ventricular conduction associated with myocardial rearrangements and fibrosis.[16] Meregalli et al[17] showed prolongation of S-wave duration in leads II and III after administration of sodium channel blockers. Their group suggested that these electrocardiographic signs included reciprocal changes in the inferior leads, mirroring the conduction slowing in the RVOT,[17,18] which may progress with aging and relate to the pathogenesis of BS. In the present study, the P-wave, QRS, S-wave durations, and PQ intervals were all significantly longer, and the S-wave amplitude was significantly deeper in the SCN5A-positive group than in the SCN5A-negative group. In addition, the PQ interval and QRS duration in lead V_2 were more markedly prolonged, and the QRS axis deviated more to the left with aging in the SCN5A-positive group than in the SCN5A-negative group during the follow-up period. The results of previous clinical studies and the present study suggest that progressive depolarization abnormalities (i.e., conduction slowing) with aging may play a key role in the pathogenesis of BS.

It has been argued recently that arrhythmic events may occur when a sufficient degree of cell damage has been reached as a result of the severity of ion channel protein mutation. Frustaci et al[19] showed that myocyte apoptosis at the right and left ventricular myocardium was significantly higher in patients with BS with SCN5A mutations than in control subjects on histologic study. They suggested that abnormalities in the function of sodium channels may lead to cellular damage because intracellular sodium homeostasis has a relevant role in myocellular function.[19] Experimentally, Aiba et al[20] used a high-resolution optical mapping system in a pharmacologic BS model and demonstrated that depolarization abnormalities (i.e., conduction slowing) is required for the maintenance of VF in BS, although the initiating premature beats were a result of a phase 2 reentry mechanism. These histologic and experimental studies also support that progressive conduction abnormalities with aging may explain why an initial VF episode appears at middle to older ages, usually 40 to 50 years, in BS. It is generally accepted that SCN5A mutation is not associated with a higher risk of cardiac events, suggesting that genetic analysis is a useful diagnostic parameter but is not helpful for risk stratification.[7] Similarly, in the present study, the presence of SCN5A mutation did not predict subsequent arrhythmic events (Table 2). Most clinical studies have reported that induction of VF by programmed electrical stimulation did not predict the clinical outcome or clinical severity in patients with BS.[6,21,22] If the progressive conduction slowing with aging often observed in patients with BS, especially SCN5A-positve patients, are really linked to VF appearance, conduction parameters, such as QRS widening, late potentials, or inducibility of VF, may still have a potential to predict new or subsequent cardiac events.[23] A much larger patient population is required to make a definitive conclusion regarding the predictive value of SCN5A mutation and the conduction parameters for cardiac events.

Several clinical studies have suggested a localized QT prolongation, a repolarization parameter, in the right precordial leads (mainly lead V_2) in patients with BS.[24,25] Castro Hevia et al[25] have suggested that a QTc >460 ms in lead V_2 was a significant risk factor for subsequent cardiac events. We recently used 87-lead body surface ECGs and reported that a corrected recovery time, another repolarization parameter, was significantly longer in the right precordial body surface ECGs, reflecting the potentials of the RVOT, than in other body surface ECGs.[26] Similarly, in the present study, the longest QTc interval was observed in lead V_2 in most patients with BS with SCN5A mutation, who usually also had a coved-type ST-segment elevation and a terminal negative T wave. The fact that the QTc interval in lead V_2 was significantly longer in the SCN5A-positive patients than in the SCN5A-negative patients at the early and late periods can be explained by more frequent and higher coved-type ST-segment elevation with a terminal negative T wave in the SCN5A-positive patients. The QTc interval in lead V_2 was significantly prolonged from the early period to the late period in the SCN5A-positive patients; however, the JTc interval in lead V_2 did not change from the early period to the late period, suggesting that the significant QTc prolongation in lead V_2 with aging occurred mainly as a result of a significant prolongation of the QRS duration in lead V_2.

There are several limitations to the present study. First, because a small number of patients with BS with SCN5A mutation could be included in a single-center study, a larger number of patients with SCN5A mutation will be required to make a definitive conclusion. Second, the study population included 44 Brugada probands who could be prospectively followed up for average of 10 ± 5 years in our hospital. Therefore, the probands represent a severely affected population, but not a consecutively referred population. Third, Veltmann et al[27] recently reported the prevalence of fluctuations between diagnostic and nondiagnostic ECGs in patients with BS, which may influence the measurement of some electrocardiographic parameters, especially QT, JT interval, and ST amplitude, and should be taken into account. However, the influence of the fluctuations on depolarization parameters such as QRS duration is expected to be less pronounced.

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J Am Coll Cardiol* 1992;20:1391–1396.
2. Brugada J, Brugada P. Further characterization of the syndrome of right bundle branch block, ST segment elevation, and sudden cardiac death. *J Cardiovasc Electrophysiol* 1997;8:325–331.
3. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in V1 through V3. A marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998;97:457–460.
4. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation* 2002;106:2514–2519.
5. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, Lemarec H, Nademanee K, Perez Riera AR, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;111:659–670.
6. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome:

insights for risk stratification and management. *Circulation* 2002;105:1342–1347.
7. Priori SG. Napolitano C. Gasparini M. Pappone C. Della Bella P. Brignole M. Giordano U. Giovannini T. Menozzi C. Bloise R. et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. *Circulation* 2000;102:2509–2515.
8. Shimizu W. Aiba T. Kamakura S. Mechanisms of diseases: current understanding and future challenges in Brugada syndrome. *Nat Clin Pract Cardiovasc Med* 2005;2:408–414.
9. Nademanee K. Veerakul G. Nimmannit S. Chaowakul V. Bhuripanyo K. Likittanasombat K. Tunsanga K. Kuasirikul S. Malasit P. Tansupasawadikul S. Tatsanavivat P. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997;96:2595–2600.
10. Chen Q. Kirsch GE. Zhang D. Brugada R. Brugada J. Brugada P. Potenza D. Moya A. Borggrefe M. Breithardt G. et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;392:293–296.
11. Alings M. Wilde A. "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. *Circulation* 1999;99:666–673.
12. Smits JP. Eckardt L. Probst V. Bezzina CR. Schott JJ. Remme CA. Haverkamp W. Breithardt G. Escande D. Schulze-Bahr E. LeMarec H. Wilde AA. Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non- SCN5A-related patients. *J Am Coll Cardiol* 2002;40:350–356.
13. Probst V. Allouis M. Sacher F. Pattier S. Babuty D. Mabo P. Mansourati J. Victor J. Nguyen JM. Schott JJ. et al. Progressive cardiac conduction defect is the prevailing phenotype in carriers of a Brugada syndrome *SCN5A* mutation. *J Cardiovasc Electrophysiol* 2006;17:270–275.
14. Bezzina CR. Shimizu W. Yang P. Koopmann TT. Tanck MWT. Miyamoto Y. Kamakura S. Roden DM. Wilde AAM. A common sodium channel promoter haplotype in Asian subjects underlies variability in cardiac conduction. *Circulation* 2006;113:338–344.
15. Probst V. Kyndt F. Potet F. Trochu JN. Mialet G. Demolombe S. Schott JJ. Baro I. Escande D. Le Marec H. Haploinsufficiency in combination with aging causes *SCN5A*-linked hereditary Lenegre disease. *J Am Coll Cardiol* 2003;41:643–652.
16. Royer A. van Veen TA. Le Bouter S. Marionneau C. Griol-Charhbili V. Leoni AL. Steenman M. van Rijen HV. Demolombe S. Goddard CA. et al. Mouse model of SCN5A-linked hereditary Lenegre's disease: age-related conduction slowing and myocardial fibrosis. *Circulation* 2005;111:1738–1746.
17. Meregalli PG. Ruijter JM. Hofman N. Bezzina CR. Wilde AA. Tan HL. Diagnostic value or flecainide test in unmasking *SCN5A*-related Brugada syndrome. *J Cardiovasc Electrophysiol* 2006;17:857–864.
18. Tukkie R. Sogaard P. Vleugels J. de Groot IK. Wilde AA. Tan HL. Delay in right ventricular activation contributes to Brugada syndrome. *Circulation* 2004;109:1272–1277.
19. Frustaci A. Priori SG. Pieroni M. Chimenti C. Napolitano C. Rivolta I. Sanna T. Bellocci F. Russo MA. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation* 2005;112:3680–3687.
20. Aiba T. Shimizu W. Hidaka I. Uemura K. Noda T. Zheng C. Kamiya A. Inagaki M. Sugimachi M. Sunagawa K. Cellular basis for trigger and maintenance of ventricular fibrillation in the Brugada syndrome model: High resolution optical mapping study. *J Am Coll Cardiol* 2006;47:2074–2085.
21. Kanda M. Shimizu W. Matsuo K. Nagaya N. Taguchi A. Suyama K. Kurita T. Aihara N. Kamakura S. Electrophysiologic characteristics and implications of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. *J Am Coll Cardiol* 2002;39:1799–1805.
22. Eckardt L. Probst V. Smits JP. Bahr ES. Wolpert C. Schimpf R. Wichter T. Boisseau P. Heinecke A. Breithardt G. et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. *Circulation* 2005;111:257–263.
23. Shimizu W. Does an overlap syndrome really exist between Brugada syndrome and progressive cardiac conduction defect (Lenegre syndrome)? *J Cardiovasc Electrophysiol* 2006;17:276–278.
24. Pitzalis MV. Anaclerio M. Iacoviello M. Forleo C. Guida P. Troccoli R. Massari F. Mastropasqua F. Sorrentino S. Manghisi A. Rizzon P. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. *J Am Coll Cardiol* 2003;42:1632–1637.
25. Castro Hevia J. Antzelevitch C. Tornes Barzaga F. Dorantes Sanchez M. Dorticos Balea F. Zayas Molina R. Quinones Perez MA. Fayad Rodriguez Y. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol* 2006;47:1828–1834.
26. Yokokawa M. Takaki H. Noda T. Satomi K. Suyama K. Kurita T. Kamakura S. Shimizu W. Spatial distribution of repolarization and depolarization abnormalities evaluated by body surface potential mapping in patients with Brugada syndrome. *Pacing Clin Electrophysiol* 2006;29:1112–1121.
27. Veltmann C. Schimpf R. Echternach C. Eckardt L. Kuschyk J. Streitner F. Spehl S. Borggrefe M. Wolpert C. A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification. *Eur Heart J* 2006;27:2544–2552.

Electrophysiologic Study-Guided Amiodarone for Sustained Ventricular Tachyarrhythmias Associated With Structural Heart Diseases

Takeshi Aiba, MD; Kenichiro Yamagata, MD; Wataru Shimizu, MD; Atsushi Taguchi, MD; Kazuhiro Satomi, MD; Takashi Noda, MD; Hideo Okamura, MD; Kazuhiro Suyama, MD; Naohiko Aihara, MD; Shiro Kamakura, MD; Takashi Kurita, MD

Background Although an electrophysiologic study (EPS) and Holter-monitoring are often helpful in evaluating the efficacy of antiarrhythmic drugs in patients with ventricular tachyarrhythmias (ventricular tachycardia/fibrillation (VT/VF)), the efficacy of EPS- or Holter-guided oral amiodarone therapy in Japanese patients is still unclear.
Methods and Results EPS was performed 1 month after starting amiodarone, and Holter-monitoring was recorded before and 1 month after amiodarone in 188 patients with sustained VT/VF because of structural heart diseases. In spite of the judgment of EPS (n=89) or Holter (n=75), all patients continued amiodarone. Patients were followed up to 3 years and the primary endpoint was VT/VF recurrence and secondary endpoint was death by all cause. Kaplan-Meier estimated the risk of VT/VF recurrence was significantly smaller with EPS-guided amiodarone (p<0.01) but not with Holter-guided amiodarone. Multivariate Cox hazard analysis revealed that EPS-guided amiodarone was an independent factor suppressing the recurrence of VT/VF (p<0.05, 95% confidence interval=0.15 to 0.96). In the subgroup analysis, EPS-guided amiodarone was effective in patients with relatively well-preserved left ventricular ejection fraction (LVEF ≥0.30) but not in patients with lower LVEF (LVEF <0.30).
Conclusion EPS-guided amiodarone was useful for preventing recurrence of VT/VF in patients with a relatively well-preserved LVEF, but not always beneficial in patients with a lower LVEF. (*Circ J* 2008; **72:** 88-93)

Key Words: Amiodarone; Electrophysiologic study; Holter monitoring; Ventricular fibrillation; Ventricular tachycardia

Ventricular tachyarrhythmias are critically important in the prognosis of patients with structural heart diseases. Amiodarone is one of the most advocated antiarrhythmic drugs available for preventing the recurrence of ventricular tachycardia (VT), ventricular fibrillation (VF), thereby reducing total mortality in patients with VT/VF.[1-4] Although an electrophysiologic study (EPS) and Holter monitoring are performed to evaluate the efficacy of antiarrhythmic drugs, oral amiodarone is often prescribed empirically because the antiarrhythmic effect as guided by EPS or Holter monitoring is controversial.[5-9] Recent clinical trials have shown that an implantable cardioverter defibrillator (ICD) is clearly superior to amiodarone for preventing sudden arrhythmic death,[10-13] but cannot prevent the recurrence of VT/VF and sometimes gives an intolerable shock to the patient. Therefore, it is still important to clarify how to optimize amiodarone and/or ICD therapies in patients with sustained VT/VF and structural heart diseases.[14,15]

On the other hand, patients with a lower left ventricular ejection fraction (LVEF) derive significantly more benefit from ICD therapy than those with a better preserved LVEF.[16-18] Moreover, a recent randomized study reported that amiodarone had no favorable effect on survival but that ICD therapy reduced overall mortality by 23% in patients with congestive heart failure and LVEF <35%.[19] Therefore, a cardiac function parameter, such as LVEF, is important in determining the prognosis of patients with sustained VT/VF. The goals of this study were: (1) to evaluate whether or not EPS- or Holter monitoring-guided therapy can stratify the risk of VT/VF recurrence after oral amiodarone, and (2) to investigate the extent to which specific patients subgroups benefit differently from amiodarone therapy.

Methods

Patients

This study retrospectively analyzed 400 patients who had been treated with oral amiodarone at the National Cardiovascular Center (Suita, Japan) from 1990 to 2004. All patients had a history of symptomatic sustained VT/VF because of structural heart diseases. We excluded 212 patients with a LVEF >0.50, treated with amiodarone for non-sustained VT or atrial arrhythmias, or who had undergone radiofrequency catheter ablation or surgical procedures for VT/VF. Therefore, this study registered 188 patients (mean age, 60±12 years; 149 males), which included 77 patients with previous myocardial infarction, 61 with dilated cardio-

(Received November 2, 2006; revised manuscript received August 21, 2007; accepted September 13, 2007)
Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan
Mailing address: Takashi Kurita, MD, Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: kuritat@hsp.ncvc.go.jp

Table 1 Patients' Characteristics

	Overall	EPS-post amiodarone		EPS (–)
		VT (–)	VT (+)	
n	188	27	62	99
Age (years)	60±12	59±9	58±11	61±14
Sex (male, %)	149 (79)	22 (81)	48 (77)	80 (81)
LVEF (%)	30±12	30±11	34±11	28±12*
Structural heart disease (%)				
Old MI	77 (41)	14 (52)	24 (39)	39 (39)
DCM	61 (33)	7 (26)	18 (29)	36 (36)
HCM	8 (4)	0 (0)	4 (6)	4 (4)
ARVC	16 (9)	1 (4)	6 (10)	9 (9)
Sarcoidosis	11 (6)	2 (7)	6 (10)	3 (3)
Valvular heart disease	12 (6)	1 (4)	3 (5)	8 (8)
Other	3 (1)	2 (7)	1 (1)	0 (0)
Presenting arrhythmias (%)				
Sustained VT	150 (80)	23 (85)	56 (91)	70 (71)
VF	26 (14)	4 (15)	2 (3)	21 (21)
Sustained VT and VF	12 (6)	0 (0)	4 (6)	8 (8)
VF total (%)	38 (20)	4 (15)	6 (9)	29 (29)*
ICD (%)	81 (43)	7 (26)	40 (65)**	34 (34)
Medication (%)				
ACEI	103 (55)	18 (67)	30 (48)	55 (55)
β-blocker	102 (55)	12 (44)	34 (55)	56 (57)
Digitalis	60 (32)	9 (33)	13 (21)	38 (38)

EPS, electrophysiological study; VT (–), VT or VF is not induced by EPS; VT (+), VT or VF is induced by EPS; LVEF, left ventricular ejection fraction; MI, myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; ACEI, angiotensin converting enzyme inhibitors.
*$p<0.05$ vs EPS-VT (+) group; ** $p<0.05$ vs EPS-VT (–) and EPS (–) group.

myopathy, 16 with arrhythmogenic right ventricular cardiomyopathy, 8 with hypertrophic cardiomyopathy, and 11 with cardiac sarcoidosis. The mean LVEF of these patients was 30±12% (Table 1).

EPS and Holter Monitoring

After written informed consent was given, EPS was performed in the fasting, nonsedated state before (pre) and 1 month after (post) starting oral amiodarone. All other antiarrhythmic drugs were discontinued. The protocols of the programmed ventricular stimuli have been described in detail previously.[4] In brief, up to 3 premature extrastimuli after an 8-beat stimulus drive were delivered from the right ventricular apex and outflow tract using a quadripolar-electrode catheter, and incremental ventricular stimulation with a constant cycle length. The stimulation protocol was terminated when sustained VT or VF was induced. The efficacy of amiodarone was determined by whether or not a run of VT >15 beats could be induced during EPS after starting amiodarone. Thus, we were not concerned about the inducibility of VT/VF before amiodarone therapy.

Twenty-four hours Holter electrocardiogram was recorded on magnetic tape before drug therapy, and repeated 1 month after administration of amiodarone and analyzed by computer to determine the frequency of arrhythmias. The efficacy of amiodarone by Holter recording was assessed by the criteria of the ESVEM trial.[20] First, patients with total premature ventricular contractions (PVC) less than 300/day before amiodarone were excluded from the Holter judgment as an "undetermined" group. Therefore, patients with total PVCs more than 300/day before amiodarone and 70% reduction in the PVC count, 80% reduction in the PVC pair count, 90% reduction in the VT count, and absence of any runs of VT >15 beats were defined as "effective", but patients with no response to these criteria were defined as "ineffective".

Table 2 EPS and Holter Judgments

	EPS post amiodarone		EPS-post (–)
	VT (–)	VT (+)	
EPS pre amiodarone			
VT (–) (n=2)	1	0	1
VT (+) (n=37)	3	16	18
EPS-pre (–) (n=149)	23	46	80
Total (n=188)	27	62	99
Holter criteria			
Effective (n=37)	7	9	21
Ineffective (n=38)	7	10	21
Undetermined (n=113)	13	43	57

EPS-pre (–), EPS before amiodarone is not performed; EPS-post (–), EPS after amiodarone is not performed. Other abbreviations see in Table 1.

Follow-up After Amiodarone

Whether or not they had EPS or Holter monitoring, all patients continued treatment with amiodarone, the loading dose of which was 300 or 400 mg/day for 2 weeks followed by a maintenance dose of 150 or 200 mg/day. However, amiodarone was discontinued when critical side effects developed or it was obviously ineffective. All patients were followed up to 36 months and the primary endpoint was recurrence of VT/VF and the secondary endpoint was death from all causes. Implantation of an ICD was recommended in patients who were considered to be "ineffective" with amiodarone or had a history of syncope because of VT/VF.

Statistical Analysis

The continuous variables are expressed as mean ± SD and were compared by an unpaired t-test when appropriate. Cumulative event rates were calculated by the Kaplan-

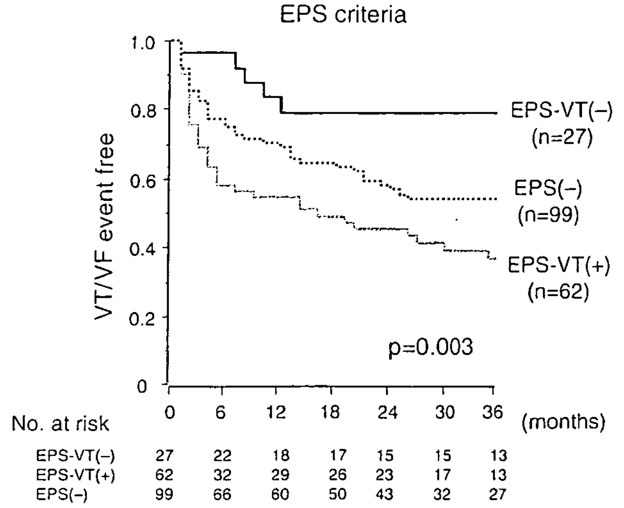

Fig 1. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by electrophysiological study (EPS) criteria. EPS stratified the risk of VT/VF recurrence after amiodarone. EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(–), patients with no inducible VT/VF by EPS after amiodarone; EPS(–), patients without EPS after amiodarone.

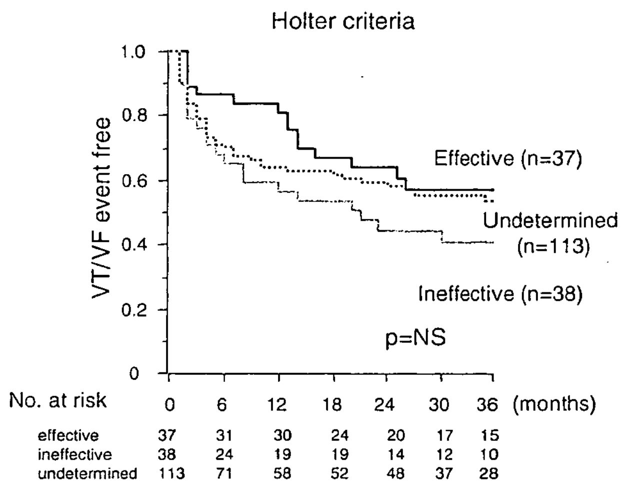

Fig 2. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by Holter-monitoring criteria. Holter-monitoring could not stratify the risk of VT/VF recurrence after amiodarone. Effective, patients judged amiodarone effective by Holter; Ineffective, patients judged amiodarone ineffective by Holter; Undetermined, patients excluded from the Holter judgment.

Table 3 Cox Hazard Regression Analysis of VT/VF Recurrence

	OR (95%CI)	*p value*
Age	*1.26 (0.80–1.99)*	*0.33*
Sex (male)	*0.93 (0.54–1.60)*	*0.78*
Basal disease (Old MI)	*0.75 (0.45–1.25)*	*0.27*
LVEF <30%	*1.47 (0.94–2.32)*	*0.09*
EPS post amiodarone		
VT (+)	*1.71 (1.07–2.75)*	*0.02*
VT (–)	*0.34 (0.15–0.96)*	*0.04*
Holter judgment		
Ineffective	*1.47 (0.87–2.50)*	*0.15*
Effective	*0.77 (0.42–1.43)*	*0.42*

Abbreviations as in Tables 1,2.

Meier method. The significance of the difference between treatment groups was assessed with the log-rank test. Cox regression analysis was performed on the patients' baseline characteristics to investigate and compare the influence of different variables. Statistical significance was established as $p<0.05$.

Results

EPS and Holter Monitoring

Table 2 summarizes the results of EPS and Holter monitoring. The EPS before amiodarone was performed in 39 patients, and induced VT/VF in 37 (95%). The EPS after amiodarone was performed in 89 patients, and could not induce VT/VF in 27 (30%) patients (EPS-VT(–) group), but still induced VT/VF in 62 (70%) patients (EPS-VT(+) group). The remaining 99 patients taking amiodarone without judgment by EPS were defined as EPS(–) group.

Holter monitoring before and after amiodarone treatment was recorded in 139 patients; however, 64 patients had less PVCs than the Holter evaluation before amiodarone (300/day). Therefore, the remaining 75 patients were judged as amiodarone effective (n=37) or ineffective (n=38) by Holter monitoring.

Follow-up

During the follow-up period of 23±13 (range 1–36) months, 82 (44%) patients had recurrence of VT. Moreover, 28 (20%) patients died during follow-up because of heart failure (n=8), sudden unexpected death (n=8), pneumonia (n=2), and unknown causes (n=10). Side-effects of amiodarone occurred in 39 (21%) patients, including hypothyroidism (n=20), proarrhythmia (n=5), pneumonia (n=11), leukocytopenia (n=1), and liver dysfunction (n=2). Amiodarone was discontinued in 13 (8%) patients because of serious side-effects.

Fig 1 illustrates the follow-up results of patients under the EPS criteria. Among those assigned to the EPS-VT(+) group, the rate of VT/VF recurrence was 45.6% and 63.9% at 1 and 3 years, respectively. Conversely, in the EPS-VT(–) group it was 21.3% and 21.3%, and for the EPS(–) group 31.0% and 46.6% at 1 and 3 year's follow-up, respectively. Therefore, the VT/VF recurrence risk after amiodarone was significantly lower in the order of EPS-VT(–), EPS(–), and EPS-VT(+) groups ($p<0.003$). Table 1 summarizes the clinical characteristics in the 3 groups. Age, sex, basal disease, and medication, except antiarrhythmic drugs, did not differ between them, although LVEF was lower in the EPS(–) group than in the EPS-VT(+) group (28±12% vs 34±11%; $p=0.01$), and VF incidence before amiodarone was higher in the EPS(–) group than in the EPS-VT(+) group (29% vs 9%; $p=0.01$). ICDs were consequently implanted in many of the EPS-VT(+) group compared with the EPS-VT(–) and EPS(–) groups (65% vs 26%, 34%, respectively; $p<0.05$).

Fig 2 illustrates the follow-up results under the Holter criteria. In the patients assigned to the effective group, the VT/VF recurrence rates were 19.1% and 42.8% (1 and 3 years, respectively), whereas in the ineffective group, they were 43.4% and 59.6% (1 and 3 years, respectively) (p=NS). Therefore, Holter monitoring cannot stratify the risk of VT/VF recurrence after amiodarone.

Table 3 shows the results of multivariate Cox hazard regression analysis for the recurrence of VT/VF after amiodarone. The clinical factors, age, gender, basal disease

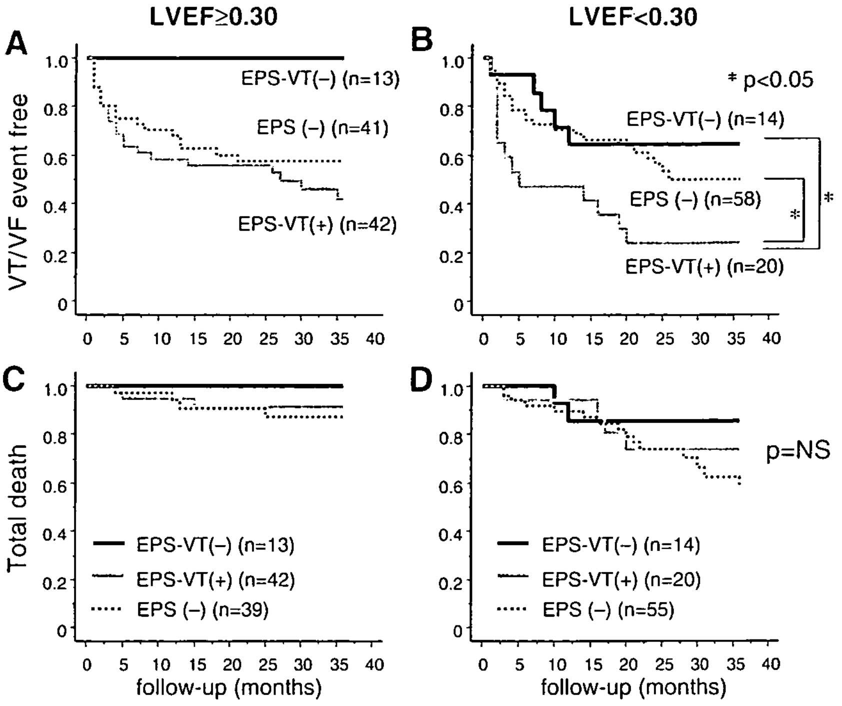

Fig 3. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) and total death after amiodarone therapy in different range of left ventricular ejection fraction (LVEF). Electrophysiological study (EPS) judgment could classify the risk of recurrent VT/VF and mortality after amiodarone in patients with LVEF ≥30% (A and C, respectively) but not in those with LVEF <30% (B and D, respectively). EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(–), patients with no inducible VT/VF by EPS after amiodarone; EPS(–), patients without EPS after amiodarone.

(myocardial infarction) and Holter judgments were not related to VT/VF recurrence. The independent clinical factors for VT/VF recurrence were inducibility of VT/VF by EPS after amiodarone (odds ratio (OR) 1.71, 95%confidence interval (CI) 1.07–2.75, p=0.02). Lower LVEF (<30%) increased the risk of VT/VF recurrence but not significantly (OR 1.47, 95%CI 0.94–2.32, p=0.09).

EPS-Guided AmiodaroneTherapy and LVEF

Because of the possibility of lower LVEF increasing risk of VT/VF recurrence after amiodarone, we evaluated the EPS-guided amiodarone therapy in subgroups. Therefore, among the patients with relatively preserved LVEF (≥30%) (n=94), there was no VT/VF recurrence in the EPS-VT(–) group, whereas the rates of VT/VF recurrence for the EPS-VT(+) group were 42.1% and 58.5%, and those for the EPS(–) group were 32.3% and 42.7% (at 1 and 3 years, respectively) (Fig 3A). Thus, the risk of VT/VF recurrence was significantly lower in the EPS-VT(–) group compared with the EPS-VT(+) and EPS(–) groups. In contrast, among patients with lower LVEF (<30%) (n=91), the rates of VT/VF recurrence for the EPS-VT(+) group were significantly higher (58.6% and 76.4% at 1 and 3 years, respectively) than those for the EPS-VT(–) (35.7% and 35.7%) and EPS(–) group (30.0% and 51.0%, respectively) (p<0.05), whereas there was no significant difference in the recurrence rate between the EPS-VT(–) and the EPS(–) groups (Fig 3B). Furthermore, in patients with LVEF ≥30%, no patients died in the EPS-VT(–) group, whereas 3 of 42 patients in the EPS-VT(+) group and 4 of 39 patients in the EPS(–) group died during follow-up (Fig 3C). However, in patients with LVEF<30%, 2 of 14 patients in the EPS-VT(–), 4 of 20 patients in the EPS-VT(+) and 15 of 55 patients in the EPS(–) group died during follow-up (p=NS) (Fig 3D).

Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for recurrence of VT/VF for Holter, EPS pre-post and EPS-post amiodarone therapy. The EPS judgment showed lower sensitivity but significantly higher specificity for recurrence of VT/VF, especially in patients with LVEF ≥30%.

Table 4 Predictors of Arrhythmic Events

	SNS	SPC	PPV	NPV	ACC
Holter-judgment (n=75)	55	59	58	56	57
EPS pre-post amiodarone (n=19)	69	100	100	38	74
EPS post amiodarone (n=89)	59	81	88	46	66
LVEF ≥30% (n=55)	52	100	100	35	62
LVEF <30% (n=34)	70	64	74	60	68

SNS, sensitivity; SPC, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy. Other abbreviations as in Table 1.

ICD and LVEF

We further analyzed the relationship between ICD and LVEF in patients treated with amiodarone. As shown in Fig 4A, the mortality of patients treated with amiodarone plus ICD did not differ between patients with higher (≥30%) and lower (<30%) LVEF. However, among patients with no ICD (amiodarone only) (Fig 4B), patients with LVEF ≥30% had a similar mortality to those with ICD, but patients with LVEF<30% had a significant worse mortality than the patients with higher LVEF (p=0.01). Therefore, patients with moderate to severe LV dysfunction achieved the greatest benefit from ICD therapy.

Discussions

Major Findings

This study retrospectively demonstrated the long-term effect of EPS-guided oral amiodarone therapy in Japanese patients with a history of life-threatening ventricular tachyarrhythmias because of structural heart diseases. EPS-guided amiodarone could reduce the recurrence of VT, especially in patients with relatively preserved (≥30%)

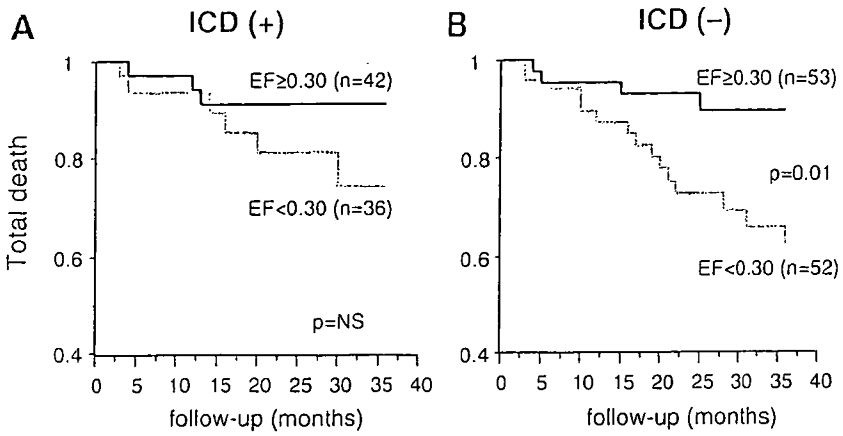

Fig 4. Cumulative risk of total death after amiodarone therapy in patients with implantable cardioverter defibrillator (ICD) (ICD(+)) and without ICD (ICD(-)). Higher (≥30%) and lower (<30%) left ventricular (LV) ejection fraction (EF) have similar risk for mortality in ICD(+) patients (A), but higher LVEF has significantly smaller risk of mortality than lower LVEF in ICD(-) patients (B).

LVEF, but was not always beneficial in patients with lower (<30%) LVEF. Therefore, amiodarone-treated patients with lower LVEF but not an implanted ICD remain at higher risk of sudden death.

EPS or Holter-Guided Amiodarone

Previous studies showed that EP-guided amiodarone therapy was useful for predicting recurrence of VT in patients at high risk for sudden cardiac death.[5,7,8,21] McGovern et al reported that the sensitivity, specificity and accuracy of EP testing for recurrent VT was 58%, 91% and 67%, respectively.[22] Those data coincide with our results showing that EPS-guided therapy has low sensitivity (59%), but high specificity (81%), for recurrence of VT after amiodarone. Moreover, this low sensitivity and high specificity of EP testing is more prominent in patients with LVEF ≥30% (52% and 100%, respectively) (Table 4). In this study, there were a small number of patients available for checking inducibility of VT before amiodarone, but the results of EPS-guided amiodarone are similar to those previously reported. Thus, it is not necessary to perform an EPS before starting amiodarone, and patients with LVEF ≥30% and non-inducible VT according to he EPS after amiodarone may remain free from recurrence of VT.

The ESVEM study showed that there was no significant difference between EPS and Holter monitoring in the probability of arrhythmic events occurring after antiarrhythmic drugs.[20] However, that study mainly examined the effectiveness of class I antiarrhythmic drugs, not amiodarone. The efficacy of amiodarone by Holter monitoring is also controversial. Veltri et al reported that Holter monitoring could predict the long-term efficacy of amiodarone.[6] Nasir et al showed that amiodarone strongly suppressed PVCs but this suppression did not predict clinical outcome.[23] Our finding that a Holter judgment could not predict the recurrence of VT after amiodarone may have resulted because (1) there was a smaller number of patients undergoing Holter monitoring before and after amiodarone, (2) twenty-four hours recording cannot detect the number of PVCs or VT precisely, and (3) the apparent number of PVCs might have no relation to the trigger of critical VT or VF. In this study EPS was clearly superior to Holter monitoring for evaluating amiodarone efficacy, but EPS is invasive and is not always performed in all patients.

Amiodarone, ICD and LVEF

Zhu et al suggested that EPS testing during amiodarone therapy was useful for predicting arrhythmia recurrence in patients without new or worsening congestive heart failure.[7] Other previous reports suggest that patients with lower LVEF (<35%) have a higher incidence of sudden cardiac death after amiodarone.[16–18] Those results are consisted with our subgroup analysis showing that EPS-guided amiodarone therapy is beneficial for patients with LVEF ≥30% but not <30%. Therefore, it is suggested that ICD is indicated in patients with lower LVEF (≤30–35%) and a history of syncope or sustained VT/VF.[17,24,25] On the other hand, patients with a relatively preserved LVEF (≥35%) do not always have better survival by ICD compared with amiodarone.[16]

In this study, EPS-guided amiodarone responders with a LVEF ≥30% were considered to be lower risk for sudden cardiac death, whereas patients judged as amiodarone non-responders or with LVEF <30% remain high risk for sudden death. Although our data could not compare between amiodarone and ICD therapy in high-risk patients, amiodarone-treated patients with lower LVEF, but not an implanted ICD, remain at higher risk of sudden death (Fig 4B) and should be considered for additional ICD therapy, as previously reported.[24]

In patients with congestive heart failure and LVEF <35%, a recent randomized study reported that amiodarone has no favorable effect on survival compared with placebo, but that ICD therapy reduced overall mortality by 23%.[19] Although ICD reduces mortality compared with antiarrhythmic drugs, it is estimated that up to 50% of patients with an ICD ultimately need antiarrhythmic drug therapy to suppress frequent episodes of VT or supraventricular tachyarrhythmias, and that amiodarone is the most commonly used drug for this purpose in Japanese patients.[15] Recently, Connolly et al reported that amiodarone plus β-blocker was effective for preventing ICD shocks, but increased the risk of drug-related adverse effect.[26] Therefore, further studies in the Japanese patient population are necessary to evaluate whether or not amiodarone can improve a patient's clinical outcome by reducing the amount of ICD shocks.[14]

Study Limitations

First, the study was not a prospective evaluation of EPS- or Holter-guided amiodarone treatment, so the direct efficacy of EPS or Holter-guided amiodarone in preventing the recurrence of VT/VF was not demonstrated; rather, an excellent prognosis for patients treated with EPS-guided amiodarone, especially in patients with a well-preserved LVEF, was demonstrated. Second, this study compared follow-up results between patients judged as amiodarone responder or non-responder by EPS, but did not compare amiodarone responders with control patients. Therefore, it might overestimate the effectiveness of EPS-guided amiodarone therapy for suppression of recurrent VT/VF. Third, this study contained a small number of patients, and a multicenter trial with a large number of patients will be necessary to demonstrate the effect of amiodarone and ICD therapy more accurately in Japanese patients![14,15] Fourth, this study focused on the risk of recurrent (secondary) VT/VF, not on primary prevention. It is still controversial whether amiodarone and/or ICD are indicated in patients with non-sustained VT and lower LVEF for primary prevention of sudden death.

References

1. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. *Circulation* 1997; **96:** 2823–2829.
2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999; **100:** 2025–2034.
3. Investigators ATM-A. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: Meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–1424.
4. Aiba T, Kurita T, Taguchi A, Shimizu W, Suyama K, Aihara N, et al. Long-term efficacy of empirical chronic amiodarone therapy in patients with sustained ventricular tachyarrhythmia and structural heart disease. *Circ J* 2002; **66:** 367–371.
5. Kadish AH, Buxton AE, Waxman HL, Flores B, Josephson ME, Marchlinski FE. Usefulness of electrophysiologic study to determine the clinical tolerance of arrhythmia recurrences during amiodarone therapy. *J Am Coll Cardiol* 1987; **10:** 90–96.
6. Veltri EP, Reid PR, Platia EV, Griffith LS. Amiodarone in the treatment of life-threatening ventricular tachycardia: Role of Holter monitoring in predicting long-term clinical efficacy. *J Am Coll Cardiol* 1985; **6:** 806–813.
7. Zhu J, Haines DE, Lerman BB, DiMarco JP. Predictors of efficacy of amiodarone and characteristics of recurrence of arrhythmia in patients with sustained ventricular tachycardia and coronary artery disease. *Circulation* 1987; **76:** 802–809.
8. Greenspon AJ, Volosin KJ, Greenberg RM, Jefferies L, Rotmensch HH. Amiodarone therapy: Role of early and late electrophysiologic studies. *J Am Coll Cardiol* 1988; **11:** 117–123.
9. Yuge M, Niwano S, Moriguchi M, Sasaki T, Hirasawa S, Imaki R, et al. Clinical significance of the electrophysiologic study (EPS)-guided therapy for the secondary prevention of ventricular tachycardia. *Circ J* 2006; **70:** 268–272.
10. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease: Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; **341:** 1882–1890.
11. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; **101:** 1297–1302.
12. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102:** 748–754.
13. Schlapfer J, Rapp F, Kappenberger L, Fromer M. Electrophysiologically guided amiodarone therapy versus the implantable cardioverter-defibrillator for sustained ventricular tachyarrhythmias after myocardial infarction: Results of long-term follow-up. *J Am Coll Cardiol* 2002; **39:** 1813–1819.
14. Kurita T, Mitamura H, Aizawa Y, Nitta T, Aonuma K, Tsuboi N, et al. Japanese randomized trial for investigation of a combined therapy of amiodarone and implantable cardioverter defibrillator in patients with ventricular tachycardia and fibrillation: The Nippon ICD Plus Pharmacologic Option Necessity study design. *Circ J* 2006; **70:** 316–320.
15. Satomi K, Kurita T, Takatsuki S, Yokoyama Y, Chinushi M, Tsuboi N, et al. Amiodarone therapy in patients implanted with cardioverter-defibrillator for life-threatening ventricular arrhythmias. *Circ J* 2006; **70:** 977–984.
16. Domanski MJ, Sakseena S, Epstein AE, Hallstrom AP, Brodsky MA, Kim S, et al. Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias: AVID Investigators: Antiarrhythmics Versus Implantable Defibrillators. *J Am Coll Cardiol* 1999; **34:** 1090–1095.
17. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials: AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study; Cardiac Arrest Study Hamburg; Canadian Implantable Defibrillator Study. *Eur Heart J* 2000; **21:** 2071–2078.
18. Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: The Canadian Implantable Defibrillator Study. *Circulation* 2000; **101:** 1660–1664.
19. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–237.
20. Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias: Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. *N Engl J Med* 1993; **329:** 452–458.
21. Horowitz LN, Greenspan AM, Spielman SR, Webb CR, Morganroth J, Rotmensch H, et al. Usefulness of electrophysiologic testing in evaluation of amiodarone therapy for sustained ventricular tachyarrhythmias associated with coronary heart disease. *Am J Cardiol* 1985; **55:** 367–371.
22. McGovern B, Garan H, Malacoff RF, DiMarco JP, Grant G, Sellers TD, et al. Long-term clinical outcome of ventricular tachycardia or fibrillation treated with amiodarone. *Am J Cardiol* 1984; **53:** 1558–1563.
23. Nasir N Jr, Doyle TK, Wheeler SH, Pacifico A. Usefulness of Holter monitoring in predicting efficacy of amiodarone therapy for sustained ventricular tachycardia associated with coronary artery disease. *Am J Cardiol* 1994; **73:** 554–558.
24. Olson PJ, Woelfel A, Simpson RJ Jr, Foster JR. Stratification of sudden death risk in patients receiving long-term amiodarone treatment for sustained ventricular tachycardia or ventricular fibrillation. *Am J Cardiol* 1993; **71:** 823–826.
25. Grimm W, Hoffmann J, Menz V, Luck K, Maisch B. Programmed ventricular stimulation for arrhythmia risk prediction in patients with idiopathic dilated cardiomyopathy and nonsustained ventricular tachycardia. *J Am Coll Cardiol* 1998; **32:** 739–745.
26. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: The OPTIC Study: A randomized trial. *JAMA* 2006; **295:** 165–171.

ELSEVIER

European Journal of Cardio-thoracic Surgery 32 (2007) 711–717

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Predictive factors for the intermediate-term patency of arterial grafts in aorta no-touch off-pump coronary revascularization

Hiroyuki Nakajima [a,*], Junjiro Kobayashi [a], Toshihiro Funatsu [a], Yusuke Shimahara [a], Masashi Kawamura [a], Atsushi Kawamura [b], Toshikatsu Yagihara [a], Soichiro Kitamura [a]

[a] Department of Cardiovascular Surgery, National Cardiovascular Center, Osaka, Japan
[b] Department of Cardiology, National Cardiovascular Center, Osaka, Japan

Received 19 February 2007; received in revised form 6 July 2007; accepted 13 July 2007; Available online 6 September 2007

Abstract

Objective: Graft flow is one of the important determinants of the arterial graft patency. To establish the optimal graft design, we examined detailed characteristics of the arterial composite and sequential grafts, and sought to delineate the risk factors of graft occlusion due to insufficient bypass flow. Methods: Angiograms of 2547 bypass grafts in 677 consecutive patients who underwent total arterial off-pump CABG without aortic manipulation followed by early postoperative angiography since December 2000 were reviewed. The angiographic flow was graded as A (antegrade), B (competitive), C (reversal), and O (occlusion). Results: The overall early graft patency rate was 98.2% (2502/2547). The rate of grade A was 91.3% (2325/2547), while the rates of grades B and C were 2.9% (73/2547) and 4.1% (104/2547), respectively. For the main trunk of the anterior descending branch (LAD), the graft patency rate was 99.3% (674/679). The grade A rate of the internal thoracic artery (ITA) grafts to LAD in an individual fashion was 99.5% (203/204), being comparable with that in the sequential or composite grafting which had two distal anastomoses (98.1%, 159/162; $p = 0.33$). The actuarial patency rates at 3 years were 84.7% for the bypass grafts with grade A flow and 33.9% for those with grade B/C flow, respectively ($p < 0.0001$). The multivariate Cox-regression analysis demonstrated that grade B/C ($p < 0.0001$, HR = 4.19) and 51–75% stenosis of the native coronary artery ($p = 0.02$, HR = 2.86) were significant predictors of graft occlusion. Conclusions: For the LAD, the results of graft flow in sequential ITA grafting or composite grafting with two distal anastomoses were comparable with that in individual ITA grafting. Prediction and prevention of competitive and reverse flow are mandatory for achieving the advantages of the arterial materials.

Keywords: Coronary disease; Surgery; Angiography; Off-pump CABG; Arterial graft

1. Introduction

The arterial grafts have beneficial characteristics in terms of expectancy of long-term patency and improved late outcome after coronary artery bypass grafting (CABG) [1–3]. For the arterial grafts, the circumstance of the blood flow in the graft lumen is considered an important determinant of the patency. It has been reported that occlusion or string sign in the arterial grafts can typically occur when the stenosis in the native coronary artery is moderate, and that these physiologic changes in the luminal diameter occurred within 2 years [4–7]. We previously reported that reverse flow in the sequential or composite graft was commonly associated with the moderately stenotic right coronary artery (RCA) and composite or sequential grafting to more than four target branches [8]. In addition, the management of a coronary branch with critical stenosis played definitive roles [9].

The objectives of this study were (1) to delineate the effects of detailed characteristics of the target coronary branches and the bypass grafts on the occurrence of competitive flow, (2) to delineate the risk of graft occlusion, and (3) to establish a theoretical basis for optimizing the strategy for graft arrangement to the left anterior descending artery (LAD) and to non-LAD branches, which include the diagonal branch, left circumflex artery (LCX), and RCA.

2. Methods

The pre- and postoperative coronary angiograms of 2547 bypass grafts in 677 consecutive patients, who underwent off-pump complete revascularization for coronary artery disease using only the internal thoracic artery (ITA) with or without the radial artery between December 2000 and May

* Corresponding author. Address: Department of Cardiovascular Surgery, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: hnakajim@hsp.ncvc.go.jp (H. Nakajima).

1010-7940/$ – see front matter © 2007 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ejcts.2007.07.025

Table 1
Baseline characteristics

No. of patients	677
Age (years)	66.1 ± 9.1
Male/female	563/114
Hypertension	357 (52.7%)
Hyperlipidemia	332 (49.0%)
Diabetes	260 (38.4%)
Left ventricular end-diastolic volume index (ml/m^2)	84.9 ± 29.0
Left ventricular ejection fraction (%)	48.1 ± 11.7
Total distal anastomoses	2547
Distal anastomoses per patient	3.76 ± 1.01
Bypass conduits used	1023
In-situ ITA	293
Composite Y-graft	391
Composite I-graft	273
Composite K-graft	66

ITA, internal thoracic artery.

2006, were reviewed. The patients who had a bypass of the gastroepiploic artery, the inferior epigastric artery or the saphenous vein, those with individual grafts only, and those who did not undergo early postoperative coronary angiography were excluded. All patients provided written informed consent after explanation of the potential risks. All procedures were performed under social insurance coverage, and institutional approval was obtained. There were 563 men and 114 women, and their mean age was 66.1 ± 9.1 years. The number of distal anastomoses was 3.76 ± 1.01 per patient (Table 1).

Early postoperative coronary angiography was performed within a month after surgery. Cardiologists independently evaluated the native coronary artery stenosis and the graft patency. The maximal severity of stenosis was recorded for all target branches. The definitions of terms used in the present study are as follows. A patent graft meant that the graft had a complete continuity of the graft lumen throughout its entire length from the origin of the ITA to the target coronary branch, irrespective of the flow direction. Whenever the continuity of the graft lumen from an in-situ ITA graft to the anastomosis with the target coronary branch was interrupted at any level, or when repeated angioplasty was performed, they were defined as Grade O (occlusion). Grade A was defined as a situation in which antegrade graft flow was found in most of the multi-plane ITA angiographs. Grade B (competitive) was defined as a situation in which the target vessel was slightly opacified from the ITA graft injection, and the bypass graft did fill by retrograde flow from the native coronary injection. Grade C (reverse flow) was defined as a situation in which the distal anastomotic site was not opacified from the ITA graft injection at all, but it did fill clearly by retrograde flow from the native coronary injection. Flow grade was recorded for each target coronary branch, and these data were collected prospectively.

An individual bypass is defined as a bypass conduit having one in-situ ITA and one distal anastomosis. A non-individual bypass graft means a bypass conduit having two or more distal anastomoses, such as sequential or composite grafting. The in-situ ITA is ITA divided only at its distal portion.

2.1. Graft design strategy

The arrangement of the bypass conduits was primarily determined by the operative risk and positional relationship of the target sites. Our current standard technique since March 2003 was based on our previous angiographic studies and introduced for minimizing competitive and reverse flow. One in-situ ITA, usually the left, supplies the LAD territory, while an I-graft of the contralateral ITA, usually the right, and the radial artery supply the LCX and RCA territories in a clockwise orientation, via a side-to-side anastomosis with LCX and an end-to-side anastomosis with RCA. The counterclockwise orientation was occasionally chosen to avoid grafting to RCA branch with 75% stenosis at the end of the conduit, because reverse flow was commonly found at the distal end of the conduit with the end-to-side anastomosis [8,9]. Before introduction of this strategy, the I-graft was used only in a counterclockwise orientation for the safety of redo operation in the future. For patients aged more than 75 years or with considerable operative risks, such as chronic obstructive pulmonary disease or diabetes mellitus treated by insulin therapy, we harvested only a single ITA. In the present series, all ITA grafts were greater than 1.5 mm in diameter at the distal end.

2.2. Late angiographic results

Follow-up angiography was performed between 3 and 66 months after the operation for 325 bypass grafts in 91 patients with recurrent angina, or ischemic findings on electrocardiography or scintigraphy. The mean follow-up period was 29 ± 19 months.

2.3. Statistical analysis

The continuous variables are expressed as the mean values ± standard deviation (SD). The data of two independent groups were compared by Fisher's exact probability test. Longitudinal data were estimated by the Kaplan–Meier method and the difference of two groups was compared by log-rank method. Cox regression analysis was used to examine the significance of the variables in predicting graft occlusion. Statistical analyses were performed using SPSS software (SPSS 8.0 Inc., Chicago, IL). The differences in the outcomes were considered statistically significant when the p-value was less than 0.05.

3. Results

The overall graft patency rate was 98.2% (2502/2547), and the grade A rate was 91.3% (2325/2547). The actuarial graft patency rates at 3 years were 84.7% for the bypass grafts graded A and 33.9% for the bypass grafts graded B/C ($p < 0.0001$). The early patency rate of the bypass grafts to 51–75% stenotic coronary branches was 98.1% (1140/1162), and their grade A rate was 85.1% (989/1162), being significantly lower than that of the bypass grafts to 76–100% stenotic branches (96.5%, 1336/1385; $p < 0.0001$). For 75% stenotic branches, the actuarial graft patency rates at 3

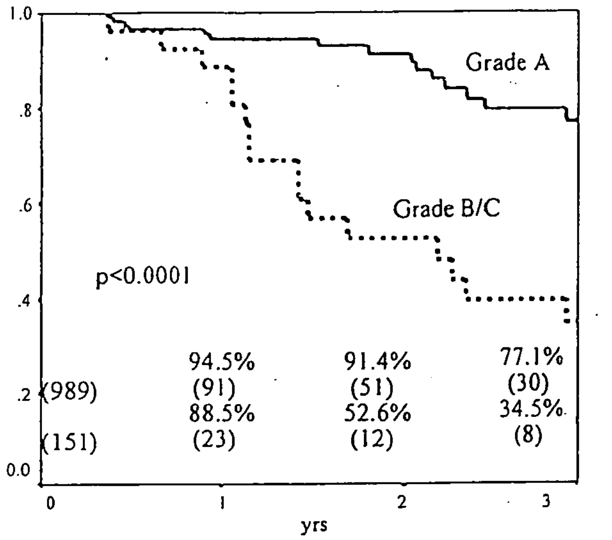

Fig. 1. The actuarial graft patency rate of the bypass grafts to 51–75% stenotic branches. Grade A vs grade B/C.

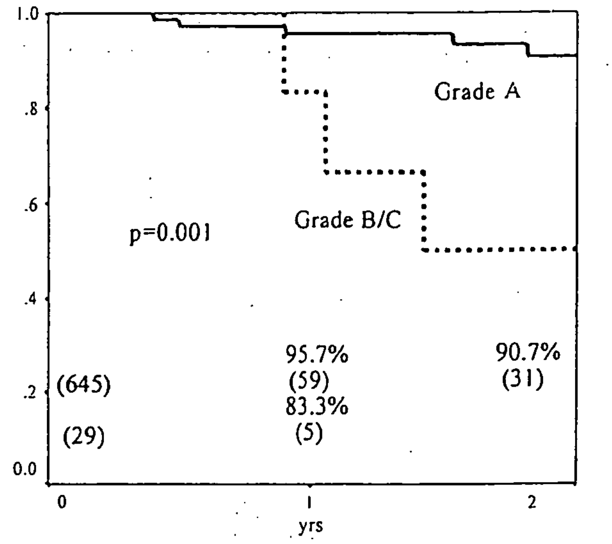

Fig. 2. The actuarial graft patency rate of the bypass grafts to the main trunk of LAD. Grade A vs grade B/C.

years were 77.1% for the bypass grafts graded A and 34.5% for the bypass grafts graded B/C ($p < 0.0001$) (Fig. 1).

Regarding the main trunk of LAD, the grade A rate of the in-situ ITA in individual fashion was 99.5% (203/204), and was significantly higher than that of non-individual conduit grafting (93.1%, 442/475; $p = 0.0001$), whereas the patency rates were similar ($p = 0.99$). The grade A rate of the conduit with two distal anastomoses was comparable with that of the individual grafting ($p = 0.33$) (Table 2). For the bypass grafts to LAD, the actuarial graft patency rates at 1 year were 95.7% for the bypass grafts graded A and 83.3% for the bypass grafts graded B/C ($p = 0.001$) (Fig. 2). The actuarial graft patency rates of the bypass graft to the LAD with 51–75% stenosis and those with 76–100% stenosis at 2 years were 79.9% and 96.7%, respectively ($p = 0.16$).

For the non-LAD branches, including the diagonal, LCX, and RCA branches, the grade A rate of the in-situ ITA was comparable to that of the Y- or K-graft or I-graft (90.8% vs 89.9%; $p = 0.87$), and the grade A rate of the individual grafts was comparable to that of the sequential and composite grafts (91.9% vs 89.9%; $p = 0.99$) (Table 3). The patency rate of the bypass grafts to 51–75% stenotic branches was similar

Table 2
Early angiographic results: flow grading of bypass grafts to main trunk of left anterior descending artery

		No. of anastomoses	Grade A	Grade A rate (%)	Grade B	%	Grade C	%	Grade O	Patency rate (%)
Native coronary stenosis	51–75%	313	288	92.0 [1]	16	5.1	6	1.9	3	99.0 [3]
	76–90%	205	196	95.6 [2]	2	1.0	5	2.4	2	99.0 [4]
	91–100%	161	161	100 [2]	0	0	0	0	0	100 [4]
Diameter of target branch	<1.5 mm	72	68	94.4 [5]	2	2.8	1	1.4	1	98.6
	≥1.5 mm	546	523	95.8 [6]	10	1.8	10	1.8	3	99.5
	Not recorded	61	54	88.5	6	9.8	0	0	1	98.4
Graft material anastomosed	ITA	679	645	95.0	18	2.7	11	1.6	5	99.3
	RA	0	0	–	0	–	0	–	0	–
	Free ITA	0	0	–	0	–	0	–	0	–
Anastomotic fashion	End-to-side (graft end)	675	642	95.1	17	2.5	11	1.6	5	99.3
	Side-to-side (sequential)	4	3	75.0	1	25.0	0	0	0	100
Conduit type	In-situ ITA	275	272	98.9 [7]	1	0.4	0	0	2	99.3
	Y-graft	343	318	92.7 [8]	17	5.0	5	1.5	3	99.1
	K-graft	61	55	90.2 [8]	0	0	6	9.8	0	100
	I-graft	0	0	–	0	–	0	–	0	–
No. of distal anastomoses of conduit	1 (individual)	204	203	99.5 [9,13]	0	0	0	0	1	99.5 [11]
	2	162	159	98.1 [10,14]	2	1.2	0	0	1	99.4 [12]
	3	204	188	92.2 [10]	12	5.9	2	1.0	2	99.0 [12]
	4∼	109	95	87.2 [10]	4	3.7	9	8.3	1	99.1 [12]
Total		679	645	95.0	18	2.7	11	1.6	5	99.3

ITA, internal thoracic artery; RA, radial artery. [1] vs [2], $p = 0.001$; [3] vs [4], $p = 0.67$; [5] vs [6], $p = 0.54$; [7] vs [8], $p = 0.0001$; [9] vs [10], $p < 0.0001$; [11] vs [12], $p > 0.99$; [13] vs [14], $p = 0.33$.

Table 3
Early angiographic results: flow grading of bypass grafts to diagonal branch, LCX, and RCA

		No. of anastomoses	Grade A	Grade A rate (%)	Grade B	%	Grade C	%	Grade O	Patency rate (%)
Target branch	Diagonal	391	368	94.1 [1]	9	2.3	7	1.8	7	98.2 [4]
	Circumflex	804	738	91.8 [2]	19	2.4	36	4.5	11	98.6 [5]
	Right coronary	673	574	85.3 [3]	27	4.0	50	7.4	22	96.7 [6]
Native coronary stenosis	51–75%	849	701	82.6 [7]	48	5.7	81	9.5	19	97.8 [9]
	76–90%	500	469	93.8 [8]	7	1.4	12	2.4	12	97.6 [10]
	91–100%	519	510	98.3 [8]	0	0	0	0	9	98.3 [10]
Diameter of target branch	<1.5 mm	614	553	90.1	15	2.4	27	4.4	19	96.9
	>1.5 mm	1121	1015	90.5	34	3.0	57	5.1	15	98.7
	Not recorded	133	112	84.2	6	4.5	9	6.8	6	95.5
Graft material anastomosed	ITA	166	147	88.6 [11]	4	2.4	7	4.2	8	95.2
	RA	1654	1488	90.0 [12]	51	3.1	83	5.0	32	98.1
	Free ITA	48	45	93.8	0	0	3	6.3	0	100
Anastomotic fashion	End-to-side (graft end)	869	709	81.6 [17]	48	5.5	80	9.2	32	96.3
	Side-to-side (sequential proximal)	999	971	97.2 [18]	7	0.7	13	1.3	8	99.2
Conduit type	In-situ ITA	109	99	90.8 [13]	1	0.9	1	0.9	8	92.7
	Y-graft	842	749	89.0 [14]	25	3.0	50	5.9	18	97.9
	K-graft	185	161	87.0 [14]	10	5.4	13	7.0	1	99.5
	I-graft	732	671	91.7 [14]	19	2.6	29	4.0	13	98.2
No. of distal anastomoses of conduit	1 (individual)	37	34	91.9 [15]	0	0	0	0	3	91.9
	2	360	319	88.6 [16]	15	4.2	12	3.3	14	96.1
	3	780	701	89.9 [16]	26	3.3	40	5.1	13	98.3
	4∼	691	626	90.6 [16]	14	2.0	41	5.9	10	98.6
Total		1868	1680	89.9	55	2.9	93	5.0	40	97.9

ITA, internal thoracic artery; LCX, left circumflex artery; RA, radial artery; RCA, right coronary artery. [1] vs [3], $p < 0.0001$; [2] vs [3], $p < 0.0001$; [4] vs [6], $p = 0.18$; [5] vs [6], $p = 0.02$; [7] vs [8], $p < 0.0001$; [9] vs [10], $p = 0.87$; [11] vs [12], $p = 0.59$; [13] vs [14], $p = 0.87$; [15] vs [16], $p > 0.99$; [17] vs [18], $p < 0.0001$.

to that of the bypass grafts to 76–100% stenotic branches (97.8% vs 97.9%; $p = 0.87$), while the grade A rate of the bypass grafts to 51–75% stenotic branches was significantly lower than that of the bypass grafts to 76–100% stenotic branches (82.6% vs 96.1%; $p < 0.0001$). The actuarial graft patency rates at 2 years were 94.5% for the bypass grafts graded A and 57.6% for the bypass grafts graded B/C ($p < 0.0001$). The actuarial graft patency rate of the bypass grafts to branches with 76–100% stenosis at 2 years was 89.8%, being significantly higher than that of the bypass grafts to branches with 51–75% stenosis (82.2%; $p = 0.009$). The actuarial graft patency rate of the bypass grafts in the end-to-side fashion at 2 years was 80.5%, being significantly lower than that of the bypass grafts in the side-to-side fashion (91.4%; $p = 0.01$) (Fig. 3A). The actuarial graft patency rates at 2 years were 85.6% for the I-grafts graded A and 88.8% for the bypass grafts graded B/C ($p = 0.31$) (Fig. 3B).

As shown in Table 4, the univariate Cox regression analysis demonstrated that the RCA territory, 51–75% stenosis, small coronary branch (diameter < 1.5 mm), and grade B/C were significant predictors of graft occlusion. The multivariate Cox regression analysis identified 51–75% stenosis (HR = 2.86, $p = 0.02$) and grade B/C (HR = 4.19, $p < 0.0001$) as significant predictors.

4. Discussion

A composite graft allowed total arterial revascularization with excellent graft patency rate and lower incidence of perioperative cardiac and cerebrovascular events [10,11]. Although various arrangements of the in-situ and free arterial grafts have already been reported [3,12,13], no optimal strategy for graft arrangement has been established yet. We have applied our grading system of angiographic graft flow for 5.5 years. The results of the present study imply some suggestions regarding the strategy for graft arrangement.

For the main trunk of the LAD, the use of the in-situ ITA graft has been generally accepted as a standard strategy, which provides a long-term patency and improves the late survival after CABG. The in-situ ITA in an individual fashion may be ideal for the main trunk of the LAD; however, sequential and composite grafting to the LAD and a diagonal branch is an important option of choice. Dion et al. reported that the long-term patency of sequential grafting with the in-situ ITA to the LAD and a diagonal branch was identical to that of the individual in-situ ITA [14]. We previously reported that early angiographic results of the Y-graft to the LAD and a diagonal branch were similar to that of sequential grafting [9]. As shown in Table 2, our present study demonstrated that, in the LAD region, the sequential graft and the Y-graft to two distal anastomoses were as reliable as individual grafting. We consider that the in-situ ITA, which is anastomosed to the LAD, can be connected with at least one diagonal branch by sequential or composite grafting without disturbance of graft flow to the main trunk of the LAD. Different from bypass grafts to LCX or RCA, the difference between the patency rate of bypass grafts to LAD 51–75% and that of bypass grafts to 76–100% stenosis was not significant. The in-situ ITA grafts could confidently supply the

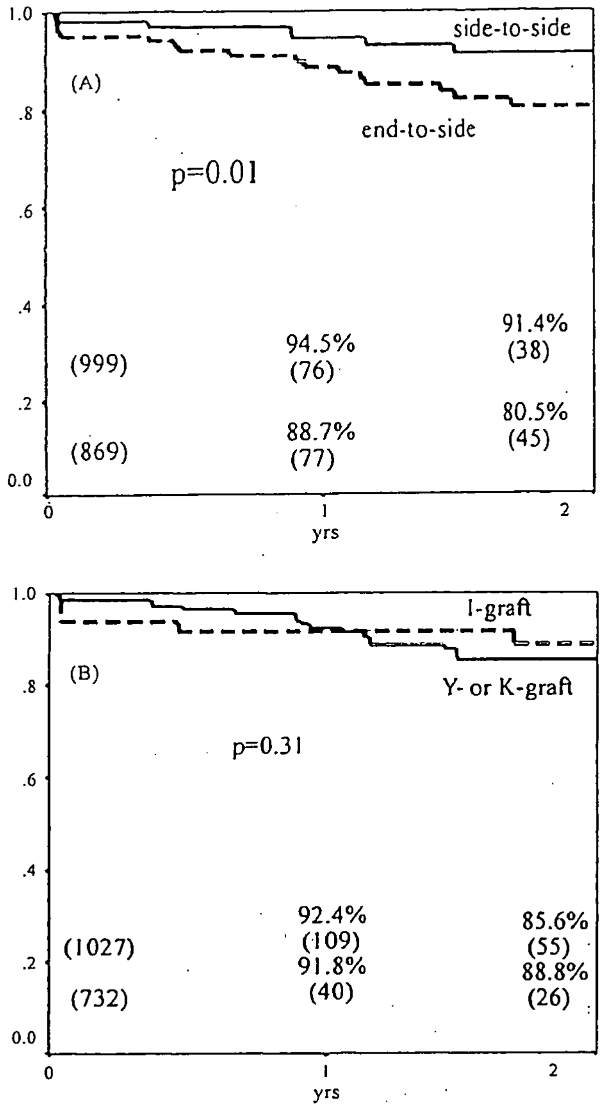

Fig. 3. (A) The actuarial graft patency rate of the bypass grafts to the non-LAD branches. End-to-side anastomoses (graft end) vs side-to-side anastomoses. (B) The actuarial graft patency rate of the bypass grafts to the non-LAD branches. I-graft vs Y- or K-graft.

sufficient antegrade flow to the LAD territory, even with moderate stenosis.

For the coronary branches besides LAD, there was no obvious disadvantage of the composite grafts versus the individual graft and the in-situ ITA. In addition, native coronary stenosis had stronger impact on the bypass grafts to the non-LAD branches than on the bypass grafts to the LAD in the follow-up angiographic results. For the bypass grafts to the non-LAD regions, both grade B/C and 51–75% stenosis in the native coronary branch significantly correlated with graft occlusion.

One of the possible explanations for these differences between the grafts to LAD and those to non-LAD branches may be the difference in the graft materials. About 90% of the anastomoses were performed with the composite radial artery. The radial artery may be more sensitive for the blood flow in the lumen than the ITA graft. More severe stenosis will be necessary for the long-term patency of the radial artery, as compared with the ITA graft.

Regarding the conduit type, no significant difference was found between the I-graft and the Y- or K-graft in the non-LAD regions. We consider that the appropriate pressure slope in each segment of the bypass conduit, highest at the proximal and lowest at the end of the conduit, was the most important for antegrade bypass flow to all target vessels. The bypass grafts with the side-to-side anastomoses presented better graft patency than those with the end-to-side anastomoses. Therefore, when the positional relationship of the target sites allows, the I-graft would be favorable, because it has only one end-to-side anastomosis and the target coronary branch at the end of the conduit can be changed by simply determining its orientation. On the other hand, the Y-graft has the advantages of increased flow capacity [15] and availability to the distant target branches.

Dion et al. reported that the patency rate of end-to-end grafting was comparable with side-to-side grafting with excellent long-term patency of sequential grafting using the ITA graft [14]. In their report, the target branches of 78% of bypass graft restudied were the LAD and a diagonal branch, whereas, in the present study, sequential ITA grafting to the LAD and a diagonal branch was only 9%, and sequential grafting to four or more target branches was performed in about 11% of patients. We consider that the difference is owing to differences in target site, graft material, and probably the number of target coronaries in sequential anastomoses.

Selection of patients suitable for this procedure would be a next concern. It has been widely accepted that the patients with severe atherosclerosis of the ascending aorta are the most suitable candidates for composite and sequential grafting [10,11]. We would suggest herein new patients' selection criteria from a viewpoint of preventing competitive flow and maximizing durability of arterial grafts. According to the results of the present study and our previous investigations, the decisive risks of competitive and reverse flow are as follows: (1) a RCA branch with 51–75% stenosis, (2) a LCX branch with 51–75% stenosis, (3) a bypass conduit with four or more distal anastomoses, and (4) three high-risk situations reported in [9]. Of 677 patients in this study, 147 (21.7%) patients had none of these risks and/or all risky situations were successfully avoided. The actuarial graft patency rate of patients who have none of the above risks at 3 years was significantly higher than that of patients with any of the risks (92.6% vs 69.7%; $p < 0.0001$). They were the best candidates for this procedure. On the other hand, when competitive or reverse flow is highly predicted, alternative strategies, such as the aortocoronary bypass, which provides the highest bypass pressure [16], may be reasonable, especially for the non-LAD regions.

The present study had some limitations. First, the patients who underwent follow-up angiography were biased toward clinically evident graft failure. Second, the peripheral vascular resistance in the myocardial tissue, which has an important role in the coronary perfusion, was not taken into account. Third, the capacity of the ITA graft was not considered. The pressure and flow capacity as the blood source of the bypass conduit and potentiality of growth or thinning and adaptability to the graft flow may also play important roles in the occurrence of insufficient flow and resultant occlusion. At the beginning of 2004, we started to harvest ITA in a skeletonized fashion to maximize the

Table 4
Predictors of graft occlusion in the intermediate-term follow-up period

Variables	Hazard ratio	95% CI	p-Value
Univariate analysis			
Female	1.17	(0.55–2.47)	0.68
Distal anastomoses of the conduit	1.00	(0.78–1.29)	0.99
Early period (Dec. 2000–Feb. 2003)	0.91	(0.50–1.66)	0.76
Type of the conduit, Y- or K-graft (vs in-situ ITA)	0.66	(0.31–1.42)	0.29
Type of the conduit, I-graft (vs in-situ ITA)	1.02	(0.45–2.32)	0.96
Graft material anastomosed, radial artery (vs in-situ ITA)	1.39	(0.81–2.38)	0.23
Graft material anastomosed, free ITA (vs in-situ ITA)	2.51	(0.74–8.55)	0.14
Location, LCX territory (vs LAD territory)	0.98	(0.51–1.90)	0.95
Location, RCA territory (vs LAD territory)	2.44	(1.41–4.23)	0.001
Stenosis (51–75%)	2.28	(1.35–3.83)	0.002
Diameter of coronary branch (<1.5 mm)	1.94	(1.12–3.36)	0.01
End-to-side anast. (graft end) (vs side-to-side = sequential proximal)	1.48	(0.87–2.53)	0.15
Grade B/C in early angiography	6.46	(3.64–11.47)	<0.0001
Multivariate analysis			
Graft material anastomosed, radial artery (vs in-situ ITA)	0.51	(0.10–2.70)	0.43
Graft material anastomosed, free ITA (vs in-situ ITA)	1.24	(0.14–11.35)	0.84
Location, LCX territory (vs LAD territory)	1.88	(0.37–9.57)	0.45
Location, RCA territory (vs LAD territory)	3.27	(0.65–16.35)	0.15
Stenosis (51–75%)	2.86	(1.17–6.99)	0.02
Diameter of coronary branch (<1.5 mm)	1.57	(0.78–3.14)	0.20
End-to-side anast. (graft end) (vs side-to-side = sequential proximal)	1.12	(0.53–2.33)	0.77
Grade B/C in early angiography	4.19	(2.02–8.69)	<0.0001

CI, confidence interval; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ITA, internal thoracic artery; RA, radial artery.

capacity of the in-situ ITA graft [17,18]. This technique will extend the application of the bilateral ITA grafting to patients with a substantial operative risk [19]. Fourth, the effects of the luminal size of arterial conduits on the long-term patency remain unclear. Previously, the grading system of the luminal size at the narrowest portion, and intimal irregularity was reported [20,21]. It was reported useful for assessment of degeneration of bypass grafts in a conventional technique. However, the luminal size of the side-to-side anastomosis in the sequential fashion is not precisely measurable, especially when the angle between the graft and the coronary branch is near 90 degrees, or when the contrast medium only fills incompletely due to mixture with the blood flow from the native coronary artery. Moreover, the regression of stenosis and the increase of the diameter were relatively common findings in the arterial materials [22,23]. At last, high-pressure injection of contrast medium may induce reverse and competitive flow and may interfere with evaluation of graft flow direction. This may be a methodological limitation. This flow grading system is not necessarily practical for postoperative evaluation for each patient and each bypass graft. In the present study, flow grading was performed independently from the catheterization team. We utilized this grading system for comparison of graft configurations and optimizing the strategy for design of the arterial grafts, based on data of a considerable number of patients and bypass grafts, and examined significance of correlations between characteristics of the bypass grafts and the occurrence of competitive and reverse flow. For these purposes, flow grading is considered useful.

In conclusion, prediction and prevention of competitive and reverse flow may be necessary to enhance the advantage of multivessel revascularization using exclusively arterial materials because insufficiency of the antegrade flow would spoil the advantage of arterial grafts.

References

[1] Maniar HS, Sundt TM, Barner HB, Prasad SM, Peterson L, Absi T, Moustakidis P. Effect of target stenosis and location on radial artery graft patency. J Thorac Cardiovasc Surg 2002;123:45–52.

[2] Royse AG, Royse CF, Tatoulis J, Grigg LE, Shah P, Hunt D, Better N, Marasco SF. Postoperative radial artery angiography for coronary artery bypass surgery. Eur J Cardiothorac Surg 2000;17:294–304.

[3] Tector AJ, Amundsen S, Schmahl TM, Kress DC, Peter M. Total revascularization with T grafts. Ann Thorac Surg 1994;57:33–9.

[4] Siebenmann R, Egloff L, Hirzel H, Rothlin M, Studer M, Tartini R. The internal mammary artery 'string phenomenon'. Analysis of 10 cases. Eur J Cardiothorac Surg 1993;7:235–8.

[5] Hashimoto H, Isshiki T, Ikari Y, Hara K, Saeki F, Tamura T, Yamaguchi T, Suma H. Effects of competitive flow on arterial graft patency and diameter. Medium-term postoperative follow-up. J Thorac Cardiovasc Surg 1996;111:399–407.

[6] Bezon E, Choplain JN, Maguid YA, Aziz AA, Barra JA. Failure of internal thoracic artery grafts: conclusions from coronary angiography: mid-term follow-up. Ann Thorac Surg 2003;76:754–9.

[7] Parvaiz I, Lund JT, Kelbek H. The arterial sling operation: one-year follow-up. Ann Thorac Surg 2005;80:1375–80.

[8] Nakajima H, Kobayashi J, Tagusari O, Bando K, Niwaya K, Kitamura S. Competitive flow in arterial composite grafts and effect of graft arrangement in off-pump coronary revascularization. Ann Thorac Surg 2004;78:481–6.

[9] Nakajima H, Kobayashi J, Tagusari O, Bando K, Niwaya K, Kitamura S. Functional angiographic evaluation of individual, sequential, and composite arterial grafts. Ann Thorac Surg 2006;81:807–14.

[10] Muneretto C, Negri A, Manfredi J, Terrini A, Rodella G, ElQarra S, Bisleri G. Safety and usefulness of composite grafts for total arterial myocardial revascularization: a prospective randomized study. J Thorac Cardiovasc Surg 2003;125:826–35.

[11] Weinschelbaum EE, Gabe ED, Macchia A, Smimmo R, Suarez LD. Total myocardial revascularization with arterial conduits: radial artery combined with internal thoracic arteries. J Thorac Cardiovasc Surg 1997;114:911–6.

[12] Wendler O, Hennen B, Markwirth T, Konig J, Tscholl D, Huang Q, Shahangi E, Schafers HJ. T grafts with the right internal thoracic artery to left internal thoracic artery versus the left internal thoracic and radial artery: flow dynamics in the internal thoracic artery main stem. J Thorac Cardiovasc Surg 1999;118:841–8.

[13] Christensen JB, Lund JT, Kassis E, Kelbaek H. Complete arterial coronary revascularization using conduit for double thoracic artery inlet flow: arterial sling operation. Eur J Cardiothorac Surg 2002;21: 391–4.
[14] Dion R, Glineur D, Derouck D, Verhelst R, Noirhomme P, El Khoury G, Degrave E, Hanet C. Long-term clinical and angiographic follow-up of sequential internal thoracic artery grafting. Eur J Cardiothorac Surg 2000;17:407–14.
[15] Royse AG, Royse CF, Groves KL, Yu G. Blood flow in composite arterial graft and effect of native coronary flow. Ann Thorac Surg 1999;68: 1619–22.
[16] Tedoriya T, Kawasuji M, Sakakibara N, Ueyama K, Watanabe Y. Pressure characteristics in arterial grafts for coronary bypass surgery. Cardiovasc Surg 1995;3:381–5.
[17] Takami Y, Ina H. Effect of skeletonization on intraoperative flow and anastomosis diameter of internal thoracic arteries in coronary artery bypass grafting. Ann Thorac Surg 2002;73:1441–5.
[18] Wendler O, Tscholl D, Huang Q, Schafers HJ. Free flow capacity of skeletonized versus pedicled internal thoracic artery grafts in coronary artery bypass grafts. Eur J Cardiothorac Surg 1999;15:247–50.
[19] Kramer A, Mastsa M, Paz Y, Locker C, Pevni D, Gurevitch J, Shapira I, Lev-ran O, Mohr R. Bilateral skeletonized internal thoracic artery grafting in 303 patients. J Thorac Cardiovasc Surg 2000;120:290–7.
[20] FitzGibbon GM, Burton JR, Leach AJ. Coronary bypass graft fate. Angiographic grading of 1400 consecutive grafts early after operation and 1132 after one year. J Thorac Cardiovasc Surg 1978;57:1070–4.
[21] FitzGibbon GM, Leach AJ, Keon WJ, Burton JR, Kafka HP. Coronary bypass graft fate. J Thorac Cardiovasc Surg 1986;91:773–8.
[22] Izumi C, Hayashi H, Ueda Y, Matsumoto, Himura Y, Gen H, Konishi T. Late regression of left internal thoracic artery graft stenosis at the anastomotic site without intervention therapy. J Thorac Cardiovasc Surg 2005;130:1661–7.
[23] Kitamura S. Does the internal thoracic artery graft have self-reparative ability? J Thorac Cardiovasc Surg 2005;130(6):1494–5.

REVIEW

CABGの現況

小林順二郎*

はじめに

1967年にKolessov[1]が左肋間開胸で左内胸動脈（左ITA：LITA）を心拍動下に左前下行枝（LAD）に吻合した症例をはじめて報告して以来，冠状動脈バイパス術（CABG）は本邦においても著しく増加してきた．日本胸部外科学会の統計では，2002年のCABGは単独手術で21,000例を超え，その手術成績も向上して，手術死亡率は1%を切るにいたっている．一方，ステントによる経皮的カテーテルインターベンション（PCI），ことに薬剤溶出ステント（DES）の導入により，3枝病変に対しても無制限にPCIが行われるようになり，2003年より単独CABG数は減少に転じて，2005年には18,000例と17%減少した（図1）．欧米においてPCIとCABGを比較した前向き無作為化比較試験[2,3]では，遠隔死亡率やmajor adverse cardiac event（MACE）発生率についてはCABGの成績がより良好であり，医療費に関しても短期的にはCABGが高いが，PCIを繰り返して入院すると逆にPCIの費用が高くなる結果であり，DES全盛時代においてもCABGは冠状動脈血行再建術の重要な手術手技であることにかわりはない．

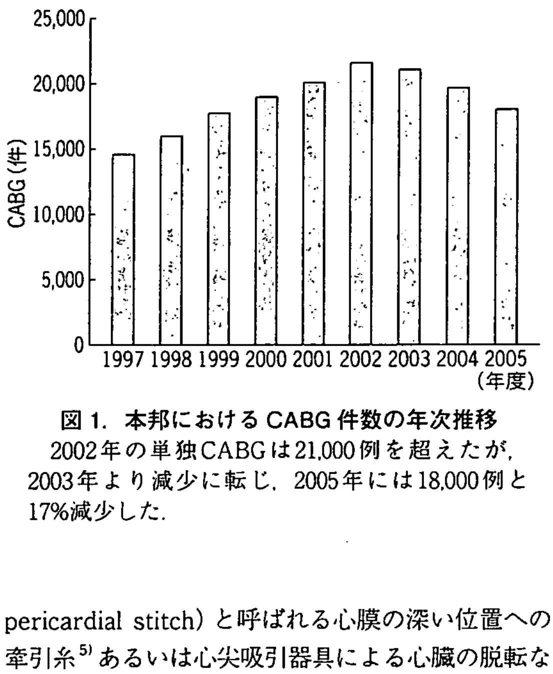

図1．本邦におけるCABG件数の年次推移
2002年の単独CABGは21,000例を超えたが，2003年より減少に転じ，2005年には18,000例と17%減少した．

これまでCABGの歴史において，二つの大きな変革があった．第一に，心臓の動きを局所的に抑えるスタビライザーの開発[4]，Lima suture（deep pericardial stitch）と呼ばれる心膜の深い位置への牽引糸[5]あるいは心尖吸引器具による心臓の脱転などの手術手技・器具の開発が，心臓の側壁・後下壁へのアプローチを可能にさせ，多枝病変に対しても胸骨正中切開下に人工心肺を使用しないCABG（off-pump CABG：OPCAB）が行われるようになり，急速に普及してきたことがあげられる．第二の変革は，大伏在静脈（SVG）がvein graft diseaseにより経時的に閉塞していくのに対し[6]，LITAは長期開存性と良好な遠隔成績が知られ，両側ITAのみ

キーワード：CABG，人工心肺，動脈グラフト

*J. Kobayashi（部長）：国立循環器病センター心臓血管外科（〠565-8565 吹田市藤白台5-7-1）．

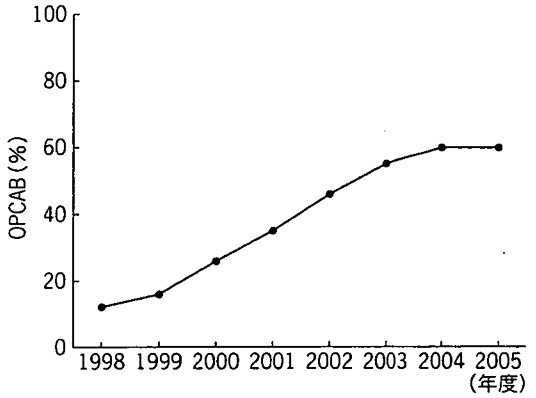

図 2. 本邦における CABG に占める OPCAB の割合

OPCABの頻度は2001年で35%, 2002年で46%, 2003年で55%, 2004年で60%と漸増している.

ならず胃大網動脈 (GEA) や橈骨動脈 (RA) などの動脈グラフトが多用されるようになったことである. 以下にCABGの現況と, 革新的な治療を含めた将来展望を述べる.

I. OPCABの現況

人工心肺技術と心筋保護法の進歩により, CABGは心停止下に安全に行えるようになったと考えられ, 一部の外科医以外はOPCABを行わなくなっていった. LADに対するPCIの再狭窄率は, bare metal stent使用では20～30%で, LADは生命予後に重要な影響を及ぼすもっとも重要な冠状動脈であり, LITAをLADに吻合することにより10年後のグラフト開存率と生存率が約90%であることが国内外で明らかにされた[6,7]. そこで1990年台後半には, LADの1枝病変の患者を中心に手術死亡・術後脳梗塞あるいは腎不全を起す術前リスクを有する患者に対して, 左肋間小開胸心拍動下にLITAをLADに吻合するMIDCAB (minimally invasive direct coronary artery bypass) がリバイバルしてきた[8,9]. しかし, 通常のCABGアプローチが胸骨正中切開心停止下手術であった心臓外科医ではグラフト採取に難渋し, 心拍動下のグラフト開存率が不良で, 術後にPCIが必要となるなどの合併症の発生が多かった. このため, 本邦では1998年をピークにほとんど行われなくなった.

一方で, 従来の人工心肺を用いたCABGは, 高い医療費と長い入院期間を要するうえに, 脳梗塞や白血球の活性化などによる全身臓器の炎症反応を惹起する侵襲的手術であることが見直され, 1990年台にBenettiら[10], Buffoloら[11]の南米におけるOPCABが再評価されるようになった.

1998年ころより技術革新が心臓の側壁・後下壁へのアプローチを可能にさせ, 多枝病変に対してもも胸骨正中切開下にOPCABが行われるようになってきた[12~14]. 本邦におけるOPCABの頻度は, 日本胸部外科学会年次統計によると, 2001年で35%, 2002年で46%, 2003年で55%, 2004年で60%となったが, 2005年では頭打ちとなった (図2). ここ3年間では, CABGの半数以上がOPCABでなされていることから, 本邦においてはOPCABが標準術式となったと考えられる. これに対して, 米国におけるOPCABの頻度は今なお20%程度であり, 一部の心臓外科医が95%以上の症例でOPCABを行っていることから考えると, 米国におけるCABGの標準術式は依然として心停止下のCABGであると考えられる.

一般的なOPCABの適応は, 人工心肺および大動脈遮断が危険であると考えられる慢性閉塞性肺疾患(喘息, 高度閉塞性肺機能障害), 脳血管病変, 慢性腎不全, 上行大動脈石灰化, 高齢者, 担癌患者などである. 逆に, 通常の人工心肺使用心停止下CABGの適応は, 不安定な血行動態, 心肺蘇生中の症例および薬剤抵抗性のショック, 低血圧, 致死的不整脈により経皮的心肺補助装置 (PCPS) 使用中の症例あるいはOPCABの続行が不可能となった症例である. これら以外の症例をOPCABで行うか否かは外科医に委ねられている. 当センターでは, OPCABの適応としては人工心肺の危険性が高い症例としていたが, 2000年3月より, OPCABが不適当な症例以外はOPCABを標準術式とし, 95%以上を占めている[15].

OPCABの禁忌としては, 重要な冠血管が筋肉内を走行したり, びまん性に石灰化したりしている患者, LADの冠状動脈径が心拍動下では吻合困難なほど細い (1.0 mm以下) 患者, 左室が拡大した高度低左心機能例 (左室駆出率30%以下, 左室収縮末期容量指数100 ml/m^{2}以上), 僧帽弁閉鎖不全などによる肺高血圧症例, 急性心筋梗塞などで血行動態が不安定で, 心室頻拍などの重症不整脈を起す症例があげられる.

OPCABが通常のCABGに比べて優位であることは, evidence-based medicine (EBM) として示されているのであろうか. 軽症例から重症例まで,

すべての症例を含めた院内死亡率に関しては conventional CABG (CCAB) とOPCABに差は認められていない[16,17]．しかし，American Heart Association/American College of Cardiology (AHA/ACC) のガイドラインに準じたOPCABに関するtask forceの報告が国際低侵襲心臓外科学会(ISMICS) から出され，その優位性が示されている[18]．

中等度以上のリスクを有する症例においては，OPCABは従来の人工心肺を用いたCCABに比べて手術時間，挿管時間，ICU滞在期間，退院までの期間が有意に短く，周術期心筋梗塞，出血量，輸血量，炎症反応，脳梗塞・脳高次機能障害が有意に少ないと報告されている[19,20]．逆に問題点としては，OPCABではバイパス本数が通常のCABGと比べて少なく，心拍動下のため吻合の質の低下を招き，グラフト狭窄あるいは閉塞による遠隔成績不良が危惧される．われわれの経験では，OPCABにおいても細い冠状動脈へのバイパスは良好に開存していた[21,22]．

以上のように，OPCAB優位な成績はレベルBのEBMにとどまり，レベルAのEBMを得るためにさまざまな無作為比較試験が行われてきた[23~28]．これらにより，OPCABはさまざまな術後合併症の減少，術後ICU滞在時間・病院滞在日数の短縮，出血量・輸血量の減少に有利に働くことが明らかになってきたが，グラフト開存率や遠隔成績に関しては定まった結論にはいたっていない．Chengら[29]は，37の無作為比較試験のmeta-analysisを行い(表1)，30日以内の手術死亡率，周術期心筋梗塞，脳梗塞，腎不全，大動脈内バルーンパンピング(IABP) 使用，創感染，再開胸止血術，再インターベンションに関してはOPCABとCCABで差がなかったとしている．一方，OPCABは心房細動の減少［オッズ比 (OR) 0.58]，輸血の減少 (OR 0.43)，強心薬使用の減少 (OR 0.48)，呼吸器感染の減少 (OR 0.41)，挿管時間短縮 (平均 −3.4時間)，ICU滞在日数の短縮 (平均−0.3日)，病院滞在日数の短縮 (平均 −1.0日) に貢献していた (表2，3)．しかし，グラフトの開存性と脳高次機能に関しては，定まった結論が得られていない (表2，4)．

われわれもOPCABとCCABを比較する前向き無作為比較試験 (JOCRI-study：Japanese Off-pump Coronary Revascularization Investigation-study)[30]を行い，中間解析として早期成績を比較・

表1．無作為比較試験のmeta-analysisにおける患者背景

背　景	報告数	OPCAB	CCAB
年　齢 (歳)	36	62.6	62.5
女　性 (%)	32	23	22
高血圧 (%)	18	55	54
非喫煙者 (%)	14	68	68
糖尿病 (%)	20	24	27
左室駆出率 (%)	9	59	60
手術時間 (分)	17	201	205
バイパス本数 ± SD	22	2.6 ± 0.6	2.8 ± 0.7

検討すると，動脈グラフトの使用率はOPCAB群で94%，CCAB群で97%といずれも90%を超えており，従来の無作為比較試験に比べて高い使用率であった．両群ともに手術死亡はなかったが，OPCAB群，CCAB群で手術時間，最高CK-MB値，術後neuron-specific enolase (NSE) 値，S-100蛋白値，無輸血率，入院医療費 (保険請求額) で両群間に有意差を認め，OPCAB群で有意に良好な結果であった．OPCAB群，CCAB群のおのおのでバイパス本数，開存率に有意差を認めなかった．しかし，グラフト開存率は同じであったが，OPCAB群において狭窄のない開存率ではRAグラフトと右冠状動脈への吻合において劣ることが示された．以上の結果から，OPCAB群において，手術時間の短縮および輸血量の減少が得られ，心筋障害・脳障害が少なくなることが示された．

OPCABの大きな利点として，脳梗塞の頻度を減少させることが知られている．しかし，OPCABにおいても上行大動脈を部分遮断してグラフト吻合を行うと，粥腫塞栓による脳梗塞が発生する危険性がある．上行大動脈にSVGあるいはRAを吻合する場合には，この可能性を認識しなければならない．われわれはOPCABのメリットを最大限に活かし，脳合併症を回避すべく，RAをITAとのcompositeグラフトとして使用することで，上行大動脈をまったく触らない，いわゆるaorta no-touch techniqueを適用している[31,32]．

Ⅱ．動脈グラフトの重要性と問題点

先述したように，近年LITAに加えて*in situ*グラフトとして右ITA (RITA)[33~35]やGEA[36,37]，さらにfree graftとしてのRA[38,39]，下腹壁動脈など[40,41]が使用されるようになっている．日本冠動脈外科学会の2004年統計では，グラフト材料とし

表2. 無作為比較試験のmeta-analysisにおける臨床成績 (1)

結　果	患者数 (研究数)	OPCAB (%)	CCAB (%)	OR	95% CI	p値
手術死亡 (30日以内)	3,082 (29)	1.2	1.0	1.02	0.58～1.80	0.9
遠隔死亡 (1～2年)	1,135 (6)	2.3	2.6	0.88	0.41～1.88	0.8
心筋梗塞 (30日以内)	2,721 (24)	2.0	2.8	0.77	0.48～1.26	0.2
脳梗塞 (30日以内)	2,859 (21)	0.4	1.0	0.68	0.33～1.40	0.3
(1～2年)	864 (4)	1.1	2.3	0.50	0.17～1.50	0.2
心房細動 (30日以内)	2,425 (17)	17.6	26.8	0.58	0.44～0.77	<0.0001
輸血率	2,412 (17)	28.4	42.5	0.43	0.29～0.65	<0.0001
腎不全 (30日以内)	1,467 (19)	0.9	2.1	0.58	0.25～1.33	0.2
胸痛再発 (30日以内)	765 (5)	6.5	7.6	0.85	0.49～1.49	0.6
再インターベンション (30日以内)	978 (4)	0.8	0.6	1.18	0.28～5.06	0.8
(1～2年)	1,120 (6)	2.9	1.6	1.61	0.71～3.65	0.3
呼吸器感染 (30日以内)	896 (7)	4.6	9.9	0.41	0.23～0.74	<0.0001
IABP使用	1,262 (10)	1.1	1.0	1.07	0.39～2.89	0.9
強心薬使用	1,655 (16)	15.1	23.6	0.48	0.32～0.73	<0.0001
縦隔炎・創感染	2,076 (15)	3.0	4.8	0.65	0.41～1.04	0.07
再開胸止血術	2,307 (15)	1.7	2.2	0.81	0.44～1.49	0.5
脳高次機能障害 (30日以内)	335 (3)	40.0	50.6	0.57	0.21～1.54	0.3
(2～6ヵ月)	393 (3)	20.3	31.8	0.56	0.35～0.89	0.01
(1～2年)	334 (2)	27.2	30.9	0.91	0.57～1.46	0.7

CI：信頼区間

表3. 無作為比較試験のmeta-analysisにおける臨床成績 (2)

結　果	患者数 (研究数)	平均の差	(95% CI)	p値
入院期間 (日)	1,384 (17)	−1.0	−1.5～−0.5	<0.0001
ICU滞在期間 (日)	1,266 (15)	−0.3	−0.6～−0.1	0.003
挿管期間 (時)	1,425 (20)	−3.4	−5.1～−1.7	<0.0001

表4. 無作為比較試験のグラフト開存率

報告者	検査時期	患者数	OPCAB	CCAB	開存率の差 (95% CI) [%]	p値
Nathoe [25]	12ヵ月	70	63/ 69 (91%)	83/ 89 (93%)	−2.0 (−10.0～6.5)	0.76
Khan [26]	3ヵ月	83	114/130 (88%)	127/130 (98%)	−10.0 (−3.8～−16.2)	0.002
Puskas [27]	入院時	197	311/314 (99%)	300/307 (98%)	1.3 (−0.66～3.31)	0.19
	12ヵ月		234/250 (94%)	249/260 (96%)	−2.2 (−6.1～1.7)	0.27
Kobayashi [31]	入院時	167	274/280 (98%)	299/305 (98%)	−0.1 (−3.5～3.1)	>0.99

てLITA 38%, RITA 15%, GEA 9%, RA 15%, SVG 24%の割合で使用されている. すなわち, 動脈グラフトが76%も使用されている. 日本胸部外科学会の2004年度の統計では, 動脈グラフトのみのCABGは全体で52%, OPCABでは66%とさらに高い. このことから, OPCABでの動脈グラフトの使用率は80%を超えていることが推察される.

LADの血行再建にはLITAを第一選択とすべきであるとする強いエビデンスがある[6, 7, 42～47]. クロスしてLADに吻合された*in situ* RITAも, LITAと同等の成績が期待される[48, 49]. また, *in situ* RITAの吻合部位は右冠状動脈でなく, 左冠状動脈領域を優先すべきであるとの報告もある[48, 50～52]. たとえ80歳以上の高齢者においても, LADにはLITAを吻合することで手術成績が良好になることが知られており[53], これらの患者が10年後も約半数が生存することを考えると, 年齢は考慮せずともよい. 緊急CABGのグラフト材料としても, LITAが術後早期・遠隔期ともに開存性に優れ, 長期生存率を向上させることが明らかにされている[54].

LITAはSVGに比して内径が細く, *in situ*グラフトとして用いると, 長いために抵抗が高く, 血圧依存性に流量が制限される. *in situ* ITAは, CABG直後の血流供給能は大動脈-冠状動脈バイパ

スのSVGより劣るものの，吻合冠状動脈領域の血流需要に呼応して流量や内径を増大させる[55,56]．ITAは狭窄の軽い冠状動脈とのあいだでは容易に血流競合を生ずるが，この血流競合によりstringとなったITAが閉塞するか，冠状動脈の狭窄が強くなった場合に正常に機能するようになるか，長期的な運命に関する報告は少ない[57]．しかし，このような機序による閉塞では，冠状動脈病変の進行によりグラフトが再開通し再び機能を回復する可能性を示唆する現象や，術直後に吻合部狭窄を認めたLITAが遠隔期に狭窄が軽減していく報告もあり，self-reparative graftとして興味深い[58~60]．

以上のようなLITAの良好な長期成績から，多枝病変においては両側ITAによるCABGが行われており，その長期成績はLITA片側によるCABGより良好である[61~63]．このような結果から，いかなる症例に対しても両側ITAを使用すべきとも考えられるが，両側ITAの使用は縦隔炎の発生率を上昇させるとの報告がある[64,65]．一方，近年広まっている超音波メスを用いたskeletonized harvestingにより，縦隔炎の危険を高めることなく両側ITAを採取できるとの報告もある[66,67]．われわれは，片側ITA使用は75歳以上の高齢，どちらかの鎖骨下動脈に狭窄がある，糖尿病で大量のインスリンを使用，ステロイドを使用，重症閉塞性肺疾患といった患者が適応であると考えている．両側ITA使用が望ましいのは若年者，左室が大きい，バイパス吻合数が多い，75%程度の比較的狭窄の軽い大きな冠状動脈枝への吻合を要するといった患者である．

LITA使用において注意すべき点として，LADが90%狭窄以上でない場合にはcompositeグラフトをつけないで単独ITAをLADに吻合するようにしていることをあげたい．また，体格の小さい高齢の女性では，ITAが細く脆弱であることが多いため，Y compositeグラフトをつけたりsequentialバイパスを行ったりすることは避けたほうがよいと考えられる．また，RITAをクロスしてLADに吻合させる症例は，将来大動脈弁の手術や上行・弓部大動脈瘤の手術が必要にならないことを術前心エコーやCTで確かめておく必要がある．

GEAは右冠状動脈領域に対するグラフトとしてSVGより長期成績が優れていると期待されるが，今なお議論のあるところである．右GEAは5年開存率81%とSVGより良好であると報告されている[68]が，10年開存率では63%とSVGがわずかに良好である[69]．エビデンスは十分でないが，GEAは腹部大動脈の第3分枝でITAに比べ10～15 mmHg血圧が低いため，右冠状動脈の狭窄が中等度である場合にはいわゆる血流競合が起りやすい[70~72]．Skeletonization techniqueによってGEAのグラフト長は増加し，グラフト径も拡大してグラフト流量の増加も期待されるが，血流競合を避けうるに十分かどうかは明らかでない[73~75]．

近年SVGにかわって頻繁に使用されるようになったRAは，バイパスとして使用した場合にSVGより開存性に優れているとする報告が多い[76~78]．また，RAをcompositeで使用しても，大動脈-冠状動脈バイパスとして使用しても，開存率に有意差はないと考えられる[79~81]が，前者では血流競合を起す可能性はより高くなると考えられ，遠隔期の閉塞が危惧される．吻合する冠状動脈の狭窄が50～75%であれば，この冠状動脈を最終の吻合部においた場合や，4ヵ所以上のsequential吻合を行った場合に血流競合の危険性が高くなる[82~85]．LITAに加えてSVGのみでCABGを行うか，RAを追加するかの比較でも，後者のほうが遠隔成績を改善したと報告されている[86]．

SVGの10年開存率は60%程度であり，その45%程度には重度の動脈硬化を認め，動脈グラフトより長期開存率が不良である[7,42,87]．しかし，日本人のSVGの長期開存率は欧米人の開存率より高いことが知られている[88]．右冠状動脈の狭窄が軽い場合の動脈グラフトの開存率がわるいことからも，この場合にSVGを使用する妥当性はある．上行大動脈の性状がわるい場合には，SVGをITAに吻合することが選択肢として考えられる．しかし，SVGをY compositeにした場合のわれわれの早期開存率は82%と不良で，慢性腎不全患者ではSVGの狭窄が急激に進行した症例がある[89]．また，SVGをY compositeにした部位より末梢のITAが，72%の症例で狭窄あるいは閉塞をきたしたとの報告もあり[90]，SVGをY compositeにすることは避けるべきと考えられる．ITAをSVGで延長してI compositeとする方法はしばしば行われているが，SVGを上行大動脈に吻合する場合に比べてグラフト流量が少なくなることが考えられる．これが早期および遠隔期のグラフト開存性を低下させることが危惧されるため，この方法も可能な限り避けるべきと考えられる．

SVGを用いても，LADはもっとも高い遠隔開存