

Effects of Vanadate on Cellular Ca^{2+} Movements in Guinea Pig Papillary Muscles

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The effects of vanadate on cellular Ca^{2+} movements across the sarcolemma of cardiac muscle cells were investigated by measuring the intracellular and extracellular Ca^{2+} activities of guinea pig papillary muscle with Ca^{2+} -selective electrodes. During the rest period following a steady-state of 2 contractions per second, the extracellular Ca^{2+} concentration was increased over the basal level within a minute. During the rest period, Ca^{2+} was transported across the sarcolemma into the extracellular space. Vanadate decreased the change in extracellular Ca^{2+} concentration during the rest period, implying that the Ca^{2+} efflux across the sarcolemma was decreased by vanadate. Vanadate increased intracellular Ca^{2+} activities significantly (from 1.9×10^{-7} M to 10^{-6} M) resulting in an increase in resting tension. These results suggest that vanadate decreases Ca^{2+} efflux from the cells into the extracellular space by blocking Ca^{2+} transport across the sarcolemma, possibly blocking the $\text{Na}^+ - \text{Ca}^{2+}$ exchange transport.

Key Words: Guinea pig papillary muscle, $\text{Na}^+ - \text{Ca}^{2+}$ exchange transport, Ca^{2+} -selective electrodes, intracellular Ca^{2+} activity, vanadate

It has been known that Na^+ has an important role in cardiac muscle contractility (Sulakhe and St. Louis 1980; Mullins 1981). In 1968 Reuter and Seitz reported that Ca^{2+} efflux from the guinea pig auricle is not directly dependent upon metabolism but upon the ratio of Ca^{2+} and Na^+ in the bathing medium (Reuter and Seitz 1968; Reuter 1974). Ca^{2+} is moved across the membrane coupled with a Na^+ influx, the driving force of which is maintained through the active transport of Na^+ ($\text{Na}^+ - \text{Ca}^{2+}$ exchange process).

The contribution of the $\text{Na}^+ - \text{Ca}^{2+}$ exchange process to the maintenance of a low Ca^{2+} concentration in the sarcoplasm (and a relaxed state of the contractile system) was shown by producing a net release of Ca^{2+} from the sarcoplasmic reticulum (SR) by caffeine (Jundt *et al.* 1975). The rate of net efflux of Ca^{2+} from the cell, in the presence of caffeine, depends

upon the Na^+ concentration of the bathing medium. Caffeine-contraction in a Na^+ -free solution relaxes upon addition of Na^+ to the bathing medium; this is correlated with the increase in net efflux of Ca^{2+} . However, the relaxation is rather slow requiring many minutes and it is more likely that a $\text{Na}^+ - \text{Ca}^{2+}$ exchange is involved in the maintenance of total intracellular Ca^{2+} at an appropriate level rather than being important in the rapid regulation of sarcoplasmic Ca^{2+} during a normal twitch.

In attempts to investigate the cellular movements of Ca^{2+} , the extracellular Ca^{2+} concentration of guinea pig atrium was measured during rest periods (Suh 1983; Suh and Sleator 1982, 1983). The extracellular Ca^{2+} concentration was decreased for a few seconds before it started to increase during the rest period (Suh and Sleator 1982). A low concentration of ryanodine (5×10^{-8} M), which blocked the post-rest contraction, enhanced the increase in extracellular Ca^{2+} concentration. Changes in extracellular Ca^{2+} concentration during rest periods were dependent upon the extracellular Na^+ concentration (Suh and Sleator 1983). It was suggested that the amount of Ca^{2+} leaving the cell decreases for a few seconds as Ca^{2+} is retained within intracellular stores and then the cell starts to lose Ca^{2+} across the sarcolemmal membrane into the extracellular space via a Na^+ -dependent process, a $\text{Na}^+ - \text{Ca}^{2+}$ exchange (Suh 1983). The involvement of a $\text{Na}^+ - \text{Ca}^{2+}$ exchange in the transsarcolemmal Ca^{2+}

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* The term "extracellular space" in this study represents the immediate space outside the cells but within the tissue. This has been called "paracellular space" by other authors (Martin and Morad 1982). The space outside the tissue is referred to here as the bathing medium.

transport can be tested by employing pharmacological blocking agents. However, no agent with this single function is known at present.

Vanadate is known to have a negative inotropic effect on guinea pig atria (Borchard *et al.* 1979; Grupp *et al.* 1979; Takeda *et al.* 1982) and a positive inotropic effect on ventricular muscle and other cardiac tissues (Hackbarth *et al.* 1978; Borchard *et al.* 1979; Grupp *et al.* 1979; Takeda *et al.* 1980). The mechanism of these effects is not yet understood. However, interference with the Ca^{2+} efflux by blocking of the Na^+ - Ca^{2+} exchange transport would be one possible mode for vanadate's positive inotropic action (Suh and Sleator 1983). Recently, the effects of vanadate on Ca^{2+} fluxes across the sarcolemma of guinea pig cardiac tissues were studied (Park 1986). Ca^{2+} efflux rates from intracellular Ca^{2+} pools of guinea pig left atria and right ventricular tissue were significantly decreased by vanadate and the pool sizes of both tissues were significantly increased by vanadate. Ca^{2+} influx into the left atria was decreased by vanadate, while Ca^{2+} influx into the right ventricular tissue was not affected by vanadate. These data imply that the positive inotropic effect of vanadate on ventricular muscle is due to a reduced efflux of activator Ca^{2+} and that a reduced influx of Ca^{2+} is responsible for its negative inotropic effect on atrial muscle.

Thus, in this study, the effects of vanadate on Ca^{2+} movements across the sarcolemma of ventricular tissue were investigated by measuring the intracellular Ca^{2+} activities and the changes in Ca^{2+} concentration in the extracellular space* of cardiac muscle preparations during the rest period with Ca^{2+} -selective electrodes. Transmembrane Ca^{2+} movements were correlated with the positive inotropic effect of vanadate on ventricular tissue.

METHODS

Guinea pigs of either sex ranging in size from 200 to 500 grams were sacrificed with a blow to the head. The heart was rapidly excised and placed in oxygenated (95% O_2 , 5% CO_2) modified Krebs-Henseleit (KH) solution. Right ventricular papillary muscles were dissected free of other tissue, the base and the apex were tied with surgical silk threads, and then were transferred to a recording chamber which was continuously perfused with the oxygenated KH solution. Tension was monitored by a Model 400A Force Transducer System (Cambridge Technology, Inc.) and displayed on a Tektronix 7313 Oscilloscope and on a Gould Brush 220 recorder along with the signal from

the differential electrometer for the Ca^{2+} -selective electrode (CSE). Stimulating current provided by a Grass S11 stimulator was passed through a pair of platinum wires. The temperature in the recording chamber was maintained at $32.5 \pm 0.2^\circ\text{C}$. The KH solution had the following composition in millimoles per liter (mM): NaCl 119; KCl 4.8; KH_2PO_4 1.2; NaHCO_3 24.8; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 1.2; CaCl_2 2.53; dextrose 10.

Transmembrane action potentials were recorded between 3 M KCl-3% agar bridge in the bath and a standard microelectrode (RE) filled with 3M KCl. The microelectrodes, pulled from microfiber capillary tubings (WPI Inc.), had a typical resistance in the range of 5-20 megohms and tip diameters of less than 0.5 microns.

The resin used for the Ca^{2+} -selective electrodes was provided by Professor W. Simon. The mixture was that of Oehme *et al.* (Oehme *et al.* 1976). Polyvinylchloride (PVC), approximately 10% by weight, was added to the mixture for the better stability of CSE.

Glass microelectrodes were pulled from borosilicate glass capillaries (WPI 1B200F6) which had been cleaned with alcohol, boiled in distilled water, and dried completely. Glass pipettes were inserted, tip upward, into holes drilled into a small Teflon plate. The Teflon plate with the pipettes was placed on the top of a bottle containing a small drop of pure dichlorodimethylsilane and then placed in an oven at 200°C . The silane vapor was allowed to react with the glass for 30 minutes. The silanized pipettes were filled with a 100 mM CaCl_2 reference solution. A column of exchanger resin was forced into the electrodes by means of a partial vacuum. The electrode was observed to be filled with resin to the tip length up to several 100 microns.

The e.m.f. from the CSE was measured with an electrometer (Analog Devices 311J or AD515 operational amplifier, Norwood, MA U.S.A.), and membrane potential measured by the RE was electronically subtracted from the e.m.f. measured with the CSE. Ca^{2+} -selective electrodes were normally checked before and after the experiments.

Generally, the performance of the CSE is quite variable. Each electrode was tested for response and left in the KH solution for at least one hour before being used. The Ca^{2+} -standard solutions containing pCa 2, 3, and 4 were made by dilution from a 100 mM CaCl_2 solution. The solutions for pCa 5, 6, 7, and 8 were made from a Ca^{2+} buffer containing EGTA (Suh 1983). Figure 1 shows the calibration curves for one electrode. Without a major monovalent cation (Na^+), a calibration plot virtually gives a Nernstian response down to pCa 7 and further useful responses down to pCa 8. The major monovalent cation starts to in-

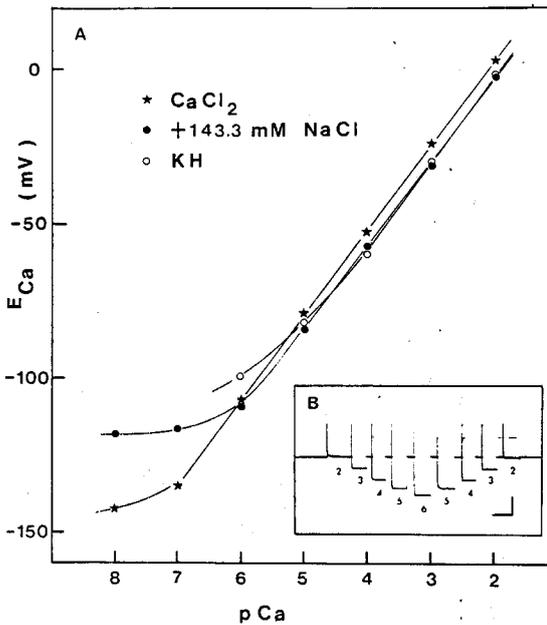


Fig. 1. Calibration curves for the Ca^{2+} -selective electrode. A. Interference from Na^+ in the KH solution appear at pCa 6. B. A chart-recording of the calibration in the KH solution. Horizontal scale = 10 seconds. Vertical scale = 50 mV.

terfere at pCa 6, and the KH solution has a similar interference. For intracellular recordings Ca^{2+} -standard solutions were made with an ionic background of 100 mM KCl instead of the KH solution. The Ca^{2+} activity coefficient of 0.32 was used to calculate Ca^{2+} activity in the solution (Lee 1981).

RESULTS

Vanadate's effects on contractility of papillary muscle

The steady-state contractions of papillary muscle were measured at various stimulation frequencies (Fig. 2). After the tissue was equilibrated for 1 hour at 1 contraction per second (cps), steady-state contractions of stimulation frequencies, in the order of 1, 2, 0.1, 0.2, 0.5, and 1 cps, were measured. Vanadate ($200 \mu\text{M}$) was then added to the perfusion solution while the tissue was stimulated at a frequency of 1 cps. When a new steady state of 1 cps was reached, steady-state contractions were measured with the same sequence of stimulation frequencies as that of the control. While vanadate increased contractile strength at all frequencies, the increase in contractility

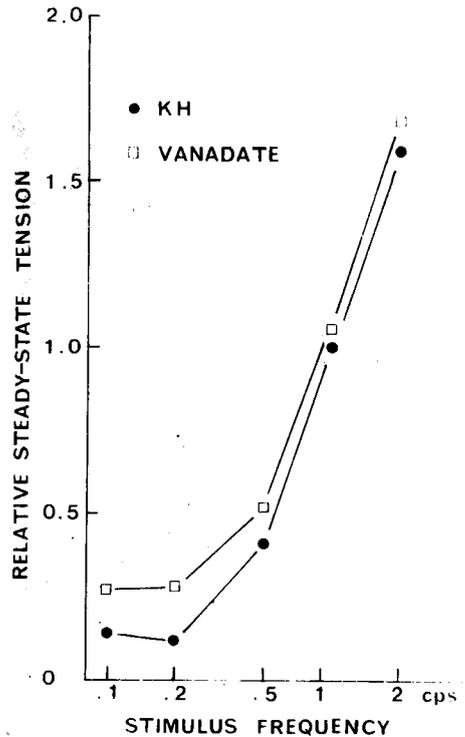


Fig. 2. Vanadate's effects on the steady-state contraction of guinea pig papillary muscle. Heart tissue was treated with vanadate ($200 \mu\text{M}$) while the tissue was stimulated at 1 cps. Effects of vanadate on steady-state contractions were measured after a steady-state of 1 cps with vanadate was reached.

was much larger at low stimulation frequencies.

The increase in contractile strength was significant when vanadate's effects on contractions and action potentials were measured at one of the low stimulation frequencies (0.2 cps). Fig. 3 shows that the resting and twitch tensions were significantly increased when the tissue was perfused with a vanadate-containing solution ($200 \mu\text{M}$) for 10 minutes. The increased contractile strength attributed to vanadate was diminished after the tissue was perfused with the normal KH solution. However, there were no significant changes in the action potential configurations.

Changes in extracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_e$) during the rest period

Rest periods were given after a steady-state of 2 cps was reached, and the extracellular Ca^{2+} concentrations during the rest periods were measured (Fig. 4). When the stimulus was stopped and a rest period was given, $[\text{Ca}^{2+}]_e$ started to increase and reached a

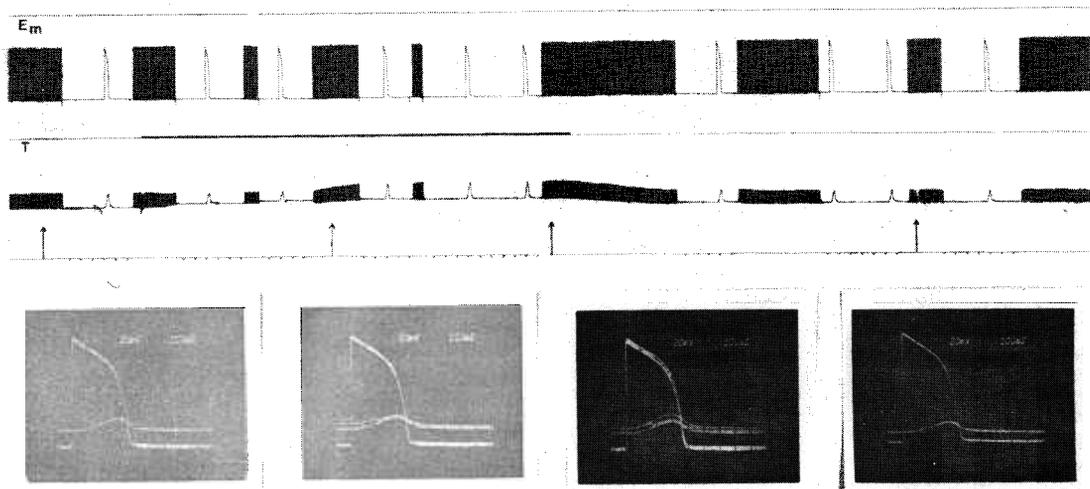


Fig. 3. Effects of vanadate on contractility and action potential.

Heart tissue was stimulated at 0.2 cps. When the tissue was treated with vanadate (200 μ M), there was an increase in resting tension and steady-state contractions. There was no significant change in action potential configurations. Arrows indicate the times when a series of polaroid pictures were taken. The sequence is as follows; control, 5 minutes, 10 minutes after vanadate's treatment, recovery. Horizontal scale = 200 msec. Vertical scale = 50 mV.

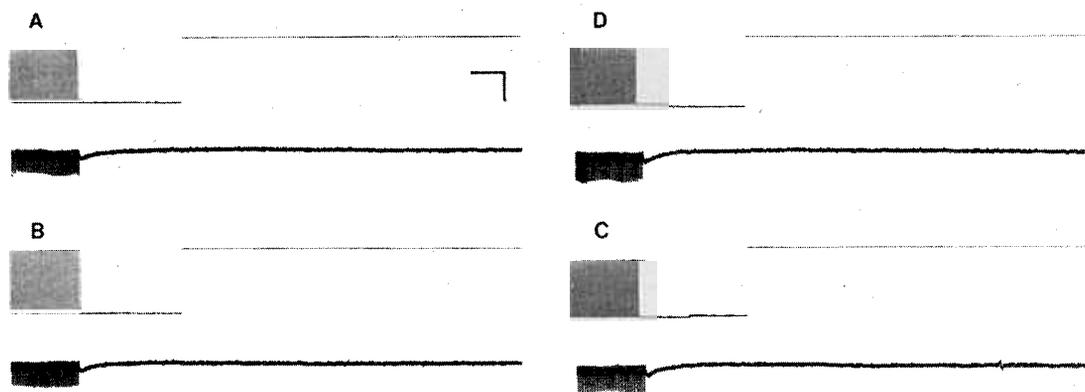


Fig. 4. Changes in extracellular Ca^{2+} concentration during rest period.

A, KH solution; B, vanadate (200 μ M) treated; C, recovery; D, ryanodine (5×10^{-8} M). Horizontal scale = 10 seconds. Vertical scale = 10 mg for tension (upper trace); 5.0 mV for E_m (lower trace).

maximum level in approximately 30 seconds as shown in Fig. 4A (about 1.7 mV, which is equivalent to an extracellular Ca^{2+} concentration change of 330 μ M). As the rest period lasted longer, $[Ca^{2+}]^e$ slowly decreased to the basal level. When the tissue was treated with vanadate (200 μ M), the steady-state contraction of 2 cps was increased with a slight increase in resting tension. The change in extracellular Ca^{2+} concentration during the rest period was much smaller (250 μ M in Fig. 4B) with vanadate. When vanadate was removed from the perfusion solution, the steady-state

contractions were decreased to the level of the control prior to the vanadate treatment, and the magnitude of the change in extracellular Ca^{2+} was again increased (340 μ M in Fig. 4C). When the tissue was treated with ryanodine (5×10^{-8} M), the increase in $[Ca^{2+}]^e$ was much greater (about 400 μ M in Fig. 4D). (This ryanodine-enhanced Ca^{2+} -efflux was used in order to produce maximum responses when Ca^{2+} efflux from the tissue was not clearly detected.)

After the papillary muscle was treated with ryanodine (5×10^{-8} M), the effects of vanadate (200

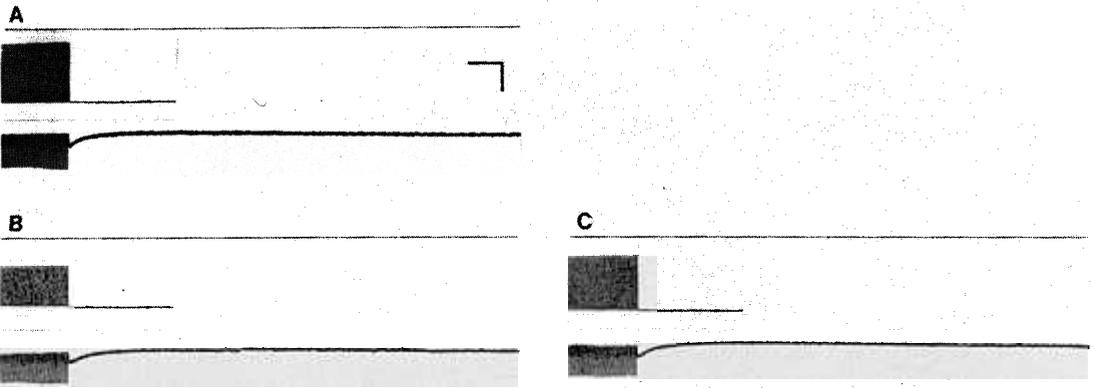


Fig. 5. Vanadate's effect on extracellular Ca^{2+} concentration of ryanodine-treated papillary muscle. Heart tissue was pretreated with ryanodine (5×10^{-8} M). A, ryanodine; B, vanadate; C, recovery. Upper records in each panel are tensions and lower records are E_{Ca} . (See the legend in Fig. 4 for other explanation.)

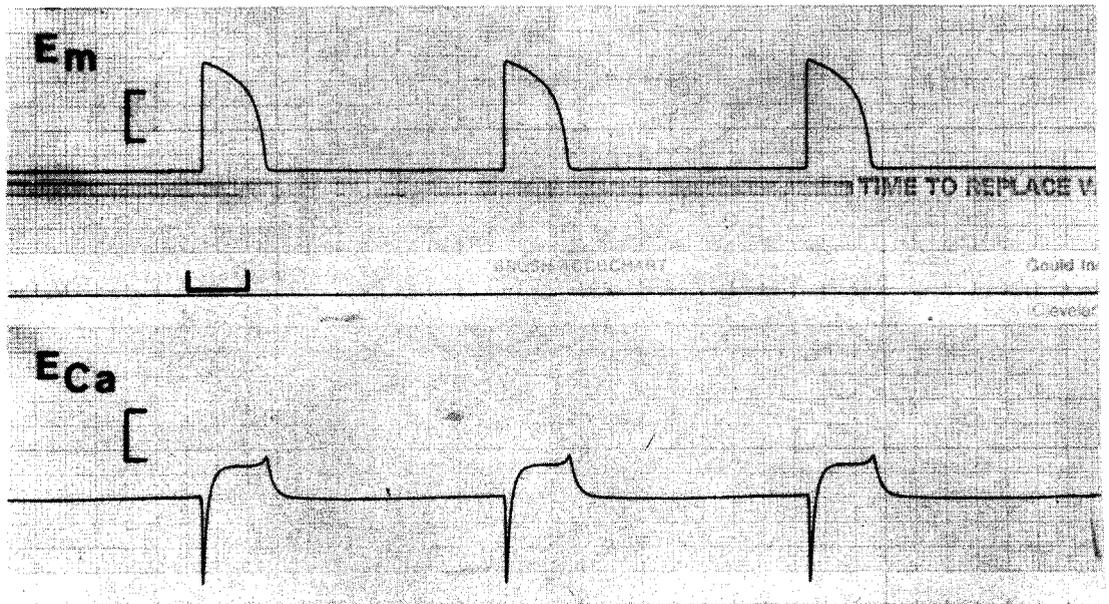


Fig. 6. Measurements of intracellular Ca^{2+} activities. Heart tissue was stimulated at 0.5 cps. Transmembrane potentials (upper trace) and intracellular Ca^{2+} activities (lower trace) were measured simultaneously. Horizontal scale = 400 msec. Vertical scale = 50 mV.

μM) on $[\text{Ca}^{2+}]^e$ during rest periods were measured (Fig. 5). The change in extracellular Ca^{2+} concentration during rest period, which was enhanced by ryanodine, was decreased by vanadate ($420 \mu\text{M}$ in Fig. 5B vs. $510 \mu\text{M}$ in Fig. 5A and $560 \mu\text{M}$ in Fig. 5C). The rate of change in $[\text{Ca}^{2+}]^e$ was also decreased by vanadate (1.0 mV in 5 seconds in Fig. 5B vs. 1.5 mV in 5 seconds in Fig. 5A) and returned to the faster rate when vanadate was removed from the perfusion solution (1.5 mV in 5 seconds in Fig. 5C).

Changes in intracellular Ca^{2+} activity

Intracellular Ca^{2+} activities were measured with CSE and RE impaling closely neighboring cells. The measured values of intracellular Ca^{2+} activities were scattered in a range of 1.8×10^{-8} to 5.1×10^{-7} M and had an average value of 1.9×10^{-7} M with S.E. of 3.1×10^{-8} M ($n=29$, out of four tissues).

Figure 6 shows one of the intracellular Ca^{2+} recordings along with the transmembrane potential. When

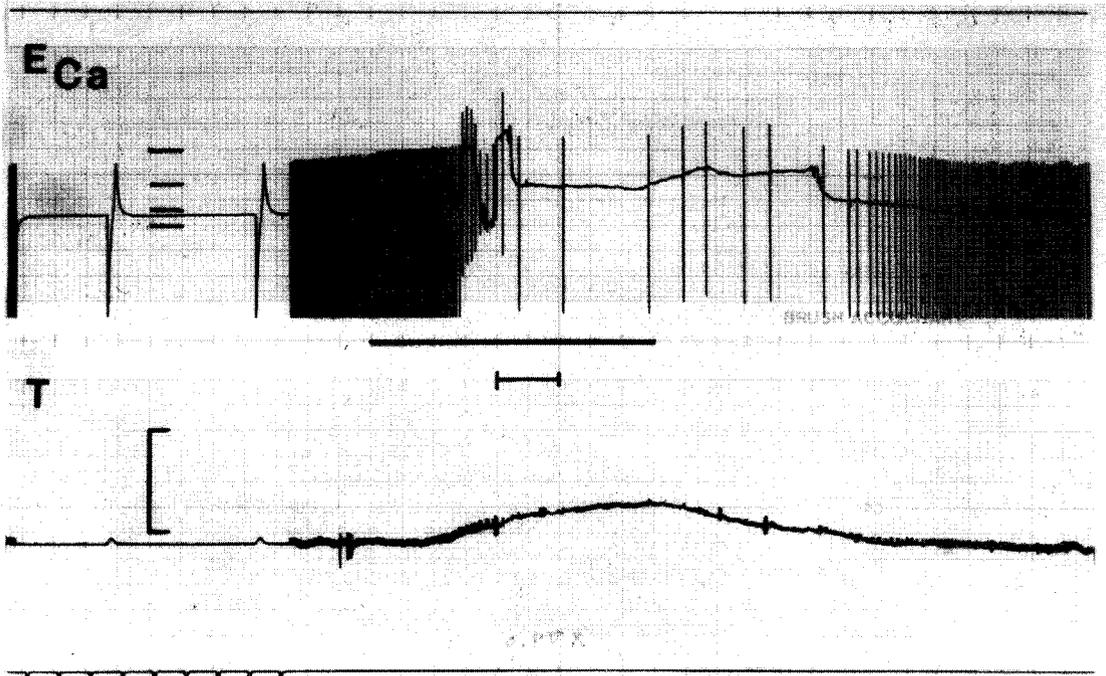


Fig. 7. Vanadate's effect on intracellular Ca^{2+} activities.

Heart tissue had spontaneous beatings and the rate of beating was decreased by vanadate. A horizontal bar represents when the tissue was treated with vanadate ($200 \mu M$). Horizontal scale = 2 minutes. Vertical scale = 10 mg for tension. Vertical scale of upper trace was converted to $pCa_{ca} = 5, 6, 7,$ and 8 from the top to bottom.

the tissue was stimulated at a frequency of 0.5 cps, the resting membrane potential (E_m) was about -80 mV and E_{Ca} was about 105 mV negative to the value E_{Ca} of the bathing solution. This value of E_{Ca} was calibrated to intracellular Ca^{2+} activity of 3.2×10^{-7} M. When the tissue was stimulated at a frequency of 0.2 cps an intracellular Ca^{2+} was about 1.8×10^{-7} M, which is slightly less than that at 0.5 cps. When the same tissue was treated with vanadate ($200 \mu M$) for 10 minutes, intracellular Ca^{2+} activities were increased by 0.5 unit of pCa to 9.0×10^{-7} M at both frequencies.

Fig. 7 shows a recording from other tissue with spontaneous beating. Vanadate increased intracellular Ca^{2+} activities from 7.2×10^{-8} M to 1.6×10^{-6} M with an accompanying increase in resting tension of about 4 mg. When the tissue was perfused with normal KH solution intracellular Ca^{2+} activities were returned to the values of 3.8×10^{-8} M and resting tension was also decreased.

DISCUSSION

Since it was proposed that vanadate could act as an "ideal endogenous regulator" of Na^+ , K^+ -ATPase ac-

tivity (Cantley *et al.* 1979), numerous studies on its physiological effects have been reported (for a review see Nechay 1984). Vanadate is known to have a negative inotropic effect on guinea pig atria with greatly shortened action potentials (Takeda *et al.* 1980) and a positive inotropic effect on the ventricular muscles of the guinea pig and other experimental animals (Hackbarth *et al.* 1978; Borchard *et al.* 1979; Grupp *et al.* 1979). Vanadate's other effects, which occur at high concentration, such as stimulating adenylate cyclase and inhibiting Na^+ , K^+ -ATPase, have been reported as possible mechanisms for its cardiac inotropism (Borchard *et al.* 1979; Krawietz *et al.* 1979). However, the mechanism of these effects is not yet well understood.

During the plateau phase of the action potential, a small but significant amount of Ca^{2+} enters the myocardial cells from the extracellular space as a slow inward current (for a review see Reuter 1979). In mammalian cardiac muscle this Ca^{2+} is not immediately available for contraction, but can replenish or augment the amount of Ca^{2+} in intracellular stores (for a review see Winegrad 1979). Since Ca^{2+} enters the cardiac cell during each action potential, to attain a steady-state

there must be a mechanism to get Ca²⁺ out of the cell. Although a Ca²⁺-activated ATPase in SR vesicles has been shown to be associated with Ca²⁺ pump, this has not been clearly identified in cardiac sarcolemma. Thus the Ca²⁺ efflux across the sarcolemma is believed to be accomplished by means of a Na⁺-Ca²⁺ exchange process (Mullins 1981). Interference of these two Ca²⁺ movements, i.e. Ca²⁺ influx via a slow inward current and Ca²⁺ efflux via a Na⁺-Ca²⁺ exchange process, would cause changes in the sarcoplasmic Ca²⁺ content and consequently changes in contractility (Mullins 1981; fleckenstein 1983).

Recently, the development of Ca²⁺-selective electrodes has made it possible to continuously measure the Ca²⁺ flux across the sarcolemma (Suh 1982; Bers and MacLeod 1986). Measurements of extracellular Ca²⁺ during a rest period reflect the movement of Ca²⁺ across the sarcolemmal membrane. As the stimulation ceases the cell, while retaining some Ca²⁺ for a post rest contraction, begins to lose Ca²⁺ probably via Na⁺-Ca²⁺ exchange transport and the concentration of extracellular Ca²⁺ increases. When stimulation is resumed intracellular stores pick up Ca²⁺, which has crossed the sarcolemma during the action potential. As the cell retains more Ca²⁺, contractions gradually become stronger and the extracellular Ca²⁺ concentration decreases (Fig. 5).

Interference with Ca²⁺ efflux by the blocking of the Na⁺-Ca²⁺ exchange transport would be one possible mode for vanadate's positive inotropic action (Suh 1983). A decrease in Ca²⁺ efflux by vanadate would increase intracellular Ca²⁺ content thus producing a positive inotropic effect.

This theme was examined with guinea pig papillary muscle which shows a positive inotropism (Fig. 2). Vanadate does not seem to increase the Ca²⁺ influx via a slow inward current as the action potentials were not significantly affected (Fig. 3). Findings from Ca²⁺ uptake experiments also support the suggestion that Ca²⁺ influx into ventricular tissue is not affected by vanadate (Park 1986).

Vanadate decreased the extracellular Ca²⁺ concentration in both untreated (Fig. 4) and ryanodine-pretreated tissue (Fig. 5). This can be interpreted as a consequence of decrease in Ca²⁺ efflux across the sarcolemma into the extracellular space since there is no reason to believe that vanadate makes faster the diffusion of Ca²⁺ into the (bulk) bathing solution from the extracellular space (the immediate vicinity of the cells). The decrease in Ca²⁺ efflux during a rest period attributed to vanadate was also reported in guinea pig atria, resulting in the reappearance of a post-rest contraction which was diminished by ryanodine (Suh 1983).

Measurements of intracellular Ca²⁺ activity with Ca²⁺-selective electrodes encounter technical difficulties (Lee 1981; Thomas 1982). To minimize the artifacts due to the slow response of the electrodes, the tissue was stimulated at low frequencies and the e.m.f. registered between action potentials (to maximize the period when the membrane potential does not change) was measured for analysis. Intracellular Ca²⁺ activities of guinea pig papillary muscle measured in this study are about 190 nM, and this number is in good agreement with other reported values (Lee 1981). Vanadate significantly increased intracellular Ca²⁺ activities resulting in an increase in resting tension. The correlation between resting tension and intracellular Ca²⁺ was not examined in this study, but will be studied in near future.

The results of this study indicate that vanadate decreases the loss of activator Ca²⁺ from cardiac muscle cells by blocking Ca²⁺ efflux across the sarcolemma, and consequently results in an increase in intracellular Ca²⁺ activities for positive inotropism of cardiac muscle tissue. They further suggest that vanadate may be a blocking agent of the Na⁺-Ca²⁺ exchange transport in mammalian cardiac cells.

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