valve Symposium — Current Controversies in Valve Management | March 28–30, 2007, St. Petersburg, Florida, USA | Email: siestavc@aol.com  
Website: http://www.floridavalvesymposium.com/ |
| Valves in the Heart of the Big Apple: Evaluation Management of Vascular Disease 2007 | April 12–14, 2007, New York, USA | Email: info@heartvalvesocietyofamerica.org  
Website: http://www.heartvalvesocietyofamerica.org/ |
| 5th Vienna Interdisciplinary Symposium on Aortic Repair (VISAR) | April 19–21, 2007, Vienna, Austria | Email: visar@eurocongress.org  
Website: http://www.eurocongress.org/ |
| 27th Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation (ISHLIT) | April 25–28, 2007, San Francisco, California, USA | Email: meeting@ishlt.org  
Website: http://www.ishlt.org/ |
| 1st Meeting of the World Society for Pediatric and Congenital Heart Surgery | May 3–4, 2007, Washington, DC, USA | Email: contacts@wspchs.org  
Website: http://www.wspchs.org/ |
| 87th Annual Meeting of the American Association for Thoracic Surgery (AATS) | May 6–9, 2007, Washington, D.C., USA | Email: aats@prri.com  
Website: http://www.aats.org/ |
| 15th Annual Meeting of the Asian Society for Cardiovascular Surgery (ASCVS) | May 17–20, 2007, Beijing, China | Email: ASCVS2007@cma.org.cn  
Website: http://www.ascvs2007.com/ |
| Euro PCR — 2007 (The Paris Course on Revascularization) | May 22–25, 2007, Barcelona, Spain | Email: europa@europa-organisation.com  
Website: http://www.europa-organisation.com/ |
| 15th European Conference on General Thoracic Surgery (ESTS) | June 3–6, 2007, Leuven, Belgium | Email: sue@ests.org.uk  
Website: http://www.ests.org/ |
| 10th Annual Scientific Meeting of the International Society for Minimally Invasive Cardiothoracic Surgery (ISIMICS) | June 6–9, 2007, Rome, Italy | Email: ismics@prri.com  
Website: http://www.ismics.org/ |
| 12th European Congress on Extracorporeal Circulation Technology | June 6–9, 2007, Kyiv, Ukraine | Email: congress.fecct@reedbusiness.nl  
Website: http://www.fecct.org/ |
| 4th Biennial Meeting of the Society for Heart Valve Disease (SHVD) | June 15–18, 2007, New York, USA | Email: secretariat@shvd.org  
Website: w02-0566.web.dircon.net/biennial2007 |
| 7th International Congress on Complications during Coronary Intervention: Management and Prevention | June 20–22, 2007, Lausanne, Switzerland | Email: coronarycomplications@eurocongress.org  
Website: http://www.coronarycomplications.org/ |
| XXVth Meeting of the Society of Cardiac Surgeons | June 21–23, 2007, Pamplona, Navarra, Spain | Email: jherreros@unav.es  
Website: http://www.cardiasurgeons.ca/ |
<table>
<thead>
<tr>
<th>Congress</th>
<th>Time-Location</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>17th World Congress of the World Society of Cardio-Thoracic Surgeons (WSCTS)</td>
<td>July 11–13, 2007, Kyoto, Japan</td>
<td>Email: <a href="mailto:wscts2007@congre.co.jp">wscts2007@congre.co.jp</a> Website: <a href="http://www.wscts2007.com/">http://www.wscts2007.com/</a></td>
</tr>
<tr>
<td>21st Annual Meeting of the European Association for Cardio-Thoracic Surgeon (EACTS)</td>
<td>September 15–19, 2007, Geneva, Switzerland</td>
<td>Email: <a href="mailto:info@eacts.co.uk">info@eacts.co.uk</a> Website: <a href="http://www.eacts.org/">http://www.eacts.org/</a></td>
</tr>
<tr>
<td>19th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery (MACCS 2007)</td>
<td>September 27–30, 2007, Opatija, Croatia</td>
<td>Email: <a href="mailto:info@alphastudio.it">info@alphastudio.it</a> Website: <a href="http://www.maccs2007.org/">http://www.maccs2007.org/</a></td>
</tr>
<tr>
<td>7th International Congress on Coronary Artery Disease - From Prevention to Intervention</td>
<td>October 7–10, 2007, Venice, Italy</td>
<td>Email: <a href="mailto:coronary@kenes.com">coronary@kenes.com</a> Website: <a href="http://www.kenes.com/cad7">www.kenes.com/cad7</a></td>
</tr>
<tr>
<td>VIII Annual International Symposium on Advances in Understanding Aortic Diseases</td>
<td>October 13–14, 2007, Tokyo, Japan</td>
<td>Email: <a href="mailto:ctskyo-ikyoku@umin.ac.jp">ctskyo-ikyoku@umin.ac.jp</a></td>
</tr>
<tr>
<td>60th Annual Scientific Meeting of the Japanese Association for Thoracic Surgery (JPATS)</td>
<td>October 17 – 20, 2007, Sendai, Japan</td>
<td>Email: <a href="mailto:jats-adm@umin.ac.jp">jats-adm@umin.ac.jp</a> Website: <a href="http://www.asian-annals.org/general/jpats.org">http://www.asian-annals.org/general/jpats.org</a></td>
</tr>
<tr>
<td>Eighth Biennial Congress of the Syrian Cardiovascular Association</td>
<td>November 1-3, 2007 Damascus, Syria</td>
<td>E-mail: <a href="mailto:scva@scs-net.org">scva@scs-net.org</a> Tel/Fax: 00963 94 27 27 55</td>
</tr>
<tr>
<td>18th Biennial Congress of the Association of Thoracic &amp; Cardiovascular Surgeons of Asia (ATCSA)</td>
<td>November 25–28, 2007, Bali, Indonesia</td>
<td>Tel/Fax: 62 21 566 5993</td>
</tr>
<tr>
<td>ISMICS Winter Workshop 2007</td>
<td>November 28–December 2, 2007, Antalya, Turkey</td>
<td>Email: <a href="mailto:oztekinoto@oztekinoto.com">oztekinoto@oztekinoto.com</a></td>
</tr>
<tr>
<td>Pioneering Techniques in Cardiac Surgery, the Fifth in the Series</td>
<td>December 6–7, 2007, Leipzig, Germany</td>
<td>Email: <a href="mailto:blaeser@medizin.uni-leipzig.de">blaeser@medizin.uni-leipzig.de</a></td>
</tr>
<tr>
<td>38th Annual Meeting of the Japanese Society for Cardiovascular Surgery (JSCVS)</td>
<td>February 20–22, 2008, Fukuoka, Japan</td>
<td>Email: <a href="mailto:JSCVS38@med.kurume-u.ac.jp">JSCVS38@med.kurume-u.ac.jp</a> Website: square.umin.ac.jp/jsevs</td>
</tr>
<tr>
<td>16th Annual Meeting of the Asian Society for Cardiovascular Surgery</td>
<td>May 2–4, 2008, Singapore</td>
<td>Email: <a href="mailto:mice@themeetinglab.com">mice@themeetinglab.com</a> Website: <a href="http://www.ascvs2008.com/">http://www.ascvs2008.com/</a></td>
</tr>
<tr>
<td>Endoscopic &amp; Laparoscopic Surgeon of Asia 2008 (ELSA 2008)</td>
<td>September 2 – 6, 2008, Yokohama, Japan</td>
<td>Email: <a href="mailto:elsa2008@convention.co.jp">elsa2008@convention.co.jp</a> Website: www2.convention.co.jp/elsa2008</td>
</tr>
</tbody>
</table>
## International Cardiovascular Meeting And Congresses Calendar (2007-2008)

<table>
<thead>
<tr>
<th>Title</th>
<th>City</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>26th Annual Scientific Meeting of the Belgian Society of Cardiology</td>
<td>Belgium, Brussels</td>
<td>01 February 2007</td>
<td>03 February 2007</td>
</tr>
<tr>
<td>1st European Forum, Heart Exercise &amp; Prevention</td>
<td>France, Paris</td>
<td>02 February 2007</td>
<td>03 February 2007</td>
</tr>
<tr>
<td>34th Annual Congress of the Egyptian Society of Cardiology</td>
<td>Egypt, Cairo</td>
<td>20 February 2007</td>
<td>23 February 2007</td>
</tr>
<tr>
<td>Acute Coronary Syndromes: from Plaque to Imagery</td>
<td>Luxembourg</td>
<td>03 March 2007</td>
<td>03 March 2007</td>
</tr>
<tr>
<td>7th Annual Spring Meeting on Cardiovascular Nursing: “Changing Practice to Improve Care”</td>
<td>United Kingdom, Manchester</td>
<td>23 March 2007</td>
<td>24 March 2007</td>
</tr>
<tr>
<td>Title</td>
<td>City</td>
<td>Start Date</td>
<td>End Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>6th International Workshop on Interventional Pediatric Cardiology</td>
<td>Italy, San Donat Milanese (Milan)</td>
<td>28 March 2007</td>
<td>31 March 2007</td>
</tr>
<tr>
<td>The 3rd Local Annual Meeting of the Libyan Cardiac Society</td>
<td>Libyan Arab Jamahiriya, AL Baida</td>
<td>30 March 2007</td>
<td>01 April 2007</td>
</tr>
<tr>
<td>73nd Annual Meeting of the German Cardiac Society</td>
<td>Germany, Mannheim</td>
<td>12 April 2007</td>
<td>14 April 2007</td>
</tr>
<tr>
<td>8th International Congress of Cardiology and Cardiac Surgery</td>
<td>Lebanon, Beirut</td>
<td>18 April 2007</td>
<td>21 April 2007</td>
</tr>
<tr>
<td>XXVIII Annual Congress of the Portuguese Society of Cardiology</td>
<td>Portugal, Vilamoura</td>
<td>21 April 2007</td>
<td>25 April 2007</td>
</tr>
<tr>
<td>Spring Meeting of the Netherlands Society of Cardiology</td>
<td>Netherlands, Amsterdam</td>
<td>26 April 2007</td>
<td>27 April 2007</td>
</tr>
<tr>
<td>8th International Conference of Nuclear Cardiology - ICNC8</td>
<td>Czech Republic, Prague</td>
<td>29 April 2007</td>
<td>02 May 2007</td>
</tr>
<tr>
<td>Annual Meeting of the Norwegian Society of Cardiology (Spring Meeting)</td>
<td>Norway, Oslo</td>
<td>03 May 2007</td>
<td>05 May 2007</td>
</tr>
<tr>
<td>1st All Africa Conference on Heart Disease, Stroke and Diabetes</td>
<td>Kenya, Nairobi</td>
<td>13 May 2007</td>
<td>16 May 2007</td>
</tr>
<tr>
<td>IV Congress of Cardiologists and Angiologists</td>
<td>Bosnia and Herzegovina, Mostar</td>
<td>17 May 2007</td>
<td>19 May 2007</td>
</tr>
<tr>
<td>Annual Meeting of the Austrian Society of Cardiology “Jahrestagung 2007”</td>
<td>Austria, Salzburg</td>
<td>30 May 2007</td>
<td>02 June 2007</td>
</tr>
<tr>
<td>Annual Meeting of the Danish Society of Cardiology</td>
<td>Denmark, Nyborg</td>
<td>31 May 2007</td>
<td>02 June 2007</td>
</tr>
<tr>
<td>Title</td>
<td>City</td>
<td>Start Date</td>
<td>End Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>11th Danubian Forum of Cardiac Surgery</td>
<td>Romania, Timisora</td>
<td>01 June 2007</td>
<td>02 June 2007</td>
</tr>
<tr>
<td>Annual Meeting of the Estonian Society of Cardiology</td>
<td>Estonia, Tallinn</td>
<td>01 June 2007</td>
<td>02 June 2007</td>
</tr>
<tr>
<td>Annual Meeting of the Italian Association of Hospital Cardiologists (ANMCO)</td>
<td>Italy, Florence</td>
<td>03 June 2007</td>
<td>06 June 2007</td>
</tr>
<tr>
<td>Annual Scientific Conference of the British Cardiovascular Society</td>
<td>United Kingdom, Glasgow (Scotland)</td>
<td>04 June 2007</td>
<td>07 June 2007</td>
</tr>
<tr>
<td>Heart Failure 2007</td>
<td>Germany, Hamburg</td>
<td>09 June 2007</td>
<td>12 June 2007</td>
</tr>
<tr>
<td>76th Congress of the European Atherosclerosis Society</td>
<td>Finland, Helsinki</td>
<td>10 June 2007</td>
<td>13 June 2007</td>
</tr>
<tr>
<td>Annual Congress of the Swiss Society of Cardiology</td>
<td>Switzerland, Geneve</td>
<td>13 June 2007</td>
<td>15 June 2007</td>
</tr>
<tr>
<td>17th Scientific Meeting of the European Society of Hypertension</td>
<td>Italy, Milan</td>
<td>15 June 2007</td>
<td>19 June 2007</td>
</tr>
<tr>
<td>The 34th International Congress on Electrocardiology</td>
<td>Turkey, Istanbul</td>
<td>27 June 2007</td>
<td>30 June 2007</td>
</tr>
<tr>
<td>The Annual Interventional Cardiology Conference - CARDIOALEX</td>
<td>Egypt, Bibliotheca Alexandrina</td>
<td>27 June 2007</td>
<td>29 June 2007</td>
</tr>
<tr>
<td>World Heart Federation Teaching Seminar on CVD 2007</td>
<td>Norway, Sommarøy</td>
<td>20 August 2007</td>
<td>01 September 2007</td>
</tr>
<tr>
<td>ESC Congress 2007</td>
<td>Austria, Vienna</td>
<td>01 September 2007</td>
<td>05 September 2007</td>
</tr>
<tr>
<td>The 46th National Congress of Cardiology of the Romanian Society of Cardiology</td>
<td>Romania, Sinaia</td>
<td>15 September 2007</td>
<td>18 September 2007</td>
</tr>
<tr>
<td>XI International Congress of the Polish Cardiac Society</td>
<td>Poland, Wroclaw</td>
<td>20 September 2007</td>
<td>22 September 2007</td>
</tr>
<tr>
<td>Bleeding Complications in the treatment of Acute Coronary Syndrome</td>
<td>Sweden, Lund</td>
<td>03 October 2007</td>
<td>05 October 2007</td>
</tr>
<tr>
<td>XVI International Symposium on Drugs Affecting Lipid Metabolism</td>
<td>United States of America, New York</td>
<td>04 October 2007</td>
<td>07 October 2007</td>
</tr>
<tr>
<td>XII Congress of the Slovak Society of Cardiology</td>
<td>Slovak Republic, Bratislava</td>
<td>04 October 2007</td>
<td>06 October 2007</td>
</tr>
<tr>
<td>7th International Congress on Coronary Artery Disease - from Prevention to Intervention</td>
<td>Italy, Venice</td>
<td>07 October 2007</td>
<td>10 October 2006</td>
</tr>
<tr>
<td>Title</td>
<td>City</td>
<td>Start Date</td>
<td>End Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Venice Arrhythmias 2007 - Tenth International workshop on Cardiac Arrhythmias</td>
<td>Italy, Venice</td>
<td>07 October 2007</td>
<td>10 October 2007</td>
</tr>
<tr>
<td>Annual Autumn Meeting of the Finnish Cardiac Society</td>
<td>Finland, Helsinki</td>
<td>10 October 2007</td>
<td>12 October 2007</td>
</tr>
<tr>
<td>European Conference on Myocardial and Pericardial Diseases with focus on heart diseases in women</td>
<td>Germany, Marburg</td>
<td>11 October 2007</td>
<td>14 October 2007</td>
</tr>
<tr>
<td>Annual General Meeting of the Irish Cardiac Society</td>
<td>Ireland, Holywood (Co. Antrim)</td>
<td>11 October 2007</td>
<td>13 October 2007</td>
</tr>
<tr>
<td>Annual Meeting of the Spanish Society of Cardiology</td>
<td>Spain, Madrid</td>
<td>17 October 2007</td>
<td>20 October 2007</td>
</tr>
<tr>
<td>XXIII National Cardiology Congress of the Turkish Society of Cardiology</td>
<td>Turkey, Antalya</td>
<td>20 October 2007</td>
<td>23 October 2007</td>
</tr>
<tr>
<td>Autumn Meeting of the Netherlands Society of Cardiology</td>
<td>Netherlands, Ermelo</td>
<td>25 October 2007</td>
<td>27 October 2007</td>
</tr>
<tr>
<td>The 8th biennial meeting of the Syrian Cardiovascular Association</td>
<td>Syrian Arab Republic, Damascus</td>
<td>01 November 2007</td>
<td>03 November 2007</td>
</tr>
<tr>
<td>National Meeting of the Algerian Society of Cardiology</td>
<td>Algeria, Algiers</td>
<td>07 December 2007</td>
<td>09 December 2007</td>
</tr>
<tr>
<td>4th Asian Pacific Congress of Heart Failure</td>
<td>Australia, Melbourne</td>
<td>31 January 2008</td>
<td>03 February 2008</td>
</tr>
<tr>
<td>The 4th International Annual Meeting of the Libyan Cardiac Society</td>
<td>Libyan Arab Jamahiritya, Benghazi</td>
<td>21 March 2008</td>
<td>23 March 2008</td>
</tr>
<tr>
<td>XVI World Congress of Cardiology</td>
<td>Argentina, Buenos Aires</td>
<td>18 May 2008</td>
<td>21 May 2008</td>
</tr>
<tr>
<td>ESC Congress 2008</td>
<td>Germany, Munich</td>
<td>30 August 2008</td>
<td>03 September 2008</td>
</tr>
<tr>
<td>National Congress of the Latvian Society of Cardiology</td>
<td>Latvia, Riga or Jurmala</td>
<td>26 September 2008</td>
<td>27 September 2008</td>
</tr>
</tbody>
</table>
Information for Authors

The first three consecutive issues of “The Journal of Tehran University Heart Center” were published under the title of “The Journal of Tehran Heart Center” with ISSN: 1735-5370. From the fourth issue onward, however, the journal has been entitled “The Journal of Tehran University Heart Center” with ISSN:1735-8620.

Scope of the journal
“The Journal of Tehran University Heart Center” aims to publish the highest quality material, both clinical and scientific, on all aspects of Cardiovascular Medicine. It includes articles related to research findings, technical evaluations, and reviews. In addition, it provides a forum for the exchange of information on all aspects of Cardiovascular Medicine, including educational issues. “The journal of Tehran University Heart Center” is an international, English language, peer reviewed journal concerned with Cardiovascular Medicine. It is an official journal of the Tehran University Heart Center and is published quarterly. Papers submitted to this journal which do not adhere to the Instructions for Authors will be returned for appropriate revision to be in line with the Instructions for Authors. They may then be resubmitted. Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis), that it is not under consideration for publication elsewhere, that its publication is approved by all Authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher.

Article Categories
“The Journal of Tehran University Heart Center” accepts the following categories of articles:

- Guest Editorial
- Original Article
- Clinical and pre-clinical papers based on either normal subjects or patients and the result of cardiovascular pre-clinical research will be considered for publication provided they have an obvious clinical relevance.
- Brief communication
- Case report
- Review Article
- “The Journal of Tehran University Heart Center” publishes a limited number of scholarly, comprehensive reviews whose aims are to summarize and critically evaluate research in the field addressed and identify future implications. Reviews should not exceed 5000 words.
- Letter to editor
- Letters to the editor must not exceed 500 words and should focus on a specific article published in “The Journal of Tehran University Heart Center” within the preceding 12 weeks. No original data may be included. Authors will receive pre-publication proofs, and the authors of the article cited invited to reply.

Submission of manuscripts
Four double spaced copies on 8 1/2 × 11 in. paper should be sent to:
Dr. A. Karimi,
Editor in Chief,
“The Journal of Tehran University Heart Center”,
Tehran Heart Center,
North Kargar Street,
Tehran, Iran
1411713138

Photocopies or good reproductions of illustrations are acceptable only on the spare copies. Included also should be a set of the electronic files of the manuscript on floppy – disk or CD-ROM. For preparation of electronic files, see the instructions herein below.

Also, manuscripts can be submitted electronically via the journal’s website: http://jthc.tums.ac.ir. On-line submission allows the manuscript to be handled in electronic forms throughout the review process.

Review of manuscripts
All manuscripts correctly submitted to will first be reviewed by the Editors. Some manuscripts will be returned to authors at this stage if the paper is deemed inappropriate for publication in “The Journal of Tehran University Heart Center”, if the paper does not meet submission requirements, or if the paper is not deemed to have a sufficiently high priority. All papers considered suitable by the Editors to progress further in the review process will undergo appropriate peer review and all papers provisionally accepted for publication will undergo a detailed statistical review.

Preparation of manuscripts
All submitted manuscripts must not exceed 5000 words, including References, Figure Legends and Tables. The number of Tables, Figures and References should be appropriate to the manuscript content and should not be excessive.
**Style and spelling**

Authors whose first language is not English are requested to have their manuscripts checked carefully before submission. This will help expedite the review process and avoid confusion. Abbreviations of standard SI units of measurement only should be used.

**Declaration of Helsinki**

The Authors should state that their study complies with the Declaration of Helsinki that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects (or their guardians).

**Section of the manuscript**

Original articles should be divided into the following sections: (1) Title page, (2) Abstract and Keywords, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Conclusion, (8) Acknowledgements, (9) References, (10) Figure legends, (11) Tables, (12) Figures.

**General format**

Prepare your manuscript text using a word processing package. Submissions of text in the form of PDF files are not permitted. Manuscripts should be double –spaced, including text, tables, legends and references. Number each page. Please avoid footnotes; use instead, and as sparingly as possible, parenthesis within brackets. Enter text in the style and order of the Journal. Type references in the correct order and style of the journal. Type unjustified, without hyphenation, except for compound words. Type headings in the style of the journal. Use the TAB key once for paragraph indents. Where possible use Times New Roman for the text font and Symbol for the Greek and special characters. Use the word processing formatting features to indicate Bold, Italic, Greek, Maths, Superscript and subscript characters. Clearly identify unusual symbols and Greek letters. Differentiate between the letter o and zero, and the letters I and i and the number 1. Mark the approximate position of each figure and table. Check the final copy of your paper carefully, as any spelling mistakes and errors may be translated into the typeset version.

**Title page**

The title page should include the following: (1) the title, (2) the name (s) of authors and their highest degree ( no more than 12 authors are acceptable), (3) the institution (s) where work was performed, (4) institution, and location of all authors, (5) the address, telephone number, fax number and e-mail address of the corresponding author.

**Abstract**

All abstracts may not contain more than 250 words and should also be submitted as a separate file. The abstract should be formatted with the following heading: (1) Background, (2) Methods, (3) Results, (4) Conclusion. A maximum of six Keywords may be submitted.

**Figures**

The review process will not begin until all figures are received. Figures should be limited to the number necessary for clarity and must not duplicate data given in tables or in the text. They must be suitable for high quality reproduction and should be submitted in the desired final printed size so that reduction can be avoided. Figures should be no larger than 125 (height) × 180 (width) mm (5× 7 inches) and should be submitted in a separate file from that of the manuscript.

**Electronic submission of figures**

Figures should be saved in TIFF format at a resolution of at least 300 pixels per inch at the final printed size for colour figures and photographs, and 1200 pixels per inch for black and white line drawings. Although some other formats can be translated into TIFF format by the publisher, the conversion may alter the tones, resolution and contrast of the image. Digital colour art should be submitted in CMYK rather than RGB format, as the printing process requires colours to be separated into CMYK and this conversion can alter the intensity and brightness of colours. Therefore authors should be satisfied with the colours in CMYK (both on screen and when printed) before submission. Please also keep in mind that colours can appear differently on different screens and printers. Failure to follow these guides could result in complications and delays. Photographs: Photographs should be of sufficiently high quality with respect to detail, contrast and fineness of grain to withstand the inevitable loss of contrast and detail inherent in the printing process. Please indicate the magnification by a rule on the photograph Colour figures: There is a special charge for the inclusion of colour figures. Figure legends: These should be on a separate, numbered manuscript sheet grouped under the heading “Legends” on a separate sheet of the manuscript after the References. Define all symbols and abbreviations used in the figure. All abbreviations and should be redefined in the legend.

**Tables**

Tables should be typed with double spacing, but minimizing redundant space and each should be placed on a separate sheet. Tables should be submitted, wherever possible, in portraits, as opposed to landscape, layout. Each Table should be numbered in sequence using Arabic numerals. Tables should also have a title above and an explanatory footnote below. All abbreviations and should be redefined in the Footnote.

**Acknowledgements**

All sources of funding and support, and substantive contributions of individuals, should be noted in the Acknowledgements, positioned before the list of references.

**Reference format**

Number references sequentially and use Arabic number in superscript to cite the reference in the text. All references should be compiled at the end of
the article in the Vancouver style. Complete information should be given for each reference including the title of the article, abbreviated journal title and page numbers. All authors should be listed. Personal communications, manuscripts in preparation and other unpublished data should not be cited in the reference list but may be mentioned in parentheses in the text. Authors should get permission from the source to cite unpublished data.

Titles of journals should be abbreviated in accordance with Index Medicus (see list printed annually in the January issue of Index Medicus). If a journal is not listed in Index Medicus then its name should be written out in full.

Article citation example:

Statistics
All manuscripts selected for publication will be reviewed for the appropriateness and accuracy of the statistical methods used and the interpretation of statistical results. All papers submitted should provide in their Methods section a subsection detailing the statistical methods, including the specific method used to summarize the data, the methods used to test their hypothesis testing and (if any) the level of significance used for hypothesis testing.

Conflict of interest
At submission, the editors require authors to disclose any financial association that might pose a conflict of interest in connection with the submitted article. All sources of funding for the work should be acknowledged in a footnote on the title page and in the Acknowledgements within the manuscript, as should all the institutional affiliations of the authors (including corporate appointments). Other kinds of associations, such as consultancies, stock ownership or other equity interest or patent-licensing arrangements should be disclosed to the editors in the cover letter at the time of submission. If no conflict of interest exists, please state this in the cover letter.

Proofs
Page proofs will be sent to the corresponding author. Please provide an e-mail address to enable page proofs to be sent as PDF files via e-mail. These should be checked thoroughly for any possible changes or typographic errors. Significant alterations instigated at this stage by the author will be charged to the author. It is the intention of the Editor to review, correct and publish your article as quickly as possible. To achieve this it is important that all of your corrections are returned to us in one all—inclusive mail or fax. Subsequent additional corrections will not be possible, so please ensure that your first communication is complete.
Subscription Form

The Journal of Tehran University Heart Center

New Subscription:  Continuation of Subscription:

Surname:  
First Name:  
Hospital or Organization:  
Date of subscription:  
Full mail address:  
P.O.BOX:  
Tell:  
Fax:  
E-mail:  

The annual Subscription and postage rate: 100/000 Rials for Iran and US $ 100 including postage for other countries.

Please liquidate the total amount of subscription and postal charges into:
Bank: Refah  Branch Code: 1232  Account: Tehran Heart Center  Account Number: 200001.28
and send the original bank slip along with duly completed form of subscription to the following address:

Tehran Heart Center,
North Kargar Street,
Tehran, Iran
1411713138
Tel: +98 21 88029702
FAX: +98 21 88029702
E-mail: jthc@tums.ac.ir

Tehran University Heart Center