In the name of God

IRANIAN SOCIETY OF CARDIAC SURGEONS

The Iranian Journal of Cardiac Surgery

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Contents

Information for Authors

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Evaluation and Comparison of Using Low Dose Aprotinin and Tranexamic Acid in CABGS: A Double –Blinded, Prospective, Randomized Study of 150 Patients

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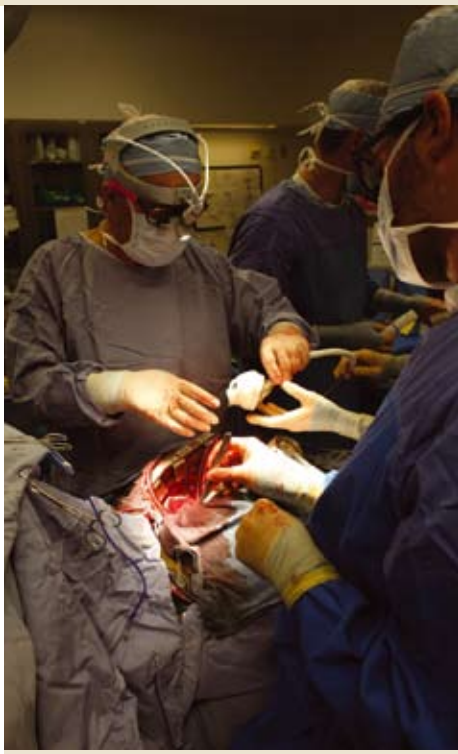

Abstract

Background. Cardiovascular operations are associated with an inherented bleeding tendency that some time leads to severe bleeding and transfusion requirement. Pharmacologic intervention to minimize post bypass bleeding and blood product transfusions has received increasing attention for both medical and economic attention.

Methods: In this double-blind randomized placebo-controlled clinical trial, three groups of patients undergoing on-pump Coronary Artery Bypass Surgery(CABG), each group composed of 50 patients, were blindly randomized to receiving either low aprotinin, tranexamic acid or placebo, and then results were evaluated and compared in each group.

Results: The following variables were similar in groups and there were no statistically significant differences in these variables: Age(P=0.308), Sex(P=0.973), ypelipidemia(P=0.720),Hypertention(P=0.786),Smoking(P=0.72),Diabetes(P=0.960). The amount of drainage from chest tubes were less in aprotinin and tranexamic acid groups compared to placebo, and this was statistically important(P<0.001). There were no statistically significant differences in need for reoperation for bleeding in three groups(P=0.998). Complications following surgery in three groups were statistically the same and not significantly different (table below). All complications had a good course and all patients were discharged from hospital uneventfully. There were no mortality in any group.

Conclusions: low dose aprotinin and tranexamic acid can significantly reduce blood loss and transfusion requirement in CABG surgery without importantly increasing mortality and morbidity.

Bleeding after cardiopulmonary bypass (CPB) is still a concern for CABG operation and an important factor affecting the morbidity and mortality in patients undergoing cardiac operation. Between 30% and 70% of open heart patients will require blood product transfusion (1). Although small, the risk of transmitting hepatitis, human immunodeficiency virus, cytomegalovirus, or other infectious agents remain a concern. The coagulopathy is multifactorial with platelet dysfunction and plasmin-induced fibrinolytic activity the major contributors to the process (2). Aprotinin, a serine protease inhibitor from bovine lung, and the synthetic antifibrinolytic drugs, Tranexamic acid (TA) and-amino-N-caproic acid (EACA) given before CPB have been shown to reduce mediastinal bleeding postoperatively (3-7). The antifibrinolytic drugs have been shown to be equally effective as aprotinin in reducing bleeding and the use of allogeneic blood products, both in high risk patients and routine patients populations undergoing cardiac operastion(8).

Because antifibrinolytic drugs are much cheaper than aprotinin, and equally effective in reducing bleeding during cardiac operations and also recently mentioned

adverse effect of aprotinin on graft patency and survival (9,10), we studied a homogeneous patient population undergoing elective CABG to estimate the influence of low dose aprotinin and TA on perioperative bleeding, need for allogeneic transfusion, and heamostasis.

Materials and Methods:

After institutional approval was obtained in a double blind clinical randomized trial all patients scheduled for coronary bypass surgery in our Center between the 21st of march 2008 and 21 march 2009 were included in this study. Inclusion criteria were: on pump CABG and patients' acceptance.

Exclusion criterias were: History of hemorrhagic tendency and blood dyscrasia, history of plavix usage, known hepatic, renal and metabolic diseases, use of other anti coagulation drugs like coumadin for valvular disease and arrhythmias and streptokinase, emergency surgery, rheumatic heart disease, known allergy to aprotinin or transamine and prohibition for their use like: acquired visual defects and retinal disease, subarachnoid hemorrhage, disseminated Intravascular coagulation, gall bladder disease, leukemia, embolization and vein thrombosis.

Patients demographic and clinical data as age, sex, history of cigarette smoking and other concomitant diseases were collected (Table 1).

All patients received 300 IU /Kg of bovine lung heparin. Additional heparin was administered for activated clotting times less than 400 seconds. The activate clothing time was monitored every 30 minutes. After we obtained written informed consent all patients were put in three groups randomly. In group A (aprotinin) after test dose 1 million units of aprotinin was added to pump prime solution. In group B (transamine) 1 gr of Transamine was added to pump prime solution and another 1 gr was used intravenously after discontinuation of pump. In group C (control) 250 cc of normal saline were used as placebo after the induction of anesthesia. Cardiac surgeons and cardiac surgery residents didn't know anything about the groups. Heparin was reversed with protamine sulfate after removal of all cannulaes. Shed mediastinal and plural blood, were estimated after 6, 12 and 24 hours and data were stored in a computer. Packed red cell was transfused for a hematocrete concentration under 30% and fresh frozen plasma was transfused based on abnormal prothrombin time and the rate of bleeding. Platlete transfusion threshold was a platelet count of 1000000 or less and bleeding tendency with one or more of the followings:

Post-operative complications like post-operative MI (based on cardiac enzyme rising, ECG changing and EF changing estimated by echocardiography), Neurological complications (estimated by clinical examination and CT-Scanning), redo operation for surgical bleeding and pericardial effusion, kidney complication(rising of serum creatinin and low urinary out put under 0.5 cc per minute) and other complications were studied.

Data was expressed as mean+/_ standard deviation. comparison of parametric patients' data was done using an unpaired student's t-test for quantitative data and K2 for qualitative data. P-value of less than 0.05 was considered significant.

Results:

We compared patients in three groups .Sex (P Value0.308), Age (P Value0.973), Cigarette smoking (P Value 0.720), Hyperlipidemia (P Value 0.707), Diabetes (P Value 0.960) and Hypertension (P Value 0.786) distribution were the same in all groups, (Table 1,Table 2) and there were no important statistical differences in these variables.

Table 1.Patient Demographics

Variable	Transamine	Aprotinin	Placebo	sum	P Value
Age(y)	54.6+_10.4	53.6+_9.1	54.2+_9.7	54.5+_9.4	0.973
Male%	41(82%)	40(80%)	35(70%)	116(77%)	0.308
Female%	9(18%)	10(20%)	15(30%)	34(23%)	

Table 2.Risk Factors

Variable	Transamin	Aprotinin	Placebo	Sum	P Value
Cigarette smoking	31(62%)	27(54%)	29(58%)	87(59%)	0.720
Hyperlipidemia	16(32%)	20(40%)	18(36%)	54(36%)	0.707
Hypertension	25(50%)	28(56%)	25(50%)	78(52%)	0.786
Diabetes Mellitus	40(80%)	40(80%)	39(78%)	119(79%)	0.960

The amount of blood drainage from chest and mediastinal drains were significantly less in aprotinin and transamine groups compare to placebo group, and this was Statistically important.(P Value <0.001),We used repeated measurement analysis of variances in this manner.(Table 3)

Only two patients needed reoperation for bleeding, one in group B and one in group C, both of them were surgical bleeding and there were no statistically important difference in need for reoperation in three groups.(P Value 0.998). (Table 4)

Table 3.Amount of bleeding

Variable	Transamine	Aprotinin	Placebo	P Value
Bleeding after 6h	115+_88.7	109+_86.7	240+_182.9	0.001
Bleeding after 12h	219+_119.9	223+_134.1	393+_280.1	0.001
Bleeding after 24h	355+_178.7	382+_217.7	540+_346.9	0.001
Bleeding after 48h	432+_210.3	469+_237.2	649+_365.3	0.001

Other complications after surgery in three groups were statistically the same and not importantly different in the three groups. (Table 4)

There were 8 cases of post operative myocardial infarction 8% (based on cardiac enzyme rising, ECG changing and EF changing estimate by echocardiography ,4 in group C, 2 in group A and 2 in group B.(P Value 0.730) (table 4)

Table 4.Post operative complications

Variable	Transamine	Aprotinin	Placebo
Myocardial Infarction	2(4%)	2(4%)	4(8%)
Pericardial Effusion	0	0	2(4%)
Neuralgic Complications	0	1(2%)	1(2%)
Renal Complications	2(4%)	1(2%)	1(2%)
Reoperation for bleeding	1(2%)	0	1(2%)
Mortality	0	0	0

2 patients in group C were reoperated for pericardial effusion, two patients; one in placebo group and one in aprotinin group had neurological complications. Renal complications were 2 in transamine group (4%) and one in each other group, all neurology and renal complications were reversed before patients being discharged from hospital. There were no mortality in three groups and all complications had a good course and all patients discharged uneventfully from hospital. (Table 4)

In transamine group 35 patients (70%) didn't need blood transfusion, 4 patients needed 1 unit of packed cell and one patient received 6 units of packed cell, in aprotinin group 19 patients (38%) received 1 unit of packed cell and in placebo group 23 patients (46%) received 1 unit of packed cell, 5 Patients (10%) received 2 units and one received 4 units of packed cell.

Discussion:

Meta-analysis of multiple studies has shown aprotinin and antifibrinolytics to reduce mediastinal chest tube drainage by 30% versus placebo (11). Although delivery protocols were uniform for aprotonin, they still vary widely for TA and EACA. Whereas the effect of TA and aprotonin on reducing blood loss after cardiac operation is clear (12), a meta-analysis of randomized studies of EACA versus placebo could not show a significant effect in reducing transfusion requirements (13). Tranexamic acid has been shown as effective as aprotinin in reducing coagulopathy-caused bleeding after CPB and cheaper than aprotinin (12).

As TA is emerging as the presently available drug of choice to reduce coagulopathy-caused bleeding and because there are some concerns regarding adverse effect of aprotinin on renal system and final outcome (10), we designed our study to glean knowledge about the benefit of using low-dose TA and low-dose aprotinin in terms of reducing blood loss and allogeneic transfusion and its effect on various coagulation factor.

In a low risk patient population, TA was shown to decrease mediastinal bleeding after cardiac operation as early as 1990(14). A similar result was found in studies by Karski and associates from Toronto (15). The first significant study of a uniform patient population undergoing coronary operation was reported by Roussou and colleagues (16). They retrospectively studied 415 patients undergoing CABG excluding emergency and redo operations. The first 209 patients were operated on without TA, and the subsequent 206 patients with a 2-g bolus of TA followed by 8-g during the procedure. Chest tube drainage in the control group was 1114 ml versus 803 mL in the study group. A double-blind randomized placebo controlled study was reported from Brook-Army medical center (17) on patients undergoing primary coronary artery operation. The dose of TA was 15mg/Kg started before CPB and 1 mg/Kg continued for 5 hours.The bleeding was reduced from 1202 mL in placebo group versus 1020 mL in the TA group. Since then multiple studies have shown the efficacy of TA in prospective studies comparing patients receiving aprotinin or EACA (9,18). These studies mostly included patient populations that were at high risk for bleeding mixed with those of primary myocardial revascularization. The few studies since 1998 that had a placebo group with primary myocardial revascularization used high-dose TA or administration of TA well into postoperative period. With improved CPB and surgical techniques, blood loss is small after routine primary CABG even without the use of antifibrinolytics (18). Therefore it is a valid question to ask whether addition of low-dose TA or aprotinin as given in our study is beneficial. From our findings, TA and aprotinin both are beneficial in this setting. Although control patients only bled 540mL in 24 hours, the use of TA and aprotinin significantly reduced this even further to 355 and 380 mL.

Conclusion:

Both aprotinin and tranexamic acid can significantly reduce blood loss and transfusion requirement even in low doses in coronary artery bypass surgery without importantly increasing mortality and morbidity.

Refferences:

1. Katsaros D, Petricievic M, Snow NJ, Woodhall DD, Bergen RV. Tranexamic acid reduces postbypass : a double blinded, prospective, randomized study of 210 patients. Ann Thorac Surg. 1996;61:1131-5
2. Wong BI, McLeanRF, Fremes SE, Deemar KA, Harrington EM, ChristakisGT, Goldman B. Aprotinin and tranexamic acid for high transfusion risk cardiac surgery. Ann Thorac Surg. 2000;69:808-16
3. Zabeeda D, Medalion B, Sverdlov M, Ezra S, Schakner A, Ezri T, Cohen AJ. Tranexamic acid reduces bleeding and the need for blood transfusion in primary myocardial revascularization. Ann Thorac Surg. 2002;74:733-8
4. Horrow JC, Van Riper DF, Strong MD, GrunewaldKE, Parmet JL. The dose response relationship of tranexamic acid. Anesthesiology 1995;82:383-91
5. RoystonD, Bidstrap BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 1987;2:1289-91

6. Horrow JC, Halvacek J, Strong MD, et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 1990;99:70-4
7. Horrow JC, Van Ripper DF, Strong MD et al. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation 1991;84:2063-70
8. Casati v, Guzzon D, Oppizi M, et al. Tranexamic acid compared with high dose aprotinin in primary elective operations: effects on perioperative bleeding and allogeneic transfusions. J Thorac Cardiovasc Surg 2000;120:520-7
9. Misfield M, Dubbert S, Eleftheriadis S, et al. Fibrinolysis adjusted perioperative low dose aprotinin reduces blood loss in bypass operations. Ann Thorac Surg 1998;66:792-9
10. Westaby S, Katsumata T. Editorial: aprotinin and vein graft occlusion-the controversy continues. J Thorac Cardiovasc Surg 1998;116:731-3
11. Fremese SE, Wong BI, Lee E, et al. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. Ann Thorac Surg 1994;58:1580-8
12. Casati V, Guzzon D, Oppizi M, et al. Hemostatic effects of aprotinin, tranexamic acid and-aminocaproic acid in primary cardiac surgery. Ann Thorac Surg 1999;68:2252-6.
13. Leupasis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery. Anesth Analg 1997;85:1258-67
14. Horrow JC, Hlavacek J, Stong MD, et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 1990;99:70-4
15. Karski JM, Teasdale SJ, Norman PH, et al. prevention of post-bypass bleeding with tranexamic acid and-aminocaproic acid. J Cardiothorac Vasc Anesth 1993;7:431-5
16. Rossou JA, Englman RM, Flack JE, et al. Tranexamic acid significantly reduces blood loss associated with coronary revascularization. Ann Thorac Surg1995;59:671-5.
17. Brown RS, Thwaits BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary bypass operation. Anesth Analg;1997:936-70
18. Hardly JF, Belisle s, Dupont C, et al. Prophylactic tranexamic acid and-aminocaproic acid for primary myocardial revascularization. Ann Thorac Surg 1998;65:371-6

Assessment of Papillary Muscle Repositioning in Mitral Valve Replacement in Patients With Ischemic Mitral Regurgitation

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Abstract:

Background: The aim of this study was to investigate the feasibility of performing papillary muscle repositioning (PMR) for subvalvular-sparing mitral valve replacement procedures in patients with ischemic mitral regur-gitation and to determine the early and late effects of this procedure on the clinical outcome and left ventricular mechanics.

Methods: We prospectively randomly allocated 50 patients with severe ischemic mitral regurgitation and left ventricle dysfunction who were candidates for coronary artery bypass graft surgery and mitral valve replacement into a total chordal-sparing mitral valve replacement group or a PMR group. Echocardiography was performed preoperatively, at discharge, and after 3 years to determine the left ventricular dimensions, shape, and function.

Results: The reduction in the left ventricle volumes and sphericity index in the PMR group was more significant than that in the other group. With regard to the left ventricular end-systolic and left ventricular end-diastolic volumes, sphericity index, and ejection fraction, the PMR group showed better results ($p < 0.05$), but the difference in New York Heart Association functional class after 3 years was not statistically significant between the two groups ($p > 0.05$).

Conclusions: The PMR technique described herein can dramatically help ischemic patients by affecting the left ventricular shape and function more efficiently compared with the complete retention of the mitral subvalvular apparatus if the mitral valve is to be replaced.

The myocardium experiences remodeling in the wake of myocardial infarction: the ventricle dilates and the papillary muscles become displaced and, thus, ischemic mitral regurgitation (IMR) occurs [1-3].

It is known that IMR is not only the dysfunction of the valve but also the subvalvular structure, with the latter comprising the left ventricle (LV) free wall, papillary muscles, and chorda tendinea [4]. This process is done through the annuloventricular continuity [5], which becomes of particular importance in patients with LV dysfunction and low preoperative ejection fraction.

Valve repair is favored over replacement in most cases of IMR. However when repair is not possible, valve replacement is performed. The earliest mitral valve replacement techniques destroyed the subvalvular structure and put the patient at risk of low cardiac output syndrome after operation [6]. Recommendations to preserve the subvalvular structure by keeping the native chordae or bioprostheses with a view to maintaining ventricular annular continuity had promising results [7] and lowered the incidence of low cardiac output syndrome [5]. Be that as it may, some surgeons are still reluctant to opt for subvalvular sparing operations in that they are more complex and time consuming and there remains a risk of complications such as LV outlet obstruc-

tion with some of the chordae preservation techniques or prosthetic valve malfunction due to the interaction of the preserved chordate with prosthetic leaflet motion.

In our previous study, we introduced a new papillary repositioning technique for subvalvular sparing mitral valve replacement in a LV dysfunction population with degenerative or rheumatic valves [8]. In this study, we sought to evaluate the efficacy of this technique and its early and late outcomes with respect to the LV mechanics in patients with IMR and LV dysfunction undergoing mitral valve replacement during coronary artery bypass graft surgery (CABG).

Material and Methods

From May 2005 through January 2006, 50 patients with IMR and LV dysfunction were selected for mitral valve replacement and CABG at Day General Hospital in Tehran. The patients were randomly divided into a complete (anterior and posterior) chordal-sparing mitral valve replacement (CMVR) group (n = 25) and apapillary muscle repositioning (PMR) group (n = 25; TI Table 1).

The ejection fraction of all the selected patients was less than 40%, and all the valves were considered irreparable at the time of surgery by the surgeon. Patients requiring additional surgical procedures were excluded from the study. Patients were randomly assigned into two treatment groups using block randomization (using two or three blocks).

Informed consent was obtained from all the patients, and the protocol was approved by our Review Board.

Surgical Technique

All the surgical procedures were performed during moderate hypothermic (approximately 28°C) cardiopulmonary with cold hyperkalemic cardioplegia delivered both through antegrade and retrograde routes. At our center, when papillary muscle distance is more than 20 cm and coaptation depth is more 10 cm, annuloplasty is performed with another procedure such as papillary muscle approximation or second order chordae cutting; but if the patient is evaluated and considered as not being able to tolerate the increased operative time, then the surgeon decides to proceed with replacing the valve. In this center, the patients with effective regurgitant orifice area more than 20 mm2 and right ventricle more than 30 mL are selected for mitral valve replacement. It is also important to emphasize that in this center, the decision on the type of repair or replacement is made by the group, the echocardiographist, the cardiologist, and the surgeon, and the surgeon is not the sole decision maker. The CMVR group patients had their entire subvalvular apparatus preserved, as indicated in our previous study

Fl (Fig 1) [8]. In the PMR group patients, all the chordal structures were excised, and the leaflets were resected from the base at a distance of 2 mm from the annulus. The heads of both papillary muscles were subsequently sutured with a 2-0 Ethibond suture (Ethicon, Somerville, NJ) to the posterior side of the corresponding annulus, leaving no space between the heads of the papillary

F2 muscles and the annulus (Fig 2). The choice of a smaller distance in this series of ischemic patients by comparison with those in our previous study was prompted by the fact that the former predominantly had posterior LV dilation and increased papillary muscle distance. If the papillary muscle had fibrous tissue, 2-0 Ethibond suture on a double-armed needle was sewn to the fibrous tip. If there was no fibrous tissue, the suture was buttressed with a small soft felt pledget or pericardium and was tied snugly. Both needles of each suture were then passed through the annulus of the mitral valve at about 5 o'clock and 7 o'clock. The valve was finally implanted on the annulus, so that the heads of the papillary muscles were directly underneath the ring of the prosthetic valve.

A St. Jude mechanical prosthesis (St. Jude Medical, St. Paul, MN) or On-X mechanical prosthesis (Medical Research Institute, Austin, TX) were used in all the patients (31 mm, 38 patients; 29 mm, 24 patients; and 27 mm, 12 patients)

Table 1. Baseline Patient Characteristics

Variable	CMVR	PMR	p Valu
Age, mean ± SD	58.3 ± 7.13	53.8 ± 7.58	0.036
Male, %	60	80	0.123
Sinus rhythm, %	76	72	0.747
Diabetes mellitus, %	24	24	1.000
Hypertension, %	52	48	0.777
COPD, %	12	16	1.000

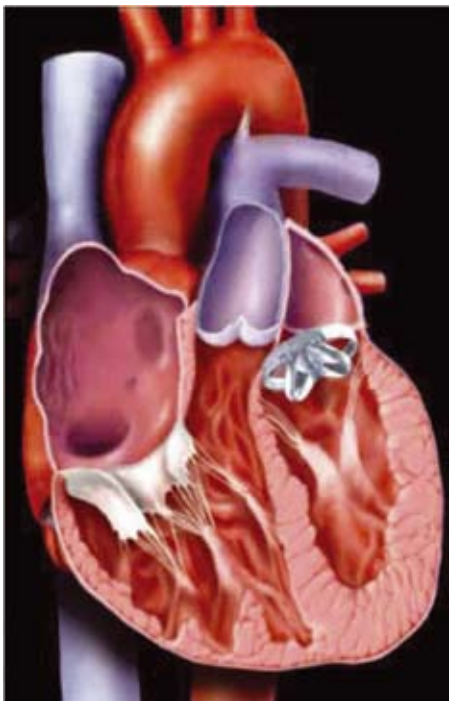

Fig 1. In the complete chordal preservation group, the subvalvular apparatus was retained in its anatomical position.

without significant differences between the two groups. In addition, all the patients received full revascularization.

Postpump transesophageal echocardiography was performed in all the patients. One patient in the CMVR group exhibited prosthetic valve malfunction due to the interference of prosthetic leaflet with the preserved chordae; the patient had to undergo a second pump for the valve to be removed and reimplanted. In all the other patients, postpump transesophageal echocardiography demonstrated no LV outflow tract obstruction or other prosthesis-related complications. In addition, the leaflets of all the prostheses were completely mobile without any limitation.

Echocardiographic Studies

All the patients underwent transthoracic echocardiography in addition to two-dimensional, M-mode, and color-flow Doppler echocardiographic studies with standard F3 acoustic windows preoperatively (Fig 3) and postopera-F4 tively (Fig 4), at hospital discharge and 3 years afterward, with GE Medical System, Vivid 7 (GE, Horton, Norway). Upon the completion of the study, all the results were interpreted by two experienced cardiologists in a blind fashion. The mean values for each measurement were derived from three consecutive heart beats in the patients in sinus rhythm and from five beats in patients in atrial fibrillation. The follow-up of all the patients was complete.

Simpson's rule method was used to measure the ejection fraction based on relative LV end-systolic volume and end-diastolic volume.

The LV sphericity index was calculated as the ratio of the LV internal diameter in the short axis compared with the LV length, measured as the distance from the mitral annulus to the apical endocardium in the LV long-axis view.

The echocardiographic data were determined according to the criteria of the American Society of Echocardiography.

Statistical Analysis

The numerical values were expressed as mean and standard deviation. The data were compared between the two groups using the unpaired t test for the continuous variables and \2 test for the categorical variables. Longitudinal changes in the parameters were compared between the two groups by repeated measurements.

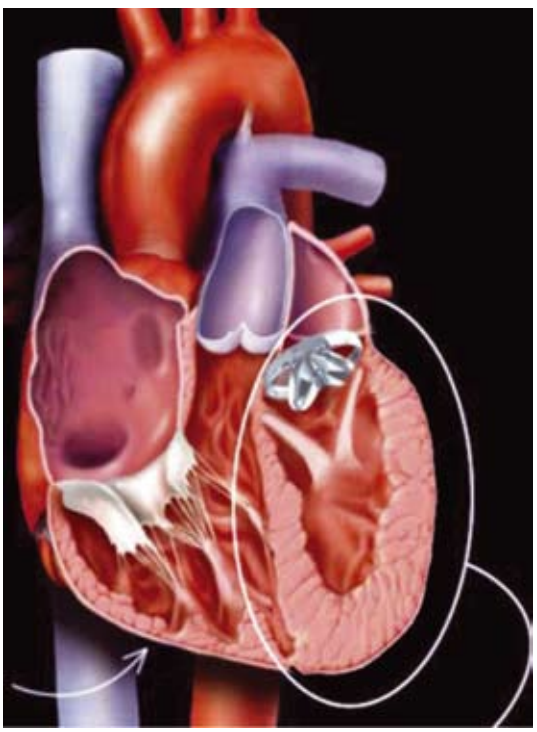

Fig 2. In the papillary muscle repositioning group, all the chordal structures were excised, and the heads of both papillary muscles were sutured to the corresponding annulus mitral valve at about 5 and 7 o'clock.

All the statistical analyses were performed using the SPSS Version 11.0 program (SPSS, Chicago, IL). A p value less

than 0.05 was considered statistically significant.

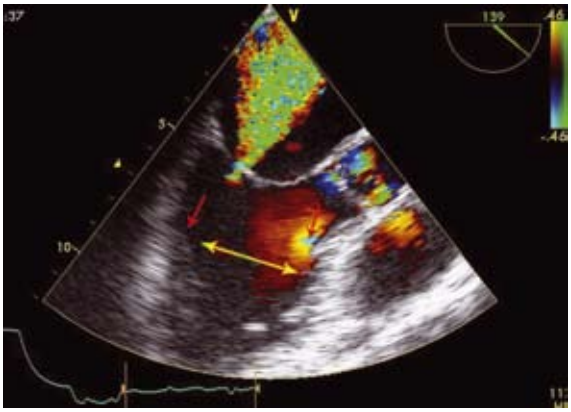

Fig 3. On transesophageal echocardiography, severe preoperative mitral regurgitation and increased papillary muscle distance is ob-served in the ventricle long-axis view. AQ: 1

Results

The number of male patients was higher in the PMR group (80%) than in the CMVR group (60%); this difference, however, was not statistically significant (p — 0.123). The mean age of the patients in the PMR group (53.8 ± 7.58 years) was not statistically significantly different (p = 0.036) from that of the patients in the CMVR group (58.3 ± 7.13 years). Other baseline patient characteristics, including ejection fraction, LV end-systolic and end-diastolic volumes, sphericity index, and preoperative New York Heart Association functional classification, were not sta-tistically significantly different between the two groups, nor was the statistical difference significant between the number of grafts received in the PMR group (3.54 ± 0.83) and that received in the CMVR group (3.54 ± 0.83; p > 0.05).

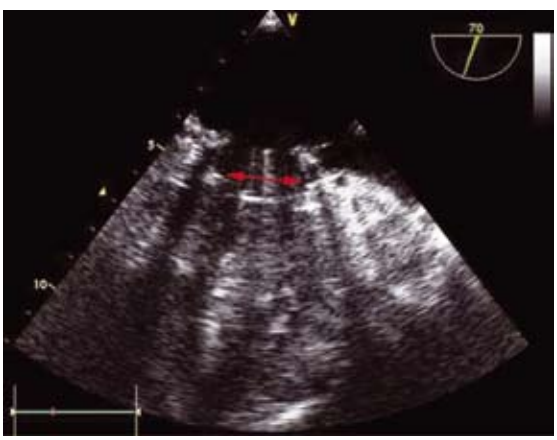

Fig 4. On transesophageal echocardiography, the left ventricle long-axis view, the retracted papillary muscle head below the prosthetic valve is observed. The transverse axis between the papillary muscles is reduced.

One patient in the CMVR group died in the operating room owing to postoperative pump failure, and another patient in the PMR group died on the fifth postoperative day as a result of respiratory failure. Moreover, 3 patients in the CMVR group and 1 in the PMR group died at follow-up in consequence of ischemic events or heart failure; these patients were not included in further analysis. No bleeding and thrombosis/embolic complications were detected in the follow-up period.

Whereas the CMVR group had a mean cross-clamp time of 33 ± 12 minutes, the PMR group scored a time of 31 ± 13 minutes, which was not longer than that in conventional mitral valve replacement operations. The cardiopulmonary bypass time was 45 ± 11 minutes in the CMVR group versus 42 ± 14 minutes in the PMR group.

With regard to the LV end-systolic and LV end-diastolic volumes, sphericity index, and ejection fraction, the PMR group showed better results (p < 0.05), but the difference in New York Heart Association class after 3 years was not statistically significant between the two T2 groups (p > 0.05; Table 2).

In the PMR group, the ejection fraction exhibited a considerable increase from the baseline (34% ± 4.79%) after surgery as demonstrated on transthoracic echocar-diography before discharge (43.13% ± 4.62%); ejection fraction continued its increase and reached 45.83% ± 1.90% at the third year of follow-up. In the CMVR group, the increase in ejection fraction from baseline (34% ± 4.79%) was not significant, and it reached 35.42% ± 4.4% before discharge and 35.83% ± 4.34% after 3 years.

Left ventricular end-diastolic volume showed a significant decline postoperatively, and this trend continued even after 3 years in both groups; the change in LV end-diastolic volume was more significant in the PMR group. Left ventricular end-systolic volume also demonstrated significant changes in the PMR group, showing a marked reduction in volume on postoperative transthoracic echocardiography, which was sustained even after 3 years. By contrast, changes in the LV end-systolic volume of the CMVR group were not significant.

The sphericity index also showed a significant decline postoperatively in the PMR group, which was sustained after 3 years; these changes were less significant in the CMVR group.

The New York Heart Association classification was better in the PMR group (1.33 ± 0.56) compared with the CMVR

group (2 ± 0.78) after 3 years, but this difference was not statistically significant (p = 0.108).

Comment

Although for most patients with IMR, the best option is mitral valve repair with ring annuloplasty, this technique does not address the ventricle etiology of IMR, and a number of these patients suffer recurrence [9]. Reports exist that mitral valve replacement in high-risk patients has yielded equal or even possibly better results compared with mitral valve repair [10, 11]. For patients suffering from acute or chronic IMR with multiple comor-bidities, complex regurgitant jets (central jet or more than one jet), or severe tethering of both mitral leaflets, mitral valve replacement can be a better option [10, 12, 13]. Therefore, replacement tends to be the viable option when the feasibility of repair is minimal.

The early methods of valve replacement resulted in the excision of the chorda tendinea structure [6] and the disruption of ventriculoannular continuity, which contributed to ventricular contraction and maintenance of ejection fraction [5,14]. Preserving the ventriculoannular continuity is thought to be more important in patients with low preoperative LV function because they have a potential risk of postoperative heart failure.

Previous reports have indicated that a low preoperative LV function and ejection fraction is associated with a poor surgical outcome after mitral valve surgery [15]. Over the years, several methods of subvalvular structure preservation have been introduced to avert the possible worsening of LV function, but most of them are much too complex and time consuming to be employed in high-risk patients. Moreover, consensus has yet to emerge about which method can achieve a more optimal result in the early and late postoperative periods.

Table 2. Patient Characteristics According to Operative Procedure Group

	Group	Baseline Mean (SD)		Before Discharge Mean (SD)		Third Year Follow-Up Mean (SD)		p Value
Ejection fraction	CMVR	32.60	5.42	35.42	4.40	35.83	4.34	0.000
	PMR	34.00	4.79	43.13	4.62	45.83	1.90	
LVEDV	CMVR	173.88	23.67	155.54	20.57	141.33	19.14	0.000
	PMR	167.08	30.19	126.21	21.95	108.96	16.14	
LVESV	CMVR	97.25	17.58	88.79	16.98	85.50	17.20	0.017
	PMR	104.46	18.33	75.17	14.19	59.54	10.87	
Sphericity index	CMVR	67.17	5.12	63.96	4.23	61.17	4.03	0.000
	PMR	64.38	4.63	54.29	2.91	49.75	2.05	
NYHA	CMVR	3.13	0.54			2.00	0.78	0.108
	PMR	3.38	0.65			1.33	0.56	

LVEDV = left ventricular end-diastolic volume; abbreviations as in Table 1.
LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; other

These techniques were first introduced by Lillehei and colleagues [16], who reported a significant reduction in mortality in the chordal preserving technique. Further modifications were made thereafter because the majority of the earliest methods involved the preservation of the bulk of both valves and were thus associated with LV outflow obstruction [17]. David and colleagues [18] resected a trapezoid section of the anterior leaflet, Sintek and associates [19] excised the major portion of the anterior leaflet, and Feikes and coworkers [20] reattached the chordae to the posterior annulus. The existing literature abounds with other more or less similar techniques introduced over recent years [5, 21, 14]. Replacement of the chordae with polytetrafluoroethylene expanded sutures from the papillary mus-

cles to the annulus has also been proposed to prevent the interference of the normal tissue with the implanted mitral valve [25]. It has been demonstrated that the preservation of all the chordae confers lower chamber volumes and better postoperative systolic functions compared with partial preservation [26], and that is the technique which we adopted in our CMVR group.

Chordal-sparing mitral valve replacement, albeit proven to yield better results, is still out of favor with many surgeons, on account of its technical complexity, prolonged cross-clamp time, potential interference with the mechanical valve leaflet motion, and the use of a smaller sized prosthetic valve. The insertion of a prosthetic mitral valve is often associated with redundant chorda tendinae, reduction in the LV size after surgery, and especially systolic anterior motion of the native anterior mitral leaflet, while the native intact valve may give rise to LV outflow tract obstruction [17, 26-29].

Seeking a straightforward and reproducible technique that would preserve the subvalvular apparatus and better restore the original ventricle geometry in patients with LV dysfunction, we excised both leaflets and all chorda tendi-nae structures and attached the papillary muscles to the annulus. Our technique resulted in a more elliptical ventri-cle, which is of particular importance in patients with functional mitral regurgitation who usually have a dilated and a more spherical ventricle. Ventricular modeling is known to persist even despite the surgical correction of IMR. Indeed, surgical techniques that limit ventricular dilation have been more effective in preventing LV remodeling and dilatation and worsening LV function when compared with the correction of IMR [30, 31].

In our previous study [8], we presented the papillary muscle repositioning technique and reported improvement in a group of patients with chronic degenerative or rheumatic mitral regurgitation and LV dysfunction. In this study, we utilized the same technique for patients with chronic IMR and LV dysfunction undergoing CABG and achieved good results, as attested to by improvement in the ejection fraction and reduction in the sphericity

index even after 3 years compared with the chorda tendinae preservation group. This improvement was achieved by preserving the subvalvular apparatus, reducing the volume load and the maintenance of better LV geometry.

We believe that our safe and straightforward technique of repositioning the papillary muscles in patients with IMR and LV dysfunction undergoing mitral valve replacement is capable of slowing the process of remodeling and maintaining a small and elliptical ventricle with a favorable ejection fraction for a relatively long period of time.

Uncited References

This section consists of references that are included in the reference list but are not cited in the article text. Please either cite each of these references in the text or, alternatively, delete it from the reference list. If you do not provide further instruction for this reference, we will retain it in its current form and publish it as an "uncited reference" with your article [22, 23, 24].

References

1. Otsuji Y, Handschumacher MD, Schwammenthal E, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation 1997;96:1999-2008.
2. Liel-Cohen N, Guerrero JL, Otsuji Y, et al. Design of a new surgical approach for ventricular remodeling to relieve isch-emic mitral regurgitation: insights from 3-dimensional echocardiography. Circulation 2000;101:2756-63.
3. Carabello BA. The current therapy for mitral regurgitation. J Am Coll Cardiol 2008;52:319-26.
4. Sarris GE, Cahill PD, Hansen DE, Derby GC, Miller DC. Restoration of left ventricular systolic performance after reattachment of the mitral chordae tendineae. The importance of valvular-ventricular interaction. J Thorac Cardio-vasc Surg 1988;95:969-79.
5. Athanasiou T, Chow A, Rao C, et al. Preservation of the mitral valve apparatus: evidence synthesis and critical reappraisal of surgical techniques. Eur J Cardiothorac Surg 2008;33:391-401.
6. Starr A, Edwards ML. Mitral replacement: clinical experience with a ball-valve prosthesis. Ann Surg 1961;154:726-40.
7. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. Circulation 1983;68:II76-82.
8. Yousefnia MA, Mandegar MH, Roshanali F, Alaeddini F, Amouzadeh F. Papillary muscle repositioning in mitral valve replacement in patients with left ventricular dysfunction. Ann Thorac Surg 2007;83:958-63.
9. Zhu F, Otsuji Y, Yotsumoto G, et al. Mechanism of persistent ischemic mitral regurgitation after annuloplasty: importance of augmented posterior mitral leaflet tethering. Circulation 2005;112(Suppl):I396-401.
10. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? J Thorac Cardiovasc Surg 2001;122:1125-41.
11. Magne J, Girerd N, Senechal M, et al. Mitral repair versus replacement for ischemic mitral regurgitation: comparison of short-term and long-term survival. Circulation 2009; 120(Suppl):104-ll.
12. Miller DC. Ischemic mitral regurgitation redux—to repair or to replace? J Thorac Cardiovasc Surg 2001;122:1059-62.
13. Calafiore AM, Di Mauro M, Gallina S, et al. Mitral valve surgery for chronic ischemic mitral regurgitation. Ann Thorac Surg 2004;77:1989-97.

14. Moon MR, DeAnda A, Daughters GT, Ingels NB, Miller DC. Experimental evaluation of different chordal preservation methods during mitral valve replacement. Ann Thorac Surg 1994;58:931-44.
15. Rothenburger M, Rukosujew A, Hammel D, et al. Mitral valve surgery in patients with poor left ventricular function. Thorac Cardiovasc Surg 2002;50:351-4.
16. Lillehei CW, Levy MJ, Bonnabeau RC. Mitral valve replacement with preservation of papillary muscles and chordae tendineae. J Thorac Cardiovasc Surg 1964;47:532-43.
17. Waggoner AD, Perez JE, Barzilai B, Rosenbloom M, Eaton MH, Cox JL. Left ventricular outflow obstruction resulting from insertion of mitral prostheses leaving the native leaflets intact: adverse clinical outcome in seven patients. Am Heart J 1991;122:483-8.
18. David TE. Mitral valve replacement with preservation of chordae tendinae: rationale and technical considerations. Ann Thorac Surg 1986;41:680-2.
19. Sintek CF, Pfeffer TA, Kochamba GS, Khonsari S. Mitral valve replacement: technique to preserve the subvalvular apparatus. Ann Thorac Surg 1995;59:1027-9.
20. Feikes HL, Daugharthy JB, Perry JE, Bell JH, Hieb RE, Johnson GH. Preservation of all chordae tendineae and papillary muscle during mitral valve replacement with a tilting disc valve. J Card Surg 1990;5:81-5.
21. Miki S, Ashraf M, Salka S, Sperelakis N. Myocardial dys function and ultrastructural alterations mediated by oxygen metabolites. J Mol Cell Cardiol 1988;20:1009-24.
22. 22. Rose EA, Oz MC. Preservation of anterior leaflet chordae tendineae during mitral valve replacement. Ann Thorac Surg 1994;57:768-9.
23. Vander Salm TJ, Pape LA, Mauser JF. Mitral valve replacement with complete retention of native leaflets. Ann Thorac Surg 1995;59:52-5.
24. Sasaki H, Ihashi K. Chordal-sparing mitral valve replacement: pitfalls and techniques to prevent complications. Eur J Cardiothorac Surg 2003;24:650-2.
25. Soga Y, Nishimura K, Ikeda T, et al. Chordal-sparing mitral valve replacement using artificial chordae tendineae for rheumatic mitral stenosis: experience of the "oblique" method. Artif Organs 2002;26:802-5.
26. Yun KL, Sintek CF, Miller DC, et al. Randomized trial comparing partial versus complete chordal-sparing mitral valve replacement: effects on left ventricular volume and function. J Thorac Cardiovasc Surg 2002;123:707-14.
27. Hennein HA, Swain JA, Mclntosh CL, Bonow RO, Stone CD, Clark RE. Comparative assessment of chordal preservation versus chordal resection during mitral valve replacement. J Thorac Cardiovasc Surg 1990;99:828-37.
28. Lillehei CW. New ideas and their acceptance. As it has related to preservation of chordae tendinea and certain other discoveries. J Heart Valve Dis 1995;4 (Suppl 2):106-14.
29. Le Tourneau T, Grandmougin D, Foucher C, et al. Anterior chordal transection impairs not only regional left ventricular function but also regional right ventricular function in mitral regurgitation. Circulation 2001;104 (Suppl l): I41-6.
30. Guy TS, Moainie SL, Gorman JH, et al. Prevention of ischemic mitral regurgitation does not influence the out come of remodeling after posterolateral myocardial infarc tion. J Am Coll Cardiol 2004;43: 377-83.
31. Enomoto Y, Gorman JH, Moainie SL, et al. Surgical treat ment of ischemic mitral regurgitation might not influence ventricular remodeling. J Thorac Cardiovasc Surg 2005;129: 504-11.

Stem Cell Transplantation and Cardiac Repair: A Review of Its Current and Future Status

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Abstract

After myocardial infarction, injured cardiomyocytes are replaced by fibrotic tissue promoting the development of heart failure. Stem cells are multipotent, undifferentiated cells capable of multiplication and differentiation. Preliminary experimental evidence suggests that stem cells derived from embryonic or adult tissues (especially bone marrow) may develop into myocardial cells. The overall clinical experience also suggests that stem cell therapy can be safely performed, if the right cell type is used in the right clinical setting. Preliminary efficacy data indicate that stem cells have the potential to enhance myocardial perfusion and/or contractile performance in patients with acute myocardial infarction, advanced coronary artery disease, and chronic heart failure. However, at the present time, the results have been mixed and inconclusive, and the mechanism of stem cell transplantation therapy remains unclear. This review discusses the controversies and problems that need to be addressed in future investigations.

Introduction

Coronary artery occlusion leads to ischemia and cell death in the heart (1). Cardiomyocyte death results in scar formation and reduced contractility of the ventricle. Although the traditional concept that the adult cardiomyocyte is erminally differentiated has been challenged by evidence that some myocytes are mitotic in adult hearts (2, 3), the ratio of myocytes undergoing proliferation is only 0.015-0.08% (3,4). The number of resident cardiac muscle stem cells within the heart is also too small to significantly repair the damage after myocardial infarction (5). The rreversible loss of muscle after acute myocardial infarction followed by fibrosis of myocardial scar, infarct xpansion, concentric hypertrophy, and left ventricular dilatation ultimately leads to progressive heart failure (6). While the uality of life after acute myocardial infarction has been improved due to the enormous progress in the cardiovascular therapeutics (7), the root cause of heart failure, which is characterized by cardiomyocyte death and ventricular emodeling, remains a major contributor to cardiac morbidity and mortality. Cellular cardiomyoplasty provides a potential approach to the treatment of heart failure after myocardial infarction. The basic concept of cellular cardiomyoplasty is to increase the number of functional cardiomyocytes by cell transplantation. Many types of cells, such as cardiomyocytes, skeletal myoblasts and stem cells, have been used in the attempt to regenerate myocardium and treatment of heart failure (8). In this review, we focus on the use of stem cell transplantation for cardiac repair.

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Definition

Stem cells are a group of undifferentiated cells that have the capacity to self-renew, as well as the ability to generate differentiated cells. There are somatic stem cells and embryonic stem cells. Somatic stem cells are derived from adult somatic tissue, such as bone marrow, adipose tissue, peripheral blood, umbilical cord blood, and skeletal muscle. Embryonic stem cells are isolated from the embryo at the blastocyst stage and can form all fully differentiated cells of the body, including true cardiomyocytes. Embryonic stem cells have the greatest potential for cardiac regeneration. Every type of stem cell has advantages and disadvantages for cardiac regeneration. Embryonic stem cells are more versatile than somatic stem cells for cardiac regeneration. Although somatic stem cells may be autologous and no immunological or ethical constraints exist, their potential to differentiate is more restricted than embryonic stem cells. Determining which is the most appropriate stem cell for cardiac regeneration and revascularization remains a crucial unanswered question.

Ventricular remodeling and stem cell therapy

The concept of ventricular remodeling was focused in 1985, from fundamental work that has come to have immense clinical application. Janice Pfeffer et al. (9) studied the causes and patterns of increased leftventricular dilation and impaired ventricular function after coronary artery ligation in rats (10). They referred to such changes in the ventricular architecture as remodeling. Post-infarct remodeling was further defined in 1990 as the changes in ventricular topography, occurring both acutely and hronically after infarction and identified as an important therapeutic target. (11) Since then, the concept has been applied to various ventricular patterns occurring in response to the mechanical stresses of other heart diseases. Innovative animal experiments have shown that progenitor cells from various sources can populate acutely damaged regions of the myocardium, refurbishing functional units and reversing remodeling (12). Whether bone-marrow-derived stem cells can acquire sufficient cardiomyocyte-like properties to reconstitute myocardium lost by infarction is uncertain. By contrast, both myocytes and coronary vessels can be regenerated from a cardiac stem-cell ompartment that can regenerate in vitro. (13,14) Injection of cardiac stem cells with bioengineered scaffolding and selective growth factors such as insulin-like growth factor could provide enough myocardial regeneration and mechanical support to rescue severely damaged hearts. Clinical evidence does not directly support this theory, but is proceeding briskly. Studies are under way in which skeletal myoblasts harvested from peripheral tissue and grown in culture are injected directly into scarred regions of the myocardium with improved ejection fraction. (15) Other ongoing approaches are using prompt extraction of autologous mesenchymal stem cells harvested from bone marrow, with intracoronary delivery to the necrotic region during the acute phase of myocardial infarction. In a well-designed study of 67 patients, this approach decreased myocardial infarct size and improved recovery of regional systolic function; long-term follow-up is still awaited. (14) The harsh scrutiny of clinical trials is needed, proceeding in tandem with basic science investigations.

Cell homing

Defining the events in progenitor cell homing may enable better targeting of cells, most obviously when cells are mobilized from the bone marrow into the bloodstream. Later steps in homing, though, are instrumental to the impact even of progenitor cells infused locally into coronary arteries. Homing is a multistep cascade including the initial adhesion to activated endothelium or exposed matrix, transmigration through the endothelium, and, finally, migration and invasion of the target tissue. The capacity to migrate and invade may be pivotal to functional integration even when cells are injected intramuscularly. Particularly in patients who lack the endogenous stimuli incited by acute ischemic injury, the enhancement of local homing signals or cells' ability to respond may be of critical importance.

Neoangiogenesis

To date, there is no direct clinical evidence that cellular cardiomyogenesis in fact occurs in the human heart after transplantation of progenitor cells. Angiogenesis, improvements in scar tissue, and cytoprotection must be considered, along with transdifferentiation, as among the most important possible consequences of cell-based therapies for cardiac repair Of these, most obviously, progenitor cells may improve neovascularization, which in turn would augment oxygen supply. Progenitor cells are expected to be of most benefit to cardiac regeneration or performance when used to treat jeopardized or hibernating cardiomyocytes. Neo-

vascularization, in turn, can be mediated by the physical incorporation of progenitor cells into new capillaries (17, 18) or, in some settings, perivascular cells (19). Incorporated progenitor cells of most if not all types may release growth factors that promote angiogenesis by acting on mature endothelial cells (20).

Embryonic stem cells

ES cells derived from the inner cell mass of blastocysts are considered to have virtually unlimited self-renewal and developmental potential. These claims are based on multiple in vitro cell doublings and generation of cell types for nearly every lineage. However, injection of ES cells into the myocardium of animal models results in formation of teratomas (21). Thus ES cells are routinely placed in culture to induce early stage cardiomyogenesis. The ifferentiation of mouse (22) and human (23) ES cells into immature cardiomyocytes is achieved when aggregates of ES cells are plated in media lacking supplemental leukemia inhibitory factor but containing a number of additives such as growth factors (22, 24). Within 7-10 days the immature cardiomyocytes display spontaneous rhythmic contractions and generate cardiac-specific proteins, including myosin light chain, a-tropomyosin and several transcription factors, typically expressed in early cardiomyocyte development (22, 25). Importantly, the in vitro generation of cardiomyocytes from ES cells has

Table 1. Differentiation of bon marrow stem cells into cardiomyocytes

Type of induction	Key references on cardiomyocyte differentiation experiments	BMC
In vitro	Spontaneous	
	Stimulation with 5-azacytidine/oxy- tcin	
	Co- culturing	
In vivo	Direct injection	Ishida et al.
	of undifferentiated cells into myocardial injury	Nygren et al.
	Direct injection of stimulated cells into myocardial injury	Tomita et al.
		Bittner et al.
		Orlic et al.
	Integration of circulating cells	Agbulut et al.
		Tomita et al.
		Balsam et al.
Clinical		Perin et al.
	Direct injection into myocardial injury	Assmus et al.
		Wollert et al.
		Kang et al.
	Integration of circulating cells	Quaini et al.
		Laflamme et al.

provided a valuable basis for in vivo experiments testing efficacy in repair of injured myocardium (26). Human ES cell-derived cardiomyocytes were injected into the wall of the left ventricle of a swine model of atrioventricular block resulting from ablation of the His bundle responsible for the major electrical conduction pathway linking atria with ventricles. At 1-3 weeks posttransplant, the hES cell-derived cardiomyocytes were integrated into the myocardial tissue, where they demonstrated an lectromechanical property and paced the ventricles. To prevent an immune reaction the animals were placed on a daily regimen of methylprednisolone. If we are to realize the full restorative potential of ES cell-derived cardiomyocytes and move these experiments forward, it will be necessary to overcome the obstacles of istocompatability and long-term survival.

Somatic stem cells

Bone marrow

The cardiomyogenic properties of bone marrow derived cells in vivo were observed for the first time by Bittner et al. After sex-mismatched bone marrow transplantation in female dystrophic mdx mice suffering from cardiac muscle degeneration, Y-chromosome containing cardiomyocytes had integrated into the myocardium. This indicated that irculating bone marrow-derived cells can be recruited to the injured heart and differentiate into cardiomyocytes (27). To further understand the capacity of bone marrow cells to differentiate into cardiomyocytes and repair the injured myocardium, stem cells were instantly delivered to the demanding area by injecting cells directly into the ocardium or coronary arteries. Few animal studies have been performed to investigate the possibilities of injecting crude bone marrow into the myocardium (Table 1). In most cases, the bone marrow mononuclear cell fraction, harboring most of the stem and progenitor cells, was cultured in vitro before injection. This will inevitably lead to the selection of either HSCs or MSCs. The population of cells with cardiomyogenic properties likely represents only a small fraction of total bone marrow.

Table 2. Differentiation of Hematopoietic stem cells (HSCs) into cardiomyocytes

Type of induction	Key references on cardiomyocyte differentiation experiments	HSC
In vitro	Spontaneous	
	Stimulation with 5-azacytidine/oxy- tcin	
	Co- culturing	Hierlihy et al.
In vivo		Nygren et al.
	Direct injection	Orlic et al.
	of undifferentiated cells into myocardial injury	Balsam et al.
		Murry et al.
	Direct injection of stimulated cells into myocardial injury	
		Jackson et al.
	Integration of circulating cells	Nygren et al.
		Kawada et al.
Clinical	Direct injection into myocardial injury	
	Integration of circulating cells	

a. Hematopoietic stem cells

Bone marrow-derived HSCs have been investigated for their differentiation potential in vivo (Table 2). The first indication that HSCs may participate in cardiac regeneration came from Jackson et al. They isolated a specific HSC population called the side population, and transplanted these cells into lethally irradiated mice. Subsequently, the transplanted mice were used in a myocardial ischemia-

reperfusion model, and hearts were analyzed after 2 and 4 weeks. Although their prevalence was not very high, donor-derived cardiomyocytes were found, primarily in the peri-infarct zone, demonstrating the cardiomyogenic ability of circulating HSCs (28). Direct injection of HSCs into the infarcted myocardium has also been investigated by Orlic et al. After ligating the coronary artery, a population of was injected into the contracting wall bordering the infarcted area. After 9 days, 40% of the mice showed regeneration of the cardiac muscle.

Approximately 68% of the infarcted area was occupied by newly formed myocardium. Donor cells were shown not only to differentiate into cardiomyocytes but also to form endothelial cells and fibroblasts. Evidence for the restoration of the myocardium was further supported by a prolonged survival of the mice and a recovery of cardiac function (29). Although these studies demonstrate that different populations of HSCs appear to have a very high capacity both in homing to and regeneration of the damaged myocardium, some groups argue otherwise. It should be noted that Balsam et al. found a small but significant increase in cardiac function 6 weeks after MI (30). Therefore, it remains unclear what the potential morphological and physiological contribution of HSCs to the regeneration of the myocardium is.

b. Mesenchymal stem cells

MSCs have been studied extensively for their in vivo cardiomyogenic potential, especially since they have the capacity to differentiate into cardiomyocytes in vitro (Table 3). Wang and colleagues show that murine MSCs participate in the formation of new cardiomyocytes in the normal, uninjured heart. Starting 4 weeks after the injection of in vitro-expanded, labeled MSCs into the healthy heart, donor cells expressing cardiac markers were detected (31).

The same in vivo potential has been demonstrated for human MSCs, which were injected into the heart of mice. Although the human MSCs were only present in a small percentage (0.44%), the engrafted cells did express cardiac markers (32). In addition to the use of healthy animals, MSCs have also been injected into the myocardium of experimental models for cardiac damage. Autologous MSCs were injected into the left ventricle (LV) of rats 3 weeks after myocardial cryoinjury. Transplanted MSCs were identified in all animals 8 weeks after injury. Immunohistochemistry revealed muscle cells expressing troponin I and myosin heavy chain. Moreover, injections of MSCs lead to a decreased scar area and a thicker LV free wall. The animals injected with pre-treated cells also had a decreased LV chamber size/body weight and improved cardiac function compared to controls (32).

Table 3. Differentiation of mesenchymal stem cells (MSCs) into cardiomyocytes

Type of induction	Key references on cardiomyocyte differentiation experiments	MSC
In vitro	Spontaneous	
		Makino et al.
	Stimulation with 5-azacytidine/oxy- tcin	Hakuno et al.
		Rangappa et al.
		Xu et al.
		Liu et al.
In vivo	Co- culturing	Fukuhara et al.
		Wang et al.
	Direct injection	Toma et al.
	of undifferentiated cells into myocardial injury	Mangi et al.
Clinical	Direct injection of stimulated cells into myocardial injury	
	Integration of circulating cells	Kawada et al.
	Clinical Direct injection into myocardial injury	
	Integration of circulating cells	

c. CD133+ Cells

The cell surface antigen CD133+ is expressed on early HSCs, which collaborate to promote vascularization of chemic tissues (34). CD133+ cells can integrate into sites of neovascularization and differentiate into mature endothelial cells. Less than 1% of nucleated BMCs are CD133+, and because these cells cannot be expanded ex-vivo, only limited numbers of CD133+ cells can be obtained for therapeutic purposes.

Table 4. Cell therapy trials in patients with acute myocardial infarction

Cell				Outcomes Time After			
Study	(n)	Type	Dose	Delivery	AMI	Improved	No Change
Strauer et al	10 treated, 10 controls*	MNC	$2.8 \pm 2.2 \times 10^7$	IC	5-9 days	Regional wall motion; Infarct size ; Perfusion	Global LVEF; LVEDV
TOPCARE- AMI	29 MNC, 30 CPC,	MNC	$2.1 \pm 0.8 \times 10^8$	IC	5 ± 2 days	Regional wall motion ; Global LVEF;	LVEDV
	11 controls*	CPC	$1.6 \pm 1.2 \times 10^7$			Infarct size ↓ ; Coronary flow	
Fernandez-Aviles et al	20 Treated, 13 controls*	MNC	$7.8 \pm 4.1 \times 10^7$	IC	14 ± 6 days	Regional wall motion ; Globl LVEF	LVEDV
Kuethe et al	5 treated	MNC	$3.9 \pm 2.3 \times 10^7$	IC	6 days		Regional wall motion ; Global LVEF
BOOST	30 treated, 30 controls	NC	$2.5 \pm 0.9 \times 10^9$	IC	6 ± 1 day	Regional wall motion: Global LVEF	LVEDV; infarct size
Chen et al , 35 controls	34 treated	MNC	$4.8 \pm 6.0 \times 10^{10}$	IC	18 days	Regional wall motion: Global LVEF; Infarct size ↓; LVEDV ↓	
Venderheyden et al	12 treated, 10 controls*	$CD133^+$	$6.6 \pm 1.4 \times 10^6$	IC	14 ± 6 days	Regional wall motion; Global LVEF; Perfusion†	

MNC = mononuclear cells; CPC= circulating blood-derived progenitor cells; NC= nucleated cells; MSC= mesenchymal stem cells; IC= intracoronary; AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume

Routes of application

Transvascular Approaches

Transvascular strategies are especially suited for the treatment of recently infarcted and reperfused myocardium when chemoattractants and cell adhesion molecules are highly expressed. (35, 36). Intracoronary Artery Infusion Selective intracoronary application delivers a maximum concentration of cells homogeneously to the site of injury uring first passage. Unselected BMCs, circulating blood-derived progenitors cells, and MSCs have been delivered via the intracoronary route in patients with AMI and ischemic cardiomyopathy (Tables 4 and 5). In these studies, cells were delivered through the central lumen of an over-thewire balloon catheter during transient balloon inflations to maximize the contact time of the cells with the microcirculation of the infarct-related artery. It is unknown hether this stop flow technique is required to enhance cell retention within the infarcted area. In the hands of an xperienced operator, intracoronary delivery is relatively easy to perform within less than an hour.

Intravenous Infusion

In experimental models, intravenous delivery of HSCs or MSCs has been shown to improve cardiac function after AMI (37, 38). However, homing of cells to noncardiac organs limits the clinical applicability of this approach. (39). Indeed, in a recent study in post- AMI patients, significant myocardial homing of unselected BMCs was observed only after intracoronary stop-flow delivery but not after intravenous application (40).

Mobilization of Stem and Progenitor Cells

Considering that the acutely infarcted myocardium recruits circulating stem and progenitor cells to the site of injury, tem and progenitor cell mobilization by cytokines may offer a noninvasive strategy for cardiac regeneration (38, 41, 42). This concept has been tested in animal models and in pilot studies in patients with AMI and chronic myocardial ischemia (43, 44).

Direct Injection in the Ventricular Wall

Direct injection is the preferred route for cell delivery in patients presenting late in the disease process when an occluded coronary artery precludes transvascular cell delivery (patients with chronic myocardial ischemia) or when cell homing signals are expressed at low levels in the heart (scar tissue).

Table 5. Cell therapy trials in patients with ischemic cardiomyopathy

					Time After		
Study	(n)	LVEF	Cell Type	Dose	MI	Delivery	Outcomes†
Menasche et al	10 treated	24 ± 4%	Myoblasts	$8.7 \pm 1.9 \times 10^8$	3-228 Months	Transepicardial (during CABG)	Regional wall motion ↑; Global LVEF ↑
Herreros et al	11 treated	36± 8%	Myoblasts	$1.9 \pm 1.2 \times 10^8$	3-168 Months	Transepicardial (during CABG)	Regional wall motion ↑; Global LVEF ↑; viability in infarct area ↑
Siminiak et al	10 treated	25± 40%	Myoblasts	$0.04 \pm 5.0 \times 10^7$	4-108 Months	Transepicardial (during CABG)	Regional wall motion ↑; Global LVEF ↑
Chachques et al	20 treated	28± 3%	Myoblasts	$3.0 \pm 0.2 \times 10^8$	Not reported	Transepicardial (during CABG)	Regional wall motion ↑; Global LVEF ↑; viability in infarct area ↑
Smits et al	5 treated	36± 11%	Myoblasts	$2.0 \pm 1.1 \times 10^8$	24-132 Months	Transepicardial (guided by EMM)	Regional wall motion ↑; Global LVEF ↑
Stamm et al	12 treated	36± 11%	CD 133+	$1.0 \pm 2.8 \times 10^6$	3-12 weeks	Transepicardial (during CABG)	Global LVEF ↑; LVEDV↓; Perfusion ↑
Assmus et al	51 MNC, 35 CPC, 16 Controls	40± 11%	MNC	$1.7 \pm 0.8 \times 10^8$	3-144 Months	IC	Global LVEF ↑; (only in MNC group)
			CPC	$2.3 \pm 1.2 \times 10^7$			

LVEF = left ventricular ejection fraction; MNC = mononuclear cells; CPC = circulating blood-derived progenitor cells; MI = myocardial infarction;CABG = coronary artery bypass grafting; EMM = electromechanical mapping; IC = intracoronary; LVEDV = left ventricular end-diastolic volume.

Table 6. cell therapy trials in patients with myocardial ischemia and no revascularization option

Outcomes							
Study	(n)	LVEF	Cell Type	Dose	Delivery	Subjective	Objective
Hamano et al	5 treated		MNC	$0.3 – 2.2 \times 10^9$	Transepicardial (during CABG)		Perfusion ↑
Tse et al	8 treated	58 ± 11%	MNC	From 40 ml BM	Transepicardial (guided by EMM)	Angina ↓	Perfusion ↑ ; Regiional wall motion ↑;
Fuchs et al	10 treated	47± 10%	NC	$7.8 \pm 6.6 \times 10^7$	Transepicardial (guided by EMM)	Angina ↓	Perfusion ↑
Perin et al	14 treated 7 Controls	30 ± 6%	MNC	$3.0 \pm 0.4 \times 10^7$	Transepicardial (guided by EMM)	Angina ↓: NYHA ↓	Perfusion ↑ ; Regiional wall motion; Global LVEF ↑

LVEF = left ventricular ejection fraction; MNC = mononuclear cells; CPC = circulating blood-derived progenitor cells; MI = myocardial infarction;CABG = coronary artery bypass grafting; EMM = electromechanical mapping; IC = intracoronary; LVEDV = left ventricular end-diastolic volume.

However, direct injection of cells into ischemic or scarred myocardium creates islands of cells with limited blood supply and may lead to poor cell survival (45). Direct injection techniques are especially suited for the application of large cells, such as MSCs or myoblasts, which may cause microembolization after intracoronary delivery. Direct njection techniques have been used in patients with advanced coronary artery disease (Table 6) and in patients with ischemic cardiomyopathy (Table 5). Cell delivery by direct injection may be technically challenging in patients with AMI, particularly if cells are to be injected into the border zone of the infarct. The safety of such an approach emains to be established because perforation of the friable necrotic tissue remains a matter of concern.

Transendocardial Injection

Using an injection needle catheter advanced across the aortic valve and positioned against the endocardial surface, cells can be directly injected into the left ventricular (LV) wall (46,47) Electromechanical mapping of the ndocardial surface can be used to delineate viable, ischemic, and scarred myocardium before cell injections (46,48).

Transepicardial Injection

Transepicardial cell injection has been performed as an adjunct to coronary artery bypass grafting (CABG). Transepicardial cell injection during open heart surgery allows for a direct visualization of the myocardium and a targeted application of cells to scarred areas and/or the border zone of an infarct scar. The invasiveness of this approach hampers its use as a stand-alone therapy. Conversely, the efficiency of cell transplantation may be difficult to evaluate and ascertain if CABG is performed simultaneously.

Transcoronary Vein Injection

A catheter system incorporating an ultrasound tip for guidance and an extendable needle for myocardial access has been used to deliver BMCs through the coronary veins into normal pig myocardium.68 The same approach has been used in a pilot trial in patients with ischemic cardiomyopathy to deliver myoblasts to areas of nonviable myocardium (50) In contrast to the transendocardial approach, where cells are injected perpendicular to the ventricular wall, the composite catheter system delivers cells parallel to the ventricular wall and deep into the injured myocardium. However, positioning of the injection catheter in a specific coronary vein is not trivial in all cases (50).

Clinical Applications of Stem Cell Therapy

Acute Myocardial Infarction

Modern reperfusion strategies and advances in pharmacological management have resulted in an increasing zroportion of AMI survivors at heightened risk of developing adverse LV remodeling and heart failure. None of our urrent therapies addresses the underlying cause of the remodeling process, ie, the damage of cardiomyocytes and the vasculature in the infarcted area. Inspired by the exciting experimental data, several trials were initiated to test whether cell therapy is safe and feasible in patients after AMI. Some have decried the clinical trials as being premature without a more complete understanding of the underlying mechanisms, (51) whereas others have pointed out that the clinical trials are justified by the potential benefits of cell therapy (52) All clinical studies included patients with AMI who had undergone primary angioplasty and stent implantation to reopen the infarctrelated artery, and cells were infused intracoronarily by using the stop-flow balloon catheter approach. In this regard, the clinical studies differ significantly from the animal studies, where the infarct related artery was not reperfused and cells were directly injected into the myocardium (38, 53, 54). The clinical trials may be categorized into studies using unselected BMCs or selected cell populations (Table 4).

Myocardial ischemia with no revascularization option

Despite significant advances in coronary revascularization techniques, some patients with coronary artery disease and myocardial ischemia have no revascularization option because of the diffuse nature of their disease. A number of these patients experience anginal symptoms despite maximal medical therapy. Chronic myocardial ischemia can be associated with a regional impairment of contractile function, which is partially reversible when tissue perfusion is restored (hibernating myocardium). Moreover, ischemia increases the risk of arrhythmias and sudden cardiac death. There is a clear need for new therapeutic strategies aimed at delivering oxygenated blood to the myocardium in these patients. Unselected mononuclear BMCs have been used in several small studies in patients with coronary artery disease not amenable to conventional revascularization techniques (55, 56). A recent study investigated the effects of G-CSF on symptoms and myocardial perfusion in patients with intractable angina (57). Treatment with G-CSF promoted a strong increase in circulating progenitor cells numbers and an improvement in anginal symptoms. However, there was no objective evidence of enhanced myocardial perfusion or improved regional wall motion.

Ischemic Cardiomyopathy, Chronic Heart Failure

Chronic heart failure has emerged as a major worldwide epidemic. Recently, a fundamental shift in the underlying etiology of heart failure is becoming evident, in which the most common cause of heart failure is no longer hypertension or valvular disease, but rather long-term survival after AMI. Conceptually, replacement of akinetic scar tissue by viable myocardium should improve cardiac function and impede progressive LV remodeling. In a recent trial, 86 patients with ischemic cardiomyopathy received intracoronary infusions of unselected mononuclear BMCs or of circulating bloodderived progenitor cells by the stop-flow balloon catheter technique. The procedure was safe (58). After 3 months, LVEF in the BMC group was improved by three percentage points, but did not change significantly in control patients and in the progenitor cell group (58). Double-blind trials are needed to rigorously evaluate the safety and efficacy of cell therapy in patients with ischemic heart failure. It is interesting to note that intracoronary infusions of mononuclear BMCs or bloodderived progenitor cells promoted greater improvements of LVEF in patients with AMI as compared with patients with ischemic cardiomyopathy (58). Because cell retention may be limited after intracoronary delivery into chronically infarcted myocardium, pharmacological or genetic approaches to enhance cell retention and engraftment should be explored. Considering that functional benefits of cell transplantation have also been observed in animals with dilated cardiomyopathy, (59) future trials may want to explore the role of cell therapy in patients with nonischemic heart failure. In this regard, a pilot study suggests that intracoronary BMC transfer may be safe and potentially effective in patients with Chagas cardiomyopathy (60).

Combination of stem cell and gene therapy

Recently, several studies have investigated the effects of genetically modified stem cells as a therapy for myocardial infarction. Studies have demonstrated that this combination of stem cell and gene therapy may be a useful approach. Genetic modification can increase the survival of transplanted stem cells in ischemic tissue (61). The survival rate of mesenchymal stem cells transduced with Aktl gene was

increased fourfold in the ischemic rat myocardium, 80-90% of lost myocardial volume was regenerated, and cardiac performance was nearly normalized. Enhancing the angiogenic potential of transplanted stem cells is another goal of genetic modification. Matsumoto et al. (62) transected the human VEGF 165 gene into cultured mesenchymal stem cells. The mesenchymal stem cells with VEGF 165 gene were injected into infracted myocardium. High expression of VEGF increased the capillary density of the infracted region and improved left ventricular function. Gene therapy can be used to mobilize and recruit stem cells into myocardial infarction.

Potential problems of stem cell therapy

Besides raising intense ethical concerns in some (63), the use of human embryonic stem cell transplantation to repair damaged tissues has many other potential scientific problems. The first problem is teratoma formation. There is a possibility of spontaneous differentiation of stem cells into undesired lineages beside the cardiomyogenic differentiation after transplantation into myocardium (64). The potential for accelerated atherogenesis or enhanced restenosis induced by stem cell transplantation remains a concern. In addition, ectopic calcification of tissue is a concem. Yoon et al. (65) injected intramyocardially unselected bone marrow cells into the ped-infarct area in a rat myocardial infarction model and found that direct transplantation of unselected BM cells into the acutely infarcted myocardium induced significant intramyocardial calcification. Skeletal myoblast transplantation may cause serious ventricular arrhythmias. Some factors, such as cardiac tissue injury induced by the intramyocardial injection, electrical heterogeneity of action potentials of differentiated stem cells, or increased nerve sprouting may be involved. Immunological rejection is a potential complication for the use of human embryonic stem cell-derived cardiomyocytes in human clinical therapy. Reprograming autologous adult stem cells to express cardiomyogenic function with human embryonic stem cell-delivered cardiomyocytes is a novel approach to resolve this problem (66). The reprograming technique involves fusion of enucleated cytoplasts generated fromhuman embryonic stem cell-delivered cardiomyocytes with autologous adult stem cells to generate cytoplasmic hybrids. The hybrids function as cardiomyocytes, but are not immunogenic. Washout of directly transplanted cells from the heart may also be a new technique for cell transplantation therapy.

Direction for future clinical research

So far, flurries of small, mostly uncontrolled clinical studies exploring the safety and feasibility of stem cell therapy have been conducted. These studies have used different cell types and preparations, each in a small number of patients with different disease states. In the aggregate, this preliminary clinical evidence suggests that stem cell therapy might work. Although these initial clinical studies have generated a great deal of hope, we should take into account the lessons learned from the translation of therapeutic angiogenesis into clinical studies, where great expectations raised by open studies have not been confirmed by subsequent randomized trials. We advocate to no longer performing studies involving small numbers of patients, but rather to conduct intermediate-size, double-blind, randomizedcontrolled clinical trials to establish the effects of stem cell therapy on surrogate markers, like LVEF, myocardial perfusion, or exercise capacity. Upcoming trials should also address procedural issues such as the optimal cell type, cell dosage, and timing of cell transfer. These trials may also look at combined morbidity and mortality end points, although they may be too small to be conclusive in this regard. Safety remains the key concern as we proceed. Although these studies are underway, fundamental questions need to be addressed experimentally. What is the fate of the injected cells after transplantation? How long do they survive? Do the cells incorporate, or is transient retention sufficient to promote functional effects? Genetic and transgenic markers should be used to determine the lineage commitment of engrafted cells. Cell labeling and imaging techniques need to be developed to track stem cell fate in patients and correlate cell retention and engraftment with functional outcomes. Pharmacological and genetic strategies may help to enhance stem cell retention, engraftment, differentiation, and paracrine capability (67-69). Support from governmental organizations or charities will be required to ensure that cell therapies, which may be efficacious but commercially less attractive (eg, unselected BMCs), will undergo much-needed further clinical testing. In conclusion, although some of the current scientific data support the concept that the stem cells can be used for the myocardial regeneration, there are still many question to be cleared before this promising approach can be performed effectively, safely and routinely in

human subjects. Questions such as how to induce the transplanted stem cells to differentiate only into cardiomyocytes, and not other cells or teratomas; which type of stem cell and which model of delivery are the most efficacious; whether stem cells in the heart truly undergo functional and electrical integration; and whether this approach may have proarrhythmic consequences remain to be
answered before eventually making this stem cell therapy a clinical reality.

References

1. Connelly C, Vogel WM, Hernandez YM, Apstein CS. Movement of necrotic wavefront after coronary artery occlusion in rabbit. Am J Physiol Heart Circ Physiol. 1982; 243(5): 682-H90.
2. Kajstura J, Leri A, Finato N, Di Loreto C, Beltrami CA, Anversa P. Myocyte proliferation in end-stage cardiac failure in humans. Proc Natl Acad Sci U S A. l998; 95(15): 8801-5.
3. Quaini F, Urbanek K, Beltrami AP, Finato N, Belterami CA,Ginard BD, Kajstura J, Leri A, Anversa P. Chimerism of the transplanted heart. N Engl J Med. 2002; 346(l): 5-15.
4. Beltrami AP, Urbanek K, Kajstura J, et al. Evidence that human cardiac myocytes divide after myocardial infarction.N Engl J Med. 2001; 344(23): 1750-7.
5. Anversa P, Leri A, Kajstura J, Nadal-Ginard B. Myocyte growth and cardiac repair. J Mol Cell Cardiol. 2002; 34(2):91-105.
6. Pfeffer MA. Left ventricular remodeling after acute myocardial infarction. Annu Rev Med. 1995; 46: 455-66.
7. Seth P, Gore J. Treatment of acute myocardial infarction: better, but still not well enough. Arch Intern Med. 2003; I63(12): 1392-3.
8. Reffelmann T, Kloner RA. Cellular cardiomyoplastycardiomyocytes, skeletal myoblasts, or stem cells for regenerating myocardium and treatment of heart failure? Cardiovasc Res. 2003; 58(2): 358-68.
9. Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. Circ Res. 1985; 57: 84–95.
10. Opie L. Heart physiology. Philadelphia, PA, USA: Lippincott Williams and Wilkins. Eur Heart J. 2004; 25(20): 1768-1765.
11. 11. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990; 81: 1161–72.
12. Dimmeler S, Zeiher AM, Schneider MD. Unchain my heart: the scientific foundations of cardiac repair. J Clin Invest. 2005; 115: 572–83.
13. Dawn B, Stein AB, Urbanek K, et al. Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function. Proc Natl Acad Sci USA. 2005; 102: 3766–71.
14. Leri A, Kajstura J, Anversa P. Cardiac stem cells and mechanisms of myocardial regeneration. Physiol Rev. 2005; 85: 1373–416.
15. Dib N, Michler RE, Pagani FD, et al. Safety and feasibility of autologous myoblast transplantation in patients with ischemic cardiomyopathy: four-year follow-up. Circulation. 2005; 112: 1748–55.
16. Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrowderived stem-cell transfer in patients with STsegment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet. 2006; 367: 113–21.
17. Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. Circ Res. 2004; 95: 343–353. Jackson KA, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. J Clin Invest. 2001; 107: 1395–1402.
18. De Palma M, Venneri MA, Roca C, Naldini L. Targeting exogenous genes to tumor angiogenesis by transplantation of genetically modified hematopoietic stem cells. Nat Med. 2003; 9: 789–795.
19. Fuchs S, et al. 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.
20. Foley A, Mercola M. Heart induction: embryology to cardiomyocyte regeneration (a review). Rends Cardiovasc Med. 2004; 14: 121-5.
21. Klug MG, Soonpaa MH, Koh GY, Field LJ. Genetically selected cardiomyocytes from differentiating embryonic stem cells from stable intracardiac grafts. J Clin Invest. 1996; 98: 216-24.
22. Kehat I, Kenyagin-Karsenti D, Snir M. et al . Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. J Clin Invest. 2001; 108: 407-14.
23. Boheler KR, Czyz J, Tweedie D, et al. Differentiation of pluripotent embryonic stem cells into cardiomyocytes (a review). Circ Res. 2002; 91: 189-201.
24. Hierlihy AM, Seale P, Lobe CG et al. The post-natal heart contains a myocardial stem cell population. FEBS Letters 2002; 530:239-43.
25. Kehat I, Khimovich L, Caspi O, et al. Electromechanical integration of cardiomyocytes derived from human embryonic stem cells. Nat Biotechnol. 2004; 22: 1282-9.
26. Bittner RE, Schofer C, Weipoltshammer K, Ivanova S, Streubel B, Hauser E, Freilinger M, Hoger H, Elbe-Burger A, Wachtler F. Recruitment of bone-marrow-derived cells by skeletal and cardiac muscle in adult dystrophic mdx mice. Anat Embryol (Berl). 1999; 199: 391-396.
27. Jackson KA, Majka SM, Wang H, Pocius J, Hartley CJ, Majesky MW, Entman ML, Michael LH, Hirschi KK, Goodell MA. Regeneration of ischemic cardiac muscle and vascular ndothelium by adult stem cells. J Clin Invest. 2001; 107: 1395-1402.
28. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, nversa P. Bone marrow cells regenerate infracted myocardium. Nature. 2001; 410: 701-705.
29. Balsam L.B., Wagers A.J., Christensen J.L., Kofidis T., Weissman I.L., Robbins R.C., aematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium, Nature, 428: 668-673, 2004.
30. Wang JS, Shum-Tim D, Galipeau J, Chedrawy E,Eliopoulos N, Chiu RC. Marrow stromal cells for cellular cardiomyoplasty: feasibility and potential clinical advantages. J. Thorac. Cardiovasc Surg. 2000; 120: 999- 1005,
31. Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation. 2002; 105: 93-98.
32. Tomita S, Li RK, Weisel RD, Mickle DA, Kim EJ, Sakai T, Jia ZQ. Autologous ransplantation of bone marrow cells improves damaged heart function. Circulation. 1999; 100: II247-II256.
33. Frangioni JV, Hajjar RJ. In vivo tracking of stem cells forclinical trials in cardiovascular disease. Circulation. 2004; ll0(21): 3378-83.
34. Lee SH, Wolf PL, Escudero R, Deutsch R, Jamieson SW, Thistlethwaite PA. Early expression of angiogenesis factors in acute myocardial ischemia and infarction. N Engl J Med. 2000; 342: 626–633.
35. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res. 2002; 53: 31-47.
36. Pittenger MF, Martin BJ. Mesenchymal stem cells and their potential as cardiac therapeutics. Circ Res. 2004; 95: 9-20.
37. 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.
38. 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.
39. Wollert KC, Hofmann M, Meyer GP, Hertenstein B, Ganser A, Knapp WH, Drexler H. Monitoring of bone marrow cell homing to the infarcted human myocardium. Circulation. 2004;110(suppl II):436.
40. Shintani S, Murohara T, Ikeda H, Ueno T, Honma T,Katoh A, Sasaki K, Shimada T, Oike Y, maizumi T. Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. Circulation. 2001; 103: 2776- 2779.
41. Yeh ET, Zhang S, Wu HD, Korbling M, Willerson JT, Estrov Z. Transdifferentiation of human peripheral blood CD34-enriched cell population into cardiomyocytes, endothelial cells, and smooth muscle cells in vivo. Circulation. 2003; 108(17): 2070-2073.
42. Norol F, Merlet P, Isnard R, Sebillon P, Bonnet N, Cailliot C, Carrion C, Ribeiro M, Charlotte F, Pradeau P, Mayol JF, Peinnequin A, Drouet M, Safsafi K, Vernant JP, Herodin F. Influence of mobilized stem cells on myocardial infarct repair in a nonhuman primate model. Blood. 2003; 102(13): 4361-4368.
43. Ince H, Petzsch M, Kleine HD, Schmidt H, Rehders T, Ko¨rber T, Chatterjee T, Freund M, Nienaber C. Prevention of LV remodeling with G-CSF in acute myocardial infarction: insights from FIRSTLINE-AMI (Front- Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor). Circulation. 2004; 110(suppl III):352.
44. Bel A, Messas E, Agbulut O, Richard P, Samuel JL, Bruneval P, Hagege AA, Menasche P. Transplantation of autologous fresh bone marrow into infarcted myocardium: a word of caution. Circulation. 2003; 108(suppl II): 247-52.
45. 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: 47-9.
46. Smits PC, van Geuns RJ, Poldermans D, Bountioukos M, Onderwater EE, Lee CH, Maat AP, Serruys PW. Catheterbased 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: 2063–69.
47. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Silva GV, Mesquita CT, Belem L, Vaughn WK, Rangel FO, Assad JA, Carvalho AC, Branco RV, Rossi MI, Dohmann HJ, Willerson JT. Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. Circulation. 2004; 110(suppl II): 213-8.
48. 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: 1964-71.
49. Siminiak T, Fiszer D, Jerzykowska O, Rozwadowska N, Grygielska B, Majewski M, Kalmucki P, Kurpisz M. Percutaneous transvenous transplantation of autologous myoblasts in the treatment of postinfarction heart failure: the POZNAN trial. Eur Heart J. 2004; 25(suppl):264.
50. Chien KR. Stem cells: lost in translation. Nature. 2004; 428: 607–8.
51. Mathur A, Martin JF. Stem cells and repair of the heart. Lancet. 2004; 364: 183-92.
52. Kamihata H, Matsubara H, Nishiue T, Fujiyama S, Tsutsumi Y, Ozono R, Masaki H, Mori Y, Iba O, Tateishi E, Kosaki A, Shintani S, Murohara T, Imaizumi T, Iwasaka T. Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands, and cytokines. Circulation. 2001; 104: 1046-52.
53. Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. Nature. 2004; 428: 668-73.
54. 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: 845-47.
55. 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: 47-9.
56. Hill JM, Syed MA, Arai AE, Powell TM, Paul JD, Zalos G, Read EJ, Khuu H, Leitman SF, Horne MK, Csako G, Dunbar CE, Cannon RO. Outcomes of granulocyte colonystimulating factor administration to patients with severe coronary artery disease. Circulation. 2004; 110(suppl III):352.
57. Assmus B, Honold J, Lehmann R, Pistorius K, Hoffmann WK, Martin H, Schachinger V, Zeiher AM. Transcoronary transplantation of progenitor cells and recovery of left ventricular function in patients with chronic ischemic heart disease: results of a randomized, controlled trial. Circulation. 2004; 110(suppl III):238.
58. Pouly J, Hagege AA, Vilquin JT, Bissery A, Rouche A, Bruneval P, Duboc D, Desnos M, Fiszman M, Fromes Y, Menasche P. Does the functional efficacy of skeletal myoblast transplantation extend to nonischemic cardiomyopathy? Circulation. 2004; 110: 1626-31.
59. Vilas-Boas F, Feitosa GS, Soares MB, Pinho-Filho JA, Almeida AJ, Mota A, Carvalho C, Carvalho HG, Oliveira AD, Ribeiro-dos-Santos R. Bone marrow cell transplantation to the myocardium is safe and potentially effective in patients with advanced heart failure due to Chagas' cardiomyopathy. Circulation. 2004;110(suppl III):239.
60. Lanza R, Moore MA, Wakayama T, Perry AC, Shieh JH, Hendrikx J, Leri A, Chimenti S, Monsen A, Nurzynska D, West MD, Kajstura J, Anversa P. Regeneration of the infarcted heart with stem cells derived by nuclear transplantation. Circ Res. 2004; 94: 820-27.
61. Lee SH, Wolf PL, Escudero R, Deutsch R, Jamieson SW, Thistlethwaite PA. Early expression of angiogenesis factors in acute myocardial ischemia and infarction. N Engl J Med. 2000; 342: 626-33.
62. Fisehbaeh GD, Fischbach RL, Stem cells: seienee, policy, and ethies, J Clin Invest 2004;l 14:1364-70.
63. Gulbins H, Meiser BM, Reichenspumer H, Reiehart B, Cell transplantation—a potential therapy for cardiac repair in the future? Heart Surg Forum. 2001; 1(1): 49-56
64. Yoon YS, Park JS, Tkebuchava T, Luedeman C, Losordo DW, Unexpected severe calcification after transplantation of bone marrow cells in acute myocardial infarction. Circulation 2004;109(25):3154-7.
65. 64. Lanza R, Moore MA, Wakayama T, et al. Regeneration of the infarcted heart with stem cells derived by nuclear transplantation. Circ Res 2004; 94(6):820-7.
66. Miyagawa S, Sawa Y, Taketani S, Kawaguchi N, Nakamura T, and Matsuura N, Matsuda H. Myocardial regeneration therapy for heart failure: hepatocyte growth factor enhances the effect of cellular cardiomyoplasty. Circulation. 2002; 105:2556-61.
67. Kai C. Wollert, Helmut Drexler. Clinical Applications of Stem Cells for the Heart. Circ. Res. 2005;96;151-63.
68. Nabel EG. Stem cells combined with gene transfer for therapeutic vasculogenesis: magic bullets? Circulation. 2002; 105:672-4.

Evaluation of 56 Cases of Long Segment Anastomosis of Left Internal Thoracic Artery to Left Anterior Descending Artery in Rajaei Heart Center

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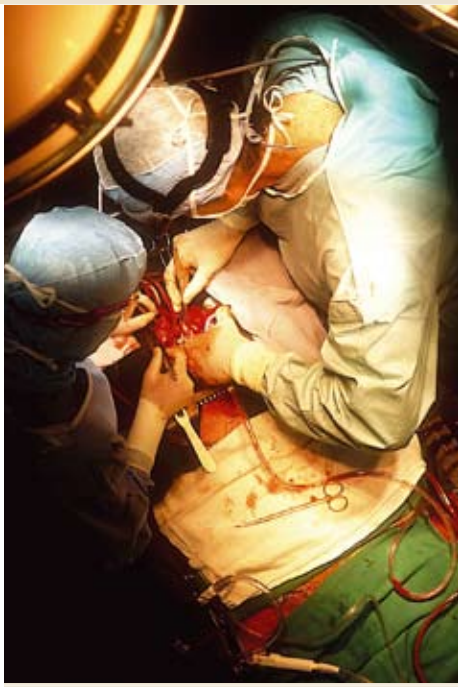

Abstract:

Background: Long segment reconstruction of the diffusely diseased Left Anterior Descending Artery (LAD) with Left Internal Thoracic Artery (LITA) has been shown to be beneficial for patients that have complicated, multiple and long segment lesions in LAD. In this prospective study we analyzed the results obtained with this technique.

Methods: From Feb. 2007 to Feb. 2009, 56 patients were operated by this technique. LITA was used as a patch along the opened narrow segment of LAD from 2 to 8 centimeter. Data from all patients were collected and all patients worked up for post operative complications, like post operative MI, ECG changes, NIHA class, enzymatic changes, post operative bleeding and CT-Angiography were done between 6 to 18 months after operation in some cases.

Results: 56 cases,42 male (75%)and 14 female (25%), from 43 to78 years with mean age of 59.8+_9.3 years with multiple and long segment lesions in LAD were included in this satudy. Preoperative risk factors were Hypertension (66.1%), Diabetes (57.1%), Hyperlipidemia (50%), cigarette smoking (50%), renal failure (1.8%) and positive family history (7.1%). 23 patients (41.1%) have had remote MI and 9 patients (16.1%) have had recent MI.Significant left main lesion were found in7 patients (12.5%), peripheral vascular disease in 3 patients (5.3%) and preoperative arrhythmias in 2 patients (3.6%). Mean number of grafts that were used in operations was 2.85 +_1.5 and other concomitant operations were done in 5 patients. Post operative complications were arrhythmias in 10 (17.8%), postoperative MI in 1 (1.8%), surgical bleeding in 7 (12.5%), infections in 3 (5.3%), plural effusion in 3(5.3%), tamponade in 2(3.6%), pericardial effusion in 1 (1.8%) and hemiparesia in 1 patient (1.8%). there was no mortality in these patients.

Conclusion: Long segment and multiple lesions in LAD are difficult challenges for cardiac surgeons and in these situations; results of long-segment LAD reconstruction are very encouraging.

Key words: Left Anterior Descending artery (LAD), Left Internal Thoracic Artery (LITA), Long segment anastomosis.

ntroduction:

CABG is an approved cardiac operation and it seems that this operation can increase life expectancy and the most important graft that can prolong the survival of the patient is the LITA to LAD anastomosis (1,2). Today, because of improvement in percutaneous techniques and more comfortable stents that can be use by interventional cardiologists, more complicated cases are referring to cardiac surgeons for coronary bypass surgery. Endarterectomy is a good solution in more complicated cases of long segment anas-

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tomosis and use of sequential (jump) graft are a resolution in multiple stenosis(3-5), also the use of vein patch for reconstruction of LAD was reported by some authors (6) but there are some reasons that endarterectomy in LAD is not as good as endarterectomy in other coronary tributaries because the origin of the rectangular septal branches that feed anterior and middle parts of ventricular septum are in risk of closure after endarterectomy and it can induce a septal MI and can jeopardize the patients' life, also it needs patient anticoagulation therapy for 6 to 8 weeks that itself it can induce more risk for hemorrhage and pericardial blood collection after CABG(7) on its owen.We decided to evaluate our technique in management of complicate LAD lesions in this study. We use LITA as a patch for reconstruction of long segment of LAD as an alternative for LAD endarterectomy, vein patch reconstruction and sequential anastomosis.

Material and methods:

From Feb 2008 to Feb 2009 in a retrospective analysis we collected data from 56 patients that we used the technique of Long segment LITA to LAD anastomosis for long segment lesion of LAD. We used our technique for patients whom have had long segment and multiple lesions on LAD especially those that have at least one patent septal artery in this region with good distal run off and usually there were at least one athromatose downstream plaque after the first stenosis in LAD. Pump circulation and standard technique for CABG were used for all patients and because of diffuse lesions in all three coronary vessels, we didnt use off pump technique in these patients. The length of long segment anastomosis should be at least 2 cm, LAD was opened and unroofed for long length where the proximal and distal point of anastomosis had good run off, then we opened the LITA for the same length and anastomosis this together with two 7-0 prolene suture one from heel and the other from the toe. Preoperative data like risk factors, sex, age and history of remote and recent preoperative MI and postoperative data like postoperative complications where collected, inserted in sheets and multivariate analysis were done in regress models with the use of chi-square and mixed model ANOVA.

Results:

From Feb 2008 to Feb 2009, 56 cases, 42 male (75%) and 14 female (25%), from 43 to 78 years with the mean age of 59.8+_9.3 years with multiple and long segment lesions in LAD were included in this study. Preoperative risk factors were Hypertension in 37 patients (66.1%), Diabetes in 32 patients (57.1%), Hyperlipidemia in 28 patients (50%), cigarette smoking in 28 patients (50%), renal failure in one patient, long term corticosteroid usage in one patient (1.8%) and positive family history in 4 patients (7.1%) (Table-1). Twenty three patients (41.1%) have had remote MI and 9 patients (16.1%) have had recent MI. Significant left main lesions were found in 7 patients (12.5%), peripheral vascular disease in 3 patients (5.3%) and preoperative arrhythmias in 2 patients (3.6%) (Table-2). Mean number of grafts that were used in operations was 2.85 +_1.5 and other concomitant operations were done in 5 patients that was VSD closure in one case and mitral valve repair in three cases and mitral valve replacement in one case. Post operative complications were arrhythmias in 10 (17.8%), postoperative MI (approved by cardiac enzyme analysis, echocardiography and ECG changes) in 1 (1.8%), surgical bleeding in 7 (12.5%), infections in 3(5.3%), plural effusion in 3(5.3%), tamponade in 2(3.6%), pericardial effusion in 1(1.8%) and hemiparesia in 1 patient (1.8%) (Table-3).

There was no mortality in these patients. Mean clamp time was 35.9+_14 and mean pump time was 70+_22 minutes. Mean length of LIMA to LAD anastomosis was 4+_1.2 cm the longest was 8 cm and the shortest was 2 cm, We don't say long segment anastomosis to grafts length shorter than 2 cm.Mean ICU stay was 2.57+_0.9 days in females and 2.33+_0.48 days in males and mean hospital stay was 6.8 +_2.5 days in females and 6.3+_1.9 days in males. Follow up period was 1.4 |+_0.4 months (Table-4). Mean NYHA class preoperative was 2.3 and it reduced to 1.5 that p_value<0.001 is significant. We didn't use Balloon pump in this group of patients.

Table-1: Classic preoperative risk factors

Hypertension	37	66.1%
Diabetes	32	57.1%
Hyperlipidemia	28	50%
Cigarette smoking	28	50%
Positive family history	4	7.1%
Renal failure	1	1.8%
Chronic corticosteroid usage	1	1.8%

Table-2: Preoperative variants

Remote MI	23 (41.1%)
Recent MI	9 (16.1%)
LM lesion	7 (12.5%)
Peripheral Vascular Disease	3 (5.3%)
Preoperative Arrhythmias	2 (3.6%)
Cerebro vascular accident	0 (0%)

Discussion:

Today, cardiac surgeons have different number of patients with diffuse lesions in LAD .With new interventional techniques simple lesions can be corrected with stents, and more diffuse lesions with long segment LAD lesions and multiple lesions are going for CABG. Endarterectomy in LAD is a known method and different authors have controversial ideas about it (4, 5, 6, and 7).some authors report good results but other are still reluctant to use this technique because of its high rate of perioperative and postoperative mortality (7,8). The origin of the rectangular septal branches that feed anterior and middle parts of ventricular septum are in risk of closure after endarterectomy and it can induce a septal MI and can jeopardize the patients life, also denuded endothelium after endarterectomy enhances the development of myofibrointimal proliferation that can produce new thrombus formation and decrease the long term survival of the graft, then it needs patient anticoagulation therapy for at least 6 to 8 weeks that itself can induce more risk for hemorrhage and pericardial blood collection after CABG (7,8). Also the use of vein as onlay patch is an alternative technique. Its use is more difficult and the athromatouse process can progress in vein portion of graft.(6,9). The main goal of this study is to introduce an alternative technique that we use in our surgical ward that may be useful in some situations for other surgeons. With the creation of a long opening in the roof of LAD until a good distal and proximal run off point can be accessed, we can see all side and septal branches and a secure anastomosis can be reconstructed. We think reconstruction of LAD with LITA can destroy all plaques and the plaque can not create stenosis circumferentially, neointimal proliferation doesn't exist any more and a wide lumen for this part of LAD can be reconstructed. in this series of 56 patients that all have had long segment or multiple lesions on LAD we reconstructed LAD with LITA for above 2 cm and we collect all the data from patients. Results shown that, mean pump time was 70+_22 minutes and mean clamp time was 35.9+_14 minutes it means that the time of clamp and pump time doesn't increase from other CABG operations. the mean ICU stay was 2.57+_0.9 days in females and 2.33+_0.48 days in males and the mean hospital stay was 6.8+_2.5 days in females and 6.3+_1.9 days in males this is in the range of simple uncomplicated CABG operations. Post operative complications in our group was surgical bleeding needs reoperation in 7 cases (12.5%) that is more than simple on pump CABG.Other complications were not more than other CABG operations(Table-3). Postoperative MI was seen in one case (1.8%) that is very low and we didn't have had any mortality in this study. Mean NYHA class preoperative was 2.3 and it reduced to 1.5 that p_value<0.001 is significant and this mean that the quality of life is better with this kind of CABG operation. We didn't use Balloon pump in this group of patients and this is valuable in our study. After all we didn't use long term anticoagulation therapy after operation in this study except for prophylaxis against deep vein thrombosis and pulmonary emboli, that was Heparin at the doses of 500 unit per hour started 6 hours after operation and discontinued after patient ambolization.We think that this technique is a good alternative for endarterectomy, sequential anastomosis and onlay vein patch technique that is simple and we can use it in all complicated situations. Limitation of our study is lake of long term postoperative follow-up and lake of postoperative angiography.

Table-3: Postoperative Complications

Surgical bleeding	7	12.5%
Arrhythmia	4	7.1%
Infection	3	5.3%
Plural effusion	3	5.3%
Thrombosis	2	3.6%
Tamponade	2	3.6%
pneumothorax	1	1.8%
Pericardial effusion	1	1.8%
Hemiplesia	1	1.8%

Table-4: Mean ICU and hospital stay and mean follow-up time

ICU stay	Female	2.57+_0.9 Days	0.219
	Male	2.33+_0.48 Days	
Hospital stay	Female	6.8+_2.5 Days	0.437
	Male	6.3+_1.9 Days	
Follow up	Female	1.8+_0.4 Days	0.69
	Male	1.9+_0.6 Days	
	Sex	Mean+_SD	P_value

Conclusion:

Long segment and multiple lesions in LAD are difficult challenges for cardiac surgeons and in these situations; results of long-segment LAD reconstruction are very encouraging and in this era could be comparing with endarterectomy and multiple sequential anastomosis.

References:

1. Ron T. van Domburg*, Arie Pieter Kappetein and Ad J.J.C. Bogers,The clinical outcome after coronary bypass surgery: a 30-year follow-up study, Eur Heart J (2008) doi: 10.1093/eurheartj/ehn530 First published online: December 9, 2008
2. Fulvia Seccareccia, Carlo Alberto Perucci , Paola D'Errigo, Massimo Arcà, Danilo Fusco, Stefano Rosato, Donato ,Greco,The Italian CABG Outcome Study: short-term outcomes in patients with coronary artery bypass graft surgery Eur J Cardiothorac Surg 2006;29:56-62
3. Thomas A. Schwann, MD, Anoar Zacharias, MD, Christopher J. Riordan, MD, Samuel J. Durham, MD, Aamir S. Shah, MD, Robert H. Habib, PhD Survival and Graft Patency after Coronary Artery Bypass Grafting With Coronary endarterectomy: Role of Arterial Versus Vein Conduits, Ann Thorac Surg 2007;84:25-31
4. Mitsumasa Hata, MD, Motomi Shiono, MD, Tatsuya Inoue, MD, Akira Sezai, MD, Nanao Negishi, MD, Yukiyasu Sezai, MD, :Midterm results of coronary artery bypass graft surgery with internal thoracic artery under low free-flow conditions, Ann Thorac Surg 2004; 78:477-480
5. Oguz Omay, M.D.*, Emre Ozker, M.D.†, Cenk Indelen, M.D.‡, Kaya Suzer, M.D. Revascularization of Left Anterior Descending (LAD) Artery with In Situ Left Internal Thoracic Artery (LITA) and Coronary-Coronary Free LITA Grafts: 12-Year Patency, Journal of Cardiac Surgery Volume 23 Issue 6, Pages 722 – 724 Published Online: 27 Oct 2008
6. Lemma M, Beretta L, Vanelli P, Santoli C. Open coronary endarterectomy, saphenous vein patch reconstruction, and internal mammary artery grafting Ann Thorac Surg 1992;53:1151-1152
7. Minale C, Nikol S, Zander M, Uebis R, Effert S, Messmer BJ. Controversial aspects of coronary endarterectomy Ann Thorac Surg 1989; 48:235-241
8. Ferraris VA, Harrah JD, Moritz DM, Striz M, Striz D, Ferraris SP. Long-term angiographic results of coronary endarterectomy Ann Thorac Surg 2000;69:1737-1743.
9. Lemma M, Beretta L, Vanelli P, Santoli C. Open coronary endarterectomy, Ladowski JS, Schatzlein MH, Underhill DJ, Peterson AC. Endarterectomy, vein patch, and mammary bypass of the anterior descending artery Ann Thorac Surg 1991; 52:1187-1189.

Intraoperative Magnesium Sulfate can Reduce Narcotic Requirement after Coronary Bypass Surgery.

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Abstract:

Background: Narcotics are the most common drugs that have been used after cardiac surgery. Everyone knows that their side effects including respiratory depression, hemodynamic instability, and nausea, vomiting and itching are dose dependent. Magnesium is both N Methyl D Aspartate (NMDA) – receptor and calcium receptor antagonist and can modify important mechanisms of nociception. The purpose of this study was to investigate the effect of magnesium sulfate on pain score and reducing narcotic requirement in coronary artery bypass surgery patients.

Methods: In a randomized, double blinded, placebo-controlled trial One hundred and eighty five patients (105 male and 80 female) undergoing elective coronary artery bypass graft surgery were studied. Mean age were 58+_11 (from 24 to79 years).We enrolled them in two groups randomly. Group1 received magnesium sulfate as an IV infusion 80 mg/kg during one hour after induction and the second group received the same volume of normal saline as placebo. During the postoperative period, Morphine requirement and pain score (visual analogue scale: scaled as 0 to 10, 0=no pain and 10= worst possible pain) in 6, 12, 18, and 24 hours were recorded and documented.

Results: There were no significant differences between two groups with respect to baseline data. In MG group, only 30 patients (32%) needed to receive Morphine Sulfate , but in placebo group, 75 patients (83%) needs some doses of Morphine Sulfate (p value < 0.001); The odds ratio showed that MG could strongly prevent the needs for receiving opioid analgesics for controlling of the pain.

Conclusion: Intra operative use of magnesium sulfate can reduce receiving opioids after (CABG) operations.

Key words: Magnesium Sulfate, Coronary Artery Bypass, Narcotics.

Introduction

Narcotics are the most common drugs that have been used after cardiac surgery and they are used as analgesic from 1853. Everyone knows that their side effects including respiratory depression, hemodynamic instability, and nausea, vomiting and itching are dose dependent. Morphine in dose of 2 Mg/Kg plus scopolamine were used as complete anesthesia 1n the

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19th century (1). Magnesium – sulfate is a common used drug in the field of anesthesiology, critical care and pain control. It is also use as a supplement in treating eclampsia, pre – eclampsia, hypokalemia, premature labor, myocardial protection after ischemia, asthma crisis , postoperative pain control and hemodynamic stability during intubation (2,3,4).

The most important mechanisms of magnesium effect is its role in the N Methyl D Aspartate (NMDA) part of Gamma Amino Butyric Acid (CABG) receptors. These receptors are found in nerve endings and can modulate pain and inflammatory responses (5,6,7). This theory is the basis for this study that suppressing the inflammatory response induced by cardiopulmonary bypass and surgical stimulation in CABG patients could decrease the postoperative pain intensity and also, can help to extubate the patients as soon as possible (8). After surgery, Pain may inhibit the effective coughing, deep inspiration, and early mobilization of the patients. Thus, management of pain is an important part of postoperative care. Opening of the Sternum and Preparation of the internal mammary artery (IMA) graft may cause severe pain after the surgery. Manipulation of the muscles, adjacent tissues of the chest, parietal pleura, the periostium of the ribs and sternum are common causes of the pain. Analgesia after CABG operation is very important for both physicians and the patients. There are numbers of adverse effects due to post operative narcotic over usage that affect the outcome of surgery.

This study was designed and executed to assess the effects of magnesium sulfate solution infusion on postoperative narcotic requirement in patients undergoing elective coronary artery bypass graft surgery.

Methods

The study population selected from Rajaei Heart Center (RHC) patients, a tertiary center of cardiovascular diseases in Tehran that patients from all parts of IRAN are referred to. All the patients were between 18 to 65 years old who scheduled for an elective coronary artery bypass graft (CABG) surgery. Exclusion criteria in this study were:

Left ventricular ejection fraction (LVEF) less than 30%, peptic ulcer disease or history of gastrointestinal bleeding, liver or renal failure, history of sleep apnea, abused other substances or had any sign or history of denoting past or present neuropathy.

This study was approved by the RHC medical ethics committee. The objectives of the study were explained for all patients by the anesthesiologist and an inform consent was signed.

Using a random digits table, the patients were randomly assigned to intervention group (which received magnesium sulfate [MG]) and /or comparison group (which received normal saline as placebo). Randomization sequences had been prepared by one of the study collaborates, who was not participated in administration of drugs, data collection or data handling or analysis. The results of randomization had been put into sealed envelopes and these envelopes were sent to operating room. Patient's allocation was performed in the operating room, before surgery. When a patient enrolled in the study, another study collaborate, who wasn't involved in treatment process, data collection or analysis, opened an envelope according their serial numbers and was informed the grouping the related patient. Then, he prepared Magnesium Sulfate (80 mg per kilogram of body weight for intervention group) or normal saline (with the same volume for placebo group) in similar syringes. He also recorded the patients' group in their file by predefined codes. Nobody was aware of this coding system, except study designer and the mentioned participant. The medical staff who had no contribution in medical care or data collection were not aware of the actual group of the patients.

All patients were visited the night before the surgery by an anesthesiologist (among the authors) and enrolled the study according to the study protocol. One hundred and eighty five patients were participated in the study. Patients were premedicated intramuscularly by Morphine Sulfate (1mg/kg) and Promethazine (1 mg/kg) one hour before coming to operating room. Then, they were allocated to the study groups (as mentioned before). Induction was achieved with intravenous administration of thiopental, 3 mg/kg; Fentanyl, 2.5 µg/kg; and Atracurium, 0.6 mg/kg. After tracheal intubation, patients were mechanically ventilated to give an initial tidal volume of 8 mL/kg, with inspiratory 100% oxygen and a respiratory rate of 12 breaths/min; the ventilatory pattern was subsequently adjusted according to the arterial blood gases. General anesthesia was maintained with a continuous intravenous infusion of Fentanyl, 10 µg/kg/h; Propofol and Atracurioum 0.007 mg/kg/h. Further boluses of Fentanyl (50-100µg) were administered if required at

the skin incision and sternotomy field. Also, in the operating room, electrocardiography and radial artery pressure monitoring were begun. Peripheral venous, central venous and urethral catheters were inserted. Body temperature was monitored with rectal and esophageal probes. The patients were then positioned and prep and drape was done for them. After induction, the anesthesiologist started intravenous Magnesium Sulfate or normal Saline infusion through a peripheral large bore catheter during one hour. Operated patients were transferred intubated to the post operative intensive care unit. The patients were extubated after full recovery of muscular forces and full awakening and with the establishment of hemodynamic stability.

CPB flow started at a perfusion index of 2.4 L/min/m2. The mean arterial pressure was maintained at about 80 mmHg. Mild hypothermia was achieved and maintained during perfusion. The arterial pressure was controlled using a vasodilator (nitroglycerin, 0.5_g/kg/min) or a vasoconstrictor (nor epinephrine, 0.05µg/kg/min) to maintain the mean pressure value in a range of 40 to 100 mmHg. A diuretic (furosemide, 20 mg) was administered if urine output during CPB was less than 0.5 mL/kg 30 minutes after the beginning of perfusion.

Statistical analysis was performed with intention-to-treat approach. Data were classified as mean ± standard deviation for interval and count (%) for categorical variables. Comparison of baseline data between the groups of study was performed by student's test or its non-parametric equivalent, Mann Whitney U test for interval data and Chi square test for nominal data. Odds ratio (OR) with 95% confidence interval (CI 95%) also computed to find the epidemiologic associations. P value less than 0.05 considered as statistically significant.

The trend of pain severity and changes of VAS results (among time intervals and between study groups) were investigated by a repeated measure analysis of variance (ANOVA) model.

Survival analysis was performed by Kaplan – Meier method to study the time of receiving the first dose of morphine sulfate, as a proxy of the time of intolerable pain by patients. Log rank test was used to compare the results between the study groups.

SPSS 15 for windows (SPSS Corporation, Chicago, Illinois) was used for statistical analysis.

Results

One hundred and eighty five patients (F/M = 80/105; mean age = 58 ± 11.0 years, range 24 to 79 years) enrolled the study. Mean left ventricular ejection fraction (LVEF) was 45 ± 8.4 percent. The average time of surgery and anesthesia was 3.8 ± 0.9 and 5 ± 0.9 hours, respectively. Patients stayed in intensive care unit (ICU) after surgery with a mean time of 2.2 ± 0.5 days (range 2 to 4 days).

Ninety five patients received intravenous magnesium sul-

Table 1- Comparison of the Baseline Data between Magnesium Sulfate and Placebo Groups.

	Magnesium Sulfate (n = 95)	Placebo (n = 90)	P value
Age years	57 ± 11.5	59 ± 10.4	0.19
Sex			0.54
Female	39 (41%)	41 (46%)	
Male	56 (59%)	49 (54%)	
Left Ventricular Ejection Fraction percent	44 ± 7.3	44 ± 9.5	0.64
Duration of Anesthesia hours	5 ± 0.7	5 ± 1.1	0.43
Duration of Operation hours	4 ± 0.7	4 ± 1.0	0.57
Cardio-Pulmonary Pump Time minutes	103 ± 58.3	104 ± 41.5	0.63
ICU Stay days	2 ± 0.4	2 ± 0.5	0.52
Number of the Grafts	3 ± 0.4	3 ± 0.3	0.19
Intubation Time hours	14.1 ± 4.3	16.5 ± 14.9	0.32

fate (MG) and 90 patients received normal saline as placebo instead. Baseline data of the study groups are presented in Table 1. No important differences were observed between the groups.

Severity of pain was measured by a 10-point visual analogue scale (VAS) in different time intervals. The results are summarized in Table 2

Table 2 –Pain Score in Different Time Intervals after Cardiac Surgery in Magnesium Sulfate and Placebo Groups

	Mean Score ± Standard Deviation					
	1st Hour	3rd Hour	6th Hour	12th Hour	18th Hour	24th Hour
MG	0.29 ± 1.17	0.0 ± 0.0*	0.97 ± 2.02*	0.23 ± 1.0*	0.0 ± 0.0*	0.0 ± 0.0
Placebo	0.09 ± 0.59†	0.36 ± 1.26†	2.53 ± 2.43†	0.89 ± 1.83†	0.0 ± 0.0†	0.0 ± 0.0

MG: Magnesium Sulfate
P value for comparison between MG and Placebo (based on repeated measure ANOVA) < 0.001
P value for comparison among time intervals (based on repeated measure ANOVA) < 0.001
* and †: Statistically significant difference in pairwise comparisons (based on Bonferroni post-hoc test). P values range <0.001 to 0.006.

Note that the most severe pain had a point which was less than 3. Immediately after surgery, patients experienced a period of analgesia. The pain appeared gradually and became more severe by the 6th hour after finishing the operation. Then, the severity of pain decreased until it disappeared at 18th hour after surgery (figure 1). The significance of this trend was proved by repeated measure ANOVA in both MG and placebo groups (p value < 0.001).

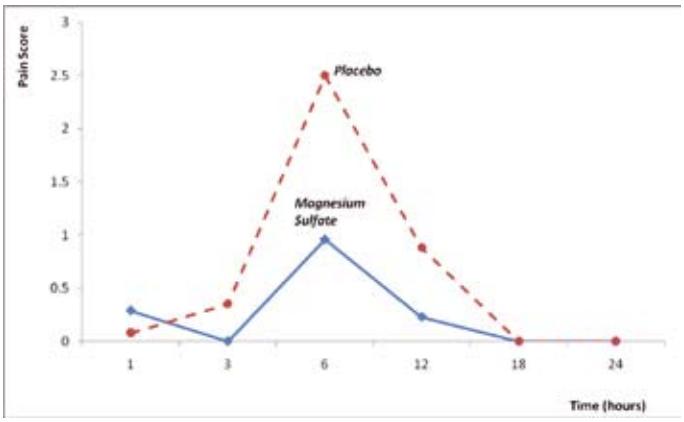


Figure 1- Changes of Pain Severity in the Study Groups.

The severity of pain was equal in two groups in the first hour after operation. The period of analgesia continued in patients who received MG until the 3rd hour after surgery, while in placebo group, the severity of pain was rising. It was observed that in any time interval, the patients in MG group experienced a less severe pain, compared to placebo group. This difference was statistically significant (p value < 0.001). According to the protocol of the study, patients could receive morphine sulfate (MS) as analgesic agent for controlling the pain, if they needed.

In MG group, only 30 patients (32%) needed to receive any dose of MS, but in placebo group, 75 patients (83%) got some doses of it (p value < 0.001; OR = 0.09, CI 95: [0.05 – 0.19]). The odds ratio showed that MG could strongly prevent the need for receiving opioid analgesic for pain controlling. Among the patients who needed the analgesics, the mean dose of Morphin Sulfate was 1.0±1.5 mg in magnesium group and 2.8±1.4 mg in placebo group (p value < 0.001). It means that magnesium may reduce the average dose of Morphin Sulfate needed for controlling the pain.

The time of prescription the first dose of morphine sulfate could be considered as a proxy for the beginning of intolerable pain (pain score between 4 and 5). This was investigated using Kaplan-Meyer method (figure 2). The results proposed that in most of the patients who needed extra analgesia, the pain became relatively intolerable 6 hours after finishing the surgery. Log-rank test showed no significant difference between two groups (p value = 0.09); then, the pattern of receiving the first dose of Morphin Sulfate could be considered similar in both magnesium and placebo groups.

Discussion

In this study, we demonstrated that the continuous infusion of magnesium sulfate in dose of 80 Mg/Kg during elective CABG surgery can reduce acute postoperative pain scores that is in concordance with the other similar studies performed on acute postoperative pain in other surgi-

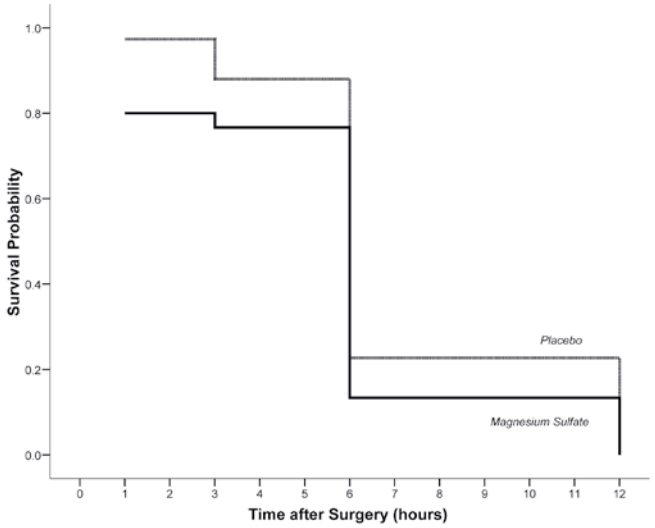


Figure 2 – Kaplan – Meier Curve for Estimation of the Time to Receive the First Dose of Opioid Analgesics.

cal procedures (9).The mechanism of this analgesic effect of magnesium is not clear, but interference with calcium channels and NMDA receptors can play an important role in the reduction of inflammatory response and can show its effect on pain control by the way of central and peripheral nervous system (10).

Magnesium also has a vasodilator effect on both the cardiac epicardium and resistance coronary arteries in humans. Furthermore, the coronary arterial response to magnesium is dose dependent (11).This vasodilator effect can be useful in CABG operations especially patients that needs arterial grafts .The preventive effect of magnesium on arterial graft vasospasm is also useful. After on pump CABG the inflammatory responses of extracorporeal circulation are common. The effects of magnesium sulfate in decreasing the general inflammatory response in these patients, both intra-operatively and postoperatively can lead to a more rapid recovery of them. This rapid recovery also takes in to consideration the effects of decreased postoperative pain scores and can lead to reducing narcotics and intubation time. (12)

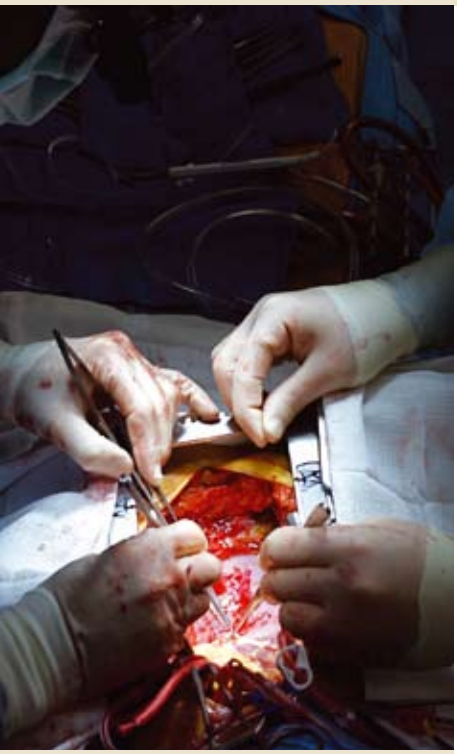
It seems that one of the most potent proposed mechanisms involved in the effects of magnesium in decreasing the postoperative pain scores is its role in affecting the N Methyl D Aspartate (NMDA) part of Gamma Amino Butyric Acid (GABA) receptors all over the body (13). In one study in gynecologic surgical patients loading dose of 50 Mg/Kg of Magnesium Sulfate maintained with continuous dose of 15 Mg/Kg/h after awhile can cause 40% decrease in post operative use of Morphine. This amount of magnesium sulfate (maximum dose up to 5 gr) can't produce any side effect in patients (14).

Conclusion: We concluded that prescription of magnesium sulfate could prolong the analgesic time of patients and reduce the severity of pain after cardiac surgery, the need for receiving opioid agents and the total dose of Morphine Sulfate, compared to the placebo group. The time of prescription of the first dose of Morphine Sulfate didn't differ between two groups.

Reference

1. Miller RD. Anesthesia, 5th rd. Churchill Livingstone, New York, USA, 2000, 274
2. Buvacndran A.Robert J. Jeffrey S. Warren L. Patricia P. Kenneth J. Intrathecal Magnesium Prolongs Fentanyl Analgesia: A Prospective, Randomized, Controlled Trial. Anesth-Analg.2001(95): 661-6
3. Terui K. Kawasaki J. Yokota K. Kawamura C. Miyao H. The effect of magnesium on coaugulation in parturients with preterm labor. Anesthesiology.2002:(96): 1065-7
4. Grigore AM, Mathew JP, Grocott HP, Reves JG, Blumenthal JA, White WD, Smith PK, Jones RH, Kirchner JL, Mark DB, Newman MF. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. Anesthesiology 2001; (95): 1110-1119.
5. James MF. Beer RE, Esser JD. Intravenous magnesium sulfate inhibits cathecholamine release associated with tracheal intubation. Anesth analg. 1989; 68): 772-6)
6. Wilder OH. Wilder-Smith OH, Arendt-Nielsen L, Gäumann D, Tassonyi E, Rifat KR. Sensory changes and pain after abdominal hysterectomy: a comparison of anesthetic supplementation with fentanyl versus magnesium or ketamine. Anesth Analg. 1998;(86):95-101
7. Koinig H, Wallner T, Marhofer P, Andel A, Horauf K, Mayer N.Magnesium sulfate reduces intra – and post- operative analgesic requirements. Anesth Analg. 1998:(87) : 206-10
8. Dube L and Granry JC. The therapeutic use of magnesium in anesthesiology, iIntensive care and emergency medicine: A review. Can J Anaesth 2003(50): 732-46
9. Zarauza R, Zarauza R, Sáez-Fernández AN, Iribarren MJ, Carrascosa F, Adame M, Fidalgo I, Monedero P. et al. A comparative study with oral nifedipine and magnesium sulfate in postoperative. Anesth Analg. 2000(91): 938-43
10. Herbert Koinig, MD,Thomas Wallner, MD, Peter Marhofer, MD, Magnesium Sulfate Reduces Intra-and Postoperative Analgesics Requirements. (Anesth Analg 1998(87): 206-10)
11. Teragawa H, Kato M, Yamagata T, Matsuura H, and Kajiyama D. Magnesium causes nitric oxide independent coronary artery vasodilation in humans. Heart. 2001 (86): 212–16.
12. Ferasatkish R, Dabbagh A, Alavi M, Mollasadeghi G, Hydarpur E, Moghaddam AA, Faritus SZ and Totonchi MZ Effect of magnesium sulfate on extubation time and acute pain in coronary artery bypass surgery Acta Anes Scon 2009(52)1348-52
13. Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996(84): 340-47
14. Seyhan T O; Tugrul M; Sungur M O; Kayacan S; Telci L; Pembeci K; Akpir K Effects of three different dose regimens of magnesium on propofol requirements… Br J Anaesth. 2006 (96):247-52

The Addition of a Tramadol Infusion to Morphine Patient-Controlled Analgesia after Coronary Artery Bypass Graft



Rasul Farasatkish[1], *Seyed Mostafa Alavi[2], Bahadour Baharestani[3] , Ziaa totonchi[4], Ali Sadeghpour Tabaee[5]

Abstract:

Background: Patient-controlled analgesia (PCA) has been advocated as superior to conventional controlled analgesia with less risk to patients in cardiac surgery. In this double-blinded, randomized controlled trial, we tested whether the addition of Tramadol to morphine for patient-controlled analgesia (PCA) resulted in improved analgesia efficacy and smaller morphine requirements compared with morphine PCA alone after Coronary Artery Bypass Graft (CABG) surgery in adults.

Methods: Seventy patients who were randomly allocated into two groups underwent anesthesia by Total IV anesthesia, midazolam, fentanyl and atracurim and, in end of surgery each group received morphine sulfat 0.2 mg/kg after arrived in ICU, morphin PCA was started with demand (bolus) dose 1mg, lockout interval 10 minutes. The Tramadol group after separated from cardiopulmonary bypass received an intra operative initial loading dose of Tramadol (1mg/kg) and a postoperative infusion of Tramadol at 0.2 mg• kg-1• h-1. The control group received an intra operative equivalent volume of normal saline and a postoperative saline infusion (placebo). The demographic data of both groups were the same. Post-operative data were recorded in the cardiac intensive care unit at 30 min, 1 h, 2 h, 4 h, 12 h and 24 h after extubation by the same anesthesiologist, who had no knowledge of the groups, and the side-effects were also evaluated.

Results: Postoperatively, Tramadol was associated with improved subjective analgesic efficacy ($P = 0.031$) and there was significantly less PCA morphine use in the Tramadol group ($P = 0.023$). No differences between the groups were found with regard to nausea dizziness, itching, antiemetic use, sedation, or quality of recovery (all $P > 0.05$).

Conclusions: We conclude that a Tramadol infusion combined with PCA morphine improves analgesia and reduces morphine requirements after cardiac surgery compared with morphine PCA alone.

Key words: patient control analgesia, tramadol, CABG

Introduction

Pain after cardiac surgery may be intense and requires the administration of large doses of opioids (1,2). Pure opioids have a dose-dependent analgesic effect. However, opioid administration is also associated with a number of adverse effects, such as nausea, vomiting, depressed gastrointestinal motility, drowsiness, and, especially with larger doses, respiratory

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depression (3).Non-opioid analgesics, such as nonsteroidal antiinflammatory drugs and paracetamol (acetaminophen), may be useful adjuncts to opioids for postoperative pain relief. Non-opioid analgesics may significantly reduce opioid consumption and the resultant side effects. However, the efficacy of these adjuncts may be limited (4), or they may have potentially serious adverse effects after cardiac surgery, such as increased bleeding and renal failure with nonsteroidal antiinflammatory drugs (5). Tramadol is a unique analgesic with multiple sites of action. It is classified as an atypical centrally acting analgesic, and has opioid and nonopioid properties. Its action on μ-opioid receptors is weak, and naloxone antagonizes only 30% of its analgesic activity (6); -2 adrenoceptor antagonists such as yohimbine significantly reverse Tramadol analgesia (7). Therefore, much of its antinociceptive actions are likely to be via inhibition of reuptake of neurotransmitters, such as norepinephrine and serotonin in the central nervous system (8). Whereas there are data comparing the efficacy of morphine to Tramadol in several surgical populations (9–11), early extubation after cardiac surgery is an important part of fast-track cardiac anesthesia. Immediate extubation is usually safe if good analgesia can be achieved. Patient-controlled analgesia (PCA) has been advocated as superior to conventional controlled analgesia with less risk to patients. In this double-blinded, randomized controlled trial, we tested whether the addition of Tramadol to morphine for patient-controlled analgesia (PCA) resulted in improved analgesia efficacy and smaller morphine requirements compared with morphine PCA alone after Coronary Artery Bypass Graft (CABG) surgery in adults.

Methods:

The study population selected from Rajaei Heart Center, a tertiary center of cardiovascular diseases in Tehran which admitted patients from any part of IRAN. Seventy patients who scheduled for an elective coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass and younger than 70 yrs of age were considered eligible for the study, Patients with poor ventricular function (ejection fraction, > 40%), chronic opiate usage, allergy to opiates or Tramadol , epilepsy, psychiatric disorders involving the use of monoamine oxidase inhibitor or selective serotonin reuptake inhibitor drugs, sleep apnea, impaired hepatic or renal function, diabetes mellitus, unstable angina and previous sternotomy were excluded. All patients continued to receive their cardiac drugs until the morning of the operation, and were informed by the same anaesthesiologist 1 day prior to surgery about PCA, and the visual analogue scale (VAS). The technique of anaesthesia was standardized for all patients. Anaesthesia was induced with midazolam, 0.2mg/kg, and fentany l, 5 -10μg/kg. pancrunume 0.1 mg/kg, was used to facilitate endotracheal intubation. Anaesthesia was maintained with fentanyl, 5–10 μg/kg, and midazolam, 0.1–0.3 mg/kg/h ;and propofol 1.5mg /kg/h N2O was not used. The depth of anesthesia was adjusted with cerebral status monitoring. Throughout the operation, fentanyl, 3 μg/kg, was administered as a standard application before the incision and sternotomy, and at the beginning of cardiopulmonary bypass (CPB). Additional propofol was administered at a dose ranging from 1 to1. 5 mg/kg if the mean arterial pressure (MAP) was more than 100 mmHg before cannulation, more than 80 mmHg during cannulation, or more than 100 mmHg after CPB. In addition, the TNG(nitroglyserin) infusion dose was adjusted to 0.1–0.3 mg/kg/h according to the same criteria. Surgery was performed in a standard fashion through a median sternotomy with saphenous veins and internal thoracic arteries harvested as conduits. A standard crystalloid prime was used in the cardiopulmonary bypass (CPB) circuit. Myocardial protection was achieved with intermittent, antegrade, solution of cardioplegia. Nonpulsatile CPB flow was maintained between 1.5 and 2 L•min–1•m–1 using a membrane oxygenator. Patients were not actively cooled, but their core temperature was allowed to drift to 32 to 34°C. Active rewarming to 37°C was completed before aortic cross-clamp removal. Tracheal extubation was performed when the patient met the following criteria: chest tube output, < 100 ml/h; no arrhythmia; urine output, > 0.5 ml/kg/h; absence of residual muscle paralysis; adequate ventilatory parameters [vital capacity, > 12 ml/kg; respiratory rate, < 25 breaths/min; minute ventilation, > 90 ml/kg/min; fraction of inspired oxygen (Fio2) < 0.6; positive end-expiratory pressure (PEEP) < 7.5 cmH2O; oxygen pressure (Po2) > 90 mmHg].

After operation, all patients were transferred to the intensive care unit (ICU) Patients were randomly put into one of the two groups (group T, n = 35; group C, n = 35) post-operatively, and then Immediately after extubation, all patients

were allowed to use the morphine PCA device (Abbott Pain Management Provider, Class II, Type CF, North Chicago, IL) for 24 h post-operatively, with the initial settings for intravenous morphine as bolus dose of 1 mg, lockout time of 7 min and 4-h limit dosage of 20 mg. The Tramadol group after separated from cardiopulmonary bypass received an intra operative initial loading dose of Tramadol (1mg/kg) and a postoperative infusion of Tramadol at 0.2 mg • kg-1 • h-1 . The control group received an intra operative equivalent volume of normal saline and a postoperative saline infusion (placebo).

Post-operative data (VAS, Ramsay sedation, total morphine consumption and number of PCA demands and boluses) were recorded in the cardiac ICU at 30 min, 1 h, 2 h, 4 h, 12 h and 24 h after extubation by the same anaesthesiologist who had no knowledge of the groups. Furthermore, the side-effects, such as itching, nausea, drowsiness vomiting and respiratory depression, were also evaluated.

Statistical analysis: was performed with intention-to-treat approach. Data were classified as mean ± standard deviation for interval and count (%) for categorical variables. Comparison of baseline data between the groups of study was performed by students' t test or its non-parametric equivalent, Mann Whitney U test for interval data and Chi square test for nominal data. Odds Ratio (OR) with 95% confidence interval (CI 95%) also computed to find the epidemiologic associations. P value less than 0.05 considered as statistically significant.

The trend of pain severity and changes of VAS results (among time intervals and between study groups) were investigated by a repeated measure analysis of variance (ANOVA) model.

Survival analysis was performed by Kaplan – Meier method to study the time of receiving the first dose of morphine sulfate, as a proxy of the time of intolerable pain by patients. Log rank test was used to compare the results between the study groups.

SPSS 15 for windows (SPSS Corporation, Chicago, Illinois) was used for statistical analysis.

Results:

seventy patients (mean age = 58 ± 11.0 years, range 24 to 69 years) enrolled the study. Mean left ventricular ejection fraction (LVEF) was 45 ± 8.4 percent. The average time of surgery and anesthesia was 3.8 ± 0.9 and 5 ± 0.9 hours, respectively. Amounts of fentanyl used peri-operatively were similar in both groups. Patients stayed in intensive care unit (ICU) after surgery with a mean time of 2.2 ± 0.5 days (range 2 to 4 days). (Table-1).Thirty five patients received intravenous tramadol and 35 got normal saline as placebo instead. Baseline data of the study groups are presented in Table-1. No important differences were observed between the groups.

Table-1- Comparison of Baseline Data between tramadol and Placebo Groups.

	tramadol (n = 35)	Placebo (n = 35)	P value
Age years	57 ± 11.5	59 ± 10.4	0.19
Weight (kg)	70 ± 11	68 ± 9	0.54
Height (cm)	168 ± 7	166 ± 7	0.52
Intra-operative fentanyl (µg)	1115 ± 323	1024 ± 288	0.55
Left Ventricular Ejection Fraction percent	44 ± 7.3	44 ± 9.5	0.64
Duration of Anesthesia hours	5 ± 0.7	5 ± 1.1	0.43
Duration of Operation hours	4 ± 0.7	4 ± 1.0	0.57
Cardio-Pulmonary Pump Time minutes	103 ± 58.3	104 ± 41.5	0.63
ICU Stay days	2 ± 0.4	2 ± 0.5	0.52
Number of the Grafts	3 ± 0.4	3 ± 0.3	0.19
Intubation Time hours	14.1 ± 4.3	16.5 ± 14.9	0.32

Severity of pain was measured by a 10-point visual analogue scale (VAS) in different time intervals. The results are summarized in Table-2. Note that the most severe pain had a point which was less than 3. After surgery, patients experienced a period of analgesia. The pain appeared gradually and became more severe by the 6th hour after finishing the operation. Then, the severity of pain decreased until it disappeared the 18th hour after surgery. The significance of this trend was proved by repeated measure ANOVA in both tramadol and placebo groups (p value < 0.001).

The severity of pain was equal in two groups in the first time after operation. The period of analgesia continued in patients

who received tramadol until the 3rd hour after surgery, while in placebo group, the severity of pain was rising. It was observed that in any time interval, the patients in tramadol group experienced a less severe pain, compared to placebo group. This difference was statistically significant (p value < 0.001). In the evaluation of the Ramsay sedation scores, no difference was found between the groups (Figure-1),

Table 2 –Pain Score in Different Time Intervals after Cardiac Surgery in Tramadol and Placebo Groups

	Mean Score ± Standard Deviation					
	1st Hour	3rd Hour	6th Hour	12th Hour	18th Hour	24th Hour
tramadol	0.29 ± 1.17	0.0 ± 0.0*	0.97 ± 2.02*	0.23 ± 1.0*	0.0 ± 0.0*	0.0 ± 0.0
Placebo	0.09 ± 0.59†	0.36 ± 1.26†	2.53 ± 2.43†	0.89 ± 1.83†	0.0 ± 0.0†	0.0 ± 0.0

P value for comparison between tramadol and Placebo (based on repeated measure ANOVA) < 0.001
P value for comparison among time intervals (based on repeated measure ANOVA) < 0.001
* and †: Statistically significant difference in pair wise comparisons (based on Bonferroni post-hoc test). P values range <0.001 to 0.006.

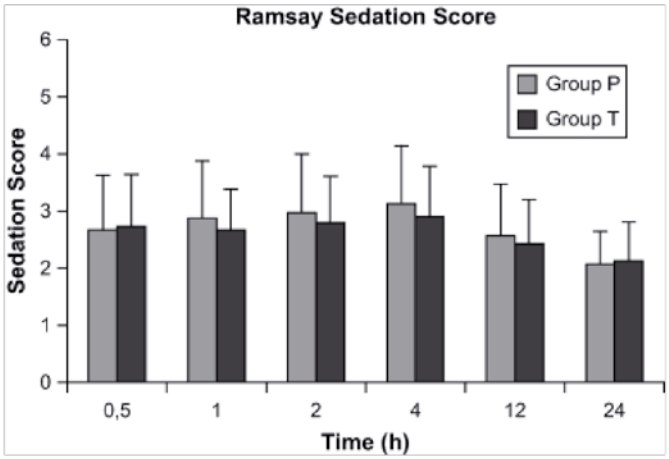

Fig.-1. Post-operative sedation scores. Scores were measured using a Ramsay sedation scale (1, agitated and uncomfortable; 2, cooperative and oriented; 3, obeys simple directions; 4, sleepy with strong reply to stimulation; 5, sleepy with slow reply to stimulation; 6, asleep and does not reply to stimulation). Sedation scores are expressed as the mean ± standard deviation for each group. Group P, saline; group T, tramadol.

The total morphine consumption was higher in group P at all evaluation times and the number of PCA demands and boluses were also higher in group P (P < 0.01) (Table-3).

Table-3:Number of patient-controlled analgesia (PCA) demands and boluses.

	Total demand (*n*)	**Total bolus (*n*)**
Group P	36.9 ± 9.2	30.6 ± 11.3
Group T	29.2 ± 12.3	23.1 ± 8.7

Group P, saline; group T, tramadol. Data are the mean ± standard deviation.

***P* < 0.01, between groups.**

The numbers of post-operative complications are shown in Table-4; there was no statistically significant difference between the two groups.

Table-4:Post-operative side-effects.

	Nausea	Vomiting	Itching	Respiratory depression
Group P	7	1	3	1
Group T	5	0	1	0

Group P, saline; group T, tramadol.

Conclusion:

This study has demonstrated infusion of tramadol following CABG is associated with reduction morphine consumption, a decrease in the VAS scores and an improvement in patient comfort within the first 4 h post-operatively.

Previous studies have demonstrated reduced morphine consumption with various agents employed in the post-operative period of cardiac surgery (5–7, 9). In this way, adverse effects caused by increased morphine doses are minimized. Rapanos et al. (6) reported a 38% decrease in morphine consumption within the first 24 h post-operatively after cardiac surgery with the administration of rectal indometacin, with VAS scores (when not coughing) reduced by 26–66%. Pettersson et al. (7) found a sharpes decrease (22%) in morphine consumption with intravenous rather than oral acetaminophen. In line with previous findings, Hynninen et al. (5) reported that non-steroidal

anti-inflammatory drugs, such as diclofenac, ketoprofen and indometacin, reduce morphine consumption after cardiac surgery, diclofenac being the most potent. Magnesium administration resulted in a decrease in VAS scores and morphine consumption after cardiac surgery in the study by Bolcal et al. (9). In contrast with the above findings, Lahtinen et al. (14) was unable to find a significant difference in pain scores or pulmonary function when propacetamol was administered with an opioid (i.e. oxycodone), and Rauf et al. (15) demonstrated an increase in morphine consumption with remifentanil infusion.

Immer et al. (16) compared the effects of diclofenac, etodolac and tramadol on pain and morphine consumption up to the fourth post-operative day after coronary surgery. Despite the absence of any significant difference between the agents in terms of VAS, morphine consumption and anti-emetic requirements up to the end of the first post-operative day, higher VAS scores and larger anti-emetic requirements were found in the tramadol group between the second and fourth post-operative days, and less morphine was consumed in the etodolac group than in the tramadol group on the fourth post-operative day.

Unlugenc et al. (10) used tramadol for pre-emptive purposes, and found a decrease in morphine consumption after major abdominal surgery. No study regarding pre-emptive agent use in the management of post-operative pain after CABG has been reported to our knowledge, and this may be because of the large amount of narcotics used in the peri-operative period and late extubation. Therefore, in the present study, we used tramadol as a single dose immediately before extubation, instead of pre-emptively.

In the present study, tramadol administration resulted in decreases in morphine consumption of 17%, 20%, 21%, 23%, 27% and 23% at 30 min, 1 h, 2 h, 4 h, 12 h and 24 h post-operatively, respectively. This was accompanied by decreases in the VAS score of 33%, 29%, 34% and 18% at 30 min, 1 h, 2 h and 4 h post-operatively, respectively. The comfort scores of patients receiving tramadol were higher within the first 4 h post-operatively. In addition, less patients required morphine (17%) or bolus doses administered via PCA (21%) in the tramadol group within the first 24 h post-operatively. Overall, these results indicate that the effects of tramadol are more prominent within the first 4 h post-operatively, suggesting a potential for better results with an additional tramadol dose administered at the end of the fourth hour.

When additional analgesic agents are used in the post-operative period, resulting in decreased morphine consumption, the anti-emetic requirement is reduced, gastrointestinal function is restored more rapidly and the post-operative morbidity and time needed for recovery from anaesthesia are decreased (6, 22). In our study, tramadol administration resulted in less frequent nausea, vomiting, respiratory depression and pruritus; however, the differences were not statistically significant.

References:

1. Gurbet A, Goren S, Sahin S et al. Comparison of analgesic effects of morphine, fentanyl, and remifentanil with intravenous patient-controlled analgesia after cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18: 755–8.
2. Mailis A, Umana M, Feindel CM. Anterior intercostal nerve damage after coronary artery bypass graft surgery with use of internal thoracic artery graft. Ann Thorac Surg 2000; 69: 1455–8.
3. Watt-Watson J, Stevens B, Katz J et al. Impact of preoperative education on pain outcomes after coronary artery bypass graft surgery. Pain 2004; 109: 73–85.
4. Checketts MR, Gilhooly CJ, Kenny GN. Patient-maintained analgesia with target-controlled alfentanil infusion after cardiac surgery: a comparison with morphine PCA. Br J Anaesth 1998; 80: 748–51.
5. Hynninen MS, Cheng DC, Hossain I et al. Non-steroidal anti-inflammatory drugs in treatment of postoperative pain after cardiac surgery. Can J Anaesth 2000; 47: 1182–
6. Rapanos T, Murphy P, Szalai JP et al. Rectal indomethacin reduces postoperative pain and morphine use after cardiac surgery. Can J Anaesth 1999; 46: 725–30.
7. Pettersson PH, Jakobsson J, Owall A. Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2005; 19: 306–9.
8. Krishnan K, Elliot SC, Berridge JC, Mallick A. Remifentanil patient-controlled analgesia following cardiac surgery. Acta Anaesthesiol Scand 2005; 49: 876–9.
9. Bolcal C, Iyem H, Sargin M et al. Comparison of magnesium sulfate with opioid and NSAIDs on postoperative pain management after coronary artery bypass surgery. J Cardiothorac Vasc Anesth 2005; 19: 714–8.
10. Unlugenc H, Ozalevli M, Gunes Y et al. Pre-emptive analgesic efficacy of tramadol compared with morphine after major abdominal surgery. Br J Anaesth 2003; 91: 209–13.
11. Duthie DJR. Remifentanil and tramadol: recent advances in opioid pharmacology. Br J Anaesth 1998; 81: 51–7.
12. Roques F, Nashef SA, Michel P et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999; 15: 816–23.
13. Ramsay MA, Savege TM, Simpson BR et al. Controlled sedation with alphaxalone–alphadolone. Br Med J 1974; 22: 656–9.
14. Lahtinen P, Kokki H, Hendolin H et al. Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. Anesth Analg 2002; 95: 813–9.

15. Rauf K, Vohra A, Fernandez-Jimanez P et al. Remifentanil infusion in association with fentanyl–propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia. Br J Anaesth 2005; 95: 611–5.
16. Immer FF, Immer-Bansi AS, Trachsel N et al. Pain treatment with a COX-2 inhibitor after coronary artery bypass operation: a randomized trial. Ann Thorac Surg 2003; 75: 490–5.
17. Sachs CJ. Oral analgesics for acute nonspecific pain. Am Fam Physician 2005; 71: 913–8.
18. Stubhaug A, Grimstad J, Breivik H. Lack of analgesic effect of 50 and 100 mg oral tramadol after orthopaedic surgery: a randomized, double-blind, placebo and standard active drug comparison. Pain 1995; 62: 111–8.
19. Turturro MA, Paris PM, Larkin GL. Tramadol versus hydrocodone–acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial. Ann Emerg Med 1998; 32: 139–43.
20. Stiller CO, Lundblad H, Weidenhielm L et al. The addition of tramadol to morphine via patient-controlled analgesia does not lead to better post-operative pain relief after total knee arthroplasty. Acta Anaesthesiol Scand 2007; 51: 322–30.
21. Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. J Pain Symptom Manage 2002; 23: 121–30.
22. Reuben SS, Connelly NR, Lurie S et al. Dose–response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. Anesth Analg 1998; 87: 98–102.

Influences of Posterior Pericardiotomy in Early and Late Postoperative Effusion of Pericardium.

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Abstract:

Background:Pericardial effusion resulting in cardiac tamponade is uncommon after open heart surgery and is associated with significant morbidity and mortality.

Methods: In a clinical randomized trial 80 patients that have undergone CABG, were divided in two groups, posterior pericardectomy group and control group. Both groups were evaluated after operation by TEE and clinical parameters for early and late post-operative pericardial effusion.

Results: In this study 45% of control group and 5% in study group developed postoperative pericardial effusion, also the incidence of late pericardial effusion was 10% in study group and 57% in control group. Age, Gender, Smoking, Diabetes Mellitus and the Number of grafts didn't have any effect on the incidence of pericardial effusion.

Conclusion: Posterior pericardiotomy as a safe and simple procedure can significantly reduce the incidence of early and late pericardial effusion.

Key words: Pericardial effusion, posterior pericardiotomy.

Introduction

Clinically insignificant pericardial effusion is common following CABG and other open heart surgeries (1), cardiac tamponade; a potentially lethal complication occurs in a minority of patients and is associated with increased perioperative mortality and morbidity (2). Depending on the methodology used for its detection, pericardial effusion have been reported in 4.7 to 85% and cardiac tamponade in 0 to 8.8% of patients(3) early pericardial effusion defined accumulation of fluid in pericardial sac during the first 3 days and late pericardial effusion after 5 to 7 days of CABG, it is often loculated and can result in homodynamic compromise, pre operative and post operative anticoagulation therapy, comorbid disease such as renal failure and hepatic insufficiency are considered to be major contributing factors to the development of pericardial effusion and cardiac tamponade after an open heart surgery(4).

Material and methods:

This study considered a prospective analysis of 80 adult patients that have undergone CABG due to ischemic heart disease over 1 year period from 2009 to 2010.08 CABG patients randomly divided in two equal groups, posterior pericardiotomy group and control group. Posterior pericardiotomy is a 4 to 6 cm incision along the posterior length of left pherenic nerve and initiated near the origin of left inferior pulmonary vein and extended to diaphragm. Patients with the past history of coagulation disorder, renal and hepatic insufficiency and previous open heart surgery and anticoagulation drugs usage were excluded from this study. Echocardiography was performed in all patients to confirm the diagnosis of pericardial effusion or tamponade after surgery. There

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were no risk factors and statistical differences like: age, sex, smoking, DM, HTN, hyperlipidemia, number of grafts and types of grafts for the development of pericardial effusion in both groups. All demographic data were collected in sheets and were analyzed with SPSS 15th version software and examined with T_test and K2, significant P_value was 0.05.(Table.1)

Table 1: Demographic data in two groups

	Case	Control	P_Value
Mean age	60.68+_8.49	60.3+_12.6	0.1
Sex	31(77.5)	32(80%)	0.12
Hyperlipidemia	30(75%)	18(45%)	0.006
DM	26(65%)	15(37.5%)	0.014
Cigarette Smoking	26(65%)	8(20%)	0.01

Results:

Echocardiography was performed in all patients to confirm the diagnosis of pericardial effusion or tamponade. Among 40 patients in control group 18 developed early pericardial effusions in contrast to 2 patients in pericardiotomy group. Also 57% of control group patients developed late effusion Vs 10% in case group (Table 3).

There was no case of readmission for pericardial drainage in 2 groups; anticoagulation drugs were not used in both groups after CABG.

Mean age was 60.5+_10.7 years, mean pump time was 103.8+_43.7 mins and mean cross clamp time was 48.6+_24.9 mins. (Table 1) Number of grafts was the same in 2 groups (Table 2). Criteria for chest tube removal included: out-put less than 100 cc in the last 24 hours on third postoperative day. Mean total drainage of pericardial tubes after surgery was 411.8+|_333 cc.

Table 2: Number of grafts in two groups

Number of grafts	1	2	3	4	5	P_Value
Case	0	6(15%)	23(57.5%)	10(25%)	1(2.5%)	0.621
Control	2(5%)	6(15%)	17(42.5%)	11(27.5%)	4(10%)	

Table 3: Incidence of pericardial effusion after CABG in two groups

	Case	Control	P_Value
Pericardial effusion	2(5%)	18(45%)	0.01
Early PE	2(5%)	23(57.5%)	0.01
Late PE	1(2.5%)	20(50%)	0.01

Discussion:

Complete drainage of fluid and blood from pericardial and pleural cavity after cardiac surgery is very important because the residual blood in there, directly or indirectly, increases morbidity or mortality. The main goal of this study was to find the best method of pericardial and pleural drainage after cardiac surgery.

Pericardial effusion is common after CABG operations with an incidence as high as 85 %(5), few effusions however progress to become hemodynamically significant and results in cardiac tamponade (6).

With regard to high incidence of early and late post operative pericardial effusion, posterior pericardiotomy can be done as a safe and rapid technique at the end of operation in order to reduce the accommodation of fluid and blood in pericardial sac.

Conclusion:

We conclude to perform posterior pericardiotomy in all patients after CABG in order to diminish the amount of fluid and blood accumulation in pericardium, because this is a safe and rapid technique and can reduce early and late pericardial effusion after surgery.

References:

1.Weitzman LB, Tinker WP, Kronzon I, Cohen ML, Glassman E, Spencer FC: The incidence and history of pericardial effusion after cardiac surgery: An echocardiography study. Circulation 1984; 69:506

2.Bora Farsak, Sedar Gunaydin, Hilmi Tokmakoglu, et al .Posterior pericardiotomy reduces the incidence of supra_ventricular arrhythmias and pericardial effusion after CABG.Eeropean journal of cardiothoracic Surgery 22(2002)278_281.

3.Stevenson LW, Child JS, Laks H, Kern L: Incidence and significance of early pericardial effusion after cardiac surgery. American J of Cardiol 1984, 54:848.

4.Ikaheimo MJ, Huikuri HV, et al: pericardial effusion after cardiac surgery, incidence, relation to type of surgery, antithrombotic therapy and early coronary graft patency.American Heart J 1988, 116, 97.

5.John W. Kirklin, Brian G. B-B: Postoperative Care. John W. Kirklin, Brian G. B-B, Nicholas T. Kouchoukos, Eugene H. Blackstone. Cardiac Surgery. 3rd ed. 2003; p: 250

6.D'Cruz IA, Overton DH, Pai GM: Pericardial complications of cardiac surgery: Emphasis on the diagnostic role of echocardiography. J Card Surg 1992; 7(3):257

What's New in Cardiac Surgery?

Abstracts Selected & Summarized by: R.Baghaei M.D; Shahid Rajaee Heart Center, Tehran, Iran

Aortic root aneurysm: Principles of repair and long-term follow-up

J Thorac Cardiovasc Surg 2010;140:S14-S19

Objectives: This study was undertaken to examine clinical and echocardiographic outcomes of aortic valve–sparing operations to treat aortic root aneurysms.

Methods: From May 1988 to December 2007, a total of 228 patients underwent reimplantation of the aortic valve, and 61 underwent remodeling of the aortic root. Patients were followed up prospectively and had echocardiographic evaluation of valve function. Mean follow-up was 7.28 ± 4.33 years.

Results: There were 5 operative and 26 late deaths. Survival at 12 years was 82.9 ± 3.7% and similar between types of operations. Age and aortic dissection were independent predictors of mortality. Seven patients have had reoperations on the aortic valve: 6 for aortic insufficiency and 1 for endocarditis. Five of these patients had undergone remodeling of the aortic root. Freedoms from reoperation at 12 years were 94.3% ± 2.6% among all patients, 90.4% ± 4.7% after remodeling, and 97.4% ± 2.2% after reimplantation (P = .09). Postoperatively, moderate aortic insufficiency developed in 14 patients (8 remodeling and 6 reimplantation) and severe aortic insufficiency in 5 (3 remodeling and 2 reimplantation). The remaining patients had mild, trace, or no aortic insufficiency. Freedoms from moderate or severe aortic insufficiency at 12 years were 86.8% ± 3.8% among all patients, 82.6% ± 6.2% after remodeling, and 91.0% ± 3.8% after reimplantation (P = .035). Only age—by 5-year increments—was an independent predictor of postoperative aortic insufficiency.

Conclusions: Aortic valve–sparing operations provide excellent patient survival and stable aortic valve function, particularly after reimplantation of the aortic valve.

Abbreviations and Acronyms AA = aortic annulus; AI = aortic insufficiency; STJ = sinotubular junction

Outcomes of Surgical Aortic Valve Replacement in High-Risk Patients: A Multiinstitutional Study

Ann Thorac Surg 2011;91:49-56. doi:10.1016/j.athoracsur.2010.09.040

Background: The introduction of transcatheter aortic valves has focused attention on outcomes after open aortic valve replacement (AVR) in very high-risk patients. This study analyzes the short-term and midterm outcomes of AVR in this patient cohort in the current surgical era.

Methods: A retrospective review was performed on 159 patients who underwent isolated, primary AVR with a STS PROM (Society of Thoracic Surgeons predicted risk of mortality) of 10% or greater from January 2002 to December 2007 at four US academic institutions. Patients with previous valve operations were excluded. A multivariable model was constructed to determine predictors of in-hospital mortality. Estimates of the cumulative event rate mortality were calculated by the Kaplan-Meier method.

Results: The mean age of all patients was 76.1 ± 11.2 years, most were men (92 of 159, 57.9%), and mean STS PROM was 16.3% ± 7.3%. Significant preoperative factors included the following: peripheral vascular disease, 33.3% (53 of 159); stroke, 23.3% (37 of 159); renal failure, 50.3% (80 of 159); New York Heart Association class III-IV heart failure, 78.0% (124 of 159); and previous coronary artery bypass grafting, 39.0% (62 of 159). Mean ejection fraction was 0.461 ± 0.153 and median implanted valve size was 23 mm. Postoperative complications included the following: stroke, 4.4% (7 of 159); heart block, 5.0% (8 of 159); multisystem organ failure, 6.9% (11 of 159); pneumonia, 7.5% (12 of 159); and dialysis, 8.2% (13 of 159). Postoperative length of stay was 12.6 ± 11.0 days and in-hospital mortality was 16.4% (26 of 159). One-, three-, and 5-year survival was 70.9%, 56.8%, and 47.4%, respectively.

Conclusions: In the current era, high-risk surgical patients undergoing open AVR have respectable short and mid-term survival. These results should serve as a benchmark for evaluating outcomes of transcatheter aortic valve implantation.

What type of valve replacement should be used in patients with endocarditis?

Interact CardioVasc Thorac Surg 2010;11:784-788. doi:10.1510/icvts.2010.234450

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was 'in patients undergoing a surgery for endocarditis is a biological valve or mechanical valve superior for achieving long-term low rates of reinfection?' Altogether more than 41 papers were found using the reported search, of which nine represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Out of the studies that include statistical comparisons, in mechanical valve replacement the average endocarditis recurrence rate ranged from approximately 3 to 9% and in biological valves from approximately 7 to 29%. Out of the studies that specifically compared the outcomes of the two valves, 50% concluded there to be no significant difference when separated from other risk factors and 50% recommended a mechanical valve for lower recurrence and higher survival rates. The Euro Heart Survey found that 63% of valve replacements were mechanical, due to young age (90%) and physician preference (75%) and only 21% bioprosthetic. Current guidelines from American College of Cardiology/American Heart Association (ACC/AHA) recommend a mechanical valve in patients <65 years old and a bioprosthetic valve if >65, without risk factors for thromboembolism, but this is based on class II evidence (conflicting evidence or opinion). These guidelines are not specific to patients with infective endocarditis, so it is vital to review the literature related to this. Three of the studies in the search specify that for patients under 60–65 years old, a mechanical valve has greater benefit, but this was not found to be true for the over 65 years. It can be concluded that for patients under 65 years old, a mechanical valve may offer greater freedom from reoperation and increased long-term survival when compared to a bioprosthetic valve (assuming no other comorbidities), although this divide is narrowing with the use of newer generation bioprosthetic valves and has to be off-set against potential bleeding risks. For patients over 65 years, other important variants need to be considered including patient choice, correct protocols of antibiotics and radical debridement.

Key Words: Review; Endocarditis; Bioprosthetic valve; Mechanical valve; Reinfection

Robotic repair of posterior mitral valve prolapse versus conventional approaches: Potential realized

J Thorac Cardiovasc Surg 2011;141:72-80.e4

Objective: Robotic mitral valve repair is the least invasive approach to mitral valve repair, yet there are few data comparing its outcomes with those of conventional approaches. Therefore, we compared outcomes of robotic mitral valve repair with those of complete sternotomy, partial sternotomy, and right mini-anterolateral thoracotomy.

Methods: From January 2006 to January 2009, 759 patients with degenerative mitral valve disease and posterior leaflet prolapse underwent primary isolated mitral valve surgery by complete sternotomy (n = 114), partial sternotomy (n = 270), right mini-anterolateral thoracotomy (n = 114), or a robotic approach (n = 261). Outcomes were compared on an intent-to-treat basis using propensity-score matching.

Results: Mitral valve repair was achieved in all patients except 1 patient in the complete sternotomy group. In matched groups, median cardiopulmonary bypass time was 42 minutes longer for robotic than complete sternotomy, 39 minutes longer than partial sternotomy, and 11 minutes longer than right mini-anterolateral thoracotomy (P < .0001); median myocardial ischemic time was 26 minutes longer than complete sternotomy and partial sternotomy, and 16 minutes longer than right mini-anterolateral thoracotomy (P < .0001). Quality of mitral valve repair was similar among matched groups (P = .6, .2, and

.1, respectively). There were no in-hospital deaths. Neurologic, pulmonary, and renal complications were similar among groups (P > .1). The robotic group had the lowest occurrences of atrial fibrillation and pleural effusion, contributing to the shortest hospital stay (median 4.2 days), 1.0, 1.6, and 0.9 days shorter than for complete sternotomy, partial sternotomy, and right mini-anterolateral thoracotomy (all P < .001), respectively.
Conclusions: Robotic repair of posterior mitral valve leaflet prolapse is as safe and effective as conventional approaches. Technical complexity and longer operative times for robotic repair are compensated for by lesser invasiveness and shorter hospital stay.

Abbreviations and Acronyms ANT = mini-anterolateral thoracotomy; CST = complete sternotomy; MR = mitral regurgitation; MV = mitral valve; PST = partial sternotomy; ROB = robotic

Extracorporeal Membrane Oxygenation in Primary Graft Failure After Heart Transplantation

Ann Thorac Surg 2010;90:1541-1546. doi:10.1016/j.athoracsur.2010.05.066

Background: The aim of this review was to analyze our results with extracorporeal membrane oxygenation (ECMO) support for primary graft failure (PGF) in heart transplant recipients.
Methods: A retrospective review of 239 consecutive patients who underwent heart transplantation between January 2000 and August 2009 was performed. Orthotopic, heterotopic, and heart lung transplants were included in this analysis. Over that time period, 54 patients developed PGF, of whom 39 patients required ECMO support. These 39 patients form the basis of this review.
Results: Thirty-four patients (87%) were successfully weaned from ECMO and 29 (74.3%) survived to hospital discharge. There were no significant differences in wean rates or complications between central and peripheral ECMO. Comparison of survival in the 39 ECMO patients to the non-PGF patients (n = 185) showed a significantly worse survival in the ECMO group (p = 0.007). When those patients who died in the first 30 days were excluded, there was no difference in overall survival between groups (p = 0.73).
Conclusions: Extracorporeal membrane oxygenation provides excellent circulatory support for patients with PGF after heart transplantation with good wean and survival to discharge rates.
6- Risk factors of stroke and delirium after off-pump coronary artery bypass surgery

Interactive CardioVascular and Thoracic Surgery 2010, doi:10.1510/icvts.2010.248872
Off-pump coronary artery bypass surgery (CABG) has not abolished the risk of postoperative stroke and delirium seen for on-pump CABG. Advanced arteriosclerotic changes are common in both on-pump and off-pump CABG. We sought to analyze if advanced arteriosclerotic changes are risk factors of stroke or transient ischemic attack (TIA), and delirium after off-pump CABG. Patients undergoing off-pump CABG between 2001 and 2005 were reviewed using medical records (n=685). Potential risk factors of postoperative stroke and delirium were identified from previous studies. Further, variables retrieved from carotid artery duplex scanning as indices of advanced arteriosclerosis, were examined. The incidences of postoperative stroke/TIA and delirium after off-pump CABG were 2.6% (n=18) and 16.4% (n=112), respectively. Carotid artery stenosis >50% was a significant risk factor of stroke or TIA (P=0.02) as well as delirium (P=0.04) after off-pump CABG. A history of atrial fibrillation (AF) (P=0.037) or diabetes mellitus (P=0.041) was a risk factors of postoperative stroke or TIA. In contrast, age over 75 years (P=0.006), creatinine >1.3 mg/dl (P=0.011), a history of hypertension (P=0.001), past history of AF (P=0.024), and smoking (P=0.048) were significant risk factors of postoperative delirium. Keywords: Brain; Coronary artery bypass surgery; Stroke

Myocardial injury is decreased by late remote ischaemic preconditioning and aggravated by tramadol in patients undergoing cardiac surgery: a randomised controlled trial

Interact CardioVasc Thorac Surg 2010;11:758-762. doi:10.1510/icvts.2010.243600

The purpose of this study was to test, whether the late phase of remote ischaemic preconditioning (L-RIPC) improves myocardial protection in coronary artery bypass grafting (CABG) with cold-crystalloid cardioplegia and whether preoperative tramadol modifies myocardial ischaemia–reperfusion injury using the same group of patients in a single-blinded randomized controlled study. One hundred and one adult patients were randomly assigned to either the L-RIPC, control or tramadol group. L-RIPC consisted of three five-minute cycles of upper limb ischaemia and three five-minute pauses using blood pressure cuff inflation 18 hours prior to the operation. Patients in the tramadol group received 200 mg tramadol retard at 19:00 hours, the day before the operation and at 06:00 hours. Serum troponin I levels were measured at eight, 16 and 24 hours after surgery. Myocardial samples for inducible and endothelial nitric oxide synthases (iNOS, eNOS) estimation were drawn twice: before and after cannulation for cardiopulmonary bypass from the auricle of the right atrium. We found that L-RIPC can reduce injury beyond the myocardial protection provided by cold-crystalloid cardioplegia, and tramadol worsened myocardial injury after CABG. Expressions of iNOS were increased in the control (significantly) and L-RIPC groups and dampened in the tramadol group.

Key Words: Myocardial protection; Ischaemic preconditioning; Troponin I; Inducible nitric oxide synthases; Endothelial nitric oxide synthases

Left Atrial Ganglion Ablation as an Adjunct to Atrial Fibrillation Surgery in Valvular Heart Disease

Ann Thorac Surg 2011;91:97-102. doi:10.1016/j.athoracsur.2010.08.037

Background: Our aim was to evaluate early results of ganglionic plexus (GP) ablation with modified Cox maze lesion sets for concomitant atrial fibrillation (AF) during corrective valve surgery.

Methods: Between December 2006 and April 2008, 20 patients (7 men; median age, 65 years; range, 52 to 82 years) with valvular heart disease and AF (intermittent in 12 [60%]) underwent corrective valve surgery with maze and GP ablation. Patients were then compared with a case-matched control cohort who underwent radiofrequency ablation maze alone.

Results: Procedures included mitral valve repair in 7 patients (35%), multivalve procedures in 5 (25%), mitral valve replacement in 4 (20%), aortic valve replacement in 3 (15%), and valve-sparing aortic root replacement in 1 (5%). All patients underwent concomitant AF ablation procedures (biatrial maze in 11 [55%], left-sided maze in 9 [45%]). Ganglionic plexus stimulation was performed in all patients. Sites at which the R-R interval doubled were considered active and were ablated. There were no early deaths. Freedom from AF at 1 year was significantly higher (90% versus 50%; $p = 0.01$) and mean New York Heart Association functional class was better (1 versus 1.7; $p < 0.001$) in the group that underwent maze and GP ablation compared with maze alone.

Conclusions: Active left atrial GP are frequently present in patients with AF and valvular heart disease, and GP ablation can be safely performed as an adjunct to AF ablation during valve surgery. Early results are promising and may yield higher freedom from AF compared with radiofrequency ablation maze alone.

Predictors for hemodynamic improvement with temporary pacing after pediatric cardiac surgery

J Thorac Cardiovasc Surg 2011;141:183-187

Objectives: Temporary epicardial pacing wires are commonly placed during pediatric cardiac surgery. Data are sparse on postoperative pacing in this population. The objective of this study was to determine the frequency of use and identify predictors for the use of temporary epicardial pacing wires.

Methods: Perioperative data were prospectively collected on all patients who underwent cardiac surgery at our institution (n = 162).

Results: A total of 117 (72%) patients had temporary epicardial pacing wires placed. Postoperatively, 23 (20%) of 117 patients had hemodynamic improvement with the use of temporary epicardial pacing wires. Indications for pacing were slow junctional rhythm (11/23 [48%]), junctional ectopic tachycardia (7/23 [31%]), pace termination of supraventricular tachycardia (3/23 [13%]) and atrial flutter (1/23 [4%]), and complete heart block (1/23 [4%]). By using univariate analysis, single-ventricle anatomy, heterotaxy, the Fontan procedure, use of circulatory arrest, intraoperative arrhythmia, pacing in the operating room, and use of vasoactive medications were predictors for hemodynamic improvement with the use of temporary epicardial pacing wires ($P < .05$). On multivariate analysis, the Fontan procedure, circulatory arrest, and intraoperative arrhythmias were independent predictors ($P < .01$). When excluding all patients with any of these 3 risk factors, only 2% were paced. Patients with clinically significant pacing had longer chest tube drainage ($P < .01$) and intensive care unit length of stay ($P < .01$). There were no complications associated with temporary epicardial pacing wires.

Conclusions: The Fontan procedure, use of circulatory arrest, and intraoperative arrhythmias were associated with hemodynamic improvement with postoperative pacing and might represent indications for empiric intraoperative placement of temporary epicardial pacing wires. Patients without these risk factors were less likely to require pacing. Temporary epicardial pacing wires were safe and useful in the management of arrhythmias after pediatric cardiac surgery.

Abbreviations and Acronyms CICU = cardiac intensive care unit; OR = odds ratio

The role of ascorbic acid in the prevention of atrial fibrillation after elective on pump myocardial revascularization surgery: a single center experience-pilot study

Interactive CardioVascular and Thoracic Surgery 2010, doi:10.1510/icvts.2010.240473

Atrial fibrillation (AF) is a common arrhythmia that occurs postoperatively in cardiac surgery. There is evidence for the role of oxidative stress in the etiology of AF. In our study, we examined whether antioxidant ascorbic acid (vitamin C), could help in the reduction of the incidence of postoperative AF. Patients who were scheduled to undergo elective isolated on-pump coronary artery bypass grafting (CABG) were included in our study. One hundred and seventy patients were randomly divided in two groups: Group A (n=85) received vitamin C preoperatively and postoperatively whereas Group B (n=85) did not receive any (control group). The incidence of AF was 44.7% in the vitamin C group and 61.2% in the control group (P=0.041). The hospitalization time, the intensive care unit stay and the time interval for the conversion of AF into sinus rhythm was significantly shorter in the vitamin C group. Patients that developed AF also had longer hospital length of stay (9.5±2.8 days vs. 6.7±1.9, P=0.034). Supplementation of vitamin C reduces the incidence of postCABG AF, and decreases the time needed for rhythm restoration and length of hospital stay. Keywords: PostCABG atrial fibrillation; Oxidative stress; Ascorbic acid; Vitamin C

class I or II, and 61.2% had some degree of persistent mitral regurgitation or stenosis, despite stable hemodynamics. Stenosis is a statistically significant risk factor for surgical intervention at less than 1 year of age and is related to higher overall mortality and incidence of late cardiac failure and mitral dysfunction; parachute mitral valve is related to higher mortality and morbidity.

Conclusions: Mitral valve repair shows acceptable early mortality and reoperation rates. Mitral malformations in the complex group are related to a significantly higher risk of reoperation on the mitral valve. Parachute mitral valve is associated with a higher rate of early mortality.

Abbreviations and Acronyms CI = confidence interval; CMV = congenital mitral valve; MR = mitral regurgitation; MV = mitral valve; NYHA = New York Heart Association; OR = odds ratio

Intermediate-term clinical outcomes of primary biventricular repair for left ventricular outflow tract obstruction and ventricular septal defect

J Thorac Cardiovasc Surg 2011;141:200-206

Objective: Primary biventricular repair for left ventricular outflow tract obstruction and ventricular septal defect remains challenging. The intermediate-term outcomes and risk factors for mortality remain undefined.

Methods: All patients undergoing primary biventricular repair of left ventricular outflow tract obstruction and ventricular septal defect from 1995 to 2008 at the C. S. Mott Children's Hospital, University of Michigan Health Systems were analyzed.

Results: Thirty-one patients (mean age, 18 days; 20 male) with a median follow-up of 6.7 years (range, 0.3–13.5 years) were identified. The ventricular septal defect was enlarged in 15 patients, and a limited atrial septal defect was constructed in 16 patients. There were 6 hospital and 2 late deaths. Ten-year patient survival was 72.3%. Lower body weight (P = .040), complete atrial septal defect closure (P = .026), and longer cardiopulmonary bypass time (P = .026) were risk factors of hospital mortality. An atrial septal defect was patent in 16 patients at discharge, 2 of whom required later surgical closure. Relief of recurrent left ventricular outflow tract obstruction was performed in 1 patient. No patient required pacemaker implantation. Five-year freedom from right ventricle-to-pulmonary artery conduit replacement was 39.3%. Smaller-sized conduit (P = .020) and use of aortic allograft (P = .048) were risk factors for early failure.

Conclusion: Primary biventricular repair for patients with left ventricular outflow tract obstruction and ventricular septal defect provides good early and intermediate-term outcomes. Maintaining a small atrial septal defect may improve hospital mortality. Selective ventricular septal defect enlargement and careful construction of the intraventricular pathway result in a low incidence of recurrent left ventricular outflow tract obstruction, as well as avoidance of heart block. Maximizing valve diameter and avoiding aortic allografts may lengthen conduit longevity.

Abbreviations and Acronyms ASD = atrial septal defect; LV = left ventricle; LVOT = left ventricular outflow tract; LVOTO = left ventricular outflow tract obstruction; MV = mitral valve; PA = pulmonary artery; RV = right ventricle; VSD = ventricular septal defect

Impact of Off-Pump Coronary Artery Bypass Graft Surgery on Postoperative Pulmonary Complications in Patients With Chronic Lung Disease

Ann Thorac Surg 2011;91:8-15. doi:10.1016/j.athoracsur.2010.08.003

Background: Off-pump coronary artery bypass graft surgery (OPCAB) has proven to be beneficial in many high-risk subgroups. This study aims to determine whether OPCAB lowers the incidence of pulmonary complications among patients with chronic lung disease (CLD) when compared with on-pump coronary artery bypass graft surgery (ONCAB).

Methods: From 2002 to 2007, 7,060 patients underwent isolated coronary artery bypass graft surgery in an academic center. Patients were classified according to surgery type (ONCAB or OPCAB) and presence or absence of CLD. A propensity score was produced to estimate each patient's likelihood of being assigned to OPCAB on the basis of 39 preoperative risk factors. Multiple logistic regression models and adjusted odds ratios with 95% confidence intervals were used to evaluate the effect of surgery type, CLD, and their interaction on pulmonary-related complications and mortality.

Results: Among OPCAB patients, 15.3% (720 of 4,693) had CLD compared with 11.2% (264 of 2,367) for ONCAB. Off-pump coronary artery bypass graft surgery was performed in 73.2% of CLD patients compared with 66.5% in those without CLD ($p < 0.0001$). Chronic lung disease was associated with a greater incidence of prolonged ventilation, reintubation, pneumonia, intensive care unit hours, and non–home discharge. After propensity score adjustment, OPCAB was associated with a significantly reduced incidence of prolonged ventilation, pneumonia, intensive care unit stay, and mortality. No significant interactions existed between surgery type and CLD status, suggesting that OPCAB was equally beneficial to patients with and without CLD.

Conclusions: In this series, patients with CLD were more likely to undergo OPCAB. Patients with CLD are at significantly greater risk of pulmonary-related complications than patients without CLD. Off-pump coronary artery bypass graft surgery reduced the incidence of pulmonary complications and mortality in all patients. Importantly, this benefit was seen similarly for patients with and without CLD.

Comparative effects of norepinephrine and vasopressin on internal thoracic arterial graft flow after off-pump coronary artery bypass grafting

J Thorac Cardiovasc Surg 2011;141:151-154

Objective: Vasoconstrictors such as norepinephrine and vasopressin are commonly used to raise the blood pressure during myocardial revascularization. The internal thoracic artery is commonly used for coronary artery grafting because of its long-term patency. However, the internal thoracic artery is a living conduit that responds to vasoactive substances. The objective of this study was to measure change in internal thoracic arterial flow after infusion of norepinephrine or vasopressin.

Methods: Forty-one patients undergoing elective off-pump coronary artery bypass grafting participated in this study. After the median sternotomy, the left internal thoracic artery was dissected with a pedicle and grafted to the left anterior descending artery. After all anastomoses were performed and hemodynamic parameters were stable, the grafted internal thoracic arterial blood flow was measured by transit time flowmeter on the distal portion of the graft as a baseline. Norepinephrine or vasopressin was then infused until mean arterial pressure was increased to 20% of baseline. Graft flow and hemodynamic variables were measured when mean arterial pressure reached the intended level.

Results: Baseline grafted internal thoracic arterial flows were similar (norepinephrine 57.1 ± 17.7 mL min–1, vasopressin 66.0 ± 34.3 mL min–1). With norepinephrine, flow

increased significantly relative to baseline (77.2 ± 31.0 mL min–1); with vasopressin, it remained unchanged (68.3 ± 37.0 mL min–1).

Conclusions: For patients needing vasopressor support after coronary artery bypass grafting, norepinephrine appeared superior to vasopressin because of increased internal thoracic arterial flow.

Abbreviations and Acronyms CVP = central venous pressure; ITA = internal thoracic artery; MAP = mean arterial pressure; PAP = pulmonary arterial pressure

Ventricular Performance in Long-Term Survivors After Fontan Operation

Ann Thorac Surg 2011;91:172-180. doi:10.1016/j.athoracsur.2010.07.055

Background: Ventricular function and arrhythmia in patients with Fontan circulation in long-term follow-up are still unknown.

Methods: We retrospectively reviewed 48 patients who survived and were followed up for more than 15 years, among 110 patients who underwent Fontan operation in our institute from 1979 to 1992. Atriopulmonary connection was performed in 26 patients and total cavopulmonary connection in 22. The patients were categorized into right ventricle, left ventricle, and biventricle groups. Follow-up cardiac catheterization and exercise test were performed routinely every 5 years post surgery. Median age at Fontan operation was 5 years.

Results: Mean follow-up was 18.5 years. Cardiac index in the total cavopulmonary connection group was higher than in the atriopulmonary connection group at 10 and 15 years post surgery ($p < 0.05$). Ejection fraction in the left-ventricle group was higher than in the right-ventricle group. End-diastolic volume at 5, 10, and 15 years was significantly lower than at 1 year ($p < 0.05$). End-diastolic pressure at 10 years was significantly higher than at 1 and 5 years ($p < 0.05$). Beyond 15 years, 6 patients developed ventricular tachycardia. The only significant risk factors for the onset of ventricular tachycardia in a multivariate analysis were age at Fontan operation and absolute age ($p < 0.05$).

Conclusions: Long-term follow-up of patients demonstrated that postoperative ventricular systolic performance seemed to become steady. Ventricular tachycardia was detected 15 years post surgery, especially in older patients with older age at Fontan operation, possibly revealing a risk factor in the long-term postoperative period, thereby meriting further consideration.

Complete atrioventricular septal defect: Outcome of pulmonary artery banding improved by adjustable device

J Thorac Cardiovasc Surg 2011;141:179-182

Objective: We sought to evaluate pulmonary artery banding in infants with complete atrioventricular septal defects.

Methods: From 2000 to 2009, 20 infants with complete atrioventricular septal defects underwent pulmonary artery banding because of unsuitable anatomy (unbalanced ventricles, associated lesions, or both) or clinical condition (infection, chronic lung disease, or noncardiac malformation). Patients were divided into 2 groups: the conventional PAB group (n = 13 [65%]; mean age, 74 ± 56 days [range, 6–187 days]; mean weight, 3.3 ± 1.1 kg [range, 2.1–5.8 kg]) and the FloWatch-PAB group (n = 7 [35%]; mean age, 111 ± 40 days [range, 81–187 days]; mean weight, 4.3 ± 1.2 kg [range, 3.2–6.1 kg]). There was no statistical difference in age or weight. Preoperative mechanical ventilation was required in 3 (23%) of 13 infants in the conventional PAB group and 5 (71%) of 7 infants in the FloWatch-PAB group ($P < .05$).

Results: Ten (77%) of 13 infants in the conventional PAB group died versus 0 (0%) of 7 infants in the FloWatch-PAB group ($P < .001$). Sternal closure was delayed in 6 (46%) of 13 infants in the conventional PAB group and 0 (0%) of 7 infants in the FloWatch-PAB group ($P < .05$). The mean

duration of mechanical ventilation, intensive care unit stay, and hospital stay was significantly longer ($P < .05$) in the conventional PAB group than in the FloWatch-PAB group (21 ± 17 days [range, 4–61 days] vs 3 ± 2 days [range, 1–8 days], 22 ± 18 days [range, 5–61 days] vs 7 ± 6 days [range, 2–21 days], and 54 ± 12 days [range, 40–71 days] vs 29 ± 25 days [range, 9–81 days], respectively). Left atrioventricular valve regurgitation increased (mild to moderate) in 2 infants in the conventional PAB group and decreased (severe to moderate) in 2 infants in the FloWatch-PAB group. Six of 10 survivors (1 in the conventional PAB group and 5 in the FloWatch-PAB group) underwent pulmonary artery debanding and repair after a median interval of 125 days (range, 34–871 days); 4 of 10 are awaiting repair.

Conclusions: In selected patients with complete atrioventricular septal defects, pulmonary artery banding followed by late repair is a viable alternative strategy. In our study the FloWatch-PAB device resulted in improved survival and made later repair possible in a better clinical state.

Abbreviations and Acronyms cAVSD = complete atrioventricular septal defect; PAB = pulmonary artery banding

Do Patients With Complete Transposition of the Great Arteries and Severe Pulmonary Hypertension Benefit From an Arterial Switch Operation?

Ann Thorac Surg 2011;91:181-186. doi:10.1016/j.athoracsur.2010.07.022

Background: Whether an arterial switch operation benefits patients with transposition of the great arteries and severe pulmonary hypertension (PH) remains controversial. Therefore, we evaluated the relationship between preoperative PH and early and midterm clinical outcomes after an arterial switch procedure.

Methods: In this retrospective study, 101 consecutive patients with transposition of the great arteries underwent an arterial switch operation between February 2004 and October 2007. Seventy had a ventricular septal defect as well; patients with intact ventricular septum and complicated concomitant abnormities were excluded. Preoperative medical records were reviewed and mean follow-up was 22.4 ± 15.2 months. After sternotomy, we directly measured pulmonary artery pressure before and after instituting extracorporeal circulation. Patients were divided into three groups according to mean pulmonary artery pressure (mPAP): control group (mPAP < 25 mm Hg, n = 23), moderate PH group (mPAP 25 to 50 mm Hg, n = 37), and severe PH group (mPAP ≥50 mm Hg, n = 10). Early and midterm results were compared among groups.

Results: Postoperatively, pulmonary artery pressure of both the moderate and severe PH groups decreased significantly. There were no significant differences in occurrence of postoperative complications or in-hospital mortality in the three groups (control group, 8.7%; moderate PH group, 8.1%; severe PH group, 10%; $p = 0.98$). However, midterm mortality differed significantly (control group, 4.3%; moderate PH group, 2.7%; severe PH group, 40%; $p < 0.01$).

Conclusions: Patients with transposition of the great arteries and mPAP less than 50 mm Hg can achieve satisfying results after an arterial switch operation. However, even though the operation can decrease pulmonary artery pressure, patients with preoperative mPAP greater than 50 mm Hg still suffer from high midterm mortality.

Blood Transfusion After Pediatric Cardiac Surgery Is Associated With Prolonged Hospital Stay

Ann Thorac Surg 2011;91:204-210. doi:10.1016/j.athoracsur.2010.07.037

Background: Red blood cell transfusion is associated with morbidity and mortality among adults undergoing cardiac surgery. We aimed to evaluate the association of transfusion with morbidity among pediatric cardiac surgical patients.

Methods: Patients discharged after cardiac surgery in 2003 were retrospectively reviewed. The red blood cell volume

administered during the first 48 postoperative hours was used to classify patients into nonexposure, low exposure (≤15 mL/kg), or high exposure (>15 mL/kg) groups. Cox proportional hazards modeling was used to evaluate the association of red blood cell exposure to length of hospital stay (LOS).

Results: Of 802 discharges, 371 patients (46.2%) required blood transfusion. Demographic differences between the transfusion exposure groups included age, weight, prematurity, and noncardiac structural abnormalities (all $p < 0.001$). Distribution of Risk Adjusted Classification for Congenital Heart Surgery, version 1 (RACHS-1) categories, intraoperative support times, and postoperative Pediatric Risk of Mortality Score, Version III (PRISM-III) scores varied among the exposure groups ($p < 0.001$). Median duration of mechanical ventilation (34 hours [0 to 493] versus 27 hours [0 to 621] versus 16 hours [0 to 375]), incidence of infection (21 [14%] versus 29 [13%] versus 17 [4%]), and acute kidney injury (25 [17%] versus 29 [13%] versus 34 [8%]) were highest in the high transfusion exposure group when compared with the low or nontransfusion groups (all $p < 0.001$). In a multivariable Cox proportional hazards model, both the low transfusion group (adjusted hazard ratio [HR] 0.80, 95% confidence interval [CI]: 0.66 to 0.97, $p = 0.02$) and high transfusion group (adjusted HR 0.66, 95% CI: 0.53 to 0.82, $p < 0.001$) were associated with increased LOS. In subgroup analyses, both low transfusion (adjusted HR 0.81, 95% CI: 0.65 to 1.00, $p = 0.05$) and high transfusion (adjusted HR 0.65, 95% CI: 0.49 to 0.87, $p = 0.004$) in the biventricular group but not in the single ventricle group was associated with increased LOS.

Conclusions: Blood transfusion is associated with prolonged hospitalization of children after cardiac surgery, with biventricular patients at highest risk for increased LOS. Future studies are necessary to explore this association and refine transfusion practices

Deep Hypothermic circulatory arrest does not impair neurodevelopmental outcome in school-age children after infant cardiac surgery

Ann Thorac Surg 2010;90:1985-1995. doi:10.1016/j.athoracsur.2010.08.005

Background: The purpose of this study was to assess deep hypothermic circulatory arrest (DHCA) as a modifier of neurodevelopmental (ND) outcomes in preschool children after cardiac surgery in infancy for repair of congenital heart defects (CHD).

Methods: This is a planned analysis of infants enrolled in a prospective study of apolipoprotein E polymorphisms and ND outcome after cardiac surgery. The effect of DHCA was assessed in patients with single or biventricular CHD without aortic arch obstruction. Neurodevelopmental assessment at 4 years of age included cognition, language, attention, impulsivity, executive function, social competence, and visual-motor and fine-motor skills. Patient and procedural variables were evaluated in univariate and multivariate models.

Results: Neurodevelopmental testing was completed in 238 of 307 eligible patients (78%). Deep hypothermic circulatory arrest was used at the discretion of the surgeon at least once in 92 infants (38.6%) with a median cumulative duration of 36 minutes (range, 1 to 132 minutes). By univariate analysis, DHCA patients were more likely to have single-ventricle CHD ($p = 0.013$), lower socioeconomic status ($p < 0.001$), a higher incidence of preoperative ventilation ($p < 0.001$), and were younger and smaller at the first surgery ($p < 0.001$). By multivariate analysis, use of DHCA was not predictive of worse performance for any ND outcome.

Conclusions: In this cohort of children undergoing repair of CHD in infancy, patients who underwent DHCA had risk factors associated with worse ND outcomes. Despite these, use of DHCA for repair of single-ventricle and biventricular CHD without aortic arch obstruction was not predictive of worse performance for any ND domain tested at 4 years of age.

Long-term coronary artery outcome after arterial switch operation for transposition of the great arteries

Eur J Cardiothorac Surg 2010;38:714-720. doi:10.1016/j.ejcts.2010.03.055

Objective: To analyse the long-term patency of coronary arteries after neonatal arterial switch operation (ASO). Methods: A retrospective study of the operative reports, follow-up and postoperative catheterisation data of 119 patients, who underwent the great arteries (TGA) repair since 1991, has been carried out. Patient population: Among the 133 survivors of the 137 ASOs performed between 1991 and 2007, 119 patients have been studied by routine control cardiac catheterisation and form the study population. Median time between repair and the coronary angiography was 2.9 ± 1.9 years. A comparison between the eight patients (6.7% out of the entire study population), known to have postoperative coronary obstructions (group I) and the rest of the cohort with angiographic normal coronary vessels (group II) was performed by univariate analysis of variance and logistic regression models. One patient had surgical plasty of the left coronary main stem with subsequent percutaneous angioplasty, three patients had primary coronary stent implantation and four patients had no further intervention at all. In group I, all but one patient denied symptoms of chest pain and echocardiography failed to show any difference between the two groups in terms of left ventricular systolic function (ejection fraction group I 61 ± 2% vs 62 ± 6% of group II, p = 1.0). Results: The association of coronary obstruction with complex native coronary anatomy (Yacoub type B to E) was evident at both univariate (62% of group I vs 22% of group II, p = 0.04) and logistic regression (p = 0.007, odds ratio (OR) 8.1) models. The type of coronary reimplantation (i.e., coronary buttons on punch vs trap-door techniques) was similar between the two groups (punch reimplantation in 25% of patients of group I vs 31% of group II, p = 0.1) as was the relative position of the great vessels (aorta anterior in 100% of patients of group I vs 96% of group II; univariate, p = 0.1). Conclusions: The late outcome in terms of survival and functional status after ASO is excellent. Nevertheless, the risk of a clinically silent late coronary artery obstruction of the reimplanted coronary arteries warrants a prolonged follow-up protocol involving invasive angiographic assessment.

Key Words: Transposition of the great arteries • Arterial switch operation • Coronary arteries

Surgical repair of congenital mitral valve malformations in infancy and childhood: A single-center 36-year experience

J Thorac Cardiovasc Surg 2010;140:1238-1244

Objective: We sought to evaluate the results of surgical repair and determine predictors for the late outcome of congenital mitral valve dysplasia.

Methods: Preoperative, operative and postoperative data were obtained from an institutional database; follow-up data came from regular clinical evaluation at our institution or elsewhere. Patients were divided into isolated and complex cases according to the complexity of associated lesions.

Results: Between 1972 and 2008, 93 patients (43 male and 50 female patients) underwent mitral repair (median, 4.5 years; range, 0.16–19.8 years). Predominant mitral regurgitation was present in 52%. Associated cardiac anomalies were present in 72%. Sixty-one patients were in the complex group. All patients underwent successful mitral repair. Surgical repair was tailored to the patient's valve anatomy. Early death was 7.5%. The postoperative course was uneventful in 86% of patients. At a mean follow-up of 10.3 years (median, 8.4 years; completeness, 94%), late mortality is 8% (7 patients). Twelve patients underwent mitral reintervention (11 replacements and 1 repair). Among the 80 survivors, 82.5% were in New York Heart Association

Chylothorax secondary to Obstruction of the Superior Vena Cava: A late Complication of the Atrial Septal Defect Repair

Asadollah Mirzai ,MD*,Afsoon Fazlinezhad ,MD ,Mahmood Hosseinzadeh Maleki ,MD, Ali Azari ,MD

Abstract:

A case of thorombosis of the superior vena cava (SVC) was complicated by unilateral chylothorax . Removal of the SVC clot and repairing its stenosis with geor-tex patch led to the prompt resolution of the chylothorax .

Chylothorax is an uncommon result of obstruction of the SVC. The most reported cause is the placement of the central venous catheters.(1-6)

We describe a case of chylothorax after atrial septal defect(ASD) repair with single pericardial patch.

Case Report: A 30-year-old man with exertional dyspnea and cyanosis was referred to this center. The diagnosis of ASD and partial anomalous pulmonary venous connection(PAPVC)was established by transesophageal echocardiography

The patient was treated with single pericardial patch repair and discharged without any complication, Postoperative echocardiography was normal. After two months the patient came back with dyspnea and swelling of the face and neck .

In physical examination the patient was afebrile and had respiratory distress. He was noted to have edema and plethora of the face and signs of the right sided pleural effusion.

Laboratory examination showed a hemoglobin level of 12gr/dl, white cell cunt of 4500/ml. platlets 440000/ml and normal arterial blood gas analysis.

Chest x-ray confirmed a massive right sided pleural effusion. Transesophageal echocardiography (TEE) showed no residual flow across the ASD repair patch and strong evidence of SVC obstruction syndrome due to large obstructing clot in SVC by 2D, color and contrast study. (FIG-1,2)

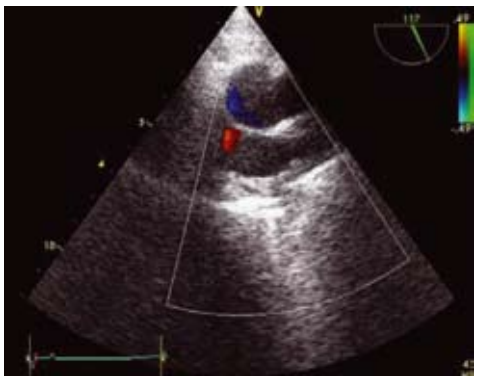

FIG-1: A-Large clot in high transesophagial long axis view of SVC

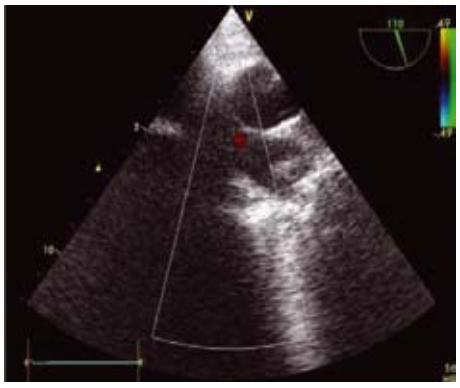

FIG-1: B-Large clot in high transesophagial short axis view of SVC

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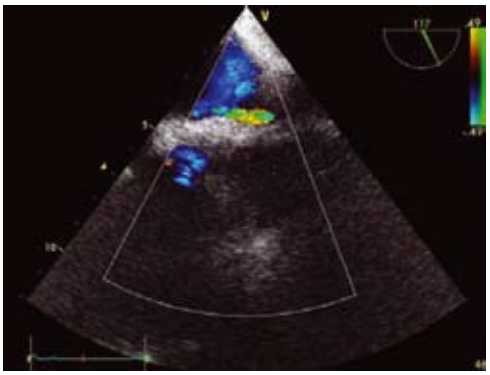


FIG-2:Significant turbulancy in color Doppler study of SVC flow

Right sided cardiac catheterism showed stenosis of SVC.
Thoracocentesis established that the right pleural fluid was chylous .
The patient was reoperated. SVC clot removed and SVC stenosis repaired with geor-tex patch. Chylothorax was resolved after reoperation.(FIG-3)

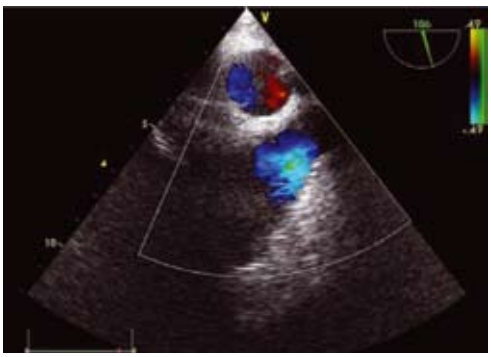


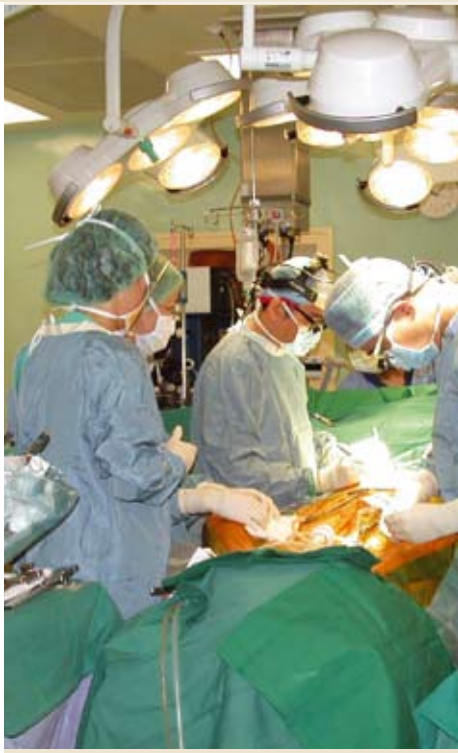
FIG-3:SVC flow by color Doppler study after clot removed

Discussion: The repair of sinus venous arterial septal defect with PAPVC entering the SVC has been a surgical challenge since the earliest reports. (7-8)
Numerous surgical modification have been made to repair the defect and redirect the pulmonary venous return . Although the early problems of persistent PAPVC and residual arterial septal defect have largely been eliminated, problems with SVC stenosis, pulmonary vein stenosis and sinoatrial node dysfunction have remained in many cases.
Chylothorax has been identified as a complication of thorombosis of the superior vena cava.
Blalock et al in 1943 showed that acute interruption of the SVC led to the development of a chylothorax in 60% of cats and dogs(1). Chylothorax has been reported in man as a complication of spontaneous thorombosis or obstruction of the SVC, innominate vein, or sub clavian vein (6). Other cases, occurring in new born infants, children and adults, have been attributed to the placement of centeral venous catheters (2-5).
Ligation of the SVC in animal, causes mediastinal tissues and lymph nodes to become considerably congested with chylous fluid (1).
According to the previous reports, the syndrome of obstructed SVC with chylothorax has a poor prognosis (3-4). Some have observed that, without relief of the venous obstruction, the lungs become lymphangiectatic themselves and this contributes to the long term morbidity(9).
We believe that early relief of the superior vena cava obstruction is important in the management of the chylothorax.

References:

1. Blalock A, Cunningham RS, Robinson CS.Experimental Production of Chylothorax by Occlusion of Superior Vena Cava,.Ann Surg. 1936 Sep;104(3):359-64.
2. Thurer RJ. Chylothorax: a complication of subclavian vein catheterization and parenteral hyperalimentation.J Thorac Cardiovasc Surg. 1976 Mar;71(3):465-8.
3. Kramer SS, Taylor GA, Garfinkel DJ, Simmons MA.Lethal chylothoraces due to superior vena caval thrombosis in infants.AJR Am J Roentgenol. 1981 Sep;137(3):559-63.
4. Seibert JJ, Golladay ES, Keller C .Chylothorax secondary to superior vena caval obstruction.Pediatr Radiol. 1982;12(5):252-4.
5. Vain NE, Swarner OW, Cha CC.Neonatal chylothorax: a report and discussion of nine consecutive cases. J Pediatr Surg. 1980 Jun;15(3):261-5.
6. Golomb HM, Catovsky D, Golde DW.Hairy cell leukemia: a clinical review based on 71 cases.Ann Intern Med. 1978 Nov;89(5 Pt 1):677-83.
7. Schuster SR, Gross RE, Colodny AH. Surgical management of anomalous right pulmonary venous drainage to the superior vena cava, associated with superior marginal defect of the atrial septum.Surgery. 1962 Jun; 51:805-8.
8. Kyger ER 3rd, Frazier OH, Cooley DA, Gillette PC, Reul GJ Jr, Sandiford FM, Wukasch DC.Sinus venosus atrial septal defect: early and late results following closure in 109 patients.Ann Thorac Surg. 1978 Jan; 25(1):44-50.
9. BRANDT M .[Angiomyomatosis of the lungs with honeycomb structure.] Virchows Arch. 1952; 321(6):585-98.

A One-year old infant with multiple cardiac masses and congenital heart disease (A case report)



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Abstract:

We present a one-year old male infant with heart murmurs discovered at birth. Transthoracic echocardiography revealed a perimembranous ventricular septal defect (VSD) as well as multiple cardiac masses. Pediatric cardiologists recommended closure of the VSD and biopsy of the uncertain cardiac masses. The VSD was repaired, and one of the masses was excised and sent for histopathological examination.

Here, we discuss a case of multiple rhabdomyomas in an infant whose associated finding was congenital heart disease, rather than tuberous sclerosis. He was discharged in good clinical condition and his parents were given instructions to have routine follow-up visits for the evaluation of the possible regression of the remaining masses.

Key words: Congenital heart disease- Cardiac masses - Rhabdomyoma

Introduction

Rhabdomyomas are hamartomatous lesions of cardiac myocytes (1), most common in infancy and childhood (2). A well-known association exists between rhabdomyomas and tuberous sclerosis; however, sporadic cases of rhabdomyomas which are solitary and endocardial-based may be seen as well (1,3). The latter is linked with congenital heart disease (2,3). Grossly, the lesions are well-demarcated and yellow-tan; they may exist singly or as multiple nodules or even numerous minute lesions, varying in size from 1 mm to 10 cm (1- 4).

Case Report

We present a one-year-old male infant who was first found to have cardiac murmurs soon after birth. In light of the abnormal heart examination, a transthoracic echocardiographic examination was performed shortly afterwards, which revealed a perimembranous ventricular septal defect (VSD) as well as multiple cardiac masses (Figure-1).

His follow-up by serial echocardiography studies showed two masses in the right atrium and three others in the right ventricle. Some degrees of mitral and tricuspid regurgitation were also noted.

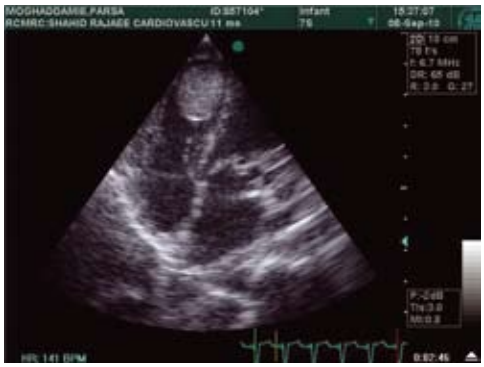

Figure-1: A well-defined mass is shown protruding into the right atrium.

Among other echocardiography findings, subsystemic pulmonary hypertension, as well as a right-sided aortic arch, was noteworthy.

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The only positive physical finding was the enlargement of the liver and spleen; other studies were, however, unremarkable.

The recommendation offered by the pediatric cardiologists was VSD closure and biopsy of the cardiac masses to determine their nature.

The patient underwent a surgical operation, during which the VSD was repaired and one of the more accessible masses in the right atrium was excised and sent to the pathology laboratory. The postoperative course was fortunately uneventful and he left the hospital, advised only to have outpatient visits for a scrutiny of possible size regression in the masses.

The surgical specimen was fleshy and brown in appearance, measuring 1.5 cm in the greatest diameter. The cut surface was solid and brown in color.

Microscopically, a well-circumscribed lesion was seen, with sheets of large cells that had clear cytoplasm (Spider cells). There was no evidence of malignancy in this specimen, and a diagnosis of cardiac rhabdomyoma was established.

The clear appearance of the cytoplasm is in consequence of the cells being embedded with glycogen, which is dissolved during the routine process of histopathology staining.

The reason why the characteristic cell is called "Spider Cell" is in the finding that only a few cytoplasmic projections are extended from the nucleus to the periphery, thus mimicking the shape of spider legs (Figure-2).

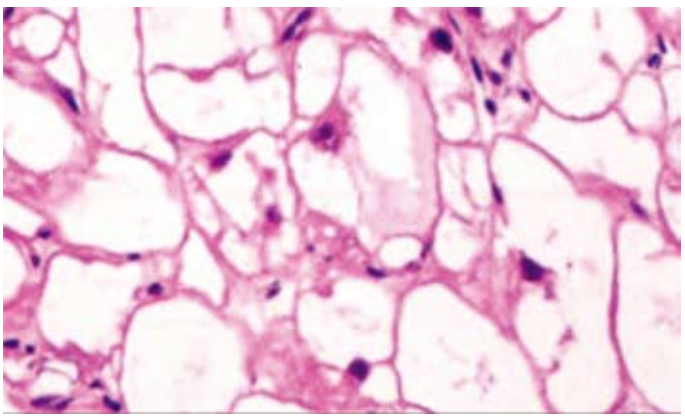

Figure-2:Plump and large clear cells are seen with central nuclei "Spider Cells".
(H& E, X 400)

Discussion:

Rhabdomyomas are considered hamartomatous lesions of cardiac myocytes (1-4) and
are the most common cardiac mass lesions seen in infancy and childhood (2,4).

Rhabdomyomas have a well-known association with tuberous sclerosis and their myriad manifestations. The lesion may, however, regress with time, if the patient survives the first month of life. Sporadic cases of rhabdomyomas, on the other hand, are solitary and endocardial-based. Nevertheless, patients in both of these groups may show certain degrees of morphological overlap (1). These masses also have an association with congenital heart disease (2,3).

Macroscopically, the lesions are well-demarcated and yellow-tan (1,3); they may exist singly or as multiple nodules or even numerous minute lesions, varying in size from 1 mm to 10 cm (2).

The hallmark of histopathological diagnosis is the presence of glycogen-rich Spider Cells. The differential diagnosis may include vacuolated myocardial cells due to glycogen storage disease, in which a diffuse distribution is found in the myocardium (1,3).

Large and single masses are amenable to surgical excision with good long-term results (2).

We herein discussed a case of multiple rhabdomyomas in an infant whose associated finding was congenital heart disease, rather than tuberous sclerosis. He was discharged in good clinical condition, while his parents were advised to have routine follow-up visits for an evaluation of possible size regression in the masses (4).

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References

1. Silver MD, Gotlieb AI, Schoen FJ. Cardiovascular Pathology. 3rd edition, New York, Churchill Livingstone Company, 2001; pp.587-8
2. Chopra P. Illustrated textbook of cardiovascular pathology.1st edition, London, Taylor & Francis Group, 2003; pp .190
3. Rosai J. Rosai and Ackerman's surgical pathology .9th edition, Edinburgh, Mosby company, 2004; pp.2426-7
4. Yuji Matsuoka, Tuyosi Nakati, Kenji Kawaguchi, and Kunio Hayakawa: Disappearance of a Cardiac Rhabdomyoma Complicating Congenital Mitral Regurgitation as Observed by Serial Two-Dimensional Echocardiography, Pediatr Cardiol 11:98-101, 1990