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Predictors of inotropic support during weaning from cardiopulmonary bypass in coronary artery bypass grafting surgery

Hideaki Hayashi[1], Rama Prabhu[2], David C. Kramer[2], and Yasu Oka[2]

[1] Department of Anesthesia, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki, Hyogo 660, Japan
[2] Department of Anesthesiology, The Albert Einstein College of Medicine, Montefiore Medical Center, 1300 Morris Park Avenue, Bronx, New York, NY 10461, USA

Abstract: Early or prophylactic inotropic drug administration is occasionally required to facilitate separation from cardiopulmonary bypass (CPB) in cardiac surgery. However, it is not without untoward effects and should be conducted on the basis of rational criteria. The purpose of our study was to clarify variables associated with the requirement for inotropic support during separation from CPB and to testify whether pre-CPB left ventricular (LV) function, as evaluated by transesophageal echocardiography (TEE), is one of the significant variables. Clinical profile data and TEE findings were retrospectively analyzed for 91 patients who had received elective primary isolated coronary artery bypass grafting (CABG) surgery. Post-CPB inotropic drug administration initiated prior to aortic decannulation was considered inotropic support for terminating CPB. Stepwise multiple logistic regression analysis identified pre-CPB LV regional wall motion abnormalities (RWMA), NYHA class, age, and duration of CPB (in order of significance) as factors associated with inotropic support for discontinuing CPB. Pre-CPB LV end-diastolic area or fractional area change was not a significant variable in the multivariate model. Our result suggests that evaluation of pre-CPB LV RWMA is useful in predicting the need of inotropic intervention during separation from CPB in patients undergoing CABG surgery.

Key words: Cardiopulmonary bypass, Coronary artery bypass grafting surgery, Inotropic support, Logistic regression, Transesophageal echocardiography

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Introduction

Improvements in anesthetic, surgical, and perfusion techniques have allowed old and sick patients who have poor left ventricular (LV) function and exhibit preexisting comorbidity to undergo myocardial revascularization surgery over the past decade [1,2]. When this population of patients receives coronary artery bypass grafting (CABG) surgery, inotropic support is often required in the post-cardiopulmonary bypass (CPB) period. Particularly for patients with preexisting LV dysfunction, early or prophylactic inotropic drug administration during separation from CPB is occasionally essential to facilitate termination of CPB and thereby minimize the detrimental effects caused by prolonged duration of CPB. The use of inotropic agents, however, is not without adverse effects. The use of inotropic agents subjects the patients to an increased risk of tachycardia, dysrhythmia, and myocardial ischemia [3,4]. Their indiscriminate use may also increase medical expense.

If variables associated with the necessity of the early inotropic support are clarified, early or prophylactic inotropic intervention can be rationally conducted. The extent of post-CPB LV dysfunction has been reported to correlate with the pre-CPB LV functional status [5]. Thus, we hypothesized that pre-CPB LV function, as evaluated by transesophageal echocardiography (TEE) intraoperatively, could be the primary factor that determines the need for inotropic intervention following CPB. TEE enables visualizing the LV motion, which cannot be assessed under direct vision from the surgical field, throughout the operation without interfering with surgery. The purpose of this study was to clarify variables associated with the requirement for inotropic support during separation from CPB in patients undergoing CABG surgery, and to test whether pre-CPB LV function, as evaluated by TEE, is one of the significant variables.

Methods

Patient population

Patients who had undergone elective primary isolated CABG surgery without requiring inotropic support or intraaortic balloon pumping (IABP) preoperatively during the period from July 1994 to January 1995 at the Weiler Division of the Albert Einstein College of Medicine were evaluated. Of the 101 patients evaluated, 3 patients were excluded because of dysrhythmia (atrial fibrillation) compromising TEE analysis, and 4 patients because of TEE image quality too poor to allow adequate evaluation. Three other patients who had inadequate revascularization (kinked graft or insufficient graft flow) failed to separate from CPB. These 3 patients were also excluded from the analysis, since they required reinstitution of CPB for surgical correction. Consequently, the data were analyzed for 91 patients [63 men and 28 women, mean age (±SD) 63.9 ± 11.2 years].

Data collection

The following data were retrospectively collected from medical records: age, sex, weight, body surface area, New York Heart Association (NYHA) class, American Society of Anesthesiologists (ASA) physical status, history of myocardial infarction and diabetes mellitus requiring medication, preoperative medication, number of coronary arteries with significant stenosis, preoperative ejection fraction (EF), intraoperative hemodynamic data, number of grafts performed, type of cardioplegia, aortic cross-clamp time, duration of CPB, requirement for electrical defibrillation following release of the aortic cross-clamp, and inotropic drug administration. Intervals of intensive care unit (ICU) and hospital stay after surgery were also surveyed as operative outcome variables.

Anesthetic and surgical technique

All patients were premedicated with morphine ($0.1\,mg \cdot kg^{-1}$), and scopolamine (0.2–0.4 mg) or diphenhydramine (25–50 mg). Upon their arrival in the operating room monitors were placed, and radial artery and pulmonary artery catheters were inserted under local anesthesia prior to induction of general anesthesia. Anesthesia was induced and maintained with sufentanil ($15–25\,\mu g \cdot kg^{-1}$), diazepam ($0.3–0.4\,mg \cdot kg^{-1}$), and a muscle relaxant (vecuronium or pancuronium). Patients were ventilated with 100% oxygen throughout surgery except during CPB.

All CPB was conducted at normothermia or mild hypothermia (core temperature >32°C). Pump flow was maintained at $2.2–3.0\ l \cdot min^{-1} \cdot m^{-2}$ throughout the CPB period. Cardiac arrest was initiated by aortic cross-clamp and administration of antegrade cold cardioplegia, and was maintained by intermittent antegrade or antegrade plus retrograde cold blood cardioplegia (29 antegrade, 62 ante- + retrograde).

Distal anastomoses of coronary grafts were performed during cardioplegic arrest following aortic cross-clamping. Proximal anastomoses were made with the heart beating and empty, using a partial occluding clamp. Fifty-three patients received both internal mammary artery and saphenous vein grafting.

Use of inotropic agents

Five cardiac anesthesiologists and four cardiac surgeons were involved in the study. The anesthesiologist and surgeon attending an operation determined the necessity of inotropic support during separation from CPB and chose the drugs to be administered.

During separation from CPB, the LV chamber size was repeatedly checked by TEE, and volume loading was adjusted to maintain the appropriate LV preload. Along with optimizing the preload condition, LV contractility was assessed by TEE, and the heart motion was observed under direct vision. When LV motion stayed sluggish, the need for inotropic support was considered. Then, hemodynamic condition was evaluated, and if systemic blood pressure and cardiac output were not in the adequate range, administration of inotropic agents was initiated.

With respect to the choice of inotropic drugs, dobutamine is the first-line agent in the institute; when a more potent inotropic effect was necessary, epinephrine was selected. When pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg) coexisted, amrinone was the drug of choice. When low blood pressure persisted, norepinephrine was added to maintain adequate perfusion pressure.

TEE evaluation

TEE was performed as one of the routine intraoperative monitoring techniques for all patients. Following induction of anesthesia, a 5-MHz biplane TEE probe (PEF-510B, Toshiba, Tokyo, Japan) connected to the echo imaging system (SSH-140A, Toshiba) was placed. TEE was monitored throughout the operation except during the period of cardioplegic arrest. Echo images were recorded on videotape.

For evaluation of pre-CPB LV function, end-diastolic area (EDA), fractional area change (FAC), and regional wall motion abnormalities (RWMA) were assessed using a LV short-axis cross-sectional view at the mid-papillary muscle level, which had been recorded when the patient's hemodynamic condition had stabilized following induction of anesthesia. The adequacy of a LV short-axis view was confirmed by switching the echo images between transverse and longitudinal scans and referring to the anatomical landmarks.

EDA and FAC were calculated from the manually determined LV endocardial border, which was traced by the leading edge—leading edge method [6], utilizing a software installed in the echo imaging system. EDA was obtained from the video frame at the peak of the R-wave of a simultaneously recorded electrocardiogram, and end-systolic area (ESA) from the frame with the smallest cross-sectional area following the image for EDA. FAC is calculated as follows:

$$FAC = (EDA - ESA)/EDA$$

FAC and EDA were averaged over three cardiac cycles.

For evaluation of RWMA, the intraoperative videotape was reviewed independently by two observers who were blinded to patient information. The LV short-axis view was subdivided into eight segments (Fig. 1) [7]. In order to evaluate the severity of RWMA, a RWMA scoring system was introduced, in which the wall motion of each subsegment was graded as (a) normokinetic (score = 0): no evidence of dysfunction; (b) mildly hypokinetic (score = 1): minimal diminution in function; (c) severely hypokinetic (score = 2): significantly abnormal movement or thickening; (d) akinetic (score = 3): total lack of movement or thickening; or (e) dyskinetic (score = 4): paradoxical outward movement or wall thickening. The RWMA score was derived by summing scores of the eight subsegments, and was averaged between the two observers.

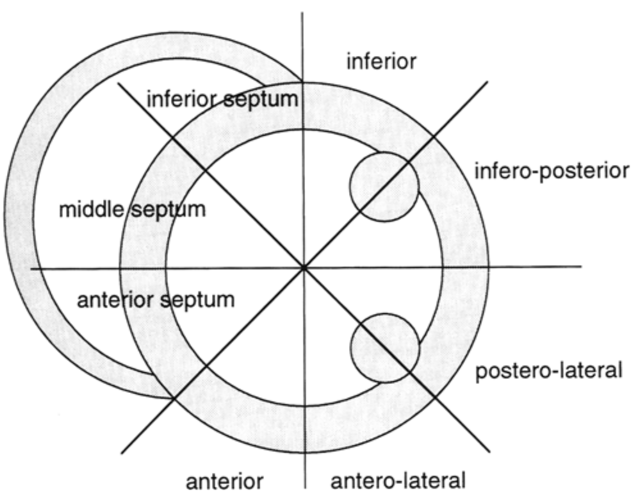

Fig. 1. Left ventricular short-axis view of the midpapillary muscle level demonstrating the subdivided eight segments. The left ventricular walls at the midpapillary muscle level are subdivided using a radial coordinate system with the papillary muscles as the fixed anatomical reference points

Statistical analysis

Prior to multivariate analysis, each variable collected was tested in a univariate fashion; the chi-square test or Fisher's exact test was used for nominal data, and the *t*-test was applied to continuous variables. Continuous data are expressed as mean ± SD. $P < 0.05$ was considered statistically significant.

Following the univariate tests, multivariate logistic regression was applied to determine the pre-CPB factors associated with the use of inotropic drugs [8]. Starting from the variables with $P < 0.25$ in univariate analysis, model fitting was performed by the stepwise logistic regression algorithm (forward selection followed by backward elimination) using 0.15 and 0.20 as P values to include and exclude variables. Interaction of significant variables was considered, but was not found. The goodness-of-fit statistic for the obtained logistic regression model was evaluated by the Hosmer-Lemeshow test [9]. Statistical computation was carried out on SYSTAT 5.2 for Macintosh (Systat, Chicago, IL, USA).

Results

Patient data

Of 91 patients, 37 required inotropic drugs to terminate CPB, and comprised the inotropic support group (ISG). The inotropic drugs given were dobutamine (n = 24), epinephrine (n = 2), amrinone (n = 1), epinephrine + amrinone (n = 8), dobutamine + epinephrine (n = 1), and dobutamine + norepinephrine (n = 1). Dobutamine was given at doses of 3–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$: n = 2; 5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$: n = 24). The doses of epinephrine administered were 0.02–0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Amrinone was infused at doses of 5–7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ following a loading dose (50–100 mg). Thirty-four patients in the ISG were given inotropic drugs for more than 6 h postoperatively. The noninotropic support group (NISG) consisted of the remaining 54 patients.

Univariate analysis revealed significant differences between the ISG and NISG with regard to age, NYHA class, ASA physical status, number of diseased vessels, and duration of CPB (Table 1). Data on EF were available in only one-third of patients, and medical documentation of previous myocardial infarction was not objectively obtained from all patients. These two variables were eliminated from the analysis.

Table 1. Comparison of patients requiring and not requiring inotropic support

	NISG (n = 54)	ISG (n = 37)	P value
Age (years)	61.9 ± 10.8	66.8 ± 11.4	0.04*
Sex (male/female)	40/14	23/14	0.23**
Weight (kg)	79.4 ± 17.4	74.5 ± 15.1	0.17*
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	0.23*
NYHA class			<0.001**
Class 2	13	2	
Class 3	37	19	
Class 4	4	16	
ASA physical status (PS)			<0.001**
PS III	38	11	
PS IV	16	26	
History of DM[a]	15	15	0.20**
Preop. β-blocker[b]	31	21	0.95**
No. of diseased vessels			0.02**
2	19	5	
3	35	32	
No. of grafts			0.12**
2	26	13	
3	24	16	
≥4	4	8	
Cardioplegia			0.08**
Antegrade	21	8	
Ante- + retrograde	33	29	
Electrical defibrillation[c]	26	12	0.14**
Duration of ACC (min)	61 ± 18	69 ± 22	0.07*
Duration of CPB (min)	98 ± 24	117 ± 32	0.002*
Duration of operation (min)	232 ± 54	252 ± 41	0.06*

NISG, noninotropic support group; ISG, inotropic support group; BSA, body surface area; NYHA, New York Heart Association; ASA, American Society of Anesthesiologists; DM, diabetes mellitus; ACC, aortic cross-clamp; CPB, cardiopulmonary bypass.
[a] Diabetes mellitus requiring medication.
[b] Preoperative medication of β-blocker.
[c] Requirement for electrical defibrillation following release of aortic cross-clamp.
* Unpaired t-test; values are mean ± SD.
** χ^2-test.

There were no differences in heart rate, blood pressure, or pulmonary artery pressure following induction between the two groups. The ISG showed a lower cardiac index ($2.3 \pm 0.6\,l \cdot min^{-1} \cdot m^{-2}$ *vs* $2.6 \pm 0.7\,l \cdot min^{-1} \cdot m^{-2}$; $P < 0.05$) after induction.

In the pre-CPB TEE evaluation, the ISG exhibited greater EDA ($13.1 \pm 4.6\,cm^2$ *vs* $11.0 \pm 2.7\,cm^2$; $P < 0.01$), lower FAC (50.2 ± 17.1% *vs* 64.5 ± 14.8%, $P < 0.01$), and a higher RWMA score ($P < 0.01$, Mann-Whitney test) than NISG (Fig. 2).

The interval of ICU stay (NISG: 65.8 ± 38.1 *vs* ISG: 86.1 ± 64.5 h) or of hospital stay (8.6 ± 4.8 *vs* 10.6 ± 6.0 days) did not differ between the two groups.

Logistic regression analysis

RWMA score, NYHA class, age, and duration of CPB (in order of significance) were identified as factors associated with inotropic support during separation from CPB (Table 2). Factors such as ASA physical status, number of stenosed coronary vessels, EDA, and FAC showed significance in univariate analysis, but they were eliminated from the multivariate model.

The relationship between RWMA score, NYHA class, age, and duration of CPB to the need for inotropic support is expressed using the probability $P(\mathbf{x})$.

$$P(\mathbf{x}) = \exp[g(\mathbf{x})]/(1 + \exp[g(\mathbf{x})])$$

$$g(\mathbf{x}) = 1.290 \cdot WM1 + 2.880 \cdot WM2 + 0.876 \cdot NYHA1 + 3.772 \cdot NYHA2 + 0.089 \cdot Age + 0.030 \cdot CPB - 11.795$$

where $P(\mathbf{x})$ is the probability of requiring inotropic support,

and $\mathbf{x}$ = (WM1, WM2, NYHA1, NYHA2, Age, CPB)

WM1 = 0, WM2 = 0 when RWMA score = 0 to 3

WM1 = 1, WM2 = 0 when RWMA score = 4 to 6

WM1 = 0, WM2 = 1 when RWMA score ≥ 7

NYHA1 = 0, NYHA2 = 0 when NYHA class = 1 to 2

Table 2. Factors associated with requirement for inotropic support during separation from CPB

Variable		Coefficient	SE	OR	95% CI for OR	*P* value
RWMA score	4 to 6	1.290	0.769	3.6[a]	(0.8, 16.4)	0.09
	≥7	2.880	0.819	17.8[a]	(3.6, 88.7)	<0.001
NYHA class	3	0.876	1.066	2.4[b]	(0.3, 19.4)	0.41
	4	3.772	1.356	43.5[b]	(3.0, 620.2)	0.005
Age		0.089	0.033	2.4[c]	(1.2, 4.6)	0.007
Duration of CPB		0.030	0.013	1.6[d]	(1.1, 2.3)	0.02

CPB, cardiopulmonary bypass; SE, standard error; OR, odds ratio; CI, confidence interval; RWMA, regional wall motion abnormalities.
[a] *Vs* RWMA score 0 to 3.
[b] *Vs* NYHA class 1 or 2.
[c] For a change of 10 years of age.
[d] For a change of 15 min of CPB time.
P values were obtained from the Wald test statistic (coefficient/SE), which follows the standard normal distribution.

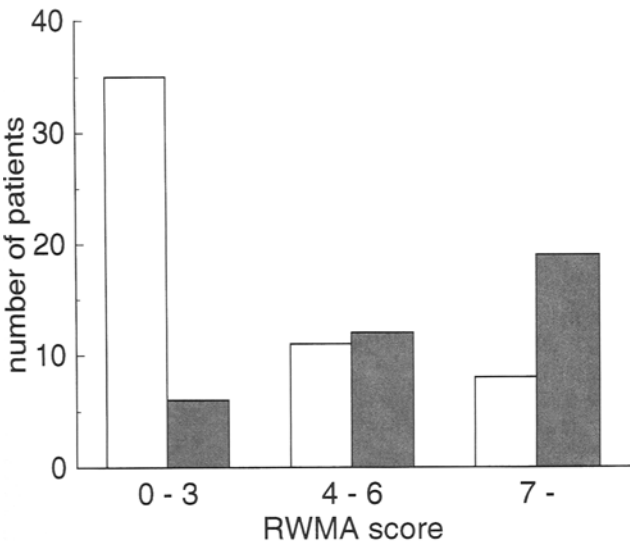

Fig. 2. Prebypass left ventricular regional wall motion abnormalities (*RWMA*) score for the noninotropic support group (NISG, *open bars*) and the inotropic support group (ISG, *solid bars*). The left ventricular short-axis view at the midpapillary muscle level was subdivided into eight segments, and each segment was scored regarding RWMA. The RWMA score was calculated by summing the scores of the eight segments

NYHA1 = 1, NYHA2 = 0 when NYHA class = 3

NYHA1 = 0, NYHA2 = 1 when NYHA class = 4

(Age, age in years; CPB, duration of CPB in minutes)

Goodness-of-fit of the model was tested by the Hosmer-Lemeshow statistic. The statistic was computed from decile of risk based on the values of estimated probabilities. The corresponding *P* value computed from chi-square distribution with eight degrees of freedom showed satisfactory fitness of the model ($P = 0.93$; $P < 0.05$ suggests a poor fit).

Discussion

Improvements in anesthetic, surgical, and perfusion techniques have enabled old and sick patients with poor LV function and profound coexisting morbidity to undergo CABG surgery [1,2]. When this population of patients receives surgical myocardial revascularization, inotropic drugs are often used to improve cardiac performance and maintain adequate systemic circulation after CPB. In patients with critically reduced LV function, early or prophylactic inotropic intervention during separation from CPB is occasionally essential to expedite termination of CPB and thereby to minimize detrimental effects caused by prolonged duration of CPB. It may also circumvent the need for mechanical intervention (IABP or ventricular assist devices) [4]. Prolonged duration of CPB is thought to result in an increased risk of myocardial distention and damage to the already jeopardized heart, a potential need for additional blood products, and the augmented unfavorable "whole-body inflammatory response" including intrinsic coagulation, the classic complement pathway, fibrinolysis, kinin function, and neutrophil activation [10].

The use of inotropic agents, however, is not free of risks. Injudicious use of these agents may be associated with tachycardia, dysrhythmias, hyperglycemia, increased reperfusion injury, and additional medical expense [3,4]. If predictors identifying patients who should be given early inotropic intervention during separation from CPB are clarified, the administration of early inotropic support could be judiciously conducted. Our study revealed that RWMA score, NYHA class, age, and duration of CPB were factors associated with requirement for early inotropic support during emergence from CPB in patients undergoing CABG surgery.

Previously, Royster and coworkers [11] have reported that in addition to age and female sex, preoperative EF and cardiac enlargement on ventriculography, as well as elevated LV end-diastolic pressure during cardiac catheterization, are predictors of the need for inotropic support after CABG surgery. Despite the similarity of the design, size, and variables analyzed, inconsistency in the derived models is seen between their investigation and ours. This inconsistency may be attributed to some differences between the two studies. First, we focused on identifying factors associated with the necessity of early inotropic intervention during separation from CPB. Thus, we defined only the patients who had required inotropic agents prior to aortic decannulation as the ISG. Royster et al., however, judged patients who received inotropic drugs in the operating room and at least 12h postoperatively to have required inotropic support [11]. This difference in definition of the ISG could affect the derived model. Second, we did not test preoperative EF, LV end-diastolic pressure, or cardiac enlargement in the analysis as parameters of LV function. Alternatively, we used EDA, FAC, and the RWMA score, evaluated by TEE in the pre-CPB period, to assess LV function. EDA and FAC have previously been shown to provide reasonable estimates of LV volume and EF [12,13].

Our model demonstrated that the presence of RWMA in the pre-CPB period was the most significant predictor of the need for inotropic support during weaning from CPB. Although EDA and FAC were found to be significant by univariate analysis, neither of them was significant in the multivariate model. Simon and coworkers [5] have echographically shown effects of CABG on global and regional myocardial function. According to their study, normal or moderately hypokinetic segments display significantly decreased regional function immediately after CPB. These seg-

Table 3. Conditions relating to the estimated probability of inotropic support >0.5

RWMA score	NYHA class	Age (years)	Duration of CPB (min)
0 to 3	1 or 2	50	>245
		60	>215
		70	>186
		80	>156
	3	50	>216
		60	>186
		70	>156
		80	>127
	4	50	>119
		60	>89
		70	>60
		80	>30
4 to 6	1 or 2	50	>202
		60	>172
		70	>143
		80	>113
	3	50	>173
		60	>143
		70	>113
		80	>84
	4	50	>76
		60	>46
		70	>17
		80	>0
7 or greater	1 or 2	50	>149
		60	>119
		70	>90
		80	>60
	3	50	>120
		60	>90
		70	>60
		80	>31
	4	50	>23
		60	>0
		70	>0
		80	>0

CPB, cardiopulmonary bypass; RWMA, regional wall motion abnormalities.
Probability of the need for inotropic support during separation from CPB was estimated from the derived logistic regression model, using RWMA score, NYHA class, age, and duration of CPB as predictors. Conditions relating to the probability exceeding 0.5 are stratified.

ments regain their pre-CPB functional status by 30 min after termination of CPB. Although severely dysfunctional segments may exhibit improvement in function following revascularization, the function of these segments remains depressed. These findings in their investigation indicate that the severity of pre-existing RWMA is the major factor which determines myocardial function following CPB, and it is therefore thought to correlate with the necessity of inotropic support during separation from CPB. Our result that pre-CPB RWMA is the significant predictor of the necessity of inotropic support during separation from CPB is consistent with their findings. In contrast, since pre-CPB EDA and FAC do not directly reflect the severity of preexisting RWMA, these variables may be less predictive of the extent of LV dysfunction and the necessity of inotropic support following CPB.

Our prediction model indicates that patients with $P(\mathbf{x}) > 0.5$ are likely to require inotropic support for separation from CPB. Table 3 shows conditions relating to $P(\mathbf{x}) > 0.5$. According to the table, patients with an RWMA score of 0 to 3 are unlikely to have difficulties in weaning from CPB without inotropic support, unless NYHA class is 4. In patients with an RWMA score of 4 to 6, an evaluation of combined risk factors is necessary, and our model estimates the probability of the need for inotropic support. Patients with an RWMA score of 7 or greater are most likely to require inotropic support.

This study, admittedly, has some limitations because of its retrospective nature. Although we assumed that the use of inotropic agents reasonably reflected the need for them, the possibility that some patients may have received inotropic support prophylactically beyond its indication needs to be considered. In order to address this distinction specifically, a prospective study should be conducted. Another factor which needs to be considered in the future study is to evaluate the adequacy of myocardial protection and graft patency objectively. The use of modalities such as contrast TEE might improve the sensitivity of prediction by demonstrating the adequacy of surgical revascularization and myocardial preservation during CPB [14,15].

In summary, our study showed that pre-CPB LV RWMA, NYHA class, age, and duration of CPB (in order of significance) were significant factors associated with the requirement for inotropic support during separation from CPB in patients undergoing CABG surgery. This result suggests that evaluation of pre-CPB LV RWMA is useful in predicting the need for early inotropic intervention to facilitate smooth termination of CPB in those patients.

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