Angiographic flow grading and graft arrangement of arterial conduits

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Objective: We sought to delineate the effects of competitive and reverse flow on the intermediate-term patency of arterial conduits and examined graft arrangements for maximizing antegrade bypass flow.

Methods: The angiograms of 2083 bypass grafts in 570 patients who underwent off-pump total arterial revascularization without aortic manipulation since December 2000 were reviewed. The blood flow in the bypass grafts were graded A (antegrade), B (competitive), C (reverse), or O (occlusion). The mean number of distal anastomoses was 3.65 ± 0.94 per patient.

Results: In the early angiography 91.3% (1901/2083) of the bypasses were grade A. Thirty (1.4%) bypasses were grade O, whereas 2.9% (61/2083) were grade B, and 4.4%(91/2083) were grade C. In the multivariate analysis the end-to-side anastomosis ($P < .0001$), 4 or more distal anastomoses of the conduit ($P = .01$), native coronary stenosis of less than 75% ($P < .0001$), and target branch location of the right coronary artery territory ($P < .0001$) and left circumflex artery territory ($P = .02$) significantly correlated with grade non-A. The patency rate in the late angiography of the bypasses graded B or C in the early angiography was 7 (28.0%) of 25, whereas that of the bypasses graded A was 164 (89.1%) of 184 ($P < .0001$). The actuarial graft patency rate of the bypasses graded A was 72.3% at 3 years and was significantly higher than that of the bypasses graded B or C (28.6% at 3 years after surgical intervention, $P < .0001$).

Conclusions: The sufficient antegrade bypass flow had a favorable effect on the graft patency of arterial conduits. The graft arrangement should be adjusted for each patient so as to maximize the antegrade bypass flow and to confirm the advantage of arterial grafts.

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The use of the in situ internal thoracic artery (ITA) graft to the left anterior descending artery (LAD) is widely accepted as a standard strategy that provides long-term patency and improves late survival. The radial artery is also useful as a free graft for coronary artery bypass grafting (CABG). For the radial artery, the graft patency mostly depended on the severity of the native coronary stenosis rather than on the proximal anastomotic site[1,2] and was equivalent to that of ITA, even when the target coronary branch was small in diameter or had severe atherosclerosis.[3,4]

In the bypass conduits having 2 or more distal anastomoses, dominant reversal flow is not quite rare. Because the bypass grafts with reverse flow do not contribute to the coronary perfusion in the grafted territory, the efficacy of CABG might be unpromising, even when the bypass graft is anatomically patent. In addition, as a consequence of inappropriate graft flow, graft failure, such as diffuse narrowing or occlusion, can occur because it has been reported that the arterial materials have shown adaptability of their own diameter to the circumstances of the blood flow in the graft lumen.[5-9]

Abbreviations and Acronyms
CABG = coronary artery bypass grafting
ITA = internal thoracic artery
LAD = left anterior descending artery
LCX = left circumflex artery
RCA = right coronary artery

Despite the various graft configurations that have previously been reported,[10-12] the optimal strategy for graft arrangement remains unknown. Because an excellent early graft patency rate can be highly expected when arterial graft materials are exclusively used, the patency rate of the bypass grafts might not necessarily be useful for evaluation and comparison of the graft arrangements.

The objectives of this study were to delineate the effect of the graft flow in the sequential and composite arterial grafts on the late graft patency and to establish the optimal strategy for the graft arrangement of the arterial conduits for minimizing competitive and reverse flow.

Materials and Methods

The coronary angiograms of 570 patients who underwent off-pump coronary revascularization with single or bilateral ITA grafts and the radial artery without aortic manipulation between December 2000 and June 2005 were reviewed. There were 475 men and 95 women with a mean age of 66.0 ± 9.3 years (Table 1), and all patients provided written informed consent. These patients were consecutive after eliminating those who had a bypass of the saphenous vein, gastroepiploic artery, or inferior epigastric artery; underwent no early postoperative coronary angiography; or had bypass grafting in an individual fashion only. During the same period, off-pump CABG was performed for 821 patients. Early coronary angiography was performed for all 570 patients at about 2 weeks after the operation. The native coronary artery stenosis and the graft patency were independently evaluated by cardiologists. The degrees of stenosis in the precise measurement of the luminal diameter were graded as 51% to 75%, 76% to 90%, and 91% to 100%. The maximal severity of stenosis was recorded for all coronary branches.

TABLE 1. Baseline characteristics

No. of patients	570
Age (y)	66.0 ± 9.3
Male/female sex	475/95
Hypertension	301 (52.8%)
Hyperlipidemia	270 (48.9%)
Diabetes	218 (38.2%)
Left ventricular end-diastolic volume index (mL/m^2)	86.2 ± 29.7
Left ventricular ejection fraction (%)	47.8 ± 11.9
Total distal anastomoses	2083
Distal anastomoses per patient	3.65 ± 0.95
Bypass conduits used	830
Individual in situ ITA	151
Individual composite I-graft	28
Composite Y-graft	358
Composite I-graft	173
Composite K-graft	63
In situ ITA sequential	57

ITA, Internal thoracic artery.

TABLE 2. Concept of flow grading system

	Grade			
	A	B	C	O
Flow direction	Antegrade	Competitive	Reverse	No-flow
Patency	Patent	Patent	Patent	Occluded
Function	Functioning	Functioning	Nonfunction	Nonfunction
Durability	Durable (?)	(?)	(?)	No

A, Antegrade; *B*, competitive; *C*, reverse; *O*, occlusion.

The definitions of terms in the present study are as follows. An *in situ ITA graft* is an ITA that was divided only at its distal portion. A *composite graft* is a bypass conduit consisting of one in situ graft and a free graft anastomosed to it (in end-to-end, end-to-side, or side-to-side fashion). A combination of Y-grafts, K-grafts, and I-grafts and the individual conduit were used in this study. An *individual bypass* was defined as a conduit having one distal anastomosis and one in situ graft. This included an in situ graft that was extended by a free graft and bypassed to one target coronary branch. A bypass conduit having one in situ graft and 2 or more distal anastomoses, such as a sequential graft or a composite Y-graft (or K-graft), was defined as *nonindividual*.

Flow Grading

The concept of determining grading of the graft flow focused on 2 factors: (1) the function as a blood supply to the ischemic myocardium and (2) the possibility of graft failure in the future (Table 2). A patent graft meant that the graft had a complete continuity of the graft lumen in the overall length from the subclavian artery to the anastomotic site with the coronary branch, irrespective of the flow direction. When 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, it was defined as grade O (occlusion), which was regarded as a no-flow situation with closure of the lumen of the bypass graft. Grade A was defined as a situation in which antegrade graft flow (ie, from the in situ graft to the target coronary branch) was found in most of the multiplane ITA angiography. Grade B (competitive) was defined as a situation in which the target vessel was barely opacified from the ITA graft injection and the bypass graft was filled by retrograde flow from the native coronary injection. In the worst of multiplane angiography, the contrast medium from the in situ ITA did not surely reach the target branch. Grade C (reverse) was defined as a situation in which the distal anastomotic site was not opacified from the ITA graft injection at all but was filled clearly by retrograde flow from the native coronary injection. The difference between grades B and C was whether the contrast medium from the in situ ITA finally reached the target branch in the best frame of multiplane examinations. Grades C and O meant that the bypass

TABLE 3. Early angiographic results

	Characteristics of coronary branches	No. of anastomoses	Grade			
			A (%)	B (%)	C (%)	O (%)
Location	LAD main trunk	574	541 (94.3)	17 (3.0)	11 (1.9)	5 (0.9)
	Diagonal	314	296 (94.3)	7 (2.2)	7 (2.2)	4 (1.3)
	LCX	646	587 (90.9)	15 (2.3)	35 (5.4)	9 (1.4)
	RCA	549	477 (86.9)	22 (4.0)	38 (6.9)	12 (2.2)
Stenosis	51%-75%	957	815 (85.2)	53 (5.5)	76 (7.9)	13 (1.4)
	76%-90%	553	521 (94.2)	8 (1.4)	15 (2.7)	9 (1.6)
	91%-100%	573	565 (98.6)	0	0	8 (1.4)
Overall	—	2083	1901 (91.3)	61 (2.9)	91 (4.4)	30 (1.4)

A, Antegrade; *B*, competitive; *C*, reverse; *O*, occlusion; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *RCA*, right coronary artery.

graft did not contribute to the increase of coronary perfusion in the grafted territory. Grade B bypass grafts probably contributed to the coronary perfusion, but the durability of graft patency was considered uncertain because the retrograde flow from the native coronary branch was almost comparable with that of grade C. The flow grade was recorded for each target coronary branch.

Graft Selection and Strategy

The details of our standard technique and pharmacologic management were reported previously.[13] The bilateral ITAs were preferably used for patients aged less than 75 years with neither severe chronic obstructive pulmonary disease nor diabetes requiring insulin therapy for improvement of the late outcome.[11,14-16] All of the ITA grafts in the present series had a luminal diameter of 1.5 mm or larger. In the side-to-side anastomosis we made a longitudinal incision of approximately 6 to 10 mm in the native coronary artery and arterial graft to achieve a sufficient luminal size without turbulence. The angle of placement of the graft was adjusted to save the graft length and avoid kinking.

The various configurations of the bypass conduits used in our patients are listed in Table 1. The arrangement of the bypass conduits was determined primarily on the basis of the special relationship of the target coronary arteries. Since March 2003, we have introduced our current strategy. Our current graft arrangement consisted of the left ITA to LAD grafting concomitant with an I-graft of the right ITA and radial artery to the left circumflex artery (LCX) and right coronary artery (RCA) in a sequential fashion. In addition, we selected appropriate orientation (clockwise or counter clockwise) to avoid bypass grafting to a coronary branch with 51% to 75% stenosis at the end of the I-graft as much as possible because the terminal end of the conduit was commonly associated with reverse flow.[13,17] Before March 2003, the I-graft was used only in a counterclockwise orientation for all patients.

Early Angiography of 2083 Coronary Branches

To determine the factors that predicted the grade non-A bypass grafts in the early angiography, we collected detailed data regarding the target coronary branch, the bypass conduit, and anastomotic fashion. The variables in the univariate analysis included the territory of the target coronary branch (LAD, LCX, or RCA), the diameter (1.0, 1.25, 1.5, or 2.0 mm, as determined by the intracoronary shunt used), the severity of the native coronary stenosis (51% to 75% or 76% to 100%), the kind of graft material (in situ ITA, free ITA, or radial artery), the type of conduit (in situ ITA, Y-graft, K-graft, or I-graft), the number of distal anastomoses of the conduit (3 or less, or 4 or more), and the type of anastomoses (end-to-side or side-to-side).

Analysis of Clinical Outcome in 570 Patients

We examined the effects of the bilateral in situ ITA grafts, total distal anastomotic sites, vessel disease, presence (or absence) of bypass graft grade non-A in the early angiography, and day of the operation in the period of our current strategy of graft arrangement. The mean follow-up period was 22 ± 16 months.

Statistical Analysis

The continuous variables are expressed as the mean values ± standard deviation. The univariate and multivariate analyses were performed by using the logistic regression method. The Kaplan-Meier method was used to determine the actuarial graft patency rate. Cox regression analysis was used to examine the significance of the clinical and angiographic variables in predicting the cardiac event–free time.

Results

The results of analysis of 2083 anastomoses are shown in Table 3. The overall early patency rate was 2053 (98.6%) of 2083. Sixty-one (2.9%) bypasses were graded B, 91 (4.4%) were graded C, and 1901 (91.2%) were graded A.

In the univariate analysis, the end-to-side anastomosis ($P < .0001$), conduit type (Y-graft, $P = .002$; K-graft, $P = .002$; I-graft, $P = .02$), native coronary stenosis of less than 75% ($P < .0001$), location (RCA territory, $P < .0001$; LCX territory, $P = .02$), and graft material (radial artery, $P = .04$) were correlated with grade non-A. In the multivariate analysis, the end-to-side anastomosis ($P < .0001$), 4 or more distal anastomoses of the conduit ($P = .01$), native coronary stenosis of less than 75% ($P < .0001$), and target branch location (RCA territory, $P < .0001$; LCX territory, $P = .02$) significantly correlated with grade non-A (Table 4). Neither the type of the conduit nor the graft material

TABLE 4. Predictors of grade non-A in the early angiography

Variables	Odds ratio	95% CI	*P* value
Univariate analysis			
End-to-side anastomosis	4.51	2.88-7.04	<.0001
Distal anastomoses of conduit >3	1.27	0.92-1.76	.14
Type of conduit, Y-graft (vs in situ ITA)	2.80	1.44-5.43	.002
Type of conduit, K-graft (vs in situ ITA)	3.21	1.52-6.78	.002
Type of conduit, I-graft (vs in situ ITA)	2.30	1.14-4.68	.02
51%-75% stenosis	4.73	3.29-5.80	<.0001
Location, RCA territory (vs LAD territory)	2.51	1.73-3.65	<.0001
Location, LCX territory (vs LAD territory)	1.62	1.10-2.40	.02
Graft material, free ITA (vs in situ ITA)	0.98	0.29-3.28	.97
Graft material, free RA (vs in situ ITA)	1.44	1.02-2.03	.04
Diameter of coronary branch	0.62	0.23-1.69	.35
Multivariate analysis			
End-to-side anastomosis	8.18	4.82-13.87	<.0001
Distal anastomoses of conduit >3	1.73	1.17-2.55	.01
Type of conduit, Y-graft (vs in situ ITA)	1.91	0.91-4.05	.09
Type of conduit, K-graft (vs in situ ITA)	1.71	0.70-4.17	.24
Type of conduit, I-graft (vs in situ ITA)	1.77	0.76-4.14	.19
51%-75% stenosis	6.19	4.22-9.09	<.0001
Location, RCA territory (vs LAD territory)	3.49	1.82-6.69	.0002
Location, LCX territory (vs LAD territory)	3.15	1.71-5.81	.0002
Graft material, free ITA (vs in situ ITA)	0.60	0.15-2.35	.46
Graft material, free RA (vs in situ ITA	0.89	0.47-1.72	.73

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

anastomosed with the coronary branch correlated with grade non-A.

Intermediate-term Results

In the follow-up period 10 patients died (cardiac death, 8; stroke, 2). Repeated angiography was carried out for 216 bypass grafts in 61 patients, who had some symptoms, including angina, or an ischemic region detected by means of electrocardiography or scintigraphy. Thirty-eight patients underwent percutaneous coronary intervention. The early and late angiographic results of these 216 bypass grafts are shown in Table 5. The patency rate in the late angiography of bypasses that were graded B or C in the early angiography was 7 (28.0%) of 25, whereas that of bypasses graded A was 164 (89.1%) of 184 ($P < .0001$).

TABLE 5. Early and late angiographic results of 216 bypass grafts

Flow grade in early angiography	Bypass grafts	Late angiography		
		Patent	Occluded	Patency rate (%)
A	184	164	20	89.1
B	12	4	8	33.3
C	13	3	10	23.1
O	7	0	7	0.0
Total	216	171	45	79.2

A, Antegrade; *B*, competitive; *C*, reverse; *O*, occlusion.

The actuarial graft patency rates at 3 years were 72.3% for bypasses graded A and 28.6% for bypasses graded B or C ($P < .0001$, Figure 1). There was no significant difference between grades B and C in the actuarial graft patency rate ($P = .20$). The multivariate Cox regression analysis demonstrated that the presence of bypass grafts graded non-A ($P = .007$) was a significant predictor of cardiac events in the intermediate-term outcome, and the period (March 2003-June 2005) was inversely correlated ($P = .008$; odds ratio, 0.32, Table 6).

Discussion

A composite graft, which consists of the left ITA and radial artery, provided total arterial revascularization with an excellent graft patency rate and less incidence of late cardiac events compared with those seen with conventional CABG.[18,19] Various arrangements of the in situ and free arterial grafts have already been practiced and reported.[10-12] Because an excellent early patency rate with less incidence of complications can be highly expected when arterial graft materials are exclusively used, the optimal strategy for graft arrangement remains unknown. For comparison of these graft arrangements and establishment of the optimal strategy, it is necessary to assess this with criteria more specific than "patent" or "occluded."

The angiographic luminal size, which was reported by FitzGibbon and colleagues,[20,21] might not be feasible for evaluation of arterial graft arrangements. At first, the luminal size of the anastomotic site is not precisely measurable in the sequential fashion, especially when the angle of the graft and coronary branch is near 90° or when the contrast medium fills only incompletely because of mixture with the blood flow from the native coronary artery. Additionally,

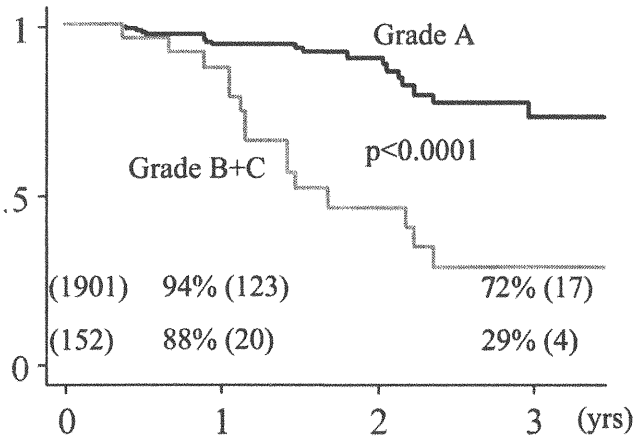

Figure 1. The actuarial graft patency rate.

TABLE 6. Predictors of cardiac events in 570 patients

Variables	Odds ratio	95% CI	*P* value
Univariate analysis			
Total distal anastomoses	1.04	0.77-1.40	.82
Period, March 2003~June 2005	0.30	0.13-0.70	.005
Bilateral in situ ITA	1.10	0.61-1.97	.76
Presence of grade non-A	1.97	1.12-3.45	.02
Vessel disease	1.02	0.61-1.69	.94
Ejection fraction <40%	1.78	0.95-3.30	.07
Hypertension	0.88	0.50-1.55	.66
Hyperlipidemia	1.01	0.63-1.93	.74
Diabetes	0.93	0.72-1.68	.81
Multivariate analysis			
Period, March 2003~June 2005	0.32	0.14-0.74	.008
Presence of grade non-A	1.85	1.05-3.24	.007
Ejection fraction <40%	1.84	0.98-3.40	.055

ITA, Internal thoracic artery.

inadequate surgical maneuvers during the operation can also strongly affect the luminal size as a result of unsuccessful anastomosis or graft kinking. Furthermore, regression of the stenosis and increase or growth of the diameter were relatively common findings in the arterial grafts.[22,23] There were 2 issues associated with insufficient bypass flow in the arterial conduits. These might be potential disadvantages of the strategy with aorta no-touch off-pump CABG using totally arterial grafts. One issue is the subject of bypass function as a blood supply to the myocardial tissue. A bypass graft presenting reverse flow, which means an obviously dominant native coronary flow, will not increase the blood supply to the myocardium in the region of the grafted coronary branch. We previously reported that not only the severity of the native coronary stenosis but also the interactions of the target coronary branches, which were connected with a composite Y-graft or sequential anastomoses, played a crucial role in the occurrence of reverse flow.[13,17] Our current graft arrangement was established to avoid development of graft nonfunction.

The other issue is the thinning or closure of the graft lumen in the postoperative period. If the flow velocity is extremely low, even when its direction is antegrade, the bypass graft might not be durable. Previously, there have been a few studies of early and late angiographies concerning physiologic characteristics of arterial grafts but only in small series.[7-9] Hashimoto and associates[8] reported serial changes of 53 arterial grafts in 38 patients after conventional CABG and demonstrated a significant correlation between "the severity of the native coronary stenosis" and "arterial graft thinning" in the early and follow-up angiographies.

In the present study it was necessary for us to demonstrate the effect of the graft flow in the composite and sequential grafts on graft patency and clinical outcomes and to rationalize the use of the flow grading system in discussing an optimal strategy for graft arrangement because there was no previous report that had been performed to delineate significant correlations between the "bypass flow" in the early angiography and the "graft patency" in the follow-up angiography after totally arterial off-pump CABG with the composite and sequential grafts. Early occlusion caused by a technical problem, which might be the most significant bias, was eliminated by the early angiography. The follow-up period in this study is considered sufficient and suitable for examining the influence of flow condition on the graft patency because physiologic changes in the luminal diameter were found at approximately 14 to 24 months[7-9] or earlier.[22,24] The results of our current study demonstrated that bypass grafts of not only grade C but also grade B were prone to close the graft lumen within the intermediate term. Therefore the flow grading system could be considered suitable and useful for discussing the optimal strategy for graft arrangement of arterial materials.

We found that the significant predictors of grade non-A were native stenosis of 75%, 4 or more distal anastomoses from a single ITA, RCA and LCX territories, and the end of the conduit. The implications of these results were as follows. The sufficient antegrade flow had a favorable effect on the intermediate-term patency of the arterial grafts. When we plan the graft configuration, especially for the multiple coronary branches in the RCA and LCX territories, we have to be conscious of the anticipated graft flow in the created bypass conduit. The most important factor in determining the antegrade flow was the appropriate pressure slope in the bypass conduit, being highest at the proximal portion of the conduit and lowest at the distal end. The Y-graft has 2 ends, and the K-graft has 3 ends, and competitive and reverse flow

was commonly found at the end of the conduit anastomosed with the moderately stenotic branch. To achieve an adequate pressure slope for 2 or 3 ends is less easy than for 1 end of the I-graft. On the other hand, the Y-graft is advantageous in terms of increased flow capacity[25] and availability to distant target branches compared with the I-graft. For the diagonal, LCX, and RCA branches, the Y-graft or K-graft might be preferred when all target branches have severe stenosis, the target diagonal branch is located at the anteroapical portion, or remarkable cardiomegaly exists. Therefore we carefully examine the indications for the Y-graft and K-graft.

Our current arrangement would be one of the simple and useful methods that can be adjusted for each coronary system. The risk of the injury during reoperation in the future is a possible disadvantage of the I-graft in a clockwise orientation. On the contrary, the evident advantage of the I-graft in clockwise orientation is that the total length of the I-graft to the LCX and RCA territories could be minimized compared with that in a counterclockwise orientation. In previous reports the right ITA to the left coronary artery, which also crosses the midline like the clockwise I-graft, is a generally accepted and often recommended procedure of choice.[26] The clockwise I-graft is considered justifiable.

Selection of suitable candidates for this procedure would be a major concern. When graft nonfunction or occlusion at a relatively early period is highly predicted, an alternative strategy, such as aortocoronary bypass, hybrid therapy with drug-eluting stent implantation, and conservation of the arterial graft for the redo operation in the future, might be a reasonable option of choice. In our experience sequential anastomoses with more than 2 moderately stenotic coronary branches were highly associated with flow insufficiency and late occlusion. Aortocoronary bypass would be reasonable because it has higher pressure potential than the in situ ITA.[27]

The present study has several limitations. First, the study is not randomized. Furthermore, the sample size of the late angiography is considered relatively small. The follow-up angiography was performed for 10.7% of the patients who were biased toward clinically evident graft failure. However, all 61 patients underwent both early and late angiographies. Early graft occlusion caused by obviously technical failure, which might be the most significant bias, was eliminated.

Second, the quality of the target branch, the amount of myocardium, peripheral vascular resistance in the myocardial tissue, and flow demands can also have important roles in the coronary perfusion. However, we do not have reliable methods for quantifying each of these factors.

The third limitation is regarding the capacity of the ITA graft. The margin of the pressure potential of the in situ ITA might also play an important role in the occurrence of competitive and reverse flow.[28] However, there is no alternative graft material for the ITA graft.

The fourth limitation might be the subject of the reproducibility of the flow grading system. Grades O and C are relatively easy to designate. Assigning grade B might be less so. Grade B probably includes both insufficient graft flow because of the strength of the native coronary flow and because of poor vascularity with high resistance in the severely impaired myocardium. Although no bypass graft might be required for the latter, we could not separately predict the insufficient antegrade flow caused by the critically damaged vasculature. In the present series there was no anastomotic stenosis, which restricted the blood flow and caused grade B bypass flow. In spite of these factors, the flow grade and angiographic data were prospectively collected and significantly correlated with the graft patency and clinical outcome. We therefore believe that the results of this study at least imply meaningful suggestions for establishing an optimal strategy for graft arrangement in the future.

In conclusion, the flow grading system was considered feasible as a criterion used for evaluation and comparison of the graft arrangements. Because the sufficient antegrade flow had a favorable effect on the durable patency of the arterial grafts, graft arrangement should be adjusted for each patient's coronary system to minimize competitive and reverse flow and to enhance the advantage of the arterial materials.

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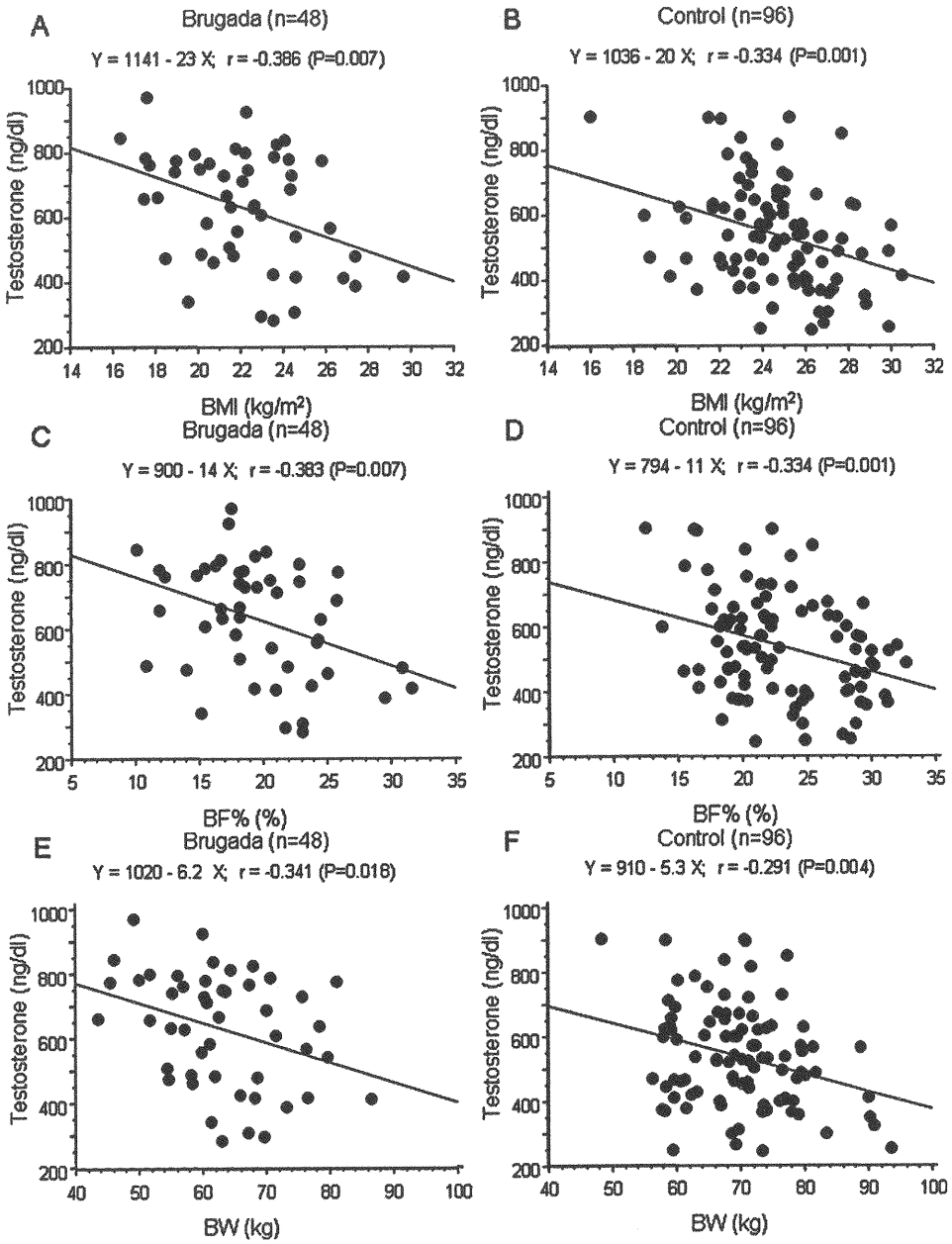

Figure 1. *Correlation between testosterone level and visceral fat parameters; body mass index (BMI) (**A** and **B**), body fat percentage (BF%) (**C** and **D**), and body weight (BW) (**E** and **F**) in the 48 Brugada males and the 96 age-matched control males. Testosterone level was inversely correlated with the BMI, BF%, or BW in both Brugada males and control males.*

syndrome. Matsuo et al. reported two cases of asymptomatic Brugada syndrome in whom typical coved ST-segment elevation disappeared following orchiectomy as therapy for prostate cancer,[21] indicating that testosterone may contribute to the Brugada phenotype in these two cases. Several experimental studies reported that testosterone increased outward potassium currents, such as the rapidly activating component (I_{Kr})[10,11] and the slowly activating component (I_{Ks})[12] of the delayed rectifier potassium current, and the inward rectifier potassium current (I_{K1}),[11] or decreased inward L-type calcium current (I_{Ca-L}).[12] Since the maintenance of the AP dome is determined by the fine balance of currents active at the end of phase 1 of the AP (principally I_{to} and I_{Ca-L}),[22,23] any agents that increase outward currents or decrease inward currents can increase the magnitude of the AP notch, leading to loss of the AP dome (all-or-none repolarization) in the epicardium, but not in the endocardium, contributing to a significant voltage gradient across the ventricular wall during ventricular activation, thus augmenting ST-segment elevation, the Brugada phenotype.[24] Therefore, testosterone would be expected to accentuate the Brugada phenotype. In the present study, males with Brugada syndrome had significantly higher testosterone level than age-matched control males, even after adjusting for age, exercise, stress, current smoking, and medication (hypertension, diabetes, and hyperlipidemia), which may affect the testosterone level. Moreover, conditional logistic regression models analysis showed strong positive association between Brugada syndrome and higher testosterone level (OR: 3.11). Our data suggest a significant role of testosterone, male hormone, in the Brugada phenotype. The

TABLE 5
Odds Ratios of Presence of Hypertestosteronemia and Confounding Risk Factors for Brugada Syndrome in Males

Variable	Odd Ratio	95% Confidence Interval	P Value
Hypertestosteronemia	3.11	1.22–7.93	0.017
Age	0.99	0.95–1.03	0.637
BMI	0.72	0.61–0.85	<0.001
Exercise	1.57	0.87–2.83	0.135
Stress	0.69	0.35–1.35	0.277
Current smoking	0.71	0.26–1.90	0.493
Hypertension	3.12	0.85–11.45	0.087
Diabetes	0.13	0.01–1.27	0.079
Hyperlipidemia	2.14	0.44–10.49	0.348

Hypertestosteronemia was defined as serum testosterone levels ≥ 700 ng/dL.

data also indicate that the male predominance in the Brugada phenotype is at least in part due to testosterone, which is present only in males.

Lower Visceral Fat May Be a Predictor for Brugada Phenotype

Matsuo et al. recently reported in their epidemiologic study that cases with the Brugada-type ECG had significantly lower BMI than that in control subjects.[16] Similarly, in the present study, males with Brugada syndrome had significantly lower visceral fat parameters, BMI, BF%, and BW than those in age-matched control males, even after adjusting for several confounding variables. Moreover, conditional logistic regression models analysis showed strong inverse association between Brugada syndrome and BMI (OR: 0.72). All of the visceral fat parameters were inversely correlated with testosterone level in both Brugada and control males, even after adjusting for the confounding variables. It has been well demonstrated that testosterone level in obese males is decreased compared to normal males of similar age.[13] Tsai et al. reported that lower baseline total testosterone level independently predicted an increase in visceral fat in the Japanese-American male cohort for 7.5 years.[15] Reversely, Marin et al. reported that testosterone treatment of middle-aged abdominally obese males was followed by a decrease of visceral fat mass measured by computerized tomography.[14] These data suggest that primarily higher level of testosterone in Brugada males compared to that in control males may result in lower visceral fat in Brugada males, which would be an "innocent bystander" sign of Brugada phenotype. In reverse, if primary lower visceral fat (body weight loss) would result in higher testosterone level, the weight loss could be a trigger for Brugada phenotype, just like fever is.[25] It is noteworthy that the visceral fat parameters at the clinical cardiac events (VF or syncope) in the 32 symptomatic Brugada males were significantly lower than those at the time of blood sampling for this study. This indicates that testosterone level is expected to be additively higher at the clinical cardiac events, which may contribute to spontaneous episodes of VF or syncope.

Other Hormonal Levels and Serum Electrolytes

Estradiol, female hormone, is reported to reduce the expression of Kv4.3 channels, which are important molecular components of I_{to} currents.[26] However, in contrast to testosterone, other sex hormonal levels including estradiol were not different between the Brugada males and the control males in the present study. Although thyroid hormones are also demonstrated to alter membrane currents, such as I_{to} and I_{Ca-L},[27,28] no significant differences were observed in the thyroid hormonal levels between the two groups in the present study.

On the other hand, serum sodium, potassium, and chloride levels were all significantly higher in the Brugada males than in the control males, even after adjusting for several confounding variables. Recently, many agents and conditions that cause an outward shift in current activity at the end of phase 1 AP have been known to unmask ST-segment elevation, as found in the Brugada syndrome, leading to the acquired form of this disorder.[4,29] Electrolyte abnormalities, such as hyperkalemia, are reported to amplify ST-segment elevation like that in Brugada syndrome.[30] The lower visceral fat found in the Brugada males is expected to decrease serum level of insulin, leptine, a novel adipocyte-derived hormone, or ghrelin, a novel growth hormone-releasing peptide, suppressing β-adrenergic receptor or plasma norepinephrine level, resulting in an increase of serum potassium level.[31,32] Further studies including measurement of levels of insulin, leptine, and ghrelin will be required to elucidate the precise mechanism.

Study Limitations

Although the testosterone level was significantly higher in the Brugada males than in the control males, no statistically significant correlations were observed between the testosterone level and the ST amplitude in the Brugada males. The degree of the ST-segment elevation is variable between Brugada patients because it is influenced by several factors other than sex hormonal levels or electrolytes levels, such as basal autonomic tone, presence of *SCN5A* mutation, or probably intrinsic current density of I_{to}, etc., in the right ventricular epicardial cells. The threshold of ST-segment elevation for spontaneous induction of VF also varies between Brugada patients. Therefore, the Brugada phenotype, such as ST-segment elevation or spontaneous induction of VF, may correlate with the testosterone level day to day individually (intra-personally) in each Brugada male, but may not correlate among the pooled data obtained from many Brugada males, probably due to inter-person difference of the ST-segment elevation.

There were no significant differences in testosterone level between symptomatic and asymptomatic Brugada males, between Brugada males with spontaneous ST elevation and those with sodium channel blocker-induced ST elevation, or between Brugada males with and without *SCN5A* mutation, all of which are probably due to a relatively small number of Brugada males in the present study. Further evaluation with increasing number of Brugada males will be required.

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