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The Journal of Tehran University Heart Center

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

The Journal of Tehran University Heart Center is indexed in Scopus, EMBASE, CAB Abstracts, Global Health, Index Copernicus, Index Medicus for the WHO Eastern Mediterranean Region (IMEMR), SID and Iranmedex

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Beauty of Autumn, IRAN

TEHRAN HEART CENTER

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Editorial

Cardiac Stem Cell Transplantation

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Cardiac stem cell transplantation is being considered as a potential alternative for many patients with ischemic heart diseases. There is a variety of cells for this purpose including embryonic and adult stem cells each with unique advantages and limitations. Nevertheless, the most suitable stem cells for cardiac cellular therapy are usually characterized by their good potential for survival, growth, differentiation, and integration into the host myocardium as well as high availability and low immunogenicity and oncogenicity. Selection of proper timing and routes of delivery and the right dosings according to the lesion size and location is also critical for success of the stem cell therapy.

Today, ischemic heart diseases and the resultant heart failure are the leading cause of death and physical disability in many countries.[1] However, there are still considerable rates of morbidity and mortality despite contemporary medical treatments and interventional options thus leaving heart transplantation as the ultimate therapeutic choice in the most complicated cases.[2-3] Because of the many limitations of the mentioned approaches, cardiac stem cell transplantation is increasingly being considered as a potentially novel alternative to conventional therapies by restoring cardiac function and improving microcirculation in the damaged heart.[3]

The innovative concept and potential application of stem cells comes from the hematological field where bone marrow and hematopoietic stem cells have been used successfully for more than 30 years to treat diseases like leukemia.[4] Stem cells are a population of immature tissue precursors found in various organs among the body capable of proliferation as well as differentiation in to a spectrum of different cell types under proper circumstances. Stem cells in general share the following characteristics and have a high capacity for: 1) proliferation or self-renewal; 2) differentiation; 3) trans-differentiation or plasticity; and 4) ex-vivo cultivation for tissue engineering applications.[5,6] On the basis of their origins and biological potentials, stem cell can be classified into either embryonic or adult categories. Embryonic stem (ES) cells are derived from the inner mass of blastocysts and can virtually give rise to any cell type found in the body (i.e. more than 200 kinds of cells) including the cardiomyocytes.[3,7] This very high differentiation capacity of ES cells is referred to as totipotency (i.e. differentiating into all cell types of the embryonic three main layers) or pluripotency (i.e. differentiating into most body cell types excluding those belonging to the germinal lineage). Adult stem cells have a much lower differentiation capacity and usually produce only limited numbers of cell types; hence they are referred to as multipotent or oligopotent stem cells. Adult stem cells in certain tissues give rise only to one type of somatic cells (monopotent stem cells). Human ES cells, on the other hand, have the disadvantage of ethical and technical limitations associated with their use in clinical trials, higher risks of arrhythmogenicity and teratogenicity, and the need for immunosuppressive therapy after transplantation.[3]

The concept of cardiomyocyte transplantation has been advocated since the late 1990s.[8] Stem cell transplantation has since then opened a new frontier in the treatment of cardiovascular disorders. In addition to regeneration of new cardiomyocytes, stem cells can participate in angiogenesis and hence prevent remodeling in the diseased heart insulted by ischemic events.[8] There are several major issues in any cardiac stem cell therapy experiment including selection of a suitable source and type of stem cells, their right dosings, the optimum timing and proper routes of cell delivery, and to decide whether to expand and differentiate them in vitro prior to implantation. These issues are the keys to success of stem cell therapy. Stem cells should also be isolated and further reintroduced in a feasible, safe and minimally invasive approach. Hence, a well-designed study should provide the following conditions to achieve the most effective tissue repair and regeneration: 1) high rates of cellular survival and proliferation (i.e. they should be able to reach the injured area, stay alive, and proliferate in the injured tissues); 2) strong

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potency for cellular differentiation; 3) potential for highly effective engraftment and integration of implanted cells into the host myocardium (i.e. implanted cells should be able to contract after differentiation and form stable intercellular gap junctions and electromechanical couplings with surrounding cardiac cells thus enhancing the cardiac function).[3]

Currently, both embryonic and adult stem cells are used in experimental cardiac cell transplantation studies, while only adult stem cells (e.g. bone marrow-derived mononuclear or mesenchymal cells, skeletal myoblasts, endothelial progenitor cells) are widely used in clinical trials.[3,9-20] Each stem cell type has unique biological properties that offer both advantages and limitations to use as mentioned earlier.[21]

Combining cell transplantation with proangiogenic growth factors or gene-transfected cells may improve cellular survival, although supporting data are not sufficient.[3] A recent evidence suggests that direct injection of undifferentiated bone marrow cells into animal leads to apparent transdifferentiation, but in fact all differentiated cells are the result of cell fusion only, at least in liver, brain, and heart.[22] This would not then appear to be a reasonable strategy. The question thus arises whether adult stem cells from any source can be adequately expanded and induced to differentiate in culture to produce sufficient cell numbers for cell therapy in patients. It seems that expansion of the cells in culture and efficient introduction of differentiation to the required cell type (ventricular cardiomyocytes) is necessary for any cell-based cardiac therapy. As many as 10^9 differentiated cardiomyocytes would be required to replace those lost after myocardial infarction.[9]

Currently there are two main approaches for cellular delivery to target myocardium: 1) cellular cardiomyoplasty; defined as direct or indirect injection of isolated cells; and 2) tissue cardiomyoplasty; or development of scaffold-based cellular constructs in vitro that can be engrafted to the damaged myocardium during open-heart surgeries. Tissue engineered scaffolds can be provided in the forms of either biologic or synthetic materials.[10] The later approach has the benefit that relatively very large scale of cells could be delivered to the scar tissue via biodegradable scaffolds. These scaffolds play a prominent role both in promoting cell proliferation and in guiding cell growth and general tissue architecture. They can induce growth and proliferation of cardiac cells into biologically relevant contractile spindle structures.[23-25] Since the first human trial published in 2001 by Menasche et al.,[26] numerous clinical trials with promising results have been published so far employing various methods of cellular cardiomyoplasty including direct intramyocardial injection of cells through thoracotomy (transepicardial)[12,14,17,27-29] or transcoronary approaches,[30-32] transcatheter endomyocardial injection,[15,20,33] intracoronary cell injection,[11,13,16,35-37] and systemic intravenous injection.[38,39] Advantages and disadvantages of each mentioned approach are outlined in table 1.

Table 1. Advantages and disadvantages of various methods for cellular cardiomyoplasty.

Method	Advantages	Disadvantages
Transepicardial intramyocardial injection	• The most precise and accurate method • The most suitable approach in candidates of CABG	• The most invasive method • Requires general anesthesia • Prolonged recovery period
Transcatheter endomyocardial injection	• Less invasive than transepicardial approach • Its safety and accuracy have been demonstrated	• Limited technical feasibility • Requires advanced imaging technologies
Intracoronary cell injection	• Technical simplicity • Can be performed at the same time with PCI	• Non-selective distribution pattern of injected cells • Cells can not reach beyond occluded coronary arteries (infarcted scar zones are excluded) • Cell aggregates may occlude small coronary arteries and lead to microembolisms
Transcoronary intramyocardial injection	• Lacks limitations of the intracoronary approach	• Safety and feasibility have not yet been proved
Systemic intravenous injection	• The simplest and least invasive delivery route • Minimal complications • Easily repeatable if necessary	• Poor selectivity • Low efficiency

References

1. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. Circulation 2000;102: IV14-IV23.
2. Miniati DN, Robbins RC. Heart transplantation: a thirty-year perspective. Annu Rev Med 2002;53:189-205.
3. Zhang Q, Madonna R, Shen W, Perin E, Angeli FS, Murad F, Yeh E, Buja LM, Caterina RD, Willerson JT, Geng YJ. Stem cells and cardiovascular tissue repair: mechanism, methods, and clinical applications. Journal of Cardiothoracic-Renal Research 2006;1:3-14.
4. McCulloch EA, Till JE, Siminovitch L. The role of independent and dependent stem cells in the control of hematopoietic and immunologic responses. Wist Inst Symp Monogr 1965;4:61-68.
5. Vats A, Bielby RC, Tolley NS, Nerem R, Polak JM. Stem cells. Lancet 2005;366:592-602.
6. Perin EC, Geng YJ, Willerson JT. Adult stem cell therapy in perspective. Circulation 2003;107:935-938.
7. Kehat I, Kenyagin-Karsenti D, Snir M, Segev H, Amit M, Gepstein A, Livne E, Binah O, Itskovitz-Eldor J, Gepstein L. Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. J Clin Invest 2001;108:407-414.
8. Li RK, Mickle DA, Weisel RD, Zhang J, Mohabeer MK. In vivo survival and function of transplanted rat cardiomyocytes. Cir Res 1996;78:283-288.
9. Moore JC, de Boer TP, van der Heyden MAG, Tertoolen LGJ, Mummery CL. Stem cells and cardiomyocytes. In: Pasterkamp G, de Kleijn DPV, eds. Cardiovascular research: new technologies, methods, and applications. New York: Springer; 2006. p. 133-155.

10. Daly CD, Campbell GR, Campbell JH. Tissue engineering. In: Pasterkamp G, de Kleijn DPV, eds. Crdiovascular research: new technologies, methods, and applications. New York: Springer; 2006. p. 207-220.
11. Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, Kogler G, Wernet P. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002;106:1913-1918.
12. Hamano K, Nishida M, Hirata K, Mikamo A, Li TS, Harada M, Miura T, Matsuzaki M, Esato K. Local implantation of autologous bone marrow cells for therapeutic angiogenesis in patients with ischemic heart disease: clinical trial and preliminary results. Jpn Circ J 2001;65:845-847.
13. Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H, Hoelzer D, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 2002;106:3009-3017.
14. Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, Schumichen C, Nienaber CA, Freund M, Steinhoff G. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet 2003;361:45-46.
15. Tse HF, Kwong YL, Chan JK, Lo G, Ho CL, Lau CP. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. Lancet 2003;361:47-49.
16. Kang HJ, Kim HS, Zhang SY, Park KW, Cho HJ, Koo BK, Kim YJ, Soo Lee D, Sohn DW, Han KS, Oh BH, Lee MM, Park YB. Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. Lancet 2004;363:751-756.
17. Menasche P, Hagege AA, Vilquin JT, Desnos M, Abergel E, Pouzet B, Bel A, Sarateanu S, Scorsin M, Schwartz K, Bruneval P, Benbunan M, Marolleau JP, Duboc D. Autologous skeletal myoblast transplantation for severe post-infarction left ventricular dysfunction. J Am Coll Cardiol 2003;41:1078-1083.
18. Herreros J, Prosper F, Perez A, Gavira JJ, Garcia-Velloso MJ, Barba J, Sánchez PL, Cañizo C, Rábago G, Martí-Climent JM, Hernández M, López-Holgado N, González-Santos JM, Martín-Luengo C, Alegria E. Autologous intramyocardial injection of cultured skeletal muscle-derived stem cells in patients with non-acute myocardial infarction. Eur Heart J 2003;24:2012-2020.
19. Pagani FD, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, Dinsmore JH, Wright S, Aretz TH, Eisen HJ, Aaronson KD. Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation. J Am Coll Cardiol 2003; 41:879-888.
20. Smits PC, van Geuns RJ, Poldermans D, Bountioukos M, Onderwater EE, Lee CH, Maat AP, Serruys PW. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. J Am Coll Cardiol 2003;42:2063-2069
21. Forrester JS, Price MJ, Makkar RR. Stem cell repair of infarcted myocardium, an overview for clinicians. Circulation 2003;108:1139-1145.
22. Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM, Fike JR, Lee HO, Pfeffer K, Loic C, Morrison SJ, Alvarez-Buylla A. Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes, and hepatocytes. Nature 2003;425:968-973.
23. Li S. Degradation of biodegradable aliphatic polyesters. In: Ma PX, Elisseeff J, eds. Scaffolding in tissue engineering. Boca Raton: CRC Press; 2006. p. 335-352.
24. Zimmermann WH, Melnichenko I, Eschenhagen T. Engineered heart tissue for regeneration of diseased hearts. Biomaterials 2004;25:1639-1647.
25. Zimmermann WH, Didie M, Wasmeier GH, Nixdorff U, Hess A, Melnychenko I, Boy O, Neuhuber WL, Weyand M, Eschenhagen T. Cardiac grafting of engineered heart tissue. Circulation 2002;106:I151-I157.
26. Menasche P, Hagege AA, Scorsin M, Pouzet B, Desnos M, Duboc D, Schwartz K, Vilquin JT, Marolleau JP. Myoblast transplantation for heart failure. Lancet 2001;357:279-280.
27. Ozbaran M, Omay SB, Nalbantgil S, Kultursay H, Kumanlioglu K, Nart D, Pektok E. Autologous peripheral stem cell transplantation in patients with congestive heart failure due to ischemic heart disease. Eur J Cardiothorac Surg 2004;25: 342-351.
28. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel HC Jr, Kormos R, Benetti F. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: A prospective randomized study. J Thorac Cardiovasc Surg 2005;130:1631-1638
29. Ahmadi H, Baharvand H, Ashtiani SK, Soleimani M, Sadeghian H, Ardekani JM, Mehrjerdi NZ, Kouhkan A, Namiri M, Madani-Civi M, Fattahi F, Shahverdi A, Dizaji AV. Safety analysis and improved cardiac function following local autologous transplantation of CD133(+) enriched bone marrow cells after myocardial infarction. Curr Neurovasc Res 2007;4:153-160.
30. Thompson CA, Nasseri BA, Makower J, Houser S, McGarry M, Lamson T, Pomerantseva I, Chang JY, Gold HK, Vacanti JP, Oesterle SN. Percutaneous transvenous cellular cardiomyoplasty: a novel nonsurgical approach for myocardial cell transplantation. J Am Coll Cardiol 2003;41:1964-1971.
31. Thompson CA, Reddy VK, Srinivasan A, Houser S, Hayase M, Davila A, Pomerantsev E, Vacanti JP, Gold HK. Left ventricular function recovery with percutaneous, transvascular direct myocardial delivery of bone marrow-derived cells. J Heart Lung Transplant 2005;24:1385-1392.
32. Ylä-Herttuala S. Percutaneous transcoronary venous access for cellular cardiomyoplasty. Lancet 2003;362:1252.
33. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ, Silva GV, Belém L, Vivacqua R, Rangel FO, Esporcatte R, Geng YJ, Vaughn WK, Assad JA, Mesquita ET, Willerson JT. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 2003; 107:2294-2302.
34. Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, Zhang JJ, Chunhua RZ, Liao LM, Lin S, Sun JP. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004;94:92-95.
35. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet 2004;364:141-148.
36. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Hölschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Intracoronary bone marrow–derived progenitor cells in acute myocardial infarction. N Engl J Med 2006;355:1210-1221.
37. Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, Endresen K, Ilebekk A, Mangschau A, Fjeld JG, Smith HJ, Taraldsrud E, Grøgaard HK, Bjørnerheim R, Brekke M, Müller C, Hopp E, Ragnarsson

A, Brinchmann JE, Forfang K. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 2006;355:1199-1209.

38. Kawamoto A, Gwon HC, Iwaguro H, Yamaguchi JI, Uchida S, Masuda H, Silver M, Ma H, Kearney M, Isner JM, Asahara T. Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia. Circulation 2001;103:634-637.

39. Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, Miller L, Guetta E, Zipori D, Kedes LH, Kloner RA, Leor J. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium. Feasibility, cell migration and body distribution. Circulation 2003;108:863-868.

TEHRAN HEART CENTER

Review Article

Cardiovascular Abnormalities in Cirrhosis: the Possible Mechanisms

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Abstract

Cirrhosis is characterized by marked abnormalities in the cardiovascular system. A hyperdynamic splanchnic and systemic circulation is typical of cirrhotic patients and has been observed in all experimental forms of portal hypertension. The hyperdynamic circulation is most likely initiated by arterial vasodilatation, leading to central hypovolemia, sodium retention, and an increased intravascular volume. Despite the baseline increase in cardiac output, ventricular inotropic and chronotropic responses to stimuli are blunted, a condition known as cirrhotic cardiomyopathy. This review briefly examines the major mechanisms that may underlie these cardiovascular abnormalities, concentrating on nitric oxide, endocannabinoids, prostaglandins, carbon monoxide, endogenous opioids, and adrenergic receptor changes. Future work should address the complex interrelationships between these systems.

J Teh Univ Heart Ctr 4 (2007) 191-200

Keywords: *Cirrhosis • Cardiomyopathy • Vasodilation*

Introduction

The clinical picture of patients with cirrhosis is dominated by the classical complications to portal hypertension, such as ascites, bleeding from esophageal varices, and encephalopathy. In addition, a considerable number of patients show signs of peripheral vasodilatation with palmar erythema and reddish skin, raised and bounding pulse, and a low systemic blood pressure indicating a hyperdynamic circulation.[1] The hyperdynamic syndrome comprises an increased heart rate, cardiac output, and plasma volume, and a reduced systemic vascular resistance and arterial blood pressure.[2,3] Despite the increased basal cardiac output, cardiac response to physiologic or pharmacologic stimuli is known to be subnormal[4,5], a phenomenon called "cirrhotic cardiomyopathy".[6,7] Cirrhotic cardiomyopathy is variably associated with a baseline increase in cardiac output, defective myocardial contractility, and lowered systo-diastolic response to inotropic and chronotropic stimuli, down-regulated β-adrenergic function, slight histo-morphological changes, and impaired electric "recovery" ability of ventricular myocardium.[8]

In addition, patients with cirrhosis develop complications from a variety of organs including the lungs, kidneys, and other organ systems.[9]

This review will summarize the recent work on pathogenic mechanisms underlying two conditions of vascular and cardiac abnormalities in cirrhosis.

Vascular Changes in Cirrhosis

Vascular abnormalities are ubiquitous in cirrhosis. It has long been known that cirrhosis may be considered as a vascular disease of the liver, owing to the marked

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anatomic changes that occur at the intrahepatic circulation.[10] A hyperdynamic splanchnic and systemic circulation is typical of cirrhotic patients and has been observed in all experimental forms of portal hypertension. Its presence is associated with extensive portal-systemic shunting and/or hepatic failure, and contributes to the severity of portal hypertension and to other manifestations of chronic liver disease. The hyperdynamic circulation is most likely initiated by arterial vasodilatation, leading to central hypovolemia, sodium retention, and an increased intravascular volume. This combination of vasodilatation and an expanded intravascular volume is necessary for the full expression of the hyperdynamic circulatory state.[11] In the vascular biologic aspect, this excessive arterial vasodilatation observed in the arterial splanchnic and systemic circulation is an extremely unique and interesting phenomenon because in the case of most diseases such as atherosclerosis and diabetes mellitus it is arterial vasoconstriction that is associated with the progressive development of symptoms.[12] For several years, efforts have been made to understand the mechanism of this arterial vasodilatation observed in the splanchnic and systemic circulation. This part of this review is to summarize our current knowledge about what molecules and factors are known to be involved in or potentially involved in the arterial vasodilatation in cirrhosis.

Nitric oxide (NO)

Nitric oxide was proposed as a putative mediator of splanchnic vasodilatation in portal hypertension in 1991.[13] Since then; a strong body of evidence from human and experimental models of cirrhosis has supported the notion that changes in NO activity affect different vascular beds in variable ways.

Nitric oxide is synthesized in the vascular endothelium from L-arginine by NO synthase (NOS)[14] , of which three isoforms have been identified: inducible NOS (iNOS), constitutive endothelial NOS (eNOS), and neuronal NOS (nNOS).[15,16] In portal hypertension, there seems to be a diminished release of NO from sinusoidal endothelial cells in the cirrhotic liver.[16,17] In the liver microcirculation, eNOS expression is decreased in a cirrhotic rat model.[18] Simvastatin enhances the hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis.[19] An NO donor or eNOS gene transfection, which compensates for the decreased hepatic eNOS expression, significantly lowers the increased portal pressure in cirrhosis.[18,20]

On the other hand, in the systemic circulation, there is evidence of increased eNOS[14,21,22], iNOS[23] or nNOS[24] upregulation. Exhaled air from cirrhotic patients contains higher NO levels than that of controls and correlates with the severity of disease and degree of hyperdynamic circulation; in animal models and cirrhotic patients, blockade of NO formation significantly increases arterial blood pressure and decreases plasma volume and sodium retention.[25]

Patients with cirrhosis have increased plasma levels of nitrites and nitrates, the NO degradation products.[26] A study performed in cirrhotic patients undergoing liver transplantation showed a higher NOS activity in the hepatic artery of these patients than that in the controls, and this abnormality was more pronounced in patients with ascites.[27] Inhibition of nitric oxide production reduces superior mesenteric artery flow[28,29], portal systemic shunting[30], and partially prevents the development of the characteristically hyperdynamic circulation of portal hypertension.[31]

Taken together, there is a growing body of evidence that the systemic NO production is increased and precedes the development of the hyperdynamic circulation in cirrhosis, thereby playing a major role in the arteriolar and splanchnic vasodilatation and vascular hyporeactivity.[15,32]

Endocannabinoids

Cannabis has been used for psychoactive and recreational purposes as well as in traditional medicine, long before the advent of modern medicine and scientific research.[33] The active component of cannabis, tetra-hydro-cannabinol (THC) was discovered in 1964.[34] This finding led to the discovery of two specific receptors of cannabinoids. The cannabinoid receptor CB1 receptor was found initially in the brain[35] and subsequently in the gut and vascular endothelium.[36-38] The CB2 receptor was isolated primarily in the immune system.[39] The first endogenous ligand for these receptors was found in 1992 and was designated as Anandamide.[40] Following this breakthrough, several other ligands were reported, e.g. 2-arachidonyl-glycerol (2-AG), noladine, and oleamide.[41]

It has been shown that anandamide increased in cirrhotic monocytes and overactivation of CB1 receptors within the mesenteric vasculature may contribute to the development of splanchnic arterial vasodilatation and portal hypertension.[42] The blockade of CB1 receptor by the antagonist SR141716A increases mean arterial pressure[42,43] and peripheral resistance[43] in rats with CCl4-induced cirrhosis.

We also showed that AM251, a selective CB1 antagonist, increased blood pressure and systemic vascular resistance of bile duct ligated-cirrhotic rats, in agreement with previous studies.[44]

Batkai et al. (2001) demonstrated that SR141716A injection caused a decrease in mesenteric arterial blood flow and portal vein pressure in CCl4-induced cirrhotic animals.[42] We also showed that AM251 administration induced the same effect on superior mesenteric artery blood flow in bile duct ligated rats.[44]

Yang et al. (2007) reported that following acute AM251 infusion, a simultaneous decrease in portal venous pressure and superior mesenteric artery blood flow and an increase in superior mesenteric artery resistance index were observed in bile duct ligated rats.[45]

Using intravital microscopy shows that acute AM251 administration significantly constricts mesenteric arterioles (first order branch) of bile duct ligated rats, while it has no effect on bile duct ligated venules or arterioles and venules (first order branch) of control rats.[44] On the other hand, chronic treatment for one week with AM251 significantly decreases portal venous pressure and superior mesenteric artery blood flow in bile duct ligated rats.[45]

Anandamide-induced relaxation is significantly potentiated in mesenteric vascular beds of cholestatic rats preconstricted with phenylephrine. Chronic treatment of bile duct-ligated animals with L-NAME (a non-selective iNOS inhibitor) and aminoguanidine (a selective iNOS inhibitor) blocks this hyperresponsiveness. Although acute L-NAME treatment of mesenteric beds completely blocks the anandamide-induced vasorelaxation in sham-operated rats, this vasorelaxation still is present in bile duct ligated animals. These effects indicate enhanced anandamide-induced vasorelaxation in 7-days' bile duct ligated rats. Moreover, NO overproduction possibly through iNOS may be involved in cholestasis-induced vascular hyperresponsiveness.[46]

In another study by Domenicali et al. (2005), mesenteric vessels of CCl4 induced-cirrhotic animals displayed greater sensitivity to anandamide than those of the control vessels, which indicated that the endocannabinoid system might have greater local vasodilator activity in the splanchnic circulation.[47] This vasodilator response was reverted by CB1 receptor blockade, but not after endothelium denudation or nitric oxide inhibition. This discrepancy for NO results between these two studies might be because of different models, as the first paper used 7-days' bile duct ligated rats induced by cholestasis, whereas in the second experiment, rats were completely cirrhotic. Domenicali et al. (2005) also showed that anandamide had no effect on distal femoral arteries.[47] These results emphasize the tissue selectivity of endocannabinoids and point to anandamide as an important local regulator of vascular tonicity in the mesenteric circulation in pathological conditions such as hepatic cirrhosis.

Carbon monoxide (CO)

Studies suggest a possible role of CO, an end product of the heme oxygenase (HO) pathway, in vasodilatation in cirrhosis.[48,49] Heme oxygenase is an enzyme that catabolizes heme derived from heme-containing proteins, especially hemoglobin to biliverdin, which is then rapidly transformed to bilirubin and CO.[50] Carbon monoxide has a number of important biological effects, including vasodilatation through activation of guanylyl cyclase of vascular smooth muscle cells, and seems to play an important role in the regulation of blood flow and resistance in several vascular beds.[51]

A constitutive isoform of HO, HO-2 is mainly expressed in the spleen, but can also be found in many other tissues, including blood vessels.[52,53] Under pathologic conditions, HO activity may increase markedly due to the upregulation of an inducible isoform of the enzyme, HO-1, also known as heat shock protein 32.[54] In portal hypertension, HO-1, not HO-2, is up-regulated in systemic and splanchnic arterial circulations. Carbon monoxide produced by HO-1, synergistically with NO, plays a role in arterial vasodilatation observed in cirrhosis with portal hypertension. [48,49]

Prostaglandins

Prostacyclin (PGI2), a major product of vascular cyclooxygenase, is formed primarily in endothelial cells and also in the media and adventitia in response to both physical and humoral stimuli that also release NO.[55] Prostacyclin causes relaxation of vascular smooth muscle by activating adenylyl cyclase and increasing the production of cyclic AMP.

An increased basal release of PGI2 is thought to have a major role in the pathogenesis of vasodilatation and vascular hypocontractility associated with portal hypertension. In agreement with this hypothesis, the whole-body production of PGI2 is increased in portal hypertensive animals.[56,57] Moreover, portal venous PGI2 levels are substantially higher in portal hypertensive animals and cirrhotic patients, which suggests that portal venous release of PGI2 may play a role in the development of the splanchnic hyperemia, collateral circulation, and portal hypertensive gastropathy.[57,58]

Initial studies with indomethacin demonstrated a significant reduction in circulating PGI2 levels concomitant with a reduction in splanchnic blood flow in portal hypertensive animals.[58,59]

In addition to decreased hepatic metabolism due to pronounced portosystemic shunting (PSS), several studies have also implicated exaggerated cyclooxygenase expression and activity within the hyperemic vasculature as a possible reason for the enhanced circulating PGI2 levels.[60]

Endogenous opioids

It has been shown that cirrhosis is associated with increased plasma levels of the endogenous opioid peptides.[61,62] They are also reputed to be possible mediators of some chronic liver disease complications such as ascites[63] and bleeding esophageal varices.[62] Furthermore, in our previous experiments, we demonstrated the endogenous opioid peptides' role in the hyporesponsiveness of the cardiovascular system to exogenous stimulation in cholestatic rats.[64-66] The precise reason for the increased opioid activity in cirrhosis is not yet completely understood, but it is likely that both the overproduction of the endogenous opioid peptides and protection of these peptides from degradation may contribute to the elevation of total opioid activity.[61,62]

Recently, we showed that biliary cirrhosis is accompanied with a decrease in baseline perfusion pressure in mesenteric vascular bed and that chronic opioid receptor blockade with

naltrexone significantly increases this pressure. The maximum mesenteric vascular bed pressure response to phenylephrine is decreased significantly in cirrhosis, and chronic naltrexone treatment completely improves it. Chronic opioid receptor blockade did not modulate the increased nitrite/nitrate levels following cholestasis. These results provided evidence on the contribution of the endogenous opioid system to vascular hyporesponsiveness in cirrhosis independent of NO production.[67]

Cirrhotic Cardiomyopathy

The possibility of heart dysfunction in cirrhosis, first described in 1953,[1] was regarded as just related to the eventual metabolic complications of alcohol intake or haemochromatosis.[68] However, during the past 2 decades, it has become clear that blunted ventricular contractility with stress is also present in nonalcoholic patients and animal models of cirrhosis. In the 1990s, numerous studies in patients with nonalcoholic cirrhosis conclusively demonstrated that depressed ventricular contractile responses to stimuli are found in *all* forms of cirrhosis.[69]

In the absence of consensus definitions, the term "cirrhotic cardiomyopathy" is defined at present as: 1) baseline increased cardiac output but blunted ventricular response to stimuli, 2) systolic and/or diastolic dysfunction, 3) absence of overt left ventricular failure at rest, and 4) electrophysiological abnormalities including prolonged QT interval on electrocardiography and chronotropic incompetence.[7,70,71] Not all features are required for the diagnosis; for example, only 30–60% of patients show a prolonged QT interval.[69]

Baik et al. (2007), believe that at least one feature of cirrhotic cardiomyopathy, such as electrocardiographic QT prolongation or diastolic dysfunction, is present in the majority of patients with cirrhosis who have reached Child-Pugh stage B or C (representing moderately or severely advanced liver failure). Moreover, diastolic dysfunction is probably present in virtually all patients with cirrhotic cardiomyopathy, and simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. Indeed, once cirrhosis has advanced to a moderate stage, with the accumulation of peripheral edema or ascites, it appears that some element of diastolic dysfunction is universally present.[69]

Cirrhotic cardiomyopathy is usually clinically latent or mild, likely because the peripheral vasodilatation significantly reduces the left ventricle after-load, thus actually "auto-treating" the patient and masking any severe manifestation of heart failure. In cirrhotic patients, the presence of cirrhotic cardiomyopathy may become unmasked and clinically evident by certain treatment interventions that increase the effective blood volume and cardiac pre-load, including surgical or transjugular intrahepatic porto-systemic shunts, peritoneo-venous shunts (LeVeen), and orthotopic liver transplantation. Under these circumstances, an often transient overt congestive heart failure may develop, with increased cardiac output as well as right atrial, pulmonary artery, and capillary wedge pressures.[8] We herein review possible pathogenic mechanisms reported by our laboratory and others.

β- adrenergic signaling

In the subjects suffering from liver cirrhosis, a deep alteration of the autonomic adrenergic function has been reported, [72,73] which correlates with the severity of the disease. In these patients, both inotropic and chronotropic responses to β-adrenergic agonist stimulation are actually diminished. In this way, the response to norepinephrine, angiotensin II, and dobutamine is decreased, and no significant heart rate increase occurs during the Valsalva maneuver, ice-cold skin stimulation, or mental stress.[8] Moreover, the dose of isoproterenol required for heart rate to increase 25 beats/min is significantly higher in cirrhotic patients than that in controls.[74,75] We also showed that the maximum effects of isoproterenol on chronotropic and inotropic responses were significantly reduced in isolated atria and papillary muscles of cirrhotic rats.[76]

The response to posture variations is reduced too, due to a blunted baroreflex function, with a tendency to orthostatic hypotension, and no significant increase in heart rate during tilting test.[8] A significant downregulation of the β-adrenergic receptors, which has been demonstrated in cirrhosis, may account for the above-mentioned clinical and experimental data.[77,78]

It has been shown that the expression and responsiveness of β-adrenergic receptors[77] as well as their post-receptor signaling pathway is blunted in the cardiac tissue of cirrhotic rats. Post-receptor impairment was found at different levels including content and function of stimulatory Gs proteins[79], uncoupling of the β-adrenoceptor-ligand complex from G protein[80], and responsiveness of adenylyl cyclase to stimuli.[79,81]

The cell membrane fluidity is critical in the correct function of several membrane-bound receptors, including β-adrenergic ones.[82] In fact, a decreased membrane fluidity (due to an increased cholesterol content and cholesterol/phospholipid ratio) in the cardiomyocytes of bile duct ligated rats was reported to be associated with a blunted β-adrenergic receptor response, with an alteration of the signal transduction pathway[79,82] and of the conductance of the gap–junction channels.[79,83]

Nitric oxide

Nitric oxide is known to negatively regulate cardiac contractile function. It has been shown to be involved in

some types of cardiac dysfunction including ischemic heart disease.[84] Balligand et al. (1993) found that the inhibition of NO synthesis by L-NMMA significantly increased the contractile response of rat ventricular myocytes to the β-agonist isoproterenol without affecting baseline contractility.[85] In terms of a cirrhotic model, van Obbergh et al. (1996) reported on the role of NO in bile duct ligated cirrhotic rat.[86] They showed that L-NMMA significantly increased contractile function in isolated working cirrhotic hearts but had no effect on controls. It has been also shown that in the cirrhotic rats, baseline isoproterenol- stimulated papillary muscle contractile force was lower than that in the control groups. But when the papillary muscles were preincubated with the NOS inhibitor L-NAME, contractile force increased significantly in the cirrhotic rats, whereas control muscles were unaffected. In addition, cirrhotic cardiomyocytes showed an increased iNOS mRNA and protein expression, whereas eNOS showed no significant difference in the expression between the bile duct ligated and the sham control hearts. Moreover, the NO donor S-nitroso-N-acetyl penicillamine inhibited papillary muscle contractility. Whether the effects of NO are mediated by the inhibition of adenylyl cyclase activity or through cGMP remains to be further clarified. However, it has been reported that TNF-α and cGMP content in cardiac homogenates showed a significant increase in bile duct ligated rats, suggesting a possible cytokine-iNOS-cGMP mediated pathway of action for NO in the pathogenesis of cirrhotic cardiomyopathy.[87]

In our recent paper, we showed that the basal abnormalities and the attenuated chronotropic and inotropic responses to isoproterenol were completely corrected by the administration of L-NAME and aminoguanidine in cirrhotic rats, implying the role of iNOS in these events.[76] We also reported that despite QT prolongation, epinephrine induced fewer arrhythmias in cirrhotic rats compared to sham-operated animals. Chronic, but not acute, L-NAME administration corrected the QT prolongation in cirrhotic rats[88] and restored the susceptibility of cirrhotic and cholestatic rats to arrhythmias.[88,89]

Endocannabinoids

Hypotension and bradycardia are the most important features elicited by the systemic administration of cannabinoids,[90] and endocannabinoids are known to have a negative inotropic effect on cardiac contractility in both humans[91] and rats.[92]

The plasma level of an anandamide is known to be increased in cirrhosis.[42] Gaskari et al. (2005) demonstrated a negative inotropic effect of anandamide in the left ventricular papillary muscles of cirrhotic rats. This inhibitory effect on contractility was completely blocked by incubation with AM251, a known CB1 antagonist, thus confirming that the effect of anandamide is mediated by CB1 receptors. They also showed a major role for an increased local cardiac production of endocannabinoids in cirrhotic cardiomyopathy. That conclusion was based on the restoration of blunted contractile response of isolated left ventricular papillary muscles from bile duct ligated cirrhotic rats after preincubation with a CB1 antagonist, AM251. Additionally, endocannabinoid reuptake blockers (VDM11 and AM404) enhance the relaxant response of cirrhotic papillary muscle to higher frequencies of contraction in an AM251-sensitive fashion, suggesting an increase in the local production of endocannabinoids acting through CB1 receptors.[93]

Bolus intravenous injection of the CB1 antagonist AM251 (3 mg/kg) acutely increased mean blood pressure, as well as both load-dependent and -independent indexes of systolic function, whereas no such changes were elicited by AM251 in the control rats. Furthermore, the tissue levels of the endocannabinoid anandamide increased 2.7-fold in the heart of the cirrhotic compared with control rats, without any change in 2-arachidonoylglycerol levels; whereas in the cirrhotic liver, both 2-arachidonoylglycerol (6-fold) and anandamide (3.5-fold) were markedly increased. CB1-receptor expression in the heart was unaffected by cirrhosis, as verified by Western blotting. Activation of cardiac CB1 receptors by endogenous anandamide contributes to the reduced cardiac contractility in liver cirrhosis, and CB1-receptor antagonists may be used to improve contractile function in cirrhotic cardiomyopathy and, possibly, in other forms of heart failure.[94]

Endogenous opioids

Previous experiments have shown that the endogenous opioid peptides are produced and secreted by the cardiac myocytes as well as the sympathetic nerves and adrenal glands.[95,96] It is well known that the endogenous opioid peptides are involved in the regulation of the cardiovascular system through both peripheral and central receptors. Besides modulating the autonomic nervous system[97], they have been demonstrated to have effects on the cardiac rhythm[98] and contractility.[99] Abnormalities of the endogenous opioid peptides system have been reported in several pathophysiological conditions in both human and animal models of cardiovascular diseases such as acute or chronic heart ischemia and genetic hypertension.[100-102] In our previous experiments, we demonstrated the endogenous opioid peptides' role in bradycardia and hyporesponsiveness of cardiovascular system to exogenous stimulation in cholestatic rats.[64-66,103] We also showed that the incubation of the cirrhotic papillary muscles with naltrexone restored the basal contractile impairment to the sham-control level, and also corrected the chronotropic and inotropic hyporesponsiveness of cirrhotic rats to isoproterenol stimulation. These findings provide the evidence for the endogenous opioid peptides regulatory role on the basal cardiac contractile impairment in cirrhosis.[76]

Carbon monoxide

An increased expression of inducible HO and cGMP levels was demonstrated in the left ventricle of the bile duct ligated rats, whose isolated papillary muscles did exhibit a blunted contractility. The treatment with Zn-protoporphyrine IX (an HO inhibitor) reduced cGMP levels, thus normalizing the myocardial inotropic ability.[104] These findings suggest that the activation of the HO-CO pathway in cirrhosis involves the catalytic action of HO-1, with the cardiodepressant effects of increasing levels of CO occurring via the stimulation of cGMP.[105]

Conclusion

Splanchnic vasodilatation in relation to portal hypertension is responsible for the hyperdynamic circulation and abnormal distribution of blood volume with a reduced "effective arterial blood volume" and activation of baroreceptor and volume-receptor reflexes as the outcome. The enhanced vasodilatation and counter regulatory overactivity of vasoconstrictor systems play major roles in the development of the multi-organ failure in cirrhosis with impaired function and perfusion of kidneys, lungs, brain, skin, and muscles. Underlying mechanisms of vascular abnormalities in cirrhosis have been extensively explored in recent years, and a number of vasoactive mediator systems including nitric oxide, endocannabinoids, carbon monoxide, prostaglandins, and endogenous opioids may be common to the genesis of these conditions.

Experimental and clinical studies of patients with cirrhosis strongly suggest the presence of latent heart failure with impaired reactions to standardized provocations. This has given rise to the introduction of the clinical entity cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy is clinically and pathophysiologically different from alcoholic heart muscle disease. Cirrhotic cardiomyopathy comprises changes in impaired cardiac contractility during the preload and afterload, decreased b adrenergic receptor function, post-receptor dysfunction, defective excitation contraction coupling, and in some patients conductance abnormalities. Cirrhotic cardiomyopathy may cover different pathophysiological mechanisms including β- adrenergic signaling, nitric oxide, endocannabinoids, endogenous opioids, and carbon monoxide abnormalities. Considering the undeniable interrelation of different systems in both hyperdynamic circulation and cardiomyopathy, further studies are required to elucidate the complex interactions between these mechanisms.

References

1. Møller S, Henriksen JH. The systemic circulation in cirrhosis. In: Arroyo V, Gines P, Rodes J, Schrier RW, eds. Ascites and renal dysfunction in liver disease. Pathogenesis, Diagnosis and Treatment. 1st ed. Malden: Blackwell Science; 1999. p. 307-329.
2. Groszmann RJ, Jensen JE. Pathophysiology of portal hypertension. In: Kaplowitz N, ed. Liver and Biliary Diseases. 2nd ed. Baltimore: Williams & Wilkins; 1996. p. 551-562.
3. Møller S, Wiinberg N, Hernriksen JH. Noninvasive 24-hour ambulatory arterial blood pressure monitoring in cirrhosis. Hepatology 1995;22:88-95.
4. Liu H, Lee SS. Cardiopulmonary dysfunction in cirrhosis. J Gastroenterol Hepatol 1999;14:600-608.
5. Myers RP, Lee SS. Cirrhotic cardiomyopathy and liver transplantation. Liver Transpl 2000;6:44-52.
6. Lee SS. Cardiac abnormalities in liver cirrhosis. West J Med 1989;151:530-535.
7. Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. Gastroenterol Clin Biol 2002;26:842-847.
8. Milani A, Zaccaria R, Bombardieri G, Gasbarrini A, Pola P. Cirrhotic cardiomyopathy. Dig Liver Dis 2007;39:507-515.
9. Moller S, Henriksen JH. Cardiopulmonary complications in chronic liver disease. World J Gastroenterol 2006;12:526-538.
10. Bosch J. Vascular deterioration in cirrhosis: the big picture. J Clin Gastroenterol 2007;41:247-253.
11. Groszmann RJ, Loureiro-Silva MR, Tsai MH. The Biology of Portal Hypertension. In: Arias IM, Boyer JL, Chisari FV, Fausto N, Schachter D, Shafritz DA, eds. The Liver: Biology and Pathobiology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 680-697.
12. Iwakiri Y, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. J Hepatol 2007;46:927–934.
13. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991;337:776-778.
14. Farzaneh-Far R, Moore K. Nitric oxide and the liver. Liver 2001;21:161-174.
15. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. Hepatology 2002;35:478-491.
16. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. Gastroenterology 1998;114:344-351.
17. McNaughton L, Puttagunta L, Martinez-Cuesta MA, Kneteman N, Mayers I, Moqbel R, Hamid Q, Radomski MW. Distribution of nitric oxide synthase in normal and cirrhotic human liver. Proc Natl Acad Sci USA 2002;99:17161-17166.
18. Van de Casteele M, Omasta A, Janssens S, Roskams T, Desmet V, Nevens F, Fevery J. In vivo gene transfer of endothelial ni tric oxide synthase decreases portal pressure in anaesthetized carbon tetrachloride cirrhotic rats. Gut 2002;51:440-445.
19. Zafra C, Abraldes JG, Turnes J, Berzigotti A, Fernandez M, Garca-Pagan JC, Rodes J, Bosch J. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. Gastroenterology 2004;126:749-755.
20. Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol 1985;1:325-337.
21. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151-1157.
22. Tazi KA, Barriere E, Moreau R, Heller J, Sogni P, Pateron D,

Poirel O, Lebrec D. Role of shear stress in aortic eNOS upregulation in rats with biliary cirrhosis. Gastroenterology 2002;122:1869-1877.

23. Lee FY, Wang SS, Tsai YT, Lin HJ, Lin HC, Chu CJ, Wu SL, Tai CC, Lee SD. Aminoguanidine corrects hyperdynamic circulation without ameliorating portal hypertension and portal hypertensive gastropathy in anesthetized portal hypertensive rats. J Hepatol 1997;26:687-693.

24. Xu L, Carter EP, Ohara M, Martin PY, Rogachev B, Morris K, Cadnapaphornchai M, Knotek M, Schrier RW. Neuronal nitric oxide synthase and systemic vasodilation in rats with cirrhosis. Am J Physiol Renal Physiol 2000;279:1110-1115.

25. Liu H, Gaskari SA, Lee SS. Cardiac and vascular changes in cirrhosis: pathogenic mechanisms. World J Gastroenterol 2006;12:837-842.

26. Guarner C, Soriano G, Tomas A, Bulbena O, Novella MT, Balanzo J Vilardell F, Mourelle M, Moncada S. Increased serum nitrite and nitrate levels in patients with cirrhosis: relationship to endotoxemia. Hepatology 1993;18:1139–1143.

27. Albornoz L, Motta A, Alvarez D, Estevez A, Bandi JC, McCormack L, Matera J, Bonofiglio C, Ciardullo M, De Santibañes E, Gimeno M, Gadan A. Nitric oxide synthase activity in the splachnic vasculature of patients with cirrhosis: relationship with hemodynamic disturbances. J Hepatol 2001;35:452-456.

28. Pizcueta MP, Piqué JM, Bosch J, Whittle BJR, Moncada S. Effects of inhibiting nitric oxide biosynthesis on the systemic and splanchnic circulation of rats with portal hypertension. Br J Pharmacol 1992;105:184-190.

29. Pizcueta P, Piqué JM, Fernández M, Bosch J, Rodés J, Whittle BJ, Moncada S. Modulation of the hyperdynamic circulation of cirrhotic rats by nitric oxide inhibition. Gastroenterology 1992;103:1909-1915.

30. Lee FY, Colombato LA, Albillos A, Groszmann RJ. Administration of N Omega-Nitro-L-Arginine ameliorates portal-systemic shunting in portal-hypertensive rats. Gastroenterology 1993;105:1464-1470.

31. García-Pagán JC, Fernández M, Bernadich C, Pizcueta P, Piqué JM, Bosch J, Rodés J. Effects of continued nitric oxide inhibition on the development of the portal hypertensive syndrome following portal vein stenosis in the rat. Am J Physiol 1994;267:984-990.

32. Helmy A, Newby DE, Jalan R, Johnston NR, Hayes PC, Webb DJ. Nitric oxide mediates the reduced vasoconstrictor response to angiotensin II in patients with preascitic cirrhosis. J Hepatol 2003;38:44-50.

33. Mechoulam R. The pharmacohistory of Cannabis sativa. In: Mechoulam R, ed. Cannabinoids as Therapeutic Agents. 1st ed. Boca Raton: CRC Press, 1986. p. 1-19.

34. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of Hashish. J Amer Chem Soc 1964;86:1646-1647.

35. Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;35:605-613.

36. Goutopoulos A, Makriyannis A. From cannabis to cannabinergics: new therapeutic opportunities. Pharmacol Therapeut 2002;95:103-117.

37. Matsuda LA, Lolait SJ, Brownstein MJ. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561-564.

38. Liu J, Gao B, Mirshahi F, Sanyal AJ, Khanolkar AD, Makriyannis A, Kunos G. Functional CB1 cannabinoid receptors in human vascular endothelial cells. Biochem J 2000;346:835-840.

39. Munro S, Thomas K, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61-65.

40. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946-1949.

41. Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. Endocannabinoids and liver disease--review. Liver Int 2005;25:921-926.

42. Bátkai S, Járai Z, Wagner JA, Goparaju SK, Varga K, Liu J, Wang L, Mirshahi F, Khanolkar AD, Makriyannis A, Urbaschek R, Garcia N Jr, Sanyal AJ, Kunos G. Endocannabinoids acting at vascular CB1 receptors mediate the vasodilated state in advanced liver cirrhosis. Nat Med 2001;7:827-832.

43. Ros J, Clària J, To-Figueras J, Planagumà A, Cejudo-Martín P, Fernández-Varo G, Martín-Ruiz R, Arroyo V, Rivera F, Rodés J, Jiménez W. Endogenous cannabinoids: a new system involved in the homeostasis of arterial pressure in experimental cirrhosis in the rat. Gastroenterology 2002;122:85-93.

44. Moezi L, Gaskari SA, Liu H, Baik SK, Dehpour AR, Lee SS. Anandamide mediates hyperdynamic circulation in cirrhotic rats via CB(1) and VR(1) receptors. Br J Pharmacol 2006;149:898-908.

45. Yang YY, Lin HC, Huang YT, Lee TY, Hou MC, Wang YW, Lee FY, Lee SD. Effect of chronic CB1 cannabinoid receptor antagonism on livers of rats with biliary cirrhosis. Clin Sci (Lond) 2007;112:533-542.

46. Moezi L, Rezayat M, Samini M, Shafaroodi H, Mehr SE, Ebrahimkhani MR, Dehpour AR. Potentiation of anandamide effects in mesenteric beds isolated from bile duct-ligated rats: role of nitric oxide. Eur J Pharmacol 2004;486:53-59.

47. Domenicali M, Ros J, Fernandez-Varo G, Cejudo-Martin P, Crespo M, Morales-Ruiz M, Briones AM, Campistol JM, Arroyo V, Vila E, Rodes J, Jimenez W. Increased anandamide induced relaxation in mesenteric arteries of cirrhotic rats: role of cannabinoid and vanilloid receptors. Gut 2005;54:522-527.

48. Chen YC, Ginès P, Yang J, Summer SN, Falk S, Russell NS, Schrier RW. Increased vascular heme oxygenase-1 expression contributes to arterial vasodilation in experimental cirrhosis in rats. Hepatology 2004;39:1075-1087.

49. Fernandez M, Bonkovsky HL. Increased heme oxygenase-1 gene expression in liver cells and splanchnic organs from portal hypertensive rats. Hepatology 1999;29:1672-1679.

50. Maines MD. The heme oxygenase system: a regulator of second messenger gases. Annu Rev Pharmacol Toxicol 1997;37:517-554.

51. Naik JS, Walker BR. Heme oxygenase-mediated vasodilation involves vascular smooth muscle cell hyperpolarization. Am J Physiol Heart Circ Physiol 2003;285:220-228.

52. Ishizaka N, Griendling KK. Heme oxygenase-1 is regulated by angiotensin II in rat vascular smooth muscle cells. Hypertension 1997;29:790-795.

53. Zakhary R, Gaine SP, Dinerman JL, Ruat M, Flavahan NA, Snyder SH. Heme oxygenase 2: endothelial and neuronal localization and role in endothelium-dependent relaxation. Proc Natl Acad Sci USA 1996;93:795-798.

54. Cruse I, Maines MD. Evidence suggesting that the two forms of heme oxygenase are products of different genes. J Biol Chem 1988;263:3348-3353.

55. Marnett LJ, Rowlinson SW, Goodwin DC, Kalgutkar AS, Lanzo CA. Arachidonic acid oxygenation by COX-1 and COX-2. Mechanisms of catalysis and inhibition. J Biol Chem 1999;274:22903-22906.

56. Yin J, Leng X, Zhu J. Plasma prostacyclin (PGI2) levels in

peripheral venous, arterial and portal venous blood in cirrhotic patients with portal hypertension and their clinical implication. Chung Hua Wai Ko Tsa Chih 1995;33:563-565.
57. Ohta M, Kishihara F, Hashizume M, Kawanaka H, Tomikawa M, Higashi H, Tanoue K, Sugimachi K. Increased prostacyclin content in gastric mucosa of cirrhotic patients with portal hypertensive gastropathy. Prostaglandins Leukot Essent Fatty Acids 1995;53:41-45.
58. Sitzmann JV, Campbell K, Wu Y, St. Clair C. Prostacyclin production in acute, chronic, and long-term experimental portal hypertension. Surgery 1994;115:290-294.
59. Hou MC, Cahill PA, Zhang S. Enhanced cyclooxygenase-1 expression within the superior mesenteric artery of portal hypertensive rats: role in the hyperdynamic circulation. Hepatology 1998;27:20-27.
60. Birney Y, Redmond EM, Sitzmann JV, Cahill PA. Eicosanoids in cirrhosis and portal hypertension. Prostaglandins Other Lipid Mediat. 2003;72:3-18.
61. Thornton JR, Losowsky MS. Plasma leucine enkephalin is increased in liver disease. Gut 1989;30:1392-1395.
62. Thornton JR, Dean HG, Losowsky MS. Do increased catecholamines and plasma methionine enkephalin in cirrhosis promote bleeding oesophageal varices? Q J Med 1988;68:541-551.
63. Thornton JR, Dean H, Losowsky MS. Is ascites caused by impaired hepatic inactivation of blood borne endogenous opioid peptides? Gut 1988;29:1167-1172.
64. Borhani AA, Houshmand G, Samini M, Namiranian K, Hajrasouliha AR, Tavakoli S, Ebrahimi F, Dehpour AR. alpha2-Adrenoceptor subsensitivity in mesenteric vascular bed of cholestatic rats: the role of nitric oxide and endogenous opioids. Eur J Pharmacol 2005;514:183-189.
65. Namiranian K, Samini M, Mehr SE, Gaskari SA, Rastegar H, Homayoun H, Dehpour AR. Mesenteric vascular bed responsiveness in bile duct-ligated rats: roles of opioid and nitric oxide systems. Eur J Pharmacol 2001;423:185-193.
66. Gaskari SA, Mani AR, Ejtemaei-Mehr S, Namiranian K, Homayoun H, Ahmadi H, Dehpour AR. Do endogenous opioids contribute to the bradycardia of rats with obstructive cholestasis? Fundam Clin Pharmacol 2002;16:273-279.
67. Moezi L, Ebrahimkhani MR, Kiani S, Karoon A, Farsam H, Dehpour AR. Endogenous opioid system modulates mesenteric bed responsiveness in cirrhotic rats. J Hepatol 2004;40:93-94.
68. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec cirrhosis. J Clin Invest 1953;32:1025-1033.
69. Baik SK, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. Orphanet J Rare Dis 2007;27:2-15.
70. Blendis L, Wong F. Is there a cirrhotic cardiomyopathy? Am J Gastroenterol 2000;95:3026-3028.
71. Gaskari SA, Honar H, Lee SS. Therapy insight: cirrhotic cardiomyopathy. Nat Clin Pract Gastroenterol Hepatol 2006;3:329-337.
72. MacGilchrist AJ, Reid JL. Impairment of autonomic reflexes in cirrhosis. Am J Gastroenterol 1990;85:288-292.
73. Trevisani F, Sica G, Mainquà P, Santese G, De Notariis S, Caraceni P, Domenicali M, Zacà F, Grazi GL, Mazziotti A, Cavallari A, Bernardi M. Autonomic dysfunction and hyperdynamic circulation in cirrhosis with ascites. Hepatology 1999;30:1387-1392.
74. Lenz K, Hörtnagl H, Magometschnigg D, Kleinberger G, Druml W, Laggner A. Function of the autonomic nervous system in patients with hepatic encephalopathy. Hepatology 1985;5:831-836.
75. Ramond MJ, Comoy E, Lebrec D. Alterations in isoprenaline sensitivity in patients with cirrhosis: evidence of abnormality of the sympathetic nervous activity. Br J Clin Pharmacol 1986;21:191-196.
76. Ebrahimi F, Tavakoli S, Hajrasouliha AR, Sadeghipour H, Dehghani M, Ahmadi SH, Dehpour AR. Involvement of endogenous opioid peptides and nitric oxide in the blunted chronotropic and inotropic responses to beta-adrenergic stimulation in cirrhotic rats. Fundam Clin Pharmacol 2006;20:461-671.
77. Lee SS, Marty J, Mantz J, Samain E, Braillon A, Lebrec D. Desensitization of myocardial beta-adrenergic receptors in cirrhotic rats. Hepatology 1990;12:481-485.
78. Hausdorff WP, Caron MG, Lefkowitz RJ. Turning off the signal: desensitization of beta-adrenergic receptor function. FASEB J 1990;4:2881-2889.
79. Ma Z, Meddings JB, Lee SS. Membrane physical properties determine cardiac beta-adrenergic receptor function in cirrhotic rats. Am J Physiol 1994;267:87-93.
80. Ma Z, Miyamoto A, Lee SS. Role of altered beta-adrenoceptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats. Gastroenterology 1996;110:1191-1198.
81. Ma Z, Lee SS, Meddings JB. Effects of altered cardiac membrane fluidity on beta-adrenergic receptor signalling in rats with cirrhotic cardiomyopathy. J Hepatol 1997;26:904-912.
82. Le Grimellec C, Friedlander G, el Yandouzi EH, Zlatkine P, Giocondi MC. Membrane fluidity and transport properties in epithelia. Kidney Int 1992;42:825-836.
83. Ladbrooke BD, Chapman D. Thermal analysis of lipids, proteins and biological membranes. A review and summary of some recent studies. Chem Phys Lipids 1969;3:304-356.
84. Smith TW, Balligand JL, Kaye DM, Wiviott SD, Simmons WW, Han X, Michel T, Singh K, Kelly RA. The role of the NO pathway in the control of cardiac function. J Card Fail 1996;2:141-147.
85. Balligand JL, Kelly RA, Marsden PA, Smith TW, Michel T. Control of cardiac muscle cell function by an endogenous nitric oxide signaling system. Proc Natl Acad Sci USA 1993;90:347-351.
86. van Obbergh L, Vallieres Y, Blaise G. Cardiac modifications occurring in the ascitic rat with biliary cirrhosis are nitric oxide related. J Hepatol 1996;24:747-752.
87. Liu H, Ma Z, Lee SS. Contribution of nitric oxide to the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. Gastroenterology 2000;118:937-944.
88. Tavakoli S, Hajrasouliha AR, Jabehdar-Maralani P, Ebrahimi F, Solhpour A, Sadeghipour H, Ghasemi M, Dehpour AR. Reduced susceptibility to epinephrine-induced arrhythmias in cirrhotic rats: the roles of nitric oxide and endogenous opioid peptides. J Hepatol 2007;46:432-439.
89. Hajrasouliha AR, Tavakoli S, Jabehdar-Maralani P, Shafaroodi H, Borhani AA, Houshmand G, Sadeghipour H, Dehghani M, Dehpour AR. Resistance of cholestatic rats against epinephrine-induced arrhythmia: the role of nitric oxide and endogenous opioids. Eur J Pharmacol 2004;499:307-313.
90. Randall MD, Harris D, Kendall DA, Ralevic V. Cardiovascular effects of cannabinoids. Pharmacol Ther 2002;95:191-202.
91. Bonz A, Laser M, Küllmer S, Kniesch S, Babin-Ebell J, Popp V, Ertl G, Wagner JA. Cannabinoids acting on CB1 receptors decrease contractile performance in human atrial muscle. J Cardiovasc Pharmacol 2003;41:657-664.
92. Ford WR, Honan SA, White R, Hiley CR. Evidence of a novel site mediating anandamide-induced negative inotropic and coronary vasodilatator responses in rat isolated hearts. Br J Pharmacol 2002;135:1191-1198.

93. Gaskari SA, Liu H, Moezi L, Li Y, Baik SK, Lee SS. Role of endocannabinoids in the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. Br J Pharmacol 2005;146:315-323.
94. Bátkai S, Mukhopadhyay P, Harvey-White J, Kechrid R, Pacher P, Kunos G. Endocannabinoids acting at CB1 receptors mediate the cardiac contractile dysfunction in vivo in cirrhotic rats. Am J Physiol Heart Circ Physiol 2007;293:1689-1695.
95. Canossa M, Ventura C, Vaona I, Carboni L, Guarnieri C, Spampinato S. Prodynorphin mRNA expression in adult cultured rat ventricular cardiac myocytes. Biochim Biophys Acta 1993;1172:247-250.
96. Springhorn JP, Claycomb WC. Preproenkephalin mRNA expression in developing rat heart and in cultured ventricular cardiac muscle cells. Biochem J 1989;258:73-78.
97. Wong TM, Shan J. Modulation of sympathetic actions on the heart by opioid receptor stimulation. J Biomed Sci 2001;8;299-306.
98. Xia Q, Sheng JZ, Tai KK, Wong TM. Effects of chronic U50,488H treatment on binding and mechanical responses of the rat hearts. J Pharmacol Exp Ther 1994;268:930-934.
99. Mantelli L, Amerini S, Rubino A, Ledda F. Characterization of opioid receptors modulating the function of capsaicin-sensitive neurons in guinea-pig atria. Eur J Pharmacol 1990;180:325-330.
100. Yu XC, Wang HX, Pei JM, Wong TM. Anti-arrhythmic effect of kappa-opioid receptor stimulation in the perfused rat heart: involvement of a cAMP-dependent pathway. J Mol Cell Cardiol 1999;31:1809-1819.
101. Yu XC, Wang HX, Zhang WM, Wong TM. Cross-talk between cardiac kappa-opioid and beta-adrenergic receptors in developing hypertensive rats. J Mol Cell Cardiol 1999;31:597-605.
102. Shan J, Yu XC, Fung ML, Wong TM. Attenuated “cross talk” between kappa-opioid receptors and beta-adrenoceptors in the heart of chronically hypoxic rats. Pflugers Arch 2002;444:126-132.
103. Ebrahimi F, Tavakoli S, Hajrasouliha AR, Shafaroodi H, Sadeghipour H, Riazi K, Borhani AA, Houshmand G, Ahmadi SH, Dehpour AR. Contribution of endogenous opioids and nitric oxide to papillary muscle contractile impairment in cholestatic rats. Eur J Pharmacol 2005;523:93-100.
104. Liu H, Song D, Lee SS. Role of heme oxygenase-carbon monoxide pathway in pathogenesis of cirrhotic cardiomyopathy in the rat. Am J Physiol Gastrointest Liver Physiol 2001;280:68-74.
105. Lee RF, Glenn TK, Lee SS. Cardiac dysfunction in cirrhosis. Best Pract Res Clin Gastroenterol 2007;21:125-140.

TEHRAN HEART CENTER

Original Article

Stem Cell Transplantation in Patients with Acute Myocardial Infarction: a Single Center Registry

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Received 12 April 2007; Accepted 28 July 2007

Abstract

Background: *Early clinical investigations indicate that an infusion of autologous bone-marrow cells into the infarct-related coronary artery is feasible after acute myocardial infarction. There is increasing evidence that cell transplantation may improve the perfusion and contractile function of the ischemic myocardium. The present study reports primarily the safety of intracoronary bone marrow mononuclear cell (BMMNC) injections and secondarily the hypothesis that intracoronary injections of autologous BMMNC in patients with acute myocardial infarction may have a favorable impact on tissue perfusion and contractile performance.*

Methods: *Twelve patients with acute ST-elevation myocardial infarction of the anterior wall treated with percutaneous coronary intervention were enrolled in this prospective, nonrandomized, open-label study. Left ventricular function and number of nonviable segments were assessed with the use of echocardiography and Technetium-sestamibi single photon emission tomography respectively at baseline and after a 4-month follow-up.*

Results: *At 4 months' follow-up, global left ventricular ejection fraction in echocardiography increased from a mean of 31.78±7.56% at baseline to 38.89±6.97% (p=0.018). Mean wall motion score in rest echocardiography was 29.5±6.67 in basal and 26.75±5.44 at 4 months' follow-up (p=0.05). Nuclear perfusion imaging studies in the patients for the mean number of nonviable segments were 6.5 at baseline and 6 in 4 months' follow-up (p=0.17). Three patients were lost to follow-up and did not undergo the 4-month evaluations.*

Conclusion: *This study is small and very preliminary. Data from large, randomized, controlled trials are needed to clarify the effect of stem-cell injection in myocardial function.*

J Teh Univ Heart Ctr 4 (2007) 201-206

Keywords: Stem cell transplantation • Myocardial infarction • Ventricular function

Introduction

Myocardial infarction (MI) leads to the loss of tissue and impairment of cardiac performance. The irreversible loss of cardiomyocytes after MI begets left ventricular remodeling, eventually resulting in ischemic heart failure. Remodeling of

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the left ventricle after MI represents a major cause of infarct-related heart failure and death.[1,2] Despite the application of pharmacotherapeutics and mechanical interventions, the cardiomyocytes lost during MI cannot be regenerated. The recent finding that a small population of cardiac muscle cells is able to replicate itself is encouraging but is still consistent with the concept that such regeneration is restricted to viable myocardium.[3] One approach to reverse myocardial remodeling is to repair myocardial tissue by using bone marrow-derived cells. In recent years, stem cell transplantation has emerged as a potential modality for the treatment of cardiovascular disease on the basis of its possible ability to induce neovascularization and tissue replacement. Several recent experimental studies have confirmed the potential of pluripotential cells in differentiating into cardiomyocytes and endothelial cells.[4-6] Early clinical investigations indicate that the infusion of autologous bone-marrow cells into the infarct-related coronary artery is feasible after acute MI[7-8] and there is increasing evidence that cell transplantation may improve the perfusion and contractile function of the ischemic myocardium.[8-12] In this way, the present study reports primarily the safety of intracoronary bone marrow mononuclear cell (BMMNC) injections and secondarily the hypothesis that intracoronary injections of autologous BMMNC in patients with acute MI may have a favorable impact on tissue perfusion and contractile performance of the injured heart.

Methods

Patient selection

This is a prospective, nonrandomized, open-label study on 12 patients with ST- elevation MI. The following inclusion criteria were required for patient enrollment: 1) age between 18 and 75 years; 2) first acute ST- elevation MI and in left anterior descending coronary artery (LAD) territory; 3) left ventricular ejection fraction (LVEF)<45% in echocardiography; 4) at least 2 nonviable segments in dipyridamole single photon emission computed tomography (SPECT); 5) akinetic and nonviable scar, as demonstrated by a lack of response to low-dose dobutamine echocardiography; 6) successful revascularization procedure with stent implanting; and 7) signed, informed consent. Patients were not enrolled in the study if any the following exclusion criteria was met: 1) presence of cardiogenic shock (defined as systolic blood pressure<80 mm Hg requiring intravenous pressors or intra-aortic balloon counterpulsation); 2) major bleeding requiring blood transfusion after reperfusion treatment; 3) a history of leucopenia, thrombocytopenia, or hepatic or renal dysfunction; 4) evidence for malignant disease, and 5) unwillingness to participate. The ethics committee of Tehran Heart Center, affiliated with Tehran University of Medical Sciences approved the study protocol, and a written informed consent was obtained from each patient.

Study protocol

All 12 patients had suffered transmural infarction according to World Health Organization criteria with the involvement of the LAD. We assessed patients with left-heart catheterization and coronary angiography, transthoracic dobutamine echocardiography, and ^{99m}Tc-mibi SPECT perfusion scan. After coronary angiography, mechanical treatment was initiated by balloon angioplasty and stent implantation in infarct-related artery and other arteries. According to the inclusion criteria, if the patient was eligible for stem cell implantation, he/she was prepared for this procedure.

TC-mibi SPECT

Baseline Technetium-Sestamibi single photon emission tomography (^{99m}Tc-mibi SPECT) was performed after angioplasty and stenting for the assessment of viable myocardium. All the patients underwent rest-redistribution ^{99m}Tc-mibi SPECT imaging according to a standardized clinical protocol. Several minutes after the injection of ^{99m}Tc-mibi, rest imaging was performed. Then, 3 to 4 h later the patient returned for redistribution imaging.

Stress echocardiography

Baseline dobutamine stress echocardiography was carried out to assess viable myocardium. Dobutamine was infused with doses of 5, 10, and 15 μg/kg per minute in 3-minute stages. Regional wall motion analysis was performed as described by the Committee on Standards of the American Society of Echocardiography[13] dividing the left ventricle into 16 segments and scoring wall motion of 1=normal, 2=hypokinesia, 3=akinesia, and 4=dyskinesia for each segment. Contractile reserve was defined as an improvement of ≥1 in the wall motion score between the baseline images and the dobutamine low- dose stage (15μg/kg per minute). The wall motion score index (WMSI) was calculated as the sum of the scores of the segments divided by the number of the segments evaluated. Echocardiograms were read by investigators unaware of the clinical, angiographic, and SPECT imaging findings in each patient.

Bone marrow aspiration and isolation of mononuclear cells

Within the first week after angioplasty, bone marrow (≈50

ml) was aspirated under local anesthesia from the posterior iliac crest. Bone marrow mononuclear cells (BMMNC) were isolated by Ficol density separation on Lymphocyte Separation Medium 199 before the erythrocytes were lysed with H_2O. Mononuclear cells were exhaustively washed with heparinized saline containing 1% human serum albumin. The cells were finally resuspended in saline with 1% human serum albumin for injection. A small fraction of the cell suspension was used for cell counting and viability testing by trypan blue exclusion. Post-hoc characterization of leukocyte differentiation markers by flow cytometry and functional assay were performed on another fraction of the cells.

Intracoronary transplantation of Bone marrow cells (BMC)

A day after bone marrow harvest, the final preparation of bone marrow cells was infused into the infarct-related artery via the central lumen of an over-the- wire balloon catheter. To allow bone marrow cells maximum contact time with the microcirculation of the infarct-related artery, the balloon was inflated inside the stent to transiently interrupt antegrade blood flow during infusions. The entire bone marrow cell preparation was infused during four to five coronary occlusions, each lasting 3 minutes. Between occlusions, the coronary artery was reperfused for 3 minutes.

Assessment of outcomes

Follow-up visits were performed by physicians 1 and 4 months post transplantation. Specific attention was paid to any potential signs or symptoms of arrhythmia during the follow-up. Four months after stem cell injection, stress echocardiography and ^{99m}Tc-mibi SPECT were repeated to measure LVEF, WMSI, and number of nonviable segments. The primary end points were feasibility and safety. Feasibility was defined as the ability of the expansion procedure to yield the target numbers of cells within two to three weeks. Safety referred to any procedural complication, including: ventricular arrhythmia, visible thrombus formation, distal embolization, injury of the coronary artery associated with the cell-infusion catheterization procedure or any adverse events related to cell injection within the follow-up period. The secondary end point was efficacy, which was primarily assessed by two-dimensional echocardiographic analysis of LV function at four months' follow-up.

Statistics

Results are reported as mean±SD. A comparison of the preoperative and postoperative data was done using the paired t test, with $p<0.05$ as the limit of significance.

Results

Between July 2003 and August 2004, 12 patients were informed and enrolled in this prospective study. Table 1 shows the clinical and interventional details of the 12 patients in this series. Although 12 patients were enrolled in this study, 3 patients were not included in the analysis. One patient was lost to follow-up and did not undergo the 4-month evaluations, the second patient had additional non-ST elevation MI 2 weeks after cell therapy. A Third patient had pulmonary edema 2 hours after the procedure; Cardio pulmonary resuscitation (CPR) was done successfully and in repeated angiogram the related artery was patent. The patient was subsequently transferred to CCU ward. However, the patient's situation was complicated with fever, pneumonia, acute renal failure, and acute respiratory distress syndrome (ARDS). After 8 days, the patient died in CCU.

In all the patients, aspirin, plavix, statin, β-blocker, and angiotensin converting enzyme (ACE) inhibitor therapy were initiated during the hospitalization for acute MI and continued until the 4-month follow-up examination. After the exclusion of above-mentioned patients, there were no deaths, and none of the patients had any malignant arrhythmias during the follow-up. At 4 months' follow-up examination, none had any clinical findings suggestive of heart failure.

On average, 43±5 ml of bone marrow was aspirated from the posterior iliac crest during a brief general analgesia with morphine. No bleeding complications at the harvest site were noted. During the preparation of bone marrow cells, the sedimentation process reduced the volume of bone marrow cells to a mean of 7.5±3.5 ml. The final preparation of bone marrow cells contained $15.5\times10^6\pm6.4\times10^6$ nucleated cells (mean viability 90%), 1.55×10^6 CD34+ cells, and 7.75×10^6 CD45+cells.

As is shown in Figure 1, at 4 months' follow-up, global LVEF in echocardiography increased from a mean of 31.78±7.56% at baseline to 38.89±6.97% at 4 months ($p=0.018$). Mean WMS in rest echocardiography was 29.5±6.67 in basal and 26.75±5.44 at 4 months' follow-up ($p=0.05$). Figure 2 illustrates WMSI at resting and 15 μg dobutamine stress echocardiography at baseline before stem cell therapy as well as the WMSI at resting echocardiography at 4 months' follow-up. Nuclear perfusion imaging studies in the patients for the mean number of nonviable segments were 6.6 at baseline and 6.1 at 4 months' follow-up ($p=0.17$). Two patients showed improvement of nonviable segment in SPECT at 4 months' follow-up.

Table 1. Patients' Characteristics

Patient No	Age (y)	Sex	LVEF (%) (pre inj)	LVEF (%) (post inj)	No of nonviable segments (pre inj)	No of nonviable segments (post inj)	WMS (pre inj)	WMS (post inj)
1	39	Male	25	30	6	6	27	28
2	46	Female	35	30	8	8	28	28
3	62	Male	25	40	6	6	26	26
4	52	Male	25	35	9	9	42	38
5	36	Female	40	45	5	5	22	22
6	62	Male	30	45	7	4	34	26
7	42	Male	36	40	7	5	34	28
8	53	Male	45	50	6	6	25	20
9	65	Female	30	35	6	6	24	24
10	75	Male	30	-	-	-	-	-
11	50	Female	40	-	-	-	-	-
12	69	Male	35	-	-	-	-	-

LVEF, Left ventricalar ejection fraction: Inj, Injection; WMS, Wall motion score

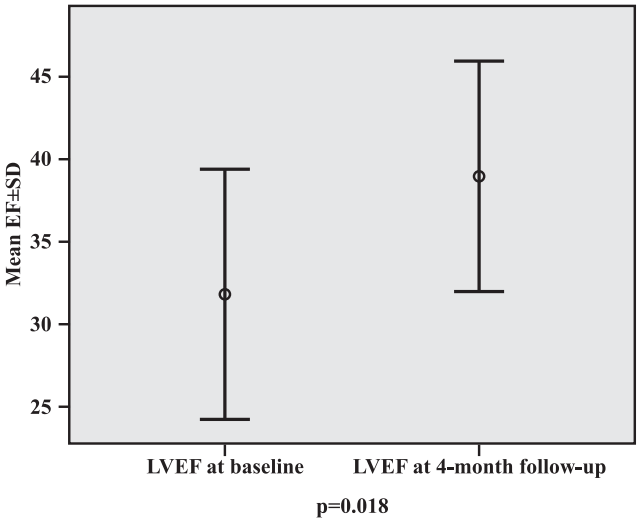

Figure 1. Mean left ventricular ejection fraction (LVEF) of patients at baseline and 4-month follow-up

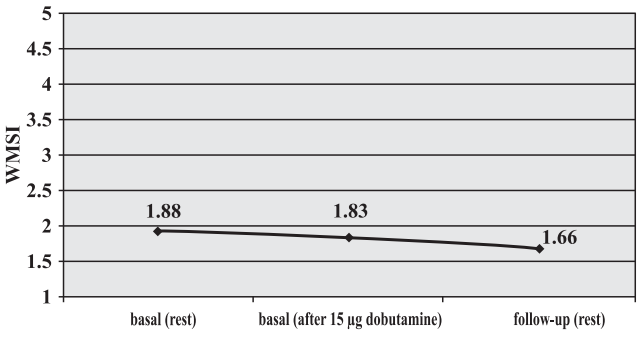

Figure 2. Wall motion score index (WMSI) before injection of bone marrow stem cell (rest and after dobutamine injection) and at 4-month follow-up

Follow-up visits were continued after 4 months. Mean follow-up visit duration was 24±4.5 months. There were no deaths, and none of the patients had any malignant arrhythmias during follow-up visit duration.

Discussion

A reduced LVEF during the acute phase of myocardial infarction is the most important independent predictor of a poor outcome, even in the era of optimal reperfusion therapy with the stenting of the infarct-related artery.[14] Thus, enhanced recovery of contractile function may be beneficial, especially in patients with large infarcts and depressed left ventricular function.[15]

Our findings indicate that a catheter-based intramyocardial implantation of bone marrow cells is relatively safe and feasible for the treatment of patients with acute MI. The present report describes the effect of intracoronary, autologous, mononuclear bone marrow cell transplantation on improving heart function and myocardial perfusion in patients after acute MI. After 4 months, the global LVEF was significantly higher compared with basal LVEF. However, the number of patients is not sufficient to conclude that an intracoronary infusion of bone marrow stem cell (BMS) is associated with persistent improvements in global left ventricular function and improved functional status among patients who have had MI at least 4 months prior to the transplantation. The enhanced recovery of global left ventricular contractile function after the intracoronary administration of BMS was due to a significant reduction in the extent and magnitude of regional left ventricular dysfunction within the territory of the infarct. This finding is in agreement with other studies where unfractionated BMC was utilized.[7,16-18] Our 4-month follow-up showed that the mean number of nonviable segments and WMSI were not significantly higher compared with the basal evaluation.

Some previous studies have shown no improvement in left ventricular function after treatment with BMC.[10,19] Technical differences in the characteristics or handling of the infused BMC might explain the different outcome. Also, differences in cell preparation and cell population may be important.

Although stem cell therapy has been shown to be safe, feasible, and effective in both animal and human studies,

the mechanism by which this therapy improves healing after ischemic injury remains unexplored. Other unanswered questions include: Is stem cell therapy safe and effective in the long term? Which stem cell (unfractionated bone marrow, bone marrow-derived mononuclear, or any of the multiple subpopulations of the latter) will produce optimal therapeutic effect in damaged myocardium? What is the optimal delivery approach (intravenous, intracoronary, intramyocardial, or transepicardial)? What is the optimal dosage and timing of the administration of cell therapy? Answers to these questions may require additional animal and human studies.

The major limitations of this study are the small number of the patients enrolled; the study design, which limits any conclusions about efficacy; and the lack of a randomized control group, which did not receive intracoronary infusion of BMC.

Additionally, as assessment of whether intracoronary infusion of BMCS can reduce the risk of complications and death among patients with acute MI was beyond the scope of the present study.

In summary, after acute MI, the intracoronary administration of BMC enhances left ventricular contractile recovery. Given the safety profile of this treatment and the beneficial effects in patients with the most severely impaired left ventricular function, large scale studies are warranted to examine the potential effects of this novel approach on the risk of death and complications in patients with large acute MI and depressed left ventricular contractile function. We emphasize the fact that all reported attempts of clinical cell transplantation for myocardial regeneration, including our study; have been done in association with surgical or interventional revascularization, so that the effectiveness of cell transplantation alone cannot clarify the role of cell transplantation in myocardial regeneration.

Conclusions

This study is small and very preliminary. Data from large, randomized controlled trials are needed to clarify the effect of stem cell injection in myocardial function.

Acknowledgments

This study has been approved by Tehran Heart Center's Review Board and Ethics Committee; and has been supported by Tehran Heart Center, Tehran University of Medical Sciences.

Reference

1. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation 1990;81:1161-1172.
2. Ertl G, Gaudron P, Hu K. Ventricular remodeling after myocardial infarction: experimental and clinical studies. Basic Res Cardiol 1993;88:125-137.
3. Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadal-Ginard B, Kajstura J, Leri A, Anversa P. Chimerism of the transplanted heart. N Engl J Med 2002;346:5-15.
4. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infracted myocardium. Nature 2001;410:701-705.
5. Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, Wang J, Homma S, Edwards NM, Itescu S. Neovascularazation of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. Nat Med 2001;7:430-436.
6. Menasché P, Hagège AA, Vilquin JT, Desnos M, Abergel E, Pouzet B, Bel A, Sarateanu S, Scorsin M, Schwartz K, Bruneval P, Benbunan M, Marolleau JP, Duboc D Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. J Am Coll Cardiol 2003;41:1078-1083.
7. Strauer BE, Brehm M, Zeus T, Köstering M, Hernandez A, Sorg RV, Kögler G, Wernet P. Repair of infracted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002;106:1913-1918.
8. Assmus B, Schächinger V, Teupe C, Britten M, Lehmann R, Döbert N, Grünwald F, Aicher A, Urbich C, Martin H, Hoelzer D, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 2002;106:3009-3017.
9. Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, Schümichen C, Nienaber CA, Freund M, Steinhoff G. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet 2003;361:45-46.
10. Tse HF, Kwong YL, Chan JK, Lo G, Ho CL, Lau CP. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. Lancet 2003;361:47-49.
11. Tomita S, Mickle DA, Weisel RD, Jia ZQ, Tumiati LC, Allidina Y, Liu P, Li RK. Improved hear function with myogenesis and angiogenesis after autologous porcine bone marrow stromal cell transplantation. J Thorac Cardiovasc Surg 2002;123:1132-1140.
12. Fuchs S, Baffour R, Zhou YF, Shou M, Pierre A, Tio FO, Weissman NJ, Leon MB, Epstein SE, Kornowski R. Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. J Am Coll Cardiol 2001;37:1726-1732.
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-367.
14. Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, Garcia E, Cox DA, Turco M, Stuckey TD, Na Y, Lansky AJ, Gersh BJ, O'Neill WW, Mehran R, Stone GW. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 2005;45:1397-1405.
15. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R,

Hölschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Intra coronary bone marrow-derived progenitor cell in acute myocardial infarction. N Engl J Med 2006;355:1210-1221.

16. Fernández-Avilés F, San Román JA, García-Frade J, Fernández ME, Peñarrubia MJ, de la Fuente L, Gómez-Bueno M, Cantalapiedra A, Fernández J, Gutierrez O, Sánchez PL, Hernández C, Sanz R, García-Sancho J, Sánchez A. Experimental and clinical regenerative capability of human bone marrow cells after myocardial infarction. Circ Res 2004;95:742-748.

17. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomized controlled clinical trial. Lancet 2004;364:141-148.

18. Schächinger V, Assmus B, Britten MB, Honold J, Lehmann R, Teupe C, Abolmaali ND, Vogl TJ, Hofmann WK, Martin H, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. J Am Coll Cardiol 2004;44:1690-1699.

19. Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, Endresen K, Ilebekk A, Mangschau A, Fjeld JG, Smith HJ, Taraldsrud E, Grøgaard HK, Bjørnerheim R, Brekke M, Müller C, Hopp E, Ragnarsson A, Brinchmann JE, Forfang K. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 2006;355:1199-1209.

TEHRAN HEART CENTER

Original Article

Effects of Phase III Cardiac Rehabilitation Programs on Anxiety and Quality of Lifein Anxious Patients after Coronary Artery Bypass Surgery

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Received 19 March 2007; Accepted 28 June 2007

Abstract

Background: *Patients with psychological problems after coronary artery bypass graft surgery (CABG) show poorer outcomes; nevertheless, there is a paucity of research into the effects of cardiac rehabilitation programs on such patients. The purpose of this study was to determine the effect of phase III cardiac rehabilitation programs on the anxiety and quality of life of anxious patients who had undergone CABG in Iran.*

Methods: *Six weeks after CABG, 83 anxious patients participated in an 8-week cardiac rehabilitation program that consisted of formal supervised exercise training and educational sessions. The state/trait anxiety inventory and SF-36 questionnaire were two instruments for collecting data in the present study. Of the total of 83, 66 participants saw out the eight-week period.*

Results: *With the exception of the mental health aspect, significant improvements were noted in the following components of the quality of life measures after the cardiac rehabilitation program: physical functioning (P<0.001), role-physical (P<0.001), bodily pain (P<0.001), social functioning, (P=0.003), general health (P=0.020), vitality (P=0.006), and role-emotional (P=0.003). Additionally, significant reductions were observed in state anxiety (P=0.010) and trait anxiety (P=0.010).*

Conclusion: *These findings suggest that phase III cardiac rehabilitation may be an effective therapy for improving psychological outcomes of patients with psychological problems after CABG.*

J Teh Univ Heart Ctr 4 (2007) 207-212

Keywords: *Phase III cardiac rehabilitation • Coronary artery bypass graft surgery • Anxiety • Quality of life*

Introduction

Cardiac surgery may evoke anxiety, stress, and emotional responses from patients and their families.[1] Anxiety is one of the earliest and most intense psychological responses to ischemic coronary events.[2] Most patients are relieved when

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the surgery is complete, and the biggest reductions in anxiety occur from preoperative to early postoperative times.[3] However, anxiety levels remain higher than normal for some time following surgery.[3-5,6] More than 40% of coronary artery bypass graft surgery (CABG) patients were anxious in the week after discharge.[7] Major personal stress in patients' lives is a stronger predictor of anxiety during recovery post-CABG discharge than are any clinical or demographic factors.[6] Patients with more anxiety after surgery have worse long-term psychological outcomes and poorer quality of life (QOL).[8,9] Anxiety exerts a profoundly negative effect on QOL and adversely influences the outcomes of ischemic heart disease from many standpoints, including recurrent hospitalization, an increased incidence of ischemic events, and higher mortality.[10] Although anxiety is less often investigated,[11] considerable epidemiological evidence indicates that persons with anxiety symptomatology are at increased risk of recurrent ischemic and arrhythmic events.[12-14]

A cardiac rehabilitation (CR) program is a well-established program of secondary prevention for patients with acute coronary disease that leads to clinical benefits and a significant reduction in all-cause mortality and total cardiac mortality through modification of coronary risk factors and unhealthy behaviors.[15] Anxiety may be addressed by CR through reducing uncertainty, providing patients with an optimistic but realistic outlook on recovery, providing psychological support, and promoting coping.[16] Improvement in QOL is an important goal for individuals participating in outpatient CR programs.[17]

It is useful to consider the four phases of CR inasmuch as each presents a different component of the journey of care: inpatient care (phase I), the early post discharge period (phase II), exercise training (phase III), and finally long-term follow-up (phase IV).[18]

The provision of CR services for CABG patients in late period after discharge is new in Iran, which is why only a few heart hospitals possess well-equipped clinic CR facilities. Fortunately, efforts are underway to increase the number of these centers and improve their qualities. Lack of research on this field in Iran is tangible: to date there has been no evidence for the effect of CR programs on the psychological outcomes of anxious Iranian patients after CABG. We, consequently, sought to address this issue by hypothesizing that post-CABG patients participating in phase III CR program would have greater QOL (in the subscales of QOL) and less state/trait anxiety than before the program.

Methods

This study is a quasi-experimental type. The program aimed to decrease the anxiety and improve the QOL of the patients who participated in phase III CR program (6 weeks after discharge) of Tehran Heart Center.

The independent variable was an 8-week exercise training session and 1-week education sessions. The major dependent variables were state anxiety, trait anxiety, and QOL. This convenience sample included 66 patients referred to the CR clinic of Tehran Heart Center 6 weeks after CABG. Patients were selected through the random sampling procedure. The selection criteria were: patients' consent to participate, CABG treatment, no history of a major comorbidity (e.g. cancer, chronic renal failure, or major neurological disorder) except for the risk factors of heart disease (e.g. diabetes), no indication of receiving treatments for anxiety and depression, the age-range of 40 to 65, and the summation of in 120>score>40 of state anxiety and trait anxiety score. Whereas medication for patients with severe anxiety it is possible to necessitate, were excluded patients having severe anxiety. All subjects completed questionnaires at baseline (Time1) and after 8 weeks (Time 2). The completion of the questionnaires lasted 30 to 35 min**.**

Assessment of anxiety and quality of life

The anxiety and QOL of the patients were measured with two questionnaires. Anxiety was measured with the State-Trait Anxiety Inventory (STAI), developed by Charles Spilberger and his colleagues. The state anxiety scale, consisting of 20 statements, evaluates how respondents feel at the moment via a four-point scale. The trait anxiety scale, comprising 20 statements, assesses how people generally feel via a four-point scale (Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory [Self-Evaluation Questionnaire]. Palo Alto: Consulting Psychologist Press; 1970. Available from: http://www.mindgarden.com/products/staisad.htm. Access: 9 Feb 2008). This scale was adapted and translated into Persian by Dadsetan et al (Dadsetan P, Mansour M. Mental illness. Tehran: Roshd Press;1998). The reliability estimate through Coronbach's ά was 0.82 for state STAI and 0.92 for trait STAI in the present study.

QOL was measured with the Sf-36 instrument. Sf-36 comprises 36 items covering eight domains: physical function (10 items), role limitation caused by physical problems (4 items), bodily pain (2 items), mental health (5 items), role limitations due to emotional problems (3items), vitality-energy (4 items), and general health perception (5 items). This scale was adapted and translated into Persian by Montazeri et al. in 1996.19 Test–retest correlation coefficients were 0.76 with a 2-week interval. A higher score indicated a better QOL.

Interventional program

Exercise training was performed 3 days/week for 24 weeks at an intensity of 70-85% of maximal heart rate for 30 minutes. During each session, the patients utilized a cycle ergometer for 8 minutes and an arm ergometer for 12 minutes.

The participants also utilized treadmills from the third session. The risk levels of the patients were determined on the basis of the results of the exercise test and other variables such as history of heart surgery and myocardial infarction, existence of heart disease, risk factors, and ejection fraction. These parameters helped determine the duration and speed of treadmill exercise. Systolic and diastolic blood pressures were measured before and after treadmill exercise. The duration of the exercise on the treadmill varied from 10 to 15 minutes. While exercising with cycle and arm ergometers, the patients were monitored. Initial exercise intensity was 40-55 % of $VO2_{peak}$ (peak oxygen consumption), which was progressively increased by 0.5 MET (Metabolic equivalent) per week to 70-85%. In the first and fifteenth sessions, electrocardiogram and exercise test for indicating MET and heart rate were done for the patients. Finally, the subjects were encouraged to perform to walk at home. The patients and their family participated in group educational classes 3 times per week. These educational sessions focused on strategies to modify the participants' coronary risk factors. In these classes, a psychologist and a nutrition expert taught the patients about nutrition regimes, coping methods with pain, anxiety, depression and problems after surgery, as well as safe sexual activity, smoking cessation, and exercise. Two educational pamphlets were given to everyone.

Statistical analysis

SPSS for Windows (version 13.0) was used for all the analyses. The independent sample t test was performed to obtain the correlation between the genders and dependent variables (overall QOL and state/trait anxiety). The Pearson correlation test was conducted to obtain the correlation coefficients between age and dependent variables. The One-way ANOVA was utilized to obtain the correlation between education level, marital status and dependent variables. Differences in the QOL domains, state anxiety, and trait anxiety scores between Time 1 and 2 were tested using student's t test for paired sample. The outcome data were presented as mean (S.D.). All P-values were two-tailed and regarded significant if below 0.05.

Results

The average age of the participants in this study was 56.5 years. 68.2 percent of the patients were male and 30.3 percent women. The survey of the education level showed that a majority of the patients (37.9%) had a high school diploma. While 36.3 percent of the patients were employed, 30.3 percent of them were retired. Most of the patients (81.8%) were married. The mean scores of the state and trait anxiety of the subjects at Time 1 (6 weeks after CABG and before CR) and Time 2 (after the end of CR) are depicted in Table 1.

Table 1. Comparison of state and trait anxiety scores between Time 1 and Time 2*

Variable	Time 1	Time 2	P value
State anxiety	44.2±10.9	40.5±10.5	0.01
Trait anxiety	43.7±9.7	41.1±10.7	0.01

* All variables are presented as Mean±SD
Time 1 denotes time before the cardiac rehabilitation program; Time 2 denotes time after the program

Table 2 demonstrates the QOL domains of the patients at Time 1 and Time 2.

Table 2. Comparison of the quality of life domains scores between Time 1 and Time 2*

Variable	Time 1	Time 2	P value
Physical functioning	56.2±18.6	73.5±16.1	<.001
Role physical	18.7±25.1	39±31.3	<.001
Bodily pain	44.5±23.7	61±21.9	<.001
General health	60.6±20.5	67.7±18.9	0.020
Vitality	49.7±17.5	56.4±19.8	0.006
Social functioning	57.2±26	56.4±19.8	0.003
Role emotional	31.4±30.2	50±37.4	0.003
Mental health	58±19.3	61.9±20.5	0.060

* All variables are presented as Mean±SD
Time 1 denotes time before the cardiac rehabilitation program; Time 2 denotes time after the program

No significant difference was observed in the state/trait anxiety scores between the males and females at baseline (Time 1) and 8 weeks (Time 2). A significant difference was, however, observed between sex and overall QOL score at baseline. The women had a lower QOL than the males at baseline.

The education level had no significant correlation with the dependent variables at Time 1 and Time 2. Also, there was no significant association between age and three dependent variables at Time 1 and Time 2. A significant difference was observed between marital status and the dependent variables at Time 1 and Time 2. The subjects who were unemployed had a lower QOL than that of the participants who had employment at Time 1 (P=0.03).

Discussion

This study measured the effects of cardiac rehabilitation on improving psychological outcomes in patients who participated in a cardiac rehabilitation program in Iran. The findings of this study demonstrated that the 8-week cardiac rehabilitation program (phase III) improved all domains QOL as well as decreased state and trait anxiety of patients after CABG.

Our findings are consistent with many studies, which evaluate the effects of cardiac rehabilitation on patients, psychological outcome. For example, Lindsay et al reported that CR programs improving four of the eight components of QOL (general health (P=0.01), physical functioning (P=0.01), role physical (P=0.02) and social functioning (P=0.04)) in attenders to CR than nonattenders.[20] Kennedy et al reported that 14-weeks cardiac rehabilitation (exercise training and life style education) can improve of quality of life and risk factors, patients.[21] Similarly, Benzer et al considered that exercise cardiac rehabilitation will reduce of anxiety and improve the quality of life in patients attending to cardiac rehabilitation than non attending.[22] Also, Choo et al. demonstrated that cardiac rehabilitation program (CRP) can increase greater in the overall quality of life, the health/functioning and the psycho/spiritual subscales in the MI patients receiving CRP than the control group (no receiving CRP) too.[23] Ades and Coello found that CR can improving quality of life and physical functioning in patients with coronary heart disease.[17] Also, Oldridge et al and Stahle et al. demonstrated that CR improving QOL and reducing state anxiety in the experimental group than the control group after 12 months.[24,25]

In the present study, cardiac rehabilitation programs had no significant effect on mental health component of QOL (shows table 2). Since, the aim of a CR program is to improving all components of QOL of patients, we may assume this intervention aren't sufficient and CR in need of specific psychological interventions (e.g. relaxation techniques) for improving mental health and more decreasing anxiety scores. Where it needs for more psychological inputs in cardiac rehabilitation for increasing quality of CR services are sensible.

It was astonished to find that cardiac rehabilitation had equality effect on trait and state anxiety. These findings are different from, other results indicating that trait anxiety is part of one, s personality make up, and therefore, more resistant to change.[26] Further clinical trials may be needed to confirm the effect of cardiac rehabilitation on reducing trait anxiety.

In the present study, women had lower level of state anxiety and trait anxiety as well quality of life in components of role physical, bodily pain, general health, social functioning and overall quality of life than men at baseline. Improving in all components of quality of life except of social functioning and reducing state anxiety and trait anxiety were statistically similarly in men and women after participating in CR program.

These data affirm that women should be routinely referred to and vigorously encouraged to participate in outpatient cardiac rehabilitation after CABG. Similarly Lavie et al found that CR has similarly effects on total scores and all components of quality of life in women and men.[27] But, these findings are different from some study. For example, O, Farrell et al found that women have significantly lower QOL and exercise capacity at first CR and 3 months after CR program than men.[28] Also, Frasure-Smith et al demonstrated that women had more symptomatology and functional impairment at entry to CR program than men and although they made significant physical gains in the program, they continued to exhibit more depressive symptomatology upon completion of the program.[29] Randomized trials are need to better define the role of CR for safely improving QOL and psychological outcomes among female with heart patients.

In the present study, observed that approximately 22% of participants drop out from program in tenth session. This finding is consistent with reviewed literatures, since its shows that approximately 20-25% of patients drop out of CR program within the first three months and about 40-50% at between 6 and 12 months.[30] To investigate the predictors of early drop-out from a CR program, it is clear that three major categories must take into consideration: the health care system, the cardiac rehabilitation program and patients, characteristics.[31] Yohannes et al. demonstrated that Psychological distress, younger age and lower perceptions of consequences, higher perception personal control and lower illness perception of treatment control were personal predictors of early drop-out from a cardiac rehabilitation program.[32] As thought that, one effect factor on drop-out from CR program in Iran may be explained through economic situations, patients (particularly income) and the lake of insurance coverage for CR after discharge.

Although the findings of this study showed that cardiac rehabilitation program in Iran can produce significant improvements in psychological outcomes and QOL of heart patients, a little number of patients refers to cardiac rehabilitation clinics. An understanding of the factors that contribute to this low participation rate is of extreme importance for planning to attract participation. Studies showed that various factors are associated with CR attendance. For example, Cooper et al. found that job status, gender and health concerns play an indirect role in attendance behavior to CR. They demonstrated that nonattenders to CR programs are more likely to be older, to have lower income/greater deprivation, to deny the severity of their illness; they are less likely to believe they can influence its outcomes or to perceive that their physician recommends cardiac rehabilitation.[33] King et al. examined the relations between demographic factors, specific psychological factors, and CR attendance. They found that cardiac patients may have misconceptions about that mandate and potential benefits of rehabilitation programs.[34] It is necessary that personality, demographic and psychosocial factors associated with CR attendance and early drop-out from CR, determine throughout qualitative and quantitative researches.

The limitations of this study include small size of subjects, absence of a control group and short duration of follow-up. Randomized control trials are needed to better define the role of CR programs for improving physical and psychological outcomes of patients. Future studies should include comparisons of the effectiveness of supervised versus home-

based CR interventions. However results in present study can demonstrate the important of CRP in Iran and the point of start, for set up studies related to this field.

Conclusion

What can be concluded is that cardiac rehabilitation programs can serve as a resource for improving psychological outcomes and quality of life in anxious heart patients. It is necessary that more attention be paid to CR programs for such patients.

Acknowledgment

The authors gratefully acknowledge the Institutional Review Board of Tarbiat Modares University, which approved and financially supported this project. They also thank all the cardiac rehabilitation staff in Tehran Heart Center for their cooperation.

References

1. Gaw-Ens B. Informational support for families immediately after CABG surgery. Crit Care Nurse 1999;14:41-42.
2. Frasure-Smith N. In–hospital symptoms of psychological stress as predictors of long-term outcomes after acute myocardial infarction in men. Am J Cardiol 1991;67:121-127.
3. Duits AA, Duivenvoorden HJ, Boeke S, Taams MA, Mochtar B, Krauss XH, Passchier J, Erdman RA. The course of anxiety and depression in patients undergoing coronary artery bypass graft surgery. J Psychosom Res 1998;45:127-138.
4. Boudrez H, De Backer G. Psychological status and the role of coping style after coronary artery bypass surgery: results of a prospective study. Qual Life Res 2001;10:37-47.
5. McCrone S, Lenz E, Tarzian A, Perkins S. Anxiety and depression: incidence and patterns in patients after coronary artery bypass graft surgery. Appl Nurs Res 2001;14:155-164.
6. Gallagher R, McKinley S, Dracup K. Effects of a telephone counseling intervention on psychosocial adjustment in women following a cardiac event. Heart &Lung 2003;32:79-87.
7. Davies N. Patients' and carers' perceptions of factors influencing recovery after cardiac surgery. J Adv Nurs 2000;32:318-326.
8. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. Psychosom Med 2001; 63:221-230.
9. Mayou RA, Gill D, Thompson DR, Hicks N, Neil A. Depression and anxiety as predictors of outcome after myocardial infarction. Psychosom Med 2000;62:212-219.
10. Januzzi JL, Stern TA, Pasternak RC, Desanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. Arch Intern Med 2000;160:1913-1921.
11. Abbey S, Stewart DE. Gender and psychosomatic aspects of ischemic heart disease. J Psychosom Res 2000;48:417-423.
12. Vingerhotes G. Cognition, emotional, and psychosomatic complains, and their relation to emotional status, and personality following cardiac surgery. Br J Health Psychol 1998;3:159-169.
13. Moser DK, Dracup K. Is anxiety early after myocardial infraction associated with subsequent ischemic and arrhythmic events? Psychosom Med 1996;58:395-401.
14. Williams RB. Do benzodiazepines have a role in the prevention or treatment of coronary heart disease and other major disorders? J Psychiatr Res 1990;24:51-56.
15. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trial. Am J Med 2004;116:682-692.
16. Yoshida T, Kohzuki M, Yoshida K, Hiwatari M, Kamimoto M, Yamamoto C, Meguro S, Endo N, Kato A, Kanazawa M, Sato T. Physical and psychological improvements alter phase II cardiac rehabilitation in patients with myocardial infraction. Nurs Health Sci 1999;1:163-170.
17. Ades PA, Coello CE. Effects of exercise and cardiac. rehabilitation on cardiovascular outcomes. Med Clin North Am 2000;84:251-265.
18. Thompson DR. A randomized controlled trial of in-hospital nursing support for first time myocardial infarction patients and their partners: effects on anxiety and depression. J Adv Nur 1989;14:291-297.
19. Montazeri A, Goshtasebi A, Vahdaninia M, Gandek B. The short form health study (Sf-36): translation and validation study of the Iranian version. Qual Life Res 2005;14:875-882.
20. Lindsay GM, Hanlon WP, Smith LN, Belcher PR. Experience of cardiac rehabilitation after coronary artery surgery: effects on health and risk factors. Int J Cardiol 2003;87:67-73.
21. Kennedy MD, Haykowsky M, Daub B, Van Lohuizen K, Knapik G, Black B. Effects of a comprehensive cardiac rehabilitation program on quality of life and exercise tolerance in women: a retrospective analysis. Curr Control Trials Cardiovasc Med 2003;4:1-6.
22. Benzer W, Platter M, Oldridge NB, Schwann H, Machreich K, Kullich W, Mayr K, Philippi A, Gassner A, Dörler J, Höfer S. Short-term patient-reported outcomes after different exercise-based cardiac rehabilitation programmes. Eur J Cardiovasc Prev Rehabil 2007;14:441-447.
23. Choo J, Burke LE, Hong KP. Improved quality of life with cardiac rehabilitation for post-myocardial infarction patients in Korea. Eur J Cardiovasc Nurs 2007;6:166-171.
24. Oldridge N, Guyatt G, Jones N, Crowe J, Singer J, Feeny D, McKelvie R, Runions J, Streiner D, Torrance G. Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction. Am J Cardiol 1991;67: 1084-1089.
25. Stahle A, Mattsson E, Ryden L, Unden AL, Nordlander RI. Improved physical fitness and quality of life following training of elderly patients after acute coronary events: a 1-year follow-up randomized controlled study. Eur Heart J 1999;20 (20):1475-1484.
26. Rashid ZM, Parish TS. The effects of two types of relaxation training on students levels of anxiety. Adolescence 1998;33:99-101.
27. Lavie CJ, Milani RV. Effects of cardiac rehabilitation and exercise training on exercise capacity, coronary risk-factors, behavioral-characteristics, and quality of life in women. Am J Cardiol 1995;75:340-343.
28. O'Farrel P, Murray J, Huston P, Legrand C, Adamo K. Sex differences in cardiac rehabilitation. Can J Cardiol 2000;16:319-25.
29. Frasure-Smith N, Lespérance F, Prince RH, Verrier P, Garber

RA, Juneau M, Wolfson C, Bourassa MG. Randomized trial of home-based psychological nursing intervention for patients recovering from myocardial infarction. Lancet 1997;350:473-479.

30. Oldridge NB. Compliance and exercise in primary and secondary prevention of coronary heart disease: a review. Prev Med 1982;11:56-70.

31. Drory Y. Cardiac rehabilitation after coronary artery bypass graft surgery: urgently needed !Isr Med Assoc J 2001;3:427-429.

32. Yohannes AM, Yalfani A, Doherty P, Bundy C. Predictors of drop-out from an outpatient cardiac rehabilitation program. Clin Rehabil 2007;21:222-229.

33. Cooper AF, Jackson G, Weinman J, Horne R. Factors associated with cardiac rehabilitation attendance: a systematic review of the literature. Clin Rehabil 2002;16:541-552.

34. King K, Humen D, Smith H, Phan C, Teo K. Psychological components of cardiac recovery and rehabilitation attendance. Heart 2001;85:290-294.

TEHRAN HEART CENTER

Original Article

An Ovine Model of Dilated Cardiomyopathy Induced by Doxorubicin

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Received 25 April 2007; Accepted 7 June 2007

Abstract

Background: Dilated cardiomyopathy is associated with a progressive deterioration in cardiac function and eventually death. Initial interest in this hypothesis was to create another large animal model for dilated cardiomyopathy in addition to pigs and dogs.

Methods: After the induction of anesthesia to 10 female sheep, a carotid-jugular shunt was created in all the animals via a 1-cm fistula between the carotid artery and jugular vein. Six sheep out of the total of 10, were given intravenous Doxorubicin. Echocardiographic studies were performed before surgery and 3 months after that. The 4 animals not injected with Doxorubicin were evaluated for echocardiographic parameters after one year.

Results: There was no abnormality in echo parameters in the 4 sheep that had not received Doxorubicin; in addition, their valves and cardiac output were normal. As regards the six sheep injected with Doxorubicin, 4 received a dose of 2 mg/kg weekly and expired after the second injection due to the toxicity of the drug, 1 was given Doxorubicin 1 mg/kg and died after one week, and 1 had Doxorubicin 0.5 mg/kg but showed no abnormality in terms of dilated cardiomyopathy.

Conclusion: We conclude that the sheep is sensitive to Doxorubicin and that the dosage that is enough for creating dilated cardiomyopathy in dogs is very toxic for the sheep.

J Teh Univ Heart Ctr 4 (2007) 213-216

Keywords: *Sheep • Dilated cardiomyopathy • Doxorubicin • Carotidojugular shunt*

Introduction

Dilated cardiomyopathy is associated with a progressive deterioration in cardiac function and eventually death.[1] Heart failure is an unresolved problem in the human despite advances in pharmacological therapy. Initial interest in this hypothesis was to create another large animal model for dilated cardiomyopathy besides pigs and dogs.

Methods

Ten adult female Iranian sheep at a mean weight of 40±5 kg were selected for this study. The study was approved by the ethical committee of Tehran University of Medical Sciences. All the experiments received humane care in accordance with the "Guide for the Care and Use of Laboratory Animals", published by the US National Institute of Health (NIH

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Publication NO. 85-23, revised 1996)

During the study, the animals were held in metabolic cages, had free access to water, and were fed with a mixed diet of hay and sheep pellets. All the sheep were housed for one week in the animal house for adaptation. They were examined by a veterinarian and a cardiologist both clinically and echocardiographically and excluded out of the study if any serious morbidity was detected.

The sheep were NPO (nil per os) from 24h prior to surgery. The animals received intramuscular xylazine, 0.2 mg/kg to become sedated for hair shaving and instrumentation. Neck hair was shortened and then shaved. The saphenous vein was cannulated with a #20 gauge (pink) intravenous catheter. A central venous cannula was placed in the jugular vein using the Seldinger technique. An intravenous infusion of lactated Ringer's solution (20 cc/kg in 1h) was delivered before anesthesia and was maintained at the rate of 10 cc/kg per hour. The urethra was catheterized with a #10 Foley catheter connected to a urine bag. A pulse oximeter transducer was connected to the ear to monitor O_2 saturation. Five electrocardiogram (ECG) electrodes were connected to the extremities and on the chest. Anesthesia was induced via an intravenous injection of sodium thiopental, 5 mg/kg and was maintained with halothane (2.0-3.0%) in oxygen.[2] The animals were then immediately intubated with a 7.5-mm endotracheal tube and were mechanically ventilated (Draeger Ventilog3®) with 100% O_2 at a respiratory rate of 12-14/min and in-to expiratory cycle ratio of 1:1 and a tidal volume of 10 mL/kg. Gastric decompression was accomplished by the insertion of an orogastric tube. An anticholinergic (atropine, 2 mg) to prevent hypersalivation and an antibiotic (cefazolin, 1g) for prophylaxis were administered intravenously upon the induction of anesthesia. Prophylactic antibiotic was repeated 8 and 16 hours after surgery.

After surgical prep/drape, heparinization was performed by injecting 100 IU/kg heparin intravenously and then a 5-cm longitudinal skin incision was made anterior to sternomastoid muscle. The carotid artery and jugular vein were dissected and exposed. Between the cross clamps, a 1-cm incision was created on both jugular vein and carotid artery. The vessels were, thereafter, anastomosed together with a 7/0 Prolene suture and a carotidojugular shunt was created (Figure 1). Muscles and skin were sutured with a Vicril 3/0 suture. Echocardiographic studies were performed before surgery and 3 months after that.

In 6 animals Doxorubicin was injected intravenously (IV) in the following regimens: 4 animals 2 mg/kg weekly; 1 animal 1 mg/kg one dose; and 1 animal 0.5 mg/kg one dose.

Results

All the animals had a carotid-jugular shunt. The four sheep not injected with Doxorubicin were evaluated for echocardiographic parameters after one year, which showed no abnormality (Table 1).

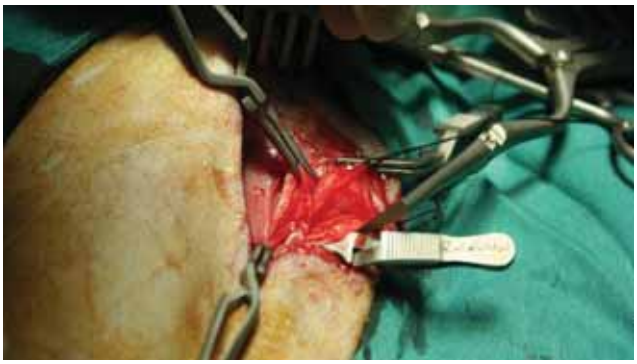

Figure 1 .Creating a carotid-jugular shunt

Table 1. Echo Parameters

Sheep No	Doxorubicin	EF (%) (primary)	EF (%) (3 months after surgery)
1	-	73	72
2	-	68	70
3	-	66	68
4	-	72	74
5	2 mg/kg	73	Died
6	2 mg/kg	68	Died
7	2 mg/kg	65	Died
8	2 mg/kg	75	Died
9	1 mg/kg	69	Died
10	0.5 mg/kg	70	69

EF, Ejection fraction

Furthermore, their valves and cardiac output were normal.

With respect to the six sheep injected with Doxorubicin, the 4 sheep that received a dose of 2 mg/kg weekly expired after the second injection due to the toxicity of the drug, the sheep that was given Doxorubicin 1 mg/kg died after one week, and the one that had Doxorubicin 0.5 mg/kg showed no abnormality in terms of dilated cardiomyopathy.

All the animals that had received Doxorubicin became weak and afflicted and showed alopecia due to the toxicity of Doxorubicin (Figure 2)

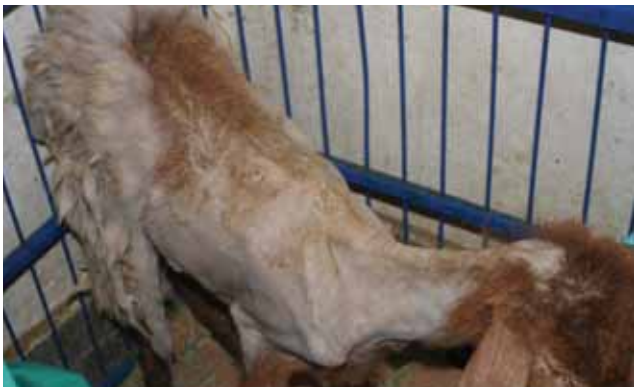

Figure 2. Alopecia after injection of doxorubicin

Discussion

Doxorubicin or hydroxyldaunorubicin is a DNA-interacting drug widely used in chemotherapy. It is an anthracycline antibiotic and structurally closely related to daunomycin and also intercalates DNA. It is commonly used in the treatment of a wide range of cancers.

The exact mechanism of action of Doxorubicin is complex and still somewhat unclear, although it is thought to interact with DNA by intercalation.[3] Doxorubicin is known to interact with DNA by intercalation and inhibition of macromolecular biosynthesis.[4] This inhibits the progression of the enzyme topoisomerase II, which unwinds DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication

Doxorubicin is commonly used to treat some form of leukemias, Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and others.

Combination therapy experiments with sirolimus (rapamycin) and Doxorubicin have shown promise in treating Akt-positive lymphomas in mice.[5]

Recent animal research coupling a murine monoclonal antibody with doxorubicin has created an immunoconjugate able to eliminate HIV-1 infection in mice. Current treatment with antiretroviral therapy (ART) still leaves pockets of HIV within the host. The immunoconjugate could potentially provide a complimentary treatment to ART to eradicate antigen-expressing T cells.

Acute side-effects of Doxorubicin can include nausea, vomiting, and heart arrhythmias. It can also cause neutropenia (a decrease in white blood cells), as well as mild alopecia. The risks of developing cardiac side effects, including congestive heart failure, dilated cardiomyopathy, and death, dramatically increase by the administration of Doxorubicin. Doxorubicin cardiotoxicity is characterized by a dose-dependent decline in mitochondrial oxidative phosphorylation.[6] Reactive oxygen species, generated by the interaction of Doxorubicin with iron, can then damage the myocytes, causing myofibrillar loss and cytoplasmic vacuolization.

Melissa J. Byrne et al. developed a model of long-term progressive heart failure in sheep.[7] They induced tachycardia with rapid ventricular pacing for 21 days at 160-190 bpm, which begot moderate heart failure. The animals were then paced at 205-215 bpm for 42 days (severe heart failure) and for 28 days (advanced heart failure). Data collected from echocardiography showed an increased left ventricular area, mitral valve regurgitation, and left ventricular end-diastolic pressure and decreased left ventricular wall thickness and left ventricular ejection fraction. This ovine heart failure model allows an examination of both structural changes and hemodynamic parameters of heart failure.

Peter Feindt et al. induced dilated cardiomyopathy in pigs with rapid ventricular pacing (220 bpm) for at least 4 weeks.[8]

Masami Takagaki et al. created a dog model of dilated cardiomyopathy by rapid ventricular pacing (230 bpm) for 4 weeks and maintained it by reducing the rate (190 bpm) for another 4 weeks.[9]

Mikhail Vaynblat et al. induced dilated cardiomyopathy by an intracoronary administration of Doxorubicin weekly for 4 weeks in 10 dogs.[10] Left ventricular end-diastolic pressure and diameter, as well as right ventricular end-diastolic diameter increased, and ejection fraction fell from 0.60±0.10 to 0.40±0.04 ($p = 0.0009$).

Valery chekanov et al. created a dog model of dilated cardiomyopathy by a carotidojugular shunt and Doxorubicin injection (2.5 mg/kg IV) weekly for six weeks.[11] After that, the mean ejection fraction of the dogs decreased about 30 percent.

We conclude that the sheep is sensitive species to Doxorubicin and that the dosage that is enough for creating dilated cardiomyopathy in dogs is very toxic for the sheep.

References

1. Muders F, Elsner D. Animal models of chronic heart failure. Pharmacol Res 2000;41:605-612.
2. Rabbani S, Ahmadi H, Fayazzadeh E, Sahebjam M, Boroumand MA, Sotudeh M, Nassiri SM. Induced myocardial infarction using ligation of the left anterior descending coronary artery major diagonal branch: development of an ovine model. J Teh Univ Heart Ctr 2006;1:89-93.
3. Lomovskaya N, Otten SL, Katayama Y, Fonstein L, Liu XC, Takatsu T, Inventi-Solari A, Filippini S, Torti F, Colombo AL, Hutchinson CR. Doxorubicin overproduction in streptomyces peucetius: cloning and characterization of the dnrU ketoreductase and dnrV genes and the doxA cytochrome P-450 hydroxylase gene. J Bacteriol 1999;181:305-318.
4. Arcamone F, Cassinelli G, Fantini G, Grein A, Orezzi P, Pol C, Spalla C. Adriamycin, 14-hydroxydaunomycin, a new antitumor antibiotic from S. peucetius var. caesius. Biotechnol Bioeng 1969;11:1101-1110.
5. Hutchinson CR, Colombo AL. Genetic engineering of doxorubicin production in streptomyces peucetius: a review. J Ind Microbiol Biotechnol 1999;23:647-652.
6. Pigram WJ, Fuller W, Hamilton LD. Stereochemistry of intercalation: interaction of daunomycin with DNA. Nat New Biol 1972;235:17-19.
7. Byrne MJ, Raman JS, Alferness CA, Esler MD, Kaye DM, Power JM. An ovine model of tachycardia-induced degenerative dilated cardiomyopathy and heart failure with prolonged onset. J Card Fail 2002;8:108-115.
8. Feindt P, Boeken U, Litmathe J, Gams E. Ventricular containment in the prophylaxis of experimental dilated cardiomyopathy. Interact Cardiovasc Thorac Surg 2003;2:575-580.
9. Takagaki M, McCarthy PM, Tabata T, Dessoffy R, Cardon LA, Connor J, Ochiai Y, Thomas JD, Francis GS, Young JB, Fukamachi K. Induction and maintenance of an experimental

model of severe cardiomyopathy with a novel protocol of rapid ventricular pacing. J Thorac Cardiovasc Surg 2002;123:544-549.
10. Vaynblat M, Chiavarelli M, Shah HR, Ramdev G, Aron M, Zisbrod Z, Cunningham JN. Cardiac Binding in Experimental Heart Failure. Ann Thorac Surg 1997;64:81-85.
11. Chekanov V, Dumcius A, Karakozov P, Cayton M, mirkhani H, Mirhoseini M. Adaptive cardiac binding: a new method for treatment of dilated cardiomyopathy. IHJ 2006;7:5-14.

TEHRAN HEART CENTER

Original Article

Immediate Small Side Branch Occlusion after Percutaneous Coronary Intervention

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Received 16 April 2007; Accepted 28 July 2007

Abstract

Background: *Small side branches, albeit less important than their larger counterparts, have not yet received due attention in the literature. Nor has there ever been a comparison between drug-eluting stents and bare metal stents apropos side branch occlusion. The aim of this study was to compare the patency of small (≥0.5 and ≤1.5 mm in diameter) side branches with respect to bare metal vs. drug-eluting stents immediately after their deployment.*

Methods: *This prospective bi-center study, conducted between June 2005 and January 2007, enrolled 82 patients treated with ≥1 of two stents (TAXUS™ Liberte™ or Liberte™). Side branches ≥0.5 and <1.5 mm in diameter arising from the main vessel at the lesion site were evaluated.*

Results: *Thirty-eight patients were treated with 42 Liberte™ stents (58 side branches) and forty-four patients with 50 TAXUS™ Liberte™ (102 side branches). The rate of small side branch occlusion was 35.3% (36) in the TAXUS™ Liberte™ group compared to 29.31% (15) in the Liberte™ group (P-value= 0.7). The presence of type 1 side branch morphology (Lefevre classification) was the most powerful predictor of small side branch occlusion (P-value=0.03).*

Conclusion: *This study shows that drug-eluting stents are not inferior to bare metal stents as regards small side branch occlusion during coronary stenting.*

J Teh Univ Heart Ctr 4 (2007) 217-222

Keywords*: Side branch angioplasty • Coronary occlusion • Stent*

Introduction

Despite its widespread use and relative success in the treatment of ischemic coronary artery disease, percutaneous coronary intervention (PCI) is associated with a number of well-known risks, the most notable of them being iatrogenic occlusion (nipping) of the side branches in the proximity of the stenosis for which stent insertion has been attempted. PCI of the lesion in the territory of a side branch is linked with an increased risk of procedure-related myocardial infarction, chest pain, cardiac enzyme elevation, and restenosis.[1] It is important that the diameter of both branch vessels be taken into account when describing a bifurcation lesion. If one branch is ≤1.5 mm in diameter, it is generally considered to be small and not suitable for PCI. In such situations, the small branch can be ignored and stenting is performed in the larger vessel only.[2, 3]

For all the studies into the risks of large side branch occlusion during PCI,[4-6] there is a paucity of data regarding the fate of small side branches during PCI. This study was conducted to compare the direct immediate effect of two stents (with similar stent design), namely TAXUS™ Liberte™ and

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Liberte™, on the risk of small side branch occlusion during PCI. We sought to investigate whether or not the presence of polymers on the stent struts, a smaller cell-surface area, and higher metal (stent)-to-artery ratio in drug-eluting stents (DES) could compromise the ostium of tiny side branches by comparison with bare metal stents (BMS) (Liberte™) [Boston Scientific announces Liberte design.

http://www.bostonscientific.com/med_specialty/deviceDetail.jsp?task=tskBasicDevice.jsp&sectionId=4&relId=2,74,75,76&deviceId=11044&uniqueId=MPDB4399 &clickType=endeca (accessed 25 July 2007)].[7]

Methods

Patient selection

This prospective bi-center study was carried out between June 2005 and January 2007 on 82 consecutive patients treated at Shahid Faghihi and Kowsar Hospitals with two stents: TAXUS™ Liberte™ and Liberte™. Side branches ≥0.5 and ≤1.5 mm in diameter arising at the lesion site from the main vessel were assessed. Thirty-eight patients were treated with Liberte™ stents and 44 patients with TAXUS™ Liberte™ stents. Patients were eligible if they had been diagnosed with symptomatic ischemic heart disease: stable or unstable angina and/or objective evidence of myocardial ischemia. Additionally, the luminal diameter of the lesion had to have a stenosis of at least 51%.The exclusion criteria were myocardial infarction (MI) within 72 hours preceding the index procedure, angiographic evidence of thrombus within the target lesion, poor distal run-off, and presence of total occlusion. Side branches that were compromised or lost during balloon predilatation were excluded. Written informed consent was obtained from each patient for the utilization of data in this study, and the study protocol was approved by the hospital ethics committees.

Stents

The TAXUS™ Liberte™ Paclitaxel-Eluting coronary stent system (Boston Scientific Corporation, Natic, MN) is a device/drug combination product comprised of two regulated components: a device (TAXUS™ Liberte™ stent mounted onto the Liberte delivery system) and a drug product (a formulation of Paclitaxel contained in a polymer coating). On the other hand, Liberte™ Monorail stent (Boston Scientific Corporation, Natic, MN) is a balloon expandable Liberte™ stainless steel stent premounted on Maverick™ catheter technology. Both stents have a Liberte™ stent design (both have small open cell areas). TAXUS™ Liberte™ stents have a lower cell-surface area (2.65 vs. 2.75 mm^2), with the polymer thickness of 0.0006 inch, higher crossing profile (0.047 vs.0.041 inch), and higher metal-to-artery ratio (percentage of artery wall covered by the outer surface of the stent) (22.3% vs. 17%).[7]

Study procedures

Premedication treatment included chronic treatment (>5 days) of aspirin (75-100 mg/day) and clopidogrel (75 mg/day) or ticlopidine (250 mg bd). In the non-pretreated patients, a loading dose of clopidogrel 300 mg the day before or 600 mg (if given <8 hours from PCI) was administered. During the procedure, the patients received 10,000 U bolus of heparin with a repeat bolus of 5000 to maintain the activated clotting time ≥250 seconds. The lesions were treated with the use of contemporary techniques and manufacturer's instruction for use. Predilatation and high pressure stent post dilation (≥14 atm) was advised but direct stenting was also allowed. After the stent was implanted, further dilatation was performed to ensure that the residual stenosis was ≤20% as assessed with the Siemens Koroscope viewer 1997 (Siemens Medical Imaging, Germany).

Coronary angiographic data management

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrate (solution 1/40%). The analyses of all the angiographic data before, during, and after the procedure were performed with the use of the Siemens Koroscope viewer 1997 (Siemens Medical Imaging, Germany) by two independent interventionists blinded to the stent type. Visual assessments included main vessel lesion type according to the American College of Cardiology/ American Heart Association (ACC/AHA) classifications and side branch type according to the Lefevre classification[7] (practical and easily applicable classification among many bifurcation classifications).[3,7-9] The diameter of the normal segment proximal to the traced area in the parent vessel was used to determine the parent reference diameter (RD), and the side branch RD was determined from the diameter of the traced area in the normal segment distal to the lesion in the branch. The minimal luminal diameter (MLD), RD, and the percent of stenosis were calculated as the mean values from two projections. The lesion length was defined as the distance from the proximal to the distal shoulder of the lesion. The angle between the distal main vessel and side branch was defined as the distal angle and was measured by joining the two centerlines of the daughter vessels in the middle of the bifurcation using the angiographic projection with the widest opening of the two branches.

Study endpoints

Primary end point was comparison of immediate small Side branch (SB) compromise during PCI with two stents. SB compromise was divided into two groups: 1) Side branch occlusion (SBO) was defined as abrupt loss or TIMI flow grade ≤II in SB during the procedure, 2) SB compromise without occlusion was defined as abrupt decrease in the diameter during the procedure without any decrease in the SB

TIMI flow grade. Secondary endpoints were determination of predictors of small SBO.

Study statistical analysis

The continuous data were presented as mean±standard deviation and discrete data as frequencies. The continuous variables were compared using the independent sample t-test, and the categorical variables were compared with the Pearson Chi-square or Fisher exact test. The Fisher exact test was employed when any expected cell count was <5 (not resulting from missing rows or columns in a larger table). P-value ≤0.05 was considered statistically significant. All the analyses were performed using SPSS 13 for Windows.

Results

Thirty-eight patients were treated with Liberte™ stents and forty-four patients received TAXUS™ Liberte™ stents. As is shown in Table 1, there were no significant differences between the two groups in terms of baseline clinical characteristic. The angiographic and procedure–related characteristics of the 92 main vessel lesions and 160 side branches are summarized in Tables 2, 3, and 4, respectively. Lesions treated with TAXUS™ Liberte™ stents were longer than those treated with Liberte™ stents. Meanwhile, the baseline MLD and RD and post-procedure MLD of the main vessel lesions were matched in the two groups. Overall, there were 33.12 % (53) side branch compromises: 10.62 % (17) of the side branches were completely occluded, whereas 22.5% (36) were compromised without complete occlusion. The rate of side branch compromise was 35.3% (36) in the TAXUS™ Liberte™ group compared to 29.31% (15) in the Liberte™ group (P-value= 0.7).

Side branch compromise primarily developed in the side branches with type 1 Lefevre classification morphology (24/52; 46.15 %). However, other morphologies, DES, and Y angle of the side branches were not related to side branch occlusion.

Table 1. Baseline demographics and clinical characteristics*

	TAXUS Liberte (44)	Liberte (38)
Age (y) (mean±SD)	61.9±9.6	62.1±9.4
Male	72.72(32)	65.79(25)
Medically Treated diabetes	27.27(12)	26.31(10)
Insulin requiring	9.09(4)	7.90(3)
Non-insulin requiring	18.18(8)	18.41(7)
Medically treated hyperlipidemia	68.18(30)	65.79(25)
Medically treated hypertension	56.82(25)	55.26(21)
Current smoking	34.09(15)	28.94(11)
Renal failure	6.82(3)	7.90(3)
Prior myocardial infarction	34.09(15)	31.58(12)
Unstable angina	27.27(12)	26.31(10)
2 vessel disease	13.63(6)	10.52(4)

*All the p values were non significant
The numbers in the parenthesis show the number of cases, and the numbers out of the parenthesis show the related percentage

Table 2. Baseline angiographic characteristics of the main vessel lesions*

Variables	TAXUS ™ Liberte™ (n=50)	Liberte™ (n=42)
Length** (mm) (mean±SD)	24.16±6.17	14.96±5.55
Reference dimension (mm)	2.85±0.40	2.92±0.64
Minimal luminal diameter (mm)		
Base line	0.99±0.83	1.25±1.02
Finial	2.76±0.45	2.82±0.55
Calcification % (n)	28 (14)	28.57 (12)
Infarct related artery % (n)	14 (7)	11.90 (5)
Lesion location % (n)		
LAD	56 (28)	47.62 (20)
LCX	20 (10)	28.57 (12)
RCA	24 (12)	23.81 (10)
Lesion Type % (n)		
A	10 (5)	9.52 (4)
B_1	20 (10)	26.20 (1)
B_2	30 (15)	28.57 (12)
C	40 (20)	35.71 (15)

*All p values were non significant except for** which was 0.001
LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery

Table 3. Procedural characteristics*

Variables	TAXUS Liberate (n=50)	Liberate (n=42)	p value
Stent			
Length (mm)	28.08±4.67	16.81±4.44	0.001
Diameter (mm)	2.87±0.17	3.03±0.38	0.009
Number of stents per patient	1.13	1.10	NS
Maximal balloon inflation (atm)	13.5±0.8	13.3±1	NS
Balloon to artery ratio	1.03±0.04	1.01±0.05	NS

*Data are presented as mean±SD
NS, Non significant

Table 4. Baseline angiographic characteristics of 160 side branches*

Variables	TAXUS Liberate (n=102)	Liberate (n=58)	p value
Minimal luminal diameter (mm)	0.77±0.34	0.80±0.36	0.56
Reference diameter (mm)	0.90±0.46	0.88±0.33	0.71
Angle Y % (n)	49.02 (50)	51.72 (30)	0.43
Morphology			
Type 1 % (n)	28.43 (29)	32.76 (19)	0.37
Type 2 % (n)	39.21 (40)	34.48 (20)	0.37

*Data are presented as mean±SD

Table 5. Predictors of small side branch occlusion

Variables	Odds ratio	95%CI	p value
Morphology			
Type 1	4.266	1.12-16.25	0.03
Type 2	0.55	0.12-2.56	0.45
Angle Y	1.37	0.67-2.82	0.38
Taxus™ Liberte™	1.29	0.6-2.47	0.51

CI, Confidence interval

Discussion

Despite the fact that there have been many studies focusing on the fate of side branches in bifurcation lesions after coronary stenting,[4,10,11] no published report exists concerning the destiny of small side branches during main vessel PCI. Experimental evidence suggests although the metal struts of the stent do not completely cover the orifices of a side branch, the blood flow into the side branch after stenting may be compromised. Fishman et al.,[12] reporting the outcome of side branches in patients with the Palmaz-Schatz stent, demonstrated that 5% of the side branches were occluded immediately after stenting. Mazur et al.[13] reported the results of Gianturco-Roubin stenting for the treatment of acute or threatened closure after balloon angioplasty. They reported that side branch occlusion developed in 6% of the major side branches after stenting. Cho et al.[4] found 10% side branch occlusion during PCI with three different BMSs. In our series, 33.12% of the side branches were compromised: 10.6% were occluded completely and 22.5% were just compromised without occlusion. These differences could be interpreted in multiple ways: the criterion for side branch occlusion in the Cho et al.,[4] Fishman et al.,[12] and Mazur et al.[13] studies was a persistent reduction in the thrombolysis in myocardial infarction (TIMI) flow grade <1. They did not consider side branches that developed TIMI flow grade II as side branch occlusion, and nor did they take into account side branches that were compromised during stenting but had a normal TIMI flow. In the aforementioned studies, fewer than 20% of the side branches had a type D morphology (equivalent to type 1 Lefevre classification in our study), which is important to consider because this was the most important predictor of side branch occlusion in their study.[4] The other interesting finding in our study was that the small side branches were compromised more than they were occluded totally (22.5 % vs. 10.6%).

Side branches originating from a stenosed segment of a coronary artery are indeed in some jeopardy during the PCI of the segment. The possible mechanism of side branch occlusion after stenting is 'the snow plow effect', where atheroma is shifted into the ostium of the small side branch from the parent vessels.[14] Other mechanisms may include the spasm of the side branch, embolization of atherosclerotic material, thrombus formation, and stent material itself.

In our series, the presence of ostial narrowing that arose from within or just beyond the diseased portion of the parent vessel (type 1 Lefevre classification morphology) was the most powerful predictor of side branch compromise immediately after stenting. This finding suggests that the plaque volume of the parent vessel and the side branch is a major determinant of the fate of a side branch (as was confirmed for larger side branches).[4,15] It is also deserving of note that in the present study, other lesions and side branch characteristics (angel, RD, MLD) had no correlation with side branch compromise.

This study demonstrated that despite a lower cell-surface area, presence of polymer, higher metal-to-artery ratio, and crossing profile, normally associated with a higher chance of spasm and side branch occlusion,[16] there was no statistically significant difference between the two groups regarding small side branch compromise. It seems that these differences are less important than was previously assumed.[3,17]

Although the occlusion of small side branches are less important than that of their larger counterparts, it can occasionally lead to clinically important events such as prolonged chest pain, ECG changes, MI, or hemodynamic instability (esp. if such occlusion leads to right ventricular infarction or papillary muscle dysfunction).[3,15,16]

Conclusion

This study demonstrated that with respect to small side branches (≥0.5 and ≤1.5 mm in diameter), TAXUS Liberte™ stents showed no immediate inferiority to BMSs (Liberte™) after stent insertion: the rate of small side branch occlusion was 35.3% (36) in the TAXUS™ Liberte™ group and 29.31% (15) in the Liberte™ group (P-value= 0.7). The presence of type 1 side branch morphology (Lefevre classification) seems to be the most important predictor of small side branch compromise (including total occlusion and compromise only) during PCI.

Our study had some limitations. First, it was relatively underpowered by the inclusion of a small number of patients. If the trend remains constant (P-value=0.7), there is a need for at least 1300 side branches to compare side branch compromise more precisely. It should also be noted that our study did not randomize the patients into one of the two treatment strategies. Another point that the present study omitted to address was the difference between the two groups in terms of the stent diameter and length.

Acknowledgement

We are indebted to M. T. Heidari, biostatistician for his important contribution to data analysis. This study has been supported by Shiraz University of Medical Sciences.

References

1. Al Suwaidi J, Yeh W, Cohen HA, Detre KM, Wiliams DO, Holmes DR Jr. Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). Am J Cardiol 2001;87:1139-1144.

2. Di Mario C, Morici N, Godino C, Goktekin O, Tamburino C, Barbagallo R, Antoniucci D, Grube G, Airoldi F, Zoccai GB, Colombo

A, Sangiorgi. G. Predictors of restenosis after treatment of bifurcational lesions with paclitaxel eluting stents: a multicenter prospective registry of 150 consecutive patients. Catheter cardiovasc interven 2007;69:416-424.

3. Movahed MR, Stinis CT. A new proposed simplified classification of coronary artery bifurcation lesions and bifurcation interventional techniques. J Inv Cardiol 2006;18:199-204.

4. Cho GY, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. Effects of stent design on side branch occlusion after coronary stent placement. Catheter Cardiovasc Interv 2001;52:18-23.

5. Furukawa E, Hibi K, Kosuge M, Nakatogawa T, Toda N, Takamura T, Tsukahara K, Okuda J, Ootsuka F, Tahara Y, Sugano T, Endo T, Kimura K, Umemura S. Intravascular ultrasound predictors of side branch occlusion in bifurcation lesions after percutanous coronary intervention. Circ J 2005;69:325-330.

6. Kuchulakanti P, Rha SW, Satler LF, Suddath WO, Pichard AD, Kent KM, Pakala R, Canos DA, Pinnow EE, Waksman R. Impact of major side branch on periprocedural enzyme elevation and long-term outcome in patients undergoing percutaneous coronary intervention and brachytherapy for in-stent restenosis. Am J Cardiol 2004;93:1394-1397.

7. Lefevre T, Louvard Y, Morice MC, Dumas P, Loubeyre C, Benslimane A, Premchand RK, Guillard N, Piechaud JF. Stenting of bifurcation lesions: classification, treatments and results. Catheter Cardiovasc Interv 2000; 49:274-283.

8. Sianos G, Morel MA, Pieter Kappetein A, Morice M.C, Colombo A, Dawkins K, Van den Brand M, Van Dyck N, Russell ME, Serruys PW. The SYNTAX score: An angiographic tool grading the complexity of coronary artery disease. Eurointervention 2005;1:219-227.

9. Medina A, Suarez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. Rev Esp Cardiol 2006;59:183.

10. Assali AR, Assa HV, Ben-Dor I, Teplitsky I, Solodky A, Brosh D, Fuchs S, Kornowski R. Drug-eluting stents in bifurcation lesions: to stent one branch or both? Catheter Cardiovasc Interv 2006;68:891-896.

11. Pan M, Suarez de Lezo J, Medina A, Romero M, Delgado A, Segura J, Ojeda S. Drug-eluting stents for the treatment of bifurcation lesions: a randomized comparison between paclitaxel and Sirolimus stents. Am Heart J 2007; 153:15.e1-7.

12. Fischman DL, Savage MP, Leon MB, Schatz RA, Ellis S, Cleman MW, Hirshfeld JW, Teirstein P, Bailey S, Walker CM, Goldberg S. Fate of lesion-related side branches after coronary artery stenting. J Am Coll Cardiol 1993;22:1641-1646.

13. Mazur W, Grinstead WC, Hakim AH, Dabaghi S, Abukhalil JM, Ali NM, Joseph J. Fate of side branches after intracoronary implantation of the Gianturco-Rubin Flex-Stent for acute or threatened closure after percutanous transluminal coronary angioplasty. Am J Cardiol 1994;74:1207-1210.

14. Aliabadi D, Tilli FV, Bowers TR, Benzuly KH, Safian RD, Goldstein JA, Grines CL, O'Neill WW. Incidence and angiographic predictors of side branch occlusion following high pressure intracoronary stenting. Am J Cardiol 1997;80:994-997.

15. Meier B, Gruentzig AR, King SB, Douglas JS, Hollman J, Ischinger T, Aueron F., Galan K. Risk of side branch occlusion during coronary angioplasty. Am J Cardiol 1984;53:10-14.

16. Cervinka P, Stasek J, Pleskot M, Maly J. Treatment of coronary bifurcation lesions by stent implantation only in parent vessel and angioplasty in side branch: immediate and long term outcome. J invasive Cardiol 1994;14:735-740.

17. Nguyen T, Douglas JS Jr, Hieu NL, Grines CL. Basic stenting. J Interv Cardiol 2002;15:237-241.

Original Article

Accuracy of Dobutamine Stress Echocardiography in Detecting Recovery of Contractile Reserve after Revascularization of Ischemic Myocardium

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Received 9 May 2007; Accepted 21 July 2007

Abstract

Background: *This study was designed to investigate the accuracy of dobutamine stress echocardiography (DSE) in detecting the post-revascularization recovery rate of contractile reserve (CR) in ischemic myocardium.*

Methods: *A total of 112 segments from seven patients with low ejection fraction (<35%) and coronary artery disease were evaluated with DSE one week before and 12 weeks after coronary artery bypass graft surgery (CABG). Sensitivity, specificity, and positive and negative predictive values of DSE for detecting the recovery rate of CR were calculated based upon their standard definition and were presented with 95% confidence intervals (CI).*

Results: *The mean baseline left ventricular ejection fraction was 31±4%, which reached 35±7% after CABG unremarkably. The recovery rates of resting function and CR were 18.2% and 50% for hypokinetic and 15.6% and 24.1 for akinetic segments respectively. Specificity, sensitivity, and positive and negative predictive values of DSE for detecting the recovery of CR were 83% (CI=69-97), 89% (CI=83-96), 94% (CI = 88-99), and 73 % (CI = 55-88), respectively.*

Conclusion: *Despite acceptable sensitivity, specificity, and positive predictive value, DSE has a relatively lower negative predictive value for detecting the recovery of CR in ischemic myocardium and, consequently, the full extent of myocardial viability. Further sensitive techniques may, therefore, be needed to provide complementary information regarding long-term functional outcome.*

J Teh Univ Heart Ctr 4 (2007) 223-228

Keywords: *Echocardiography • Dobutamine • Myocardial ischemia*

Introduction

Hibernating myocardium defines the reversible contractile function of dysfunctional left ventricular (LV) segments subtended by stenotic coronary arteries in patients with chronic coronary artery disease following revascularization.[1-4] Detection of the contractile reserve (CR) of hibernating myocardium by noninvasive testing currently helps make clinical decisions regarding recommendation for revascularization in patients with severe ischemic LV dysfunction.[5]

Among different noninvasive imaging techniques, dobutamine stress echocardiography (DSE) is usually the initial approach for detecting hibernating myocardium

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because it is inexpensive, widely available, and has a good predictive value.[6] It is now becoming increasingly clear that certain myocardial segments are resistant to dobutamine stimulation but eventually show recovery of function after revascularization and, hence, are defined as hibernating.[7] It has been suggested that the recovery of resting function may be an inappropriate standard viability assessment and that improvement in CR is even more important in terms of functional capacity, preventing LV remodeling, and long-term prognosis.[4,8]

Improvement in left ventricular ejection fraction (LVEF) and heart failure symptoms after revascularization is associated with the presence of CR in a substantial number of segments in DSE; therefore, findings of DSE may guide therapeutic management in patients with severely ischemic LV dysfunction. We investigated the diagnostic accuracy of DSE to predict the degree of recovery in CR after surgical revascularization of the ischemic myocardium.

Methods

The study population comprised 7 patients with chronic coronary artery disease and severe LV dysfunction (EF<35) who underwent coronary artery bypass grafting (CABG). Patients with a recent acute myocardial infarction, significant valve disease, or inadequate image quality were not included. All the patients underwent DSE one week before intervention and repeated DSE at 3 months post-CABG. All the studies were observed by two independent experienced observers. The study findings were analyzed using the rest and dobutamine echocardiography report. The study was approved by the Ethics Committee of the hospital.

Dobutamine stress echocardiography

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

After baseline echocardiography, dobutamine infusion was initiated using a mechanical pump. Dobutamine was delivered intravenously beginning at 5 μ/kg/min for three minutes and increased by 5 μ/kg/min increments every three minutes to 15 μ/kg/min, at which dose it was administered for an additional three minutes. Blood pressure was measured periodically. 12-lead ECG was continuously monitored throughout the study and during the recovery phase. Infusion was terminated when severe hypotensive or hypertensive response, significant arrhythmias, prolonged angina, significant electrocardiographic changes, appearance of new wall motion abnormalities in at least two segments, or completion of the protocol was observed. Echocardiographic images were analyzed off-line using a 16-segment model.[7] Segmental wall motion was scored on a four-point scale: 1; normal, 2; hypokinetic (severely reduced wall thickening and inward wall motion), 3; akinetic (absence of systolic thickening and wall motion), and 4; aneurismal (dyskinetic regions with a diastolic contour abnormality). Regional LV function was assessed by resting and dobutamine echocardiography one week before and 3 months after intervention. A regional wall motion score index (WMSI) was quantified by summing the grades for each segment and dividing it by the total number of segments analyzed for each patient.

Demonstration of wall thickening in a previously akinetic segment or normalization of thickening in a previously hypokinetic segment was considered as criteria for myocardial viability. Improvement in segmental wall motion at stress by at least one grade compared with the baseline rest study was considered as recovery of CR in the follow-up study. Recovery of resting function in the follow-up studies was expressed by improvement on resting segmental wall motion after CABG at least one grade or more compared with the baseline rest study before CABG.

Left ventricular ejection fraction was measured at baseline, and peak dobutamine dosage was determined using an available software program that applied Simpson's rule on the apical two-chamber and four-chamber views.

CABG

Surgery was performed by cardiac surgeons using cardiopulmonary bypass and mild hypothermia (32-34 ºC). Every effort for complete revascularization was made during the operation to graft all epicardial vessels with significant stenosis. The median number of grafts was three (range 1-5); the cardiopulmonary bypass time was 64 minutes and the aortic clamp time 41 minutes.

Statistical analysis

Recovery rates at rest and stress are given with 95% confidence interval (CI). Continuous data are expressed as mean±SD and compared using the Student's t-test for paired and unpaired data when appropriate. Univariate analysis for categorical variables was performed using the chi-square test. Sensitivity, specificity, and positive and negative predictive values (PPV & NPV) are based upon their standard definition and presented with their 95% CI. A p value<0.05 was considered significant.

Results

In all, 7 patients (mean age of 51.6±8.9 years, one woman), were enrolled in the study. There was no death or ischemic event during surgery or follow-up period. The mean baseline

LVEF of all the patients was 31±3.7%. Clinical, laboratory, and operative characteristics are shown in Table 1.

Table 1. Clinical, angiographic and operative data of study patients (n = 7)

variables	No of patients
EF 25-30%	1
EF 30-35%	6
History of myocardial infarction	6
Stable angina	7
Dyspnea (NYHA I-II)	7
Previous CABG	0
Diabetes	2
Hypertension	3
Dyslipidemia	5
Smoking	2
2-vessel disease	1
3-vessel disease	6
Number of distal coronary anastomoses	
2	1
3	1
4	4
5	1

EF, Ejection fraction; NYHA, New York heart association classification; CABG, Coronary artery bypass grafting

DSE before surgery

A total of 112 myocardial segments were analyzed (16 segments per patient), of which 76 (68%) had baseline wall motion abnormalities: 44 (39%) were hypokinetic and 32 (29%) akinetic. The responses of the 76 dysfunctional segments to dobutamine were as follows: continuous improvement in 43 segments (56.5%) and no change in 33 (43.4%). Evidence of CR was demonstrated in 9.4% (3/32) of the akinetic segments, while there was no CR in 90.6% (29/32) of them. Evidence of CR was demonstrated in 90.9% (40/44) of the hypokinetic segments, while there was no CR in 9.1% (4/44) of them. Thus, myocardial viability was detected more frequently in hypokinetic than in akinetic segments (P<0.0001).

After dobutamine injection, CR was presented in 79 (70.5%) of 112 segments and absent in 33 (29.5%). Wall motion score index was 1.96 at rest and decreased to 1.71 when stressed.

The mean baseline LVEF of all the patients was 31±3.7%, which reached 43.6±10% after dobutamine infusion.

Effect of coronary revascularization on LV function

Mean LVEF at rest increased insignificantly from 32±4% preoperatively to 35±7% post surgery. Wall motion score index at rest decreased from 1.96 preoperatively to 1.89 at follow-up insignificantly. Recovery of resting function was evident in 18% of hypokinetic and 15.6% of akinetic segments, whereas recovery in CR was evident in 50% of hypokinetic and 24.1% of akinetic segments.

Accuracy of DSE in predicting the recovery of CR after revascularization

Main findings are summarized in Table 2, Table 3 and Figure 1 Calculated sensitivity and specificity of DSE in detecting the recovery of CR in all segments were 89.2% (95%CI, 83-96) and 82.8% (95%CI, 69-97), respectively. The PPV of DSE for detecting CR was 93.7% (95%CI, 88-99) and NPV was 72.7% (95%CI, 57-88). From 33/112 segments without CR before surgery, 9 (27.3%) presented CR and 27(72.7%) showed no CR after CABG. From 79/112 segments with CR before CABG, 74 (93.5%) showed CR while 5 (6.5%) did not show CR after surgery.

Results of DSE before and after surgical intervention are depicted in Table 2.

Table 2. Comparison of myocardial segments with different function in terms of the presence of CR, detected by DSE, before and after CABG in 112 segments

Wall motion	Before CABG			After CABG		
	With CR N (%)	Without CR N (%)	Total N	With CR N (%)	Without CR N (%)	Total N
Normal	36 (100)	0	36	47 (100)	0	47
Hypokinetic	40 (91)	4 (9)	44	31 (94)	2 (6)	33
Akinetic	3 (9)	29 (91)	32	5 (16)	27 (84)	32
Total	79 (71)	33 (29)	112	83 (74)	29 (26)	112

CR, Contractile reserve; DSE, Dobutamine stress echocardiography; CABG, Coronary artery bypass grafting; N, Number

Of 29/32 akinetic segments without CR before CABG, 7/29 had CR after CABG, and 5/7 of them recovered resting function while 22/29 had neither recovery of CR nor recovery of resting function after CABG. All 3/32 akinetic segments with CR before surgery showed CR after surgery, but none of them recovered resting function.

From 40/44 hypokinetic segments with CR before surgery, 36/40 had CR after surgery and 8/36 of them recovered resting function while 4/40 had neither recovery of CR nor recovery of resting function after CABG. From 4/44

hypokinetic segments without CR before surgery, 2/4 had CR after surgery and 2/4 did not, while none of them had recovered resting function.

Outcome of wall motion at baseline (resting function) in 112 left ventricular segments is demonstrated in Figure1.

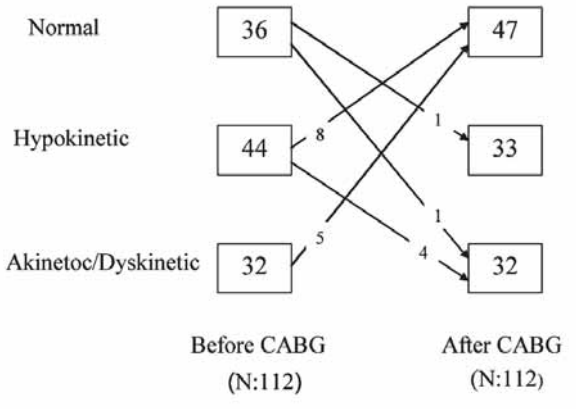

Figure1: Outcome of wall motion at baseline in 112 left ventricular segments after revascularization. The numbers in the boxes show the number of normal, hypokinetic, and akinetic/dyskinetic segments. The numbers on the arrows indicate the number of segments showing wall motion changes after coronary artery bypass grafting (CABG)

Table 3. Accuracy of dobutamine stress echocardiography for recovery of contractile reserve in 112 segments at 3 months after coronary artery bypass grafting

Accuracy	% (95%CI)
Recovery rate	27.3 (12-43)
Sensitivity	89.2 (83-96)
Specificity	82.8 (69-97)
PPV	93.7 (88-99)
NPV	72.7 (57-88)

CI, Confidence interval; NPV, Negative predictive value; PPV, Positive predictive value

Discussion

In agreement with previous reports[4,8,9] this study provides evidence to confirm high sensitivity and specificity of DSE to detect the recovery of CR in ischemic myocardium after revascularization.

It has been reported that CR is present more frequently in hypokinetic than in akinetic segments.[4] In line with this report, in our study, 90.9% of hypokinetic segments demonstrated CR before CABG and 86.4% of them showed CR after CABG. In contrast, among akinetic regions, 9.4% showed CR before CABG and 31.3% showed CR after CABG respectively.

The results of this study also indicate that the recovery rate of resting function is quite low (18%) for hypokinetic segments. This indicates that low-dose DSE is less effective in identifying improvement of resting function in hypokinetic segments that will improve function after revascularization. Possible reasons for this judgment have been explained previously.[10,11] Hypokinetic segments may contain a mixture of a considerable amount of scar tissue and some normal myocardium.[11] In this case, inotropic stimulation may provoke hypercontraction of normally perfused myocardium, thus showing a positive response. This, however, would not translate into an improvement of function after revascularization. In addition, in our study the recovery rate of akinetic segments was 15.6% and the amounts of increase in EF and decrease in WMSI were insignificant. Zaglavara et al. reported recovery rate of 52% in hypokinetic and 39% in akinetic segments and significant increase in EF (10%) 6 months after CABG. Also, they reported a significant decrease in WMSI at 6 weeks after CABG.[4] The possible reasons for these different results may be firstly, longer follow-up time of their study, and secondly, relatively long waiting list of CABG in our center (mean of 6 months). A reduction in myocardial contractility in hibernating myocardium conserves metabolic demand and may be protective, but prolonged and severe hibernation may lead to severe ultrastructural abnormalities, irreversible loss of contractile units, and apoptosis.[12]

Apparently, a relatively intact contractile apparatus is required for the demonstration of CR, and myocardial segments with advanced ultrastructural changes may not respond to dobutamine despite the presence of other markers of viability such as preserved metabolism or membrane function.[13,14] On the basis of these observations, it has been suggested that nuclear imaging may be more suitable than DSE for the assessment of myocardial viability in patients with depressed LV function and presumably more advanced myocardial ultrastructural damage.

Being able to predict early recovery in CR is of major clinical importance, particularly in patients with severely depressed LV function, because it can give an estimate of myocardial response to inotropes during the early postoperative period and, thus, an indication of early postoperative and in-hospital morbidity and mortality.[15]

Severely depressed LV ejection fraction and worse functional status independently increase the risk of CABG.[16] In these patients, the decision for CABG must balance the perioperative risk against the benefit of long-term functional improvement in the presence of myocardial viability. It seems that more than one method for viability detection is necessary to make the correct treatment decision in such cases. DSE may be valuable for the prediction of the early response of the hibernating myocardium to revascularization, whereas other more sensitive techniques may provide complementary information regarding long-term functional outcome. Using nuclear techniques (known to be more sensitive but less specific than DSE) in conjunction can be helpful in detecting the recovery of CR as an end point.

Conclusion

Despite acceptable sensitivity, specificity, and positive predictive value, DSE has a relatively lower negative predictive value for detecting the recovery of CR and, consequently, full extent of myocardial viability in ischemic myocardium. Further sensitive techniques like nuclear techniques may, therefore, be required to provide complementary information on long-term functional outcome.

This Study had the following limitation. We only indicated patients with severe LV impairment so that despite the relatively small number of patients, the number of dysfunctional segments was adequate to give statistical significance to the results. Because of the low percentage of women, findings may not fully apply to women, who are reported to have worse outcomes after CABG compared with men.[17]

Acknowledgment

This study was supported by Tehran Heart Center, University of Medical Sciences. We thank Dr. Mahmood Sheikh Fathollahi, for assistance with analysis; and Dr. Sirous Jahangiri and Dr. Mohammad Majd For data collection.

References

1. Diamond G, Forrester J, deLuz P, Wyatt HL, Swan HJC. Post-extrasystolic potentiation of ischemic cardiomyopathy by atrial stimulation. Am Heart J 1978;95:204-209.
2. Rahimtoola Sh. Coronary bypass surgery for chronic angina-1981: a perspective. Circulation 1982;65:225-241.
3. Rahimtoola Sh. The hibernating myocardium. Am Heart J 1989;117:211-221.
4. Zaglavara T, Karvounis HI, Haverstad R, Hasan A, Parharidis GE, Louridas GE, Dark JH, Kenny A. Dobutamine stress echocardiography is highly accurate for the prediction of contractile reserve in the early postoperative period, but may underestimate late recovery in contractile reserve after revascularization of the hibernating myocardium. J Am Soc Echocardiogr 2006;19:300-306.
5. Pasquet A, Robert A, D Hondt AM, Dion R, Melin Ja, vanoverschelde JL. Prognostic value of myocardial ischemia and viability in patients with chronic left ventricular dysfunction. Circulation 1999;100:141-148.
6. Bonow R. Identification of viable myocardium. Circulation 1996;94:2674-2678.
7. La canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O. Echocardiography during infusion if dobutamine for identification of reversible dysfunction in patients with chronic coronary artery disease. J Am Coll Cardiol 1994;23:617-626.
8. Lombardo A, Loperfido F, Trani C, Pennestri F, Rossi E, Giordano A, Possati G, Maseri A. Contractile reserve of dysfunctional myocardium after revascularization: a dobutamine stress echocardiography study. J Am Coll Cardiol 1997;30:633-640.
9. Elhendy A Cornel JH, Van Domburg RT, Bax JJ, Roelandt JRTC. Effect of coronary artery bypass surgery on myocardial perfusion and ejection response to inotropic stimulation in patients without improvement in resting ejection fraction. Am J Cardiol 2000;86:490-494.
10. Pace L, Filardi PP, Cuocolo A, Prastaro M, Acampa W, Dellegrottaglie S, Storto G, Della Mortre AM, Piscione F, Chiariello M, Salvatore M. Diagnostic accuracy of low-dose dobutamine echocardiography in predicting post-revascularisatin recovery of fnction in patients with chronic coronary artery disease: relationship to thallium-201 uptake. Eur J Nucl Med 2001;28:1616-1622.
11. Cornel JH, Bax JJ, Elhendy A, Maat APWM, Kimman GJP. Geleijnse ML, Rambaldi R, Boersma E, Fiorettip PM. Biphasic Response to Dobutamine Predicts Improvement of Global Left Ventricular Function After Surgical Revascularization in Patients With Stable Coronary Artery Disease, Implications of Time Course of Recovery on Diagnostic Accuracy. J Am Coll Cardiol 1998;31:1002–1010.
12. Morrow DA, Gersh BJ, Braunwald E. Chronic coronary artery disease. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. Braunwald's Heart Disease: a text book of cardiovascular medicine. 7th ed. Philadelphia: Elsevier Sanders; 2005. p. 1281-1335.
13. Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, Lammertsma AA, Liedtke AJ, Paternostro G, and Vatner SF. Pathophysiological mechanisms of chronic reversible left ventriculay dysfunction due to coronary artery disease (hibernating myocardium). Circulation 1997;96:3205-3214.
14. Baumgartner H, Porenta G, Lau YK, Wutte M, Klaar U, Mehrabi M, Siegel RJ, Czernin J, Laufer G, Sochor H, Schelbert H, Fishbein MC, Maurer G. Assessment of myocardial viability by dobutamine echocardiography, positron emission tomography and thalium-201 SPECT: correlation with histopathology in expanded hearts. J Am Coll Cardiol 1998;32:1701-1708.
15. Redwod SR, Ferrari R, and Marber MS. Myocardial hibernation and stuning from physiological principles to clinical practice. Heart 1998;80:218-222.
16. Pagano D, Townend JN, and Bonser RS. What is the role of revascularization in ischemic heart failure? Heart 1999; 81: 8-9.
17. Pepine CJ. Ischemic heart disease in women: facts and wishful thinking. J Am Coll Cardiol 2004; 43:1727-1730.

TEHRAN HEART CENTER

Original Article

One-Year Outcome of Patients with Acute Myocardial Infarction

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Received 16 April 2007; Accepted 10 July 2007

Abstract

Background: *Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide. Acute myocardial infarction (AMI) represents the most dramatic presentation of CVD and is one of the most commonly seen acute medical emergencies. According to Iran's Ministry of Health, 966,779 people (46%) died of CVD and 575, 257 (27%) potential years of life were lost to CVD in 2000. We, therefore, set out to evaluate the one-year outcome of the patients admitted to Loghman-Hakim Hospital between 2003 and 2004.*

Methods: *This historical cohort study selected patients that had been discharged from hospital a year earlier. The subjects were asked by telephone to come to the hospital so that their records could be assessed, and data on the following categories were extracted: coronary angiography results, revascularization (percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG]), re-admission, mortality and drug compliance.*

Results: *Among 132 AMI patients at a mean age of 59.2 years, 76.5% were male. Seventy nine point five percent of all the patients had had ST-elevation myocardial infarction (STEMI) and 20.5% non-STEMI. Fifty-eight percent of the subjects had received streptokinase and 42.4% had undergone cardiac catheterization. Revascularization had been performed on 12.8% via PCI and on 21.2% through CABG. The mortality and re-admission rates within one year of treatment stood at 6.1% and 14.3%, respectively. One year after discharge, the respective rates of drug compliance with beta-blockers, ASA, ACEI and statins were 74.2%, 98.5%, 71.2% and 67.4%.*

Conclusion: *Patients with AMI show satisfactory long-term drug compliance. Our patients' mortality rate was comparable to that in other studies, and their adherence to prescribed medicines and recommended procedures (PCI, CABG) was relatively high.*

J Teh Univ Heart Ctr 4 (2007) 229-232

Keywords: *Acute myocardial infarction • Outcome • Mortality • Revascularization • Drug compliance*

Introduction

In recent decades, coronary artery disease (CAD) has become the leading cause of death worldwide. Acute myocardial infarction (AMI) is known to be one of the biggest problems of ischemic heart disease (IHD), and for all

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the progress made in the treatment of CAD in recent years, it remains the main cause of mortality in developed and underdeveloped countries.

According to WHO's report (The World Health Report 2002: Reducing risks promoting healthy life. Geneva WHO; 2002) in 2001, 7,200,000 people lost their lives as a result of heart disease in the world; 78% of these deaths occurred in underdeveloped countries. At the same time, heart diseases caused 59,000,000 years of potential life lost in 2001, 86% of which took place in underdeveloped countries.

According to Iran's Ministry of Health report (The picture of death in 18 provinces of Iran in 2000, Iran Ministry of Health and Medical Educations publications. 2002), 966,779 people (46%) died of CAD and 575,257 (27%) potential years of life were lost in 2000. Nowadays, the use of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in conjunction with appropriate and timely drug therapy has lessened AMI-related deaths by one-third.

Methods

This historical cohort study selected patients with AMI who had been discharged from Tehran Loghman Hakim Hospital one year previously, i.e. between November 2003 and 2004. The patients were recruited over the telephone for an evaluation of their records on the following categories: 1) mortality rate; 2) coronary angiography; 3) re-admission; 4) revascularization by PCI and CABG on indication; and 5) drug compliance.

The patients with one of the following criteria had undergone coronary angiography: 1) 1-14 days post MI angina; 2) sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) after 48 hours of MI; 3) congestive heart failure (CHF) symptoms and signs or ejection fraction (EF)≤40%; and 4) positive exercise tolerance test (ETT) or myocardial perfusion scan.

The above data were analyzed with SPSS 13.

Results

The research was carried out on 132 patients out of a total of 166 patients who had been discharged from hospital during the period in mind. The subjects, 101(76.5%) males and 31(23.5%) females, had a mean age of 59.2 years (standard deviation [SD]=13.1 years). Of all our patients, 105 had had ST-elevation myocardial infarction (STEMI) and 27 non-STEMI.

The frequencies of the risk factors; namely, hypertension, diabetes mellitus, current smoking, previous MI and cerebrovascular accident (CVA), were 28%, 21.2%, 32.6%, 10.6% and 3%, respectively.

The anatomical locations of AMI are depicted in Table1.

Table 1. The anatomical locations of myocardial infarction (MI)

MI Location	Frequency	Percent
Anterior (V1-V4)	16	12.1
Anterior, Inferior	3	2.3
Anteroseptal (V1-V2)	15	11.4
Antertolateral (V4-V6)	5	3.8
Extensive Anterior (V1-V6, I, aVL)	16	12.1
Inferior (II, III, aVF)	37	28.0
Inferior, RV (II, III, aVF, V3R-V6R)	6	4.5
Inferolateral (II, III, aVF, V4-V6)	5	3.8
Inferoposterior (Inf + tall R V1or V2)	5	3.8
Inferoposterolateral	1	0.8
Non-specified	2	1.5
Non-ST-elevation MI	21	15.9
Total	132	100.0

The average of left ventricular ejection fraction (LVEF) was 43.3%. From 105 patients with STEMI, 58.1% of them had received streptokinase (SK). Sixty-two patients had been initially candidated for coronary angiography, which had been finally carried out in 90.3% of them. The results of angiography were single-vessel (17.8%), 2-vessel (26.7%), 3-vessel (53.5%) and multi-vessel disease (1.8%).

Fifty-nine patients had been selected for CABG and PCI based on indications, which are represented by Figures 1 and 2, respectively.

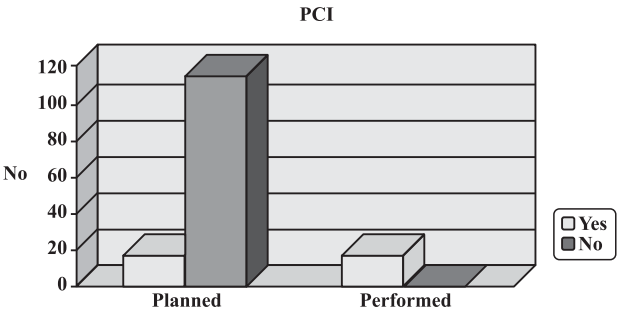

Figure 1. The number of patients with percutaneous coronary intervention (PCI)

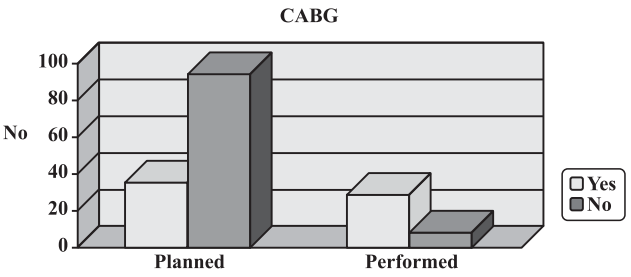

Figure 2. The number of patients who underwent coronary artery bypass grafting (CABG)

Within a year, 19 patients had been readmitted: eight patients due to angina pectoris, six due to congestive heart failure exacerbation, two due to palpitation (one with VT and the other with AF) and the remaining three due to cerebrovascular disease. It is worthy of note that for different

reasons access to 34 patients was not possible, which precluded the determination of the exact number of those who had been re-admitted.

Among the smokers, 16.2% had completely quit smoking and 27.9% had given up on a temporary basis.

Eight patients (6.1%) had died within one year after discharge: all were male and older than sixty years, 4 of them had had STEMI (two receiving SK) and the other 4 NSTEMI. No significant relation was found between mortality and age, sex, hypertension, diabetes mellitus, smoking, drug consumption and thrombolytic therapy presumably because of our low sample volume.

The rates of drug compliance with ASA, beta-blockers, ACEI and statins a year after discharge were 98.5%, 74.2%, 71.2% and 67.4%, respectively.

Discussion:

It was observed in the course of this study that AMI had occurred mostly in male patients. Other studies have yielded the similar results.[1-4]

In our study, 25.7% of the patients were in their fifth decade; and by comparison with other studies, such risk factors as diabetes mellitus and high blood pressure had occurred earlier in them.[1,2,5]

Additionally, reperfusion had been performed with SK in 58.1% of our patients. The reasons for not receiving SK are as follows: 26 (24.8%) of the patients due to a delay, 8 (7.6%) due to misdiagnosis, 5 (4.7%) due to BP>200/110 mmHg, 3 (2.8%) due to a recent CVA, 1 (0.9%) due to recent eye surgery and another one (0.9%) due to prolonged cardiopulmonary resuscitation.

In the Schiele F et al.[2] study in France, 77.5% of their patients received thrombolytic therapy. The skills of emergency medical staff, the timely arrival of victims to hospital and availability of necessary diagnostic and therapeutic procedures and especially cardiologists for decision-making in opting for thrombolytic therapy are the key factors that can explain this difference.[6,7] The use of thrombolytic therapy can be increased by raising public awareness of AMI symptoms especially among those at higher risk, namely the elderly, smokers, diabetics, and hypertensives, as well as by providing necessary equipment and transportation facilities for the timely transfer of patients to emergency departments with adequately trained medical staff.

Forty-two point four percent of our patients had undergone coronary angiography, 12.8% PCI and 21.2% CABG. In the Tesak et al.[5] , 9% of their patients underwent PCI and 16% CABG. In the Mehta et al.[1] study, 59.3% underwent coronary angiography, 22.6% PCI and 10.6% CABG.

A comparison between our patients and those in other studies[1,2,8,9] with respect to drug compliance is made in Table 2.

Table 2. A comparison between different studies with respect to drug compliance

STUDY / DRUG	O'Neill et al	Prabhakaran et al	Mehta et al	Schiele et al	Our study
ASA	81	98.2	93.3	100	98.4
β-blocker	41	72.1	75	47	72.4
Statin	-	-	-	99	67.4
ACEI	-	-	20.2	68	71.2

*Data are presented as percentage
ASA, Acetly salicylic acid; ACEI, Angiotensin converting enzyme inhibitors

The low use of beta-blockers in the Schiele F et al.[2] study was due to chronic obstructive pulmonary disease and bradycardia. The reasons for the high use of ACEI in our study, however, were EF<40%, which was present in 31% of our patients, and hypertension, which existed in 28%.

Drug therapy compliance in our patients was high compared to that in other studies, which could be the result of the proper training of the patients.

Unfortunately, 6.1% of our patients had died within one year after discharge from hospital. In the Prabhakaran D et al.[9] during two-year follow-up of their patients, 9.9% had died; Yan at et al.[10] in Canada reported the death of 6.5 % of their subjects, and 11.5% of the patients of the Schiele F et al.[2] study in France had died during a one-year follow-up.

As was previously mentioned, the most prevalent reason for some of our patients' not have received SK was delay. Consequently, mortality in their case must have occurred before hospitalization. This idea could affect our study mortality. As for the 34 patients whom we were not able to access, we contacted the Tehran Behesht-e-Zahra Cemetery, there was no record of these patients there.

Conclusion

Our patients' mortality rate was comparable to that in other studies and their long-term adherence to prescribed medicines and recommended procedures (PCI, CABG) was relatively high. Be that as it may, in comparison with studies carried out in developed countries we had more patients lost to follow-up, which was the result of a lack of integrated database in Iran.

It is essential that an integrated database be established to record patient data in hospitals and during their follow-up anywhere in our country. Also, it is advisable that, in addition to the telephone number of the patients, we obtain the numbers of some of their relatives as well so that we could have fewer patients lost to follow-up.

Acknowledgments

We thank Mohamad Sadegh Sayadi M.D., Seyed Hamidreza Ghafelebashi M.D., Maryam Tavakoli, Biglari, Ghorbani, and many other colleagues for their tireless efforts to ensure completeness, and accuracy of these data. We thank in particular Mohamad Delafkar for his help's in preparing this article.

References

1. Mehta RH, Criger DA, Granger CB, Pieper KK, Califf RM, Topol EJ, Bates ER. Patient outcomes after fibrinolytic therapy for acute myocardial infarction at hospitals with and without coronary revascularization capability. J Am Coll Cardiol 2002;40:1034-1040.
2. Schiele F, Meneveau N, Seronde MF, Caulfield F, Fouche R, Lassabe G, Baborier D, Legalery P, Bassand JP; the Réseau de Cardiologie de Franche Comté group. Compliance with guidelines and 1-year mortality in patients with acute myocardial infarction: a prospective study. Eur Heart J 2005;26:873-880.
3. Vaccarino V, Berkman LF, Krumholz HM. Long-term outcome of myocardial infarction in women and men: a population perspective. Am J Epidemiol 2000;152: 965-967.
4. Kam R, Cutter J, Chew SK, Tan A, Emmanuel S, Mak KH, Chan CN, Koh TH, Lim YL. Gender differences in outcome after an acute myocardial infarction. Singapore Med J 2002;43:243-248.
5. Tesak M, AdamKova R, Janousek S. Long term prognosis in patients with acute myocardial infarction. SCRIPTA MEDICA (BRNO) 2000;73:289-298.
6. Berger PB, Tuttle RH, Holmes DR Jr, Topol EJ, Aylward PE, Horgan JH, Califf RM. One-year survival among patients with acute myocardial infarction complicated by cardiogenic shock, and its relation to early revascularization: results from the GUSTO-I trial. Circulation 1999;99:873-878.
7. Thiemann DR, Coresh J, Oetgen WJ, Powe NR. The association between hospital volume and survival after acute myocardial infarction in elderly patients. N Engl J Med 1999;340:1640-1648.
8. O'Neill JO, Nash PJ, Bourke W, McGarry K, Bedford D. Management of acute myocardial infarction: practical problems in implementing the evidence. Ir Med J 2002;95:270-272.
9. Prabhakaran D, Yusuf S, Mehta S, Pogue J, Avezum A, Budaj A, Cerumzynski L, Flather M, Fox K, Hunt D, Lisheng L, Keltai M, Parkhomenko A, Pais P, Reddy S, Ruda M, Hiquing T, Jun Z. Two-year outcomes in patients admitted with non-ST elevation acute coronary syndrome: results of the OASIS registry 1 and 2. Indian Heart J 2005;57:217-225.
10. Yan AT, Tan M, Fitchett D, Chow CM, Fowlis RA, McAvinue TG, Roe MT, Peterson ED, Tu JV, Langer A, Goodman SG; Canadian Acute Coronary Syndromes Registry Investigators. One-year outcome of patients after acute coronary syndromes (from the Canadian Acute Coronary Syndromes Registry). Am J Cardiol 2004;94:25-29.

TEHRAN HEART CENTER

Case Report

Successful Implantation of Coronary Sinus Lead after Balloon Angioplasty of a Coronary Vein Stenosis

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Received 10 March 2007; Accepted 21 July 2007

Abstract

A 55-year-old man referred for cardiac resynchronization therapy (CRT) due to severe heart failure. A severe stenosis in the coronary sinus vein after the posterior branch disallowed the insertion of the lead. Nevertheless, the stenosis was dilated and the left ventricle (LV) lead was implanted in the lateral marginal branch.

J Teh Univ Heart Ctr 4 (2007) 233-234

Keywords: *Coronary sinus lead • Coronary vein stenosis • Coronary vein angioplasty*

Introduction

Currently available tools and techniques achieve a greater than 90% transvenous left ventricle (LV) lead placement success rate. However, failure to implant the coronary sinus (CS) lead is reported in 8-10% of procedures.[1] This is mainly due to failure to cannulate the CS, inappropriate coronary vein, unstable lead position, high stimulation threshold, and unavoidable phrenic nerve stimulation.[2] This report describes a patient in whom coronary vein stenosis disallowed the normal insertion of the CS lead, but the LV lead was subsequently implanted in the lateral marginal branch following balloon angioplasty.

Case report

A 55-year-old man presented with dilated cardiomyopathy, and further investigations revealed the following: New York Heart Association (NYHA) class III, left bundle branch block (LBBB), left ventricular ejection fraction (LVEF) of 20% and left ventricular end-diastolic diameter of 7cm. He was candidated for biventricular pacing therapy. A Tissue Doppler Imaging study showed compatibility for cardiac resynchronization (CRT) therapy.

Anesthesia having been established with lidocaine 2%, a temporary pace maker was inserted in the right ventricular apex and coronary sinus cannulation was performed. A retrograde venography showed severe stenosis in the CS after the posterior branch. Although a 0.014-inch guide wire could easily cross the stenotic area, a Medtronic 4194 lead (inserted over the guide wire) could not pass. As shown in

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Figure 1, despite the fact that there were no suitable venous branches before the stenosis, a good lateral marginal branch after the stenosis was noted.

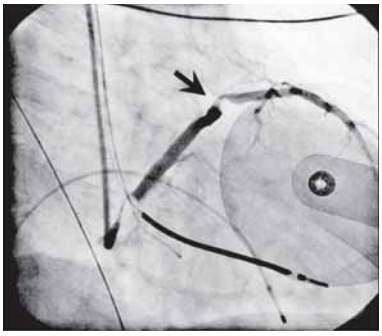

Figure 1. Coronary sinus stenosis

A VOYGER balloon, 3 mm in diameter and 15 mm in length, was negotiated through the lesion before it was inflated up to 8 atm (Figure 2).

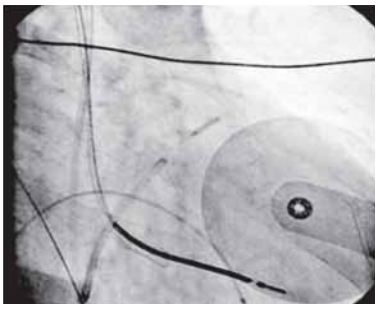

Figure 2. Coronary sinus balloon angioplasty

After angioplasty, the percutaneous transluminal coronary angioplasty (PTCA) catheter was exchanged for a Medtronic lead 4194, and it was passed through the dilated area without any difficulty and was inserted in the lateral marginal branch. A satisfactory stable lead position with acceptable threshold of LV lead and 890-ohm impedance without phrenic nerve stimulation was obtained. After the insertion of the other leads (right atrium and right ventricle) in suitable positions, all the leads were connected to the Medtronic INSYNC III MARQUIS pace maker and biventricular pace maker was commenced (Figure 3). Due to the relatively bad situation of the patient and successful implantation of the coronary sinus lead, second retrograde venography was not performed.

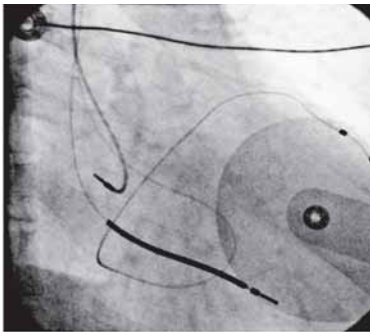

Figure 3. Coronary sinus lead implantation

Discussion

To our knowledge, symptomatic coronary vein stenosis has not been reported yet. This could be in part explained by the presence of an abundant collateral circulation.

Coronary vein angiograms performed during biventricular pacemaker implantation elucidate the presence of an asymptomatic coronary venous stenosis in approximately 10% of the authors' patients.

In this patient, we were unable to pass the CS lead through the stenotic area; therefore, we chose to dilate the coronary vein stenosis.

Venous stenting within the context of pacemaker-induced superior vena cava syndrome for symptomatic patients or to gain access to the central venous circulation has been previously reported.[3,4]

For this patient, we dilated a relatively large vein. Although there is risk of a subsequent occlusion of the smaller coronary veins, the extensive collateral circulation of the cardiac veins avoids clinical sequel. Only in the event of lead extraction can such an occlusion cause problems.

References

1. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite stimulation in cardiomyopathies (MUSTIC) study investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-880.

2. Walker S, Levy T, Rex S, Brant S, Paul V. Initial United Kingdom experience with the use of permanent, biventricular pacemakers: implantation procedure and technical considerations. Europace 2000;2:233-239.

3. Francis CM, Starkey IR, Errington ML, Gillespie IN. Venous stenting as treatment for pacemaker-induced superior vena cava syndrome. Am Heart J 1995;129:836-837.

4. Ing FF, Mullins CE, Grifka RG, Nihill MR, Fenrich AL, Collins EL, Friedman RA. Stent dilation of superior vena cava and innominate vein obstructions permit transvenous pacing lead implantation. Pacing Clin Electrophysiol 1998;21:1517-1530.

Photo Clinic

A Case of Twiddler's Syndrome

Mehran Asgari, MD*, Jocelyn Bridge, BSc, Helen Talyor, BSc
Kayvan Kamalvand, MD, FRCP, FACC

William Harvey Hospital, Ashford, Kent, UK.

A 65-year-old male patient with a background of extensive anteroapical myocardial infarction, severely impaired left ventricular function and renal failure had a biventricular cardiac defibrillator implanted on 28/06/07. The following day's checks were all normal including the chest X-ray (Figure 1).

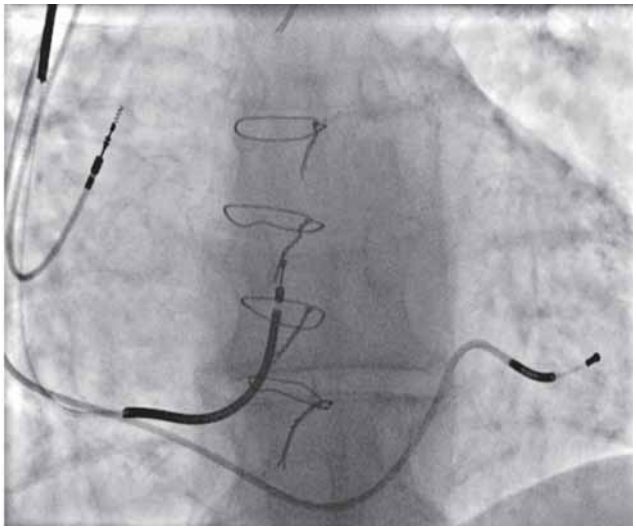

Figure 1. Post implant x-ray showing the appropriate lead location

He was brought back on 16/08/07 for intracardiac defibrillator dermatitis (ICD) induction. There was neither sensing nor capturing on the right and left ventricular leads. The lead position was screened on the table (Figure 2), followed by the defibrillator implant site (Figure 3).

This is a classical case of the Twiddler's syndrome, in which the patient had played with the generator in the pocket in such a way that the leads were wound around it. The patient exhibited the early signs of dementia and memory loss and denied interfering with his device; however, his wife had spotted bleeding over the site of implant on a couple of occasions after the wound had healed.

We would like to emphasise the importance of suturing the device routinely in order to secure it in the pocket.

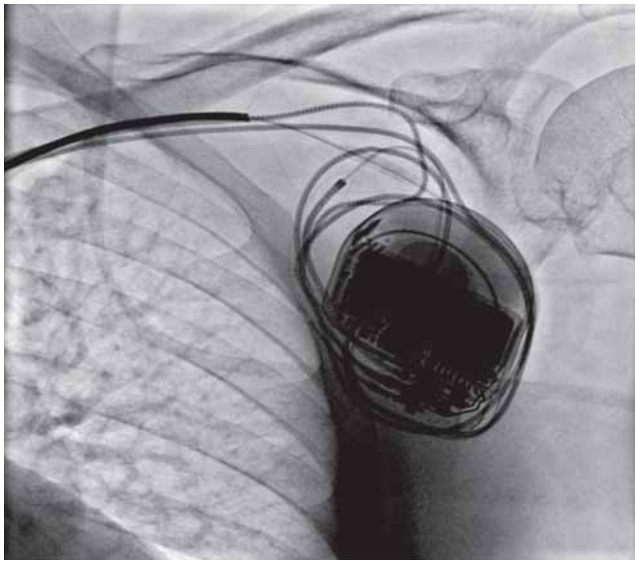

Figure 2. X-ray of the Implant site showing the leads wound around the device

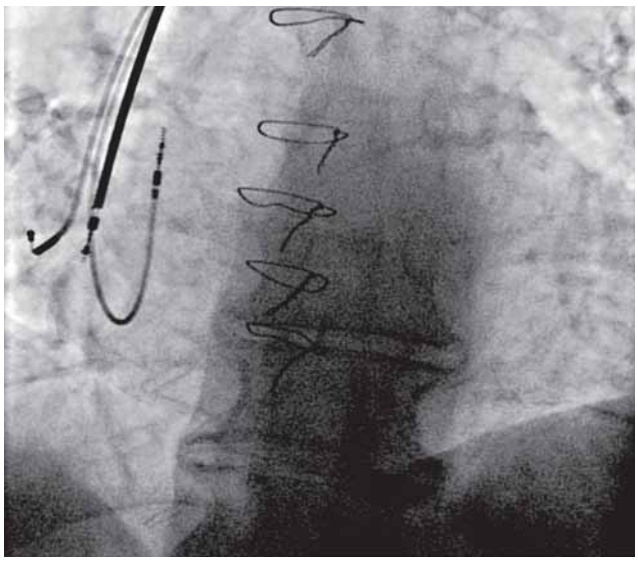

Figure 3. Displaced leads confirmed by x-ray

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Letter To The Editor

Arrhythmia in Acute Right Ventricular Infarction

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Received 5 July 2007; Accepted 21 July 2007

Acute inferior myocardial infarction (MI) frequently involves the right ventricle (RV).[1-3] We assessed the prognostic impact of RV myocardial involvement in patients with inferior MI. One hundred seventy patients were admitted to the cardiac care unit of Madani Heart Hospital (Tabriz-Iran) with the diagnosis of inferior MI with (group1) or without (group2) the simultaneous involvement of RV during the study period (from 2005 to 2006). Patients presenting within 12h of symptom onset were eligible for inclusion. Patients with simultaneous anterior wall MI or renal impairment (creatinine > 2 mg/dl), as well as those undergoing primary percutaneous translational coronary angioplasty, were excluded. Eighty eight percent of the patients with RVMI and 75% of those with isolated inferior MI had some type of arrhythmia. Atrioventricular (AV) block occurred in 42% of the infarctions with RV involvement and only in 29% of the control group. Intra-ventricular conduction disturbance (IVCD) was also more frequent in RVMI (29.4% vs. 13.1%, p=0.021), especially right bundle branch block (RBBB) (20% vs. 7.4%, P=0.003). There was, however, no meaningful difference in the incidence of left bundle branch block (LBBB) between the two groups (3.5% vs. 2.35%, P=0.95). Ventricular fibrillation (VF) was observed in 5.2% and 1.2% and ventricular tachycardia in 26% and 12.2% of the patients in groups 1 and 2, respectively. In 27% of patients with RVMI, it was necessary to implant a pacemaker as compared to 10% of those in the control group. Mortality was higher in the patients with inferior infarction extended to the RV (15.3% vs. 3.5%, P= 0.0001).

Thus, the differences between the findings in the two groups in terms of the occurrence of post-MI arrhythmias and conduction disorders were quite significant, but there was no meaningful difference with respect to the incidence of LBBB between the two groups. Additionally, patients with inferior MI who also had RV myocardial involvement were at increased risk of death and arrhythmias. This suggests that the RV may be more arrhythmogenic than the LV; a hypothesis that warrants further investigation.

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References

1. Kinch JW, Ryan TJ. Right ventricular infarction. N Engl J Med 1994;28:1211-1217.
2. Zehender M, Kasper W, Kauder E, Schonthaler M, Geibel A, Olschewski M. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. N Engl J Med 1993;328:981-988.
3. Dell'Italia LJ, Starling MR, Crawford MH, Boros BL, Chaudhuri TK, O'Rourke RA. Right ventricular infarction: identification by homodynamic measurements before and after volume loading and correlation with noninvasive techniques. J Am Coll Cardiol 1984;4:931-939.

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International Cardiovascular Surgery Meetings Calender (2007-2008)




Congress	*Time-Location*	*Address*
Singapore LIVE 2007 (16th Annual Live Interventions in Vascular Endotherapy)	January 22-24, 2007, Singapore	Email: contact@singlivecourse.com Website: http://www.singlivecourse.com/
43rd Annual Meeting of The Society of Thoracic Surgeons (STS)	January 29 – 31, 2007, San Diego, California, USA	Email: sts@sts.org Website: http://www.sts.org/
53rd Annual conference of the Indian Association of Cardio Vascular Thoracic Surgeons (CTCON 2007)	February 8 – 11, 2007, Jaipur, Rajasthan, India	Email: email-info@ctcom2007.com Website: http://www.ctcon2007.com/
7th Indian Society of Extra-Corporeal Technology (ISECT CON 2007)	February 9 – 10, 2007, Jaipur, Rajasthan, India	Tel: 91 0935 135 2897 Email: info@ctcon2007.com
37th Annual Meeting of the Japanese Society for Cardiovascular Surgery (JSCVS)	Feburary 21 – 23, 2007, Tokyo, Japan	Email: JSCVS37@hij.twmu.ac.jp Website: jscvs37.umin.jp
25th International Cardiovascular Surgical Symposium Annual Meeting	March 3–10, 2007, Zürs, Arlberg, Austria	Email: congress@herzchirurgie.at Website: http://www.asian-annals.org/general/www.surgery-zur.at
71st Annual Scientific Meeting of the Japanese Circulation Society	March 15 – 17, 2007, Kobe, Japan	Email: 71junkan@congre.co.jp Website: www.congre.co.jp/jcs71
CREF 27 - The San Diego Cardiothoracic Surgery Symposium: Science and Techniques of Perfusion	March 15 – 18, 2007, San Diego, California, USA	Email: info2007@amainc.com Website: http://www.amainc.com/

Congress	*Time-Location*	*Address*
First Annual Florida Valve Symposium-Current Controversies in Valve Management	March 28–30, 2007, St. Petersburg, Florida, USA	Email: siestavc@aol.com Website: http://www.floridavalvesymposium.com/
Valves in the Heart of the Big Apple: Evaluation Management of Vascular Disease 2007	April 12 –14, 2007, New York, USA	Email: info@heartvalvesocietyofamerica.org Website: http://www.heartvalvesocietyofamerica.org/
5th Vienna Interdisciplinary Symposium on Aortic Repair (VISAR)	April 19–21, 2007, Vienna, Austria	Email: visar@ieurocongress.org Website: http://www.eurocongress.org/
27th Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation (ISHLT)	April 25–28, 2007, San Francisco, California, USA	Email: meeting@ishlt.org Website: http://www.ishlt.org/
1st Meeting of the World Society for Pediatric and Congenital Heart Surgery	May 3–4, 2007, Washington, DC, USA	Email: contacts@wspchs.org Website: http://www.wspchs.org/
87th Annual Meeting of the American Association for Thoracic Surgery (AATS)	May 6 – 9, 2007, Washington, D.C., USA	Email: aats@prri.com Website: http://www.aats.org/
15th Annual Meeting of the Asian Society for Cardiovascular Surgery (ASCVS)	May 17–20, 2007, Beijing, China	Email: ASCVS2007@cma.org.cn Website: http://www.ascvs2007.com/
Euro PCR-2007 (The Paris Course on Revascularization)	May 22–25, 2007, Barcelona, Spain	Email: europa@europa-organisation.com Website: http://www.europa-organisation.com/
15th European Conference on General Thoracic Surgery (ESTS)	June 3–6, 2007, Leuven, Belgium	Email: sue@ests.org.uk Website: http://www.ests.org/
10th Annual Scientific Meeting of the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS)	June 6–9, 2007, Rome, Italy	Email: ismics@prri.com Website: http://www.ismics.org/
12th European Congress on Extracorporeal Circulation Technology	June 6–9, 2007, Kyiv, Ukraine	Email: congress.fecect@reedbusiness.nl Website: http://www.fecect.org/
4th Biennial Meeting of the Society for Heart Valve Disease (SHVD)	June 15–18, 2007, New York, USA	Email: secretariat@shvd.org Website: w02-0566.web.dircon.net/biennial2007
7th International Congress on Complications during Coronary Intervention: Management and Prevention	June 20–22, 2007, Lausanne, Switzerland	Email: coronarycomplications@eurocongress.org Website: http://www.coronarycomplications.org/
XXVth Meeting of the Society of Cardiac Surgeons	June 21–23, 2007, Pamplona, Navarra, Spain	Email: jherreros@unav.es Website: http://www.cardiasurgeons.ca/

Congress	*Time-Location*	*Address*
17th World Congress of the World Society of Cardio-Thoracic Surgeons (WSCTS)	July 11–13, 2007, Kyoto, Japan	Email: wscts2007@congre.co.jp Website: http://www.wscts2007.com/
21st Annual Meeting of the European Association for Cardio-Thoracic Surgeon (EACTS)	September 15–19, 2007, Geneva, Switzerland	Email: info@eacts.co.uk Website: http://www.eacts.org/
19th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery (MACCS 2007)	September 27–30, 2007, Opatija, Croatia	Email: info@alphastudio.it Website: http://www.maccs2007.org/
7th International Congress on Coronary Artery Disease - From Prevention to Intervention	October 7–10, 2007, Venice, Italy	Email: coronary@kenes.com Website: www.kenes.com/cad7
VIII Annual International Symposium on Advances in Understanding Aortic Diseases	October 13–14, 2007, Tokyo, Japan	Email: ctstokyo-ikyoku@umin.ac.jp
60th Annual Scientific Meeting of the Japanese Association for Thoracic Surgery (JPATS)	October 17 – 20, 2007, Sendai, Japan	Email: jats-adm@umin.ac.jp Website: http://www.asian-annals.org/general/www.jpats.org
Eighth Biennial Congress of the Syrian Cardiovascular Association	November 1-3, 2007 Damascus, Syria	E-mail: scva@scs-net.org Tel/Fax: 00963 94 27 27 55
18th Biennial Congress of the Association of Thoracic & Cardiovascular Surgeons of Asia (ATCSA)	November 25–28, 2007, Bali, Indonesia	Tel/Fax: 62 21 566 5993
ISMICS Winter Workshop 2007	November 28–December 2, 2007, Antalya, Turkey	Email: oztekinoto@oztekinoto.com
Pioneering Techniques in Cardiac Surgery, the Fifth in the Series	December 6–7, 2007, Leipzig, Germany	Email: blaeser@medizin.uni-leipzig.de
4th Asian Pacific Congress of Heart Failure (APCHF)	January 31–February 3, 2008, Melbourne, Australia	Email: apchf@tourhosts.com.au Website: http://www.apchf.com.au/
38th Annual Meeting of the Japanese Society for Cardiovascular Surgery (JSCVS)	February 20–22, 2008, Fukuoka, Japan	Email: JSCVS38@med.kurume-u.ac.jp Website: square.umin.ac.jp/jscvs
16th Annual Meeting of the Asian Society for Cardiovascular Surgery	May 2–4, 2008, Singapore	Email: mice@themeetinglab.com Website: http://www.ascvs2008.com/
Endoscopic & Laparoscopic Surgeon of Asia 2008 (ELSA 2008)	September 2 – 6, 2008, Yokohama, Japan	Email: elsa2008@convention.co.jp Website: www2.convention.co.jp/elsa2008

International Cardiovascular Meeting And Congresses Calender (2007-2008)




Title	City	Start Date	End Date
XVII Annual Meeting of the French Society of Cardiology	France, Paris	17 January 2007	20 January 2007
Singapore 2007 Live, 16th Annual Live Interventions in Vascular Endotherapy	Singapore, Singapore	22 January 2007	24 January 2007
39th Annual Business Meeting of the Finnish Cardiac Society and 33rd Progress Report Meeting	Finland, Nilsiä	26 January 2007	27 January 2007
Annual Meeting of the Norwegian Society of Cardiology (Winter Meeting)	Norway, Lillehammer	26 January 2007	28 January 2007
26th Annual Scientific Meeting of the Belgian Society of Cardiology	Belgium, Brussels	01 February 2007	03 February 2007
1st European Forum, Heart Exercise & Prevention	France, Paris	02 February 2007	03 February 2007
Cardiology Update 2007: Educational Programme	Switzerland, Davos	12 February 2007	16 February 2007
Annual Meeting of the Belorussian Scientific Society of Cardiologists	Belarus, Minsk	15 February 2007	16 February 2007
34th Annual Congress of the Egyptian Society of Cardiology	Egypt, Cairo	20 February 2007	23 February 2007
International Summit on Syncope: State of the Art 2007	United States of America, Amelia, Florida	23 February 2007	25 February 2007
Acute Coronary Syndromes: from Plaque to Imagery	Luxembourg	03 March 2007	03 March 2007
7th Annual Spring Meeting on Cardiovascular Nursing: "Changing Practice to Improve Care"	United Kingdom, Manchester	23 March 2007	24 March 2007

Title	City	Start Date	End Date
6th International Workshop on Interventional Pediatric Cardiology	Italy, San Donat Milanese (Milan)	28 March 2007	31 March 2007
13th Annual Transoesophageal Echocardiography Course	United Kingdom, London	29 March 2007	30 March 2007
The 3rd Local Annual Meeting of the Libyan Cardiac Society	Libyan Arab Jamahiriya, AL Baida	30 March 2007	01 April 2007
73nd Annual Meeting of the German Cardiac Society	Germany, Mannheim	12 April 2007	14 April 2007
8th International Congress of Cardiology and Cardiac Surgery	Lebanon, Beirut	18 April 2007	21 April 2007
EuroPrevent 2007	Spain, Madrid	19 April 2007	21 April 2007
XXVIII Annual Congress of the Portuguese Society of Cardiology	Portugal, Vilamoura	21 April 2007	25 April 2007
Annual Meeting of the Swedish Society of Cardiology	Sweden, Gothenburg	25 April 2007	27 April 2007
4th Global CardioVascular Clinical Trialists Forum	France, Cannes	26 April 2007	28 April 2007
Spring Meeting of the Netherlands Society of Cardiology	Netherlands, Amsterdam	26 April 2007	27 April 2007
8th International Conference of Nuclear Cardiology - ICNC8	Czech Republic, Prague	29 April 2007	02 May 2007
Annual Meeting of the Norwegian Society of Cardiology (Spring Meeting)	Norway, Oslo	03 May 2007	05 May 2007
Cardiology and Vascular Medicine - update and perspective	Netherlands, Rotterdam	07 May 2007	09 May 2007
Annual Scientific Congress of Cardiology of the Hugarian Society of Cardiology	Hungary, Balatonfüred	09 May 2007	12 May 2007
15th Alpe-Adria Cardiology Meeting	Czech Republic, Brno	11 May 2007	13 May 2007
1st All Africa Conference on Heart Disease, Stroke and Diabetes	Kenya, Nairobi	13 May 2007	16 May 2007
IV Congress of Cardiologists and Angiologists	Bosnia and Herzegovina, Mostar	17 May 2007	19 May 2007
EuroPCR 2007	Spain, Barcelona	22 May 2007	25 May 2007
25th Anniversary Meeting of the Slovenian Society of Cardiology	Slovenia, Radenci	24 May 2007	26 May 2007
VI Annual Congress of the Armenian Cardiologists Association	Armenia, Yerevan	24 May 2007	26 May 2007
Annual Meeting of the Austrian Society of Cardiology "Jahrestagung 2007"	Austria, Salzburg	30 May 2007	02 June 2007
Annual Meeting of the Danish Society of Cardiology	Denmark, Nyborg	31 May 2007	02 June 2007

Title	City	Start Date	End Date
11th Danubian Forum of Cardiac Surgery	Romania, Timisora	01 June 2007	02 June 2007
Annual Meeting of the Estonian Society of Cardiology	Estonia, Tallinn	01 June 2007	02 June 2007
Annual Meeting of the Italian Association of Hospital Cardiologists (ANMCO)	Italy, Florence	03 June 2007	06 June 2007
Annual Scientific Conference of the British Cardiovascular Society	United Kingdom, Glasgow (Scotland)	04 June 2007	07 June 2007
Heart Failure 2007	Germany, Hamburg	09 June 2007	12 June 2007
76 th Congress of the European Atherosclerosis Society	Finland, Helsinki	10 June 2007	13 June 2007
Annual Congress of the Swiss Society of Cardiology	Switzerland, Geneve	13 June 2007	15 June 2007
17th Scientific Meeting of the European Society of Hypertension	Italy, Milan	15 June 2007	19 June 2007
RHYTHM 2007- ARRHYTHMIAS AND HEART FAILURE: pharmacological and non- pharmacological therapies	France, Cannes	15 June 2007	17 June 2007
Mayo International Vascular Symposium in Iceland, June 2007	Iceland, Reykjavik	19 June 2007	23 June 2007
Europace 2007	Portugal, Lisbon	24 June 2007	27 June 2007
The 34th International Congress on Electrocardiology	Turkey, Istanbul	27 June 2007	30 June 2007
The Annual Interventional Cardiology Conference - CARDIOALEX	Egypt, Bibliotheca Alexandrina	27 June 2007	29 June 2007
World Heart Federation Teaching Seminar on CVD 2007	Norway, Sommarøy	20 August 2007	01 September 2007
ESC Congress 2007	Austria, Vienna	01 September 2007	05 September 2007
The 46th National Congress of Cardiology of the Romanian Society of Cardiology	Romania, Sinaia	15 September 2007	18 September 2007
43rd EASD Annual Meeting 2007	Netherlands, Amsterdam	17 September 2007	21 September 2007
XI International Congress of the Polish Cardiac Society	Poland, Wroclaw	20 September 2007	22 September 2007
Bleeding Complications in the treatment of Acute Coronary Syndrome	Sweden, Lund	03 October 2007	05 October 2007
XVI International Symposium on Drugs Affecting Lipid Metabolism	United States of America, New York	04 October 2007	07 October 2007
XII Congress of the Slovak Society of Cardiology	Slovak Republic, Bratislava	04 October 2007	06 October 2007
7th International Congress on Coronary Artery Disease - from Prevention to Intervention	Italy, Venice	07 October 2007	10 October 2006

Title	City	Start Date	End Date
Venice Arrhythmias 2007 - Tenth International workshop on Cardiac Arrhythmias	Italy, Venice	07 October 2007	10 October 2007
National Cardiology Congress of the Society of Cardiology of the Russian Federation	Russian Federation, Moscow	09 October 2007	11 October 2007
Annual Autumn Meeting of the Finnish Cardiac Society	Finland, Helsinki	10 October 2007	12 October 2007
European Conference on Myocardial and Pericardial Diseases with focus on heart diseases in women	Germany, Marburg	11 October 2007	14 October 2007
Annual General Meeting of the Irish Cardiac Society	Ireland, Holywood (Co. Antrim)	11 October 2007	13 October 2007
Wonca Europe 2007	France, Paris	17 October 2007	20 October 2007
Annual Meeting of the Spanish Society of Cardiology	Spain, Madrid	17 October 2007	20 October 2007
XXIII National Cardiology Congress of the Turkish Society of Cardiology	Turkey, Antalya	20 October 2007	23 October 2007
Autumn Meeting of the Netherlands Society of Cardiology	Netherlands, Ermelo	25 October 2007	27 October 2007
The 8th biennial meeting of the Syrian Cardiovascular Association	Syrian Arab Republic, Damascus	01 November 2007	03 November 2007
Cardio Lipid 2007 Egypt	Egypt, Ain Sokhna - Red Sea	15 November 2007	17 November 2007
National Meeting of the Algerian Society of Cardiology	Algeria, Algiers	07 December 2007	09 December 2007
4th Asian Pacific Congress of Heart Failure	Australia, Melbourne	31 January 2008	03 February 2008
16th Annual Meeting of the Asian Society For Cardiovascular Surgery (ASCVS 2008)	Singapore,	13 March 2008	16 March 2008
The 4th International Annual Meeting of the Libyan Cardiac Society	Libyan Arab Jamahiriya, Benghazi	21 March 2008	23 March 2008
XVI World Congress of Cardiology	Argentina, Buenos Aires	18 May 2008	21 May 2008
ESC Congress 2008	Germany, Munich	30 August 2008	03 September 2008
National Congress of the Latvian Society of Cardiology	Latvia, Riga or Jurmala	26 September 2008	27 September 2008

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.

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"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.

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The Journal of Tehran University Heart Center" accepts the following categories of articles:"

Guest Editorial

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Brief communication

Case report

Review Article

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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.

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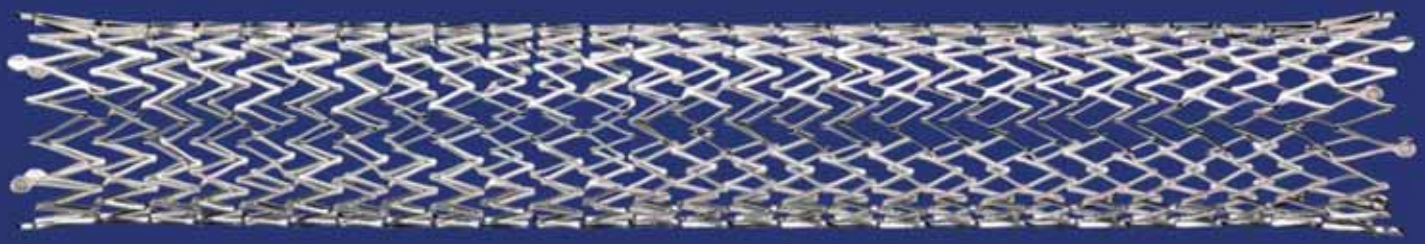

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