Hemodynamic Effect of Diltiazem Cardioplegia Following Cardiopulmonary Bypass

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Diltiazem, one of the calcium channel blockers, has various pharmacological effects including dilatation of the coronary artery and peripheral vessels, and reduction of heart rate by blocking calcium channels in sinus and atrio-ventricular nodes[1]. It is commonly used for the treatment of essential hypertension, angina on effort and variant angina characterized by coronary artery spasm[2,3].

Recently some studies have reported on the myocardial protective effect of calcium channel blockers added to cardioplegic solution during cardiopulmonary bypass (CPB) in cardiac surgery[4-11].

Since May 1983, we have used diltiazem cardioplegia in all aorto-coronary bypass (A-C bypass) operations for myocardial protection and prevention of coronary artery spasm after CPB. Following the use of diltazem cardioplegia, however, hypotension, bradycardia, and fugitive atrio-ventricular block were frequently recognized. We studied hemodynamics before and after CPB to evaluate problems associated with diltiazem cardioplegia in the anesthetic management.

Materials and Methods

This study was carried out on 397 patients who underwent elective A-C bypass surgery, with their informed consent, from November 1982 to March 1987. Characteristics of patients are given in table 1. From November 1982 to May 1983, potassium cardioplegia was used for 87 patients. From May 1983 to March 1987, diltiazem cardioplegia was used for the other 310 patients. Coronary artery spasm was diagnosed by surgeons and anesthesiologists, based on the criteria of Buxton et al.[12], when sudden onset of hypotension, electrocardiographic ST-segment elevation and various types of arrhythmia were recognized. Hemodynamic variables were measured in 24 patients randomly selected from the 87 patients who received potassium cardioplegia (potassium group), and 30 from the 310 patients who received diltiazem cardioplegia (diltiazem group).

A thermistor-tipped flow-directed pulmonary artery catheter was inserted from the basilic vein on the day before the operation. Patients were premedicated intramuscularly with scopolamine 0.008 $mg \cdot kg^{-1}$, hydroxyzine 1 $mg \cdot kg^{-1}$ and pethidine 1 $mg \cdot kg^{-1}$, or scopolamine 0.008 $mg \cdot kg^{-1}$, diazepam 0.2 $mg \cdot kg^{-1}$ and morphine 0.2 $mg \cdot kg^{-1}$ 30 min before arrival in the operating room. Anesthesia was induced with diazepam 0.2 $mg \cdot kg^{-1}$, fentanyl 0.01–0.02 $mg \cdot kg^{-1}$, and pancuronium 0.1–0.15 $mg \cdot kg^{-1}$, and maintained with high dose fentanyl (0.075–0.1 $mg \cdot kg^{-1}$). Nitrous oxide

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Table 1. Characteristics of patients

	KCP Group (n = 24)	DLCP group (n = 30)
Male/Female	20/4	26/4
Age (y.o.)	54.1 ± 9.9	58.6 ± 6.9*
Weight (kg)	59.1 ± 8.2	59.1 ± 7.1
Height (cm)	158.8 ± 6.8	161.9 ± 6.7
BSA (m^2)	1.6 ± 0.1	1.6 ± 0.1
Hypertension	8	6
Diabetes Mellitus	6	7
Diltiazem administration	3	8
Nifedipine administration	20	23
Nitroglycerin administration	20	30
β-blocker administration	2	5
Antiarrhythmic drugs administration	2	1
Diuretics administration	3	2
LVEDP (mmHg)	10.5 ± 7.2	9.9 ± 8.7

*: different from KCP group ($P < 0.05$).

Values are expressed as mean ± SD

KCP = potassium cardioplegia. DLCP = diltiazem cardioplegia, BSA = body surface area (m^2), LVEDP = left ventricular end diastolic pressure (mmHg).

Table 2. Demographics during operation

	KCP Group (n = 24)	DLCP group (n = 30)
Number of Bypass Graft	2.5 ± 0.7	2.2 ± 0.8
Duration of Anesthesia (min)	553.4 ± 71.4	567.0 ± 78.2
Duration of Operation (min)	452.0 ± 67.9	464.1 ± 76.1
Duration of CPB (min)	119.5 ± 38.0	121.7 ± 33.2
Diltiazem in Cardioplegia ($mg \cdot kg^{-1}$)	—	0.23 ± 0.05
at CPB discontinuation period		
A-V block	1 (4%)	10 (33%)*
Dopamine	18 (75%)	26 (87%)
Norepinephrine	7 (29%)	23 (77%)*
Isoproterenol	1 (4%)	5 (17%)
RA-pacing	3 (13%)	11 (37%)*
after CPB		
systolic blood pressure > 150 mmHg	4 (17%)	0 (0%)*
coronary spasm	10/87 (11.5%)	2/310 (0.6%)*

*: different from KCP group ($P < 0.05$).

Values are expressed as mean ± SD.

KCP = potassium cardioplegia. DLCP = diltiazem cardioplegia, CPB = cardiopulmonary bypass, A-V block = atrioventricular block, RA-pacing = right atrial-pacing.

and/or halothane were used when necessary. Nitroglycerin (0.3–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused intravenously during the operation. Systemic moderate hypothermia (22–28°C), topical cooling method (the heart was directly cooled with ice slush) and cardioplegia were applied for myocardial protection during cardiac arrest. The potassium cardioplegia consisted of 500 ml of 5% glucose solution, 15 mEq of potassium (30 mEq/L), and 10 units of insulin (20 units/L). Diltiazem cardioplegia I consisted of 500 ml of potassium cardioplegia and 0.15 $mg \cdot kg^{-1}$ (body weight) of diltiazem. Diltiazem cardioplegia II consisted of 500 ml of CPB blood, 7.5 mEq of potassium chloride (15 mEq/L), and 0.075 $mg \cdot kg^{-1}$ (body weight) of diltiazem. Cardioplegic solutions were given at the intervals of 25–35 min from cardioplegic line into the aortic root as required. In the diltiazem group, first, diltiazem cardioplegia I was administered and subsequently, diltiazem cardioplegia II was administered. Catecholamines such as dopamine and norepinephrine were used to maintain optimal systemic blood pressure after CPB.

Hemodynamic measurements were performed 1) before induction of anesthesia, 2) before CPB, 3) immediately after CPB, 4) one hour after CPB, and 5) two hours after CPB. Hemodynamic variables monitored were heart rate, systolic, diastolic and mean blood pressure, right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output. Cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular resistance, left and right ventricular stroke work indices were calculated by standard formulas.

All the data were presented as mean ± standard deviation. Hemodynamic values of both groups were compared by non-paired t-test, and continuous variance of hemodynamic data in each group was shown by analysis of variance (ANOVA). Scheffe's methods were used to specify differences when ANOVA indicated a significant difference. Clinical data were compared by Chi square test. Difference was considered to be statistically significant at a P value of less than 0.05.

Results

In the preoperative data, age and right atrial pressure showed significant difference between both groups ($P < 0.05$) (table 1,3). Coronary artery spasm was recognized in 2 of the diltiazem group (0.6%), and in 10 of the potassium group (11.5%) (table 2). After CPB, heart rate significantly increased in both groups, but immediately after CPB it was significantly lower in the diltiazem group (101.6 ± 12.1/min) than in the potassium group (111.2 ± 17.2/min) ($P < 0.05$) (table 3, fig. 1). Mean blood pressure decreased after CPB in both groups, but showed a significantly lower value in the diltiazem group (53.7 ± 11.4 mmHg) than in the potassium group (64.1 ± 7.3 mmHg) ($P < 0.05$) (table 3, fig. 1). Cardiac index was also lower in the diltiazem group and remained so until two hours after CPB. The diltiazem group also showed lower right atrial pressure, pulmonary artery pressure, left ventricular stroke work index, and right ventricular stroke work index after CPB, than the potassium group (table 3). There was no significant difference between both groups in systemic vascular resistance (table 3, fig. 2).

At the time of discontinuation of CPB, 5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine was required in 26 of the diltiazem group (87%), and in 18 of the potassium group (75%) (table 2). Moreover, 0.03 to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of norepinephrine was required in 23 of the diltiazem group (77%) and 7 of the potassium group (29%). The number of patients treated with norepinephrine was significantly larger in the diltiazem group than in the potassium group. One hour after CPB, the difference in mean blood pressures between both groups was not significant, but blood pressure tended to be lower in the diltiazem group than in the potassium group. After CPB, there were no patients in the diltiazem group whose systolic blood pressure was elevated above 150 mmHg, but 4 patients in the potassium cardioplegia group showed hypertension (> 150 mmHg).

After the discontinuation of CPB, 10

Table 3. Hemodynamic data during operation

		(1)	(2)	(3)	(4)	(5)
HR	DLCP	76.6 ± 15.1	74.5 ± 13.7	101.6 ± 12.1*	102.2 ± 13.0*	100.3 ± 13.7*
	KCP	80.9 ± 15.3	81.1 ± 16.3	111.2 ± 17.2*	115.4 ± 14.5*	113.5 ± 16.1*
	t-test	NS	NS	$P < 0.05$	$P < 0.05$	$P < 0.05$
mBP	DLCP	94.8 ± 13.2*	79.9 ± 8.4	53.7 ± 11.4*	65.4 ± 12.7*	70.1 ± 12.3
	KCP	99.8 ± 12.9*	83.5 ± 10.4	64.1 ± 7.3*	70.9 ± 11.1*	75.3 ± 9.6
	t-test	NS	NS	$P < 0.05$	NS	NS
mPA	DLCP	14.8 ± 4.5	9.8 ± 3.3	12.9 ± 3.3*	15.1 ± 4.3*	14.9 ± 4.2*
	KCP	13.3 ± 4.2	10.4 ± 2.4	15.5 ± 3.6	16.2 ± 2.3*	16.2 ± 3.0*
	t-test	NS	NS	$P < 0.05$	NS	NS
RA	DLCP	5.3 ± 2.2	3.3 ± 2.7	4.1 ± 2.5	5.5 ± 3.5*	5.8 ± 2.5*
	KCP	3.8 ± 2.0	4.5 ± 1.8	5.8 ± 1.7	7.0 ± 2.4	7.7 ± 2.1
	t-test	$P < 0.05$	NS	$P < 0.05$	NS	$P < 0.05$
PCWP	DLCP	7.8 ± 2.8	4.7 ± 2.8	6.6 ± 2.9	7.5 ± 3.5*	7.6 ± 2.6*
	KCP	6.7 ± 3.5	5.7 ± 1.7	8.6 ± 3.3*	9.0 ± 2.2*	9.7 ± 2.7*
	t-test	NS	NS	NS	NS	$P < 0.05$
CI	DLCP	3.13 ± 0.89	2.08 ± 0.37	3.33 ± 0.58*	3.84 ± 0.96*	2.98 ± 0.90*
	KCP	3.43 ± 0.78	2.07 ± 0.50	4.44 ± 1.26*	4.35 ± 0.90*	3.95 ± 1.19*
	t-test	NS	NS	$P < 0.05$	NS	$P < 0.05$
SVR	DLCP	1502 ± 459*	1890 ± 411	764 ± 221*	827 ± 347*	1192 ± 506*
	KCP	1465 ± 367*	2048 ± 715	765 ± 306*	781 ± 239*	839 ± 250*
	t-test	NS	NS	NS	NS	$P < 0.05$
LVSWI	DLCP	51.7 ± 14.8*	29.8 ± 8.0	22.2 ± 6.6	29.0 ± 7.0	24.8 ± 7.4
	KCP	54.4 ± 13.4*	27.7 ± 8.3	31.6 ± 9.9	31.6 ± 6.3	28.8 ± 7.2
	t-test	NS	NS	$P < 0.05$	NS	NS
RVSWI	DLCP	6.3 ± 3.0*	3.0 ± 1.3	3.8 ± 1.4	5.2 ± 2.0*	3.6 ± 1.8
	KCP	5.6 ± 2.4*	2.2 ± 1.1	6.0 ± 2.7*	4.8 ± 1.6*	4.3 ± 1.9
	t-test	NS	NS	$P < 0.05$	NS	NS

(1): awake, (2): before CPB, (3): immediately after CPB, (4): 1 hour after CPB, (5): 2 hours after CPB.

Values are expressed as mean ± SD.

*: different from before CPB by ANOVA & Scheffe ($P < 0.05$).

HR = heart rate (/min), mBP = mean blood pressure (mmHg), mPA = mean pulmonary artery pressure (mmHg), RA = right atrial pressure (mmHg), PCWP = pulmonary capillary wedge pressure (mmHg), CI = cardiac index (L/min/m^2), SVR = systemic vascular resistance (dyn·sec/cm^2), LVSWI = left ventricular stroke work index (grm·m/m^2), RVSWI = right ventricular stroke work index (grm·m/m^2), CPB = cardiopulmonary bypass, DLCP = diltiazem cardioplegia, KCP = potassium cardioplegia.

of the diltiazem group (10/30: 33%) had atrio-ventricular block, whereas only one of the potassium group (1/24: 4%) had atrio-ventricular block. Right atrial pacing was applied to 11 of the diltiazem group (11/30: 37%), and to 3 of the potassium group (3/24: 13%) (table 2).

Discussion

During aorto-coronary bypass surgery, coronary artery spasm is a major complication which must be prevented if possible, and treated adequately when it occurs. Coronary artery spasm is noticed with sudden hypotension associated with electrocardiographic ST-segment elevation, sinus bradycardia, atrio-ventricular block, and paroxysms of ventricular tachycardia[12]. In the period from November 1982 to May 1983, 10 of 87 patients undergoing CPB in our institution who received potassium cardioplegia developed coronary artery spasm. Three of

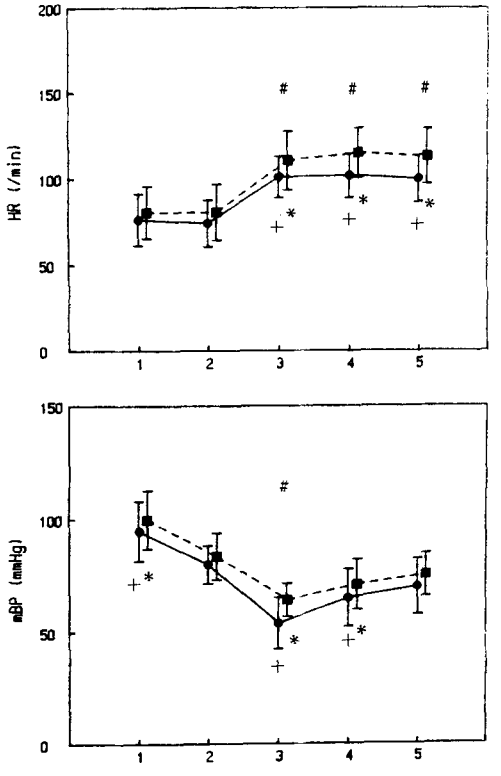

Fig. 1. Changes in heart rate (HR) and mean blood pressure (mBP) before and after cardiopulmonary bypass (CPB).

Heart rate after CPB increased in both groups, and was lower in DLCP group than in KCP group. Mean blood pressure decreased after CPB in both groups and was lower in DLCP group than in KCP group immediately after CPB.

1: awake, 2: before CPB, 3: immediately after CPB, 4: one hour after CPB, 5: two hours after CPB.

●——●: DLCP group, ■ – – ■: KCP group.

#: Significantly different between both groups by t-test ($P < 0.05$).

+: Significantly different from values before CPB by ANOVA & Scheffe in DLCP group ($P < 0.05$).

*: Significantly different from values before CPB by ANOVA & Scheffe in KCP group ($P < 0.05$).

DLCP: diltiazem cardioplegia, KCP: potassium cardioplegia.

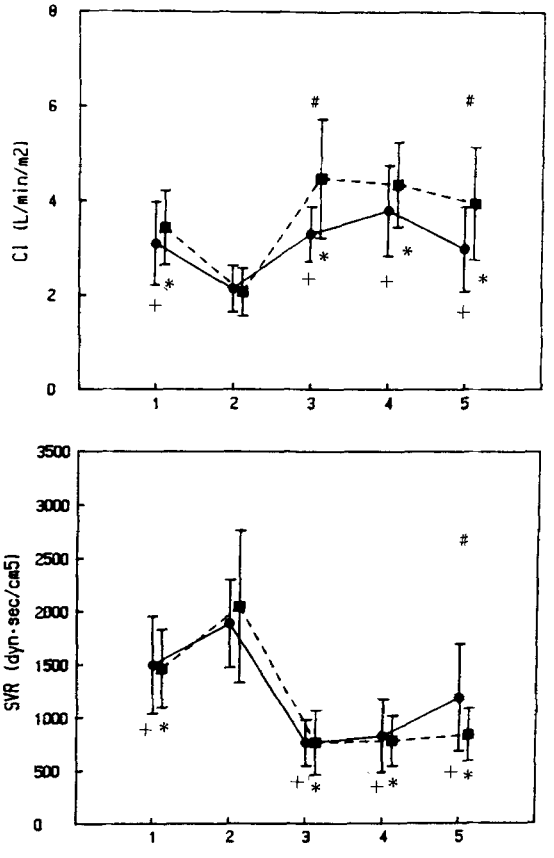

Fig. 2. Changes in cardiac index (CI) and systemic vascular registance (SVR) before and after cardiopulmonary bypass (CPB).

Cardiac index was lower in DLCP group than in KCP group for two hours after CPB. Systemic vascular resistance was lower after CPB than values before CPB in both groups and no difference was seen between both groups after CPB.

1: awake, 2: before CPB, 3: immediately after CPB, 4: one hour after CPB, 5: two hours after CPB.

●——●: DLCP group, ■ – – ■: KCP group.

#: Significantly different between both groups by t-test ($P < 0.05$).

+: Significantly different from values before CPB by ANOVA & Scheffe in DLCP group ($P < 0.05$).

*: Significantly different from values before CPB by ANOVA & Scheffe in KCP group ($P < 0.05$).

DLCP: diltiazem cardioplegia, KCP: potassium cardioplegia.

them fell into myocardial infarction and two died postoperatively. Possible causes of intraoperative spasm include elevation of blood pH, excessive alpha-adrenergic activity, physical manipulation of a coronary artery during dissection for placement of a bypass graft, and release of vasoconstrictor substances by platelets[12]. Insufficient myocardial protection during CPB may also be responsible for spasm after CPB. As a result of using diltiazem cardioplegia since May 1983, the incidence of spasm has been significantly reduced (only 2 of 310 patients (0.6%)) between May 1983 and March 1987. When diltiazem is contained in a cardioplegic solution, it usually dilates the coronary artery and efficiently gets to the every cardiac cell. In this way it ensures cardiac arrest by inhibiting pacemaking cells in which impulse is generated by the slow calcium current, and by blocking calcium flux into cardiac constriction cells[5,6]. Diltiazem is also reported to protect the myocardium from reperfusion injury by preventing calcium influx during the reperfusion period[13]. Similar beneficial effects have been observed in other calcium channel blockers such as nifedipine or verapamil[10,11].

The patients who received the diltiazem cardioplegia showed significant hypotension immediately after CPB and lower cardiac index during the two hours after CPB. They required norepinephrine more frequently than the patients who received the potassium cardioplegia. This suggests that the diltiazem cardioplegia may have caused negative inotropic effect after CPB, because a large dose of diltiazem would spread to the myocardium during CPB and remain in high concentration even after CPB. In our experience, the plasma concentration of diltiazem is about 200 $ng \cdot ml^{-1}$ immediately after CPB[9], and therefore, during aortic cross-clamp, a larger quantity of diltiazem might affect the myocardium. Kapur et al. demonstrated that when the plasma level of diltiazem was less than 200 $ng \cdot ml^{-1}$, only mild bradycardia and prolongation of atrioventricular conduction were observed in the presence of enflurane, but plasma diltiazem levels of between 200–500 $ng \cdot ml^{-1}$ were associated with decreased blood pressure and left ventricular dp/dt[14]. Probably, diltiazem, when employed as an additive to cardioplegic solution, might have greater depressant effects on the myocardium compared with its use in intravenous administration. Moreover, since the biological half life of intravenous diltiazem is as long as 1.9 hr, diltiazem may remain effective for several hours. In our study, left ventricular stroke work index and right ventricular stroke work index were low immediately after CPB in the diltiazem group and no patients showed hypertension (systolic blood pressure > 150 mmHg) for two hours after CPB. This may be evidence of the effects of diltiazem cardioplegia.

After the administration of diltiazem cardioplegia, sympathomimetic drugs such as dopamine and norepinephrine were frequently required to maintain optimal blood pressure. Van Breemen et al.[15] reported that the occurrence of vasoconstriction with low dosage of norepinephrine was directly related to calcium flux into vascular smooth muscle cells, and could be prevented by diltiazem. Therefore we used a small dose of norepinephrine (0.03–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in anticipation of the counteractive effect on calcium antagonists, and could maintain proper blood pressure.

Heart rate after CPB was significantly lower in the diltiazem group than in the potassium group. This seems to be due to the inhibition of the sinus node by diltiazem and contribute to the reduction of myocardial oxygen consumption. However, 11 patients (37%) receiving diltiazem cardioplegia temporarily needed right atrial pacing because of remarkable sinus bradycardia. Furthermore, the patients who received diltiazem cardioplegia showed a high incidence of atrio-ventricular block (33%) after DC cardioversion, probably due to excessive inhibition of the atrio-ventricular node by diltiazem.

Concerning the adequacy of the diltiazem dose to be added to cardioplegic solution, Christakis et al.[4] suggested that 150–250 $\mu g \cdot kg^{-1}$ (body weight) would be adequate

to minimize postoperative artificial pace maker dependency and to improve postoperative myocardial metabolism. Grondin et al.[8] reported that diltiazem cardioplegia was safe at as wide a dosage range as 150–650 $\mu g \cdot kg^{-1}$. Although the dosage limit in our study (230 ± 50 $\mu g \cdot kg^{-1}$) complied with the above ranges, the consequent effects of diltiazem cardioplegia on hemodynamics after CPB offered both merit and demerit. Meanwhile, Yamamoto et al.[7] proposed 0.5 $\mu mol \cdot \ell^{-1}$ (0.21 $mg \cdot \ell^{-1}$) as the optimal concentration of diltiazem in cardioplegia, and claimed that diltiazem offered no improvement in protection under conditions of hypothermic (at 20°C) ischemic arrest. Therefore, adequate dosage of diltiazem and its application should be studied further so that diltiazem cardioplegia could effect sufficient myocardial protection and prevention of coronary spasm, and would cause no remarkable cardiovascular depression after CPB.

In conclusion, diltiazem is effective for prevention of coronary artery spasm after CPB, but it shows negative inotropic and chronotropic effects when employed as an additive to cardioplegic solution.

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