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Is Calcium a Coronary Vasoconstrictor In Vivo?

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Background: **Calcium produces constriction in isolated coronary vessels and in the coronary circulation of isolated hearts, but the importance of this mechanism *in vivo* remains controversial.**

Methods: **The left anterior descending coronary arteries of 20 anesthetized dogs whose chests had been opened were perfused at 80 mmHg. Myocardial segmental shortening was measured with ultrasonic crystals and coronary blood flow with a Doppler flow transducer. The coronary arteriovenous oxygen difference was determined and used to calculate myocardial oxygen consumption and the myocardial oxygen extraction ratio. The myocardial oxygen extraction ratio served as an index of effectiveness of metabolic vasodilation. Data were obtained during intracoronary infusions of $CaCl_2$ (5, 10, and 15 mg/min) and compared with those during intracoronary infusions of dobutamine (2.5, 5.0, and 10.0 μg/min).**

Results: **$CaCl_2$ caused dose-dependent increases in segmental shortening, accompanied by proportional increases in myocardial oxygen consumption. Although $CaCl_2$ also increased coronary blood flow, these increases were less than proportional to those in myocardial oxygen consumption, and therefore the myocardial oxygen extraction ratio increased. Dobutamine caused dose-dependent increases in segmental shortening and myocardial oxygen consumption that were similar in magnitude to those caused by $CaCl_2$. In contrast to $CaCl_2$, however, the accompanying increases in coronary blood flow were proportional to the increases in myocardial oxygen consumption, with the result that the myocardial oxygen extraction ratio remained constant.**

Conclusions: **Calcium has a coronary vasoconstricting effect and a positive inotropic effect *in vivo.* This vasoconstricting effect impairs coupling of coronary blood flow to the augmented myocardial oxygen demand by metabolic vascular control mechanisms. Dobutamine is an inotropic agent with no apparent direct action on coronary resistance vessels *in vivo.* (Key words: Canine hearts; coronary circulation; dobutamine; inotropic drugs.)**

CALCIUM has long been recognized as a positive inotropic substance.[1] Increasing the concentration of ionized calcium with $CaCl_2$ or calcium gluconate is widely used to treat cardiac depression found in a variety of clinical conditions, including after transfusion of citrated blood, during administration of volatile anesthetic agents, and after termination of cardiopulmonary bypass.[1,2] Calcium is essential for excitation-contraction coupling in vascular smooth muscle,[1] but despite many years of investigation, the effect of exogenous calcium on coronary vasomotor tone remains unresolved.[3] Calcium has been shown to cause constriction of isolated coronary artery rings[4] and to reduce coronary blood flow (CBF) in isolated, crystalloid-perfused, beating hearts,[5] although it increased CBF in isolated, blood-perfused, fibrillating hearts.[6] Further, when calcium was administered *in vivo,* it either increased, decreased, or had no effect on CBF or coronary vascular resistance.[7-15] These inconsistent findings *in vivo* are likely attributable to methodologic differences, including those relating to the animal preparation and to dose, mode (bolus *vs.* infusion), and site (intravenous *vs.* intracoronary) of calcium administration. Interpretation of the *in vivo* studies was hindered frequently by the lack of measurements of myocardial oxygen consumption (MV_{O_2}) or of the myocardial oxygen extraction ratio (E_{O_2}), which made it difficult to separate the direct vascular effects of calcium from those secondary to the increased rate of cardiac metabolism.

In the current study, measurements of CBF, MV_{O_2},

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and segmental shortening (SS), an index of local myocardial contractility, were obtained during graded intracoronary infusions of $CaCl_2$ in *in situ* canine hearts. Values for E_{O_2}, which reflect the relationship between MV_{O_2} and CBF, served as an index of the effectiveness of metabolic vasodilation during infusion of $CaCl_2$.[3] Findings during intracoronary infusions of $CaCl_2$ were compared with those during intracoronary infusions of the β-adrenergic receptor agonist dobutamine, an inotropic drug that has been demonstrated to possess no apparent direct effect on the coronary vasculature.[16]

Materials and Methods

Canine Preparation

The current study was conducted in compliance with the guidelines of the Institutional Animal Research Committee. Experiments were performed on 20 healthy mongrel dogs of both sexes (weight, 20.4–23.2 kg). Anesthesia was induced with intravenous bolus injections of thiopental (15 mg/kg) and maintained by continuous intravenous infusion of fentanyl and midazolam at rates of 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 0.6 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively. After tracheal intubation and left thoracotomy in the fourth intercostal space, the lungs were ventilated mechanically with room air enriched with oxygen to maintain arterial oxygen tension (P_{O_2}) >200 mmHg. The tidal volume and respiratory rate were adjusted to maintain arterial carbon dioxide tension (P_{CO_2}) and *p*H at physiologic levels (P_{CO_2},35–40 mmHg; *p*H, 7.38–7.42). P_{O_2}, P_{CO_2}, and *p*H of arterial and venous blood samples (see subsequent section) were measured electrometrically (model 413; Instrumentation Laboratories, Lexington, MS). Muscle paralysis was achieved with an intravenous injection of vecuronium bromide (0.1 mg/kg), with supplements of 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$. Body temperature was maintained at 38°C with a heating pad. Lactated Ringer's solution was administered continuously at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ intravenously to compensate for evaporative fluid losses. Heparin (400 U/kg with supplementation) was used for anticoagulation.

The left anterior descending coronary artery (LAD) was isolated for cannulation approximately 2 cm from its origin. A thin-walled, stainless steel cannula (ID 2.5 mm) was introduced into the isolated segment of the LAD so that the artery could be perfused selectively by an extracorporeal perfusion system.[16–18] The perfusion system contained a pressurized reservoir, which was supplied with blood from the left femoral artery.

The tubing connecting the reservoir to the LAD was equipped with (1) a heat exchanger to maintain the temperature of coronary arterial blood at 38°C; (2) a Doppler flow transducer (Transonics Systems, Inc., Ithaca, NY) to measure CBF; (3) ports for collecting samples of coronary arterial blood and for infusing drugs; and (4) a mixing chamber for drugs infused into the perfusion tubing. Coronary perfusion pressure was measured through a small-diameter tube positioned at the outlet of the perfusion cannula.

Measurements of aortic, left atrial, and left ventricular pressures; maximum rate of increase of left ventricular pressure (dP/dt max); and heart rate were obtained using standard methods.[16–18] A continuous record of these variables was obtained on a physiologic recorder (model 2800S; Gould, Cleveland, OH).

Experimental Measurements

Myocardial Segmental Shortening. Measurements of myocardial segmental length in the LAD bed were obtained with a pair of ultrasonic crystals.[16] Changes in distance between the crystals were recorded from measurements of the ultrasonic transit time between the crystals (Triton Technology, San Diego, CA). The end-diastolic and end-systolic lengths were identified by the beginning of the rapid increase in left ventricular pressure just before isovolumetric contraction and the peak negative dP/dt, respectively. Percent segmental shortening was calculated from the formula:

$$SS = [(EDL - ESL)/EDL] \times 100$$

where EDL and ESL are end-diastolic and end-systolic lengths, respectively.

Myocardial Oxygen Consumption. Measurements of MV_{O_2} were obtained in the LAD perfusion territory. The anterior interventricular vein was cannulated at the same level as the LAD cannula for collection of regional coronary venous effluent.[19] The venous cannula was allowed to drain freely into a beaker to prevent venous stagnation and interstitial edema. This venous blood was returned intermittently to the dog to maintain isovolemic conditions. At specified times in the study, 1-ml blood samples were collected from the coronary venous cannula under mineral oil to maintain anaerobic conditions. These venous samples were paired with 1-ml arterial samples from the perfusion tubing so that the coronary arteriovenous difference for oxygen could be determined. Hemoglobin concentrations and percent hemoglobin oxygen saturation of the blood sam-

ples were measured with a CO-Oximeter (model 482; Instrumentation Laboratories) and used to calculate oxygen bound to hemoglobin, assuming an oxygen carrying capacity for hemoglobin of 1.39 ml O_2/g. The oxygen dissolved in the blood was computed (O_2 dissolved = [0.003 ml $O_2 \cdot 100$ ml blood$^{-1} \cdot$ mmHg^{-1}]) and added to the bound component to compute total oxygen content. MV_{O_2} (in ml $\cdot$ min$^{-1} \cdot 100$ g^{-1}) was computed using the Fick equation, *i.e.,* from the product of the coronary arteriovenous oxygen difference and CBF. E_{O_2} (in percent) was calculated by dividing the arteriovenous oxygen difference by the arterial oxygen content.

The increases in E_{O_2} caused by $CaCl_2$ in our initial studies in series 1 (see Experimental Protocols section) suggested that this agent may precipitate myocardial ischemia. To assess this possibility, in the final four calcium studies in series 1, paired 1-ml arterial and venous samples were obtained from the LAD perfusion field and analyzed for plasma lactate concentrations using an enzymatic method (Paramax Analytical System; Baxter, Irvine, CA) before (control) and during the highest intracoronary dose of $CaCl_2$ (15 mg/min). Myocardial lactate uptake (in μmol $\cdot$ min$^{-1} \cdot 100$ g^{-1}) was calculated by substituting the coronary arteriovenous difference for plasma lactate concentration and plasma flow (determined from CBF and hematocrit) into the Fick equation. Myocardial lactate extraction (in percent) was calculated by dividing the arteriovenous lactate difference by the arterial lactate concentration. Because the balance of oxygen supply *versus* demand was maintained during administration of dobutamine, *i.e.,* E_{O_2} remained constant, there was no reason to suspect that it was causing myocardial ischemia. Therefore, lactate measurements were not performed in these studies.

Coronary Arterial Ionized Calcium Concentration. Ionized calcium concentration ([Ca^{++}]) in the LAD blood during infusion of $CaCl_2$ was estimated by calculating the [Ca^{++}] added to the blood (by dividing the infusion rate for calcium by the steady-state value for CBF) and adding it to the control value for [Ca^{++}]. To validate this approach, coronary arterial blood samples were obtained from four dogs (series 2) and analyzed for [Ca^{++}] using a potentiometric technique (GEM Premier System; Instrumentation Laboratory Sensor Systems, Inc., Boston, MA), and the values were compared with the calculated values for [Ca^{++}]. Measurements of [Ca^{++}] were obtained under control conditions and during the graded intracoronary infusions of $CaCl_2$. The average value for measured [Ca^{++}] under control conditions in our studies (1.22 $\pm$ 0.06 mM) was used in the calculations of [Ca^{++}].

Experimental Protocols

Series 1: Cardiac Effects of $CaCl_2$ and Dobutamine in Separate Groups of Dogs. In one group of eight dogs, the dose-dependent cardiac effects of $CaCl_2$ were evaluated. After >45 min for recovery from surgical preparation, control measurements for CBF, SS, MV_{O_2}, and E_{O_2} were obtained with coronary perfusion pressure set equal to 80 mmHg. Then $CaCl_2$ was infused into the LAD in a graded fashion (5, 10, and 15 mg/min). Measurements were obtained when steady-state conditions were achieved at each drug infusion rate (as indicated by stable increases in CBF and SS), within 2–3 min after varying the rate of infusion. The dose range used for $CaCl_2$ was selected because it has been shown previously to span a significant portion of the dose–response curve.[15] In a second group, also consisting of eight dogs, the responses to intracoronary infusions of dobutamine (2.5, 5.0, and 10.0 μg/min) were assessed using a protocol similar to that used for $CaCl_2$. This dose range for dobutamine was demonstrated in a previous investigation to cause increases in SS that were equal to those caused by $CaCl_2$.[16] $CaCl_2$ and dobutamine were dissolved in isotonic saline to achieve concentrations of 10 and 5 μg/ml, respectively, so it was possible to use identical ranges of infusion rates (0.5–2.0 ml/min) for the two inotropes. After $\geq$20 min for recovery from the effects of the inotropic drug, coronary vasodilator reserve was assessed using a maximally dilating intracoronary infusion of adenosine (8 mg/min).[17] The time required for CBF to achieve a stable maximum value during infusion of adenosine was 2 min. Adenosine was dissolved in isotonic saline to achieve a concentration of 8 mg/ml, so that the infusion rate for the adenosine solution was 1.0 ml/min. Previous studies demonstrated that infusion of the saline vehicle at rates comparable to those used in the current study had no effect on CBF or MV_{O_2} in the LAD bed.[18]

Series 2: Cardiac Effects of $CaCl_2$ and Dobutamine in the Same Group of Dogs. To rule out the possibility that the differences in the effects of $CaCl_2$ and dobutamine in series 1 were due to the use of different dogs to study each drug, additional studies were conducted in which the effects of $CaCl_2$ and dobutamine were compared in the same four dogs. The protocols used were essentially similar to those described for series 1. The order of the intracoronary infusions of $CaCl_2$, dobutamine, and adenosine was randomized. In

Table 1. Cardiac Effects of Graded Intracoronary Infusions of $CaCl_2$ and Dobutamine

			Drug Dose		
		Control	Low	Medium	High
SS (%)	$CaCl_2$	16.1 ± 5.3	20.4 ± 5.9*	22.8 ± 6.7*†	23.8 ± 7.0*†
			(132 ± 20)	(148 ± 22)	(151 ± 26)
	DOB	18.2 ± 4.4	22.5 ± 3.6*	24.2 ± 4.0*†	24.5 ± 6.2*†
			(119 ± 9)	(128 ± 9)	(135 ± 12)
EDL (mm)	$CaCl_2$	11.2 ± 1.7	11.3 ± 1.6	11.3 ± 1.7	11.4 ± 1.8
			(101 ± 6)	(101 ± 7)	(102 ± 7)
	DOB	12.3 ± 3.3	12.6 ± 3.6	12.6 ± 3.6	12.3 ± 3.3
			(99 ± 1)	(99 ± 2)	(100 ± 3)
ESL (mm)	$CaCl_2$	9.3 ± 1.0	8.9 ± 1.1	8.7 ± 1.2*†	8.6 ± 1.1*†‡
			(95 ± 5)	(92 ± 6)	(92 ± 6)
	DOB	10.1 ± 2.7	9.8 ± 2.9*	9.6 ± 2.9*†	9.3 ± 2.4*†‡
			(95 ± 3)	(93 ± 4)	(92 ± 4)
MV_{O_2} ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	$CaCl_2$	6.0 ± 1.0	7.3 ± 1.0*	8.4 ± 1.0*†	9.1 ± 1.2*†‡
			(127 ± 17)	(146 ± 22)	(155 ± 26)
	DOB	6.6 ± 1.6	8.0 ± 2.3*	9.2 ± 3.3*†	10.2 ± 3.8*†
			(117 ± 15)	(133 ± 25)	(152 ± 26)
CBF ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	$CaCl_2$	119 ± 31	128 ± 35	140 ± 39*	156 ± 35*†
			(119 ± 32)	(131 ± 38)	(135 ± 38)
	DOB	109 ± 40	119 ± 45	134 ± 52*†	171 ± 61*†‡
			(125 ± 15)	(140 ± 23)	(159 ± 33)
E_{O_2} (%)	$CaCl_2$	42 ± 7	49 ± 10*	51 ± 10*†	52 ± 8*†
			(117 ± 9)	(124 ± 10)	(125 ± 11)
	DOB	47 ± 7	47 ± 7	47 ± 7	47 ± 7
			(96 ± 11§)	(97 ± 15§)	(101 ± 14§)

Values are mean ± SD in 12 dogs. Values in parentheses are percent of control. Drug doses were 5, 10, and 15 mg/min for $CaCl_2$ and 2.5, 5.0, and 10.0 μg/min for DOB.

DOB = dobutamine; SS = segmental shortening; EDL = end-diastolic length; ESL = end-systolic length; MV_{O_2} = myocardial oxygen consumption; CBF = coronary blood flow; E_{O_2} = myocardial oxygen extraction ratio.

$P < 0.05$: * *versus* control, † *versus* low, ‡ *versus* medium, § versus respective $CaCl_2$ value.

these studies, additional samples of blood were obtained from the LAD perfusion tubing (distal from the site of infusion of $CaCl_2$) and analyzed for $[Ca^{++}]$ as described previously. In two of the dogs, a blood sample was obtained from the aorta just before terminating the intracoronary infusion of $CaCl_2$ at the highest dose (15 mg/min) and its $[Ca^{++}]$ compared with the pre-$CaCl_2$ level.

At the termination of each experiment, 5 ml of Evans blue dye (10 mg/ml saline) was injected into the LAD to identify its perfusion territory. After the heart was stopped with a 10-ml bolus injection of KCl (80 mg/ml saline) into the left ventricular cavity, it was removed and trimmed. The dyed tissue was excised and weighed so that CBF could be expressed per 100 grams. The average weight of the LAD perfusion territory was 33 ± 3 g.

Statistical Analyses

A two-way analysis of variance for repeated measurements was used to assess the dose-dependent effects of $CaCl_2$ and dobutamine.[20] *Post hoc* comparisons were made using the Student's *t* test with the Bonferroni correction.[20] Additional statistical analyses were performed using the paired and unpaired versions of the Student's *t* test.[20] Because results in series 2 were similar to those in series 1, the data were pooled for analysis. In some cases, data were normalized to percent of control (*e.g.,* table 1) to facilitate comparisons between the effects of $CaCl_2$ and dobutamine. Linear regression analysis[20] was used to evaluate the relation between (1) the measured and the calculated values for $[Ca^{++}]$, and (2) the increases in E_{O_2} and the log of calculated $[Ca^{++}]$ during infusion of $CaCl_2$. Data are presented as mean ± SD. A probability value <0.05 was considered significant.

Results

Table 1 presents the dose-related effects of $CaCl_2$ and dobutamine on SS, MV_{O_2}, CBF, and E_{O_2} using data

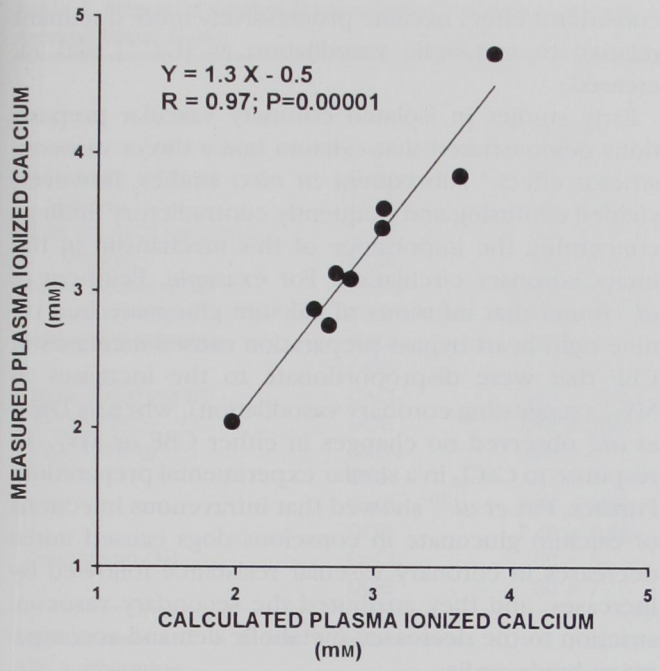

Fig. 1. Linear relationship between the calculated and measured values for coronary arterial [Ca^{++}].

pooled from series 1 and 2. $CaCl_2$ caused increases in SS and MV_{O_2} that were dose-dependent, except that the increases in SS at 10 mg/min were not significantly different from those at 15 mg/min. The increases in CBF during infusion of $CaCl_2$ were less than proportional to the increases in MV_{O_2}, with the result that E_{O_2} increased. The $CaCl_2$-induced increases in E_{O_2} at 10 and 15 mg/min were greater than those at 5 mg/min, although this difference was modest. The increases in SS and MV_{O_2} during administration of dobutamine were similar to those during $CaCl_2$. During dobutamine administration, however, CBF increased in proportion to MV_{O_2}, and therefore E_{O_2} was constant across the entire dose range.

Figure 1 compares the calculated and measured values for coronary arterial [Ca^{++}]. Three of the 12 values for measured [Ca^{++}] in series 2 exceeded 5.0 mM, which was the upper limit of the ion analyzer, and thus these data were excluded from the analysis. Figure 1 demonstrates a strong linear relationship between the calculated and measured values for coronary arterial [Ca^{++}]. Table 2 shows that the values for calculated [Ca^{++}] varied directly with the rate of infusion of $CaCl_2$. In two animals, the values for [Ca^{++}] in the aortic blood just before termination of the intracoronary infusions of $CaCl_2$ were 1.35 and 1.39 mM, which represented

Table 2. Effect of Graded Intracoronary Infusions of $CaCl_2$ on Calculated Values for Plasma Ionized Calcium*

Infused $CaCl_2$ (mg/min)	Calculated Ionized Calcium (mM)
5	2.38 ± 0.37
10	3.37 ± 0.64
15	4.21 ± 0.86

Values are mean ± SD in 12 dogs.

* The control value for measured ionized calcium was 1.22 ± 0.06 mM.

only a modest increase from the pre-$CaCl_2$ control values in these animals (1.19 and 1.18 mM, respectively).

Figure 2 demonstrates a linear relationship between the increases in E_{O_2} and the log of the calculated values for [Ca^{++}].

Table 3 compares the cardiac effects of high-dose $CaCl_2$ and dobutamine in the same dogs (series 2). These findings, like those at the low and medium doses (not shown), were similar to those in series 1, which justified the pooling of results in table 1.

Table 4 indicates that (1) myocardial lactate extraction and lactate uptake were pronounced under control conditions, and (2) $CaCl_2$ had no effect on lactate extraction, although it increased lactate uptake.

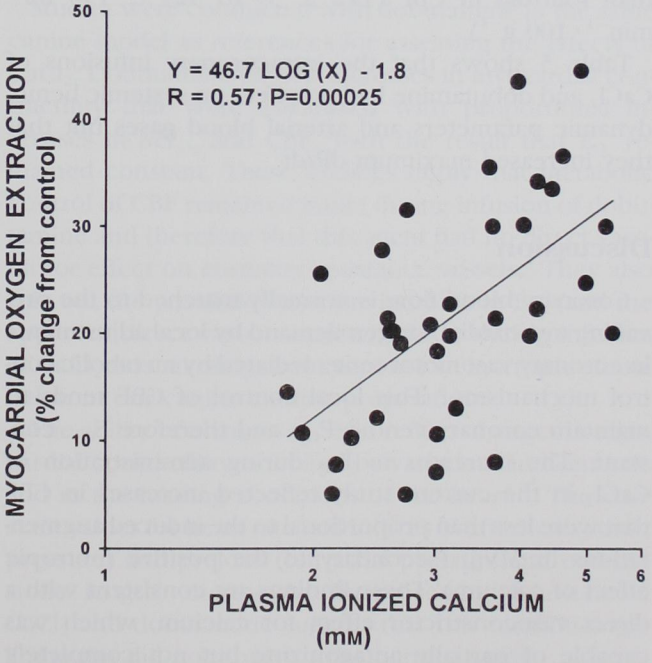

Fig. 2. Linear relationship between the increases in the myocardial extraction ratio and the log of the calculated values for [Ca^{++}].

Table 3. Cardiac Responses to Intracoronary Infusions of High-dose $CaCl_2$ and Dobutamine in the Same Dogs (Series 2)

	Control	$CaCl_2$	Control	DOB
SS (%)	18.8 ± 4.4	25.6 ± 7.2* (137 ± 30)	19.5 ± 4.0	25.8 ± 5.3* (133 ± 12)
EDL (mm)	11.5 ± 1.7	11.6 ± 1.6 (100 ± 2)	11.4 ± 1.8	11.7 ± 1.7 (103 ± 3)
ESL (mm)	9.3 ± 1.0	8.6 ± 1.0* (92 ± 7)	9.2 ± 1.1	8.7 ± 1.0* (95 ± 1)
MV_{O_2} ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	6.3 ± 1.0	9.2 ± 1.0* (149 ± 27)	5.9 ± 1.5	8.8 ± 1.3* (152 ± 17)
CBF ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	126 ± 48	156 ± 25* (133 ± 35)	126 ± 44	195 ± 39* (164 ± 50†)
E_{O_2} (%)	45 ± 7	55 ± 6* (122 ± 10)	43 ± 5	44 ± 6 (103 ± 13†)

Values are mean ± SD in four dogs. Abbreviations are same as in table 1. The doses for $CaCl_2$ and dobutamine were 15 mg/min and 10 μg/min, respectively.

* $P < 0.05$ *versus* control.

† $P < 0.05$ *versus* $CaCl_2$ response.

The infusions of adenosine caused increases greater than fourfold in CBF (112 ± 39 to 529 ± 145 $ml \cdot min^{-1} \cdot 100\ g^{-1}$).

Table 5 shows that the intracoronary infusions of $CaCl_2$ and dobutamine had no effect on systemic hemodynamic parameters and arterial blood gases but that they increased maximum dP/dt.

Discussion

Coronary blood flow is normally matched to the prevailing myocardial oxygen demand by local adjustments in coronary vasomotor tone mediated by metabolic control mechanisms.[3] This local control of CBF tends to maintain coronary venous P_{O_2}, and therefore E_{O_2}, constant. The increases in E_{O_2} during administration of $CaCl_2$ in the current study reflected increases in CBF that were less than proportional to the induced augmentations in MV_{O_2} (secondary to the positive inotropic effect of calcium). These findings are consistent with a direct vasoconstrictor effect for calcium, which was capable of partially antagonizing but not completely overriding metabolic vasodilation. The observed direct relation between E_{O_2} and $[Ca^{++}]$ implies that this vasoconstrictor effect became progressively more dominant relative to metabolic vasodilation as $[Ca^{++}]$ was increased.

Early studies in isolated coronary vascular preparations demonstrated that calcium had a direct vasoconstrictor effect.[4] Subsequent *in vivo* studies, however, yielded confusing and frequently contradictory findings concerning the importance of this mechanism in the intact coronary circulation. For example, Feinberg *et al.*[7] found that infusions of calcium gluconate in a canine right heart bypass preparation caused increases in CBF that were disproportionate to the increases in MV_{O_2} (suggesting coronary vasodilation), whereas Drop *et al.*[8] observed no changes in either CBF or MV_{O_2} in response to $CaCl_2$ in a similar experimental preparation. Further, Pitt *et al.*[10] showed that intravenous injections of calcium gluconate in conscious dogs caused initial decreases in coronary vascular resistance followed by increases, and they attributed the secondary vasoconstriction to the decreased metabolic demand accompanying bradycardia.

The regional coronary perfusion model used in the current study permitted exposure of a circumscribed region of the left ventricular wall to $CaCl_2$, which avoided its systemic effects (*e.g.*, bradycardia[10]), thus simplifying interpretation of the data. Moreover, local samples of venous blood were obtained so that the changes in CBF caused by $CaCl_2$ could be evaluated in the context of the accompanying changes in MV_{O_2} and E_{O_2}. Our model of regional coronary perfusion has been used in previous studies to evaluate (during stable hemodynamic conditions) the direct coronary effects of drugs and of physiologic factors, including hypercapnia.[16–18,21,22] Drawbacks of this model are its invasive nature and the instrumentation required. This dictates that caution be exercised in extrapolating the current findings to humans.

The control values for E_{O_2} in the cannulated LAD bed were moderately lower than those usually found in an-

Table 4. Effect of Intracoronary Infusion of $CaCl_2$ on Myocardial Lactate Extraction and Lactate Uptake

	Control	$CaCl_2$
Lactate extraction (%)	29 ± 8	36 ± 15
Lactate uptake ($\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$)	45 ± 4	86 ± 31*

Values are mean ± SD in four dogs.

* $P < 0.05$ *versus* control.

Table 5. Effects of Graded Intracoronary Infusions of $CaCl_2$ and Dobutamine on Systemic Hemodynamic Parameters and Arterial Blood Gases

			Drug Dose		
		Control	Low	Medium	High
Mean aortic pressure (mmHg)	$CaCl_2$	76 ± 18	84 ± 15	84 ± 15	81 ± 17
	DOB	79 ± 23	87 ± 20	88 ± 20	80 ± 24
Mean left atrial pressure (mmHg)	$CaCl_2$	3.6 ± 1.7	4.4 ± 1.8	4.4 ± 1.8	3.9 ± 1.8
	DOB	4.9 ± 2.3	5.2 ± 1.8	5.2 ± 1.8	4.4 ± 2.0
Left ventricular dP/dt max (mmHg/s)	$CaCl_2$	1,250 ± 252	1,344 ± 155*	1,413 ± 217*	1,438 ± 267*
	DOB	1,255 ± 304	1,507 ± 372*	1,629 ± 340*†	1,615 ± 342*†
Heart rate (beats/min)	$CaCl_2$	119 ± 32	118 ± 38	120 ± 38	117 ± 30
	DOB	117 ± 31	116 ± 35	116 ± 37	115 ± 32
Arterial blood values	$CaCl_2$	225 ± 188	184 ± 163	184 ± 163	201 ± 185
P_{O_2} (mmHg)	DOB	313 ± 166	352 ± 153	352 ± 153	306 ± 165
P_{CO_2} (mmHg)	$CaCl_2$	36 ± 6	35 ± 6	35 ± 6	36 ± 6
	DOB	37 ± 7	35 ± 4	35 ± 4	37 ± 7
*p*H	$CaCl_2$	7.40 ± 0.05	7.41 ± 0.05	7.40 ± 0.05	7.39 ± 0.05
	DOB	7.40 ± 0.06	7.40 ± 0.06	7.40 ± 0.06	7.40 ± 0.06
Hematocrit (%)	$CaCl_2$	30 ± 5	30 ± 6	30 ± 6	29 ± 5
	DOB	30 ± 7	31 ± 7	31 ± 7	30 ± 7

Values are mean ± SD in 12 dogs. Drug doses were 5, 10, and 15 mg/min for $CaCl_2$ and 2.5, 5.0, and 10.0 μg/min for DOB.

DOB = dobutamine.

* $P < 0.05$ *versus* control.

† $P < 0.05$ *versus* low.

esthetized dogs with an intact coronary circulation.[23] This suggests modest vasodilation in the control preparation, probably because of dilators released from blood cells in the pumps, bottles, and tubing contained in the extracorporeal circuit.[24] Nevertheless, vascular responsiveness to both endothelium-dependent (*e.g.,* acetylcholine) and endothelium-independent vasodilators (*e.g.,* sodium nitroprusside) has been demonstrated to remain pronounced with this preparation.[17,21] Moreover, vasodilator reserve is appreciable, as shown by the increases greater than fourfold in CBF during infusion of adenosine in the current study. These latter findings indicated that the increases in CBF during inotropic stimulation were not limited by the vasodilator reserve of the preparation.

The increases in E_{O_2} during the infusions of $CaCl_2$ were associated with reductions in coronary venous P_{O_2} and presumably in myocardial P_{O_2}. Production of lactate was not evident, however, suggesting lack of anaerobic metabolism and myocardial ischemia.[25] The ability of the myocardium to experience reductions in P_{O_2} without adverse metabolic consequences may be because of high values for P_{O_2} (secondary to vasodilation) in the control preparation. The increase in myocardial uptake of lactate during infusion of $CaCl_2$ probably reflected its increased use as a substrate to meet a higher oxygen demand.[26]

Studies were conducted with dobutamine in the same canine model as references for assessing the effects of $CaCl_2$. Dobutamine caused increases in myocardial contractility that were associated with proportional increases in MV_{O_2} and CBF, with the result that E_{O_2} remained constant. These findings imply that metabolic control of CBF remained intact during infusion of dobutamine and therefore that this agent had no direct vasomotor effect on coronary resistance vessels.[3] They also rule out the possibility that the increase in E_{O_2} (and the apparent direct vasoconstrictor effect) during infusion of $CaCl_2$ was an obligatory response to inotropic stimulation in our canine cardiac preparation.

The ability of changes in SS to reflect changes in myocardial contractility is limited by variations in heart rate and in the loading conditions of the heart.[27] The constant values for heart rate and indices of afterload (aortic pressure) and preload (left atrial pressure and end-diastolic length) during the intracoronary infusions of $CaCl_2$ and dobutamine suggest that this methodologic limitation did not apply to the current study.

$[Ca^{++}]$ in the coronary arterial blood during infusion of $CaCl_2$ was calculated by dividing the infusion rate

for calcium by the steady-state value for CBF, assuming a constant control value for $[Ca^{++}]$, *i.e.,* that no recirculation of the infused calcium occurred. This assumption was based on our finding that $[Ca^{++}]$ increased only negligibly in the aortic blood just before termination of the intracoronary infusion of $CaCl_2$. The strong correlation between our calculated values for $[Ca^{++}]$ and those measured directly (fig. 1) validated our approach for estimating $[Ca^{++}]$ in the coronary arterial blood.

Continuous infusions of $CaCl_2$, rather than bolus injections, were used in the current study to establish the steady-state conditions required for application of the Fick principle. The intracoronary infusion rates for $CaCl_2$ were chosen to produce dose-related increases in myocardial contractility (and therefore oxygen demand), as shown previously by Ito *et al.*[15] In clinical practice, $CaCl_2$ is usually administered intravenously as a bolus infusion.[1] The clinically reported and recommended doses for $CaCl_2$ vary widely, from 3–15 mg/kg.[1] In adult patients, an intravenous bolus administration of $CaCl_2$ in a dose of 7 mg/kg caused a maximum increase in $[Ca^{++}]$ of 0.1–0.2 mM, whereas a dose of 15 mg/kg caused a maximal increase of approximately 0.8 mM.[28,29] Therefore, our findings at the lowest rate of intracoronary infusion of $CaCl_2$ (5 mg/min) appear to have the most clinical relevance.

We have shown that selective intracoronary infusions of $CaCl_2$ are accompanied by increases in myocardial contractility, MV_{O_2}, and CBF; however, the increases in CBF were less than proportional to those in MV_{O_2}, leading to an increase in E_{O_2}. These findings suggest that a direct coronary vasoconstrictor effect competes with metabolic vasodilation during administration of $CaCl_2$. Although calcium-induced coronary vasoconstriction did not produce myocardial ischemia in the normal hearts in the current study, it is conceivable that it could do so in a variety of pathologic conditions, including (1) when vasodilator reserve is compromised by a proximal stenosis, hypoxemia, or anemia, or (2) when the generation of metabolic vasodilators, *e.g.,* nitric oxide or adenosine, is obtunded because of diminished responsiveness of the myocardium to the inotropic effects of calcium or to endothelial dysfunction or disease.

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