



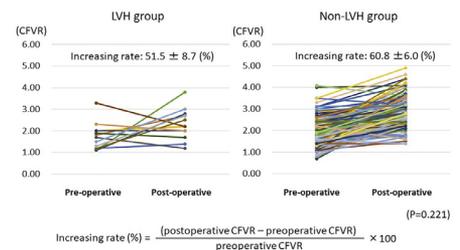
Functional Evaluation of the Myocardial Ischemia After Coronary Artery Bypass Surgery Using Coronary Flow Velocity Reserve in Left Ventricular Hypertrophy

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Patients with left ventricular hypertrophy (LVH) have reportedly higher than normal mortality and incidences of cardiovascular events. Coronary microvascular pathophysiology also appears to differ from other populations. Such coronary microcirculation dysfunctions are considered strong causes of cardiac events. We compare the functional improvement of myocardial ischemia between LVH patients and other patients after successful coronary artery bypass surgery (CABG) using coronary flow velocity reserve (CFVR) by transthoracic echo cardiography. Patients who underwent isolated coronary artery bypass surgery, including left anterior descending artery (LAD) revascularization via “in situ” internal thoracic artery (ITA) between June 2008 and July 2017 ($n = 155$), were retrospectively reviewed. ITA grafts were patent in postoperative graft evaluation in all patients. CFVR was evaluated pre- and postoperatively, and data were compared between patients with severe LVH group and those without (non-LVH group). Preoperative mean CFVR was 1.77 ± 0.75 in LVH group and 1.91 ± 0.63 in non-LVH group ($P = 0.188$). After the operation, ITA to LAD graft patency was confirmed in all patients. Postoperative CFVR was 2.23 ± 0.70 in LVH group and 2.85 ± 0.71 in non-LVH group, respectively ($P = 0.002$). Significant difference was observed between the 2 groups. CFVR values improved after ITA to LAD bypass grafting in both LVH and non-LVH groups, but postoperative CFVR was significantly lower in patients with severe LVH than in patients without. Myocardial ischemia may exist in patients with LVH, despite patent graft, due to microvascular dysfunction. Comprehensive treatment, including long-term oral medication to improve microvascular dysfunction, is necessary for patients with LVH.

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Increasing rate of the CFVR value after CABG.

Central Message

Confirmation of the graft patency by anatomical methods is important after CABG. Evaluation of the functional improvement of the myocardial ischemia is also essential in microvascular disorders.

Perspective Statement

We have to recognize that in patients with microvascular disorders, myocardial ischemia might not improve to the normal range in spite of the successful bypass grafting. After CABG, functional evaluation is also important and in patients with microvascular disorders, postoperative comprehensive therapy including medication is necessary.

Abbreviations: LVH, left ventricular hypertrophy; CABG, coronary artery bypass grafting; CFVR, coronary flow velocity reserve; TTE, transthoracic echocardiography; LAD, left anterior descending artery; ITA, internal thoracic artery; LVMI, left ventricular mass index; MDCT, multiple detector computed tomography; MRI, magnetic resonance imaging; CTO, chronic total occlusion; CAG, coronary angiography

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Conflicts of Interest: None declared.

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INTRODUCTION

Coronary artery bypass surgery is considered successful if the graft is patent in postoperative evaluation. Functional evaluation of preoperative myocardial ischemia and improvement after CABG, however, have not been considered to the same extent.

In patients with left ventricular hypertrophy (LVH), mortality and incidences of cardiovascular events are reportedly higher than in normal populations.^{1,2} In LVH patients, myocardial microvascular disorders are often observed, and dysfunction of coronary microcirculation is considered to be one of the most common causes of cardiac events.^{3,4} In CABG candidates, hypertension and LVH are observed in many patients, among whom there is a possibility that the myocardial ischemia would not improve after successful bypass grafting.

We used coronary flow velocity reserve (CFVR) to evaluate functional improvement of myocardial ischemia in patients with severe LVH with patent graft in this study. CFVR is useful to assess the function of myocardial blood flow, including microcirculation. The usefulness of CFVR in assessing the effect of percutaneous coronary intervention (PCI) and CABG was reported in several previous articles.^{5–8}

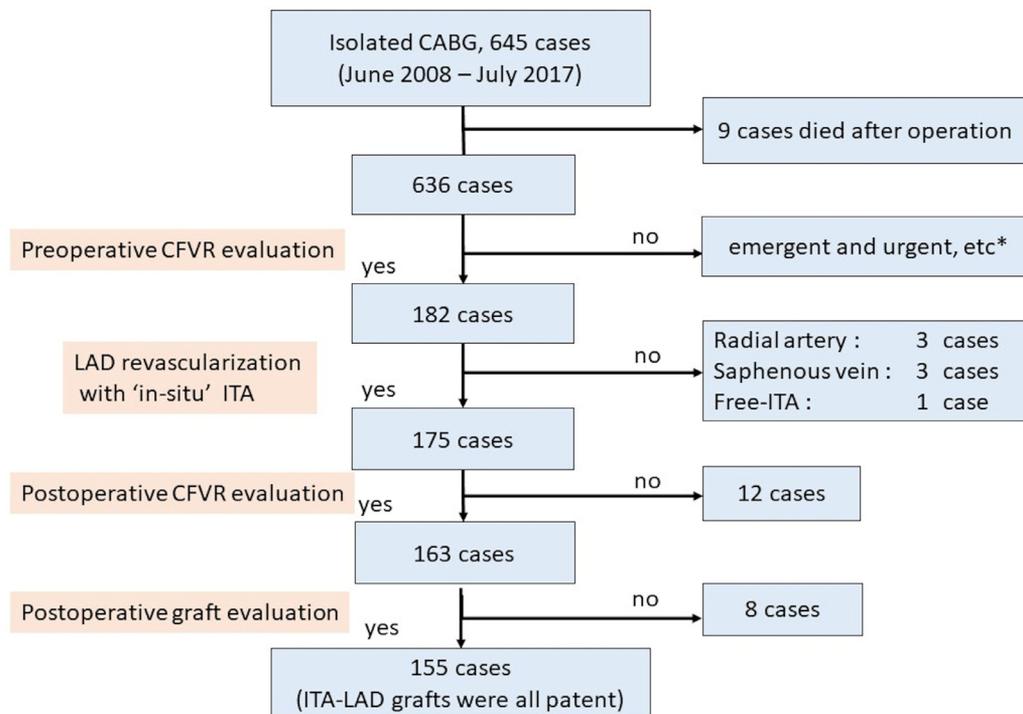
In the present study, we evaluate functional improvement of myocardial ischemia after CABG in severe LVH patients and compare it with nonsevere LVH patients.

METHODS

Patient Populations and Design

This is a single-center, retrospective study. Data collection was performed retrospectively and was approved by our institutional review board. Between June 2008 and July 2017, 645 patients underwent isolated CABG in our institute. Pre- and postoperative CFVR was measured in selected patients. Emergent and urgent cases, history of asthma, drug allergy for adenosine triphosphate, total or subtotal occlusion of the left anterior descending (LAD) were excluded during this study period, preoperative CFVR measurement was performed in 182 patients. Seven patients underwent LAD revascularization other than the “in situ” internal thoracic artery (ITA) graft (radial artery: 3 cases, saphenous vein: 3 cases, and free ITA: 1 case), and postoperative CFVR data were not obtained from 12 patients. Of the remaining 163 cases, postoperative graft evaluation was not obtained from 8 cases, leaving 155 (129 men, 26 women, mean age 66.9 ± 9.4 years) patients finally enrolled in this study. Study profile is shown in Figure 1.

Patients were classified into 2 groups; LVH group was patients with severe LVH defined by preoperative echocardiography, non-LVH group was patients without LVH. To assess the functional improvement of myocardial ischemia, we performed CFVR evaluation of the LAD by transthoracic echocardiography (TTE). CFVR of the LAD was evaluated before and after CABG, and the graft flow and pulsatility index (PI) were



* Including CTO lesion in LAD (68 cases), drug allergy, etc

Figure 1. Study profile.

also evaluated during the operation using transit time flow meter (TTFM) to confirm whether the bypass grafting was successful.

After the operation, graft patency to the LAD was confirmed in all patients. Occluded grafts to the LAD were not observed in any of the 155 patients. Changes in the CFVR value after operation were then evaluated and compared between the 2 groups.

Transthoracic Echocardiographic Examination (CFVR Measurement)

All transthoracic CFVR measurement was performed using TTE by 2 medical laboratory technicians. Two-dimensional, M mode, color Doppler, and tissue Doppler echocardiographic data were obtained using an ultrasound system (GE Healthcare Vivid 7 Dimension, Little Chalfont, United Kingdom). A high-frequency transducer (5–7 MHz) was used to visualize the distal part of the LAD. For color Doppler flow mapping, the velocity range was set between 12 and 24 cm/s. Coronary flow of the LAD territory was visualized using a high-frequency color Doppler technique, and the flow was measured by pulse wave Doppler echocardiography.

Adenosine triphosphate was used as the vasodilator for measuring the CFVR. It has a short half-life and a rapid onset of action, allowing CFVR to be measured more rapidly than other vasodilators. Low-dose adenosine triphosphate (0.14 mg/kg/min) was used to measure the CFVR. Baseline spectral Doppler signals were recorded in the distal part of the LAD. To record the spectral Doppler signals during hyperemia, low-dose adenosine phosphate was administered for 2 minutes. Mean diastolic flow velocities at rest and during hyperemia were measured for CFVR assessment.⁵ CFVR was calculated as the ratio of the mean diastolic flow velocity at hyperemia to the mean diastolic flow velocity at rest. Heart rate and blood pressure were also examined during CFVR assessment.

Mean period of postoperative echocardiography after CABG was 9.6 ± 10.0 (median 2.8; interquartile range, 1–12) months.

Definition of the LVH and Groups

The definition of the LVH was evaluated using 2D guided linear measurement according to the American Society for Echocardiography guidelines.⁹ Severe LVH was defined as left ventricular mass index (LVMI) over 148 g/m^2 in males, and over 121 g/m^2 in females. In this study, LVH group was defined as LVMI over 148 g/m^2 in males, and over 121 g/m^2 in females in preoperative echo examinations.

Transit Time Flow Measurement

Intraoperative bypass graft flow assessments were performed using TTFM (VeriQ system, Medistim, Oslo, Norway). The mean graft flow and PI of the graft to the LAD graft of all patients were recorded.

PI indicates grafting accuracy and quality. A cut-off value of 5.0 for an optimal graft is suggested by manufacturers. Increased PI values indicate a poor graft caused by technical failure, competitive flow, and diffuse disease of the native coronary

arteries.¹⁰ TTFM measurements were performed after stabilizing the hemodynamic condition in both off-pump and on-pump coronary artery bypass grafting. To avoid any influence of the ischemic hyperemia just after ITA to LAD anastomosis, TTFM measurement was performed immediately prior to chest closure.

Graft Patency

Intraoperative fluorescence imaging to assess the graft patency was performed in all CABG patients, adding to the TTFM during the operation. Postoperative graft patency (patent vs occluded) was also performed in most cases. Among all 645 patients in this study period, postoperative graft evaluation was performed of 502 patients (78.9%), and of 155 patients enrolled in this study, “in situ” ITA to LAD grafts were patent in all patients. Multi detector raw computed tomography was used in 147 patients, in patients with chronic kidney disease, plane magnetic resonance imaging was used (6 patients) and coronary angiography was used in 2 cases to evaluate graft patency. Mean period of graft assessment was 13.1 ± 5.6 months (median: 3.5; interquartile range, 1.5–13 months).

Exclusion Criteria

Patients with bronchial asthma were excluded from this study because adenosine infusion is a contraindication of this procedure.¹¹ In this study population, in situ ITA graft was used for the LAD revascularization. Concomitant surgery cases were also excluded because CFVR value was influenced by other factors, such as aortic and mitral valve disorders. Patients with total or subtotal occlusion of the LAD with coronary angiography were also excluded because the LAD flow in those patients showed reverse coronary flow and because comparison with postoperative LAD flow is difficult.

Statistical Analysis

Analyses were performed using SPSS software (Statistical package for the Social Sciences, Version 20, SPSS Inc., Chicago, IL).

Continuous data are presented as means \pm standard deviation. Variables with a normal distribution were compared using paired and unpaired *t* tests. Differences between groups and inhomogeneously distributed data were tested using the Mann-Whitney U tests. Clinical characteristics of the groups were compared using the chi-squared test. Values of $P < 0.05$ were considered statistically significant. The authors had full access to the data and take full responsibility for its integrity. All authors have read the manuscript and agree to the data interpretation as written.

RESULTS

Patients' preoperative characteristics are listed in [Table 1](#).

Mean ages in LVH group and non-LVH group were 62.4 ± 11.5 and 67.4 ± 9.0 , respectively.

There were no significant differences between the 2 groups regarding prevalence of hypertension, diabetes mellitus, dyslipidemia, or smoking.

Table 1. Patient Characteristics

No.	LVH 16	Non-LVH 139	P Value
Age (yrs)	62.4 ± 11.5	67.4 ± 9.0	P = 0.131
Male	13 (81.2%)	116 (83.4%)	P = 0.823
Height (cm)	164.4 ± 8.6	163.8 ± 8.1	P = 0.746
Weight (kg)	72.3 ± 10.3	63.4 ± 15.8	P = 0.046
Body surface area (m ²)	1.79 ± 0.16	1.68 ± 0.21	P = 0.061
Hypertension	16 (100%)	127 (91.3%)	P = 0.368
Diabetes mellitus	11 (68.8%)	78 (56.8%)	P = 0.428
Insulin	4 (25.0%)	39 (28.1%)	P = 0.796
Dyslipidemia	12 (75.0%)	112 (80.6%)	P = 0.598
Smoking	8 (50.0%)	94 (67.6%)	P = 0.173
Myocardial infarction (LAD territory)	3 (18.8%)	20 (14.4%)	P = 0.709

Table 2. Preoperative Echocardiographic Data and Coronary Lesion

No.	LVH 16	Non-LVH 139	P Value
Echocardiography			
Dd (mm)	53.3 ± 9.5	45.8 ± 5.6	P = 0.001
Ds (mm)	39.6 ± 7.2	31.8 ± 6.6	P = 0.003
IVS (mm)	11.1 ± 1.8	9.5 ± 1.3	P = 0.001
PW (mm)	11.0 ± 1.7	9.3 ± 1.2	P < 0.001
LV mass (g)	290.7 ± 74.1	164.9 ± 45.2	P < 0.001
LV mass index (g/m ²)	160.7 ± 27.7	97.3 ± 23.0	P < 0.001
EF (%)	45.6 ± 9.8	53.3 ± 8.8	P < 0.001
Coronary lesion			
SVD	1 (6.3%)	4 (2.9%)	P = 1.000
DVD	4 (25.0%)	30 (21.6%)	P = 1.000
TVD	11 (68.8%)	105 (75.5%)	P = 0.762

Dd, dimension diastolic; Ds, dimension systolic; DVD, double vessel disease; EF, ejection fraction; IVS, interventricular septum thickness; PW, posterior wall thickness; SVD, single vessel disease; TVD, triple vessel disease.

Results of the preoperative echocardiography and coronary lesions are shown in Table 2. In LVH group, left ventricular size, left ventricular wall thickness, and left ventricular mass were significantly larger.

Preoperative CFVR measurements are shown in Table 3.

Preoperative mean LAD flows at rest were 29.5 ± 19.7 (ml/min) in LVH group and 22.6 ± 8.7 (ml/min) in non-LVH group (P = 0.526), respectively. In both groups, mean LAD flow increased at hyperemia. Mean LAD flows at hyperemia

were 47.3 ± 27.0 in LVH group and 41.9 ± 18.0 in non-LVH group (P = 0.715), respectively. As a result, no significant difference was observed in preoperative CFVR value between the 2 groups.

Results of the intraoperative data and graft flow assessment are shown in Table 4.

Prevalence of the off-pump technique was higher in non-LVH group, but no significant difference was observed in the number of distal anastomosis and left ITA use. Intraoperative

Table 3. Preoperative CFVR Value

Preoperative CFVR		LVH	Non-LVH	P Value
Mean Coronary Flow Velocity (ml/min)	Rest	29.5 ± 19.7	22.6 ± 8.7	P = 0.526
	Hyperemia	47.3 ± 27.0	41.9 ± 18.0	P = 0.715
CFVR	(range; 1.1–3.5)	1.77 ± 0.75	1.91 ± 0.63 (range; 1.1–4.1)	P = 0.188

ADULT — CFVR AFTER CABG IN LEFT VENTRICULAR HYPERTROPHY

Table 4. Intraoperative Data

	LVH	Non-LVH	P Value
ONCAB	9	33	$P = 0.009$
OPCAB	7	106	
No. of distal anastomosis	2.81 ± 0.98	3.09 ± 1.08	$P = 0.363$
LAD revascularization			
LITA	12	96	$P = 0.778$
RITA	4	43	
Transit time flow meter (patients with data available: 152 patients)			
Mean graft flow (ml/min)	41.6 ± 30.9	26.8 ± 15.6	$P = 0.033$
Pulsatility index	2.90 ± 1.31	2.61 ± 1.53	$P = 0.350$

mean graft flow was significantly larger in LVH group than in non-LVH group ($P = 0.033$). PI was almost the same degree, and thus, the quality of the anastomosis did not differ between the 2 groups.

Postoperative CFVR measurements are shown in Table 5. Mean LAD flows at rest were 21.3 ± 8.9 (ml/min) in LVH group and 19.7 ± 6.8 (ml/min) in non-LVH group ($P = 0.549$), respectively, and mean LAD flows at hyperemia were 46.2 ± 20.9 (ml/min) in LVH group and 56.5 ± 24.8 (ml/min) in non-LVH group ($P = 0.131$), respectively. As a result, in spite of the larger intraoperative graft flow, the postoperative CFVR value was significantly lower in LVH group than in non-LVH group ($P = 0.002$). The increasing rate of the CFVR values of each patient after CABG is shown in Figure 2. Increasing rate was 51.5% in LVH group and 60.8% in non-LVH group. Significant difference was not observed ($P = 0.221$). In measuring the CFVR, heart rate and blood pressure were also assessed. Significant difference was observed only in preoperative heart rate in rest and postoperative systolic blood pressure in hyperemia (Table 6).

Postoperative follow-up was performed in an outpatient clinic or by telephone. The freedom from death of cardiac or unknown causes was similar between the 2 groups at 7 years of follow-up (mean follow-up duration was 4.0 years; Fig. 3).

Correlation between preoperative LVM and intraoperative graft flow was shown in Figure 4. There was a weak but significant correlation ($r = 0.210$, $P = 0.010$).

There was also a weak but significant correlation between preoperative LVMI and postoperative CFVR ($r = 0.308$, $P < 0.001$; Fig. 5). This result indicated that larger preoperative LVMI lead lower postoperative CFVR.

DISCUSSION

Functional improvement of myocardial ischemia after CABG between severe LVH patients and other patients by CFVR with TTE is compared in the present study.

Various methods to evaluate functional changes of myocardial ischemia have been reported. Of these methods, CFVR measurement by TTE is a noninvasive, relatively inexpensive, repeatable method that requires no radiation to evaluate myocardial ischemia.¹¹ CFVR is obtained as the ratio of the maximum coronary artery blood flow velocity/resting coronary artery blood flow velocity.

CFVR value depends on both epicardial vessels and microcirculation. If CFVR indicates low value, it needs to be ascertained whether the epicardial lesion, microcirculation, or a combination of both, affect the result.¹² To avoid the epicardial factor, confirmation of the graft patency was essential in this study. Here, ITA grafts to the LAD were all patent.

The usefulness of the CFVR has been reported in PCI. CFVR has enabled the evaluation of the PCI indication and the follow-up assessment of restenosis.^{13–15}

Based on these previous uses, CFVR was developed, and has been introduced in surgical situations.

Yoshitatsu et al investigated the changes in LAD flow after CABG using transthoracic Doppler echocardiography in 2002.⁶ Fukui et al also described the CFVR changes after CABG, concluding that the CFVR assessment of the LAD was useful after CABG in confirming graft patency.¹⁶ Regarding revascularization technique, Ozulku et al reported that there was no difference between on-pump and off-pump surgery on mid-term CFVR results,¹⁷ so both off-pump and on-pump patients were enrolled in this study.

Myocardial microvascular dysfunction in LVH patients is well reported³ and has several mechanisms.

Camici and Crea reported that “vascular remodeling, vascular rarefaction, and perivascular fibrosis” exist as a structural problem and “dysfunction of the smooth muscle cells” exists as a functional problem and “extramural compression” also exists as extravascular problems.⁴ In LVH patients, to meet the

Table 5. Postoperative CFVR Value

Postoperative		Group L	Group N	P Value
Postoperative data				
Mean coronary flow velocity	(ml/min)			
	Rest	$21.3 + 8.9$	$19.7 + 6.8$	$P = 0.549$
	hyperemia			
CFVR		$46.2 + 20.9$	$56.5 + 24.8$	$P = 0.131$
		$2.23 + 0.10$	$2.85 + 0.71$	$P = 0.002$
		(1.2–3.8)	(1.4–4.9)	

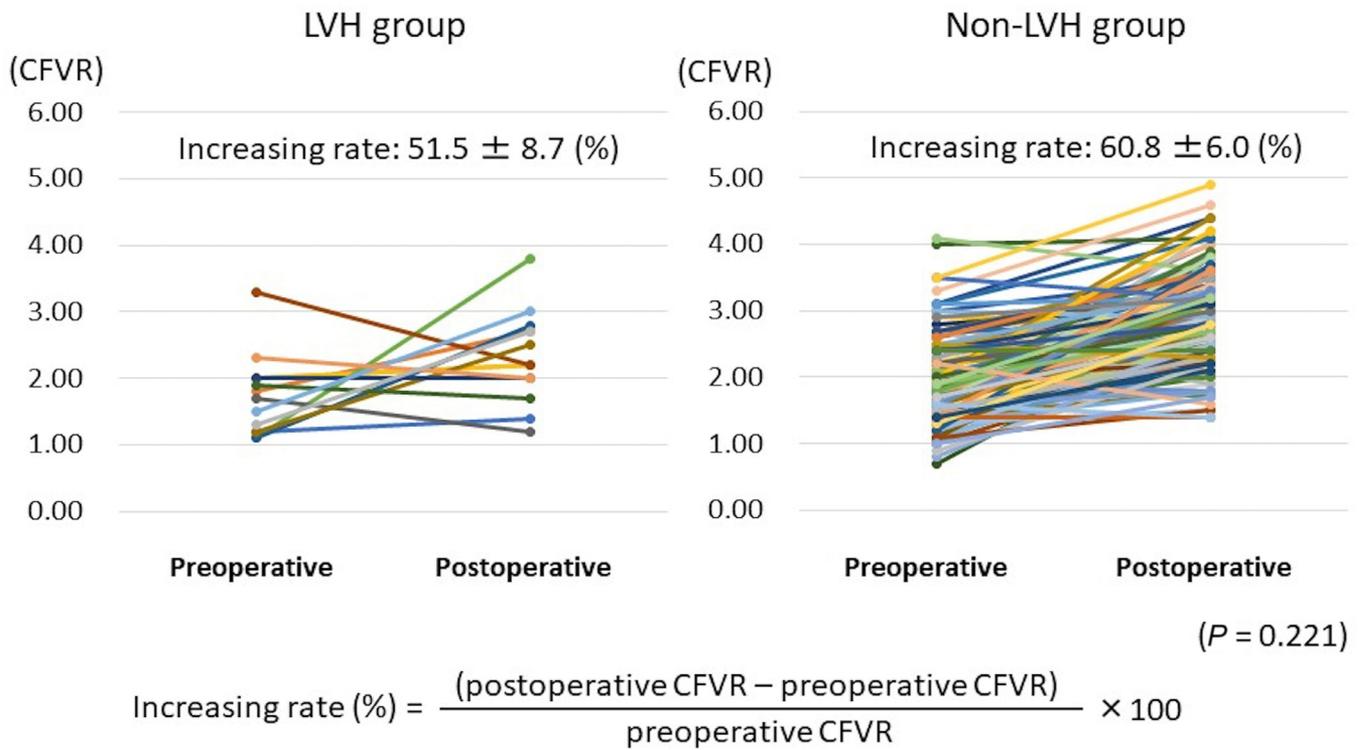


Figure 2. Increasing rate of the CFVR value after CABG.

hypertrophic myocardial demand, coronary arterial flow at rest is higher than in a normal heart. Inadequate vasodilation with endothelial dysfunction, as mentioned above, may cause insufficient coronary flow increase. In such cases, there is a

possibility of some angina in spite of the normal coronary angiograms, Syndrome X.¹⁸

Interestingly, intraoperative ITA flow was significantly larger in LVH group. The possible cause of this phenomenon is that

Table 6. Hemodynamics in CFVR Measurement

	*	LVH	Non-LVH	P Value
Preoperative Data				
<i>Rest</i>				
Heart rate (/min)	130	72.3 ± 11.0	62.8 ± 9.5	P = 0.004
Systolic blood pressure (mm Hg)	139	124.3 ± 21.3	127.0 ± 22.5	P = 0.672
Diastolic blood pressure (mm Hg)	139	64.3 ± 14.1	68.9 ± 13.8	P = 0.353
<i>Hyperemia</i>				
Heart rate (/min)	130	74.7 ± 12.0	68.6 ± 10.4	P = 0.087
Systolic blood pressure (mm Hg)	139	121.4 ± 16.1	120.6 ± 22.2	P = 0.864
Diastolic blood pressure (mm Hg)	139	62.2 ± 8.8	63.9 ± 14.1	P = 0.833
Postoperative data				
<i>Rest</i>				
Heart rate (/min)	131	69.2 ± 9.9	67.4 ± 13.4	P = 0.647
Systolic blood pressure (mm Hg)	130	138.1 ± 29.2	121.4 ± 19.4	P = 0.083
Diastolic blood pressure (mm Hg)	130	71.6 ± 13.7	68.1 ± 14.1	P = 0.427
<i>Hyperemia</i>				
Heart rate (/min)	131	72.9 ± 10.7	73.2 ± 13.7	P = 0.931
Systolic blood pressure (mm Hg)	130	137.6 ± 27.2	116.0 ± 19.2	P = 0.009
Diastolic blood pressure (mm Hg)	130	68.0 ± 13.4	62.2 ± 13.4	P = 0.155

*Patients with data available.

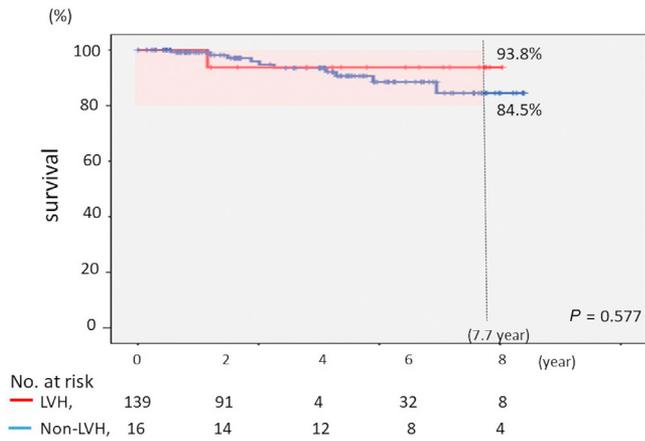


Figure 3. Kaplan-Meier overall survival curve.

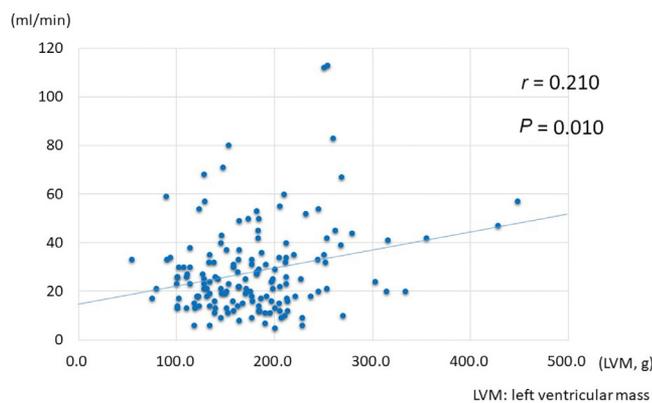


Figure 4. Correlation between preoperative LVM and intraoperative graft flow.

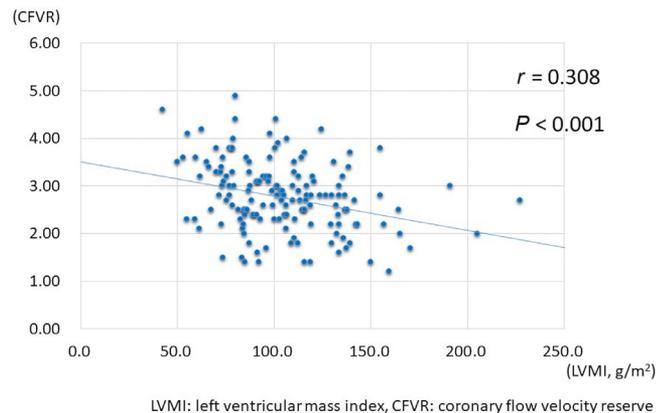


Figure 5. Correlation between preoperative LVMI and postoperative CFVR.

larger ventricular myocardium has larger vascular beds and needs more blood supply. There was a weak, but significant correlation between preoperative left ventricular mass and intraoperative graft ($r = 0.210$, $P = 0.01$; Fig. 4).

There are various opinions on the normal value of CFVR. Some authors report that $CFVR < 2.0$ is a useful cut-off value for significant coronary stenosis,^{19,20} others report that the lower limit of

normal CFVR was >3.0 .²¹ Moreover, Galderisi et al reported that aging and atherosclerotic factors could influence CFVR.²²

In Galderisi's report, the CFVR value decreased with age, even in patients with angiographically normal coronary anatomy. In the general population, the normal value of CFVR in patients under age 55 was found to be 3.01 ± 0.69 ; it was 2.67 ± 0.54 for ages 55–62, 2.47 ± 0.54 for ages 63–69, and 2.39 ± 0.49 for patients over 70 years.

In this study, the mean age was 66.6 ± 9.3 years old and with that background, postoperative CFVR value was expected to be around 2.47. Postoperative results, however, indicated that the CFVR value in non-LVH group (2.85 ± 0.71) was higher than the expected normal value. In LVH group, however, it was lower (2.23 ± 0.70) than the expected value.

This result indicates that the CFVR value in LVH patients does not reach the expected normal value after the successful CABG. Correlation between preoperative LVMI and postoperative CFVR is shown in Figure 5. It indicates that if LVMI becomes larger, CFVR could be lower.

In LVH patients who undergo CABG, confirmation of the graft patency is not a final goal.

Levy et al reported on medicines that may have a beneficial effect on LVH.²³

Clear evidence shows α -blockers and calcium antagonists can lead to increase in capillary density in animal models. Angiotensin-converting enzyme inhibitors are also considered to have an effect on LVH improvement.

Although the graft is patent, whether the coronary blood flow is satisfactory is unclear. To fulfill the exercise tolerance, comprehensive treatment including postoperative drug therapy is necessary for LVH patients.

LIMITATIONS

Our study has several limitations. First, this was a retrospective study and a relatively small study group, especially the LVH group. Second, the age distribution was wide, ranging between 48 and 84 years old. The normal CFVR value differs with the age and, therefore, it might have influenced the results. Third, as this is a retrospective study, the measurement conditions of CFVR might vary by, for example, medication and/or food intake, and if the patients smoke. Fourth, there were some missing data in hemodynamics in CFVR measurement, as described in Table 6.

CONCLUSIONS

In this study, CFVR values improved after ITA to LAD bypass grafting in both LVH and non-LVH groups. In patients with severe LVH, however, postoperative CFVR was significantly lower than in patients without and postoperative CFVR did not reach the expected normal value, despite the successful bypass grafting.

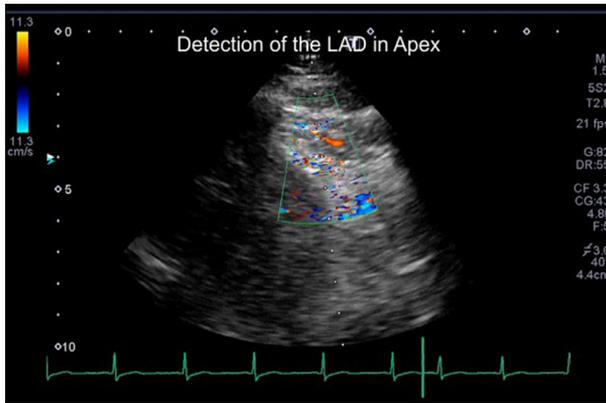
To improve microcirculation, comprehensive therapy including medication is necessary.

DECLARATION OF HELSINKI

The authors declare that this complies with the Declaration of Helsinki and was furthermore approved by the institutional ethics committee.

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



Video 1. Evaluation method of the CFVR by transthoracic echocardiography.

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