SUMMARY. The effects of verapamil (1 mg/liter, $2 \times 10^{-6}$ mol/liter), quiescence, and cardioplegia ($K^+ 16$ mmol/liter, $Mg^{2+} 16$ mmol/liter) on calcium exchange and mechanical function during ischemia and reperfusion have been investigated in the rabbit interventricular septum at $32^\circ C$. Calcium influx and efflux were recorded continuously with $^{47}$Ca$^{2+}$ and $^{45}$Ca$^{2+}$. After 60 minutes of total ischemia and reperfusion for 30 minutes, there was a net calcium gain of 4.9 mmol/kg dry tissue. Verapamil given before total ischemia reduced net calcium gain to 1.5 mmol/kg dry tissue ($n = 5, P < 0.03$). When given only on reperfusion after total ischemia, or 10 minutes before reperfusion during low flow ischemia, verapamil did not affect calcium exchange. Cardioplegia begun 10 minutes before total ischemia reduced net calcium gain to $1.0 \pm 0.26$ mmol/kg dry tissue ($n = 6, P < 0.001$). Cardioplegia during the first 10 minutes of reperfusion, or lack of electrical stimulation during reperfusion, did not reduce calcium gain. Net calcium gain correlated with the maximum rise in resting tension and with the recovery of developed tension. In control experiments, neither verapamil nor cardioplegia altered influx or efflux of slowly exchanging calcium. The cardioprotective effects of cardioplegia and the calcium channel blocker verapamil appear to be due to a reduction of myocardial work rather than to any specific direct action on calcium fluxes across the myocardial cell membrane. (Circ Res 50: 360-368, 1982)

MYOCARDIAL ischemia in humans occurs after myocardial infarction or during open heart surgery under conditions of cardiopulmonary bypass. Limitation of the size of the necrotic area in myocardial infarction and preservation of myocardial function after cardiac surgery are important therapeutic objectives. During reperfusion after a period of ischemia, calcium accumulates in myocardium (Shen and Jennings, 1972a, 1972b; Whalen et al., 1974) and particularly in mitochondria (Kloner et al., 1974; Henry et al., 1977). The cause of this calcium accumulation, its relationship to changes in mechanical function, and the ways in which it can be modified by pharmacological and other interventions remain unclear.

Since part of the total calcium influx into the myocardial cell is through the slow calcium channel of the cardiac action potential, this channel may be the pathway for calcium accumulation associated with reperfusion after ischemia. Verapamil and other calcium antagonists block the slow calcium current of the action potential (Kohlhardt et al., 1972a, 1972b; Cranefield et al., 1974; Kohlhardt and Mnich, 1978; Henry, 1980). When these drugs are given prior to or at the onset of a period of ischemia, they have been shown to preserve tissue ultrastructure (Reimer et al., 1977), to reduce enzyme release (Wende et al., 1975; Smith et al., 1977; Lefer et al., 1979), to diminish S-T elevation (Lefer et al., 1979; Selwyn et al., 1979) to improve hemodynamic function (Magee et al., 1979; Clark et al., 1979), to maintain tissue ATP (Lefer et al., 1979; Watts et al., 1979; Nayler et al., 1980; Weishaar and Bing, 1980), and to prevent calcium accumulation in whole tissue and isolated mitochondria (Henry et al., 1977; Watts et al., 1979; Lefer et al., 1979; Nayler et al., 1980). The uniformly beneficial results obtained in such experiments are in sharp contrast to the results of experiments in which calcium antagonists have been administered, not prior to ischemia, but either after the ischemic myocardium has ceased to contract or at the time of reperfusion. Under these conditions, cardiac function is not preserved (Watts et al., 1980), tissue ATP is not maintained (Watts et al., 1980), calcium accumulation is not prevented (Lefer et al., 1979; Watts et al., 1980), and enzyme release is unaltered (Karlsberg et al., 1977). However, Weishaar et al. (1979) have reported that diltiazem given after 10 minutes of ischemia halved the subsequent decrease in ATP but had no effect on mitochondrial function.

In a recent study utilizing $^{47}$Ca$^{2+}$, $^{45}$Ca$^{2+}$, and $^{51}$Cr-EDTA to measure calcium fluxes and the extracellular space during ischemia and reperfusion of the isolated interventricular septum of the rabbit (Bourdillon and Poole-Wilson, 1981), calcium accumulation on reperfusion was shown to be due to increased influx probably related not to gross disruption of the cell membrane but to a specific abnormality of ionic channels. The extent of the calcium accumulation was related to the severity and duration of ischemia and to the degree of mechanical recovery. To assess the precise role of the slow calcium channel in the myocardial accumulation of calcium after ischemia, we have used...
the same technique to compare the effects of verapamil, cardioplegia, and discontinuation of electrical stimulation (quiescence). Interventions have been made both before and after the onset of ischemia.

**Methods**

The experimental preparation was the isolated but arterially perfused interventricular septum of the adult New Zealand White rabbit (Poole-Wilson and Langer, 1975; Bourdillon and Poole-Wilson, 1981). Rabbits, weighing 2.2-2.5 kg, were heparinized (2000 U) and killed by an overdose of sodium pentobarbital (120 mg). The chest was opened and the heart removed. Within 4 minutes, the septal artery was cannulated and the septum perfused, using a roller pump (Watson-Marlow). Underperfused tissue was excised and the triangular-shaped septum was mounted with its base fixed by forceps at each side and its apex attached to a transducer (model UF1, Devices). Tension and rate of tension development were recorded continuously (model M4, Devices). Only septa with 10 g or more developed tension, and 10 g or less resting tension at 28°C and 50 beats/min were used for experiments. For each experiment, perfusate flow was constant, except during periods of ischemia. Mean flow was 2.15 ml/min per g (range 1.6-3.0 ml/min per g). The septa were electrically stimulated with impulses of 15 V and duration 5 msec (model 6032, Scientific Research Instruments). For each experiment, the rate was kept constant between 72 and 82 beats/min (mean 74 beats/min). The perfusate contained the following constituents in mmol/liter: NaCl, 114; KCl, 5.0; MgCl₂, 1.0; CaCl₂, 1.8; NaHCO₃, 28; NaH₂PO₄, 0.43; d-glucose, 5.56. The solution was equilibrated with a gas mixture of 95% O₂ and 5% CO₂; pH was 7.3.

For experiments with verapamil, a measured quantity of the drug was added to the perfusate to give a concentration of 1 mg/liter (2 × 10⁻⁶ mol/liter). For experiments with cardioplegia, the perfusate was made up to contain KCl 16 mmol/liter and MgCl₂ 16 mmol/liter, with a corresponding reduction in NaCl to 88 mmol/liter.

The septum was mounted in a Perspex chamber so that muscle temperature could be maintained constant at 32.0 ± 0.25°C during periods of ischemia. Perfusion was warmed by a thermostatically controlled heating coil adjacent to the cannula. The chamber was heated by a water-filled radiator through which nitrogen gas was bubbled. The humidified gas was circulated in the chamber by a small electric fan.

Through the side of the chamber a large sodium iodide crystal (5 cm diameter, type N599D, Ekco Electronics) was introduced so that its flat face was within 3 mm of the septum. The crystal was connected to a scintillation counter and used to monitor uptake of ⁴⁷Ca²⁺ (peak 1.30 meV) (Poole-Wilson and Langer, 1979; Harding and Poole-Wilson, 1980; Bourdillon and Poole-Wilson, 1981). The lower window was set at 600 keV to avoid counting radioactivity from ⁴⁷Sc³⁺ (peak 159 keV), the daughter of ⁴⁷Ca²⁺. Isotopes were obtained from Radiochemical Centre). A 15-cm lead screen was placed between the muscle and the perfusate store containing isotope. Effluent from the septum was returned to a waste container behind the lead screen close to the perfusate store and at a distance of one meter from the septum. With this arrangement, background counts were constant and less than 10% of total counts.

Calcium efflux was assessed by measuring the washout of ⁴⁷Ca²⁺ (Shine et al., 1971) after labeling for 40 minutes. Four drops of effluent were collected over a timed period at 20 seconds to 2 minute intervals. To these aliquots were added 10 ml of scintillant containing alcohol 500 ml, toluene 500 ml, PPO (2,5-diphenyloxazole) 4 g/liter, and POPOP (1,4-di-2-(5-phenyloxazolyl) benzene) 50 mg/liter. The activity was counted in a liquid scintillation counter (model 3380, Packard Instruments). Radioactivity was expressed as counts/min per min of perfusate flow in order to take account of any small changes in flow (Poole-Wilson and Langer, 1975, 1979).

In all experiments, an equilibration period of 90 minutes was allowed. In uptake experiments, interventions were introduced after a 40-minute labeling period with ⁴⁷Ca²⁺. In efflux experiments, interventions were introduced 8 minutes after the start of the washout of isotope. At the end of each experiment, the septum was blotted and weighed. Isotopic activity was measured in a γ counter (model 6500, ICN) and compared to the activity of a weighed quantity of perfusate. The septum then was dried to constant weight in an oven at 100°C. Tissue water was expressed as a percentage, being the volume of water (ml) per 100 g of wet tissue. From these measurements, the amount of tissue calcium that had been labeled with ⁴⁷Ca²⁺ could be calculated in mmol/kg dry tissue.

To measure total calcium in septa perfused under control conditions, tissue was dried, digested in concentrated nitric acid, and diluted to 100 ml. Lanthanum chloride (1.3 mmol) was added. Calcium was measured with an atomic absorption spectrophotometer (model 306, Perkin-Elmer).

Results are expressed as the mean ± SEM. Differences between groups of experiments were analyzed with Student's t-test.

**Control Conditions**

Resting tension and developed tension in the experimental preparation were stable over 130 minutes (Fig. 1; Table 1). Initial uptake of ⁴⁷Ca²⁺ was rapid due to labeling of the vascular and extracellular spaces. Subsequently, ⁴⁷Ca²⁺ uptake became slower and complete equilibration was not reached. Total tissue calcium was 22.7 ± 2.1 (n = 4) mmol/kg dry tissue. The amount of labeled calcium after 130 min was 21.3 ± 2.6 mmol/kg dry tissue, representing 94% of the total tissue calcium.

**FIGURE 1.** Developed tension (T), the first differential of developed tension with respect to time (dv/dt) and tissue counts (cpm) of ⁴⁷Ca²⁺ in a control experiment. The early rise is tissue counts is due to uptake into the intravascular and extracellular spaces.
With the onset of total ischemia, developed tension fell to zero within 15 minutes and resting tension fell by 0.9 ± 0.2 g (n = 6) (Table 1; Fig. 2A). During 60 minutes of ischemia, there was a gradual rise in resting tension from 6.8 ± 1.2 to 15.3 ± 1.7 g. On reperfusion, there was a further rise to a maximum of 19.2 ± 1.2 g after 4 minutes of reperfusion, with a subsequent decline to 13.9 ± 1.2 g after 30 minutes. The mean maximum rise in resting tension from the pre-ischemic level of 7.7 ± 1.2 g was 11.5 ± 1.7 g. Developed tension recovered to 27 ± 4.2% of the pre-ischemic mean value of 15.9 ± 1.7 g.

The changes in mechanical function and $^{47}$Ca$^{2+}$ uptake associated with 30 minutes of total ischemia were less than with 60-minute ischemia (Table 1). The maximum rise in resting tension was smaller (5.6 ± 1.4 g, n = 5, P < 0.05), recovery of developed tension on reperfusion for 30 minutes was greater 59.5 ± 3.1% (P < 0.001) and the calcium gain was less (4.0 ± 0.25 mmol/kg dry tissue, P < 0.01). The changes after 30 minutes of ischemia were all significantly different from control experiments (P < 0.001).

Low Flow Ischemia

With the onset of low flow ischemia (0.18 ± 0.02 ml/min per g, n = 5), the early decline in developed tension was less rapid than with total ischemia and the level to which resting tension rose during the subsequent 60 minutes was less (6.5 ± 1.5 g; P < 0.01) (Table 1, Fig. 2B). On reperfusion at the control flow rate, tissue counts increased rapidly to control levels and the increase of labeled calcium after 30 minutes was 4.4 ± 0.25 mmol/kg dry tissue, greater than in control experiments (P < 0.01) but less than with total ischemia for 60 minutes (P < 0.02).

Verapamil

The effect of the slow channel blocker verapamil on the increased uptake of $^{47}$Ca$^{2+}$ associated with ischemia and reperfusion was studied using a concentration of 1 mg/liter (2 X 10$^{-5}$ mol/liter). Preliminary experiments showed that this concentration was suf-
The developed tension recovered slowly but did not return to control levels after 70 minutes of perfusion (Fig. 3A). Verapamil given for 30 minutes caused only a minimal transient rise in 

\[ \text{Ca}^{2+} \] uptake which could be accounted for by a small rise in extracellular space (Poole-Wilson et al., 1981). On reperfusion, the counts increase rapidly due to a greater influx.

When verapamil was added to the perfusate 50 minutes before ischemia and continued during reperfusion after 60 minutes of total ischemia (Table 1; Fig. 3B), the increase in labeled calcium on reperfusion (4.3 ± 0.7 mmol/kg dry tissue, \( n = 5 \)) was less than in the absence of the drug (\( P < 0.03 \)). The rise in resting tension during ischemia and reperfusion was also less (\( P < 0.02 \)).

When verapamil was given only on reperfusion after 60 minutes of total ischemia (Table 1; Fig. 3C), the increase of labeled calcium (5.7 ± 1.1 mmol/kg dry tissue, \( n = 7 \)) and the maximum rise in resting tension (11.0 ± 1.6 g) were not significantly reduced. When given 10 minutes before reperfusion during low flow ischemia (0.20 ± 0.02 ml/min per g, \( n = 5 \)) and during reperfusion (Table 1; Fig. 3D), verapamil had no significant effect on the subsequent increase of labeled calcium (4.0 ± 0.54 mmol/kg dry tissue, \( n = 5 \)) and the maximum rise in resting tension (7.0 ± 1.6 g).

**Cardioplegia**

Under control conditions, perfusion with Mg\( ^{2+} \) (16 mmol/liter) alone resulted in a 10% fall in developed tension. With K\( ^{+} \) (16 mmol/liter) alone developed tension fell by 90%. With Mg\( ^{2+} \) (16 mmol/liter) and K\( ^{+} \) (16 mmol/liter) together, developed tension was abolished completely (Table 1; Fig. 4A). In control experiments (\( n = 4 \)), perfusion with this combined cardioplegic solution for 20 minutes caused a small transient rise in \( \text{Ca}^{2+} \) uptake which could be accounted for by a small rise in extracellular space during cardioplegia (Poole-Wilson et al., 1979). There was no significant change, when compared to controls, in mechanical function and calcium gain on subsequent reperfusion with control perfusate.

When perfusion with cardioplegic solution was given for a 10-minute period prior to 60 minutes of total ischemia (Table 1; Fig. 4B) the increase of labeled calcium on reperfusion with control perfusate was reduced to 2.8 ± 0.26 mmol/kg dry tissue (\( n = 6 \), \( P < 0.001 \)). Developed tension recovered more, to 68 ± 4.2% of pre-ischemic levels (\( P < 0.001 \)). The rise in resting tension was reduced both during ischemia and during the early part of reperfusion. The maximum rise in resting tension was less than without cardioplegia (3.1 ± 0.42 g, \( P < 0.01 \)).

When cardioplegic solution was introduced for a 10-minute period starting at the beginning of reperfusion (Table 1; Fig. 4C) the increase of labeled calcium after a further 20 minutes with control perfusate was 5.6 ± 0.5 mmol/kg dry tissue (\( n = 5 \)), not significantly less than the increase with cardioplegia. The mean rise in resting tension was 11.8 ± 1.4 g and the mean recovery of developed tension was 26 ± 2.4%, both similar to the changes in mechanical function without cardioplegia.

**Quiescence**

In order to assess further the role of the slow calcium current in the calcium accumulation on reperfusion after ischemia, we investigated the effect of discontinuing electrical stimulation of the septum during reperfusion. Without stimulation and in the absence of spontaneous activity, there is no action potential and therefore no slow calcium current. The spontaneous heart rate was not greater than 20 beats/min in any preparation; three of five muscles were virtually silent.

The mean increase in labeled calcium in this group of experiments was 5.6 ± 0.7 mmol/kg dry tissue (\( n = 5 \), Table 1, Fig. 5), not different from the group in which stimulation was continued during reperfusion. In four of the five experiments, there was a further rise in resting tension during the first 4 minutes of
reperfusion and the mean maximum rise in resting tension was 12.2 ± 1.9 g, similar to control muscles stimulated at 74 beats/min.

**Calcium Gain and Mechanical Function**

The increase in labeled calcium was related to the maximum rise in resting tension (Fig. 6). The recovery of developed tension (Fig. 7) was inversely related to the increase of labeled calcium; experiments with verapamil, in which the drug was given during reperfusion, and experiments in which stimulation was discontinued during reperfusion are excluded, since there was no recovery of developed tension.

**Efflux of 47Ca2+**

Efflux of 47Ca2+ was not altered significantly by either verapamil (Fig. 8A) or cardioplegic solution (Fig. 8B) under control conditions.

**Discussion**

Previous measurements of tissue calcium during or after a period of ischemia have been made by atomic absorption spectrophotometry (Shen and Jennings, 1972a; Whalen et al., 1974; Henry et al., 1977; Lefer et al., 1979) or using 4Ca2+ (Shen and Jennings, 1972b). Only a single value is obtained in each experiment. The effect of interventions, the timing of changes in calcium content, and the relationship to mechanical function have to be deduced from the results of many experiments. The techniques used in our study and in previous work (Poole-Wilson and Langer, 1979; Harding and Poole-Wilson, 1980; Ponce-Hornos and Langer, 1981; Bourdillon and Poole-Wilson, 1981) allow continuous monitoring of 47Ca2+ uptake so that each experiment is used as its own control and small changes can be detected with some accuracy. The tissue calcium in control muscles was 22.4 mmol/kg dry tissue and rapid changes as small as 0.2 mmol/kg dry tissue could be detected (Poole-Wilson and Langer, 1979).

During ischemia, effluent drops continue to fall away from the muscle for approximately 5 minutes. Consequently, the extracellular space, measured continuously with 51Cr EDTA (Poole-Wilson et al., 1979), is reduced and accounts for the early fall in counts of 47Ca2+ (Bourdillon and Poole-Wilson, 1981) (Fig. 2). On reperfusion after total ischemia or low flow ischemia, the extracellular space rapidly increases to the control value and thereafter alters only slightly; the efflux of calcium is essentially unchanged (Bourdillon and Poole-Wilson, 1981). The increase of the rate of 47Ca2+ uptake on reperfusion (Fig. 2) can, therefore, be interpreted as an increase of influx. We have previously argued that, on reoxygenation after hypoxia (Harding and Poole-Wilson, 1980) and on reperfusion after ischemia (Bourdillon and Poole-Wilson, 1981), the sudden increase of calcium influx is
due to a specific increase in the permeability of the cell membrane to calcium.

The present study was undertaken to determine whether the uptake of calcium on reperfusion after ischemia was inhibited by verapamil, cardioplegia, or a lack of electrical stimulation. Verapamil is a calcium antagonist which inhibits the slow calcium current associated with the myocardial action potential. The drug is not specific for the calcium current and also inhibits a slow sodium current which may pass through the same ionic channel (Henry, 1980). Under control conditions, neither verapamil nor cardioplegic solution had any effect on calcium efflux or influx as measured by our methods (Fig. 8). Shine and Douglas (1974) have shown that, although magnesium does
tension could not be studied in experiments with verapamil because, on removal of the drug, the negative inotropic effect is reversed only slowly even under control conditions (Fig. 3). The same interventions at the time of reperfusion had no effect. The results cannot be explained by supposing that the intervention did not reach the ischemic tissue until a few minutes after reperfusion when damage might be complete. The introduction of verapamil during low flow ischemia, 10 minutes before reperfusion, also failed to reduce calcium uptake.

The observation that verapamil and cardioplegia do not directly inhibit calcium entry on reperfusion is in contrast to many studies (Wende et al., 1975; Reimer et al., 1977; Smith et al., 1977; Lefer et al., 1979) which have shown that, when given prior to a period of ischemia, calcium antagonists delay or prevent tissue damage, and also reduce calcium accumulation (Henry et al., 1977; Witts et al., 1979; Lefer et al., 1979; Nayler et al., 1980). There are fewer reports of the effects of calcium antagonists given after the onset of ischemia. Karlsberg et al. (1977) showed, in dogs, that verapamil given 5 hours after occlusion of a coronary artery did not alter creatine kinase release or myocardial blood flow. Smith et al. (1977) gave verapamil 15 minutes after occlusion of the left anterior descending coronary artery in dogs; myocardial blood flow and lactate production were unchanged, although the elevation of S-T segments was tran-

-**Figure 7.** The relationship between the gain in labeled calcium and developed tension. The greater the gain in labeled calcium the smaller is the percentage recovery of developed tension. Experiments with quiescence and verapamil have been excluded because there, by definition, was no developed tension in the unstimulated muscle and the negative inotropic effect of verapamil reverses slowly (Fig. 3).

-**Figure 8.** Efflux of 45Ca2+ in single experiments compared to controls (n = 5). Verapamil (A) or cardioplegic solution (B) was given for 10 minutes, beginning 8 minutes after the start of washout of 45Ca2+. A
siently reduced. Watts et al. (1980), in globally ischemic rat hearts, showed that verapamil given after the onset of ischemia did not prevent calcium accumulation or the decline of tissue ATP. In Langendorff rabbit hearts, addition of verapamil to the perfusate, after the decline in developed tension caused by hypoxia, does not prevent the subsequent rise in resting tension (Nayler et al., 1978). These studies, taken in conjunction with our own, strongly suggest that verapamil is beneficial to ischemic myocardium not because calcium influx is directly inhibited but because of its cardioplegic effect. The reduction in developed tension, heart work, and rate of ATP consumption prevents a rapid decline of ATP at the onset of ischemia so that ATP is available to maintain cellular integrity. The similarity of our results obtained with verapamil, cardioplegia, and quiescence supports the conclusion.

In animals with an intact circulation, two further considerations are important. The systemic vasodilator effect of calcium antagonists, particularly nifedipine, may alter cardiac hemodynamics in such a manner as to increase coronary or collateral blood flow to ischemic muscle. Calcium antagonists may directly dilate collateral arteries with a resulting increase of blood flow to the ischemic myocardium. Special experimental conditions may be necessary to demonstrate such a phenomenon in animals since, in humans, collaterals develop over long periods of time. Two groups (Karlsberg et al., 1977; Smith et al., 1977) have shown that verapamil given after the onset of ischemia did not alter blood flow to the ischemic muscle, whereas Henry et al. (1979), using a model designed to detect collateral flow, were able to demonstrate that nifedipine did enhance contractile performance of ischemic myocardium and did increase collateral blood flow.

The recovery of developed tension (Fig. 7) and the increase of resting tension (Fig. 6) were both related to the extent of calcium accumulation. Calcium accumulation could be either a primary event leading to cell necrosis on reperfusion of ischemic myocardium by analogy with similar findings during reoxygenation of hypoxic myocardium (Harding and Poole-Wilson, 1980), or the result of damage occurring during ischemia but manifest only on reperfusion, or the secondary consequence of lack of tissue ATP to maintain normal calcium homeostatic mechanisms. These present experiments cannot distinguish between these possibilities but do support the contention that calcium homeostasis is linked closely to cell survival (Shen and Jennings, 1972a; Fleckenstein et al., 1979).

Whatever the role of calcium in cell necrosis, our results indicate that the influx of calcium is not primarily through the slow calcium channel. If it were, then verapamil and quiescence would be expected to alter the flux, and they do not (Figs. 3 and 5). An alternative explanation is that, under ischemic conditions, verapamil might not inhibit calcium influx through the slow channels as it does under control conditions. However, verapamil is reported to have a greater, not smaller, negative inotropic effect on ischemic compared to normal myocardium (Smith et al., 1976), suggesting that verapamil does still block calcium channels under ischemic conditions. The failure of quiescence to alter the calcium influx provides support for the argument that the influx is not through the slow calcium channel. Furthermore the gain of calcium appears not to be voltage dependent. There was no difference between the calcium gain on reperfusion with normal perfusate (Fig. 2) and the calcium gain in experiments in which the extracellular potassium (cardioplegic solution, Fig. 4) was maintained high throughout reperfusion. In the former experiments, the cell would be depolarized only early during reperfusion, before potassium that had accumulated during ischemia (Hirche et al., 1980) was washed out, whereas, in the latter experiments, the cell would be depolarized throughout reperfusion. If calcium gain were dependent on the degree of depolarization of the cell membrane (voltage dependence), a difference would have been expected. Our experiments indicate that if the calcium accumulation is due to altered membrane permeability (Bourdillon and Poole-Wilson, 1981) and not gross disruption of the cell membrane, then the movement is likely to be through a pathway other than the slow calcium channel, possibly via a sodium or hydrogen ion/calcium exchange mechanism.

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