

## Peripheral Vascular versus Direct Cardiac Effects of Calcium

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Peripheral vascular and direct cardiac effects of calcium chloride were determined in a new animal model, the unanesthetized calf, before and after replacement of its natural heart (NH) with a pneumatically driven artificial heart (AH). Calcium (5 and 10 mg/kg) significantly increased cardiac output ( $\dot{Q}$ ) and reduced systemic vascular resistance (SVR) before and after AH implantation. Increases in  $\dot{Q}$ , in AH calves and reductions in SVR in both NH and AH calves were, however, transient, being present 5 minutes but not 15 minutes after both doses of calcium. Increases in  $\dot{Q}$ , and reductions in SVR were significantly ( $P < .05$ ) greater after 10 mg/kg than after 5 mg/kg calcium in NH and AH calves. Both doses of calcium produced greater ( $P < .05$ ) increases of  $\dot{Q}$  in NH than in AH animals but similar reductions in SVR. Pulmonary vascular resistance, heart rate and pulmonary arterial and right atrial pressures were not significantly altered by either dose of calcium in NH or AH calves. Mean aortic pressure was influenced by 10 mg/kg calcium only, being transiently reduced in AH calves and increased in NH animals. Pulmonary shunt ( $\dot{Q}_s/\dot{Q}_t$ ) was increased by both doses of calcium in NH calves but only by 10 mg/kg in AH animals. Correlations of mean change in  $\dot{Q}/\dot{Q}_t$  with mean change in  $\dot{Q}$ , were high both before ( $r = .99$ ) and after ( $r = .97$ ) AH implantation. These data demonstrate that calcium significantly reduces SVR in a dose-related manner as well as exerting a positive inotropic effect on the myocardium. (Key words: Ions, calcium; Heart, calcium; Arteries, calcium.)

RECENT ADVANCES in the development of an artificial heart (AH) to replace the natural heart of the patient who has uncorrectable or untreatable heart disease have made available a unique animal model for study of the differential cardiovascular effects of drugs that have peripheral vascular and direct cardiac inotropic actions.<sup>1-5</sup> This model, the unanesthetized calf before and after its natural heart (NH) is removed and replaced with a pneumatically powered, pulsatile AH, enables not only quantitation but also separation of

### ABBREVIATIONS

AH	= artificial heart
AH calves	= calves with artificial hearts
$C_{a_{100}}$	= content of oxygen (ml) in 100 ml of arterial blood
$C_{v_{100}}$	= content of oxygen (ml) in 100 ml of mixed venous (pulmonary artery) blood
f	= respiratory rate
HR	= heart rate
LA	= left atrial
LVW	= left ventricular work
NH	= natural heart
NH calves	= calves with their natural hearts
PA	= pulmonary artery
$P_{a_{CO_2}}$	= partial pressure of carbon dioxide in arterial blood
$P_{A_{O_2}}$	= partial pressure of oxygen in alveolar air
$P_{a_{O_2}}$	= partial pressure of oxygen in arterial blood
$P_B$	= barometric pressure
$P_{H_2O}$	= partial pressure of water in pulmonary alveoli (47 torr)
PVR	= pulmonary vascular resistance
$\dot{Q}_s/\dot{Q}_t$	= pulmonary shunt
$\dot{Q}_t$	= cardiac output
RA	= right atrial
SVR	= systemic vascular resistance
$\dot{V}$	= minute respiratory volume
$V_{O_2}$	= oxygen uptake
$V_T$	= tidal volume

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the myocardial effects of a drug from its actions on the peripheral vasculature. In the present study the bovine AII model was used to differentiate the cardiac and systemic vascular actions of 5 and 10 mg/kg of calcium chloride, administered intravenously.

### Methods

The experimental subjects were 16 84–102-kg bull calves. After induction of anesthesia with 3–5 mg/kg sodium methohexital, iv, endotracheal intubation, and maintenance of anesthesia with 1–2 per cent halothane, 10-gauge needles were placed percutaneously into the right external jugular vein. With continuous pressure recording, a 7-Fr Swan-Ganz triple-lumen catheter was threaded through the needle, through the right ventricle, and into the proximal pulmonary artery (PA). Another catheter (14 Fr) was placed percutaneously into the opposite jugular vein and threaded into the right atrium. Following this a small incision was made in the groin and a third catheter (17 Fr) threaded into the central aorta through the left femoral artery. Catheter position was documented by fluoroscopy and catheter patency maintained with dilute heparinized (2 units/ml) Ringer's lactate solution administered at a rate of 1–2 ml/hr via a constant-infusion pump. Anesthesia was then terminated, the tracheas were extubated, and

the animals were allowed to recover for 24–48 hours.

### PRE-ARTIFICIAL HEART IMPLANTATION STUDY PROCEDURES

Studies before AII implantation were performed with the calves standing in a metal calf cage. Arterial blood samples were drawn for blood-gas analysis and for pH, total calcium, sodium and potassium determinations while the calves were breathing room air. Following this the animals breathed 100 per cent oxygen through a specially designed air-tight calf face mask. Warren E. Collins 3-cm ID inspiratory and expiratory "J" valves (model #P-304) were attached to the mask portals and the inspiratory valve was connected to a source of oxygen. PA and aortic blood samples were obtained (for oxygen content analysis) after 20 minutes of oxygen breathing and heart rate (HR) and systolic, diastolic, and mean PA and aortic and mean right atrial (RA) pressures recorded. Oxygen uptake ( $\dot{V}_{O_2}$ ), respiratory rate ( $\dot{f}$ ), tidal volume ( $V_T$ ) and minute volume ( $\dot{V}$ ) were then measured over a 3-minute period by removing both "J" valves from the mask portals, attaching one of the portals to a standard 9-liter, oxygen-filled Warren E. Collins closed-circuit spirometer equipped with water and CO<sub>2</sub> absorbers, and plugging the other portal of the face mask.

$\dot{Q}_T$  in l/min was calculated using the Fick equation:

$$\dot{Q}_T = \frac{\dot{V}_{O_2}}{C_{iO_2} - C_{vO_2}}$$

$\dot{Q}_s/\dot{Q}_T$  was determined utilizing the modified shunt equation given below:

$$\dot{Q}_s/\dot{Q}_T = \frac{(P_{AO_2} - P_{aO_2}) \times 0.0031}{(C_{iO_2} - C_{vO_2}) + (P_{AO_2} - P_{aO_2}) \times 0.0031}$$

where

$$P_{AO_2} = P_B - P_{H_2O} - P_{aCO_2}$$

Blood carbon dioxide tension was measured with a Severinghaus electrode, pH with a Radiometer glass electrode, and oxygen tension with a modified Clark electrode. All electrodes were maintained at 39 C and frequently recalibrated with standard solutions and gases of known concentrations and tensions. Temperature corrections were made when necessary using standard bovine blood-gas correction factors. Oxygen saturation was determined on an American Optical Company oximeter and hemoglobin on a Fisher Hemophotometer. Rectal

temperature was monitored with a Yellow Springs temperature probe and recording module. It was assumed that one gram of fully oxygenated calf blood combined with 1.39 ml of oxygen.\*\* Blood oxygen content in vol per cent was calculated from hemoglobin (Hb) capacity, oxygen saturation, and dissolved oxygen according to the equation:

$$\text{Oxygen content} = (1.39 \times \text{grams Hb}/100 \text{ ml blood}) + 0.0031 \times \text{partial pressure oxygen}$$

Left ventricular work (LVW) in kg M/min was obtained from the nomogram of Mostert *et al.*<sup>6</sup> and systemic vascular resistance (SVR) in dynes-sec/cm<sup>-5</sup> was calculated from the equation:

$$\text{SVR} = \frac{\text{mean aortic pressure} - \text{mean RA pressure}}{\dot{Q}_T} \times 80$$

Following control measurements and with the calves breathing into the spirometer, calcium chloride, 5 mg/kg, was rapidly given intravenously and after 5, 15, and 30 minutes, PA and aortic blood samples again collected;  $\dot{V}_{O_2}$ ,  $f$ ,  $V_T$ ,  $\dot{V}$ , HR, and PA, aortic, and RA blood pressures were remeasured, and  $\dot{Q}_T$  and  $\dot{Q}_L/\dot{Q}_T$  recalculated. The following day the same measurements were repeated before and after administration of 10 mg/kg calcium. Two to four days later each calf had its NH replaced with a pneumatically driven AH.

#### DESIGN OF THE ARTIFICIAL HEART AND THE ARTIFICIAL HEART DRIVING SYSTEM

A silicone rubber (Silastic)<sup>††</sup> or polyurethane elliptical type of AH (fig. 1) was used in these investigations. This type of AH has been described.<sup>1-3</sup> It is composed of four chambers (two artificial atria and two artificial ventricles), contains four Bjork-Shiley pyrolytic carbon disc valves, and weighs approximately 300 g. Each ventricle consists of a rigid outer casing and a pliable inner blood-containing chamber, between which compressed air is applied for compression and ejection of blood.

The system of AH control used in these experiments, based on the maintenance of normal atrial pressures, has been described.<sup>1</sup> Basically, the control system consists of two direct-acting, three-way solenoid valves, lo-

cated in the control module, which apply compressed air through the two air-drive lines during systole and exhaust air to the atmosphere during diastole. The two air-drive lines bring compressed air from the control module (standing next to the calf's cage) through the calf's chest wall to the AH ventricles within the chest. With this system the rate of filling, and therefore the volume of blood entering each ventricle during the diastolic period, increases with an increase in atrial pressure. This volume is expelled during the next ventricular systole. As filling of the ventricle diminishes so does stroke volume. There is, thus, an inherent balance between the pulmonary and systemic circulatory systems, as with the natural heart, and extremes of high and low atrial and venous pressures are avoided. The AH also responds, as does the NH, to increases and decreases in ventricular afterload with appropriate decreases or increases in ventricular stroke volume and cardiac output.

#### POST-ARTIFICIAL HEART IMPLANTATION PROTOCOL AND STUDY PROCEDURES

Artificial heart implantation was accomplished through a right lateral thoracotomy, as has been described.<sup>1</sup>

Post-AH implantation studies were carried out 6-9 days after operation when  $V_T$  was >400 ml,  $P_{a_{CO_2}}$  <40 torr, and  $P_{a_{O_2}}$  >70 torr for six or more hours while breathing room air. Additional criteria for acceptance in the study included  $\dot{Q}_L/\dot{Q}_T$  and mean PA, aortic, and RA pressures within 20 per cent of pre-AH levels when AH output was adjusted (via AH rate changes) to approximate pre-

\*\* It has been shown (Kosochi T and Stanley T, unpublished data) that freshly drawn, heparinized 12-16-week-old calves' blood will bind 1.38-1.41 ml of oxygen/g hemoglobin when fully oxygenated.

†† Silastic, silicone rubber of the Dow-Corning Company of Midland, Michigan.

implantation values. When these criteria were met, arterial blood samples were drawn for blood-gas, pH, and electrolyte analysis<sup>11</sup>; each calf breathed 100 per cent oxygen through the calf face mask, and pre-AH implantation study procedures were repeated.

Mean LA pressure was an additional variable available for measurement after AH implantation. LA pressure was obtained, as

were RA, PA and aortic pressures and blood samples, from high-pressure tubing connected to taps on the artificial atria and vascular grafts attaching the artificial ventricles to the natural PA and aorta. Using mean LA pressures it was possible to calculate pulmonary vascular resistance (PVR) in dynes-sec/cm<sup>-5</sup> after AH implantation using the following equation:

$$PVR = \frac{\text{mean PA pressure} - \text{mean LA pressure}}{Q_T} \times 80$$

### Results

Mean values of arterial blood pH, blood gases, and electrolytes measured prior to and after administration of 5 and 10 mg/kg calcium appear in tables 1 and 2. Arterial blood pH,  $P_{CO_2}$ ,  $P_{O_2}$ , calcium, sodium, and potassium were not significantly different during control conditions (before administration of either dosage of calcium) before and after AH replacement.  $Pa_{O_2}$  and arterial blood pH were not significantly altered by either dose of calcium at any time after administration in NH or AH calves.  $Pa_{O_2}$  was significantly ( $P < .05$ ) reduced by 5 and 10 mg/kg calcium in NH calves and by 10 mg/kg in AH calves 5 minutes after administration (table 1), but was not significantly different from control values in any of these conditions 15 and 30 minutes after administration.  $Pa_{O_2}$  was not significantly altered at any time after 5 mg/kg calcium in AH calves.

Mean values of all cardiovascular and respiratory variables studied were also not significantly different during control conditions before and after AH replacement. Calcium, 5 mg/kg, significantly increased cardiac output ( $Q_T$ ) after 5 ( $P < .025$ ) and 15 ( $P < .05$ ) minutes in NH calves, but only after 5 minutes ( $P < .05$ ) in AH calves, (fig. 2). Calcium, 10 mg/kg, produced significant increases in  $Q_T$  during all measure-

ments after administration in NH calves but only after 5 minutes in AH calves. Increases in  $Q_T$  were significantly ( $P < .05$ ) greater following 10 mg/kg calcium than after 5 mg/kg in both NH and AH calves after 5 minutes but were not significantly different 15 or 30 minutes following administration. Both doses of calcium produced greater ( $P < .05$ )§§ increases in  $Q_T$  in NH than in AH animals after 5 minutes but no significant difference after 15 or 30 minutes.

Systemic vascular resistances (SVR) were

§§ When compared utilizing Student's t test for unpaired data.

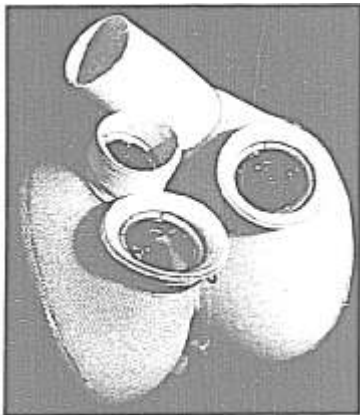


FIG. 1. Pneumatic artificial heart.

<sup>11</sup> Blood potassium, sodium and total calcium concentrations could not be measured after calcium administration either before or following AH replacement.

TABLE 1. pH and Blood-Gas Tensions in 16 Calves Receiving Calcium (Mean  $\pm$  SD)

		Control	Minutes after Calcium			
			5	15	30	
pH	Calcium, 5 mg/kg	NH	7.37 $\pm$ 0.05	7.39 $\pm$ 0.04	7.36 $\pm$ 0.05	7.36 $\pm$ 0.03
		AH	7.40 $\pm$ 0.04	7.42 $\pm$ 0.03	7.43 $\pm$ 0.03	7.43 $\pm$ 0.04
	Calcium, 10 mg/kg	NH	7.41 $\pm$ 0.03	7.40 $\pm$ 0.02	7.41 $\pm$ 0.03	7.41 $\pm$ 0.04
		AH	7.38 $\pm$ 0.03	7.40 $\pm$ 0.04	7.41 $\pm$ 0.03	7.40 $\pm$ 0.03
P <sub>aCO<sub>2</sub></sub> (torr)	Calcium, 5 mg/kg	NH	34 $\pm$ 3	32 $\pm$ 4	34 $\pm$ 5	35 $\pm$ 4
		AH	35 $\pm$ 2	34 $\pm$ 3	32 $\pm$ 3	31 $\pm$ 2
	Calcium, 10 mg/kg	NH	33 $\pm$ 2	30 $\pm$ 5	32 $\pm$ 4	32 $\pm$ 3
		AH	32 $\pm$ 3	31 $\pm$ 4	30 $\pm$ 5	32 $\pm$ 3
P <sub>aO<sub>2</sub></sub> (torr)	Calcium, 5 mg/kg	NH	76 $\pm$ 7	70* $\pm$ 4	73 $\pm$ 5	74 $\pm$ 5
		AH	75 $\pm$ 4	72 $\pm$ 5	74 $\pm$ 5	76 $\pm$ 7
	Calcium, 10 mg/kg	NH	79 $\pm$ 6	67* $\pm$ 5	73 $\pm$ 7	77 $\pm$ 5
		AH	80 $\pm$ 7	74* $\pm$ 5	77 $\pm$ 4	79 $\pm$ 3

\*  $P < .05$ , Student's *t* test for paired data.TABLE 2. Arterial Blood Electrolyte Concentrations during Control Conditions in 16 Calves (Mean  $\pm$  SD)

	Natural Heart Prior to Calcium		Artificial Heart Prior to Calcium	
	5 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg
Calcium (mg/100 ml)	9.9 $\pm$ 0.4	10.2 $\pm$ 0.6	9.7 $\pm$ 0.6	10.1 $\pm$ 0.5
Sodium (mEq/l)	140.7 $\pm$ 2.4	140.0 $\pm$ 2.3	139.6 $\pm$ 3.1	141.8 $\pm$ 3.4
Potassium (mEq/l)	4.26 $\pm$ 0.23	4.10 $\pm$ 0.25	4.67 $\pm$ 0.58	4.36 $\pm$ 0.79

significantly ( $P < .05$ ) and similarly decreased ( $-5$  versus  $-4$  per cent)<sup>ff</sup> by 5 mg/kg calcium in NH and AH calves 5 minutes following administration (fig. 3). Calcium, 10 mg/kg, produced greater reductions ( $P < .025$ ) in SVR in both NH and AH calves than 5 mg/kg of the drug after 5 minutes. SVR did not differ significantly from control values 15 or 30 minutes after administra-

<sup>ff</sup> SVR changes after 5 and 10 mg/kg were not significantly different in NH and AH animals,  $P > .6$ , when compared utilizing Student's *t* test for unpaired data.

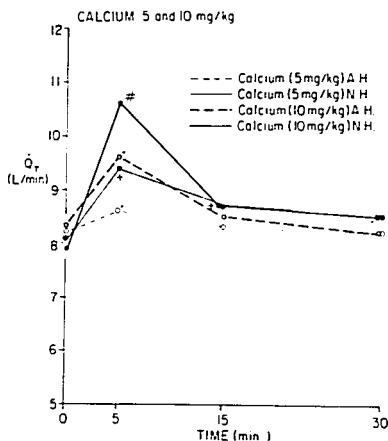


FIG. 2. Cardiac output before and after calcium. \* $P < .05$ ;  $IP < .025$ ; # $P < .01$ ; Student's  $t$  test for paired data.

tion of 5 or 10 mg/kg calcium in either NH or AH calves. Pulmonary vascular resistance was measured in AH calves only and was not significantly changed by either dose of calcium at any time after administration (fig. 4).

Heart rate, PA blood pressure, and mean RA pressure were not altered by either dosage of calcium at any time after administration in NH or AH calves (fig. 5-7). Likewise, 5 mg/kg calcium did not significantly change mean LA pressure in AH calves

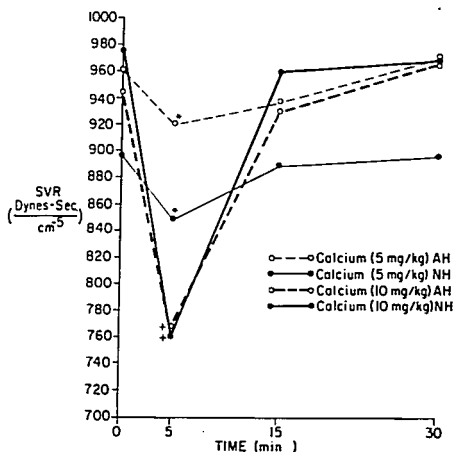


FIG. 3. Systemic vascular resistance before and after calcium. \* $P < .05$ ;  $IP < .025$ .

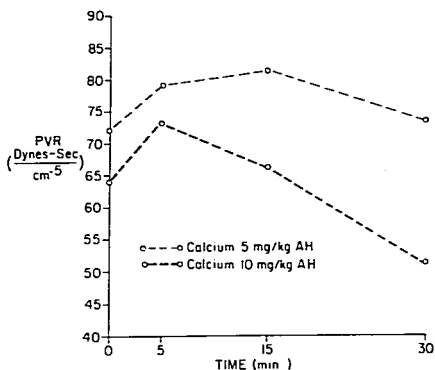


FIG. 4. Pulmonary vascular resistance before and after calcium.

or mean aortic pressure in either NH or AH calves (figs. 6 and 7). However, 10 mg/kg calcium significantly ( $P < .025$ ) reduced mean LA and aortic pressures after 5 minutes in AH calves. NH calves experienced slight but insignificant increases in aortic pressures 5 and 30 minutes after 10 mg/kg calcium and a significant ( $P < .05$ ) elevation in aortic pressure 15 minutes after receiving the compound.

Left ventricular work (LVW) was not changed by either dosage of calcium at any time after administration in AH calves but was significantly ( $P < .05$ ) increased at all times after both dosages of calcium in NH calves (fig. 8). The increase in LVW 5 minutes after 10 mg/kg calcium in NH calves was greater than that after 5 mg/kg, but the difference was not significant ( $P > .30$ ).

Calcium, 5 mg/kg, produced a significant ( $P < .05$ ) increase in the pulmonary shunt ( $\dot{Q}_p/\dot{Q}_t$ ) in NH calves after 5 minutes (fig. 9),

but no significant change after 15 or 30 minutes.  $\dot{Q}_p/\dot{Q}_t$  was slightly but not significantly increased at any time following 5 mg/kg calcium in AH calves. Calcium, 10 mg/kg, after 5 minutes produced significant increases in  $\dot{Q}_p/\dot{Q}_t$  in both NH ( $P < .025$ ) and AH ( $P < .05$ ) calves which were not present 10 and 15 minutes later. Correlations of mean changes in  $\dot{Q}_p/\dot{Q}_t$  with those in  $\dot{Q}_t$  5, 15, and 30 minutes after either dose of calcium were high both before ( $r = .99$ ) and after ( $r = .97$ ) AH implantation (fig. 10). Correlation of mean changes in  $\dot{Q}_p/\dot{Q}_t$  with those in mean LA pressure was also high,  $r = .95$  (fig. 11). Neither 5 nor 10 mg/kg calcium produced any significant change in  $\dot{V}_{O_2}$ ,  $f$ ,  $V_1$  or  $\dot{V}$  in NH or AH calves at any time.

### Discussion

The unanesthetized bovine before and after replacement of its natural heart with a

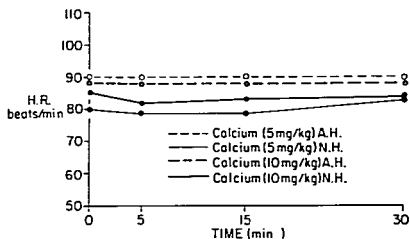


FIG. 5. Heart rate before and after calcium.

FIG. 6. Mean aortic and pulmonary arterial blood pressures before and after calcium. \* $P < .05$ .

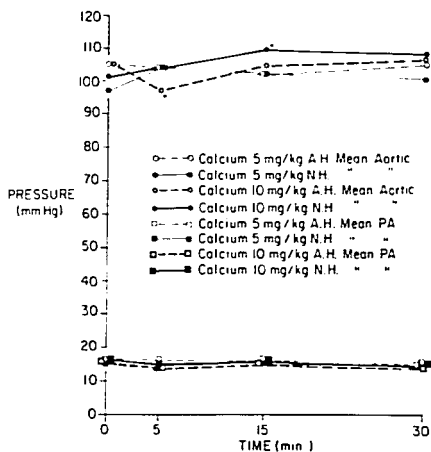
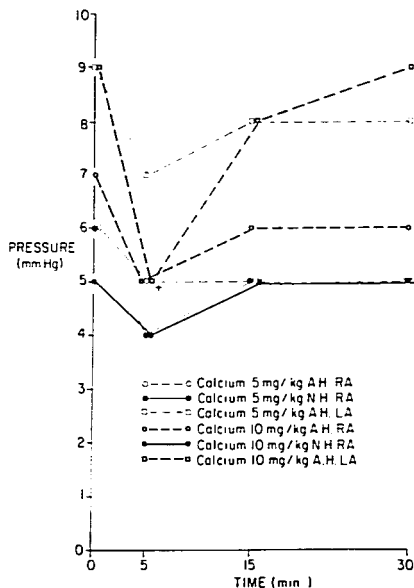


FIG. 7. Mean right and left atrial pressures before and after calcium.  $\dagger P < .025$ .





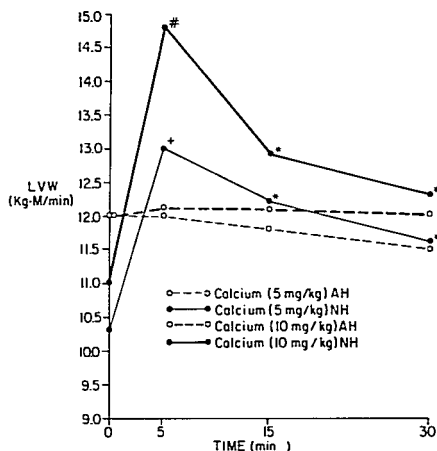


FIG. 8. Calculated left ventricular work before and after calcium. \* $P < .05$ ; † $P < .025$ ; # $P < .01$ .

pneumatically driven artificial heart is a useful model for studies of cardiovascularly active pharmacologic compounds. In addition to the advantage of the docility of the animal, ease of handling and instrumenting the bovine artificial heart model enables investi-

gation of drug action in animals in the absence of other pharmacologic or physiologic influences, *i.e.*, anesthesia or artificial respiration, which could modify the cardiovascular effects of the compound under investigation. In addition, and more important, utilization

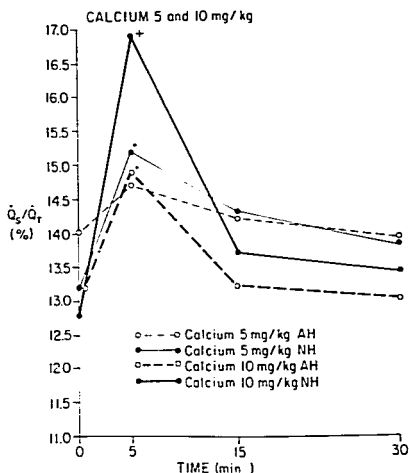
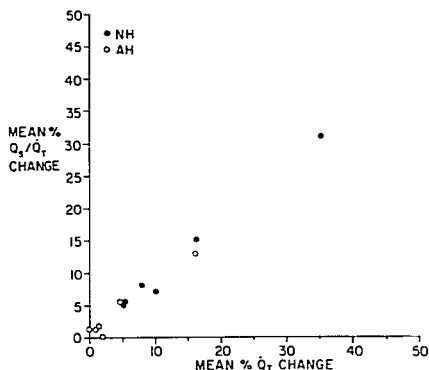


FIG. 9. Pulmonary shunt before and after calcium. \* $P < .05$ ; † $P < .025$ .

FIG. 10. Mean change in  $\dot{Q}_p/\dot{Q}_t$  versus mean change in  $\dot{Q}_t$  after calcium.



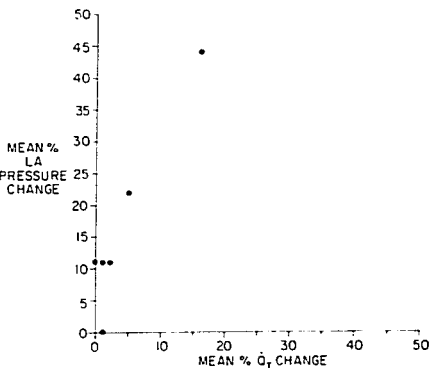
of an animal that has an artificial heart for drug investigation allows quantitation and separation of the effects of drugs on the peripheral vascular system (after AH replacement) from its effects on the heart plus the peripheral vascular system (before AH replacement).

The findings of this study using the bovine AH model document that intravenous administration of calcium chloride produces a significant, dose-related, but relatively transient reduction in peripheral arterial resistance. Our data also suggest that calcium has a significant positive inotropic effect in

the calf 5 minutes after administration, but only a minimal effect 10 or 25 minutes later.

The positive inotropic effect of calcium on the mammalian heart has been extensively investigated in isolated myocardial muscle preparations,<sup>7</sup> isolated-heart experiments,<sup>8,9</sup> intact experimental animals,<sup>10</sup> and man.<sup>11,12</sup> These reports document that calcium increases myocardial contractility and work; however, they also demonstrate that the major portion of the positive inotropic effect of calcium lasts less than 15 minutes.<sup>8,11,12</sup> Denlinger and colleagues<sup>12</sup> found that 7 mg/kg

FIG. 11. Mean change in  $\dot{Q}_p/\dot{Q}_t$  versus mean change in mean left atrial pressure after calcium.



calcium chloride administered intravenously caused significant increases in myocardial contractility in human volunteers anesthetized with halothane 1 and 3 minutes following administration but no significant change after 7 and 15 minutes. Shiner *et al.*<sup>11</sup> showed, in unanesthetized man, that peak elevations in myocardial contractility occur immediately after calcium infusion, are highly correlated with serum calcium values, and rapidly decrease thereafter. The above-mentioned data indicate that the effect of calcium on myocardial inotropy is transient. The results of our study are consistent with these findings.

Changes in  $\dot{Q}_i$  in NH calves depend on alterations in preload, afterload, and the contractile state of the heart. AH calves respond in a similar fashion except that the contractile state is fixed. Since calcium in the present study produced similar reductions in SVR in NH and AH calves after 5 minutes, differences in  $\dot{Q}_i$  in the two groups can be explained only by alterations in preload or myocardial inotropy. The response of AH hearts to changes in venous return (preload) is similar to that of NH hearts. Therefore, the difference in  $\dot{Q}_i$ 's in NH and AH calves after a given dosage of calcium must be the result of myocardial inotropic changes in NH calves. Our data demonstrate that increases in  $\dot{Q}_i$  after both doses of calcium were significantly greater in NH than in AH animals after 5 minutes. We attribute these differences to the inotropic action of calcium on the NH myocardium. Thereafter, SVR returned to control values in both NH and AH calves and  $\dot{Q}_i$  to pre-calcium levels in AH animals.  $\dot{Q}_i$  remained slightly but still significantly increased in NH calves 15 minutes after 5 mg/kg calcium and 15 and 30 minutes after 10 mg/kg. Whether  $\dot{Q}_i$  elevations at these times are the result of remaining positive inotropic activity, or reflect different sets of time constants for responses by natural ventricles and by artificial ventricles to a reduction in afterload, cannot be determined at this time.

The effect of calcium on the peripheral vasculature has not been as extensively or carefully studied as its effect on the heart, and what few data are available are contradictory.<sup>12-17</sup> Thus, while some investi-

gators<sup>12,14</sup> have shown calcium to have a constrictor effect on peripheral arterioles, others have reported the effects of calcium to be either insignificant<sup>13,16</sup> or vasodilatory.<sup>17</sup> The reason(s) for these different findings is not clear, but could be related to the methods of studying blood-vessel constriction and dilation, to use of different concentrations of calcium, or to the modifying influence of anesthetics. Most studies utilizing isolated vascular beds or measuring the peripheral vascular effects of calcium when injected into a peripheral artery have demonstrated vascular constriction.<sup>12,14</sup> The results of these studies may be attributed to the unphysiologic preparations employed, e.g., the dissected forelimb vessels of an anesthetized dog perfused with a pump and directly infused with various concentrations of calcium, or an artificial fluid perfusing an isolated vascular bed or a limb with all of its vessels ligated except one major artery or vein. Vasoconstriction in these preparations may also be related to the extremely high local concentrations of calcium following direct injection into the vessels under study. Direct injection of calcium in coronary arteries, for example, produces profound vasoconstriction and reduction in coronary-artery blood flow,<sup>10,12</sup> yet intravenous administration of similar amounts of calcium usually results in coronary-artery vasodilation with an increase in coronary-artery blood flow.<sup>10</sup> Unfortunately, as in our study, blood levels of total calcium and ionized calcium were not measured in the above-mentioned investigations.

Anesthetics can markedly alter the effect of calcium on the myocardium\*\*\* and may also modify the peripheral vascular effects of calcium. Pitt *et al.*<sup>10</sup> found that intravenous administration of calcium gluconate produced a significant increase in coronary vascular resistance in dogs anesthetized with pentobarbital but resulted in coronary vascular dilation in unanesthetized dogs trained to lie quietly. While the mechanism responsible for the findings of Pitt *et al.* is not

\*\*\* Price HL, Ohnishi T: A mechanism of anesthetic-induced myocardial depression—direct anesthetic interaction with cardiac troponin. Abstract, 1975 Annual ASA Proceedings, pp 53-54.

clear, an anesthetic that produces peripheral vasoconstriction or vasodilation could easily augment, diminish, or completely change the peripheral vascular effects of calcium.

The peripheral vascular effects of calcium in normal, unanesthetized man have not been studied in detail. However, what information is available suggests that calcium produces arterial vasodilation. Bernheim and London<sup>19</sup> and Weichsel<sup>20</sup> have shown that calcium chloride 1–2 g, decreases peripheral arterial resistance and produces a generalized cutaneous flush, a feeling of warmth, and reductions in arterial systolic and diastolic blood pressures. Because of these responses calcium chloride has been used to reduce vascular spasm in a variety of diseases. In a study of human volunteers anesthetized with halothane, Denlinger *et al.*<sup>12</sup> recently found that 7 mg/kg calcium produced a 14 per cent increase in cardiac index and a 12 per cent reduction in total peripheral resistance 7 minutes after administration. These authors discarded the likelihood that at least part of the increase in cardiac index might be due to an effect of calcium on SVR because animal work they reviewed suggested that calcium produces peripheral vasoconstriction. The findings of Denlinger *et al.*<sup>12</sup> in anesthetized man are not dissimilar to ours in unanesthetized calves. We found that 5 mg/kg calcium produced a 16 per cent increase in  $\dot{Q}_i$  and a 5 per cent reduction in SVR, while 10 mg/kg calcium increased  $\dot{Q}_i$  35 per cent and reduced SVR 22 per cent 5 minutes after administration. After AH implantation, 5 mg/kg calcium increased  $\dot{Q}_i$  5 per cent and reduced SVR 4 per cent, while 10 mg/kg calcium produced a 16 per cent increase in  $\dot{Q}_i$  and a 19 per cent reduction in SVR.

It is interesting that increases in left ventricular work (LVW) in the NH calves were similar after 5 and after 10 mg/kg calcium. AH calves, as expected, did not sustain a significant change in LVW after either dosage of calcium. These findings, coupled with the greater reductions in SVR after 10 mg/kg calcium than after 5 mg/kg in both NH and AH calves, suggest that maximal myocardial stimulation following calcium is achieved with doses approximating 5 mg/kg (at least after 5 minutes in

the calf) and further increases in  $\dot{Q}_i$  with higher doses of the compound are primarily the result of decreased afterload. The latter response appears to last only a short time irrespective of the dose of calcium employed.

In this study calcium produced significant elevations in  $\dot{Q}_i/\dot{Q}_i$  that appeared to be related to corresponding increases in  $\dot{Q}_i$ . Positive correlation of changes in  $\dot{Q}_i/\dot{Q}_i$  with simultaneous changes in  $\dot{Q}_i$  has also been found after administration of isoproterenol<sup>21,22</sup> and norepinephrine.<sup>21</sup> Recent work in this laboratory<sup>3,4,23</sup> has demonstrated that nonpharmacologic increases in  $\dot{Q}_i$  induced by changes in heart rate or left ventricular contractility in AH calves produce changes in  $\dot{Q}_i/\dot{Q}_i$  that are strongly positively correlated with  $\dot{Q}_i$  and negatively correlated with LA pressure. Although the exact mechanism(s) is unknown, these data suggest that pulmonary venous pressure and changes induced in this variable through pharmacologic or physiologic alterations in left ventricular or peripheral vascular dynamics may have a profound effect on  $\dot{Q}_i/\dot{Q}_i$ . Our data in this study present additional evidence to support this concept.

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