British Journal of Anaesthesia 88 (1): 78–86 (2002)

BJA

LABORATORY INVESTIGATIONS

Effects of intracoronary calcium chloride on regional oxygen balance and mechanical function in normal and stunned myocardium in dogs

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Background. Brief myocardial ischaemia has been demonstrated to result in mechanical and coronary endothelial dysfunction, in which calcium may play a role. We examined whether the mechanical and vascular responses to calcium are altered in postischaemic, reperfused myocardium.

Methods. Regional myocardial oxygen consumption ($M\dot{V}_{O_2}$), mechanical function and coronary blood flow (CBF) in response to calcium chloride (0.10, 0.25, 0.50 and 0.75 mg ml^{-1} of CBF) directly infused into the left anterior descending (LAD) artery were determined before (normal) and 30 min after a 15-min-period of LAD occlusion (stunned) in an open-chest canine model. Percentage segment shortening (%SS) and percentage postsystolic shortening (%PSS) in the LAD territory were determined using ultrasonic crystals and CBF using a Doppler transducer. Myocardial extraction of oxygen (E_{O_2}) and lactate (E_{lac}) was calculated.

Results. The infusion of calcium chloride resulted in dose-dependent increases in %SS and $M\dot{V}_{O_2}$ but did not affect %PSS in normal myocardium. These changes were accompanied by parallel increases in CBF, resulting in no change in E_{O_2}. In stunned myocardium, the responses to calcium chloride were not significantly altered, with the exception of a reduction in %PSS. However, ischaemia and reperfusion itself significantly reduced %SS and E_{lac} and increased %PSS.

Conclusions. These data suggest that calcium chloride improves regional systolic and diastolic function both in normal and stunned myocardium. Calcium chloride is unlikely to cause direct coronary vasoconstriction or to deteriorate regional mechanical function in postischaemic myocardium.

Br J Anaesth 2002; **88**: 78–86

Keywords: heart, coronary circulation; ions, calcium; drugs, inotropic; dog

Accepted for publication: August 3, 2001

A brief ischaemic episode followed by reperfusion results in 'stunned' myocardium, in which the myocardial contractile function is impaired for a prolonged period in the absence of cell necrosis.[1] Myocardial stunning *per se* usually requires no therapy at all, as blood flow is normal and contractile function recovers spontaneously. However, if it is severe or involves parts of the left ventricle large enough to cause impairment of global ventricular function, it can be reversed with inotropic agents.[2–5]

Clinically, calcium is frequently used as an initial therapeutic agent to reverse acute postischaemic ventricular dysfunction during separation from cardiopulmonary bypass.[6] However, calcium has been observed to reduce coronary blood flow (CBF) in an isolated beating heart.[7] A

recent *in vivo* study also demonstrated that intracoronary calcium chloride caused direct coronary vasoconstriction, in addition to its inotropic action, in normal canine heart.[8]

On the other hand, the stunned myocardium is associated with decreased coronary flow reserve and vasodilator responsiveness.[9,10] Furthermore, it shows normal oxygen consumption ($M\dot{V}_{O_2}$), despite depressed contractile function, i.e. increased oxygen cost of contractility.[11] It is speculated that calcium may exaggerate the vasoconstrictor response and hence impair myocardial oxygen balance in the stunned myocardium. Indeed, it has been demonstrated that mechanical function is not as tightly coupled as CBF and $M\dot{V}_{O_2}$, and thus oxygen extraction (E_{O_2}) increased during inotropic stimulation with dobutamine in postischaemic canine myocardium.[5]

In addition, intracellular Ca^{2+} overloading during ischaemia and reperfusion has been implicated in the pathogenesis of myocardial stunning.[12] In an isolated rat heart, postischaemic myocardium was susceptible to Ca^{2+} influx and subsequent injury.[13] Administration of calcium may therefore deteriorate rather than improve regional function, by augmenting calcium overload in postischaemic myocardium. The seeming paradox of the clinical use and known pathophysiological effects of calcium remains to be explained. In the present work we studied the effects of calcium chloride on regional oxygen balance and mechanical function in the stunned myocardium.

Methods

The study was approved by the Institutional Review Board of Experimental Animal Research. Mongrel dogs of either sex, weighing 17–35 kg, were anaesthetized with thiopental sodium (10–15 mg kg^{-1} i.v.). After tracheal intubation, anaesthesia was maintained with enflurane (1.4% end-tidal; Datex, Helsinki, Finland) in 100% oxygen by positive-pressure ventilation. In eight dogs, anaesthesia was induced with an i.v. bolus injection of fentanyl 100 μg kg^{-1} and midazolam 0.6 mg kg^{-1} and maintained by continuous infusion at rates of 20.0 μg kg^{-1} h^{-1} and 0.6 mg kg^{-1} h^{-1} respectively. Tidal volume and respiratory rate were adjusted to maintain end-tidal carbon dioxide concentration between 4.5 and 5.5%. To obtain muscle relaxation, vecuronium bromide 0.1 mg kg^{-1} was used initially as a bolus and thereafter infused at 0.05 mg kg^{-1} h^{-1}. Body temperature and electrocardiogram were monitored continuously. Ringer's lactate solution was administered i.v. at 5 ml kg^{-1} h^{-1}.

A left thoracotomy was performed via the fifth intercostal space and the heart was suspended in a pericardial cradle. Instruments were implanted in and around the heart as shown in Fig. 1. A Doppler transit time flow probe (Transonic Systems, Ithaca, NY, USA) was placed around the main pulmonary artery to measure cardiac output, and another flow probe was placed around the left anterior descending coronary artery (LAD) distal to the first diagonal branch for continuous blood flow measurement. A rubber band was placed around the LAD immediately distal to the flow probe to serve as an occluder. For the infusion of drugs, a 24-gauge catheter was inserted into the proximal LAD. A pair of ultrasonic dimension transducers (Medical Research Technology, Gaithersburg, MD, USA) were implanted approximately 10 mm apart in the subendocardium of a region of anterior wall that demonstrated myocardial cyanosis during a brief test occlusion of the LAD. A catheter-tipped micromanometer (SPR-524; Millar Instruments, Houston, TX, USA) was inserted directly into the left ventricle via an apical incision for the measurement of left ventricular pressure (LVP). The first derivative of LVP ($+dP/dt_{max}$ and $-dP/dt_{min}$) was obtained by electronic differentiation. The right femoral artery was cannulated for measurement of aortic pressure with a catheter-tipped micromanometer and for blood sampling to measure arterial oxygen and lactate contents. An 18-gauge catheter was inserted into the left atrium for the measurement of luminal pressure (Datex, Helsinki, Finland) and a 24-gauge catheter into the anterior interventricular vein at the same level as the LAD occluder for measurement of coronary venous oxygen and lactate concentrations.[14]

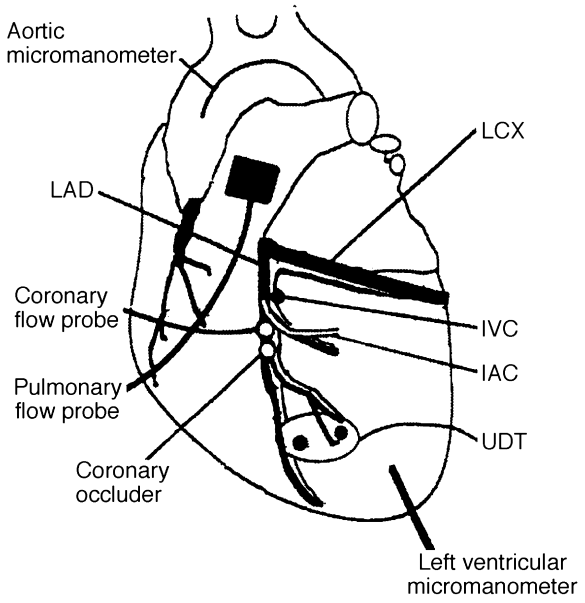

Fig 1 Schematic presentation of the experimental preparation. LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; IVC=intravenous catheter; IAC=intra-arterial catheter; UDT=ultrasonic dimension transducers.

Oxygen (Gem Premier; Instrumentation Laboratory, Lexington, MS, USA) and lactate concentrations (Vitros 950; Ortho-Clinical Diagnostics, Rochester, NY, USA) were measured in blood drawn simultaneously from the coronary vein and artery. $M\dot{V}_{O_2}$ of the anterior myocardial wall was calculated by multiplying the arteriovenous oxygen difference by total LAD flow. E_{O_2} and myocardial lactate extraction (E_{lac}) (as a percentage) were calculated by

dividing the arteriovenous difference by the arterial content. Plasma Ca^{2+} concentrations were also measured from the anterior interventricular venous blood with a blood gas analyser (Gem Premier; Instrumentation Laboratory, Lexington, MS, USA).

After a stabilization period of 60 min, pre-infusion mechanical and haemodynamic data were collected in one group of 16 dogs (series 1). Simultaneous measurements were obtained of arterial and coronary venous oxygen and lactate concentrations (metabolic data). The animals then received intracoronary infusions of calcium chloride with a syringe pump (STC 524; Terumo, Japan). Calcium chloride was infused in incremental concentrations of 0.10, 0.25, 0.50 and 0.75 mg ml^{-1} LAD flow for 3–5 min, each administered 8–10 min apart. The infusion rate was calculated by multiplying the desired concentration by LAD blood flow, resulting in a rate between 0.3 and 2.0 ml min^{-1}. All measurements except metabolic data at 0.50 mg ml^{-1} were repeated at the end of each dose and 5 min after calcium chloride infusion was stopped. Because mechanical and CBF responses to calcium chloride at 0.50 mg ml^{-1} did not differ significantly from those at 0.75 mg ml^{-1} and myocardial oxygen balance was well maintained, metabolic data at 0.50 mg ml^{-1} were not obtained. After one series of experiments in normal myocardium, all dogs were subjected to a 15-min LAD occlusion and subsequent reperfusion to stun the myocardium. Approximately 30 min after the onset of reperfusion, when haemodynamic and flow values were stable, the same calcium chloride infusion protocol was repeated.

In eight dogs (series 2), experiments were performed to evaluate whether preischaemic administration of calcium chloride altered postischaemic contractile responsiveness (preconditioning against postischaemic contractile dysfunction) and whether volatile anaesthetics affected postischaemic myocardial responsiveness. To address the first issue, calcium chloride was infused only in the postischaemic myocardium. To address the second issue, fentanyl–-midazolam instead of enflurane was used to maintain anaesthesia. The responses to intracoronary infusions of calcium chloride (0.10, 0.25, 0.50 and 0.75 mg ml^{-1} of LAD flow) were assessed using a protocol similar to that used for series 1.

Data acquisition and analysis

Blood flow (main pulmonary artery and LAD), the segmental dimension of the anterior wall and pressures (LVP and mean aortic pressure) were monitored continuously and recorded on a polygraph (TA 5000; Gould, Cleveland, OH, USA). End-systolic segment length (ESL) was determined approximately 20 ms before peak $-dP/dt_{min}$ and end-diastolic segment length (EDL) was determined at the onset of left ventricular isovolumetric contraction.[15] Steady beat data were obtained from three to five cardiac cycles. Regional myocardial contractility was determined using percentage segment shortening (%SS), calculated from the equation $\%SS=[(EDL-ESL)/EDL]\times100$. Percentage postsystolic shortening (%PSS), as a regional diastolic function, was calculated from the equation $\%PSS=[(ESL-L_{min}D)/(L_{max}-L_{min}D)]\times100$, where $L_{min}D$ and L_{max} are minimum length during diastole and maximum length in an overall contraction, respectively. Coronary perfusion pressure was calculated as aortic diastolic pressure minus left atrial pressure.

At the end of the experiment, the heart was stopped by intra-atrial injection of concentrated potassium chloride solution. The area supplied by the LAD artery was defined by injection of Evans blue into the vessel at the site of the flow transducer. Weighing of the stained muscle allowed calculation of mean flow in ml min^{-1} per 100 g of muscle. The LAD perfusion territory was 24.3 (5.6)% of the total left ventricular mass.

Statistical analysis

All data are presented as mean (SD). They were analysed using StatView software version 4.0 (Abacus Concepts, Berkeley, CA, USA) on a Macintosh computer. Statistical analysis of the calcium chloride responses in normal and stunned myocardium was performed by two-way analysis of variance for repeated measures followed by Dunnett's *t* test. Comparisons between the pre-infusion values of normal and stunned myocardium were made with the paired Student's *t*-test. Enflurane- and fentanyl–midazolam-anaesthetized groups were compared using the Mann–Whitney *U*-test. Linear regression analysis was used to examine the relationship between CBF and $M\dot{V}_{O_2}$ at all doses of calcium chloride in series 1. Significance was assumed when $P<0.05$.

Results

Two of 18 dogs anaesthetized with enflurane produced lactate before the experiment and three died of ventricular fibrillation immediately after the onset of reperfusion, whereas three of eight dogs anaesthetized with fentanyl–-midazolam developed ventricular fibrillation during coronary occlusion or immediately after the onset of reperfusion. These were excluded from data analysis.

Table 1 shows systemic haemodynamics in normal and stunned myocardium in enflurane-anaesthetized dogs. Calcium chloride was without significant effects on these variables in normal myocardium. However, there was a dose-dependent increase in $+dP/dt_{max}$. LAD occlusion produced a small increase in heart rate and left atrial pressure and decreased mean aortic pressure, $+dP/dt_{max}$, $-dP/dt_{min}$ and cardiac index. They quickly returned towards baseline values at the onset of reperfusion, with the exception of $+dP/dt_{max}$ and $-dP/dt_{min}$, which remained lower than their baseline values. In stunned myocardium,

Table 1 Effects of increasing infusion rate of intracoronary calcium chloride on systemic haemodynamics before (normal) and 30 min after a 15-min coronary occlusion (stunned) in enflurane-anaesthetized dogs. HR = heart rate; MAP = mean aortic pressure; $+dP/dt_{max}$= maximum positive left ventricular pressure derivative; $-dP/dt_{min}$= minimum negative left ventricular pressure derivative; LAP = left atrial pressure; CI = cardiac index; CPP = coronary perfusion pressure; CBF = coronary blood flow. Results are mean (SD) of data from 13 dogs. *P<0.05 compared with pre-infusion values; †P<0.05 compared with normal myocardium

Variable	Condition	Pre-infusion	Calcium chloride (mg ml^{-1} CBF)			
			0.10	0.25	0.50	0.75
HR (beats min^{-1})	Normal	132 (16)	131 (18)	131 (17)	130 (16)	131 (21)
	Stunned	133 (18)	133 (19)	134 (18)	136 (23)	139 (23)
MAP (mm Hg)	Normal	87 (12)	87 (12)	89 (13)	89 (14)	92 (15)
	Stunned	84 (10)	84 (10)	84 (10)	84 (9)	84 (8)
$+dP/dt_{max}$ (mm Hg s^{-1})	Normal	1685 (497)	1749 (489)	1873 (547)*	1896 (617)*	1987 (646)*
	Stunned	1316 (190)†	1403 (203)	1488 (266)*	1664 (209)*	1787 (251)*
$-dP/dt_{min}$ (mm Hg s^{-1})	Normal	2480 (501)	2526 (504)	1495 (438)	2478 (493)	2421 (544)
	Stunned	2149 (372)†	2165 (438)	2090 (429)	2050 (513)	2182 (426)
LAP (mmHg)	Normal	5.2 (1.0)	5.1 (1.0)	5.3 (1.0)	5.3 (1.1)	5.3 (1.2)
	Stunned	5.9 (0.9)	5.8 (0.9)	5.4 (0.9)	5.3 (1.1)	5.2 (0.9)
CI (litre min^{-1}m^{-2})	Normal	2.3 (0.5)	2.3 (0.5)	2.2 (0.5)	2.2 (0.6)	2.1.(0.5)
	Stunned	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)	2.1 (0.5)	2.1 (0.6)
CPP (mmHg)	Normal	73 (11)	74 (8)	75 (7)	76 (8)	76 (9)
	Stunned	71 (10)	71 (11)	72 (8)	72 (10)	72 (11)

Table 2 Effects of increasing infusion rate of intracoronary calcium chloride on regional mechanical function before (normal) and 30 min after a 15-min coronary occlusion (stunned) in enflurane-anaesthetized dogs. %SS = percentage systolic shortening; EDL = end-diastolic segment length; ESL = end-systolic segment length, %PSS = percentage postsystolic shortening. All length measures are normalized to an initial end-diastolic length of 10 mm at baseline. Results are mean (SD) of data from 13 dogs. *P<0.05 compared with pre-infusion values; †P<0.05 compared with normal myocardium

Variable	Condition	Pre-infusion	Calcium chloride (mg ml^{-1} CBF)			
			0.10	0.25	0.50	0.75
%SS	Normal	16.9 (4.3)	18.1 (4.5)*	20.2 (4.8)*	22.4 (5.1)*	23.6 (5.6)*
	Stunned	7.4 (4.5)†	9.9 (4.7)*	14.3 (5.9)*	18.8 (4.9)*	21.5 (6.7)*
EDL (mm)	Normal	10.0 (0.00)	9.95 (0.10)	9.88 (0.23)*	9.84 (0.13)*	9.83 (0.19)*
	Stunned	10.5 (0.37)†	10.27 (0.36)	10.20 (0.33)*	10.03 (0.25)*	9.88 (0.35)*
ESL (mm)	Normal	8.4 (0.43)	8.24 (0.43)	7.99 (0.51)*	7.79 (0.52)*	7.65 (0.51)*
	Stunned	9.68 (0.78)†	9.37 (0.85)	9.04 (0.89)*	8.34 (0.54)*	8.04 (0.59)*
%PSS	Normal	5.9 (2.9)	5.5 (3.6)	4.2 (4.5)	3.5 (6.4)	3.7 (5.6)
	Stunned	32.7 (17.6)†	20.1 (17.6)*	14.7 (19.8)*	5.5 (4.7)*	5.8 (5.3)*

the effects of calcium chloride were similar to those in normal myocardium.

Table 2 shows the effects of calcium chloride on regional mechanical function in normal and stunned myocardium in enflurane-anaesthetized dogs. Calcium chloride caused dose-dependent increases in %SS and decreases in ESL but did not affect %PSS in normal myocardium. LAD occlusion rapidly increased EDL [from 10.0 to 10.8 (0.38), P<0.01] and %PSS [from 5.9 (2.9) to 76 (10)%, P<0.01], systolic bulging apparent within 1–3 min. Subsequent reperfusion produced a transient increase in %SS followed by a gradual decline to 7.4 (4.5)% (44% of preischaemic baseline) at 30 min of reperfusion. In stunned myocardium, the responses to calcium chloride were not altered compared with those in normal myocardium, except for a progressive reduction in %PSS. When calcium chloride was stopped, %SS rapidly returned towards, but not below, pre-infusion values in stunned myocardium (data not shown).

Table 3 shows the effects of calcium chloride on CBF and metabolic data in normal and stunned myocardium in enflurane-anaesthetized dogs. Calcium chloride caused dose-dependent increases in $M\dot{V}_{O_2}$ and CBF in normal myocardium. After LAD occlusion and reperfusion, metabolic and CBF responses to calcium chloride were not altered significantly, while there was a slight decrease in $M\dot{V}_{O_2}$ from preischaemic baseline values of normal myocardium (P<0.05), despite severely impaired contractile function. During calcium chloride infusion, CBF increased linearly in relation to $M\dot{V}_{O_2}$ in normal and stunned myocardium (Fig. 2), such that that E_{O_2} remained unchanged. Plasma Ca^{2+} concentrations in the anterior interventricular vein were dose-dependently increased by the administration of calcium chloride to a similar extent in normal and stunned myocardium, implying that coronary veins draining the LAD region were correctly cannulated.

Figure 3 shows the effects of calcium chloride on lactate extraction in enflurane-anaesthetized dogs. Although significantly reduced by the ischaemia and reperfusion insult itself, E_{lac} was not affected by calcium chloride either in normal or stunned myocardium. However, four of 13

Table 3 Effects of increasing infusion rate of intracoronary calcium chloride on coronary blood flow (CBF) and metabolism before (normal) and 30 min after a 15-min coronary occlusion (stunned) in enflurane anaesthetized dogs. $M\dot{V}_{O_2}$ = myocardial oxygen consumption; E_{O_2} = myocardial oxygen extraction. Results are mean (SD) of data from 13 dogs. *P<0.05 compared with pre-infusion values; †P<0.05 compared with normal myocardium

Variable	Condition	Pre-infusion	Calcium chloride (mg ml^{-1} CBF)			
			0.10	0.25	0.50	0.75
CBF (ml min^{-1} 100 g^{-1})	Normal	73.1 (7.0)	78.9 (8.9)*	86.6 (9.4)*	95.2 (10.1)*	101.5 (9.9)*
	Stunned	70.9 (6.4)	78.0 (6.7)*	86.4 (6.0)*	93.0 (10.3)*	99.5 (11.6)*
Arterial P_{O_2} (mm Hg)	Normal	380 (67)	378 (65)	383 (65)	–	383 (65)
	Stunned	389 (85)	387 (84)	388 (85)	–	389 (85)
Coronary venous P_{O_2} (mm Hg)	Normal	30.4 (3.5)	30.7 (3.3)	30.5 (2.9)	–	30.8 (3.4)
	Stunned	32.2 (4.9)	32.5 (5.0)	32.2. (5.0)	–	31.7 (3.8)
$M\dot{V}_{O_2}$ (ml min^{-1} 100 g^{-1})	Normal	7.1 (1.5)	7.6 (1.6)*	8.4 (1.8)*	–	9.9 (2.1)*
	Stunned	6.3 (1.3)†	6.9 (1.3)*	8.0 (1.8)*	–	9.0 (2.1)*
E_{O_2} (%)	Normal	52.1 (8.2)	52.5 (7.3)	52.5 (6.9)	–	52.5 (6.9)
	Stunned	49.4 (9.0)†	49.8 (8.6)	50.5 (9.1)	–	50.7 (9.1)
Ca^{2+} in coronary vein (mmol litre^{-1})	Normal	1.08 (0.13)	1.68 (0.43)*	2.96 (0.59)*	–	5.03 (0.97)*
	Stunned	1.14 (0.11)	1.70 (0.47)*	2.88 (0.49)*	–	5.29 (0.72)*

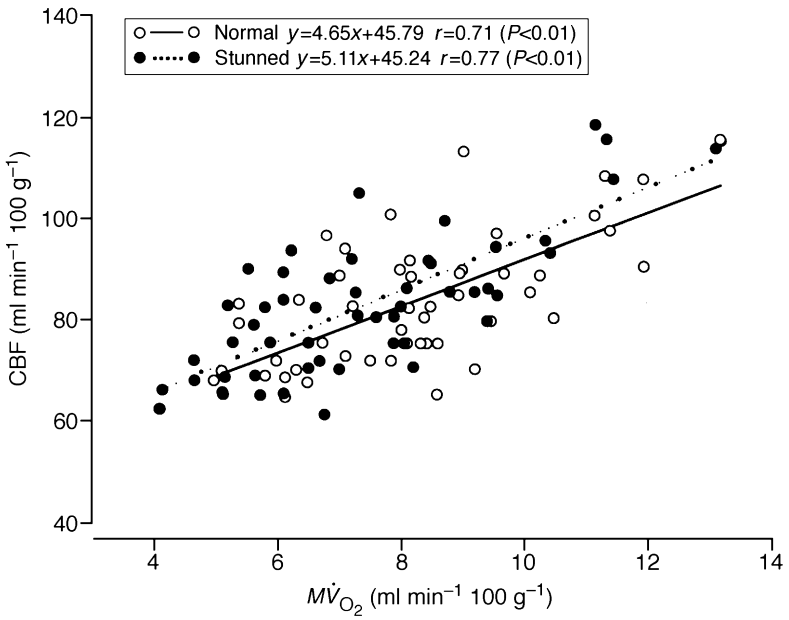

Fig 2 Relationship between myocardial oxygen consumption ($M\dot{V}_{O_2}$) and coronary blood flow (CBF) during intracoronary calcium chloride infusion in normal and stunned myocardium in enflurane anaesthetized dogs (n=13). In both normal and stunned myocardium, CBF increased in parallel with $M\dot{V}_{O_2}$.

animals anaesthetized with enflurane showed lactate production with the highest dose of calcium chloride in stunned myocardium.

Figure 4 compares the effects of calcium chloride on %SS, $M\dot{V}_{O_2}$, CBF and E_{O_2} in stunned myocardium in enflurane- and fentanyl–midazolam-anaesthetized dogs. Calcium chloride produced similar increases in %SS and $M\dot{V}_{O_2}$. The increase in CBF was proportional to $M\dot{V}_{O_2}$, and therefore E_{O_2} remained unchanged in both groups. In addition, systemic haemodynamic variables, including cardiac index, $+dP/dt_{max}$ and heart rate, did not differ significantly between enflurane- and fentanyl–midazolam-anaesthetized dogs (data not shown).

Discussion

The present study demonstrated that calcium chloride improved regional contractile and diastolic function in stunned canine myocardium. In addition, %SS returned to the postischaemic baseline value after discontinuation of inotropic stimulation with calcium chloride. Indeed, restoration of normal contractile capability during infusion of calcium has been observed in isolated globally ischaemic rat hearts[16] and *in vivo* regionally ischaemic hearts in dogs[3 12] and pigs.[4 17] These findings are contradictory to the previous notion that Ca^{2+} overloading occurring during ischaemia and reperfusion is causally related to the pathogenesis of

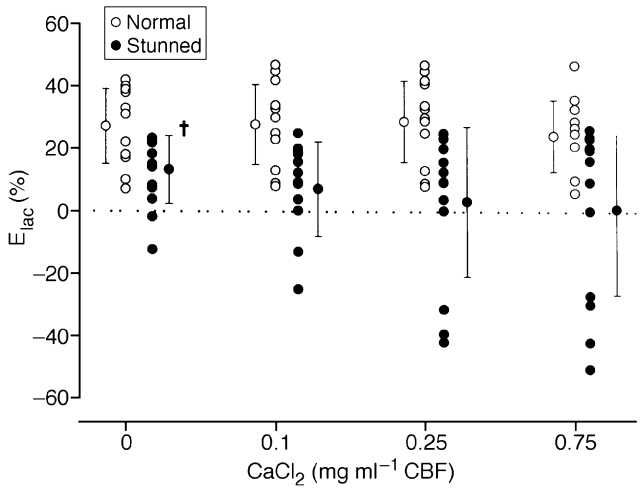

Fig 3 Effects of calcium chloride on lactate extraction (E_{lac}) in normal and stunned myocardium in enflurane-anaesthetized dogs (n=13). E_{lac} was not significantly affected by calcium chloride either in normal or stunned myocardium. Data are skewed and therefore presented as a dot plot with mean (SD). The ischaemia and reperfusion insult itself significantly reduced E_{lac}. $^{\dagger}P<0.05$ compared with normal myocardium.

myocardial stunning.[12] Moreover, calcium chloride administered early during reperfusion has been shown to elicit a dose-dependent deterioration in ventricular function in the isolated postischaemic rat heart.[13] Viable cells may restore control of cytoplasmic Ca^{2+} rapidly after ischaemia, and hence intracellular Ca^{2+} levels return to a baseline value after 20 min of reperfusion.[18] Collectively, the data suggest that calcium chloride may improve rather than deteriorate regional function if administered after, but not during, the early reperfusion period.

Vascular dysfunction may occur even after a short period of ischaemia.[9 10] The vascular response to endothelium-dependent dilators (e.g. acetylcholine) was reduced, whereas that to constrictors (e.g. the thromboxane mimic U46619) was enhanced after 15 min of regional ischaemia in canine hearts *in situ*.[10] Therefore, the vascular response to calcium chloride may differ between normal and stunned myocardium. However, the response to calcium chloride, increased CBF with no significant changes in coronary venous oxygen tension and E_{O_2}, did not differ significantly between normal and stunned myocardium (Table 3). Similarly, Buffington and Rothfield[4] observed an appropriate increase in CBF when regional contractility was stimulated by calcium chloride in stunned porcine myocardium. These findings suggest that, in stunned myocardium, calcium chloride does not interfere with normal metabolic vasoregulation but maintains CBF in proportion to the myocardial oxygen demand.

In contrast, Crystal and colleagues[8] demonstrated that intracoronary calcium chloride produced direct vasoconstriction and impaired coupling of CBF to the augmented myocardial oxygen demand in normal myocardium of dogs anaesthetized with fentanyl–midazolam. The discrepancy between these studies is not readily explained. It has been shown that volatile anaesthetics decrease Ca^{2+} sensitivity in rat aortic vascular smooth muscle *in vitro*[19] and produce coronary vasodilation directly in *in situ* canine hearts.[20] However, the vascular responses to calcium chloride were similar in fentanyl–midazolam- and enflurane anaesthetized dogs in the present study (Fig. 4). It is unlikely that anaesthetics are responsible for the discrepancy between these studies. Another possible explanation may include different experimental methods. Crystal and colleagues[8] used an extracorporeal perfusion system with a pressurized reservoir to keep coronary perfusion pressure constant, whereas we administered calcium chloride directly into the LAD. However, the coronary perfusion pressure was not affected by calcium chloride in either study.

The markedly reduced contractile function has been associated with an unaltered $M\dot{V}_{O_2}$ in stunned myocardium.[11] If contractile function increases at a higher energy cost in stunned myocardium, an elevated CBF would be expected for a given level of function (assuming unchanged E_{O_2}). However, the CBF response in relation to segment shortening was similar in normal and stunned myocardium in the present study. Chiu and colleagues[21] have demonstrated that regional inotropic stimulation with isoproterenol restores synchrony and regional work in stunned myocardium without greatly affecting $M\dot{V}_{O_2}$ in dogs. They speculated that myocardial stunning produced asynchrony between force development and segment shortening, thereby decreasing systolic regional work (but not total work) to a greater extent than $M\dot{V}_{O_2}$. It is likely that inotropic drugs, including calcium chloride, do not increase total mechanical work but restore the synchrony, resulting in no greater increases in CBF relative to regional mechanical work in stunned myocardium.

Although systolic function associated with the use of inotropic drugs has been studied extensively in stunned myocardium, the diastolic function has been overlooked. In the present study, calcium chloride did not affect peak $-dP/dt_{min}$ but produced a progressive reduction in %PSS (Table 2). Similarly, Schlack and colleagues[22] observed that intracoronary norepinephrine did not affect peak $-dP/dt_{min}$ but reduced postejection wall thickening in an open-chest canine model. It is also likely that calcium chloride improves early diastolic function. On the other hand, peak $-dP/dt_{min}$ has been demonstrated to reflect changes in contractility (i.e. peak ventricular pressure) rather than relaxation in regionally ischaemic canine hearts.[23] The unaltered aortic pressure during the infusion of calcium chloride in the present study may be related to the unaltered peak $-dP/dt_{min}$. There has been debate about whether calcium chloride increases chamber stiffness (late diastolic dysfunction) in postischaemic myocardium. Gao and colleagues[24] observed that, in response to supraphysiological increases in $[Ca^{2+}]_o$, diastolic $[Ca^{2+}]_i$ and tone increased in stunned trabeculae, with frequent occurrence of after-contractions in the isolated rat heart. They speculated that

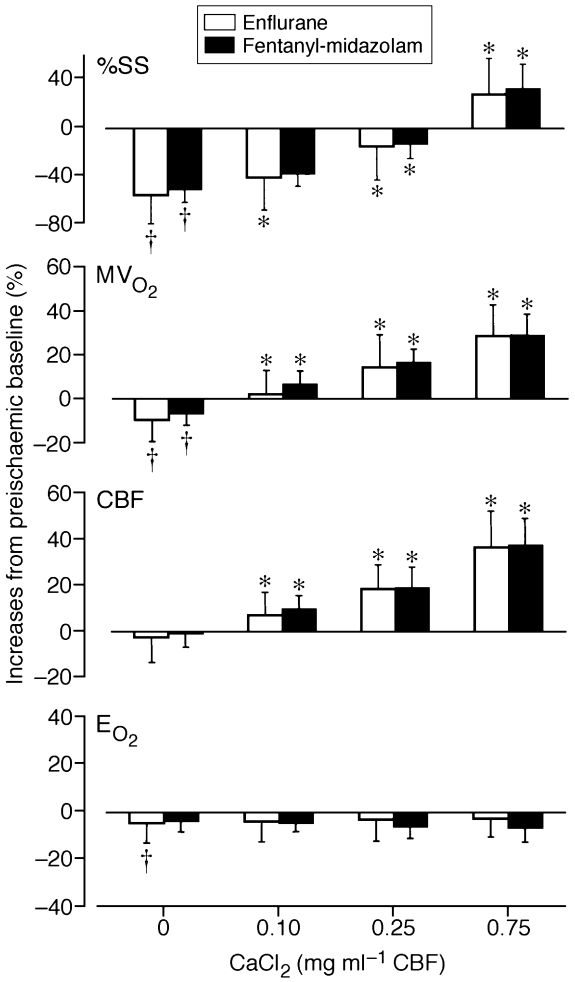

Fig 4 Changes [mean (SD)] from preischaemic baseline values of %SS, $M\dot{V}_{O_2}$, CBF and E_{O_2} during calcium chloride infusion in stunned myocardium in dogs anaesthetized with enflurane (n=13) or fentanyl–midazolam (n=5). Changes were similar in the two groups. †P<0.05 compared with preischaemic baseline values; *P<0.05 compared with postischaemic baseline values (indicated as dose 0 of calcium chloride).

increased susceptibility to Ca^{2+} results in increased diastolic tone under conditions that favour cellular Ca^{2+} accumulation. DeHert and colleagues[25] also found an increase in ventricular stiffness when calcium chloride was given early after cardiopulmonary bypass, suggesting temporary diastolic dysfunction. In contrast, Eberli and colleagues[26] observed that increased $[Ca^{2+}]_i$ was not causally related to the increase in diastolic chamber stiffness in isolated rat hearts.

The effect of calcium chloride on myocardial function is transient, despite persistent elevation of the plasma concentration of ionized calcium, whereas the effect on systemic vascular resistance is more prolonged.[27] We therefore chose to infuse calcium chloride continuously rather than use a single bolus injection to produce steady-state changes in myocardial contractility (and hence myocardial oxygen demand), as shown previously by Crystal and colleagues.[8] In general, calcium chloride at doses of 5–15 mg kg^{-1} body weight is given i.v. to improve haemodynamics while the patient is weaned from cardiopulmonary bypass.[28] An i.v. bolus administration of calcium chloride at a dose of 15 mg kg^{-1} caused a maximal increase of approximately 0.8 mmol $litre^{-1}$.[29] Therefore, our data with the lowest rate of calcium chloride (0.1 mg ml^{-1}=0.9 mmol $litre^{-1}$) appears to be clinically relevant.

Lactate production has been a reliable sign of a mismatch between myocardial oxygen demand and supply.[30] In the present study, a progressive reduction in lactate extraction was observed during the infusion of calcium chloride in stunned myocardium, albeit statistically insignificant. Moreover, lactate was produced in four of 13 animals anaesthetized with enflurane during calcium chloride infusion at 0.75 mg ml^{-1} in stunned myocardium (Fig. 3). Stahl and colleagues[31] observed increased heterogeneity of oxygen extraction with very low venous oxygen saturation in stunned myocardium despite patent microvasculature and normal perfusion, implying either focally impaired perfusion or increased metabolic activity. Calcium chloride would have induced focal microcirculatory changes with localized areas of tissue hypoxia and anaerobic metabolism, leading to lactate production, despite unaltered coronary venous oxygen tension. In addition, increased susceptibility to Ca^{2+} load in stunned myocardium has been demonstrated in isolated rat hearts.[13 24] Indeed, functional deterioration has been reported after intense inotropic stimulation with high-dose dobutamine in many reperfused segments that respond positively to low-dose dobutamine infusion, probably because of impaired intracellular Ca^{2+} handling.[32] Likewise, calcium chloride may have a deleterious long-lasting effect that differs from an immediate functional and metabolic effect, as in the present study. Therefore, caution should be exercised in extrapolating our results, showing that the postischaemic dysfunction was effectively improved by calcium chloride without impairing myocardial oxygen balance, to the clinical situation.

The present study has several limitations. First, enflurane was used to maintain anaesthesia. Volatile anaesthetics have been shown to enhance recovery of postischaemic myocardium[33] and to produce coronary vasodilation directly *in vivo*.[20] Enflurane may have protected the myocardium against ischaemia and reperfusion injury, altering the response to calcium chloride. However, we observed that responses to calcium chloride in postischaemic myocardium were similar in enflurane- and fentanyl–midazolam-anaesthetized groups (Fig. 4). Secondly, it has been demonstrated that calcium chloride has a preconditioning effect against postischaemic contractile dysfunction.[34] However, the responses to calcium chloride in the stunned myocar-

dium were similar in series 1 and series 2 (Fig. 4). It is unlikely that a preconditioning effect was exerted in our experimental protocol. Thirdly, the present study did not evaluate the time course of recovery of postischaemic, reperfused myocardium during the period corresponding to drug infusion (30–70 min of reperfusion). However, an open-chest canine model has shown constant regional contractile function (%SS) between 30 and 90 min of reperfusion.[35] Furthermore, %SS returned to the pre-infusion values after cessation of calcium chloride infusion. Finally, changes in heart rate and systemic blood pressure during calcium chloride infusion may result in increases in $M\dot{V}_{O_2}$ and CBF. However, calcium chloride did not affect aortic pressure, heart rate or coronary perfusion pressure at any time during the study.

In summary, calcium chloride improved regional systolic and diastolic functions both in normal and stunned myocardium. However, the metabolic control of CBF is unlikely to be impaired in stunned myocardium, as shown by an enhanced regional function in association with proportional increases in CBF. In addition, calcium chloride is unlikely to deteriorate regional mechanical function in postischaemic myocardium.

Acknowledgement

This work was supported by KOSEF through the Hormone Research Centre (Project no. 2001G0301).

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