Which Factors Predict the Recovery of Natural Heart Function After Insertion of a Left Ventricular Assist System?

A. Mano, MD, PhD, T. Nakatani, MD, PhD, N. Oda, MD, T. Kato, MD, PhD, K. Niwaya, MD, PhD, O. Tagusari, MD, PhD, H. Nakajima, MD, PhD, T. Funatsu, MD, PhD, S. Hashimoto, K. Komamura, MD, PhD, A. Hanatani, MD, PhD, I. H. Ueda, MD, PhD, M. Kitakaze, MD, PhD, J. Kobayashi, MD, PhD, T. Yagihara, MD, PhD, and S. Kitamura, MD, PhD

Reprinted from
JOURNAL OF HEART AND LUNG TRANSPLANTATION
Vol. 27, No. 8, 2008

Which Factors Predict the Recovery of Natural Heart Function After Insertion of a Left Ventricular Assist System?

A. Mano, MD, PhD,[a] T. Nakatani, MD, PhD,[a] N. Oda, MD,[a] T. Kato, MD, PhD,[a] K. Niwaya, MD, PhD,[a] O. Tagusari, MD, PhD,[b] H. Nakajima, MD, PhD,[b] T. Funatsu, MD, PhD,[b] S. Hashimoto,[c] K. Komamura, MD, PhD,[d] A. Hanatani, MD, PhD,[a] I. H. Ueda, MD, PhD,[e] M. Kitakaze, MD, PhD,[d] J. Kobayashi, MD, PhD,[b] T. Yagihara, MD, PhD,[b] and S. Kitamura, MD, PhD[b]

Background: Recent reports have demonstrated that use of a left ventricular assist system (LVAS) can initiate recovery of cardiac function, and subsequent weaning from the LVAS has attracted considerable interest. In this study we investigated reliable predictors of LVAS weaning.

Methods: Eighty-two patients underwent LVAS implantation between April 1994 and July 2006 at our institution. Cardiac function was restored in 8 patients, who were weaned from LVAS after a mean of 5 months (Group R). Thirty-three patients remained on LVAS support for >1 year (Group N) because natural heart function did not show adequate improvement. We retrospectively evaluated the differences between these two groups. Group R was younger, and had a shorter duration of heart failure than Group N (23.4 vs 36.7 years and 13.3 vs 56.1 months, $p < 0.01$, respectively). Pathologic findings showed that the interstitial fibrosis score was lower in Group R ($p < 0.01$). Three months after LVAS insertion, B-type natriuretic peptide (BNP) and fractional shortening (FS) were more favorable (66.6 ± 46 vs 264.5 ± 170 pg/ml, $p < 0.01$, and 23 ± 17.1 vs 12 ± 9.1%, $p < 0.05$, respectively) in Group R. Furthermore, Group R received a higher dose of β-blocker (15.4 ± 8.4 vs 5.8 ± 3.9 mg, $p < 0.05$).

Conclusions: Younger age, shorter history of heart failure, and less interstitial fibrosis were effective predictors of weaning from LVAS. Restoration of natural heart function was more rapid and more persistent in candidates for LVAS explantation, and presence of β-blocker played a prominent role in improving cardiac function after LVAS implantation. J Heart Lung Transplant 2008;27:869-74. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

The left ventricular assist system (LVAS) is a powerful tool for saving patients with end-stage heart failure. The primary objective of this device is to provide sufficient circulation, to help patients recover from secondary organ dysfunction, and to stabilize them until their own heart function recovers or suitable donor organs are found. However, relatively few patients receive the benefit of heart transplantation, especially in Japan, due to a shortage of donor organs. In a previous study, we have described the possibility of natural heart recovery after profound heart failure using long-term LVAS support.[1] Several recent reports have demonstrated the restoration of native cardiac function during LVAS support, and weaning from LVAS is recognized as a desirable option. Several factors are associated with improvement of natural heart function after LVAS implantation. Levin et al reported reverse remodeling with a decreased LV mass in LVAS-supported patients.[2] Reduced cellular edema,[3] improved myocardial metabolism,[4] reversal of neurohumoral stimulation[5] and decreased apoptosis[6] have also been suggested. Assessment of myocardial recovery during LVAS support is also an area of interest.[7] However, it remains unclear which patients are appropriate candidates for LVAS explantation. In this study we investigated the factors that could predict weaning from LVAS.

METHODS

Patient Population

Between April 1994 and July 2006, 82 patients except post-cardiotomy cases underwent LVAS implantation for end-stage heart failure at our institution. All patients had New York Heart Association Class IV status and were supported by intravenous inotropic agents and/or percutaneous mechanical support. Among these patients, natural heart function was restored and general condition was sufficiently stable in 8 patients (ages 17

From the Departments of [a]Organ Transplantation, [b]Cardiovascular Surgery, [c]Physiology, [d]Cardiology and [e]Pathology, National Cardiovascular Center, Osaka, Japan.

Submitted January 17, 2008; revised May 2, 2008; accepted May 2, 2008.

Reprint requests: Akiko Mano, MD, Department of Organ Transplantation, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. Telephone: +81-6-6833-5012. Fax: +81-6-6872-8160. E-mail: mano@hsp.ncvc.go.jp

 1053-2498/08/$-see front matter. doi:10.1016/j.healun.2008.05.007

to 38 years, 7 males and 1 female; 7 with dilated cardiomyopathy [DCM], 1 with myocarditis) and they were weaned from LVAS after 89 to 310 days (recovery group: Group R). Thirty-three patients were supported by LVAS for >1 year. They remained generally stable, but they could not be weaned from LVAS because of poor native heart function (non-recovery group: Group N). This group comprised 22 males and 11 females, ages 16 to 55 years, and whose etiologies were as follows: 27 had DCM; 3 were in the dilated phase of hypertrophic cardiomyopathy (dHCM); and 3 had secondary cardiomyopathy (sarcoidosis, myopathy and drugs). Of these, 15 patients underwent heart transplantation, 13 died (6 cerebral hemorrhages, 1 cerebral infarction, 6 infections), and 5 remain on the waiting list. Another 3 patients were weaned from LVAS due to cerebral events despite insufficient natural heart recovery. LVAS support was discontinued within 1 year in the other 35 patients because of transplantation or death.

In Group R, 3 patients were given a Toyobo LA LVAS, 4 a Toyobo LV LVAS and 1 a Novacor device. In Group N, 30 patients were given a Toyobo LV LVAS and 3 a HeartMate VE device. We retrospectively evaluated the differences between Group R and Group N. To assess natural heart function, we followed-up echocardiographic parameters and the brain natriuretic peptide (BNP) levels at 1 and 3 months after LVAS implantation. Medical therapy regimens were also evaluated. The investigations complied with the principles outlined in the Declaration of Helsinki. The study was approved by the institutional review board of the National Cardiovascular Center, and all patients provided written informed consent.

Management After LVAS Implantation

After general stabilization, we re-administered a β-blocker (carvedilol), an angiotensin-converting enzyme inhibitor (ACE-I, enarapril) and an aldosterone antagonist (spironolactone).

The maximum titrated doses were 20, 5 and 25 mg, respectively. The criteria by which we introduced or increased these drugs were as follows: systolic blood pressure >80 mm Hg; heart rate >60 beats/min; and no sign of deterioration of heart failure. Adequate rehabilitation was also combined with medical treatments. Nutritional states were assessed and the patients received nutritional intervention if necessary. The pump rate was gradually reduced to 60/min when cardiac function showed no deterioration.

Weaning Protocol

Device explantation was considered if the patients met the following criteria: left ventricular diameter in diastole (LVDd) <55 mm; fractional shortening (FS) >20%; and BNP < 100 pg/ml under minimal LVAS support (60 pumps/min). Candidates for LVAS explantation then underwent dobutamine stress testing. Dobutamine was titrated from 5 to 40 μg/kg/min, and hemodynamic and echocardiographic data were evaluated at each dose level. The test outcome was classified as favorable if the patients showed an increase in cardiac output and FS with an increase in dobutamine, without an increase in pulmonary capillary wedge pressure (PCWP), LVDd and symptoms of heart failure. Those who responded appropriately to dobutamine stress testing were considered candidates for LVAS explantation.

Statistical Analysis

We used Student's unpaired *t*-test to compare continuous variables (all data expressed as mean ± SD) and the chi-square test to compare categoric variables. In time-course analysis (Figure 1), data were analyzed by 2-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS software (version 14-J).

RESULTS

Before LVAS Implantation

Table 1 summarizes the demographics and baseline characteristics of Groups R and N. Group R was significantly younger and had a shorter duration of heart failure than Group N ($p < 0.01$, respectively). Group R had less myocardial fibrosis than Group N ($p < 0.01$). Myocardial hypertrophy tended to be milder in Group R, but the difference did not reach statistical significance. The ratio (%) of patients with dilated cardiomyopathy was similar in both groups. Hemodynamic parameters, echocardiographic parameters, dose of intravenous inotropic agents, ratio (%) of patients supported by percutaneous mechanical assist devices, BNP levels, and degree of other organ dysfunction or anemia did not significantly differ between the two groups. The regimens of medical treatment did not significantly differ between the two groups (Table 2), but the percentage of patients who were given an ACE-I, a β-blocker, a spironolactone or an amiodarone tended to be higher in Group N.

One Month After LVAS Implantation

Echocardiographic parameters (Dd and FS) and BNP levels were more favorable in Group R, but the differences were not statistically significant (Table 3). The ratio (%) of patients who tolerated treatment with a β-blocker was significantly higher in Group R ($p < 0.05$) (Table 4).

Three Months After LVAS Implantation

FS was significantly higher, and BNP levels was significantly lower ($p < 0.05$ and $p < 0.01$, respectively) in Group R than in Group N (Table 5). Furthermore, the

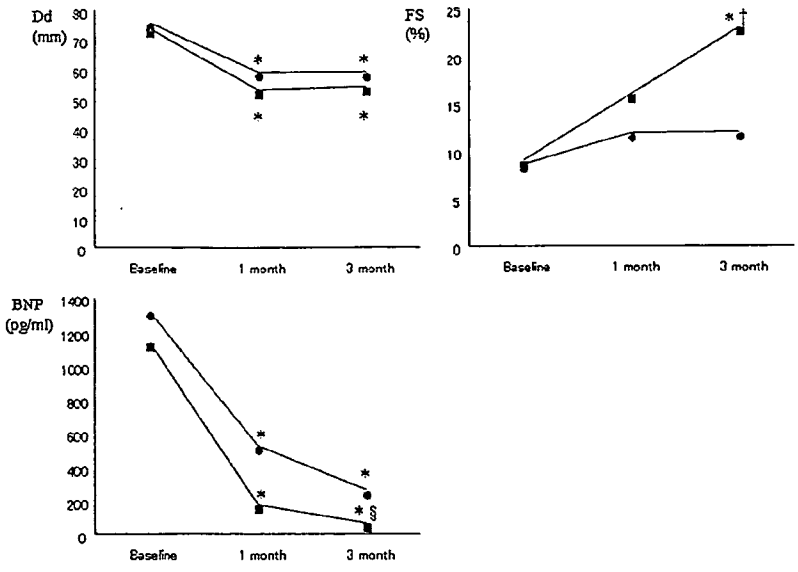

Figure 1. Changes in Dd, FS and BNP after LVAS implantation. Filled squares: Group R; filled circles: Group N. $^{*}p < 0.05$ vs baseline, $^{\dagger}p < 0.05$ vs Group N and $^{\S}p < 0.01$ vs Group N. LVDd, left ventricular end-diastolic dimension; FS, fractional shortening; BNP, brain natriuretic peptide.

increasing rate of FS and the decreasing rate of BNP (3 months after vs before LVAS implantation) were significantly higher in Group R ($p < 0.05$, respectively, data not shown). The dose of β-blocker was higher in Group R ($p < 0.05$) (Table 6). More patients tolerated treatment with an ACE-I or a β-blocker, and Dd tended to be smaller in Group R, but statistical significance was not demonstrated.

Time Course After LVAS Implantation

Figure 1 shows changes in Dd, FS and BNP after LVAS implantation. Improvement of Dd was almost complete

Table 1. Demographics and Baseline Characteristics of Study Population

	Group R ($n = 8$)	Group N ($n = 33$)	p-value
Age (years)	23.4 ± 7.1	36.7 ± 12.4	<0.01[a]
Gender (% female)	12.5	35.3	0.21
Etiology (% dilated cardiomyopathy)	87.5	79.4	0.6
Duration of heart failure (month)	13.3 ± 22	56.1 ± 52	<0.01[a]
Myocardial fibrosis (score)	1.4 ± 0.5	2.5 ± 0.6	<0.01[a]
Myocardial hypertrophy (score)	1.7 ± 0.5	2.2 ± 0.8	0.1
Dose of inotropic agents (DOA + DOB)	9.7 ± 5.6	10.2 ± 4.8	0.83
Use of mechanical support (% IABP and/or PCPS)	62.5	67.6	0.78
Systolic blood pressure (mm Hg)	93 ± 9.0	86 ± 12	0.16
Heart rate (bpm)	116 ± 13	103 ± 25	0.19
Cardiac output (liters/min)	3.21 ± 1.0	3.36 ± 1.0	0.77
Pulmonary capillary wedge pressure (mm Hg)	27.2 ± 4.3	27.2 ± 8.5	0.1
Right atrial pressure (mm Hg)	14.2 ± 5.8	10.2 ± 6.1	0.17
Left ventricular diastolic dimension (mm)	74.1 ± 8.9	75.9 ± 11	0.66
Fractional shortening (%)	9.0 ± 3.7	8.6 ± 4.6	0.84
Wall thickness (mm)	7.6 ± 0.4	7.4 ± 1.4	0.7
B-type natriuretic peptide (pg/ml)	1,140 ± 660	1,282 ± 1,074	0.76
Total bilirubin (mg/dl)	2.6 ± 1.0	1.8 ± 1.0	0.06
Creatine (mg/dl)	1.1 ± 0.5	1.4 ± 1.1	0.52
Hemoglobin (g/dl)	11.4 ± 2.5	10.5 ± 1.8	0.31

Myocardial fibrosis or hypertrophy was classified as mild, moderate or severe and scored as follows: 1 = mild; 2 = moderate; 3 = severe. Dose of inotropic agents is shown as the sum of dopamine (DOA) + dobutamine (DOB). Wall thickness is shown as the mean of the septum and posterior wall. IABP, intra-aortic balloon pump; PCPS, percutaneous cardiopulmonary support.

[a]Statistically significant.

Table 2. Medical Regimens Before LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	37.5	55.9	0.35
β-blocker (%)	12.5	47.1	0.07
Furosemide (%)	100	82.4	0.2
Spironolactone (%)	25	55.9	0.12
hANP (%)	37.5	23.5	0.42
Amiodarone (%)	12.5	50	0.05
Digitalis (%)	37.5	29.4	0.66

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system; ACE-I, angiotensin-converting enzyme inhibitor.

Table 4. Medical Regimens at 1 Month After LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	71.4	41.2	0.14
β-blocker (%)	71.4	26.5	<0.05[a]
Furosemide (%)	85.7	88.2	0.85
Spironolactone (%)	57.1	70.6	0.49
Amiodarone (%)	0	20.6	0.19
Digitalis (%)	57.1	26.5	0.11

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system.
[a]Statistically significant.

within 1 month in both groups. Augmentation of FS continued during the follow-up period in Group R, but was complete at about 1 month in Group N. BNP levels decreased during the first month and continued to decrease thereafter in both groups.

Prognosis of Patients After LVAS Explantation

Table 7 shows prognosis of patients after LVAS explantation. Three of 8 patients have continued to maintain normal ventricular function during follow-up periods ranging from 8 months to 8 years. Four patients developed recurrent but mild heart failure, and were treated in the outpatient clinic for up to 10.5 years. All are being given an ACE-I (enarapril, mean dose 3.75 mg) and a β-blocker (carvedilol, mean dose 16 mg). The other patient did well up to 8 to 9 years after LVAS removal, but then had episodes of heart failure that required re-LVAS implantation 12 years after explantation. He is now on the waiting list.

DISCUSSION

This study has demonstrated that: (1) young patients with a short history of heart failure and less myocardial fibrosis are candidates for LVAS removal; (2) patients who can be weaned from LVAS show rapid and persistent improvement of natural heart function; and (3) a β-blocker is a potent agent that can induce LVAS removal.

Several mechanisms about restoration of the natural heart by LVAS have been reported. Wohlschlaeger et al showed that ventricular pressure and volume unloading by LVAS reduces harmful neurohumoral and cytokine stimulation (systemic and local), and decreases myocardial apoptosis.[8] Heerdt et al suggested that LVAS support increases the gene and protein levels of SERCA 2a, normalizes Ca^{2+} handling[9] and improves myocardial contraction. Brodde et al demonstrated an up-regulation of a β-receptor after LVAS support.[10] The regression of myocyte hypertrophy and interstitial fibrosis has been also suggested.[11,12] These effects, which occur as a result of maximal ventricular unloading, lead to functional recovery of the native heart.

Basal cardiac states, however, might influence the process of functional improvement. Histologic analysis has demonstrated that less myocardial fibrosis is one of the predictors of LVAS weaning.[13] This finding was also demonstrated in our study. Furthermore, in the present study, myocardial hypertrophy tends to be less common in patients who could be weaned from the device, but a significant difference was not detected. Our study found that younger patients with a shorter duration of heart failure before LVAS implantation were suitable candidates for LVAS explantation. These features indicate less pre-operative myocardial degeneration. The timing of LVAS implantation is very important. LVAS implantation in necessary before myocardial damage becomes irreversible for restoration of natural heart after LVAS implantation. Cardiac function and dysfunctional severity of other organs before LVAS implantation were not statistically different between Groups R and N.

The process of natural heart improvement might reach completion within 4 to 5 months after device implantation.[14] Continued ventricular unloading be-

Table 3. Echocardiographic Parameters and BNP Levels 1 Month After LVAS Implantation

	Group R	Group N	*p*-value
Left ventricular diastolic diameter (mm)	53.7 ± 12.4	59.5 ± 17.6	0.42
Fractional shortening (%)	16.1 ± 12.7	11.9 ± 7.7	0.43
BNP (pg/ml)	176.8 ± 151.6	526.2 ± 483.8	0.09

BNP, B-type natriuretic peptide; LVAS, left ventricular assist system.

Table 5. Echocardiographic Parameters and BNP Levels 3 Months After LVAS Implantation

	Group R	Group N	*p*-value
Left ventricular diastolic diameter (mm)	54.7 ± 11.7	58.9 ± 15.4	0.49
Fractional shortening (%)	23.0 ± 17.1	12.0 ± 9.0	<0.05[a]
BNP (pg/ml)	66.6 ± 46.1	264.6 ± 170.1	<0.01[a]

BNP, B-type natriuretic peptide; LVAS, left ventricular assist system.
[a]Statistically significant.

Table 6. Medical Regimens at 3 Months After LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	85.7	55.9	0.14
β-blocker (%)	85.7	55.9	0.14
β-blocker (mg)	15.4 ± 8.4	5.8 ± 3.9	<0.05[a]
Furosemide (%)	57.1	85.3	0.09
Spironolactone (%)	57.1	70.6	0.49
Amiodarone (%)	57.1	32.4	0.22
Digitalis (%)	57.1	29.4	0.16

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system; ACE-I, angiotensin converting enzyme inhibitor.
[a]Statistically significant.

yond this time frame may induce myocardial atrophy and fibrosis. Farrar et al reported that waiting 50 days would capture half of the patients who would ultimately recover ventricular function followed by successful device removal, and waiting up to 90 days could capture 80% of them.[5] We evaluated several parameters at 1 and 3 months after LVAS implantation. Natural heart function was restored more rapidly and the improvement persisted for longer in the weaned patients (Group R). They recovered completely, essentially within 3 months, and were weaned from LVAS after a mean of 5 months of support. BNP was the first representative indicator of native cardiac recovery, which was followed by echocardiographic improvement. None of the patients in whom restoration of the native heart was not indicated for these periods could be weaned from LVAS. This timing is compatible with the findings of Farrar et al.

Recently, the β-blocker has been recognized as being highly beneficial for patients with chronic heart failure, and is becoming the first-line drug treatment for heart failure.[15-17] However, the effect of a β-blocker in patients with LVAS is unclear. We found here that the ratio (%) of patients who tolerated treatment with a β-blocker at 1 month after LVAS insertion and the dose of a β-blocker at 3 months after device implantation were significantly higher in weaned than in non-weaned patients. This result indicates that a β-blocker is useful in patients with LVAS. Several mechanisms underlying the favorable effects of β-receptor blockage have been suggested. A β-blocker restores the function of the calcium-release channel and improves cardiac muscle performance.[18] It also improves myocardial energetics, attenuates myocardial apoptosis, and abrogates induction of the fetal gene program.[19] These effects ultimately help to prevent and reverse ventricular remodeling. Also, these mechanisms might strengthen restoration of the natural heart induced by LVAS. Our findings directly show the importance of β-blocker treatment in patients with first-time LVAS. The percentage of patients who tolerated treatment with an ACE-I after LVAS implantation was also higher in the weaned group, but the values did not reach statistical significance. Conversely, more patients were given a β-blocker, ACE-I, spironolactone and amiodarone before LVAS implantation in the non-weaned group. This may be dependent on the longer duration of heart failure in those patients.

Study Limitations

The present study has several limitations. First, the population size in this investigation was relatively small because the percentage of patients able to be weaned from LVAS is small. Second, the etiologies of patients are various due to the same reason (we could not focus specifically on DCM patients). Third, we demonstrated the effect of a β-blocker. However, we could not standardize the medical regimens after LVAS implantation. Further examinations on larger numbers of patients with uniform etiology and medical treatments are necessary.

In conclusion, weaning from LVAS might be feasible in selected patients. Adjunctive treatments as well as adequate unloading are important in those who

Table 7. Prognosis After Explanation of the Left Ventricular Assist System

Patient no.	Age (years)	Gender	Left ventricular diastolic dimension (mm)	Fractional shortening (%)	B-type natriuretic peptide (pg/ml)	New York Heart Association class	Current status	Duration after explantation
1	29	M	69	5	124	I	Re-LVAS implantation, in hospital, on waiting list	12 years
2	31	M	66	17	103	II	Well, at home	10 years 5 months
3	33	M	50	28	12	I	Well, at home	8 years
4	44	F	53	36	21	I	Well, at home	5 years 7 months
5	25	M	69	10	548	I	Well, at home	5 years 5 months
6	30	M	72	8	275	II	Well, at home	4 years 1 month
7	19	M	91	12	848	II	Well, at home	3 years
8	26	M	51	31	26	I	Well, at home	8 months

have the capability of natural heart restoration. Further studies on LVAS weaning are desirable.

REFERENCES

1. Nakatani T, Sasako Y, Kumon K, et al. Long-term circulatory support to promote recovery from profound heart failure. ASAIO J 1995;41:M526-30.
2. Levin H, Oz M, Chen J, et al. Reversal of chronic ventricular dilatation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 1995;91:2717-20.
3. Schenin S, Capek P, Radovancevic B, et al. The effect of prolonged left ventricular assist support on myocardial histopathology in patients with end stage cardiomyopathy. ASAIO J 1992; 38:M271-4.
4. Lee S, Oskbakken M, Doliba N, Oz M, Mancini D. LVAD therapy improves myocardial mitochondrial metabolism in patients with heart failure. J Thorac Cardiovasc Surg 1998;116:1-6.
5. Levin H, Chen J, Oz H, et al. Potential for left ventricular assist device as out-patient therapy while awaiting transplantation. Ann Thorac Surg 1994;58:1515-20.
6. Belland S, Grunstein R, Jeevanadam V, Eisen H. The effect of sustained mechanical support with left ventricular assist devices on myocardial apoptosis in patients with severe dilated cardiomyopathy. J Heart Lung Transplant 1998;17:83A.
7. George RS, Yacoub MH, Tasca G, et al. Hemodynamic and echocardiographic responses to acute interruption of left ventricular assist device support: relevance to assessment of myocardial recovery. J Heart Lung Transplant 2007;26:967-73.
8. Wohlschlaeger J, Schmitz KJ, Schmid C, et al. Reverse remodeling following insertion of left ventricular assist devices (LVAD): a review of the morphological and molecular changes. Cardiovasc Res 2005;68:376-86.
9. Heerdt PM, Holmes JW, Cai B, et al. Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. Circulation 2000;102:2713-9.
10. Brodde OE. Beta-adrenergic receptors in failing human myocardium. Basic Res Cardiol 1996;91(suppl 2):35-40.
11. Zafeiridis A, Jeevanandam V, Houser SR, Margulies KB. Regression of cellular hypertrophy after left ventricular assist device support. Circulation 1998;98:656-62.
12. Kucuker SA, Stetson SJ, Becker KA, et al. Evidence of improved right ventricular structure after LVAD support in patients with end-stage cardiomyopathy. J Heart Lung Transplant 2004;23:28-35.
13. Loebe M, Muller J, Hetzer R. Ventricular assistance for recovery of cardiac failure. Curr Opin Cardiol 1999;14:234-48.
14. Entwistle JW III. Short- and long-term mechanical ventricular assistance towards myocardial recovery. Surg Clin N Am 2004;84:210-21.
15. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.
16. MERIT-HF. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
17. CIBIS-II. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. Lancet 1999;353:9-13.
18. Reiken S, Wehrens X, Vest J, et al. β-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. Circulation 2003;107:2459-66.
19. Sabbah HN. Biologic rationale for the use of beta-blockers in the treatment of heart failure. Heart Fail Rev 2004;2:91-7.

Replacement of the descending aorta: Recent outcomes of open surgery performed with partial cardiopulmonary bypass

Kenji Minatoya, MD, PhD, Hitoshi Ogino, MD, PhD, Hitoshi Matsuda, MD, PhD, Hiroaki Sasaki, MD, PhD, Toshikatsu Yagihara, MD, PhD, and Soichiro Kitamura, MD, PhD

Objective: Surgical replacement is our standard treatment for descending aortic aneurysm, despite the advent of thoracic endoprostheses. We retrospectively analyzed outcomes of descending aortic replacement performed with partial cardiopulmonary bypass.

Methods: Since 1994, a total of 113 patients in our institution (mean age 68 ± 12 years, n = 75 male) have undergone graft replacement of the descending aorta for nondissecting aneurysm. There were 16 emergency cases (14.2%). All operations were performed through left thoracotomy with partial cardiopulmonary bypass with segmental clamping. Since 1998, preoperative magnetic resonance angiography has been performed to detect the Adamkiewicz artery in elective cases. Motor evoked potentials are now measured intraoperatively.

Results: Early mortalities were 5.3% overall (6/113), 1.0% (1/97) in elective cases, and 31.3% (5/16) in emergency cases. Rates of spinal cord dysfunction were 2.7% overall (3/113), 1.0% (1/97) in elective cases, and 12.5% (2/16) in emergency cases. Stroke rates were 7.1% overall (8/113), 4.1% (4/97) in elective cases, and 25.0% (4/16) in emergency cases. Rates of respiratory failure were 9.7% overall (11/113), 9.2% (9/97) in elective cases, and 12.5% (2/16) in emergency cases. No patient underwent reoperation for the same lesion as a result of repair problems in the follow-up period. Kaplan–Meier overall survival estimates were 92.2% at 3 years, 90.6% at 5 years, and 70.2% at 10 years.

Conclusion: Although it is more invasive than stent graft repair, descending aorta replacement performed with partial cardiopulmonary bypass involves a risk comparable to that associated with thoracic endoprosthesis placement.

From the Department of Cardiovascular Surgery, National Cardiovascular Center, Suita, Japan.

Read at the Thirty-second Annual Meeting of The Western Thoracic Surgical Association, Sun Valley, Idaho, Jun 21–34, 2006.

Received for publication Oct 19, 2006; revisions received Feb 10, 2008; accepted for publication March 30, 2008.

Address for reprints: Kenji Minatoya, MD, PhD, Department of Cardiovascular Surgery, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka, 5658565 Japan (E-mail: minatoya@hsp.ncvc.go.jp).

J Thorac Cardiovasc Surg 2008;136:431-5

0022-5223/$34.00

doi:10.1016/j.jtcvs.2008.03.034

Surgical treatment for a descending thoracic aneurysm (DTA) is changing drastically in response to the advent of endovascular treatment. Endoprostheses have been used for DTA, with generally favorable results.[1,2] Stent graft repair for thoracic aortic diseases is a therapeutic option even for high-risk patients who are not candidates for open surgery. Open surgical replacement, however, is still our current standard treatment for DTA. There are several operative strategies for DTA, such as the single-clamp technique,[3] distal perfusion with left heart bypass,[4] hypothermic circulatory arrest,[5] and partial cardiopulmonary bypass (PCPB).[6] We have usually used PCPB for DTA, with hypothermic circulatory arrest when there is no space for crossclamping. We retrospectively analyzed the outcomes for DTA repair performed with PCPB and compared them with those reported in the literature for endoprostheses.

Materials and Methods

Patients

From 1994 to 2004, a total of 113 patients (75 men, mean age 68 ± 12 years) underwent graft replacement of the descending aorta for nondissecting aneurysm. The cases that required open

Abbreviations and Acronyms
AKA = Adamkiewicz artery
DTA = descending thoracic aneurysm
MEP = motor evoked potential
PCPB = partial cardiopulmonary bypass

proximal anastomosis under circulatory arrest were excluded, and the patients in this study had sufficient space for crossclamping next to the left subclavian artery and celiac artery. There were 16 cases of emergency surgery (14.2%), all because of rupture of the aneurysm. Fifteen patients had undergone previous abdominal aortic replacement, 3 had undergone previous thoracoabdominal aortic replacement, and 11 had undergone previous thoracic aortic replacement. Since 1998, preoperative magnetic resonance angiography has been performed to detect the Adamkiewicz artery (AKA) in elective cases.[7] The AKA was preoperatively imaged by contrast magnetic resonance angiography with gadolinium dimeglumine (0.3 mmol/kg body weight). Early- and late-phase images were used to differentiate arteries from veins. Imaging volumes covered the levels between T6 and L3. The AKA and the anterior spinal artery were identified by at least two radiologists in 0.6-mm contiguous sections processed by multiplanar reconstruction. Our institution approved this retrospective study and did not require patient consent on the condition that patients not be identified.

Operative Techniques

The patients were anesthetized and intubated with a double-lumen endotracheal tube. The patients were then positioned in the right lateral decubitus position with the hips flexed 60°. An incision was made from the vertebral border of the scapula to the costal cartilage along the intercostal space. From the 4th to the 7th intercostal space, access to the left thorax was selected according to the location of the aneurysm. The left or right femoral artery and vein were dissected and looped with umbilical tape. A cannula was inserted in the femoral artery for perfusion inflow, and another cannula was inserted in the femoral vein for perfusion outflow. The tip of the venous cannula was placed at the opening of the inferior vena cava in the right atrium, with placement confirmed by transesophageal echocardiography. PCPB was initiated, and normal proximal aortic pressure was maintained; the flow rate was usually around 1.5 to 2.0 mL/(min · m^2). The pump circuit had an extracorporeal membrane oxygenator, including a heat exchanger. The bladder temperature was cooled to between 33°C and 34°C during PCPB.[8] The DTA was exposed and clamped after establishment of PCPB. The clamps were placed sequentially when the aneurysm involved a long segment. The aorta was opened longitudinally, and intercostal arteries were ligated or oversewn for hemostasis when they were considered to be unimportant. Intercostal arteries that had to be reattached or preserved were temporarily closed with a bulldog clamp or small balloon-tip catheters. The anastomosis was always performed with complete transection of the descending aorta. An appropriately sized Dacron polyester fabric graft was chosen, and the proximal anastomosis was performed first with running 3-0 or 4-0 polypropylene suture with a polytetrafluoroethylene felt strip. Intercostal arteries were reattached with a short, small-caliber graft. The distal anastomosis was then performed with running 3-0 or 4-0 polypropylene suture with a polytetrafluoroethylene felt strip. The flow of PCPB was reduced, and the aortic clamps were then gently released. The patient was weaned from PCPB once the bladder temperature reached 36.5°C.

We have been measuring motor evoked potentials (MEPs) during surgery since 1998 to detect spinal ischemia and have previously described the details.[9] With sufficient anesthesia maintained with low doses of fentanyl (0.02–4 mg/kg), propofol (4—6 mg/[kg · h]), and vecuronium (0.04 mg/[kg · h]), the motor cortex was activated by 600 V transcranial electrical stimulation. The action potentials conducted through the anterior horn motor neurons were recorded from the skin over the upper extremity muscles (as a control), the lower extremity muscles, and the thenar muscles. The signals of the MEPs are affected by femoral arterial cannulation; the probe was therefore always placed on the contralateral side from femoral cannulation. Monitoring of MEPs is also influenced by anesthesia, including neuromuscular blockade, only a low dose of vecuronium was therefore used during the operation. During crossclamping, MEP levels were determined every 2 to 5 minutes. A fall in MEP amplitude below 25% of the baseline was taken to indicate ischemia of the spinal cord. When critical reduction of MEP amplitude was observed, rapid revascularization of the spinal cord blood supply was performed. Additionally, the blood pressures of upper and lower body were increased with use of catecholamines, transfusion, and perfusion flow.

Definitions

Early mortality was defined as death during the hospital stay. Postoperative stroke was defined as newly developing neurologic deficit confirmed by computed tomography. Neurologic diagnoses were made by neurologists. Respiratory failure was defined as the need for intubation and ventilatory support longer than 72 hours.

Statistical Analysis

Values are the mean ± SD. Data were analyzed with Fisher exact tests for categorical variables.

Results

The early mortalities were 5.3% overall (6/113), 1.0% (1/97) in elective cases, and 31.3% (5/16) in emergency cases. The rates of spinal cord dysfunction were 2.7% overall (3/113), 1.0% (1/97) in elective cases, and 12.5% (2/16) in emergency cases. Spinal cord dysfunction occurred more frequently in patients older than 75 years and was not prevented by preoperative AKA detection (Table 1). The stroke rates were 7.1% overall (8/113), 4.1% (4/97) in elective cases, and 25.0% (4/16) in emergency cases. Stroke occurred most frequently in emergency cases, but it was not related to crossclamping adjacent to the aortic arch (Table 2). The rates of respiratory failure were 9.7% overall (11/113), 9.2% (9/97) in elective cases, and 12.5% (2/16) in emergency cases.

Thirty-two patients were older than 75 years, and 9 of these underwent emergency operations. The older patients' mortality was 6.3% (2/32), and the 2 patients who died had both undergone emergency operations. The rates of spinal

TABLE 1. Spinal cord dysfunction and variables

	Total	Spinal cord dysfunction	*P* value
All	113	3 (2.7%)	
Male	76	3 (3.9%)	.55
Age			
>70 y	56	3 (5.4%)	.12
>75 y	32	3 (9.4%)	.02
Partial cardiopulmonary bypass duration			
>60 min	83	3 (3.6%)	.99
>90 min	39	1 (2.5%)	.99
>120 min	15	1 (6.7%)	.36
Emergency operation	16	2 (12.5%)	.05
Preoperative Adamkiewicz artery detection	50	2 (4.0%)	.59

cord dysfunction in this age group were 9.3% overall (3/32), 4.3% (1/23) in elective cases, and 22.2% (2/9) in emergency cases. The stroke rates were 9.4% overall (3/32), 0% (0/23) in elective cases, and 33.3% (3/9) in emergency cases. The rates of respiratory failure were 12.5% overall (4/32), 13.0% (3/23) in elective cases, and 11.1% (1/9) in emergency cases.

Overall, the mean operative time was 291 ± 93 minutes, the mean PCPB time was 84.8 ± 32.1 minutes, the mean bleeding volume was 1187 ± 1432 mL, and the mean transfusion volume was 1335 ± 2642 mL, with 45.1% of the patients not requiring transfusion. In elective cases, the mean operative time was 280 ± 78 minutes, the mean PCPB time was 80.7 ± 27.7 minutes, the mean bleeding volume was 921 ± 845 mL, and the mean transfusion volume was 851 ± 1870 mL, with 51.5 % of the patients not requiring transfusion.

Magnetic resonance angiography was performed in 65 cases, and the AKA was detected in 50 patients (76.9%). Among these patients, 2 had paraplegia; the AKA had been detected in both. Three patients had paraplegia or paraparesis: 1 had undergone surgery without MEP monitoring, another showed MEP change, and the third patient showed no change in MEPs. MEPs were altered in 2 patients; 1 had paraplegia and the other had a postoperative stroke.

None of the patients underwent reoperation for the same lesion to repair problems in the follow-up period. Kaplan–Meier overall survival estimates were 92.2% at 3 years, 90.6% at 5 years, and 70.2% at 10 years (Figure 1).

Discussion

DTA repair is usually discussed in combination with thoracoabdominal aortic aneurysms. Reports focusing solely on surgical repair for DTA are relatively uncommon. Many DTAs will probably be repaired with endoprostheses, because a DTA has no visceral branches. The advent of endovascular treatment is believed to be a great innovation in treatment for aortic aneurysm. Endoprostheses have been used for abdominal aortic aneurysms, and some surgeons are now using them for DTA repair. Makaroun and colleagues[2] used the GORE TAG thoracic endoprosthesis in 139 patients with DTA. They reported that the procedure time was 150 minutes on average, blood loss was 506 mL on average, and that mortality, stroke, and spinal ischemia rates were 1.5%, 4% and 3%, respectively. Fattori and colleagues[10] used the Talent thoracic stent graft for DTA in 457 patients. They reported mortalities of 7.9% in acute cases and 4% in elective cases, a stroke rate of 3.7%, and a spinal ischemia rate of 1.7%.

The articles on endoprostheses refer to open repair of DTA, and they often point out that the mortality associated with open repair is greater than 10% and that the risk of spinal ischemia is 4% to 5%. On the other hand, the results of open repair are improving. Coselli and colleagues[11] reported a mortality of 4.4% and a paraplegia rate of 2.6% after open repair of DTA. Estrera and associates[12] reported a mortality of 8.8%

TABLE 2. Stroke and variables

	Total	Stroke	*P* value
All	113	8 (7.1%)	
Male	76	5 (6.6%)	.72
Age			
>70 y	56	4 (7.1%)	.99
>75 y	32	3 (9.4%)	.69
Partial cardiopulmonary bypass duration			
>60 min	83	8 (9.6%)	.20
>90 min	39	5 (12.8%)	.13
>120 min	15	3 (20.0%)	.08
Emergency operation	16	4 (25.0%)	.01
Crossclamp near arch	37	4 (10.8%)	.43

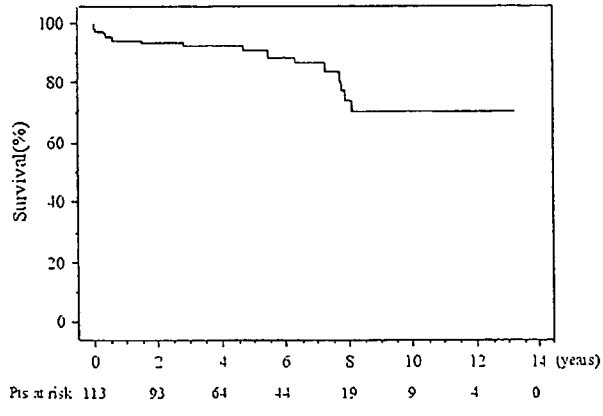

Figure 1. Kaplan–Meier cumulative actuarial survival curve.

and a paraplegia rate of 2.7% after open repair of DTA with cerebrospinal fluid drainage and distal perfusion. Even with hypothermic circulatory arrest, Patel and coworkers[13] reported a mortality of 6.0%, a stroke rate of 6.8%, and a spinal ischemia rate of 4.5%. Our results were comparable with or even better than those reported for open repair and for endoprostheses. Open repair of DTA has several merits relative to repair with an endoprosthesis, especially long-term durability. Moreover, there are no anatomic limitations such as interfere with the applicability of an endoprosthesis, including short or wide proximal or distal landing zones, severe neck angulations, and tortuous or stenotic access arteries.[14]

Stroke is a devastating complication after aortic surgery. The incidence and etiology of stroke related to DTA repair have not been frequently described. Attention is generally paid to spinal ischemia as a primary neurologic complication of DTA repair. Actually, DTA repair with PCPB involves a certain risk of stroke, as indicated in this study. Goldstein and colleagues[15] reported a stroke rate of 8.1 % in DTA repair and also noted that stroke was a significant predictor of postoperative death. Patel and coworkers[13] reported a stroke rate of 6.8% in DTA repair with hypothermic circulatory arrest. The retrograde flow of PCPB from femoral cannulation when normal proximal aortic pressure is not maintained could be a reason for the stroke risk. Moreover, crossclamping adjacent to the aortic arch has also been mentioned as a cause of stroke.[16] In our study, however, some patients without crossclamping adjacent to the aortic arch still had stroke occur under normal proximal aortic pressure. Crossclamping adjacent to the aortic arch was not a statistically significant risk factor of stroke in our study.

The preoperative detection of AKA by magnetic resonance angiography is, we believe, useful in preventing spinal cord injury during DTA repair. The utility of the detection of AKA has already been described elsewhere, and the effects were reflected in the lower rate of spinal ischemia. Although the spinal blood supply is not completely understood, we consider that reimplantation or preservation of the intercostal arteries, which connect the AKA, contributes to improved results. In this study, however, 2 patients showed spinal ischemia despite detection of the AKA. This implies that preservation of the AKA per se is not enough to prevent spinal ischemia. MEPs have been reported to be a rapid indicator of spinal cord injury during thoracoabdominal aortic repair.[17] We also believe that MEP monitoring contributes to prevention of spinal cord injury, even during DTA repair, but such an effect was not clear in this study.

Advanced age is supposed to be among the risks for DTA repair. Huynh and colleagues[18] reported a stroke rate of 9% in their series of descending and thoracoabdominal aortic replacements in patients of advanced age. In this study, the frequencies of stroke in patients older than 70 years and in those older than 75 years old were comparable. No deaths and no postoperative strokes were seen among elective cases. The rate of respiratory failure, however, was high even in elective cases, as expected.

In conclusion, outcomes of traditional open DTA repair are improving. The long-term result of this technique is in clear contrast to that of endoprosthesis. Even in patients older than 75 years, open DTA repair can be performed with acceptable risk. Although open DTA repair is by definition more invasive and should be further improved, the risks involved in replacement of the descending aorta under PCPB were comparable to those associated with thoracic endoprosthesis placement at this time.

References

1. Wheatley GH 3rd, Gurbuz AT, Rodriguez-Lopez JA, Ramaiah VG, Olsen D, Williams J, et al. Midterm outcome in 158 consecutive Gore TAG thoracic endoprostheses: single center experience. *Ann Thorac Surg*. 2006;81:1570-7.
2. Makaroun MS, Dillavou ED, Kee ST, Sicard G, Chaikof E, Bavaria J, et al. Endovascular treatment of thoracic aortic aneurysms: results of the phase II multicenter trial of the GORE TAG thoracic endoprosthesis. *J Vasc Surg*. 2005;41:1-9.
3. Cooley DA, Golino A, Frazier OH. Single-clamp technique for aneurysms of the descending thoracic aorta: report of 132 consecutive cases. *Eur J Cardiothorac Surg*. 2000;18:162-7.
4. Estrera AL, Miller CC 3rd, Chen EP, Meada R, Torres RH, Porat EE, et al. Descending thoracic aortic aneurysm repair: 12-year experience using distal aortic perfusion and cerebrospinal fluid drainage. *Ann Thorac Surg*. 2005;80:1290-6.
5. Soukiasian HJ, Raissi SS, Kleisli T, Lefor AT, Fontana GP, Czer LS, et al. Total circulatory arrest for the replacement of the descending and thoracoabdominal aorta. *Arch Surg*. 2005;140:394-8.
6. Coady MA, Mitchell RS. Femoro-femoral partial bypass in the treatment of thoracoabdominal aneurysms. *Semin Thorac Cardiovasc Surg*. 2003; 15:340-4.
7. Yamada N, Takamiya M, Kuribayashi S, Okita Y, Minatoya K, Tanaka R. MRA of the Adamkiewicz artery: a preoperative study for thoracic aortic aneurysm. *J Comput Assist Tomogr*. 2000;24: 362-8.
8. Svensson LG, Khitin L, Nadolny EM, Kimmel WA. Systemic temperature and paralysis after thoracoabdominal and descending aortic operations. *Arch Surg*. 2003;138:175-80.
9. Ogino H, Sasaki H, Minatoya K, Matsuda H, Yamada N, Kitamura S. Combined use of Adamkiewicz artery demonstration and motor-evoked potentials in descending and thoracoabdominal repair. *Ann Thorac Surg*. 2006;82:592-6.
10. Fattori R, Nienaber CA, Rousseau H, Beregi JP, Heijmen R, Grabenwöger M, et al. Results of endovascular repair of the thoracic aorta with the Talent Thoracic stent graft: the Talent Thoracic Retrospective Registry. *J Thorac Cardiovasc Surg*. 2006;132: 332-9.
11. Coselli JS, LeMaire SA, Conklin LD, Adams GJ. Left heart bypass during descending thoracic aortic aneurysm repair does not reduce the incidence of paraplegia. *Ann Thorac Surg*. 2004;77:1298-303.
12. Estrera AL, Rubenstein FS, Miller CC 3rd, Huynh TT, Letsou GV, Safi HJ. Descending thoracic aortic aneurysm: surgical approach and treatment using the adjuncts cerebrospinal fluid drainage and distal aortic perfusion. *Ann Thorac Surg*. 2001;72:481-6.
13. Patel HJ, Shillingford MS, Mihalik S, Proctor MC, Deeb GM. Resection of the descending thoracic aorta: outcomes after use of hypothermic circulatory arrest. *Ann Thorac Surg*. 2006;82:90-6.
14. Najibi S, Terramani TT, Weiss VJ, Mac Donald MJ, Lin PH, Redd DC, et al. Endoluminal versus open treatment of descending thoracic aortic aneurysms. *J Vasc Surg*. 2002;36:732-7.
15. Goldstein LJ, Davies RR, Rizzo JA, Davila JJ, Cooperberg MR, Shaw RK, et al. Stroke in surgery of the thoracic aorta: incidence,

impact, etiology, and prevention. *J Thorac Cardiovasc Surg.* 2001;122:935-45.
16. Kawaharada N, Morishita K, Fukada J, Hachiro Y, Fujisawa Y, Saito T, et al. Stroke in surgery of the arteriosclerotic descending thoracic aortic aneurysms: influence of cross-clamping technique of the aorta. *Eur J Cardiothorac Surg.* 2005;27:622-5.
17. Jacobs MJ, Mess W, Mochtar B, Nijenhuis RJ, Statius van Eps RG, Schurink GW. The value of motor evoked potentials in reducing paraplegia during thoracoabdominal aneurysm repair. *J Vasc Surg.* 2006;43:239-46.
18. Huynh TT, Miller CC 3rd, Estrera AL, Porat EE, Safi HJ. Thoracoabdominal and descending thoracic aortic aneurysm surgery in patients aged 79 years or older. *J Vasc Surg.* 2002;36:469-75.

ACD

Biochemical and Biophysical Research Communications
Volume 374, Issue 1, 12 September 2008, Pages 11-16

Abstract Figures/Tables

doi:10.1016/j.bbrc.2008.06.074
Cite or Link Using DOI

Activation of cardiac progenitor cells through paracrine effects of mesenchymal stem cells

Chiaki Nakanishi[a, b], Masakazu Yamagishi[b], Kenichi Yamahara[a], Ikuo Hagino[c], Hidezo Mori[d], Yoshiki Sawa[e], Toshikatsu Yagihara[c], Soichiro Kitamura[c] and Noritoshi Nagaya[a]

[a]Department of Regenerative Medicine and Tissue Engineering, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

[b]Division of Cardiovascular Medicine, Kanazawa University, Graduate School of Medicine, Kanazawa, Japan

[c]Department of Cardiovascular Surgery, National Cardiovascular Center, Osaka, Japan

[d]Department of Cardiac Physiology, National Cardiovascular Center Research Institute, Osaka, Japan

[e]Department of Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Received 9 June 2008. Available online 27 June 2008.

Abstract

Mesenchymal stem cells (MSC) transplantation has been proved to be promising strategy to treat the failing heart. The effect of MSC transplantation is thought to be mediated mainly in a paracrine manner. Recent reports have suggested that cardiac progenitor cells (CPC) reside in the heart. In this study, we investigated whether MSC had paracrine effects on CPC in vitro. CPC were isolated from the neonatal rat heart using an explant method. MSC were isolated from the adult rat bone marrow. MSC-derived conditioned medium promoted proliferation of CPC and inhibited apoptosis of CPC induced by hypoxia and serum starvation. Chemotaxis chamber assay demonstrated that MSC-derived conditioned medium enhanced migration of CPC. Furthermore, MSC-derived conditioned medium upregulated expression of cardiomyocyte-related genes in CPC such as β-myosin heavy chain (β-MHC) and atrial natriuretic peptide (ANP). In conclusion, MSC-derived conditioned medium had protective effects on CPC and enhanced their migration and differentiation.

Keywords: Cardiac progenitor cell; Mesenchymal stem cell; Paracrine effect; Proliferation; Migration; Differentiation

Article Outline

Biochemical and Biophysical Research Communications
Volume 374, Issue 1, 12 September 2008, Pages 11-16

Result list | previous < 4 of 34 > next
Font Size:

Abstract | Figures/Tables

doi:10.1016/j.bbrc.2008.06.074
Cite or Link Using DOI

Activation of cardiac progenitor cells through paracrine effects of mesenchymal stem cells

Chiaki Nakanishi[a, b], Masakazu Yamagishi[b], Kenichi Yamahara[a], Ikuo Hagino[c], Hidezo Mori[d], Yoshiki Sawa[e], Toshikatsu Yagihara[c], Soichiro Kitamura[c] and Noritoshi Nagaya[a]

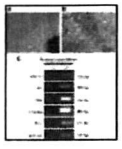

Fig. 1. Morphological features and gene expression of CPC derived from neonatal rat heart. (A,B) Representative photographs of CPC isolated by explant method. White arrows indicate CPC and black arrow indicates fibroblast-like cells. (A) Bar: 200 μm. (B) Bar: 20 μm. (C) Gene expression profile of CPC by RT-PCR.

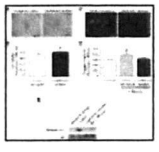

Fig. 2. Proliferative and antiapoptotic effect of MSC-derived conditioned medium on CPC. (A) Representative photographs of CPC incubated in basal culture medium (serum starvation) and MSC-derived conditioned medium for two days. Bar: 200 μm. (B) MTS assay of CPC. $^{*}p < 0.05$ vs serum starvation. (C) TUNEL staining of CPC. TUNEL-positive apoptotic CPC are stained green. Nuclei are stained with DAPI (blue). White arrows indicate TUNEL/DAPI double-positive cells. Bar: 50 μm. (D) Caspase-3 activity of cultured CPC. $^{*}p < 0.05$ vs control, $^{\dagger}p < 0.05$ vs serum starvation. (E) Western blot analysis. MSC-derived conditioned medium as well as 50 ng/mL HGF phosphorylated Akt compared to basal culture medium (standard medium).

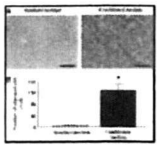

Fig. 3. Migration of CPC induced by MSC-derived conditioned medium. (A) Representative photographs of migrated CPC incubated in basal culture medium (standard medium) and MSC-derived conditioned medium. White arrows indicate migrated CPC (standard medium). Bars: 100 μm. (B) Quantitative analysis of migrated CSC. $^{*}p < 0.05$ vs standard medium.

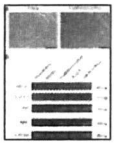

Fig. 4. Cardiomyogenesis of CPC induced by MSC-derived conditioned medium. (A) Morphological features of CPC after incubation in complete culture medium (Vehicle) and MSC-derived conditioned medium for two weeks. Cultured CPC did not beat spontaneously. (A) Bar: 50 μm. (B) RT-PCR analysis of CPC after induction of cardiomyogenesis. Adult rat heart extract was used as positive control.

Table 1.

Primer pairs for RT-PCR

Biochemical and Biophysical Research Communications
Volume 374, Issue 1, 12 September 2008, Pages 11-16

Result list | previous < 4 of 34 > next

Pediatr Cardiol (2008) 29:266–270
DOI 10.1007/s00246-007-9114-y

ORIGINAL ARTICLE

Competition Between Native Flow and Graft Flow After Coronary Artery Bypass Grafting. Impact on Indications for Coronary Artery Bypass Grafting for Localized Stenosis with Giant Aneurysms Due to Kawasaki Disease

Etsuko Tsuda · Hideki Fujita · Toshikatsu Yagihara · Osamu Yamada · Shigeyuki Echigo · Soichiro Kitamura

Received: 9 June 2007 / Accepted: 10 July 2007 / Published online: 5 October 2007

Abstract We report the postoperative course of native and graft flow after coronary artery bypass grafting (CABG) in two patients with giant aneurysms and localized stenosis due to Kawasaki disease (KD). Although both patients had undergone CABG to the left anterior descending artery (LAD) with the left internal thoracic artery (ITA), at 5 and 10 years old, respectively, the ITA grafts were occluded 1 month postsurgery. However, when the two patients suffered complete occlusion of the native LAD more than 10 years after surgery, angiograms showed that the ITA grafts had reopened. We believe that this postoperative course reflects competition between the native artery flow and graft flow after CABG. CABG in patients with severely delayed coronary flows or recurrence of thrombus in giant aneurysms was ineffective in preventing myocardial infarction or damage. We conclude that CABG in giant aneurysm without significant localized stenosis should be avoided.

Keywords Kawasaki disease · Coronary artery aneurysm · Intracoronary thrombus · Intracoronary thrombolysis · Coronary artery bypass grafting

E. Tsuda (✉) · H. Fujita · O. Yamada · S. Echigo
Department of Pediatrics, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita-shi, Osaka 565-8565, Japan
e-mail: etsuda@hsp.ncvc.go.jp

T. Yagihara · S. Kitamura
Department of Cardiothoracic Surgery, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita-shi, Osaka 565-8565, Japan

Giant aneurysm is one coronary artery lesion that characterizes Kawasaki disease (KD) [6, 7] and, after the acute episode, may lead to thrombotic coronary artery occlusion or coronary artery stenosis and eventually progress to ischemic heart disease [2, 10]. Myocardial revascularization by coronary artery bypass grafting (CABG) to prevent myocardial infarction or myocardial damage is useful for stenotic lesions due to KD [4, 11], but determining its optimal timing is difficult. We sometimes encounter recurrent thrombus in a giant aneurysm or severely delayed flow in a giant aneurysm with ischemic signs, and we discuss the decision whether or not to recommend CABG. We report unusual latent occlusion of the internal thoracic artery (ITA) graft more than 10 years postsurgery in two patients with giant aneurysms and localized stenosis. This experience might provide some basis for determining the indications for CABG in patients with giant aneurysms caused by KD.

Case Reports

Case 1

One patient had acute KD when 4 years old and was treated with flurbiprofen and steroid. Bilateral giant aneurysms were detected by two-dimensional echocardiography (2DE) 12 days after the onset of KD. She underwent cardiac catheterization and selective coronary angiograms (CAG) 2 months later, when the maximum diameter of both the right coronary artery (RCA) and the left coronary artery (LCA) was 12 mm. Aspirin was started to prevent thrombotic occlusion. Four months after the onset of KD, the patient had an acute inferior myocardial infarction. When she was 5 years old CAG revealed segmental

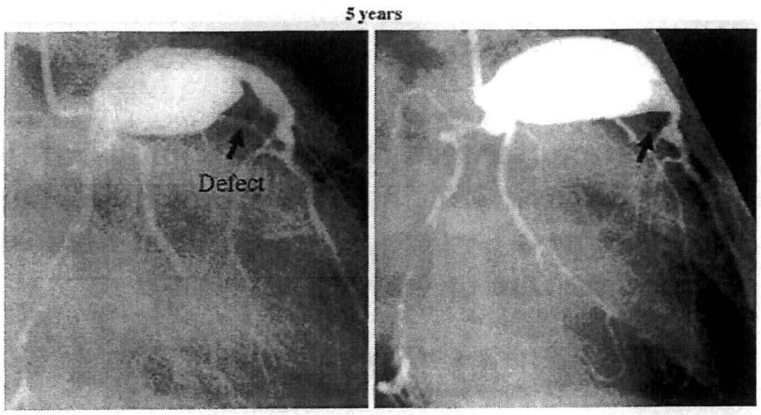

Fig. 1 Left coronary angiograms (Case 1). **Left**: The left coronary angiogram revealed a defect due to thrombus in a giant aneurysm. **Right**: The defect due to thrombus in the giant aneurysm disappeared after intracoronary thrombolysis

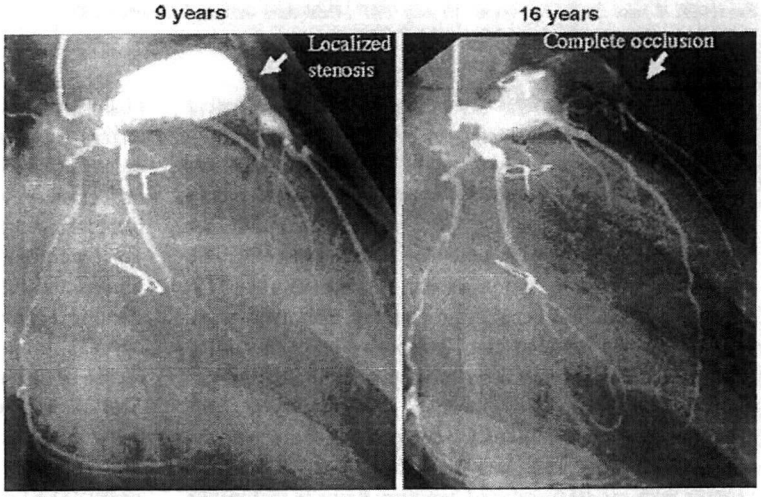

Fig. 2 Left coronary angiograms (Case 1). **Left**: The left coronary angiogram revealed segmental stenosis of the left anterior descending artery at the age of 9 years. **Right**: The left anterior descending artery was occluded at the age of 16 years

stenosis of the RCA. One week after the examination, she became pale and felt generally unwell. After 2 months, she was referred to our hospital. A thrombus in the aneurysm of the LCA was detected by 2DE, a perfusion defect was observed in the inferior and anterolateral wall of the left ventricle by dipyridamole-loaded ^{201}Tl myocardial imaging, and redistribution was detected in the anterolateral wall of the left ventricle. CAG confirmed a giant aneurysm of the LCA with a defect due to thrombus (Fig. 1, left). The left ventricular ejection fraction (LVEF) was 50%. Blood flow in the left anterior descending artery (LAD) was delayed. Intracoronary thrombolysis (ICT) by tissue plasminogen activator was performed for the LCA, and the thrombus dissolved (Fig. 1, right). There was no stenosis of LAD beyond the giant aneurysm. However, the thrombus reoccurred within 2 months despite the administration of urokinase and heparin intravenously. Warfarin was started in addition to aspirin. After 2 months, CABG to the LAD with the left internal thoracic artery (ITA) was performed at the age of 5 years 8 months. One month after surgery, angiography showed that the ITA graft was completely occluded and flow in the native LAD was detected. When the patient was 9 and 13 years old, CAGs showed localized stenosis of the LAD (Fig. 2, left). ITA graft flow was not detected in the follow-up angiograms (Fig. 3, left). Depression of ST-T segments in the left precordial leads after exercise was detected from the age of 13 years. Perfusion defects in the anterior wall, inferior wall, and apex of the left ventricle were demonstrated by exercised ^{99m}Tc myocardial imaging. The patient had remained symptom-free since surgery. When she was 16 years old, she had abdominal discomfort; CAG at that time revealed complete occlusion of the native LAD (Fig. 2, right). At that angiogram, the ITA graft, although narrow, had reopened (Fig. 3, right). The left ventricular end-diastolic volume index (LVEDVI) and the LVEF were 112 ml/m^2 and 50%, respectively. The ITA graft was patent on angiography at the age of 21 years.

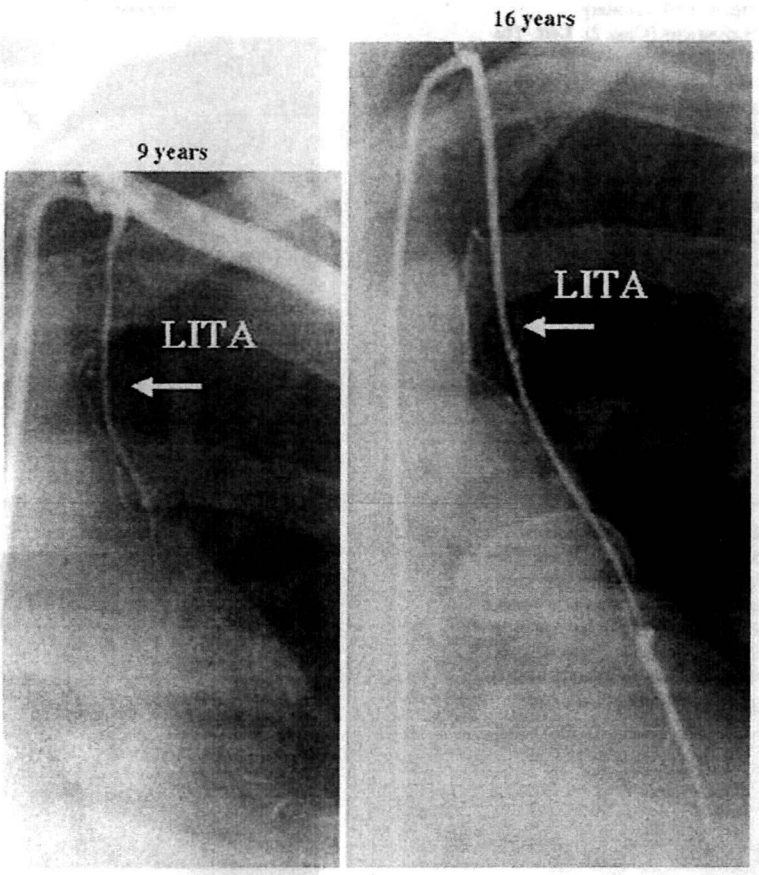

Fig. 3 Left internal thoracic angiograms (Case 1). **Left:** The left internal thoracic graft was occluded at the age of 9 years. **Right:** Flow in the left anterior descending artery was detected through the left internal thoracic graft at the age of 16 years. The stenosis at anastomosis was detected

Case 2

The second patient had acute KD when 8 years old, and she received flurbiprofen and intravenous immunogloblin within 7 days after the onset. Bilateral giant aneurysms were detected by 2DE 14 days after the onset of KD. She underwent cardiac catheterization and CAG after 52 days. At CAG, the maximum diameter of the right coronary artery (RCA) was 10 mm and that of the LAD was 11 mm. Aspirin and dipyridamole were started. CAG at 1 year after the onset of KD revealed localized stenosis of the LAD with severely delayed flow. A perfusion defect in the interventricular septum was detected by ^{201}Tl myocardial imaging after dipyridamole and isoproterenol loading. Two months after the CAG, the patient had a CABG to the LAD using the left ITA at the age of 10 years. One month after surgery, angiography showed that the ITA graft was occluded and the delayed flow in the native LAD persisted. When she was 17 years old, the patient had an acute anterior myocardial infarction. ICT by tissue plasminogen activator for the LAD was initially successful, but she had a reinfarction the next day, and ICT was repeated. The interventricular septum was akinetic by 2DE and perfusion defects were detected in the anteroseptal wall and apex of the left ventricle. The LVEF was 35% and the creatinine phosphokinase was elevated to 8415mg/dl. Warfarin and angiotensin converting enzyme were started. The patient had been asymptomatic since her previous myocardial infarction. CAGs, 3 and 7 years after myocardial infarction, revealed severe delayed flow in the LAD, although the ITA graft was occluded (Fig. 4, left, and Fig. 5, left). Although a localized stenosis of the RCA was detected by CAG when the patient was 20 years old, there was no ST-T change on treadmill testing. When she was 26 years old, CAG revealed complete occlusion of the RCA and the LAD; at that time distal LAD flow through the ITA graft was detected (Fig. 4, right, and Fig. 5, right). The LVEDVI and the LVEF were 131 ml/m^2 and 37%, respectively.

Discussion

Thrombus is often detected in giant aneurysms and presents a treatment challenge. Usually warfarin and an antiplatelet agent are administered, and if either chest pain or ischemic signs on examination occur, ICT by tissue

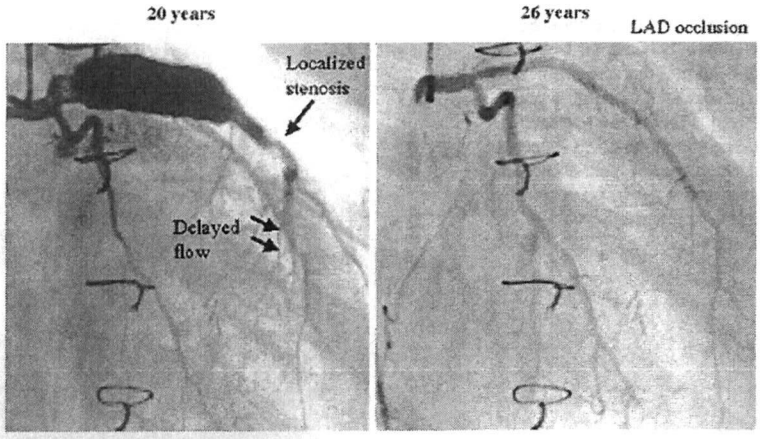

Fig. 4 Left coronary angiograms (Case 2). **Left**: The left coronary angiogram revealed severely delayed flow and localized stenosis of the left anterior descending artery at the age of 20 years. **Right**: The left anterior descending artery was completely occluded at the age of 26 years

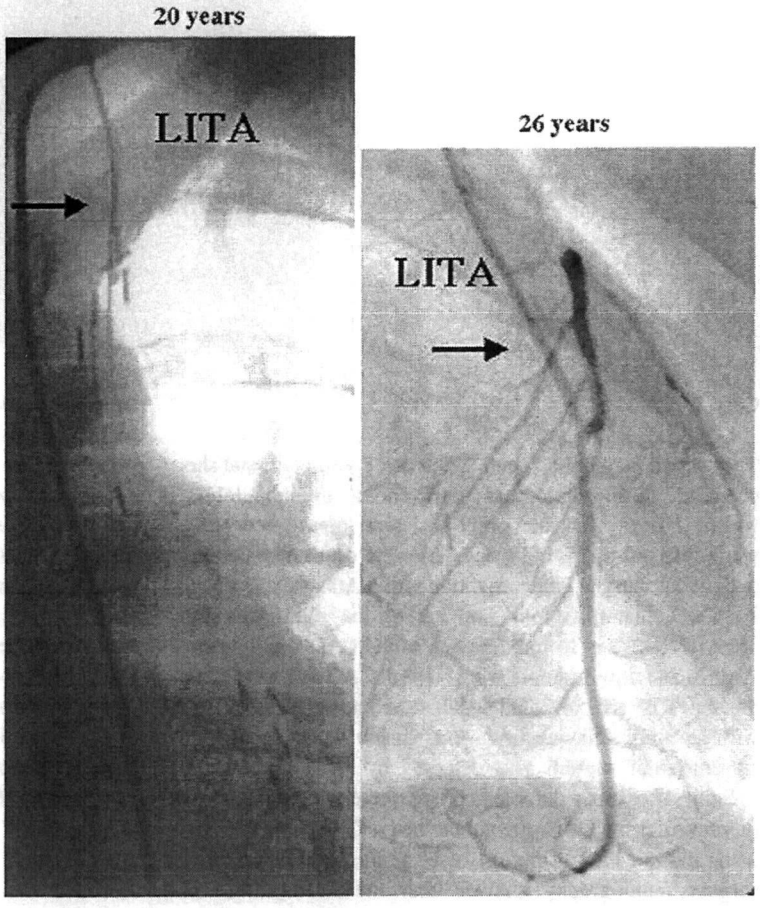

Fig. 5 Left internal thoracic angiograms (Case 2). **Left**: The left internal thoracic graft was occluded at the age of 20 years. **Right**: Flow in the left anterior descending artery was detected through the left internal thoracic graft at the age of 26 years

plasminogen activator is considered [1]. Recurrence of thrombus despite aggressive anticoagulant therapy threatens possible myocardial infarction. We sometimes observe at CAG severe delays in flow due to giant aneurysms with localized stenosis, especially in the LAD. The degree of localized stenosis is difficult to quantify because of the severe delayed flow. If ischemic signs are present, a high risk of myocardial infarction is assumed. In the middle

1980s it was difficult to decide whether or not CABG should be performed for these patients. Our patients had no symptoms or evidence of severe ischemia on examination. Prophylactic CABG at the selected time in these two patients was ineffective in preventing myocardial damage.

In these patients, the ITA grafts became occluded immediately after surgery and antegrade native LAD flow persisted. When the antegrade flow in the native LAD disappeared, the ITA reopened and provided distal LAD flow. We believe the apparent occlusion was functional, not mechanical. Although ITA grafts in children are known to grow with physical development [3], it is striking that an apparently occluded ITA graft had grown more than 10 years after surgery despite absence of flow. This is an interesting example of a "living graft." Until recently, the results of ITA graft patency in small children with stenotic lesions caused by KD have been unsatisfactory [11]. Early graft occlusion after surgery often occurred because of anastomotic stenosis and competition with the native coronary flow [8]. Our experience showed that the ITA graft flow was compromised because of competition with the native LAD flow. Recently we have reported that percutaneous transluminal balloon angioplasty for the anastomotic site performed a few months after surgery helped prevent graft occlusion in patients with giant aneurysm and localized stenosis [5].

The appropriate decision regarding CABG is very important. The existence of severe ischemia on examination and severe localized stenosis or complete occlusion would be absolute indicators for CABG [9]. However, it is not easy to diagnosis clearly the existence of ischemia in cases with recurrent thrombus or severe delayed flow in giant aneurysms. Patients with recurrent thrombosis in giant aneurysms do not always have significant localized stenosis, and severe delayed flow in giant aneurysms occurs because of the hemodynamic effects due to large aneurysms. The thrombus formation and delayed flow often occur simultaneously, and these phenomena influence reciprocally. Further, it is also difficult to detect the degree of localized stenosis accurately in such cases. Flow in the graft will be compromised if the native artery flow is not decreased. In cases with recurrent thrombus in a giant aneurysm despite aggressive anticoagulation or with severe delayed flow in the giant aneurysm without significant localized stenosis, CABG is not necessarily effective, and the indication for CABG should be considered carefully. Our experience with these two patients suggests that CABG in patients with giant aneurysm and mild localized stenosis should be avoided.

Conclusion

We encountered two patients with early ITA graft occlusion after surgery in whom the grafts reopened more than 10 years after surgery with the disappearance of the native coronary artery flow. Prophylactic CABG in patients with severely delayed coronary flow or recurrent thrombus in giant aneurysms was ineffective in preventing myocardial infarction or damage. Our experience suggests that CABG in giant aneurysm without significant localized stenosis should be avoided.

Acknowledgments We thank Professor Peter Olley and Dr. Setsuko Olley for their kind English language consultation.

References

1. Akagi T, Ogawa S, Ino T, et al. (2000) Catheter interventional treatment in Kawasaki disease: a report from the Japanese Pediatric Interventional Cardiology Investigation Group. J Pediatr 137:181–186
2. Kato H, Ichinose E, Kawasaki T (1986) Myocardial infarction in Kawasaki disease: clinical analyses in 195 cases. J Pediatr 108:923–927
3. Kitamura S, Seki T, Kawachi K, et al. (1989) Excellent patency and growth potential of internal mammary artery grafts in pediatric coronary bypass surgery: new evidence for a "live" conduit. Circulation 78(Suppl):I129–I139
4. Kitamura S (2002) The role of coronary bypass operation on children with Kawasaki disease. Coron Artery Dis 13:437–447
5. Miyazaki A, Tsuda E, Miyazaki S, et al. (2003) Percutaneous transluminal coronary angioplasty for anastomotic stenosis after coronary artery bypass grafting in Kawasaki disease. Cardiol Young 13(3):284–289
6. Nakano H, Ueda K, Saito A, et al. (1985) Repeated quantitative angiograms in coronary arterial aneurysm in Kawasaki disease. Am J Cardiol 56:846–851
7. Suzuki A, Kamiya T, Tsuda E, et al. (1997) Natural history of coronary artery lesions in Kawasaki disease. Prog Pediatr Cardiol 6:211–216
8. Tsuda E, Kitamura S (2004) The cooperative study of Japan. National survey of coronary artery bypass grafting for coronary stenosis due to Kawasaki disease in Japan. Circulation 110(Suppl II):II61–II66
9. Tsuda E, Ono Y, Tsukano S, et al. (1998) Long-term results of coronary artery bypass grafting for coronary arterial lesions due to Kawasaki disease: cases with new appearance of localized stenosis after surgery. In: Imai Y, Momma K (eds) Proceedings of the Second World Congress of Pediatric Cardiology and Cardiac Surgery. Futura, New York pp 1117–1119
10. Tsuda E, Kamiya T, Ono Y, et al. (2005) Incidence of stenotic lesions predicted by acute phase changes in coronary arterial diameter during Kawasaki disease: threshold for coronary aneurysm causing stenosis is 6.0mm. Pediatr Cardiol 26:73–79
11. Yoshikawa Y, Yagihara T, Kameda Y, et al. (2000) Results of surgical treatments in patients with coronary-arterial obstructive disease after Kawasaki disease. Eur J Cardio-thorac Surg 17:515–519