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The National Research Center for Medical Sciences of the Islamic Republic of Iran organizes the annual Razi Research Festival on medical sciences to encourage and identify talents and contribute to the improvement of research on medical sciences and encourage further development in medicine.

The prize will be presented to the researcher, faculty member, talented students of medical sciences whose works and researches have led to significant advances in medical and health sciences.

The 14th Razi Medical Sciences Research Festival will be held in collaboration with the researchers of member states of the Islamic Educational, Scientific and Cultural Organization (ISESCO) in December 2008, the year with the theme of innovation and flourishing. The objective behind holding the conference is to introduce the best practices on medical sciences researches with emphasis on innovation in the field of research and technology.

Highlight of Razi Festival

Razi Festival was initiated at Tehran University of Medical Sciences in 1995. The Festival prize for medical research is designated to encourage and reward medical researchers. The prize is awarded annually for an outstanding, ground-breaking medical research project and may be awarded to an individual or a research team. Prize recipients are selected on the basis of two principal criteria, equally scored: (1) nobility of the article; (2) mastery of the candidates. Other evaluation criteria would be:

1. Universities and student research centers will be evaluated on the basis of their quality and quantity of knowledge production, resource mobilization and capacity building in research.
2. Evaluation of the research centers are based on the annual assessment carried out by the Undersecretary for Research and Technology, MOHME
3. NGOs, institutes, companies and charities awarding research grants are nominated by the recipients.

The eligible candidates will be mainly within two categories:

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7- Approved Medical Sciences Research Centers
8- Student Medical Sciences Research Committee
9- NGO companies, charities and scientific societies that support research on medical sciences
10- Approved scientific research journals of medical sciences.
**International:**
1. Iranian researchers who stay abroad
2. Researchers from member states of ISESCO

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*Applicants should specifically address how their work meets the following criteria:*

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1. Priority;
2. Innovation;
3. Applicability;
4. Scientific Methodology;
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**Research criteria:**
- Brief biography including major scientific/technical accomplishments, published articles in credited journals indexed by Medical Journals Databases
- Significant publications (books)
- Sustained leadership contributions in improving healthcare, technology customizing, and patient care; or who have successfully pursued innovative improvement in public health with demonstrated translational benefits applied to improve quality of life.
- Curriculum vitae

**Supporting Documents:**
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3. Recent 5 year CV
4. Copies of 5 recent significant articles and a copy of published book
5. Complete list of recent 5 years publications that are indexed by Medical Journal Databases

The festival will include basic sciences, health sciences, surgical and non-surgical medical sciences, pharmacology, nutrition, dentistry, rehabilitation, modern technology, health sector reform.

- The article should be published in a credited medical journal after 2006
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## Editorial

**Bioprosthetic Heart Valve Replacement: Oral Anticoagulation or Antiplatelet Therapy? A Still Active Controversy**  
Carlos-A. Mestres, Andrea Colli, Jose I. Aramendi  
127

## Review Article

**Thoracoabdominal Aortic Aneurysms**  
Ali Azizzadeh, Anthony L. Estrera, Charles C. Miller, Hazim J. Safi  
131

## Original Articles

**Device Occlusion versus Surgery for Closure of Congenital Heart Defects: Cost Issues in Iran**  
Ali Akbar Zeinaloo, Seyyed Mahmoud Meraji, Keyhan Sayadpour Zanjani, Mohammad Reza Mirzaaghayan  
141

**Coronary Artery Bypass Surgery versus Medical Treatment in Patients with Low Ejection Fraction and Coronary Artery Disease**  
Hakimeh Sadeghian, Mojtaha Salarifar, Abbas Ali Karimi, Mehrab Marzban, Kyomars Abbasi, Masoumeh Lotfi-Tokaldany, Mahmood Sheikhfathollahi, Mohammad Majd, Sirous Jahangiri, Seyyed Hesameddin Abbasi  
145

**Transcatheter Closure of Patent Ductus Arteriosus Using the Amplatzer Ductal Occluder: Early Results and Midterm Follow-Up**  
Mostafa Behjati Ardakani, Sayed khalil Forouzannia, Majid Dehghani, Mohammad Hassan Abdollahi  
151

**Efficacy of Adenosine for Acute Treatment of Supraventricular Tachycardia in Infants and Children**  
Mohammad Yusef Aarabi Moghadam, Seyed Mohammad Dalili, Zahra Emkanjoo  
157

**Do C-Reactive Protein and Lipoprotein (a) Have Different Impacts on the Severity of Coronary Artery Disease in Diabetic and Non-Diabetic Patients?**  
Mohammad Ali Boroumand, Maryam Sotoudeh Anvari, Mehrdad Sheikhvatan, Soheil Saadat, Seyyed Hesameddin Abbasi, Mahmood Sheikhfathollahi  
163

**Lipid Profile Comparison between Opium Addicts and Non-Addicts**  
Seyedeh Seddigheh Fatemi, Mehdi Hasanzadeh, Arman Arghami, Mohammad Reza Sargolzaee  
169

## Case Report

**Significant Improvement in Severely Stunned Left Ventricle after Percutaneous Coronary Intervention**  
Ahmad Sharafi, Seyed Ebrahim Kassaian, Ahmad Yamini Sharif, Hakime Sadeghian, Gholamreza Davoodi, Abbas Soleimani  
173
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Bioprosthetic Heart Valve Replacement: Oral Anticoagulation or Antiplatelet Therapy? A Still Active Controversy

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There are a number of controversies in cardiac surgery. Among them, the issue of compulsory anticoagulant therapy after valve replacement with a tissue valve, also known as bioprosthesis, continues to be a matter of discussion. The key point is to admit that antithrombotic therapy in general may eventually be founded on shaky grounds. When referring to valve replacement with mechanical valves, there are neither doubts nor discussions that life-long oral anticoagulation therapy is the gold standard in terms of therapeutics due to the intrinsic valve structure with metallic components. The addition of immediate postoperative intravenous or subcutaneous heparin may accompany the introduction of anticoagulation usually with oral warfarin.

When referring to tissue valves, there still exists controversy with regard to the most appropriate antithrombotic therapy. Different options have been tried and are already popular within the surgical community: 1) No antithrombotic therapy, 2) Full oral anticoagulation therapy for three months with antivitamin K drugs, 3) Antiplatelet agents for three months, and 4) Combinations of all the above. In other words, there are considerable variations in practice as shown by surveys and registries.1,2

The issue of guidelines is also to be considered. Despite the fact that guidelines are luckily not the law, major scientific societies try to establish recommendations on what to do after bioprosthetic heart valve replacement, especially in patients with normal sinus rhythm, regardless of the valve position. The use of antiplatelets is a currently accepted policy.1,5 If atrial fibrillation is present, there may be fewer doubts at the time to recommend a specific therapeutic regimen. What seems to be clear is that, despite the intrinsic biological nature of tissue valves, there are still chances of early postoperative thrombotic events.6,7 On the other hand, any antithrombotic therapy has to be appropriately and carefully balanced with regard to drug-induced hemorrhagic events.6

Although it was a retrospective study and covering a long period of time, the results described in the seminal paper by Heras et al.8 helped to define the extent of the problem and showed that there exists a risk of thrombotic events within the first three months after tissue valve replacement, which is the estimated time frame for the prosthetic ring to become endothelialized. There is an expected risk that may peak around 40-60 days after the operation. Therefore, on purity, prophylactic regimens should theoretically be implemented. Real life shows that even though there is an appropriate knowledge of guidelines, the cardiothoracic surgical community has no consensus on this issue as only 60% of the surgeons do not recommend antithrombotic therapy after tissue valve replacement as has been shown by an online survey in CTSNet on this subject.1 A recently published registry has confirmed the lack of consensus on this matter, despite the guidelines.2 This renders the problem on the complex side.

There is still little evidence about what to do; however, there is recent information suggesting that anticoagulation with oral warfarin may not be the ideal approach in this setting. In the past decade, a handful of papers have indicated that antiplatelet agents may be quite useful at the time of preventing stroke and other peripheral embolic events.5,11 An early study showed that antiplatelet therapy was effective in preventing embolization; however, ticlopidine still had some risk of hemorrhagic events.6 In terms of evidence, there is only one recent prospective and randomized trial, the TRAC study, that has shown, on a pilot basis, that antiplatelet therapy was as effective as oral warfarin in preventing embolic events; in addition, the risk of hemorrhagic events was also reduced when using antiplatelet agents.2,13 A major limitation of this prospective randomized trial was the reduced sample size. So

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far no other controlled study has addressed this problem.

Joining all together, the still scanty papers published up to now are currently challenging old thinking on this particularly complex issue. Some other recent non-randomized studies are concluding in a similar way that antiplatelet therapy is useful in preventing embolic events with no increased risk of hemorrhage.\textsuperscript{14,15} A very recent abstract also indicates, despite some problems in methodology and follow-up, that no oral anticoagulation may eventually be required.\textsuperscript{16} Waiting for the publication of the data presented in this abstract, this study is another example of the renewed interest in this issue.\textsuperscript{16}

There is still not enough information to draw at strong and powerful conclusions. The ACTION registry\textsuperscript{2} has a number of important limitations that have already been discussed,\textsuperscript{7} but it may bring additional light as to what is done in real life. This is the power of a registry, which is probably not the most appropriate scientific tool, although its value should not be neglected. Up to now, this registry seems to confirm the aforementioned impression that the practices are diverse; in other words, consensus does not exist. On the other hand, guidelines do reflect society policies\textsuperscript{15} and the CTSNet Survey also confirmed that there are probably as many policies as the number of operating surgeons.\textsuperscript{1}

Bearing in mind the lack of consensus and the confirmation of the diversity of practices, something seems to be of interest: there is a trend not to use oral anticoagulation immediately after tissue heart valve replacement. This may eventually be good news. Physicians in general and cardiologists in particular have always been too rigid in this regard, and full oral anticoagulation has always been started after tissue valve replacement for at least three months. This tendency toward an increased usage of antiplatelet drugs is aimed at reducing the complications of oral anticoagulation; those are not to be neglected. We, surgeons, know that anticoagulation-related hemorrhage continues to be a major part of overall morbidity after valve replacement in general and mechanical valve in particular.\textsuperscript{17,19} Therefore, any effort to reduce bleeding should always be welcome.

The TRAC prospective and randomized pilot study,\textsuperscript{12,13} the ACTION and ANSWER registries in Europe and the USA\textsuperscript{2} and the cohort studies that have already addressed the problem\textsuperscript{6,8,11,14-16} are related in some aspects. First, they will contribute in different ways to a future body of evidence supporting the use of antiplatelet drugs in this field. Second, although all these studies have some limitations to a certain extent, they seek to create more awareness among surgeons regarding this still debatable issue. Third, it seems clear that they address the problem of hemorrhage as this continues to be the most important part of the business. For a therapy that looks at reducing thromboembolic events to a minimum and to avoid hemorrhage related to the therapy, it is encouraging to see that antiplatelet treatment is able to offer an appropriate efficacy and safety profile that needs further investigation.

References

Bioprosthetic Heart Valve Replacement...


Thoracoabdominal Aortic Aneurysms

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Abstract

Over the last 50 years, significant progress has been made in the surgical repair of thoracoabdominal aortic aneurysms (TAAA). Improvements in perioperative care and surgical techniques have resulted in reductions in complication and mortality rates. Adjunctive use of distal aortic perfusion and cerebrospinal fluid drainage has been especially helpful, reducing the incidence of neurological deficits to 2.4%. Current research is aimed at improving organ preservation. This review focuses on the current diagnosis and management of TAAA.

Keywords: Thoracoabdominal aortic aneurysm • Surgery • Review

Epidemiology

In the United States, infrarenal abdominal aortic aneurysms (AAA) occur 3 to 7 times more frequently than thoracic aortic aneurysms. Fewer than 1000 thoracoabdominal aortic aneurysms (TAAA) are repaired annually, compared to approximately 50,000 infrarenal AAA. The prevalence of AAA varies between 2.3% to 10.7%, depending on the population studied and the size used to define an aneurysm. The incidence of TAAA is estimated to be 10.4 cases per 100,000 person-years. The mean age of patients with thoracic aortic aneurysm is between 59 and 69 years with a male to female predominance of between 2 and 4 to 1.

Less than 40% of patients with untreated large TAAA survive beyond 5 years, with most deaths due to rupture. TAAA studies have shown that rupture is more likely to occur when aneurysms exceed 5 cm, with risk of rupture increasing with aneurysm size. The median size at which a TAAA will rupture is around 7.0 cm. Aneurysms equal to or greater than 8 cm have an 80% risk of rupture within a year of diagnosis. The lifetime probability of rupture for any untreated aortic aneurysm is 75% to 80%. It is difficult to predict at what size and when an aneurysm will rupture.

Pathogenesis

An aortic aneurysm is defined as a localized or diffuse dilatation that exceeds 50% of normal aortic diameter. Most TAAAs are degenerative, with an underlying pathology similar to the more frequently encountered infrarenal abdominal aortic aneurysm. For a long time, arteriosclerosis has been implicated in the development of aortic aneurysm. However, arteriosclerosis primarily affects the intima and typically causes occlusive disease, whereas aneurysmal disease usually involves the media and adventitia. Although the pathogenesis of arteriosclerotic occlusive disease and that of aneurysm disease have been shown to be distinct, the two conditions commonly occur together. Histologically, degenerative aortic aneurysms are characterized by thinning of the media with destruction of smooth muscle cells and elastin, infiltration of inflammatory cells, and neovascularization. A chronic inflammatory infiltrate, comprised of macrophages, as well as T and B lymphocytes, is consistently observed in the outer layer of aneurysm wall. The degree of vessel wall inflammation varies and the stimulus for cell migration remains unclear. These inflammatory cells, particularly macrophages, secrete proteases and elastases that can degrade the aortic wall; in
turn, the elastin degradation products may act as chemotactic agents for the influx of inflammatory cells. The role of matrix metalloproteinases (MMP), the most prominent type of elastases, in the development of aortic aneurysms has emerged from both clinical and experimental studies. Increased amounts of elastases MMP-2, MMP-9 and MMP-12 have been found in aortic aneurysmal tissue.

Familial clustering of aortic aneurysm is evident, as up to 20% of patients with aneurysms have one or more first-degree relatives with the same affliction. Marfan syndrome, characterized by skeletal, ocular, and cardiovascular abnormalities, is the most common inherited connective tissue disorder related to aortic aneurysm and dissection. Marfan syndrome occurs at a frequency of 1: 5000 worldwide. Aortic dilatation observed in Marfan patients has been linked to mutation in fibrillin-1 (FBN-1). Other known genetic syndromes that predispose individuals to thoracic aortic aneurysm and dissection include Ehlers-Danlos syndrome, Turner syndrome, and polycystic kidney disease. In addition, a familial syndrome in which multiple members have thoracic aortic aneurysm and dissection, with yet to be identified genetic abnormalities, has been reported in the literature. In the majority of these families, the phenotype for thoracic aortic aneurysm and dissection is inherited in an autosomal dominant manner with marked variability in the age at onset of aortic disease and decreased penetrance.

Approximately 25% of TAAAs are associated with chronic aortic dissection. About 20% to 40% of patients will develop aneurysms in the thoracoabdominal aorta within 2 to 5 years following acute aortic dissection. Persistent patency of the false aortic lumen is reported to be a significant predictor of aneurysmal formation. However, the presence of chronic aortic dissection or patent false lumen has not been linked to a higher risk of aortic rupture. In approximately 20% of cases, aneurysmal disease occurs in more than one part of the aorta. The so-called “mega” aorta is an “extensive” aortic aneurysm involving the ascending, transverse arch, and the entire thoracoabdominal aorta. The cause of extensive aortic aneurysm remains unknown, although associated factors include Marfan syndrome and chronic aortic dissection.

The options remain limited for patients afflicted with a large TAAA. Sudden fatal aneurysm rupture is a looming and unpredictable threat. Most patients succumb with rupture of the aneurysm. Although emergency repair of ruptured TAAA can save lives, the associated morbidity and mortality remain extremely high. Elective surgical repair of TAAA is the only effective treatment for eradicating the risk of aneurysm rupture and improving patient survival.

**Clinical manifestations**

As they increase in size, aortic aneurysms can cause compressive symptoms although most do not until they reach a large size. Symptoms include:
1. Ill-defined chronic back pain, although pain can also occur in the chest, flank or epigastrum. Acute changes in the characteristics and severity of pain can indicate sudden expansion or impending aortic rupture.
2. Hoarseness, resulting from vocal cord paralysis due to compression of the left recurrent laryngeal or vagus nerves, frequently seen in patients with large aneurysms of the distal transverse arch or proximal descending thoracic aorta.
3. Dyspnea related to compression of the tracheobronchial tree.
4. Dysphagia or weight loss related to pressure on the adjacent esophagus or duodenum, leading to obstruction or early satiety.
5. Exsanguination, presenting as massive hemoptysis or hematemesis due to direct erosion of the aneurysm into the adjacent tracheobronchial tree, esophagus, or both. Less frequently, this can cause slow intermittent blood loss.
6. Paraplegia or paraparesis rarely occurs in patients with TAAA due to acute occlusion of the intercostal or spinal arteries. This is usually associated with acute aortic dissection but can also result from thrombo-embolization.
7. Distal embolization causing acute mesenteric, renal or lower extremity ischemia is infrequent, even though there is a varying amount of mural thrombus associated with aneurysms.

In 10% to 20% of patients rupture may be the first clinical manifestation of a T AAA. A ruptured aneurysm should be suspected if there is an acute onset of severe chest, abdominal or back pain associated with hypotension. A pulsatile mass may be palpable in the abdomen unless the larger part of the TAAA is positioned deep in the thoracic cage. Most ruptured aneurysms are fatal unless treated emergently, but the ruptured arterial wall may temporarily seal for several hours or days before free rupture. The rupture is usually contained within the pleura or retroperitoneum in patients who make it to the hospital alive. Free rupture with severe hypotension usually results in death before surgical care can be obtained.

**Preoperative evaluation and preparation**

The initial consultation with the TAAA patient includes:
1. A thorough history and physical examination, primarily to detect co-morbidities, as there are generally few symptoms or physical signs related to the aneurysm itself.
2. Imaging studies to determine the extent of the TAAA.
4. Consultation with cardiologist, pulmonologist or nephrologist to aid in the stratification of risks.
5. Transthoracic echocardiography to estimate cardiac function. Ischemic heart disease is prevalent and is the most common cause of death.
Coronary artery revascularization, using either percutaneous intervention (balloon angioplasty or stent) or surgical bypass, may be indicated prior to TAAA surgery. For patients who must undergo coronary artery bypass prior to TAAA repair, our conduit of choice is the saphenous vein graft. We avoid using the left internal mammary artery to obviate the possibility of cardiac ischemia should aortic cross-clamping proximal to the left subclavian artery be required during the TAAA repair. Moreover, the internal mammary artery may be an important collateral blood supply to the spinal cord.

**Operative techniques**

The history of techniques reveals:

1- 1955: Etheredge did the first successful repair of a thoracoabdominal aortic aneurysm (TAAA) using a homograft tube.
2- 1956: DeBakey sewed his own Dacron tube grafts to replace the descending thoracic aorta and infrarenal abdominal aorta.
3- Crawford introduced the clamp-and-sew technique, encompassing three basic principles of aortic surgery: the inclusion technique, use of Dacron tube graft conduit, and reimplantation of both visceral and renal arteries.
4- A classification was developed based upon the extent of the TAAA (Figure 1).
5- Early operations had to be done with haste to avoid extended periods of organ ischemia. Now the use of adjuncts provides longer operative time, better organ protection and improved outcome.

Current operative procedures require a multidisciplinary team at a specialized cardiothoracic surgery unit. The patient is placed in the supine position on the operating table and prepared for surgery. General anesthesia is induced. Endotracheal intubation is established using a double lumen tube for selective one-lung ventilation during surgery. Electrodes are attached to the scalp for electroencephalogram (EEG) and along the spinal cord for both motor and somatosensory evoked potential (SSEP) to assess the central nervous system and spinal cord function, respectively. The patient is then positioned on the right side with the hips and knees flexed to open the intervertebral spaces. A lumbar catheter is placed in the 3rd or 4th lumbar space to provide cerebrospinal fluid (CSF) pressure monitoring and drainage. The CSF pressure is kept at 10 mmHg or less by gravity drainage of CSF fluid throughout the procedure.

We tailor the incision to complement the extent of the aneurysm. The full thoracoabdominal incision begins posteriorly between the tip of the scapula and the spinous process, curving along the sixth intercostal space to the costal cartilage, then obliquely to the umbilicus, and finally in the midline to above the symphysis pubis. The latissimus dorsi muscle is divided and at the insertion of the serratus. Usually, a full thoracoabdominal exploration is necessary for extent II, III and IV TAAA. A modified thoracoabdominal incision begins similar to the full thoracoabdominal incision but ends at the costal cartilage or above the umbilicus.

The modified thoracoabdominal incision provides excellent exposure for surgery involving the descending thoracic aorta, extent I, and extent V TAAA, when the aneurysm

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Figure 1. Thoracoabdominal aortic aneurysm classification. Extent I, distal to the left subclavian artery to above the renal arteries. Extent II, distal to the left subclavian artery to the below the renal arteries. Extent III, from the sixth intercostal space to below the renal arteries. Extent IV, the twelfth intercostal space to the iliac bifurcation (total abdominal aortic aneurysm). Extent V, below the sixth intercostal space to just above the renal arteries.
ends above the superior mesenteric artery. We extend the thoracoabdominal incision to the level of the umbilicus, for extent I and V TAAA that involve the superior mesenteric artery. A self-retaining retractor is placed firmly on the edges of the incision to maintain full thoracic and abdominal exposure during the procedure.

The dissection begins at the level of the hilum of the lung cephalad to the proximal descending thoracic aorta. We identify the ligamentum arteriosum and transect it, taking care to avoid injury to the left recurrent laryngeal nerve. The extent of the distal abdominal aneurysm is assessed. We divide the muscular portion of the diaphragm only and preserve the left phrenic nerve (Figure 2). A retroperitoneal plane is then developed, mobilizing the spleen, bowel loops, and left kidney to the right side of the abdominal aorta (medial visceral rotation). To prepare for distal aortic perfusion, the patient is anticoagulated using intravenous heparin (1 mg/kg of weight). The pericardium is opened posterior to the left phrenic nerve to allow direct visualization of the pulmonary veins and left atrium. The left atrium is cannulated through the left inferior pulmonary vein or atrial appendage. A centrifugal pump with an in-line heat exchanger is attached to the left atrial cannula and the arterial inflow is established through the left common femoral artery and the descending thoracic aorta.

Padded clamps are applied onto the proximal descending thoracic aorta just distal to the left subclavian artery and the mid-thoracic aorta. When the proximal extent of the aneurysm is too close to the left subclavian artery, we clamp the aorta between the left common carotid and left subclavian arteries and clamp the left subclavian artery separately. Because of the danger of graft-esophageal fistula, we no longer use the inclusion technique for the proximal anastomosis. Instead, we completely transect the aorta to separate it from the underlying esophagus (Figure 4a). We prefer a woven Dacron graft impregnated with collagen or gelatin for replacement. We suture the graft in an end-to-end fashion to the descending thoracic aorta, using a running 3-0 or 2-0 monofilament polypropylene suture. We check the anastomosis for bleeding and use pledgeted polypropylene sutures for reinforcement, if necessary. We use sequential clamping for all TAAAs. After completion of the proximal anastomosis, the mid-descending aortic clamp is moved distally onto the abdominal aorta at the celiac axis to accommodate intercostal reattachment. Reattachment of patent, lower intercostal arteries (T8-T12) is performed routinely, except in cases of occluded arteries, heavily calcified aorta, or acute aortic dissection. After completion of intercostal reattachment, the proximal clamp is released from the aorta and re-applied on the aortic graft beyond the intercostal patch, restoring pulsatile flow to the reattached intercostal arteries (Figure 4b). The distal clamp is moved onto the infrarenal aorta, the abdominal aorta is opened, and the graft is passed through the aortic hiatus. The
celiac, superior mesenteric and renal arteries are identified and perfused using #9 or #12 F balloon-tipped catheters, depending on the size of the ostia (Figure 4c). The delivery of cold perfusate (4°C) to the viscera is maintained between 300 and 600 mL/min. Renal temperature is directly monitored and kept at approximately 15°C. The visceral vessels are usually reattached using the inclusion technique. Upon completion of this anastomosis, the proximal clamp is moved beyond the visceral patch, restoring pulsatile flow to the viscera and kidneys (Figure 4d). The final graft anastomosis is then completed at the aortic bifurcation. In most cases an island patch accommodates reattachment of the celiac, superior mesenteric, and both renal arteries. If the right or left renal artery is located at too great a distance from other arteries, its reattachment usually requires a separate interposition bypass graft. We no longer use a visceral patch for Marfan patients, because of the high incidence of recurrent patch aneurysms in such cases. Instead we use a woven Dacron graft with side-arm grafts of 10 mm and 12 mm for separate attachment of the celiac, superior mesenteric and the left and right renal arteries.

Figure 4a. Sequential clamping and graft replacement. Padded clamps are placed on the proximal and mid distal descending thoracic aorta. The proximal part of the aneurysm is opened. The aortic neck is completely transected and separated from the esophagus.

Figure 4b. The proximal anastomosis is fashioned. Subsequently, the patent lower intercostal arteries are reattached via an elliptical hole in the graft. The proximal clamp is then moved onto the graft to restore pulsatile flow to the intercostal arteries, and the graft is pulled through the hiatus into the abdomen.

Figure 4c. The distal clamp is reapplied onto the infrarenal aorta. The remaining of the aneurysm is opened. Balloon-tipped catheters are inserted into the celiac, superior mesenteric, and renal arteries to permit perfusion. An elliptical hole is made in the graft for...
Fig 4d. Pulsatile flow is then restored to the visceral and renal arteries, and the distal anastomosis is completed.

We then wean the patient from partial bypass once the core body or nasopharyngeal temperatures reaches 36 to 37°C. Protamine is administered (1 mg/1 mg heparin) and the atrial and femoral cannulae are removed. Once hemostasis is achieved, two or sometimes three 36-F chest tubes are placed in the pleural cavity for drainage. The diaphragm is reapproximated using running #1 polypropylene suture. The left lung is re-inflated. Closure of the incision is done in a standard fashion. The patient is placed in the supine position, and the double lumen endotracheal tube is exchanged for a single lumen tube. If the vocal cords are swollen, the double lumen tube is kept in place until the swelling resolves. The patient is then transferred to the intensive care unit.

**Postoperative management**

In the intensive care unit we monitor the patient’s hemodynamics closely. We try to wake the patient as quickly as possible to check neurologic status. The patient’s mean arterial pressure is maintained between 90 and 100 mmHg to ensure good organ perfusion, particularly to the spinal cord. CSF pressure is continuously monitored. Approximately 10 to 15 mL of CSF is drained hourly to keep CSF pressure at 15 mmHg or less. We start weaning the patient off the ventilator on the first postoperative day.

After the patient recovers from anesthesia and is moving all extremities, we are on the alert for delayed neurologic deficit. Warning signs for delayed neurologic deficit are unstable arterial blood pressure, hypoxemia, low hemoglobin (<10 g/dl), or increased CSF pressure (>15 mmHg).

Cerebrospinal fluid drainage is discontinued on the third postoperative day. We recommend annual CT scan follow-up to screen for the development of new aneurysm or graft-related pseudoaneurysm formation. The frequency of follow-up visits or CT scans may vary based on TAAA etiology. For example, patients with remaining unrepaired aortic dissection, connective tissue disorders (Marfan syndrome), a family history of aortic aneurysm, or concurrent aneurysms may need closer surveillance.

**Results of Surgery**

Mortality rates for patients undergoing thoracoabdominal and descending thoracic aortic aneurysm repair range between 4% and 21%, depending on the series. The differing success rates are partly related to the heterogeneity of the patient population, and to the expertise of the treating team. In our cumulative experience, (January 1991 to February 2003), 1004 patients underwent thoracoabdominal and descending thoracic aortic aneurysm repair. Sixty-three percent of our patients were men. The median age was 65 years (range, 8 to 89 years). Approximately 7% of patients had emergency surgery for free or contained rupture of thoracoabdominal or descending thoracic aortic aneurysm. Currently, our 30-day mortality rate is 14%. The mortality rate highly correlates with preoperative renal function as determined by calculated glomerular filtration rate (GFR). Patients with a GFR greater than 90 mL/min/1.73 m² had a mortality rate of 5.6% compared to a rate of 27.8% in patients with a GFR less than 49 mL/min/1.73 m². Using multivariable analysis, we have identified advanced age, renal failure, and paraplegia as important risk factors for mortality. Patients aged 79 years or older with at least one of three factors—emergency presentation, a history of diabetes or congestive heart failure—have been identified as a particularly high-risk group with 30-day mortality as high as 50%. Overall, 70% of our patients recover from TAAA without significant postoperative complications. The 5-year survival for our patients after TAAA is between 60% and 70%. Recently, we found the negative predictors for long-term survival to include advanced age, extent II TAAA, renal failure, emergency surgery, cerebrovascular disease and active tobacco smoking.

**Neurologic Outcome**

Postoperative neurologic deficit (ND) is the most devastating complication following TAAA repair. When the descending thoracic aorta is cross-clamped, the spinal cord is quickly rendered ischemic because of the immediate
interruption of perfusion to the spinal cord and consequent increased CSF pressure. Therefore, in the clamp-and-sew era, the single most important predictor of ND was the length of the clamp time. Our method of protection is to increase spinal cord perfusion during the clamp-and-sew era because of the longer clamp time. This combination of adjuncts has reduced our cumulative rate of ND to 0.9% for descending thoracic aortic repair and to 3.3% for thoracoabdominal aortic repair. Repair of the most extensive TAAAs (extent II) has long been known to result in the highest incidence of ND. In the clamp-and-sew era, this incidence was as high as 30% to 40%. With the use of adjuncts, the rate of immediate ND for extent II TAAA has been reduced to 4% in our series. In addition to the extent of the aneurysm, other perioperative risk factors for immediate ND include age, emergency presentation, renal dysfunction, active smoking, and cerebrovascular disease. The use of intraoperative distal aortic perfusion and perioperative CSF drainage, in combination, prevents one ND in twenty cases for all patients, and one in five for extent II TAAA.

The reimplantation of intercostal arteries is critical in spinal cord protection. Reimplantation of intercostal arteries was found to be a risk factor for postoperative neurologic deficit during the clamp-and-sew era because of the longer cross-clamp time required for reimplantation. The level at which the anterior radicular artery (known as the artery of Adamkiewicz, or artery radicularis magna) originates is known to be variable. Usually it branches from one of the lower intercostal arteries with or without additional collateral branches from nearby intercostal arteries. The anterior radicular artery is believed to be the major blood supply to the anterior spinal artery of the spinal cord. We studied the relationship of neurologic deficit to ligation, reimplantation, and pre-existing occlusion of intercostal arteries in patients undergoing TAAA repair using adjuncts. We found that ligation of patent lower intercostal arteries (T9 to T12) increased the risk of paraplegia. Therefore we reattach all patent lower intercostal arteries from T9 to T12, either together as a patch to a side hole made in the Dacron graft or, when the intercostal arteries are too far apart, separately as buttons or using interposition bypass grafts. However, if the lower intercostal arteries are occluded, we will reimplant the patent upper intercostal arteries, because these are thought to assume a more important role in the collateral system to the anterior spinal artery in this situation.

**Delayed Neurologic Deficits**

Delayed neurologic deficit (DND) refers to the onset of paraplegia or paraparesis after a period of normal neurologic function. DND after TAAA repair was first reported in 1988, at which time the condition was considered irreversible and beyond the surgeon’s control. Since then numerous reports have described improvements in patients’ neurologic function by using CSF drainage for DND. We have observed DND as early as 2 hours and as late as 2 weeks following surgery (median, 3 days), in 2.7% of patients. We have found no single risk factor responsible for DND. However, using multivariable analysis, we identified acute dissection, extent II TAAA, and renal insufficiency as significant preoperative predictors for DND. In a subsequent case-control study, postoperative mean arterial pressure of less than 60 mmHg and CSF drain complications were found to be predictors in the development of DND, independent of preoperative predictors.

DND has emerged as an important clinical entity now that improved spinal cord protection during TAAA surgery has reduced the incidence of neurologic complications. The exact mechanisms involved in the development of DND remain unknown. DND after TAAA repair may result from a ‘second hit’ phenomenon. Adjuncts can protect the spinal cord intraoperatively and reduce the incidence of immediate neurologic deficit, but the spinal cord remains vulnerable during the early postoperative period. Additional ischemic insults caused by hemodynamic instability, malfunction of the CSF drainage catheter, or both may constitute a ‘second hit,’ causing DND. Furthermore, in the rigid, unyielding spinal column, any rise in CSF pressure could lead to an increase in compartment pressure, with consequent decreased spinal cord perfusion. Hence, we drain CSF freely when DND develops to relieve the compartment pressure.

To optimize postoperative spinal cord perfusion and oxygen delivery, we keep the mean arterial pressure above 90 to 100 mmHg, hemoglobin above 10 mg/dL, and cardiac index greater than 2.0 L/min. If DND occurs, measures to increase spinal cord perfusion are begun immediately. The patient is placed flat in the supine position. The patency and function of the drain is ascertained at once. If the drain has been removed, the CSF drainage catheter is reinserted immediately and CSF is drained freely until the CSF pressure drops below 10 mmHg. The systemic arterial pressure is raised, blood transfusion is liberally infused, and oxygen saturation is increased, as indicated above. CSF drainage is continued for at least 72 hours for all patients with delayed onset neurologic deficit. Using this multifaceted approach to treating delayed onset neurologic deficit, we have seen overall improvement in neurologic function, as measured from the time of onset, in 57% of these patients. Recovery was dependent on the status of the CSF drain at the time of onset. Seventy-five percent of patients recovered function when the CSF drain was still in place at the onset of delayed
Endovascular management of thoracic aortic pathology has evolved at a rapid pace since the first successful reported thoracic endograft procedure in 1991. Numerous centers have reported series of patients receiving thoracic endografts for a variety of conditions, including acute and chronic type B aortic dissections, traumatic thoracic transections, and descending thoracic and TAAAs. Although the short-term benefits of endovascular therapy are clear, with less morbidity and shorter length of hospital stay compared to conventional surgery, the reported mortality rates appear to replicate those from conventional surgery in large centers. The long-term effectiveness of endoluminal exclusion of aneurysms remains to be determined. Several cases of immediate and delayed paraplegia have been reported in the literature following thoracic endograft placement. The development of fenestrated and branched endografts allows for reimplantation of patent visceral and renal arteries. The rapid advances in this field have made endovascular treatment an alternative to open repair in selected patients with TAAA. These devices currently have to be custom made to the patient’s anatomy. Although tremendous progress has been made, the technology is still in its infancy. This approach is presently available in a very limited number of specialized centers and requires collaboration between different specialties. Surgeons who attempt this procedure must have extensive experience with endovascular techniques including treatment of abdominal and descending thoracic aortic aneurysms. There is much work that remains to be done in developing devices that are applicable to a wider range of patients with TAAA.

Conclusion

Much progress has been made in the surgical treatment of TAAA. The reduction in mortality and complication rates can be attributed to improvements in perioperative care and in surgical technique, particularly the adoption of adjunct distal aortic perfusion and cerebrospinal fluid drainage. Neurologic deficit is no longer a major threat to patients, as the use of adjuncts has brought the incidence down to 2.4% for all TAAA. Further research is needed to improve organ preservation. The evolution of endovascular technology and the development of branched devices hold great promise in the future management of TAAA.

Acknowledgement

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Device Occlusion versus Surgery for Closure of Congenital Heart Defects: Cost Issues in Iran

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Abstract

Background: Closure of patent ductus arteriosus (PDA), ventricular septal defect (VSD) and atrial septal defect (ASD) can be done surgically or by device. This study was designed to compare the total cost of surgical or device closures of PDA, ASD or VSD for Iranian patients.

Methods: This is a cross-sectional study, conducted from January 1, 2005 until January 1, 2006 in two large heart centers of Tehran. The study population consisted of 91 patients with isolated PDA, ASD or VSD who underwent either surgical or device closure.

Results: PDA device closure either with the Amplatzer device or coil was less costly than that via surgery. VSD closure with the Amplatzer device was more costly (17.6%). Although ASD closure was also more expensive (15.4%), the difference was not statistically significant.

Conclusion: It can be concluded that PDA closure is cheaper than surgery in Iran. ASD and VSD device closures are more expensive, but the added cost can be affordable in view of the advantages of device closure.

Keywords: Cost • Patent ductus arteriosus • Atrial septal defect • Ventricular septal defect

Introduction

Surgery was the standard treatment for patent ductus arteriosus (PDA), ostium secundum atrial septal defect (ASD) and ventricular septal defect (VSD) until the advent of transcatheter techniques. Nowadays, the transcatheter device closure of congenital cardiac defects is being used increasingly with excellent results.¹

A controversial issue in pediatric cardiology during the past decades has been the comparison of the transcatheter closure of PDA, ASD and VSD with surgery. Surgical closure is reserved for patients whose families choose surgical repair or whose lesions remain unsuitable for device closure.² The alleged advantages of percutaneous occlusion over surgery can include avoidance of cardiopulmonary bypass (CBP) and its potential adverse sequelae, fewer complications, shorter hospital stay and superior cosmetic results.³

The cost-effectiveness of PDA, ASD and VSD transcatheter closure versus surgery is still a controversial issue in many countries.⁴ Comparisons of costs have yielded equivocal results in different countries and at different times. Relative professional

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fees for the interventionist and cardiac surgeon, cost of the device and length of hospital stay after the procedures can be the main determinants in this regard. Comparisons in terms of hospitalization have yielded shorter durations after device closure in almost all studies reported from different parts of the world.2,11

In Iran, cost implications are an important factor for patients or parents in choosing the right procedure. The Iranian government pays subsidies for intracardiac devices (around 50% of the actual price); therefore, it can be difficult to make a comparison between the situation in Iran and that in the Western countries. To the best of our knowledge, no previous studies have compared the hospital costs of the procedures in Iran. We, therefore, sought to conduct the current study.

Methods

We conducted a cross-sectional study of a randomized sample of 91 patients (40 patients with device closure and 51 patients with surgical closure), who were hospitalized in two large public hospitals of Tehran. We recruited patients admitted for the surgical or device closure of the ostium secundum ASD, VSD or PDA at Shaheed Rajayee Cardiovascular Center (SRCVC) and Children’s Medical Center at Imam Khomeini Hospital Complex (CMC/IKHC). All the patients were hospitalized in the pediatric wards of these hospitals and were in the pediatric age group (under 18 years of age). The study period was from January 1, 2005 until January 1, 2006. The study was restricted to patients with isolated VSD (all types), ostium secundum ASD and PDA. The other inclusion criterion was Iranian citizenship as the subsidy is paid only for Iranian patients. The implanted devices included the Amplatzer Ductal Occluder (ADO), Amplatzer Septal Occluder (ASO), Amplatzer Membranous Ventricular Septal Occluder (AMVSO) (AGA Medical Corporation, Golden Valley, Minnesota, USA) and Nit-Occlude coils (pfm AG, Köln, Germany).

The number of the patients that underwent each procedure is depicted in Table 1. Of the total patients, 76 (83.5%) were hospitalized and treated in SRCVC and 15 (16.5%) in CMC/IKHC. All the VSDs were of the perimembranous type. There was no significant difference in terms of the age of the PDA or ASD patients (p values were 0.715, 0.415 and 0.283 for ADO, coil and ASO patients, respectively, in comparison with relevant surgical patients). The VSD patients treated surgically were significantly younger than those treated with the device (4.34±4.77 and 16±2.94 years, respectively, for surgical and device closure groups, p value <0.001). Sex comparisons of the patients also yielded no significant differences (p values were 0.268, 0.637 and 0.162 for PDA, ASD and VSD patients, respectively).

The total cost for the patients or their parents were calculated including professional fees and device price. Comparisons of the detailed costs were beyond the scope of this study. Intraoperative transesophageal echocardiography was not performed for the surgical cases. All the costs were calculated before applying insurance discounts for the insured patients. The results were calculated in Iranian Rials and then converted to US dollars ($1=9200 Iranian Rials).

PDA and VSD device closures were successful in all the patients, but there was significant residual PDA after surgical ligation (5%) in one patient and significant residual VSD after surgery (7.1%) in another. ASD device closure was unsuccessful in one patient due to device embolization; the device was removed and the defect was repaired surgically. A similar situation occurred for a VSD device closure. Coil embolization occurred in one patient and was, subsequently, treated via repeated device occlusion. Other complications included postpericardiotomy syndrome (2 patients), apnea and cyanosis after the ADO implantation (1 patient), anemia requiring transfusion after the ADO implantation (1 patient), temporary complete heart block after VSD surgical closure (1 patient) and temporary supraventricular tachycardia after ASD surgical closure (3 patients).

Intensive care unit (ICU) stay was shorter for both PDA device closure and ASD device closure than that for surgery (p values were <0.001, 0.005 and 0.025 for ADO, coil and ASO closures, respectively, in comparison with the relevant surgeries); however, there was no significant difference with respect to VSD device closure (p=0.141). Floor bed stay was longer for all kinds of surgical closures (p values were 0.007, 0.038, 0.004 and 0.004 for ADO, coil, ASO and AMVSO closures, respectively, in comparison with the relevant surgeries). Comparisons of the hospitalization durations are shown in Table 2.

All the data were collected and analyzed using SPSS for Windows release 11.0.0 standard version. The independent-Samples T, Fisher Exact and Pearson Chi-Square tests were utilized, and p values lower than 0.05 were considered significant. Otherwise specified, data are presented as mean±standard deviation.

<table>
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<th>Procedure</th>
<th>Number of Patients</th>
<th>Table 1. Number of patients enrolled per procedure</th>
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<td>Table 1. Number of patients enrolled per procedure</td>
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<td>Surgery</td>
</tr>
<tr>
<td>VSD</td>
<td>14</td>
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</tr>
<tr>
<td></td>
<td>ASD</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>VSD</td>
<td>14</td>
</tr>
</tbody>
</table>

PDA, Patent ductus arteriosus; ASD, Atrial septal defect; VSD, Ventricular septal defect
Device Occlusion Versus Surgery for Closure ...

Table 2. Comparison of the length of hospital stays (in days) for PDA, ASD or VSD closures (surgery versus device occlusion)*

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Amplatzer Devices</th>
<th>Coil</th>
<th>p value</th>
</tr>
</thead>
<tbody>
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<td>Floor</td>
<td>ICU</td>
<td>Floor</td>
<td>ICU</td>
</tr>
<tr>
<td>PDA</td>
<td>9.10±6.10</td>
<td>1.30±0.73</td>
<td>4.71±1.69</td>
<td>0.35±0.49</td>
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<tr>
<td>ASD</td>
<td>12.8±8.36</td>
<td>3.65±3.24</td>
<td>4.20±2.62</td>
<td>1.60±0.97</td>
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<tr>
<td>VSD</td>
<td>12.4±8.09</td>
<td>3.29±2.30</td>
<td>4.50±2.08</td>
<td>1.50±1.73</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD

PDA, Patent ductus arteriosus; ASD, Atrial septal defect; VSD, Ventricular septal defect; ICU, Intensive care unit; Amp, Amplatzer devices

Table 3. Comparison of total costs (in US dollars) for PDA, ASD or VSD closures (surgery versus device occlusion)

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Amplatzer Devices</th>
<th>Coil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Floor</td>
<td>ICU</td>
<td>Floor</td>
</tr>
<tr>
<td>PDA</td>
<td>1697±218</td>
<td>1494±264</td>
<td>1136±440</td>
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<tr>
<td>ASD</td>
<td>2739±615</td>
<td>3160±1051</td>
<td>-</td>
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<tr>
<td>VSD</td>
<td>2637±354</td>
<td>3102±76.7</td>
<td>-</td>
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</table>

PDA, Patent ductus arteriosus; ASD, Atrial septal defect; VSD, Ventricular septal defect

Discussion

There has been a debate over the cost-effectiveness of PDA device closure versus surgery over the past years. In 1993, Gray et al.² from the USA reported that PDA device closure (Rashkind PDA occluder) was less costly than surgical closure ($11466 for device closure versus $8838 for surgery). But in a later study published in 1996, Hawkins et al.³ from the USA showed that the cost of PDA coil occlusion ($7105) was almost the same as that of surgery ($7101).

Since then, all studies comparing coil occlusion with surgery have yielded favourable results for the coil, including those of Kramer et al.12 from the USA ($4964 versus $2941), Agnetti et al.¹³ from Italy, Laohaprasitiporn et al.¹⁴ from Thailand, Vázquez-Antona et al.² from Mexico ($6964 versus $4412) and Prieto et al.¹⁷ from USA ($8509 versus $5273). Vázquez-Antona et al.¹⁸ also compared Amplatzer device occlusion with surgery and found that the costs were almost the same ($6964 for device versus $6815 for device occlusion). The reason for this trend is apparently the lower cost of newer devices.

It is now accepted that PDA coil occlusion is less costly than surgery wherever it is practiced.

The relative cost of PDA occlusion with the ADO is controversial in developing countries, where the professional fees for surgery or intervention are relatively low in comparison with the device cost; the cost difference in these countries, therefore, cannot be considerable. The present study also demonstrates that PDA device closure, whether with the ADO or with the coil, is cheaper than surgery in Iran. Professional fees are relatively low in Iranian public hospitals, but what makes ADO closure more affordable is probably the subsidy that Iranian government pays for intracardiac devices (around 50% of the actual price).

As we mentioned earlier, the cost-effectiveness of ASD closure is something of an enigma: ASD device closure maybe more or less expensive than surgery in different countries even when the same device (ASO) is used at relatively the same time. The reports that are in favor of surgery include those of Durongpisitkul et al. from Thailand (Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Sritoschati S, Ponvilawan S, Subtaweesin T, Kangkagate C. Comparison of atrial septal defect closure using Amplatzer septal occluder with surgery[Abstract]. Proceedings of the 3rd World Congress of Pediatric Cardiology and Cardiac Surgery, Toronto, Canada 2001:830.) and Vida et al.¹ from Guatemala ($3330 versus $4521). Thompson et al.¹⁸ from the UK arrived at almost equal costs (£5375 for ASO versus £5412 for surgery). In contrast, there are reports in favor of device occlusion, including those of Galal et al. from Switzerland (Galal MO, von Bremen K, Sekarski N, Payot M, Bernath M, Corno A, Hurni M, von Segesser L, Fanconi S, Kappenberger L. Cost-comparison of transcatheter and surgical closure of atrial septal defect in children[Abstract]. Proceedings of the 3rd World Congress of Pediatric Cardiology and Cardiac Surgery, Tokyo, Canada, 2001: 878.). Kim and Hijazi⁹ from USA ($25126 versus $39351), Hughes et al.² from Australia (Aus$11845 versus Aus$12969) and Khelashvili et al.¹⁰ from Georgia. The present study also shows statistically non-significant higher costs of ASD device closure ($3102 versus $2637, 15.4% higher) in Iran.

VSD device closure is the least studied device closure in terms of cost comparison. In the only other study in the existing medical literature, Xunmin et al.¹¹ found a non-significant difference between the two methods of VSD.
closure, albeit Amplatzer device closure was 10% more costly (¥48521 versus ¥44058). The current study found 17.6% higher costs, which is not far from the results of the above-mentioned study.

It should be reemphasized that the Iranian government pays subsidies for the devices and the calculated costs include the discounted fees for the implanted devices. But it should be noticed that subsidy is also paid for some materials used in the operating room. Cost calculation without considering these subsidies would be difficult and only performable based on the limited number of foreign patients for whom no subsidy is granted.

Although we tried to calculate all possible payments, there may be some other charges not included in the hospital documents. In addition, the costs related to time away from work or school was not included in the study. It is deserving of note, however, that most of the other similar studies have also not included this factor due to the difficulty in assessment.

**Conclusion**

PDA device closure either with the pfm Nit-Occlud coil or ADO is less costly than surgical ligation in Iran. Although ASD and VSD device closures are more expensive than their respective surgeries, the added costs can be affordable for the patients and their parents considering the benefits of device closure.

**Acknowledgment**

We wish to thank the staff of the Accounting Department of Shaheed Rajayee Cardiovascular Center, and the staff of the Pediatric Cardiac Surgery Ward of Imam Khomeini Hospital Complex for their great help.

**References**

Coronary Artery Bypass Surgery versus Medical Treatment in Patients with Low Ejection Fraction and Coronary Artery Disease

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Abstract

Background: We compared the outcomes in patients with a low ejection fraction (EF) and multivessel coronary artery disease (CAD) who either underwent coronary artery bypass grafting (CABG) or received medical treatment (MT) after a viability study via dobutamine stress echocardiography (DSE).

Methods: We considered patients with CAD and left ventricular ejection fraction (LVEF) <40% who were referred for DSE, and enrolled 106 patients (89% male, mean age: 55.8±9.7 years) with ≥4 viable segments. According to DSE, all the 106 patients were suitable for revascularization. We compared the outcomes between the patients who underwent CABG and those who received MT at a mean follow-up time of 8 months.

Results: Both groups had similar baseline characteristics and rest EF. Thirty-three (31.1%) patients underwent CABG and 73 (68.9%) received MT. There was no significant difference between the CABG and MT groups in terms of mortality rate (9.1% vs. 11.0%) and improvement in New York Heart Association functional class at follow-up. In the CABG group, patients with LVEF <25% had higher mortality compared to patients with LVEF >25% (100% vs. 40%, P< 0.05).

Conclusion: The patients with CAD and a low EF had the same survival rate after both CABG and MT at mid-term follow-up. Long-term follow-up is needed to show the survival benefit of CABG in such patients with an acceptable extent of viable myocardium.

J Teh Univ Heart Ctr 3 (2008) 145-150

Keywords: Stress echocardiography • Coronary artery bypass • Heart failure

Introduction

Large registries and randomized trials comparing coronary artery bypass grafting (CABG) and medical treatment (MT) have shown improved survival rates in patients with reduced left ventricular ejection fraction (LVEF) and multivessel coronary artery disease (CAD) who undergo surgery. However, such patients have increased surgical risk and lower long-term survival rates than those with better ventricular function. Further trials have demonstrated that patients with CAD and low EF benefit from CABG if there is adequate viable myocardium. There is still no consensus...
about the number of viable segments that are required to perform CABG, with suggestions varying between 3 and 8 viable segments in different studies.7,8 Determining viability in areas of the myocardium with severe regional dysfunction may be important in patients with severe LV systolic dysfunction and multivessel CAD in whom CABG is contemplated.9-13 Due to the scarcity of data on the relation between myocardial viability and clinical outcome, it is still a matter of debate whether survival in patients with a low EF and multivessel CAD can be predicted by dobutamine stress echocardiography (DSE).

This study was designed to compare the outcomes of patients with a low EF and multivessel CAD who either underwent CABG or received MT with an acceptable extent of myocardial viability as assessed by DSE.

**Methods**

Between March 2003 and January 2005, 106 patients with LVEF <40% and documented CAD underwent DSE for a clinical assessment of myocardial viability. Patients with unstable angina, congestive heart failure occurring within one month of the study, significant valvular disease, and technically inadequate echocardiographic imaging were not included in this study.

Baseline characteristics and clinical findings before the study were: age, sex, risk factors for CAD (hyperlipidemia, renal failure, family history, and diabetes mellitus), EF, left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), New York Heart Association (NYHA) classification for heart failure, myocardial viability, and mortality rate. Patient status and NYHA functional class were obtained at follow-up for each patient.

Baseline evaluations before treatment (CABG or MT) included cross-sectional echocardiography at rest and during dobutamine infusion. According to DSE, all the patients were suitable for revascularization. All these patients were discussed in a committee comprised of a group of surgeons and cardiologists to make treatment decisions on the strength of clinical and revascularization characteristics. The patients were divided into 2 groups of CABG and MT according to the committee’s decision.

Echocardiography was performed with a 2.5-MHz transducer, Toshiba, version 5000, under resting condition and during each dobutamine infusion step. Beta-blockers, calcium antagonists, and nitrates were discontinued in the patients at least 2 days before DSE.

After baseline echocardiography, dobutamine infusion was started using a mechanical pump. Dobutamine was delivered intravenously beginning at 5 µg/kg/min for three minutes, followed by 5 µg/kg/min increments every three minutes and increased to 15µg/kg/min for an additional three minutes. Blood pressure was measured periodically, and 12-lead ECG was continuously monitored throughout the study and during the recovery phase. The termination of the infusion was due to severe hypotensive or hypertensive response, significant arrhythmias, prolonged angina, significant electrocardiographic changes, or completion of the protocol. The echocardiographic images were analyzed off-line, and a 16-segment model was used as suggested by the American Society of Echocardiography.14 Segmental wall motion at rest was scored on a four-point scale: normal or mildly hypokinetic=1, severely hypokinetic=2 (decreased endocardial excursion and systolic wall thickening), akinetic=3 (absence of endocardial excursion and systolic wall thickening), and dyskinetic or aneurismal=4 (paradoxical outward movement in systole).15

The demonstration of wall thickening in a previously akinetic segment or normalization of thickening in a previously hypokinetic segment was considered as a criterion for myocardial viability.16 A dysfunctional LV segment was considered viable if the infusion of dobutamine at 10 or 15µg/kg/min resulted in the improvement of wall motion of at least 1 point. A patient was considered to have adequate myocardial viability for CABG if ≥4 segments demonstrated viability. This definition was based on previous reports demonstrating that evidence of viability in ≥4 segments during DSE is associated with a significant improvement in LVEF after revascularization.9,10,17 In addition, the viability score for each patient was calculated: segments showing viability were assigned a score of 1 and segments without viability a score of zero. By summing the grades of 16 segments, and because the maximal possible viability score was 16, the viability score was divided by 16 to yield a viability index. LVEF was measured at baseline using an available software program that applied Simpson’s rule on the two-chamber and four-chamber views.

Surgery was performed by cardiac surgeons using cardiopulmonary bypass. The median number of grafts was 3 (range: 1-5). The mean cardiopulmonary bypass time was 66 minutes, and the aortic clamp time was 42 minutes.

Follow-up was commenced in April 2005 and lasted for 3 months (until June 2005). Survival status was determined by contacting all the patients or next-of-kin by telephone. Cardiac events during late follow-up were defined as cardiac death. Cardiovascular death was defined as death from stroke, acute myocardial infarction, and refractory congestive heart failure as well as any sudden, unexplained death.

The mortality rates and changes in NYHA functional class at follow-up were compared between the groups. Additionally, EF at rest and stress, amount of increase in EF by stress, LVESV, LVEDV, and viability index were compared between the two groups.

The numerical variables were presented as mean±SD, and the categorical variables were summarized in percentages. The continuous variables were compared using the Student’s t-test or paired t-test, and the categorical variables were compared using the Fisher exact test. A P value less than 0.05 was considered statistically significant.
Results

From the 106 study patients, 33 (31.1%) underwent CABG and 73 (68.9%) received MT. The CABG group was comprised of 30 (91%) men and 3 (9%) women at a median age of 56.24±9.76 years (range: 36 to 70 years), and the MT group comprised 61 (84%) men and 12 (16%) women at a mean age of 56.24±9.76 years (range: 33 to 75 years). The mean follow-up time was 8 months.

The groups had no significant difference regarding the risk factors. Table 1 depicts a comparison between the baseline and follow-up characteristics of the groups. Before treatment, the CABG group had a significantly lower NYHA score. After treatment, this difference reached a non-significant level. There was no significant difference between the mortality rates of the groups (9.1±5% vs. 11.0±3.7%). LVESV and LVEDV were not significantly different between the dead and surviving patients in both groups.

Table 1. Comparison of baseline and follow-up characteristics of patients in CABG and medical treatment groups*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CABG group (N=33)</th>
<th>MT (N=73)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54.82±9.15</td>
<td>56.24±9.76</td>
<td>NS</td>
</tr>
<tr>
<td>Men (%)</td>
<td>30 (90.9)</td>
<td>61 (83.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at rest</td>
<td>29.29±6.47</td>
<td>28.84±8.20</td>
<td>NS</td>
</tr>
<tr>
<td>at stress</td>
<td>36.63±9.32</td>
<td>37.29±10.51</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (cm³)**</td>
<td>144.79±8.94</td>
<td>141.45±5.99</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (cm³)**</td>
<td>103.77±7.99</td>
<td>100.66±5.46</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA classification</td>
<td>3.24±0.75</td>
<td>3.53±0.52</td>
<td>0.05</td>
</tr>
<tr>
<td>Viability index</td>
<td>0.61±0.15</td>
<td>0.65±0.14</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA classification</td>
<td>1.46±0.62</td>
<td>1.67±0.93</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>9.1</td>
<td>11.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD unless specified
**P values calculated using independent two-sample t-test or Fisher’s exact test
***Mean±standard error
CABG, Coronary artery bypass grafting; MT, Medical treatment; NS, Non-significant; EF, Ejection fraction; NYHA, New York heart association; LVEDV, Left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume

The viability index, EF at rest, and EF at stress of the dead and surviving patients were also compared between the two groups (Table 2).

Table 2. Comparison of viability and EF of dead and surviving patients in terms of CABG and Medical treatment groups prior to treatment

<table>
<thead>
<tr>
<th>EF rest (%)</th>
<th>CABG 25±0</th>
<th>MT 22±5</th>
<th>0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viability index</td>
<td>CABG 0.62±0.06</td>
<td>MT 0.55±0.12</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD
P values calculated via independent two-sample t-test for the number of viable segments for dead and surviving patients
EF, Ejection fraction; CABG, Coronary artery bypass grafting; NS, Non-significant; MT, Medical treatment

In both study groups, the surviving patients had a markedly higher EF at rest. In the MT group, EF at stress was markedly higher in the surviving patients; but this was not significant in the CABG group. The amount of increase in EF after dobutamine infusion had no significant effect on mortality in both groups.

It is noteworthy that the viability index was not significantly different between the dead and surviving patients in the CABG group, but the extent of viability was significantly smaller in the dead than that in the surviving patients of the MT group.
Discussion

Because ischemic LV dysfunction is the most common cause of heart failure, proper management of this group of patients is important. There are conflicting views in previous reports over whether CABG can improve survival in patients with severe LV systolic dysfunction. The identification of patients with CAD and LV systolic dysfunction that may benefit from revascularization is, therefore, important. The presence of myocardial viability has been shown to predict improvements in LV function after coronary revascularization. Nevertheless, it is not clear what extent of viable myocardium is needed to improve the outcome after revascularization.

Among different modalities, DSE has been shown as a strong predictor of the recovery of contractile function after revascularization. Afridi et al. demonstrated improved survival with revascularization in patients with CAD and LV dysfunction who showed myocardial viability in four or more segments as assessed by DSE. In their setting, the decision for revascularization was made by the physicians and the study groups were classified based on DSE findings and revascularization status. They reported that the main predictor of mortality among patients with multivessel CAD and severe LV dysfunction who did not undergo CABG was a low EF at rest. Our data also confirmed this notion, and the mortality rate in our study was higher in patients who underwent CABG with LVEF ≤25% at rest.

A "viability index" derived from thallium uptake during rest redistribution scintigraphy was shown to predict cardiac event-free survival after bypass surgery in 70 patients with LV dysfunction by Pagley PR et al. We also used the viability index to assess the prognostic value of a viability study by DSE. The viability index was not significantly different between the dead and surviving patients in our CABG group. It is probably due to the fact that our follow-up time was not long enough to show the survival benefit of CABG. It is deserving of note that previous reports have shown increased period of 8 months. Along with the number of viable segments, a reduced EF is also of great importance in selecting patients who are likely to benefit from CABG.

Acknowledgment

This study was supported by Tehran Heart Center, Tehran University of Medical Sciences. We wish to thank the surgery data base group in Tehran Heart Center for data collection. Thanks are also due to Mrs. Mahnaz Forghani and Mrs. Neda Karimi for their assistance with data entry.

Conclusion

The patients with CAD and a low EF at rest had the same survival rate after both CABG and MT at a mean follow-up period of 8 months. Along with the number of viable segments, a reduced EF is also of great importance in selecting patients who are likely to benefit from CABG.

References

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Transcatheter Closure of Patent Ductus Arteriosus Using the Amplatzer Ductal Occluder: Early Results and Midterm Follow-Up

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Abstract

Background: The transcatheter closure of patent ductus arteriosus has advanced rapidly with improvements in device designs. The aim of this study was to analyze the safety, efficacy, and early and intermediate follow-up results of the percutaneous closure of persistent ductus arteriosus (PDA) with the Amplatzer ductal occluder (ADO) in children.

Methods: Between May 2004 and March 2007, fifty patients between 7 months and 20 years of age underwent the transcatheter closure of PDA, using the ADO. The mean PDA diameter at its narrowest segment (pulmonary end) was 7.35±2.57 mm (range: 4 to 16mm). Follow-up evaluations were performed via echocardiography at 24 hours, and 1, 3, 6, and 12 months and then yearly after implantation.

Results: Successful immediate occlusion of PDA was achieved in 42 (84%) of the 50 cases. In 5 cases, there were trivial intraprosthesis shunts. In addition, there was a small residual shunt in one case, left pulmonary artery narrowing in one case, and embolization of the device immediately after the procedure in one case. At 24 hours, color Doppler flow mapping revealed complete closure in all except one case with a small shunt. At 3 months' follow-up, occlusion was complete in all the patients. At a median follow-up of 17 months (range: 3 months to 32 months), all the patients had complete closure.

Conclusion: We conclude that although the transcatheter closure of PDA using the ADO is a highly effective and safe treatment for most patients, several complications including embolization and left pulmonary artery narrowing may occur in certain cases.

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Keywords: Patent ductus arteriosus • Child • Infant • Follow-up studies

Introduction

The reported incidence of persistent ductus arteriosus (PDA) varies because of methodological differences related to the population group studied, age of consideration, and method of detection. Although ductus arteriosus is usually functionally closed within 48 hours of birth, some authors consider the patent ductus to be abnormal only after 3 months of age. In children born at term, the incidence of PDA has been reported to be about 1 in 2000 births. As an isolated lesion, PDA represents 9-12% of all congenital heart diseases. Surgical closure by ligation or division is an effective treatment, but it carries the potential risk of morbidity and rarely, mortality associated with thoracotomy, especially...
Degenerative changes such as calcification, friability, and aneurysm formation with advancing age make the conventional procedure of division and ligation difficult and may mandate the use of a more invasive approach including total cardiopulmonary bypass and trans-aortic patch closure. Currently, the benefits of the transcatheter closure of PDA compared to surgical closure seem obvious in terms of shorter in-hospital stay, high success rates, no scar, and insignificant morbidity.

The percutaneous closure of PDA using an Ivalon plug device was first described by Porstmann in 1966. The Porstmann plug was not widely used because of a large-sized arterial delivery sheath and was, therefore, followed by the Rashkind and Cuaso, later by Sideris, and recently by Amplatzer.

The transcatheter occlusion of PDA using various occluding devices and coils is a widely accepted alternative to surgical closure in most pediatric centers. The Amplatzer ductal occluder (ADO) (AGA medical, Golder Valley, MN, USA) is a new device with easy placement. It is reported to have a higher rate of occlusion than do the other occluders currently available for the transcatheter closure of PDA.

Morphologically, there have been a number of different anatomical variants of PDA described. In general, it is simplest to think in terms of three types of lesions. The main type is “the Krichenko Group A” lesion, which is typically saucer-shaped, conical, or funnel-shaped; approximately 80% of all PDAs fall within this category. The next common type is the “Krichenko Group B lesion” which is window shaped, short length and has narrowing at the aortic end. Less common is the tubular lesion (Krichenko Group C), which is long and has no focal narrowing.

The aim of this study was to evaluate the efficacy and safety of the ADO over short and intermediate terms for the closure of PDA.

**Methods**

Between May 2004 and March 2007, fifty (14 boys and 36 girls) patients underwent the transcatheter occlusion of PDA. Age at intervention ranged from 7 months to 20 years (mean age: 6.11 years). Medium weight was 18.2 kg (range: 6 to 65 kg). All the patients had clinical and echocardiographic findings of PDA. Seventeen patients had symptoms of heart failure and/or failure to thrive. Associated anomalies observed included mild aortic stenosis (2 patients), small ventricular septal defect (1 patient), medium-sized ventricular septal defect (1 patient), and mild pulmonic stenosis (1 patient). One of the patients had a residual PDA following surgical ligature.

The Amplatzer (AGA) ductal occluder is a self-expanding nitinol stent that is made up of a flat retention flange that is placed on the aortic wall and a tube (which is placed in the PDA itself) that contains thrombogenic material (a polyester patch sewn to the nitinol stent). The diameter of the retention flange is 4 mm larger than the tube sheath, which is in the form of a cone; the pulmonary end of the cone is 2 mm smaller than the end that is attached to the retention flange. Different ADO models refer to the size in millimeters of the two ends of the tube: 6/4, 8/6, 10/8, 12/10, 14/12, 16/14, and 18/16. The total length of the device is 7 mm in the 6/4 and 8/6 models, and 8 mm in the remaining models.

Informed written consent was obtained from the parents of all the patients. In brief, routine right and left heart catheterization was performed usually under local and sedation regimen. Prophylactic antibiotics with 30 mg/kg cephazoline were administered at the beginning of the procedure and two subsequent doses 8 hours apart, and 100 IU/kg of sodium heparin was administered after catheterizing the artery.

A monoplane left anteroposterior and lateral descending aortogram was performed to outline the ductus and obtain the required measurements that included the length of the PDA, the diameter at the narrowest part, the aortic ampulla, and the center of the PDA (Figure 1).

The device was chosen to be at least 1 to 2 mm larger than the narrowest part of the PDA. Under fluoroscopic guidance, the ADO was advanced via a delivery cable until the retention disk was extruded in the descending aorta across from the ampulla. The disk was opened into the distal thoracic aorta in order to avoid possible damage of the aortic wall by the small metal protrusion of the disk. The device was then pulled gently against the aortic ampulla. An angiogram was performed to assess the position of the device.
prior to the deployment of the tubular part of the prosthesis. If the position was satisfactory, then using gentle tension on the delivery cable, the sheath was pulled back to deploy the rest of the device. With the device still attached to the cable, repeat descending aortography (hand injection of contrast medium) was performed to confirm proper device position and exclude left pulmonary or aortic obstruction. Once optimal position was confirmed, the ADO was released by counter-clockwise rotation of the delivery cable. A repeat angiogram was performed 10 minutes after the release to check for residual shunt (Figure 2). Repeat pressure pullback from the ascending aorta and left pulmonary was obtained. All the patients were discharged 24 hours after the procedure and given no medication.

All the patients had complete two-dimensional and color Doppler echocardiographic studies at 24 hours after the procedure and at 1, 6, and 12 months and then serially every 1 year thereafter. Special attention was paid to residual shunts and aortic or left pulmonary obstruction. Endocarditis prophylaxis was discontinued at six months’ follow-up if the duct was completely closed.

The parametric data are expressed as mean±SD, percentage, medium, and range. The data were analyzed with statistical program SPSS 11.0.1.

### Results

The device was successfully deployed in all the patients except in one patient, in whom, distal embolization of the device occurred immediately after the procedure. After the device was retrieved percutaneously, the patient underwent surgery. The mean age was 6.11±5.35 years, and the mean weight of the time of the procedure was 18.26±14.06 kg. The mean PDA minimal diameter (pulmonary end) was 5.58±2.57 mm (range: 4-16 mm). The pulmonary to systemic flow ratio (Qp/Qs) ranged from 1.4-3.3 (mean: 2.3±0.56). All the device sizes were used. Most of the devices employed were moderate sized (8 of the 6/4 device size, 14 of the 8/6, 17 of the 10/8, 7 of the 12/10, 2 of the 14/12, 1 of the 16/14, and 1 of the 18/16). The procedure time was 54.9±11.96 min (range: 40-90 min). Fluoroscopy time was 12.6±4.4 min (range: 6-25 min) (Table 1).

<table>
<thead>
<tr>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.11</td>
<td>4.5</td>
<td>5.35</td>
<td>0.58-20</td>
</tr>
<tr>
<td>18.26</td>
<td>12.5</td>
<td>14.06</td>
<td>6-65</td>
</tr>
<tr>
<td>2.3</td>
<td>2.3</td>
<td>0.56</td>
<td>1.4-3.3</td>
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<tr>
<td>5.58</td>
<td>7.35</td>
<td>2.57</td>
<td>4-16</td>
</tr>
<tr>
<td>12.6</td>
<td>12</td>
<td>4.4</td>
<td>6-25</td>
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<td>54.9</td>
<td>51</td>
<td>11.97</td>
<td>40-90</td>
</tr>
<tr>
<td>17.8</td>
<td>16</td>
<td>9.88</td>
<td>3-32</td>
</tr>
</tbody>
</table>

SD, Standard deviation; Qp/Qs, Pulmonary to systemic flow ratio; PDA, Persistent ductus arteriosus; FT, Fluoroscopy time; PT, Procedure time; F/U, Follow-up

In 8 patients, the devices were too small to close the defect; consequently, larger ADOs were implanted. Immediate complete occlusion of PDA was achieved in 42 of the 50 cases. In 5 patients, there were trivial intraprosthetic residual shunts immediately after the procedure. In one patient, there was a small residual shunt immediately, 24 hours, and 1 month after the procedure and complete occlusion was achieved two months after the procedure. Three patients required blood transfusion due to significant blood loss. Thrombosis of the right femoral artery occurred in 7 patients, and thrombosis of the left femoral artery occurred in 1 patient. Heparin (continuous intravenous infusion 20 unit/kg/h) was administered unsuccessfully in 4 patients. Streptokinase intravenous infusion (loading does 10000 u/kg over 60 minutes followed by 10000 u/kg for three hours) produced a successful and complete turn of pulses in three patients; another one patient underwent femoral thrombectomy. Mild inguinal hematoma occurred in two patients. None of the patients had a gradient through the aortic arch on post-implant hemodynamic evaluation. One patient had left pulmonary branches obstruction due to a large-sized Amplatzer (8/6). In one patient, distal embolization of the device occurred immediately after the procedure. After the device was retrieved percutaneously, the patient was sent to surgery.

All the patients had echocardiographic evaluations within 24 hours from the procedure. A small shunt continued to be seen in one infant (age:
9 months). The remaining 48 patients showed complete closure. The patient who had a small shunt had complete closure at 2 months’ follow-up. Thus, the closure rate was 100% at 2 months post implant. All the patients underwent echocardiography at 1, 3, 6, and 12 months and then yearly after the procedure. Echocardiography showed evidence of left pulmonary artery stenosis in one case 1 month after the procedure with a 40 mmHg gradient. There was no evidence of aortic obstruction, and nor was there any clinical evidence of hemolytic, bacterial arteritis, and early or late device embolization in any patient.

**Discussion**

The percutaneous closure of PDA is a well-established technique that has a low incidence of complication.14 Percutaneous closure with the new ADO has significantly improved the results of the transcatheter closure of moderate-sized and large ducts.15

The major advantages of the ADO over previous devices (such as double umbrella, controlled removable coils, etc.) are the smaller delivery sheaths (6-8 French), the ability to reposition the device before release, and a significantly lower rate of complications and residual shunts.10,12,16

The device has the advantage of closing a large PDA that otherwise may require long or multiple coils or special additional techniques that can render the procedure more difficult with potential coil embolization or protrusion causing pulmonary artery or aortic narrowing.17

Technically, the placement of the ADO is easy without complicating mechanisms. This significantly reduces the fluoroscopy time and shortens the learning curve for each operator. Indeed, the fluoroscopy time in this study was much lower than that reported for other PDA occluders, including coils.11,18,19

Faella et al.16 reported the immediate and short-term results of the international registry of the transcatheter closure with the ADO. Three hundred and sixty patients were treated at a median age of 2.1 years. The occlusion rate was up to 100% at one year’s follow-up. Seven patients experienced significant complications including death, hemolysis, transient asystole, device embolization, device misplacement, ST depression, and blood loss.

Bikis et al.20 reported on a long series of 205 patients with PDA occluded with the ADO. Closure was successful in all the patients. Complications occurred in 6 patients: embolization in 3, mild aortic narrowing due to large device in 1, and blood loss that required transfusion in 2.

Butera G et al.21 reported on a large series of 197 infants and young children with PDA occluded with the ADO. The occlusion rate was 100% at 24 months’ follow-up. Complications occurred in 3 patients: right femoral thrombosis in 1 patient and mild left inguinal hematoma in 2 patients.

In our study, the thrombosis rate in the femoral artery was as high as 16%. The main cause was the long time for the placement of the large artery sheath in the femoral artery. Femoral artery thrombosis can be successfully cured with urokinase or streptokinase intravenous infusion.21,22

In another study, the ADO was used in large ducts and coils were employed in patients with small to moderate-sized ducts. In group I (coil ductal occluder), PDA occlusion was successful in 207 (96.7%) patients. In group II (ADO), ductus closure was successful in 134 (98.5%) patients. There was no significant difference in the success rates between groups II and I. Distal embolization occurred in 19 patients of group I and in 2 of group II, respectively. Left pulmonary artery stenosis was found exclusively in 9 patients of group I at 6 months’ follow-up (P<0.05). Nine patients in group I required second intervention to achieve complete occlusion.23

Santoro G et al.24 reported on 34 patients with large PDA occluded with the ADO. Closure was successful in 97.1% patients over a mid-term follow-up. They concluded that percutaneous closure might be considered effective and safe also in large clinically significant PDA.

Li JJ et al.25 reported the successful use of the ADO to occlude PDA over a long-term follow-up (five years). According to the report of Li JJ et al.,25 late complications occurred in 5 patients, including hemolysis in 3 patients and loss of the femoral artery in 2 patients. The incidence of residual shunts at follow-up periods of 24 hours and 1, 2, 36, 48, and 60 months after device occlusion was reported to be 9.2%, 2.8%, 1.2% 0.8% 0, 0, 0, and 0, respectively. The previous reported incidence of residual shunts was 0% to 38%.10,12 In the present study, the incidence of residual shunts was 12%. Wang JK et al.26 reported that the transcatheter closure of moderate to large-sized ducts with the ADO was effective and safe. Several studies have reported hemolysis, device embolization, infection, and significant narrowing of the left pulmonary artery or descending aorta as major complications.26-29

We used the ADO for very large PDA (≥12mm); nonetheless, unfortunately left pulmonary artery stenosis occurred in one patient with a PDA size of 14 mm and the ADO size of 12/14. Our study showed that the immediate, short, and intermediate term results of PDA closure using the ADO were excellent, although two significant complications occurred: left pulmonary artery stenosis in 1 patient and distal embolization of the device in another patient. The previous reported Amplatz embolization rates ranged from 0% to 3%.12,20,26 In the present study, the embolization rate was 2%. It is worthy of note that left pulmonary artery narrowing is an infrequent complication.30 In our study, a single patient had a gradient 20 mmHg from left pulmonary artery to main pulmonary artery. At 18 months’ follow-up, this patient had a gradient on echocardiogram over 40 mmHg. Because of the small number of significant left pulmonary artery obstruction observed, conclusion as to the etiology or means of preventing this complication is not obvious from these data. However, in general, it seems likely that the use of a
large or oversized device in small patients might be a risk factor for this complication. Transcatheter occlusion has become the treatment of choice for most patent ducts in children and adults. In cases of calcified ductus arteriosus with increased pulmonary vascular resistance, transcatheter closure offers considerable advantages over surgical closure, which frequently involves cardiopulmonary bypass with an anterior approach through a median sternotomy. The surgical repair of the ductus is considered safe and carries a low morbidity and mortality. Repair does not require the use of cardiopulmonary bypass, but it does require general anesthesia and endotracheal intubation. Cases of recanalization or incomplete initial ligation have occurred after the use of surgical ligation only. With the more detailed and sophisticated techniques of evaluating these patients using color Doppler, the incidence of residual ductal patency following ligation seems to be higher.

Serious complications of surgical repair include inadvertent ligation of the left pulmonary artery or the descending aorta with catastrophic results. Morbidity after classical surgical repair is mainly due to lateral thoracotomy.

**Conclusion**

Percutaneous PDA closure with the ADO is an effective method for the treatment of PDA. The low incidence of complications and residual shunts makes this device ideal for the percutaneous closure of PDA. The immediate, short, and intermediate term results are very encouraging. Achieving complete closure in the catheterization laboratory is desirable but unnecessary, since most residual trace flows seen immediately after device placement will cease at follow-up. The transcatheter closure of moderate to large-sized ducts with the ADO is effective and safe; however, in very large PDA, it can cause left pulmonary artery stenosis. Further studies are required to document its efficacy, safety, and long-term results in a larger number of patients.

**Acknowledgement**

The authors wish to thank Dr. M. Dehghani for teaching us the technique of the PDA closure using the new ADO. This study was approved and supported by the Cardiovascular Research Center of Afshar Hospital.

**Reference**


persistent ductus arteriosus with the Amplatzer duct occluder in very young symptomatic children. Heart 2004;90:1467-1470.
Efficacy of Adenosine for Acute Treatment of Supraventricular Tachycardia in Infants and Children

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Abstract

Background: This study was done to assess the efficacy and adverse effects of the different doses of adenosine in the pediatric age group with respect to multiple patient variables.

Methods: Over a period of 1 year, 86 occasions of supraventricular tachycardia (SVT) were treated with adenosine in 81 infants and children aged between 18 days and 12 years (median of 1.3 years, SD=3). Adenosine efficacy was evaluated in terms of the patients’ demographics, SVT rate, electrocardiogram characteristics, and route of drug administration.

Results: The dose of 50 μg/kg was effective only in 24% of the SVT cases, and the additional doses of 100 μg/kg, 150 μg/kg, and 200 μg/kg were effective in another 29% of the cases. The drug efficacy was higher in the infants than that in the older children. There were no predictors other than age for the estimation of the efficacy of the drug.

Conclusion: Our findings showed that the current recommended doses of adenosine are ineffective in the vast majority of children and infants with SVT. No patient-related factor other than age seems to affect the efficacy of the drug.

Keywords: Tachycardia, supraventricular • Child • Infant • Adenosine

Introduction

Paroxysmal supraventricular tachycardia (SVT) is the most common symptomatic arrhythmia in young patients and affects children of all ages. Its prevalence is estimated at more than one in 500 children. The diagnosis of SVT is based on thorough clinical history and electrocardiogram (ECG). The characteristic features include abrupt onset and termination, fixed cycle length, normal QRS complexes, and usually an absence of clearly discernible P waves or flutter waves. SVTs may be divided into many sub-types electrophysiologically; however, there are certain general principles of therapy which apply to all patients regardless of the type of SVT. Intravenous adenosine is the first line drug for the termination of SVT in infants and children. Most authors recommend an initial dose of 50 to 100 μg/kg, while others solely recommend an initial dose of 100 μg/kg; be that as it may, if such doses are ineffective, following doses by increments of 50 μg/kg are recommended.

There are considerable controversies in the effectiveness and dosing of adenosine. Patient-dependent factors such as heart rate and administration route are thought to be the predictive factors for the effectiveness of adenosine in a few studies, while others do not find such results. The side

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effects of the drug also remain controversial.6,16,17

The aim of this study was to assess the effectiveness of the different doses of adenosine, as well as its side effects while considering multiple patient variables.

**Methods**

We conducted a prospective observational study on hospitalized children between November 2006 and 2007. During this period, 86 episodes of SVT in 81 patients (40 male and 41 female) were treated with intravenous adenosine. The diagnosis of SVT was based on clinical and ECG findings. The criteria for the rapid diagnosis of SVT were: 1- abrupt onset of arrhythmia, 2- fixed cycle length, 3- normal QRS complex duration, 4- uniform QRS complexes, 5- absence of clearly discernible P waves or flutter waves, and 6- heart rate of more than 180 per minute.

The patients were managed by pediatric cardiology fellows and trained staff in the emergency department, pediatric intensive care units, pediatric ward, and cardiac catheterization laboratory. All the patients were monitored continuously with a single-lead ECG from admission until 24 hours after the termination of the tachycardia and restoration of permanent sinus rhythm. The heart rate was recorded just before the administration of each dose of adenosine. A 12-lead ECG was obtained from all the patients after the termination of the tachycardia and was analyzed for P wave characteristics, PR interval, QRS axis and duration, presence of a delta wave, and calculation of corrected QT interval.

Adenosine was prepared as a sterile solution in 0.9% sodium chloride with 1mg/ml concentration. Each bolus was flushed immediately with physiological saline.

The route of drug administration was peripheral venous access in 48 episodes (right arm in 24, left arm in 14, right leg in 6, and left leg in 4) and central venous access in 38.

The data were analyzed with the Statistical Package for Social Sciences (SPSS, Chicago, IL) software (version 15.0) using conventional methods for mean and SDs. The comparisons between the groups were made by means of the non-parametric Mann-Whitney, Fisher, and Chi-square tests. P values of less than 0.05 were considered significant.

**Results**

The patients were between 18 days and 12 years of age (median=1.3, SD=3 years). Thirty-nine episodes occurred in the infants (aged 1 year or less), and the remainder in the older children. The weight of the patients ranged from 3 to 23 kg (median=8.2kg). Sixty-six patients had structural cardiac anomalies, while 38 of them had undergone palliative or corrective interventions. The types of congenital heart disease (CHD) and relative interventions are summarized in Figure 1.

![Figure 1. Types of structural heart disease and interventions in supraventricular tachycardia patients](image_url)

DTGA, d- transposition of great arteries; TOF, Tetralogy of Fallot; TAPVC, Total anomalous pulmonary venous connection; AVSD, Atrioventricular septal defect; PDA, Patent ductus arteriosus; VSD, Ventricular septal defect; MVP, Mitral valve prolapse; AS, Aortic stenosis; PS, Pulmonary valve stenosis
Sixteen patients had a previous history of SVT. Fifteen patients used digoxin as a cardiac inotrope. Six patients had the Wolff-Parkinson-White (WPW) pattern on their surface ECG; two of them had a history of SVT and used propranolol. The patients’ characteristics are summarized in Table 1.

Table 1. Patients’ characteristics (n=81)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (49)</td>
</tr>
<tr>
<td>Infantile age</td>
<td>39 (48)</td>
</tr>
<tr>
<td>Older than 1 year</td>
<td>42 (52)</td>
</tr>
<tr>
<td>Structural cardiac anomaly (other than PFO and BAV)</td>
<td>66 (81)</td>
</tr>
<tr>
<td>Previous surgical intervention</td>
<td>38 (47)</td>
</tr>
<tr>
<td>History of SVT</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Digoxin usage</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Propranolol usage</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Wolf- Parkinson-White Syndrome</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

*Numbers in the parentheses show the related percentages

PFO, Patent foramen ovale; BAV, Bicuspid aortic valve; SVT, Supraventricular tachycardia

Factors other than age (sex, history of previous SVT, presence of CHD, previous cardiac surgery, anti-arrhythmic drug use, SVT rate, ECG characteristics, and route of drug administration) were not correlated statistically with adenosine efficacy.

All the patients who did not respond to adenosine were treated with other usual anti-arrhythmic drugs successfully (18 episodes with amiodarone, 12 with verapamil, 4 with digoxin, 4 with propranolol, and 2 with procainamide). No patient needed cardioversion.

No important side effect was detected after the administration of adenosine; note that transient complete heart block was not considered as a drug adverse effect.

Table 2. Treatment results in 86 episodes of supraventricular tachycardia in our study

<table>
<thead>
<tr>
<th>Adenosine dose</th>
<th>Completely controlled episodes</th>
<th>Transiently controlled episodes</th>
<th>Uncontrolled episodes</th>
<th>Controlled episodes with other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>50µg/kg (used for 76 episodes)</td>
<td>18</td>
<td>10</td>
<td>48</td>
<td>2 (Verapamil: 2)</td>
</tr>
<tr>
<td>100µg/kg (used for 66 episodes)</td>
<td>8</td>
<td>20</td>
<td>38</td>
<td>8 (Amiodarone: 4 Verapamil: 4)</td>
</tr>
<tr>
<td>150µg/kg (used for 50 episodes)</td>
<td>16</td>
<td>13</td>
<td>21</td>
<td>22 (Amiodarone: 8 Verapamil: 6 Digoxin: 4 Propranolol: 4)</td>
</tr>
<tr>
<td>200µg/kg (used for 12 episodes)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>8 (Amiodarone: 6 procainamide: 2)</td>
</tr>
</tbody>
</table>

*Adenosine was used 204 times for 86 episodes of supraventricular tachycardia (some episodes needed more than one dose of the drug). In 46 (53%) of the episodes, it was effective. All non-responding episodes to adenosine were treated with other antiarrhythmic drugs successfully.

Discussion

Adenosine is a purine nucleoside with a half-life of 15-30 seconds in humans.11 Its mechanism of action includes a direct effect on the activation of the adenosine-sensitive potassium current.18 The increase in potassium conductance shortens atrial action potential duration, hyperpolarizes the membrane potential, and decreases atrial contractility.

Similar changes occur in the sinus and atrioventricular (AV) nodes. In addition to these direct effects, adenosine antagonizes catecholamine-stimulated adenylate cyclase activity.18 When administered as a rapid intravenous bolus, adenosine should produce transient AV node block, terminating tachycardia using the AV node.19 These effects on the AV node and sinusatrial (SA) node will be brief, allowing normal sinus rhythm to resume. Even if the AV node block fails to terminate tachycardia, the resultant alteration in the AV relationship provides important diagnostic information.
Primary atrial tachycardia or ventricular tachycardia occasionally may be terminated by adenosine.1 Reinitiating of tachycardia may limit the clinical efficacy of this drug. A possible mechanism is the sinus acceleration that follows a bolus dose. This is a common mechanism of the initiation of SVT in small infants.19

The initial recommended dose of adenosine varies between 50 to 150μg/kg. Most authors recommend an initial dose of 50 to 100μg/kg,1,2,6-9 while others solely recommend an initial dose of 100μg/kg.10 Overholt et al.20 reported a mean effective dose of 114-131 μg/kg. Till et al.6 found a median dose of 150μg/kg to be effective. Dixon et al.12 reported that the dose of 50 μg/kg was effective in less than 10% of infants and children and that the dose of 100μg/kg was effective in less than 25% of infants and 50% of children.

Sherwood et al.10 found a 16% response to 50μg/kg. Losek et al.9 showed a 22% efficacy for doses up to 100μg/kg. We found that the dose of 50μg/kg was effective in 24%, doses up to 100μg/kg in 30%, doses up to 150μg/kg in 49%, and doses up to 200μg/kg in 53% of the cases.

A few researchers have reported the effect of SVT rate14 and route of drug administration11 on the efficacy of the drug. We studied multiple factors, including patient demographics (age, sex), patient history (previous SVT, CHD, antiarrhythmic drug use, and previous cardiac surgery), SVT rate, basal ECG characteristics (rate and rhythms, P wave characteristics, PR interval, QRS axis and duration, presence of delta wave, and QTc), and route of drug administration. We found that none of these factors other than age influenced the efficacy of the drug.

Dixon et al.6 found a lower response to adenosine in infants compared to children. Contrary to their findings, we found a higher response to adenosine in the infants by comparison with the children (69% vs. 40%, P=0.008).

Some researchers have demonstrated the side effects of the drug.10,14 We found no important side effects after the administration of adenosine; it is worthy of note, however, that we did not consider transient complete heart block as a drug adverse effect.

Conclusion

Our findings showed that the current recommended adenosine doses for the acute management of SVT might be ineffective in the vast majority of cases. Chiming in with some previous studies, the present study highlights the need for a review of the dose protocol of adenosine in SVT. We would propose different dose references for infants and children in light of significant differences in drug response. Our findings confirm that nearly all SVT episodes can be controlled with routine drugs and that adenosine is a safe drug with doses up to 200 μg/kg.

We found that multiple patient variables such as sex, history of previous SVT, presence of CHD, previous cardiac surgery, anti-arrhythmic drug use, SVT rate, ECG characteristics, and route of drug administration do not affect the efficacy of adenosine.

Acknowledgement

The authors wish to thank all the pediatric cardiologists and electrophysiologists of Shahid Rajaee Heart Center for their valuable assistance. We offer our special thanks to the pediatric cardiology fellows for their cooperation. Dr. H. Bakhshandeh is highly appreciated for his statistical aids.

References

Do C-Reactive Protein and Lipoprotein (a) Have Different Impacts on the Severity of Coronary Artery Disease in Diabetic and Non-Diabetic Patients?

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Received 25 January 2008; Accepted 29 March 2008

Abstract

Background: The potential role of lipoprotein (a) changes and also inflammation in coronary artery disease (CAD) have rendered these processes one of the most interesting objects of study in patients affected by type 2 diabetes mellitus. The aim of the current study was to evaluate lipoprotein (a) and other lipid profiles and also C-reactive protein (CRP) as the predictors of cardiovascular disease severity in non-insulin dependent diabetic subjects in comparison with non-diabetic CAD patients.

Methods: Between June and September 2004, 372 patients with CAD were enrolled at Tehran Heart Center. Non-insulin dependent diabetics accounted for 102 of the cases, and the remaining 270 were non-diabetics. The severity of CAD was evaluated using the Gensini score, and the effect of patient variables such as serum lipid concentrations and CRP on CAD severity in the diabetics was investigated and compared with that of the non-diabetics.

Results: The mean of the Gensini score, CRP, and serum concentrations of all the lipid profiles were similar between the diabetic and non-diabetic patients. In the diabetic group, a high CRP concentration ($\beta=0.200, Rs= 0.040; P=0.046$) was effective on the Gensini score, whereas lipoprotein (a) and lipid profiles did not influence CAD severity. In the non-diabetics, no significant relationships were found between the Gensini score and all the studied laboratory indices.

Conclusion: A high CRP level is an important predictor of the severity of CAD in diabetic patients with CAD.

Keywords: Diabetes mellitus • Coronary artery disease • Lipoprotein(a) • Inflammation

Introduction

Several studies have shown that the incidence of coronary artery disease (CAD) related to atheroma in patients with type 2 diabetes mellitus is higher than that of the general population and is accompanied with an increased total mortality rate. The greater mortality in these patients cannot be explained only by the presence of the classic risk factors.
for CAD such as smoking, hypertension, and an increased plasma cholesterol concentration. However, recent studies have presented hypotheses about a positive relationship between the occurrence of CAD and the changes in serum lipoprotein concentrations, especially high and low density lipoprotein and lipoprotein (a). Previous in vitro studies supported a pathophysiological role for lipoprotein (a) in the development of atherosclerosis and in some prospective studies; lipoprotein (a) concentrations were higher in the subjects who later developed ischemic heart disease than those in the control groups. In the Iranian population, high levels of serum lipoprotein (a) have been associated with increased risk of CAD in diabetic patients. It has also been indicated that the abnormalities in high density lipoprotein (HDL) might contribute to the well-established high risk of atherosclerosis in non-insulin dependant diabetes mellitus (NIDDM). Indeed, low HDL cholesterol has been found to be predictive of CAD events in a prospective study of NIDDM patients. Nevertheless, another study reported that the predictive value of HDL cholesterol was relatively weak. Recent research has shown that the inflammatory processes play an important role in CAD and other manifestations of atherosclerosis, that has been more highlight than in diabetic patients.

Given the potential role of lipoprotein (a) and other lipid profile changes and also inflammation in CAD, these processes have recently become one of the most interesting topics of study in patients affected by type 2 diabetes mellitus. Be that as it may, the data in the existing literature are still controversial, not least those on the Iranian population. Furthermore, most of the recent studies have demonstrated factors effective on CAD severity in diabetics and non-diabetics and confirmed significant differences between the two groups. In the present study, we sought to study the impact of these factors in CAD patients with and without diabetes mellitus so that we could determine the difference in CAD severity between diabetics and non-diabetics and also the main predictors of this severity in the two groups with the approach to the effects of lipoprotein (a) and the inflammatory index.

Method

We retrospectively searched the special angiography database for patients aged between 25 and 90 years who were candidates for angiography at Tehran Heart Center between June and September 2004. A total of 372 patients met these criteria and were, thereafter, divided into a group of 102 (27.4%) diabetics and a group of 270 (72.6%) non-diabetics. The patients were treated with insulin, and those undergoing valvular surgeries or non-cardiac procedures were excluded. CAD was considered significant if there was a 75% or greater stenosis in the cross-sectional diameter and 50% or greater stenosis in the luminal view. The severity of coronary atherosclerosis was also quantified using the Gensini score. The following data were included for analysis: 1) General characteristics: age and gender; 2) Risk factors for CAD: 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), hyperlipidemia (total cholesterol ≥5.0 mmol/l, HDL-cholesterol ≤1.0 mmol/l in men, or ≤1.1 mmol/l in women, and triglycerides ≥2.0 mmol/l), 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 ≥11.1 mmol/l or fasting plasma glucose ≥7.0 mmol/l or 2-hpp ≥11.1 mmol/l); 3) Homodynamic status: number of defected coronary vessels and severity of defected coronary vessels according to the Gensini scoring; and 4) serum C-reactive protein (CRP) level. Plasma glucose concentrations were assessed by means of a glucose hexokinase method (Pars Azmoon kits accredited by Bioactiva Diagnostica, Germany). Serum total cholesterol, HDL cholesterol, and triglycerides were measured via enzymatic techniques (Pars Azmoon kits accredited by Bioactiva Diagnostica, Germany). The Friedewald formula was used to calculate low density lipoprotein (LDL) cholesterol, except when the triglyceride level was >4.52 mmol/l. Blood pressure was calculated as the mean of two measurements, performed in the sitting position after 5 minutes of rest, using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, UK.). CRP level was measured by immunoturbidimetry (Pars Azmun, Iran), and lipoprotein(a) was measured using Tint ELIZA (Biopool, USA).

The results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student’s t-test for the continuous variables and the chi-square test or Fisher’s exact test if required for the categorical variables. Predictors exhibiting a statistically significant relationship with the Gensini score in the univariate analysis were taken for a multivariable linear regression analysis to investigate their independence. The data analyzer was anonymous, and data collection and processing were approved by the institutional review board of our heart center. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

The general characteristics and hemodynamic status of the patients are summarized in Table 1.
Table 1. Characteristics of diabetic and non-diabetic patients with coronary artery disease*  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetics (n=102)</th>
<th>Non-diabetics (n=270)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>54.9</td>
<td>76.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.0±10.1</td>
<td>57.4±10.6</td>
<td>0.026</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>50.0</td>
<td>45.6</td>
<td>0.448</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>68.6</td>
<td>35.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.9</td>
<td>34.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>76.5</td>
<td>58.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Recent MI</td>
<td>46.1</td>
<td>54.1</td>
<td>0.168</td>
</tr>
<tr>
<td>History of CVA</td>
<td>5.9</td>
<td>2.3</td>
<td>0.082</td>
</tr>
<tr>
<td>History of PVD</td>
<td>38.2</td>
<td>20.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gensini score</td>
<td>66.5±42.2</td>
<td>60.6±46.4</td>
<td>0.244</td>
</tr>
<tr>
<td>Number of coronary artery</td>
<td></td>
<td></td>
<td>0.038</td>
</tr>
<tr>
<td>involvement:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>13.7</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>30.4</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>55.9</td>
<td>43.3</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as percentage or mean±SD  
CAD, Coronary artery disease; MI, Myocardial infarction; CVA, Cerebrovascular accident; PVD, Peripheral vascular disease; PCI, Percutaneous coronary intervention

The mean age of the diabetic patients was higher than that of the non-diabetic patients (P=0.026). A history of cigarette smoking (P=0.002), hyperlipidemia (P<0.001), and hypertension (P=0.001) were also found more among the diabetics. Although a history of recent myocardial infarction and cerebrovascular disease was similar between the two groups, peripheral vascular disease had occurred more often in the diabetics. There was a significant difference in the number of defected vessels between the two groups (P=0.038). Single-vessel disease was more frequent in the non-diabetic patients, whereas three-vessel disease was detected more in the diabetics. However, the mean of the Gensini score was similar between the diabetics and non-diabetics (P=0.244), and so were the serum concentrations of lipoprotein (a) and lipid profiles (Table 2). The mean of CRP was not different between the two study groups.

Table 2. Laboratory indices of diabetic and non-diabetic patients with coronary artery disease*  

<table>
<thead>
<tr>
<th>Indices</th>
<th>Diabetics (n=102)</th>
<th>Non-diabetics (n=270)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final FBS</td>
<td>174.5±71.0</td>
<td>98.0±19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>199.8±95.6</td>
<td>184.7±103.5</td>
<td>0.190</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>209.1±47.2</td>
<td>208.3±49.1</td>
<td>0.882</td>
</tr>
<tr>
<td>LDL</td>
<td>129.9±41.1</td>
<td>134.1±41.1</td>
<td>0.397</td>
</tr>
<tr>
<td>HDL</td>
<td>38.4±10.4</td>
<td>39.2±9.0</td>
<td>0.506</td>
</tr>
<tr>
<td>Lipoprotein a</td>
<td>39.2±34.5</td>
<td>42.1±39.2</td>
<td>0.491</td>
</tr>
<tr>
<td>CRP</td>
<td>12.5±9.0</td>
<td>12.6±14.2</td>
<td>0.966</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD mg/dl  
FBS, Fasting blood sugar; LDL, Low density lipoprotein; HDL, High density lipoprotein; CRP, C-reactive protein

Our multivariate linear regression analysis showed that in the diabetic group, among all the studied patients’ laboratory indices, only a high CRP concentration was effective on the Gensini score adjusted for confounders and lipoprotein (a) and lipid profiles did not influence CAD severity (Table 3). In the non-diabetics, CRP concentration was a predictor of the severity of CAD (Table 4).

Table 3. Impact of laboratory indices on Gensini score in diabetic patients adjusted for confounders

<table>
<thead>
<tr>
<th>Indices</th>
<th>Univariate P value</th>
<th>Multivariate P value</th>
<th>Beta 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-21.026</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.069</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.143</td>
<td>0.631</td>
<td>-3.294</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.254</td>
<td>0.236</td>
<td>-10.826</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.383</td>
<td>0.205</td>
<td>-0.042</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.380</td>
<td>0.172</td>
<td>0.143</td>
</tr>
<tr>
<td>LDL</td>
<td>0.995</td>
<td>0.708</td>
<td>-1.369</td>
</tr>
<tr>
<td>HDL</td>
<td>0.062</td>
<td>0.056</td>
<td>-0.927</td>
</tr>
<tr>
<td>Lipoprotein a</td>
<td>0.994</td>
<td>0.287</td>
<td>0.118</td>
</tr>
<tr>
<td>CRP</td>
<td>0.046</td>
<td>0.005</td>
<td>1.208</td>
</tr>
</tbody>
</table>

LDL, Low density lipoprotein; HDL, High density lipoprotein; CRP, C-reactive protein

Table 4. Impact of laboratory indices on Gensini score in non-diabetic patients adjusted for confounders

<table>
<thead>
<tr>
<th>Indices</th>
<th>Univariate P value</th>
<th>Multivariate P value</th>
<th>Beta 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-21.026</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.069</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.194</td>
<td>0.160</td>
<td>-5.727</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.146</td>
<td>0.383</td>
<td>3.814</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.832</td>
<td>0.457</td>
<td>0.014</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.716</td>
<td>0.006</td>
<td>-0.129</td>
</tr>
<tr>
<td>LDL</td>
<td>0.898</td>
<td>0.543</td>
<td>-0.136</td>
</tr>
<tr>
<td>HDL</td>
<td>0.269</td>
<td>0.552</td>
<td>-0.124</td>
</tr>
<tr>
<td>Lipoprotein a</td>
<td>0.685</td>
<td>0.554</td>
<td>0.033</td>
</tr>
<tr>
<td>CRP</td>
<td>0.167</td>
<td>0.039</td>
<td>0.310</td>
</tr>
</tbody>
</table>

LDL, Low density lipoprotein; HDL, High density lipoprotein; CRP, C-reactive protein

Discussion

We studied the role of some laboratory indices such as CRP and lipoprotein (a) as predictors of CAD severity in type 2 diabetic patients and found a relation between the CRP level and CAD severity. Inflammation plays an essential role in the development of insulin resistance and type 2 diabetes mellitus, the initiation and progression of atherosclerotic lesions, and plaque disruption. CRP is a marker of low-grade inflammation and has a role in the pathogenesis of atherosclerotic lesions in humans. Pai et al. found a significant association between CRP levels and the risk of CAD. These findings are consistent with the role of these inflammatory markers in the elevated risk of...
cardiovascular events associated with type 2 diabetes. The association with the duration of diabetes mellitus supports the hypothesis that one of the mechanisms for the increased CRP in diabetic subjects may be a chronic inflammatory state. This state could result from endothelial damage and dysfunction caused by the diabetic state. Higher levels of CRP seem to be also associated with low levels of PON1 activity (an anti-inflammatory enzyme located on HDL, which protects against the development of atherosclerosis), providing a mechanistic link between inflammation and the development of atherosclerosis. Furthermore, the effects of high levels of CRP and both complications and mortality due to the progression of diabetes mellitus have been indicated. In a study by Machness et al. on patients with type 1 diabetes, CRP concentration was significantly higher in the presence of any complication, neuropathy, nephropathy, and retinopathy; whilst in the population with type 2 diabetes, a higher CRP concentration was found in the presence of any complication and CAD. Also, in another study, in patients with type 2 diabetes who had acute coronary syndrome, CRP seemed to be an independent predictor of cardiovascular death.

We also found that lipoprotein (a) was not an effective indicator of the severity of CAD in both diabetic and non-diabetic groups. Similarly, Govindaraju et al. in a study among the Indian population showed that in diabetics, there was a trend toward increased lipoprotein (a) levels compared to the controls, but the difference was not statistically significant. They also found no relationship between lipoprotein (a) levels and number of stenosed coronary arteries. In the Solfirizzi et al. study, elevated lipoprotein (a) levels did not appear to be an independent predictor of CAD among elderly patients, but high serum lipoprotein (a) was a CAD risk factor dependent on type 2 diabetes mellitus and the combined effect of high lipoprotein (a) and high LDL cholesterol increased coronary risk. However, in a cohort study by Tsimikas et al., Lp (a) lipoprotein levels showed a strong and graded association with the presence and extent of CAD. It has been demonstrated that a 10% reduction in LDL cholesterol during a lipid-lowering trial eliminates lipoprotein (a) as a predictor of subsequent angiographic progression of CAD. It seems that lipoprotein (a) is a CAD risk factor dependent on total cholesterol or LDL cholesterol, suggesting a direct atherogenic action of Lp (a) for its high affinity binding to glycosaminoglycans and fibronectin. Also, it seems that the atherogenicity of Lp (a) lipoprotein may be mediated in part by associated proinflammatory oxidized phospholipids. It has even been suggested that serum analysis for Lp (a) lipoprotein may become a useful tool for the identification in early life of members of a subgroup particularly at risk of developing CHD.

In our study, no significant difference in terms of serum Lp (a), LDL, HDL, and cholesterol concentrations was observed between the diabetic and non-diabetic patients. Similarly, Pedreno et al. found that serum Lp (a) levels were increased in patients with angiographically documented CAD, but there were no significant differences between the diabetic and non-diabetic patients, which indicated that elevated Lp (a) levels were specifically associated with CAD but not with type-2 diabetes mellitus. Also, in the Abdella et al. study, Lp (a) was not an independent risk factor for CAD in patients with diabetes mellitus. Serum Lp (a), a risk factor for coronary heart disease in some non-diabetic populations, is largely under genetic control and varies among ethnic and racial groups. Nonetheless, in the Solfirizzi et al. study, in the elderly, elevated Lp (a) levels did not appear to be an independent predictor of CAD, whereas this lipoprotein was a risk factor only in the subjects with type 2 diabetes mellitus and elevated LDL cholesterol.

**Conclusion**

The higher rate of main CAD risk factors, higher incidence of cardiovascular disease, and the effects of inflammatory factors on the progression of CAD complications in diabetic patients require multifactorial control for CAD risk reduction in this group of patients. Our findings indicate that a high CRP level could be an important predictor of CAD severity in diabetic patients with CAD and underscore the role of inflammatory processes in the progression of coronary lesions in these patients.

**Acknowledgement**

This research project was approved and supported by Medical Sciences/University of Tehran. The authors would like to thank the interviewers, who collected the information, and the participants, who devoted their time to the study.

**References**


Lipid Profile Comparison between Opium Addicts and Non-Addicts

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2Ghaem Hospital, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran.  
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Abstract

Background: This study was done to test the notion that opium can reduce serum lipids and decrease the risk of ischemic heart disease (IHD) in opium addicts; we made a comparison between the lipid profiles of opium addicts and non-addicts.

Methods: In this study, we compared 100 male opium addicts (according to the ICD-10 criteria) who had referred to addiction treatment centers with 75 healthy male non-addicts. The subjects filled out our research questionnaire and had their fasting serum lipid profile (total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride) evaluated.

Results: Among those with a body mass index (BMI) between 18 and 25, the total cholesterol level in the opium addicts was less than that in the control group; there was, however, no difference in terms of LDL, HDL, and TG between the case and control groups. There was a significant difference in BMI between the two groups, which requires further studies to investigate the reason.

Conclusion: Opium does not seem to have any impact on triglyceride, low density lipoprotein, and high density lipoprotein. Despite the lower total cholesterol levels in opium addicts (as a known side effect of opium on different body systems), it is not advisable that opium and its extracts be recommended to decrease the risk of IHD.

Keywords: Opium • Cholesterol • Lipoproteins • Triglycerides

Introduction

Ischemic heart disease (IHD) is the most frequent cause of death in most countries and is responsible for one million deaths yearly in the United States of America. There are several risk factors for IHD. Hyperlipidemia is one of the main risk factors in that it aggravates atherosclerosis and may lead to IHD.1 Controlling hyperlipidemia by nutritional regimens, exercise, and physical activity and use of anti-hyperlipidemic agents may be effective in the prevention of IHD. A change in life style is, therefore, the main step to prevent hyperlipidemia.1,2

Traditional concepts without a scientific basis in some cultures may create wrong habits. For instance, in Iran
opium users believe that opium decreases serum lipids and prevents IHD. There is not an abundance of related research in the existing medical literature, but some researchers have studied the effects of opium on diabetes\(^3\) and depression.\(^4\)

The present study compared the serum lipid profiles between opium users and a control group so as to detect any difference between these two groups for further interventions.

**Methods**

This case-control study recruited some male opium addicts who had referred to the addiction treatment centers in Mashhad, Iran and a control group comprised of men who did not use opium. Cluster randomized sampling was done, and 170 questionnaires were filled out in the case group and 140 questionnaires in the control group initially. However, the case and control groups were thereafter limited to 100 and 75 cases each.

Opium addiction was defined according to the ICD-10 criteria, and our study was conducted before the withdrawing plans. An epidemiologic questionnaire containing personal characteristics and lipid profile in fasting condition [total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG)] was filled out and subsequently evaluated by a private clinic laboratory (Imam Reza Hospital). A similar procedure was also performed for the control group. The inclusion criteria included being male and 20-50 years of age, and the exclusion criteria were a history of underlying diseases such as thyroid diseases, diabetes mellitus, end-stage renal disease, or obesity (BMI>30). The data were analyzed using SPSS software. The tables and curves were designed via the T test, and the one-way ANOVA test with covariates was utilized for data analysis.

**Results**

Both case and control groups were in the 20-50 year-old range. Other factors such as cigarette smoking were almost similar in both groups. The case group was comprised of opium addicts mainly (70.8%), the rest being addicted to opium extracts (20.8%) or both (8.4%).

The method of opium usage was by inhaling in 50%, eating in 33%, and both ways in 17%. Opium concentration was used by eating method mostly.

Forty eight percent of the cases were trying opium withdrawal for the first time, and 52% had tried it at least once before. No other medication was used simultaneously in 86% of the cases, but benzodiazepines were used in 9.8% and other sedative agents usage was reported in 4.2%.

The lipid profiles were compared between the case and control groups; and according to the T test, only the difference between the cholesterol levels of the two groups was significant (\(P=0.026\)) and the difference between the LDL levels was borderline and TG and HDL were almost similar in both groups.

In order to study the effect of BMI on lipid profile, we compared the BMI of the case and control groups. BMI was 22.27±3.25 in the case group and 24.52±2.86 in the control group, which means that the BMI of the addicts was significantly less than that of the non-addicts (\(P=0.001\)). If we do not take pseudo-correlation into account, then we can explain the lower BMI in the opium addicts. We would, accordingly, suggest the hypothesis that the low cholesterol level in the addicts was probably due to their lower BMI in comparison with the non-addicts.

We used the one-way ANOVA test to omit the effects of BMI. We focused our study on male opium addicts between 18 and 25 years of age and compared their mean cholesterol level with the control group. The mean cholesterol level in the case group was also significantly less than that of the control group (\(P=0.017\)). As a result, it could be argued that opium may decrease total cholesterol indirectly aside from weight loss in addicts.

### Table 1. Comparison between the lipid profiles of opium addicts and non-addicts

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Opium addicts</th>
<th>Non-addicts</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>178.01±31.62</td>
<td>190.90±35.44</td>
<td>0.026</td>
</tr>
<tr>
<td>TG</td>
<td>107.84±36.78</td>
<td>112.40±42.78</td>
<td>0.527</td>
</tr>
<tr>
<td>LDL</td>
<td>110.07±32.61</td>
<td>120.14±34.30</td>
<td>0.057</td>
</tr>
<tr>
<td>HDL</td>
<td>45.59±9.01</td>
<td>45.93±8.95</td>
<td>0.818</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD mg/dl
TG, Triglyceride; LDL, Low density lipoprotein; HDL, High density lipoprotein

We also studied lipid profile in the opium addicts with respect to the type of addiction and observed a significant difference between those who used opium and those who used its extracts. The only exception was HDL, which was almost similar in both groups (Table 2).

### Table 2. Lipid profile in addicts to opium and addicts to its extracts

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Opium addiction</th>
<th>Opium extract addiction</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>177.81±32.54</td>
<td>201.11±35.79</td>
<td>0.003</td>
</tr>
<tr>
<td>TG</td>
<td>107.75±36.57</td>
<td>129.22±42.35</td>
<td>0.025</td>
</tr>
<tr>
<td>LDL</td>
<td>105.74±29.03</td>
<td>121.76±23.75</td>
<td>0.017</td>
</tr>
<tr>
<td>HDL</td>
<td>45.58±9.03</td>
<td>43.5±6.77</td>
<td>0.278</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD mg/dl
TG, Triglyceride; LDL, Low density lipoprotein; HDL, High density lipoprotein
Discussion

According to our findings, there was a 20mg/dl decrease in the cholesterol level of the opium addicts with BMI in the range of 18-25 compared to the healthy subjects. The decrease in the cholesterol level was more significant in those addicted to opium compared to those addicted to its extracts. These findings, however, are not sufficient to make an exact judgment about the direct effect of opium on serum lipids because many other factors may influence lipid profile such as dietary habits, which are different between addicts and healthy people. As a result, our findings may be partly because of malnutrition among the opium addicts.

TG, LDL, and HDL levels were almost the same in both groups of our study, but a lower HDL level among addicts was previously reported in an article from Rafsanjan (2004). It is worthy of note that the difference in the HDL level between the two groups was not significant in our study.

There was a significant difference between the BMI of the addicts and non-addicts in our study. We are not able to provide a convincing explanation for the main cause. Be that as it may, the fact that drug addicts are liable to expend a considerable portion of their income on drugs renders their nutritional regimens different from those of the healthy people. The loss of appetite combined with drowsiness due to insufficient intake of opium could lead to weight loss. The direct effects of opioids and their alkaloids on weight and lipid profile require further investigations.

Wilgard et al. omitted the effects of age, sex, and cigarette smoking and reported a significant correlation between BMI and HDL or TG. Our findings also showed a significant correlation between TG and BMI in both case and control groups.

Opioids indubitably impact many body organs. Indeed, several opium derivative alkaloids such as lysine, urtinin, phenylalanine, tyrosine, tryptophan, and histidin are known to wreak havoc on the central nervous system. Furthermore, addiction to opioids imposes an extremely heavy financial burden on both the individual and the community. For instance, the cost of drug abuse during the mid 1990s in the United States of America was estimated at 110 billion dollars (International planning for drug addiction control. United National Foundation. Universal report, 2000). If these vast sums of money were, for example, allocated to the prevention of coronary artery diseases, we would witness a remarkable improvement in health indices.

Conclusion

In conclusion, our findings showed that opium had no impact on TG, LDL, and HDL. Our opium addicts had a lower total cholesterol level by comparison to the non-addicts; nevertheless, it is not advisable that opium and its extracts be recommended for effecting a decrease in the risk of IHD.

Acknowledgement

The authors wish to express their gratitude to Miss Azari R. as well as the addiction treatment centers in Mashad. We are also grateful to Dr Shojaeeeyan for statistical advice.

References

Significant Improvement in Severely Stunned Left Ventricle after Percutaneous Coronary Intervention

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

Abstract

This is a case of severely stunned left ventricle which occurred after a non-ST elevation myocardial infarction in a 76-year-old woman who was a known case of three-vessel disease. Her symptoms and cardiac function responded well to revascularization.

Keywords: Myocardial stunning • Angioplasty • Ventricular dysfunction

Introduction

For many years, the functional sequelae of chronic coronary artery disease were considered irreversible; evidence gathered over the past three decades, however, proves that this is not necessarily true.1 Cardiovascular research has led to the identification of three new and important phenomena: myocardial stunning, myocardial hibernation, and ischemic preconditioning. Myocardial stunning is characterized by transient contractile dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near normal coronary blood flow. Myocardial hibernation is a condition of sustained reduction of contractile function in hypoperfused but viable myocardium, which recovers completely upon reperfusion. Ischemic preconditioning refers to a phenomenon by which one or more brief periods of myocardial ischemia increases the ischemic tolerance against infarction by endogenous adaptive mechanisms.2 A number of studies, including non-randomized studies, have demonstrated that patients with post-ischemic heart failure may derive symptomatic and prognostic benefit from coronary revascularization, and most of this benefit is thought to be derived from the functional improvement of the hibernating myocardium.1,3

Case report

On 27 Oct. 2003, a 75-year-old woman referred to the emergency ward of our hospital for an evaluation of palpitation and chest pain. She was a case of three-vessel disease. A coronary angiography, performed three years previously, had made her a candidate for coronary artery bypass grafting (CABG) but she had refused to undergo surgery. A physical examination revealed rales on pulmonary auscultation and no cardiac murmur. In addition, S4 was
detected. An electrocardiographic study revealed ST depression on leads V4 to V6. An echocardiographic study revealed the following: ejection fraction (EF)=60%, mild aortic valve insufficiency, normal chamber size (end-diastolic diameter=5.0cm, end-systolic diameter=3.2cm), and normal left ventricular systolic function. The patient was discharged nine days later.

On 21 Feb. 2004, she referred to the emergency ward with recent chest pain and dyspnea on exertion. She was admitted with a diagnosis of non-ST elevation myocardial infarction. The findings in echocardiography included: severe left ventricular systolic and diastolic dysfunction (EF=30%, end-diastolic=3.7cm, end-systolic=3cm), anterior and lateral wall hypokinesia, apical akinesia, apicoseptal dyskinesia, mild aortic valve insufficiency, and mild mitral regurgitation.

A coronary angiography showed severe three-vessel disease with the following specifications (Figures 1A, 1B): left anterior descending artery: 95% long calcified stenosis at the proximal third and 50% stenosis at the mid third; left circumflex artery: 80% stenosis after the OM2 ostium; right coronary artery: cut-off from the proximal portion, retrograde moderate run-off; wall motion abnormality: anterolateral, anteroapical, apical, inferoapical, and mid-inferior akinesia; left ventricular (LV) size: enlarged; and left ventricular EF=20%.

The patient’s clinical condition precluded a viability study with myocardial perfusion scan or dobutamine stress echo. Due to the presumed high surgical risk, our cardiac surgeons refused to do CABG and recommended medical treatment. Unable to discharge her from CCU due to her symptoms including both refractory and repetitive chest pain and dyspnea, we opted to perform percutaneous coronary intervention (PCI) as a palliative treatment strategy. The procedure was carried out 17 days after her admission: percutaneous transcoronary angioplasty (PTCA) and primary stenting of the left anterior descending artery with two overlapping bare metal stents AVE-S660 2.75-24 (12 atm) (Medtronic Inc.) and Tron 3-28 (14 atm) (Tron, Pan medical Inc.) were performed. The procedural outcome was successful (Figures 2A, 2B).

The patient’s symptoms were relieved, and 2 days later she was discharged without any complications.

Twenty-seven months later, her cardiac symptoms were relieved significantly. She had no typical chest pain or dyspnea on exertion. Echocardiography was repeated twice and showed: EF=60%, LV size: normal (end-diastolic=5.2cm, end-systolic=3.1cm), and no regional wall motion abnormality. This is a typical case of severe myocardial stunning recovered by partial percutaneous revascularization.
Discussion

Coronary artery disease may lead to several serious outcomes including acute myocardial infarction and unstable angina, which were once believed to reflect the irreversible nature of the underlying cause(s). This point of view has been proven to be not necessarily true. Impaired resting left ventricular function due to chronically reduced coronary blood flow reserve that can be restored by revascularization has been attributed to myocardial hibernation. Hibernating myocardium is present in approximately one-third of patients with coronary artery disease and impaired left ventricular function. The time course of recovery of hibernating myocardium after revascularization is quite variable, from days to months. Slower recovery is typically associated with a longer duration of hibernation. Data obtained over the past several years have suggested that the restoration of the antegrade flow in the infarct-related artery may improve survival via a mechanism independent of the influence on the left ventricular function.

Our patient suffered from chronic myocardial ischemia, which forced her to refer to the emergency room on two separate occasions within four months. The second time she was referred with a documented non-ST elevation myocardial infarction. She was a known case of three-vessel disease and a candidate for CABG for three years.

In the clinical setting, stunning may coexist with persistently ischemic and infarcting myocardium; the benefit of therapeutic interventions on the stunned myocardium must, therefore, be weighed against potential deleterious effects on the ischemic myocardium. Interventions may be required when myocardial stunning is severe and involves large parts of the ventricle such that the ventricular pump function and the maintenance of adequate cardiac output and blood pressure are jeopardized. A few markers of myocardial viability have been detected through echocardiography and established by coronary angiography.

In our patient, the presence of angina pectoris and absence of Q waves on the ECG and a history of prior myocardial infarction were useful clues in favor of hibernation. She responded to revascularization well; her symptoms relieved noticeably and her cardiac function improved significantly.

Conclusion

The recognition of viable myocardium in a patient with LV dysfunction and symptoms of LV failure should prompt rapid revascularization. It is advisable that one not be disappointed when facing a falling ejection fraction; one should regard it as heart failure and bear it in mind that revascularization by PCI or CABG could cause significant improvements in the patient’s outcome.

Acknowledgement

We are indebted to Dr. Mehran Mahmoodian for technical assistance.

References

### International Cardiovascular Surgery Meetings Calendar (2008-2009)

<table>
<thead>
<tr>
<th>Congress</th>
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<td>61st Congress of the French Society for Thoracic and Cardiovascular Surgery</td>
<td>4-8 June 2008 Versailles, France</td>
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<td>EACTS Academy: European School for Cardio-Thoracic Surgery, Cardiac Course level B</td>
<td>9-14 June 2008 Bergamo, Italy</td>
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<td>Bypass, Balloons and Circulatory Support</td>
<td>9 June 2008 London, United Kingdom</td>
<td>Website: <a href="http://www.rcseng.ac.uk/education/courses/speciality/cardiosurgery.html">http://www.rcseng.ac.uk/education/courses/speciality/cardiosurgery.html</a></td>
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<td>IVth Biennial Conference of the Polish Society of Cardiotoracic Surgeons</td>
<td>12-14 June 2008 Warsaw, Poland</td>
<td>Website: <a href="http://www.kardiotorakokongres2008.pl">http://www.kardiotorakokongres2008.pl</a></td>
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<td>XIX National Congress of the Spanish Society for Thoracic - Cardiovascular Surgery (SECTCV)</td>
<td>19-21 June 2008 MÁLAGA, Spain</td>
<td>Website: <a href="http://19congresosectcv.unicongress.org/">http://19congresosectcv.unicongress.org/</a></td>
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<td>World Summit on Pediatric and Congenital Heart Surgery Services, Education and Cardiac Care in Children and Adults with Congenital Heart Disease</td>
<td>19-21 June 2008 Montreal, PQ Canada</td>
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<td>The 8th Symposium on Aortic and Mitral Reconstructive Surgery</td>
<td>20-21 June 2008 Brussels Belgium</td>
<td>Website: <a href="http://www.valvesymposium.org">http://www.valvesymposium.org</a></td>
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<td>APACVS 9th Annual Summer Educational Meeting</td>
<td>30 June-2 July 2008 Kailua Kona, HI United States</td>
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<td>Eurasian Workshop on Valve Repair</td>
<td>11-13 July 2008 Parumala, Kerala India</td>
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<td>Cardiac Surgical Unit Advanced Life Support</td>
<td>24-26 July 2008 Penrigh, Cumbria United Kingdom</td>
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<td>Terms and Techniques In Aortic Surgery For Trainees</td>
<td>22-24 September 2008 Liverpool, Merseyside UK</td>
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<td>Canadian Association of Thoracic Surgeons - 11th Annual Meeting</td>
<td>11-14 September 2008 Halifax, NS Canada</td>
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<td>2008 Heart Valve Summit – Case-Based Review: Medical and Surgical Management</td>
<td>18-20 September 2008 Chicago, IL United States</td>
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<td>2nd Meeting Towards Safer Repeat Cardiac and Thoracic Surgery - Hosted by The Heart Hospital, London</td>
<td>19 September 2008 London United Kingdom</td>
<td>Website: <a href="mailto:lrassociates@lycos.co.uk">lrassociates@lycos.co.uk</a></td>
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<td>International Meeting on Aortic Aneurysms</td>
<td>19-20 September 2008 Liège Belgium</td>
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<td>ESTS School of Thoracic Surgery (Practical course in the laboratory)</td>
<td>25-26 September 2008 Elanacourt France</td>
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<td>Birmingham Review Course In Cardiothoracic Surgery</td>
<td>2-5 October 2008 Bordesley East, Birmingham UK</td>
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<td>American College of Surgeons annual Clinical Congress Meeting</td>
<td>10-14 October 2008 San Francisco, CA United States</td>
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<td>13-18 October 2008 Bergamo Italy</td>
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<td>Annual Meeting of the Swedish Association for Cardiothoracic Surgery</td>
<td>16-18 October 2008 Lund Sweden</td>
<td>Website: <a href="http://www.sacts.org">http://www.sacts.org</a></td>
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<td>10th National Congress of the Turkish Cardiovascular Surgery Society</td>
<td>17-21 October 2008 Cesme, Izmir Turkey</td>
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<td>Fifty-Fifth Southern Thoracic Surgical Association Annual Meeting</td>
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<td>XXIV National Meeting of the Italian Society for Cardiac Surgery</td>
<td>8-11 November 2008 Rome Italy</td>
<td>Website: <a href="http://www.sicch.org/">http://www.sicch.org/</a></td>
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<td>10-15 November 2008 Bergamo Italy</td>
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<td>13th Congress on Cardio-Thoracic Surgery</td>
<td>15 November 2008 Woluwe, Brussels Belgium</td>
<td>Website: <a href="http://www.bacts.org">http://www.bacts.org</a></td>
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<td>Cardiac Surgical Unit Advanced Life Support</td>
<td>27-29 November 2008 Penright, Cumbria United Kingdom</td>
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<td>EACTS Academy: Cardio-Thoracic Surgery and Regenerative Medicine</td>
<td>28-29 November 2008 Bern Switzerland</td>
<td>Website: <a href="http://www.aec.org/education/programs/brochures/heartvalvesummit_08.htm">http://www.aec.org/education/programs/brochures/heartvalvesummit_08.htm</a></td>
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<tr>
<td>2nd Meeting Towards Safer Repeat Cardiac and Thoracic Surgery - Hosted by The Heart Hospital, London</td>
<td>19 September 2008 London United Kingdom</td>
<td>Website: <a href="http://courses.eacts.org/sections/CT/CTRegen/index.html">http://courses.eacts.org/sections/CT/CTRegen/index.html</a></td>
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<tr>
<td>ICR 2008: Integrated Cardiovascular Repair - Workshop 4th Interdisciplinary Workshop for Interventional Cardiologists, Cardiac Surgeons and Cardiac Intervention Teams</td>
<td>4-6 December 2008 Innsbruck Austria</td>
<td>Website: <a href="http://www.icrworkshop.at/">http://www.icrworkshop.at/</a></td>
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<td>Congress</td>
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<tr>
<td>Aortic Surgery and Anesthesia “How to do it”</td>
<td>11-13 December 2008 Milan Italy</td>
<td>Website: <a href="http://www.aorticsurgery.it">http://www.aorticsurgery.it</a></td>
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<tr>
<td>7th Biennial International Conference - Pakistan Society of Cardiovascular &amp; Thoracic Surgeons</td>
<td>18-21 December 2008 Peshawar Pakistan</td>
<td>Website: <a href="http://www.7bic.org">http://www.7bic.org</a></td>
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<tr>
<td>EACTS Academy: Cardiac and Thoracic Robotic Surgery</td>
<td>4-7 February 2009 Strasbourg France</td>
<td>Website: <a href="http://courses.eacts.org/sections/CT/RobSurg/index.html">http://courses.eacts.org/sections/CT/RobSurg/index.html</a></td>
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<tr>
<td>58th International Congress of the European Society for Cardiovascular Surgery</td>
<td>1-4 May 2009 Warsaw Poland</td>
<td>Website: <a href="http://www.escvs.org">http://www.escvs.org</a></td>
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<td>Advance Cardiac Techniques in Surgery - The Seventh in the Series - Surgical and Interventional Therapies for Heart Valve Diseases, Left Ventricular Failure, Aortic Arch Aneurysms and Atrial Fibrillation</td>
<td>6-7 May 2009 New York, NY United States</td>
<td>Website: <a href="http://www.promedicacme.com/">http://www.promedicacme.com/</a></td>
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<tr>
<td>Emergency in Cardiovascular Surgery: An Integrated Approach</td>
<td>18-23 May 2009 Erice.Sicily Italy</td>
<td>Website: <a href="http://www.ccsem.infn.it">http://www.ccsem.infn.it</a></td>
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## International Cardiovascular Meeting And Congresses Calender (2008-2009)

<table>
<thead>
<tr>
<th>Title</th>
<th>City</th>
<th>Start Date</th>
<th>End Date</th>
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<tr>
<td>American Society of Hypertension 23rd Annual Scientific Meeting and Exposition</td>
<td>New Orleans, United States</td>
<td>13 May 2008</td>
<td>17 May 2008</td>
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<tr>
<td>XVI World Congress of Cardiology</td>
<td>Buenos Aires, Argentina</td>
<td>18 May 2008</td>
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<td>Cardiology Essentials and Case Studies</td>
<td>Civitavecchia, Italy</td>
<td>21 May 2008</td>
<td>2 June 2008</td>
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<td>2nd Annual Sights and Sounds of Echocardiography in the Heart of the Big Apple</td>
<td>New York, United States</td>
<td>22 May 2008</td>
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<td>Cardiovascular CT at Concord</td>
<td>Sydney, NSW, Australia</td>
<td>23 May 2008</td>
<td>25 May 2008</td>
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<tr>
<td>Advanced Cardiac Life Support: 2 day</td>
<td>Tampa, FL, United States</td>
<td>23 May 2008</td>
<td>24 May 2008</td>
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<tr>
<td>16th Annual Congress of the Czech Society of Cardiology</td>
<td>Brno, Czech</td>
<td>24 May 2008</td>
<td>27 May 2008</td>
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<tr>
<td>The 2nd Asia-Pacific Congress of Pediatric Cardiology and Cardiac Surgery</td>
<td>Jeju Island, Korea</td>
<td>27 May 2008</td>
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<tr>
<td>Annual Congress of the Swiss Society of Cardiology</td>
<td>Berne, Switzerland</td>
<td>28 May 2008</td>
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<tr>
<td>Annual Meeting of the Austrian Society of Cardiology</td>
<td>Salzburg, Austria</td>
<td>28 May 2008</td>
<td>31 May 2008</td>
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<td>European Section Meeting of the International Society for Heart Research</td>
<td>Athens, Greece</td>
<td>28 May 2008</td>
<td>31 May 2008</td>
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<tr>
<td>Emory Symposium on Coronary Atherosclerosis (ESCAPE)</td>
<td>Amelia Island, United States</td>
<td>28 May 2008</td>
<td>28 June 2008</td>
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<tr>
<td>Annual Meeting of the Norwegian Society of Cardiology</td>
<td>Bergen, Norway</td>
<td>29 May 2008</td>
<td>31 May 2008</td>
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<tr>
<td>Certification Examination for Competency in Cardiac Rhythm Device Therapy for the Physician Preparation Course</td>
<td>Dallas, TX, United States</td>
<td>30 May 2008</td>
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<td>3C, Curso Cardiovascular de Caracas</td>
<td>Caracas, Venezuela</td>
<td>30 May 2008</td>
<td>31 May 2008</td>
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<td>XXXIX Annual Congress of the Italian Association of Hospital Cardiologists (ANMCO)</td>
<td>Firenze, Italy</td>
<td>30 May 2008</td>
<td>2 June 2008</td>
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<td>Annual Meeting of the Norwegian Society of Cardiology (Spring Meeting)</td>
<td>Manchester, United States</td>
<td>2 June 2008</td>
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<td>Cardiovascular Imaging: SPECT, PET &amp; CT</td>
<td>New Haven, United States</td>
<td>3 June 2008</td>
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<td>Duke Cardiovascular Research Symposium</td>
<td>Durham, NC, United States</td>
<td>3 June 2008</td>
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<td>18th International Symposium on Adult Congenital Heart Disease 2008</td>
<td>Toronto, Canada</td>
<td>4 June 2008</td>
<td>7 June 2008</td>
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<td>Advanced Cardiac Life Support: 2 day</td>
<td>Keywest, FL, United States</td>
<td>4 June 2008</td>
<td>5 June 2008</td>
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<td>16th Annual Meeting of the Alpe Adria Association of Cardiology</td>
<td>Portoroz, Slovenia</td>
<td>5 June 2008</td>
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<td>2nd Annual Pulmonary Hypertension Symposium</td>
<td>Westport, CT, United States</td>
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<td>Innovations in Treatment of Cardiac Structural Disease: The Mediterranean Meeting</td>
<td>Pittsburgh, United States</td>
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<td>The Annual Scientific Sessions of the American Society of Echocardiography - ASE 2008</td>
<td>Toronto, Canada</td>
<td>7 June 2008</td>
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<td>Ultrasound Techniques in Vascular Emergencies / 5°corso di Ecografia Vascolare in Emergenza</td>
<td>Florence, Italy</td>
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<td>5th Tunisian-European Congress on Cardiology Practice (Les 5 èmes Journées Tuniso Européennes de Cardiologie Pratique) pratique</td>
<td>Hammam, Tunisia</td>
<td>12 June 2008</td>
<td>14 June 2008</td>
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<td>Cardiovascular Diseases Symposium</td>
<td>Iowa City, IA, United States</td>
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<td>European Meeting on Hypertension 2008</td>
<td>Berlin, Germany</td>
<td>14 June 2008</td>
<td>19 June 2008</td>
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<td>Heart Failure 2008 Congress</td>
<td>Milan, Italy</td>
<td>14 June 2008</td>
<td>17 June 2008</td>
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<td>CARDIOSTIM - 16th world congress in Cardiac Electrophysiology and Cardiac Techniques</td>
<td>Nice, France</td>
<td>18 June 2008</td>
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<td>9th International Fetal Cardiology Symposium</td>
<td>Nice, France</td>
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<td>10th National Congress on Cardiovascular Update</td>
<td>Tehran, Iran</td>
<td>21 June 2008</td>
<td>25 June 2008</td>
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<td>Current Topics in Noninvasive Cardiovascular Imaging</td>
<td>San Diego, CA, United States</td>
<td>22 June 2008</td>
<td>27 June 2008</td>
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<td>H.E.A.R.T UK 22nd Annual Conference</td>
<td>Hatfield, UK</td>
<td>25 June 2008</td>
<td>27 June 2008</td>
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<td>ICI - Imaging in Cardiovascular Interventions</td>
<td>Frankfurt, Germany</td>
<td>28 June 2008</td>
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<td>20th International Congress on Thrombosis</td>
<td>Athens, Greece</td>
<td>25 June 2008</td>
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<td>CSI - 11th International Congress Congenital and Structural Interventions</td>
<td>Frankfurt, Germany</td>
<td>26 June 2008</td>
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<tr>
<td>14th Annual Scientific Session of the Society of Geriatric Cardiology</td>
<td>Washington, United States</td>
<td>27 June 2008</td>
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<td>The 1st World Congress on Controversies in Cardiovascular Disease Diagnosis, Treatment and Interventions (C-Care)</td>
<td>Berlin, Germany</td>
<td>3 July 2008</td>
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<td>14th World Congress on Heart Disease, International Academy of Cardiology Annual Scientific Sessions 2008</td>
<td>Toronto, Canada</td>
<td>16 July 2008</td>
<td>29 July 2008</td>
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<td>Heart Failure 2008</td>
<td>Amelia Island, United States</td>
<td>17 July 2008</td>
<td>20 July 2008</td>
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<tr>
<td>14th World Congress on Heart Disease International Academy of Cardiology Annual Scientific Sessions 2008</td>
<td>Toronto, ON, Canada</td>
<td>26 July 2008</td>
<td>29 July 2008</td>
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<tr>
<td>Cardiology &amp; Infectious Disease</td>
<td>Oslo, Norway</td>
<td>28 July 2008</td>
<td>9 August 2008</td>
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<tr>
<td>22nd Annual Echocardiographic Symposium at Vail</td>
<td>Vail, CO, United States</td>
<td>11 August 2008</td>
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<td>17th International Cardiovascular Symposium</td>
<td>Venice, Italy</td>
<td>12 August 2008</td>
<td>14 August 2008</td>
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<td>The Baltic Summer School 2008: Basic and Clinical Aspects of Cardiac Arrhythmias</td>
<td>Copenhagen, Denmark</td>
<td>17 August 2008</td>
<td>29 August 2008</td>
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<td>ESC Congress 2008</td>
<td>Munich, Germany</td>
<td>30 August 2008</td>
<td>3 September 2008</td>
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<td>Controversies and Advances in the Treatment of Cardiovascular Disease: The Eighth in the Series</td>
<td>Beverly Hills, United States</td>
<td>4 September 2008</td>
<td>5 September 2008</td>
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<td>Intraoperative Echocardiography in the 21st Century</td>
<td>Atlanta, GA, United States</td>
<td>4 September 2008</td>
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<td>19th Annual Coronary Interventions</td>
<td>San Diego, CA, United States</td>
<td>7 September 2008</td>
<td>19 September 2008</td>
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<td>Mayo Cardiovascular Review Course for Cardiology Boards and Recertification</td>
<td>Rochester, United States</td>
<td>20 September 2008</td>
<td>25 September 2008</td>
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<tr>
<td>12th International Congress of the Polish Cardiac Society</td>
<td>Poznan, Spain</td>
<td>25 September 2008</td>
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<td>6th Advanced Symposium on Congenital Heart Disease in the Adult</td>
<td>Thessaloniki, Greece</td>
<td>26 September 2008</td>
<td>27 September 2008</td>
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<td>AICT 2008: Athens Interventional Cardiovascular Therapeutics</td>
<td>Athens, Greece</td>
<td>26 September 2008</td>
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<td>3rd Georgian Congress of Cardiology</td>
<td>Tbilisi, Georgia</td>
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<td>XIII Annual Congress of the Slovak Society of Cardiology</td>
<td>Bratislave, Slovakia</td>
<td>5 October 2008</td>
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<td>National Congress of the Society of Cardiology of the Russian Federation</td>
<td>Moscow, Russia</td>
<td>7 October 2008</td>
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<td>Irish Cardiac Society Annual Scientific Meeting 2008</td>
<td>Galway, Ireland</td>
<td>10 October 2008</td>
<td>11 October 2008</td>
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<tr>
<td>Rheumatology &amp; Cardiovascular Medicine</td>
<td>Istanbul, Turkey</td>
<td>11 October 2008</td>
<td>25 October 2008</td>
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</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. Authors should comply with the manuscript formatting and the ethical conventions of the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” issued by the International Committee of Medical Journal Editors (http://www.icmje.org).

**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).

**Clinical trials**

Clinical trial reports should also comply with the Consolidated Standards of Reporting Trials (CONSORT) and include a flow diagram presenting the enrollment, intervention allocation, follow-up, and data analysis with number of subjects for each (www.consort-statement.org). Please also refer specifically to the CONSORT Checklist of items to include when reporting a randomized clinical trial.

**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.

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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 guidelines 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:


Chapter citation example:


Webpage citation example:

   http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004). Where the date in parenthesis refers to the access date.

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 the of submission. If no conflict of interest exists, please state this in the cover letter.

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<th>Full mail address:</th>
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<tr>
<th>P.O.BOX:</th>
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<th>Tell:</th>
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<th>Fax:</th>
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<tr>
<th>E-mail:</th>
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</table>

**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**
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Think S.M.A.R.T.®

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