The Hemodynamic Effects of Strontium Chloride in the Intact Dog (36714)

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Strontium ion, a divalent cation, has many interesting biological effects. It has been shown to be capable of substituting for calcium ion in maintaining excitability of certain nerve and muscle membranes (1, 2); in electro-mechanical coupling in an alga (3); and in excitation–contraction coupling in both skeletal and cardiac muscle (4). Also, in some isolated cardiac muscle preparations it has been shown to have potent positive inotropic effects (5–7).

It is not completely clear from the literature, however, whether in the presence of calcium ion, Sr^{2+} has positive or negative inotropic effects. An antagonism between the inotropic effects of Ca^{2+} and Sr^{2+} has been found in the frog heart by Thomas (8), and in the cat auricle by De Hemptine, Weyne and Leusen (7). On the other hand, in mammalian papillary muscle, Garb (5) and Buccino *et al.* (9), found that Sr^{2+} in the presence of normal Ca^{2+} concentration had a definite positive inotropic effect. It was the purpose of this study to determine the hemodynamic effect of Sr^{2+} in the intact dog, in the presence of normal serum $[Ca^{2+}]$, and to assess its toxicity and therapeutic potential as an inotropic agent.

Methods. Mongrel dogs weighing from 16 to 24 kg were studied. Dogs were anesthetized with intravenous chloralose–urethane (80 mg/kg chloralose + 0.7 g/kg urethane). Respiration was maintained through a cuffed endotracheal tube connected to a Harvard respiratory pump using room air. A left lateral thoracotomy was performed and the pericardium was opened. A solid state pressure cell (Whittaker 1017) was placed in the left ventricle through a stab wound in the apex and a Biotronex electromagnetic flow probe was positioned around the ascending aorta. A large bore fluid-filled catheter was placed in the ascending aorta via the left carotid artery, and connected to a Statham P23Db strain gauge manometer. The pressure and flow signals obtained, and a standard EKG lead II, were amplified using Honeywell Accudata 113 amplifiers. The left ventricular pressure cell was calibrated and balanced in water at 38° and gave greater than 95% full scale response to 1000 Hz. The left ventricular pressure signal was electronically differentiated using a Honeywell Accudata 132 statically calibrated differentiator with a full scale frequency response to 120 Hz. The frequency response of this left ventricular pressure recording and differentiating system allows determination of the true maximum dp/dt (10). The signals, aortic pressure, left ventricular pressure, left ventricular dp/dt, aortic flow, and the EKG, were recorded on ultraviolet sensitive photographic paper using a Honeywell Visicorder. Mean aortic pressure and flow were obtained electronically. The flow probes were calibrated *in vitro* in a gravity flow device. Flows obtained with these probes were found to vary by ± 10% from outputs determined by dye dilution curves. The animals were maintained at normal temperature (38°) by a heating pad, and arterial blood gases were monitored at regular intervals. The pH was maintained between 7.35 and 7.45, and the O_2 saturation above 90% at all times. All animals were given 5 ml/kg of 6% dextran intravenously after the surgical manipulations were completed.

Strontium chloride was administered as a 10% (w/v) solution of $SrCl_2 \cdot 6H_2O$ in infusion of 10 ml (3.75 mmoles/infusion). Infusions were given over a 15 sec period repeatedly at 3 min intervals via the left foreleg vein. One minute after administration of

the infusion, blood samples were drawn from the superior vena cava, and hemodynamic measurements were made.

Hemodynamic studies were performed in 15 dogs. Five dogs received no medication prior to $SrCl_2$ other than anesthesia. This group constituted the "nonblocked" dogs. The second group consisted of 5 dogs who received 1 mg/kg of propranolol and 0.1 mg/kg of atropine intravenously, prior to administration of strontium chloride. The third group of 5 dogs were given intravenous dibenzyline 5 mg/kg, in addition to propranolol and atropine. For each group, a 15–30 min control period of stable hemodynamic measurements was obtained prior to administration of strontium chloride. For the blocked dogs, the control period measurements were obtained at least 15 minutes after administration of blocking drugs. Adequacy of beta and alpha blockade following these doses of propranolol and dibenzyline was established by abolishment of the increase in *dp/dt* and aortic pressure following rapid infusion of 3 μg isoproterenol and 8 μg norepinephrine, respectively.

Serum strontium levels were determined using a Perkin-Elmer 290 atomic absorption spectrometer. Serum Ca, Na, K, Cl, and CO_2 levels before and after administration of strontium were also determined in the propranolol–atropine group of animals.

The data obtained were analyzed using an IBM 360/50 computer at the ACME computer facility, Stanford Medical Center. Paired or nonpaired Student's *t* tests were used, when appropriate, to assess statistical significance of the data.

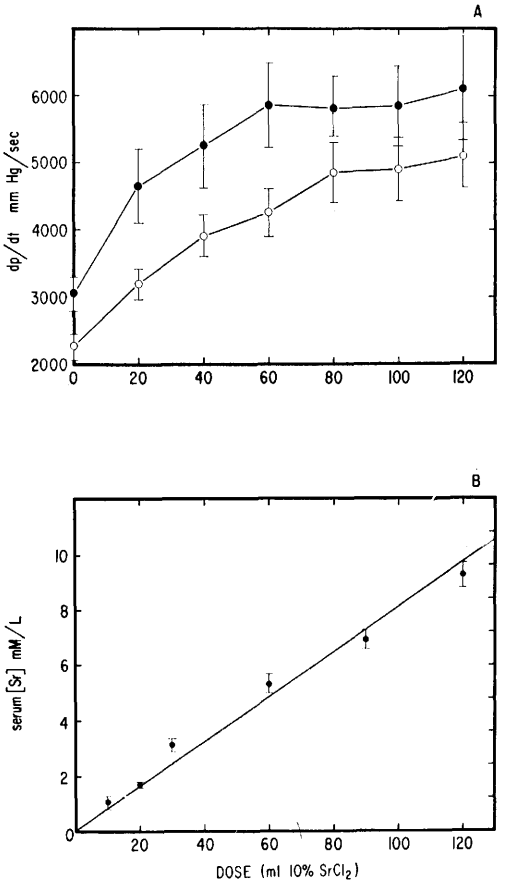

FIG. 1. Effect of 10% $SrCl_2$ (cumulative dose) given intravenously on left ventricular *dp/dt* (A) and the serum Sr concentration (B) in anesthetized dogs. Each point plotted indicates the mean, and brackets the SEM. In (A): (○) the group of dogs blocked with propranolol and atropine; (●) the unblocked dogs. In (B) the two groups were combined.

Results. The most striking effect of strontium chloride in these studies was a marked increase in LV *dp/dt* (Fig. 1A), which reached a plateau after administration of 60 to 80 ml total dose of the 10% $SrCl_2$ solution. The increase in LV *dp/dt* following strontium administration was not affected by beta blockade with propranolol. The corresponding serum concentrations of strontium are shown in Fig. 1B. The increase in LV *dp/dt* which occurred after the first 10 ml dose was statistically significant in both groups ($p \leqq .05$); this corresponded to a serum concentration of about 1 m*M*. The plateau of the effect was reached at a serum [Sr] between 5 and 7 m*M*. When the maximum increase in LV *dp/dt* was obtained, cessation of administration of strontium chloride resulted in a fairly rapid fall in *dp/dt* over the first 15 min, followed by a more gradual decline, generally paralleling the serum concentration. An example is shown in Fig. 2. Serum Ca levels were not significantly different from control levels after administration of 90 ml of 10% $SrCl_2$, although there was a significant fall in [Na] and rise in [Cl] ($p \leqq .05$) (Table I).

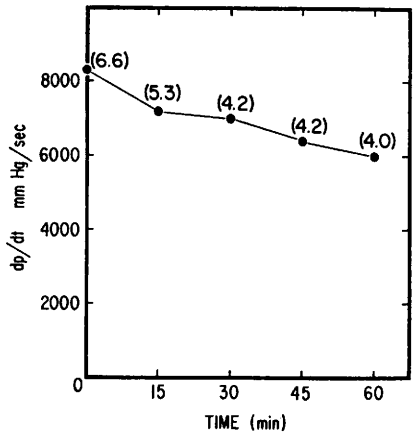

FIG. 2. This graph depicts the fall in LV *dp/dt* (ordinate) with time (abscissa) in an animal which had received 60 ml total dose of the 10% $SrCl_2$ solution. The serum concentration of strontium in m*M* at the times the *dp/dt* was determined is indicated in parentheses adjacent to each point. This dog was not treated with propranolol or atropine.

In an effort to characterize further the inotropic effect of the drug, peak velocity of the contractile element (peak V_{CE} was estimated for each dog from the isovolumetric LV pressure and simultaneous LV *dp/dt*, using the formula V_{CE} (muscle lengths/sec) $= dp/dt/32P$ (11, 12), and plotting V_{CE} against *P* (total pressure). Peak V_{CE} was determined during the control period and after that dose of $SrCl_2$ which produced the maximum increase in *dp/dt* in each animal. The averages of these data, the percentage changes in LV *dp/dt* and peak V_{CE} before and after strontium, are shown in Table II. Although the V_{CE} increased significantly after strontium in each dog ($p \leqq .05$), the magnitude of the effect of the drug on that parameter was less than the effect on LV *dp/dt*. There was no statistically significant difference in the time to peak LV *dp/dt* and time to peak V_{CE} before and after strontium in either group of dogs. It should be noted that heart rate, which was not maintained constant in this preparation, also affects time to peak LV *dp/dt*. However, the changes in heart rate were relatively minor in these animals, particularly in the nonblocked group of dogs, and therefore would be expected to cause relatively small changes in this parameter.

The effects of Sr^{2+} on other hemodynamic parameters are shown in Fig. 3. There was a significant ($p \leqq .05$) increase in the peripheral resistance (Fig. 3A) in beta-blocked dogs following administration of 60 ml of 10% $SrCl_2$. There were no significant changes in heart rate (Fig. 3B). The LVEDP (Fig. 3C) fell in both groups of dogs, and this effect was maximal after 30 ml total doses. The fall in LVEDP was significant ($p \leqq .05$) in the blocked dogs. The gradual increase in LVEDP with increasing doses above 30 ml which occurred in both groups of dogs was associated with a rise in mean aortic pressure. The average cardiac output (Fig. 3D) tended to rise slightly with increasing [Sr] in both groups, although these changes were not significant.

In the 5 dogs given dibenzyline, 5 mg/kg, in addition to propranolol and atropine, and then given strontium, there was also a significant increase in peripheral resistance ($p \leqq .05$) following administration of 30 ml of $SrCl_2$. This is shown in Fig. 4.

The electrocardiographic effects of strontium varied from T wave changes to conduction changes with alteration of the QRS. Several dogs developed ventricular premature contractions immediately after an infusion which then disappeared over the ensuing minute. There was one brief run of ventricular tachycardia in a single dog after 110 ml of the 10% solution had been administered. There was no instance of ventricular fibrillation, asystole, or heart block in animals given strontium chloride 10% solution, up to a dose of 240 ml, and a serum concentration of

TABLE I. Effect of Sr^{2+} Administration on Serum Electrolytes (Propranolol–Atropine Group).[a]

	Control	After 90 ml 10% $SrCl_2$
Na	134.4 ± 1.93	127.8 ± 1.89
K	3.00 ± 0.21	3.1 ± 0.23
CO_2	14.00 ± 1.25	12.2 ± 1.19
Cl	111.2 ± 2.5	120.2 ± 2.78
Ca	2.24 ± 0.06	2.27 ± 0.09

[a] m*M* ± SEM.

TABLE II. Effect of Sr^{2+} on Inotropic Parameters.[a]

	Nonblocked		Propranolol and atropine	
	Control	Strontium	Control	Strontium
Peak *dp/dt* (mm Hg/sec)	3040 ± 191	6708 ± 649	2280 ± 166	5060 ± 306
TTP *dp/dt* (msec)	50.04 ± 2.17	45.74 ± 2.23	52.00 ± 2.34	48.50 ± 2.56
Peak V_{CE}	1.708 ± .111	2.25 ± .176	1.312 ± .050	1.791 ± .152
TTP V_{CE} (msec)	37.26 ± 2.35	39.7 ± 2.40	32.16 ± 2.13	32.76 ± 2.31
% Δ *dp/dt*	—	126 ± 23	—	125 ± 16
% Δ V_{CE}	—	33 ± 9	—	36 ± 8

[a] Values given = mean ± SEM. Abbreviations: TTP = time to peak measured from the onset of *dp/dt* increase; V_{CE} = velocity of the contractile element in muscle lengths/sec.

18 mmoles/liter. There was a regular widening of the QRS complex and a prolongation of ventricular systole, which occurred usually after a total dose of 90 to 120 ml. This effect is illustrated in Fig. 5.

Discussion. The major hemodynamic effects of strontium chloride in an anesthetized dog appear to be: (a) an increase in the inotropic state of the ventricle, reflected by a rise in peak *dp/dt* and peak V_{CE}, and a fall in LVEDP pressure in spite of a rise in after load, and (b) an increase in peripheral resistance most apparent when the beta-adrenergic receptors have been blocked. These effects are not mediated by beta or alpha receptors, and therefore appear to be due to direct actions of the ion on cardiac muscle and arteriolar smooth muscle. This

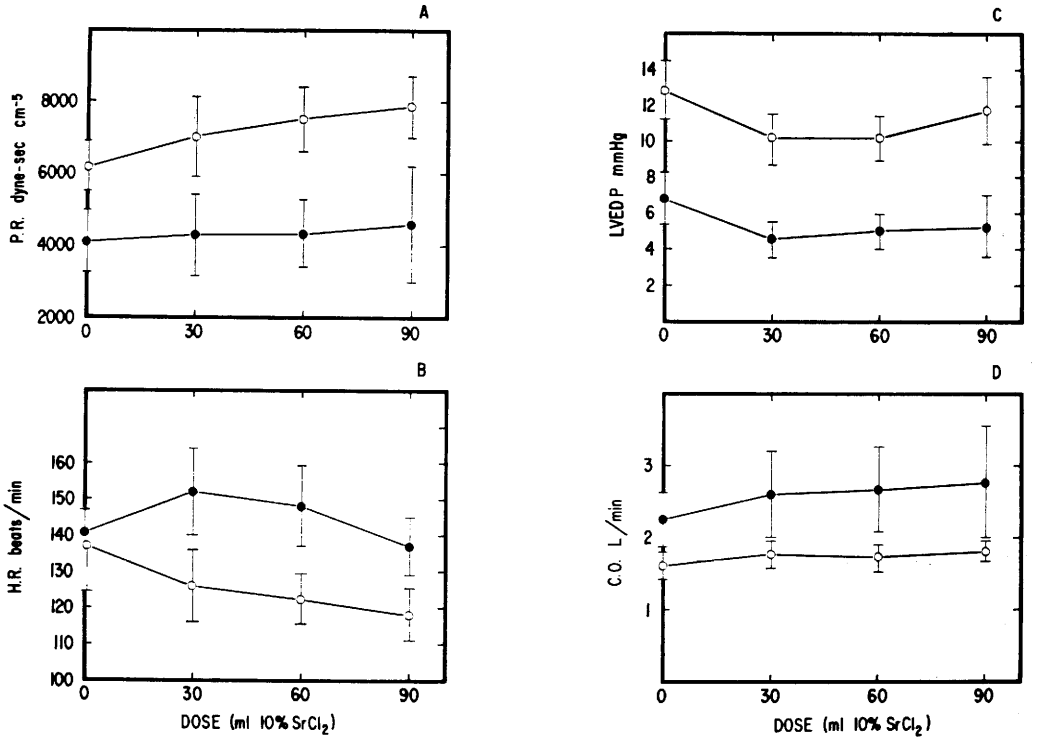

FIG. 3. Effect of 10% $SrCl_2$ given intravenously on peripheral resistance (A), heart rate (B), left ventricular end-diastolic pressure (C), and cardiac output (D). (●) Nonblocked dogs and (○) propranolol–atropine dogs; points indicate the means, and brackets the SEM.

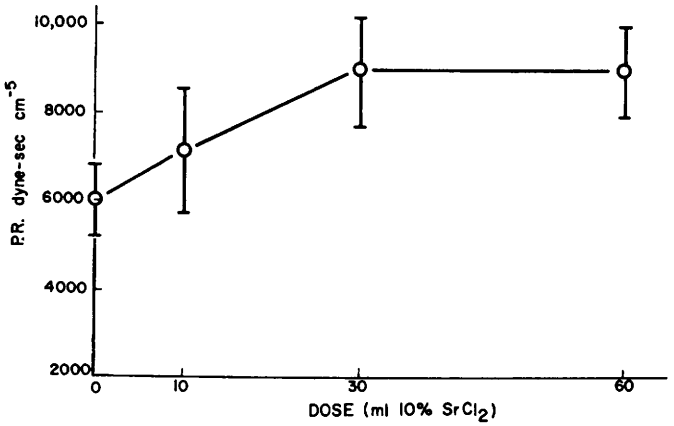

FIG. 4. Effect of $SrCl_2$ on peripheral resistance in 5 dogs in which there was pharmacological blockade of both alpha and beta receptors. (O) Means, and brackets SEM.

latter effect of the ion is consistent with the *in vitro* findings of Hudgins and Weiss (13) that Sr^{2+} is capable of substituting for Ca^{2+} in the contractile process in vascular smooth muscle, in addition to stimulating the uptake of ^{45}Ca by that tissue.

The possibility that the inotropic changes noted after $SrCl_2$ administration are due to osmotic changes or the volume load should be considered. As can be seen from Table I, and Fig. 1B, the increase in serum osmolarity after administration of 90 ml of 10% $SrCl_2 \cdot H_2O$ solution was only 6 mOsm at a time when the inotropic effect was maximal. In addition, previous studies in our laboratory have demonstrated a small but statistically insignificant increase in *dp/dt* in this same preparation following volume loading with 100 ml of 6% dextran in saline. Thus, neither a change in osmolarity nor the volume expansion following administration of $SrCl_2$ can account for the large positive inotropic effects observed.

The mechanism of the inotropic action of Sr^{2+} on cardiac muscle is not clear. Most studies on isolated tissue suggest that at least a small amount of calcium ion is necessary for this action (6, 14). However, there are clear differences between the positive inotropic effect produced by Ca^{2+} and that produced by SR^{2+}. Although both ions increase peak tension, Ca^{2+} decreases time to peak tension, and time to peak *dp/dt*, shortens the duration of contraction and the duration of the action potential; Sr^{2+} has opposite effects (7, 9, 14, 15). The present study shows that in the intact heart in the presence of a normal serum [Ca], Sr^{2+} prolongs the duration of contraction, and causes little if any change in the time to peak *dp/dt*. Therefore, in both isolated cardiac tissue and in the intact dog heart, the positive inotropic action of Sr^{2+} does not appear to be a simple "Ca^{2+}-like" effect.

Sr^{2+} by itself is capable of binding to troponin–tropomyosin from cardiac muscle and thereby overcoming the inhibition of actin-myosin interaction although it is only about 1/3 as effective as Ca^{2+} in this regard (4). Therefore, its inotropic action may be a combination of (a) a direct effect on the troponin–tropomyosin actomyosin contractile unit; (b) potentiating the effect of calcium ion by competing with Ca^{2+} for intracellular uptake binding sites (16) and (c) an alteration of the electrophysiological properties of the cardiac muscle cell, affecting excitation contraction coupling. Sr^{2+} is an unusual inotropic agent in that it appears to increase the duration of the active state in addition to increasing its intensity.

Strontium ion appears to be relatively nontoxic in the anesthetized dog, with the maximum inotropic effect occuring at serum concentrations of 5 to 7 m*M*, while serious disturbance of cardiac function usually does not

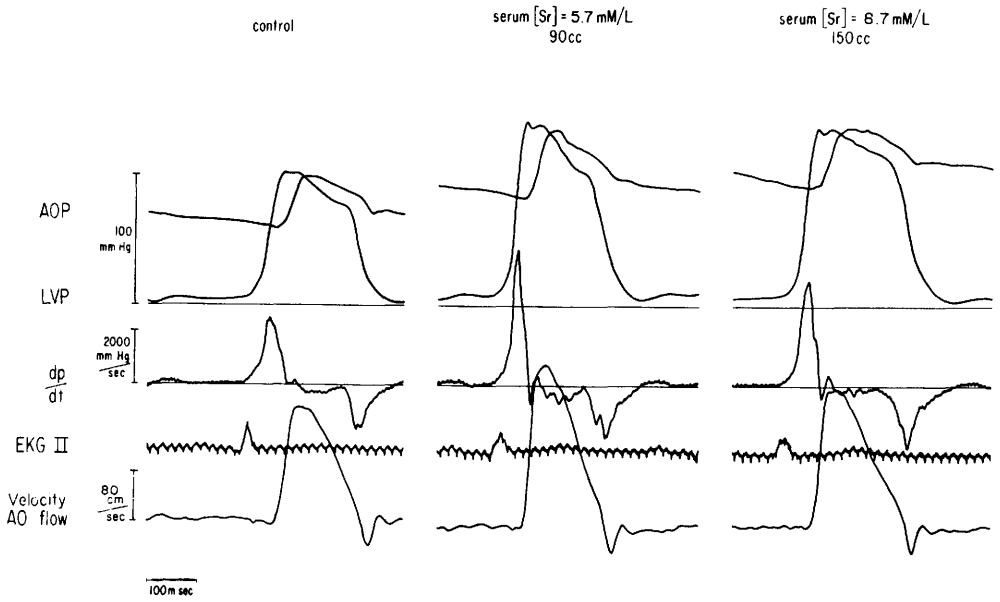

FIG. 5. Records demonstrating the effect of intravenous $SrCl_2$ on aortic pressure, left ventricular pressure, LV *dp/dt*, the QRS of lead II EKG, and aortic flow in a nonblocked dog. The dose of 10% solution of $SrCl_2$ and the corresponding serum concentration of strontium is indicated above the appropriate records. The control heart rate was 130/min, the heart rate after 90 and 150 ml of 10% $SrCl_2$ 140 and 110 beats/min, respectively. The time scale is indicated on the abscissa. After a dose of 90 ml the predominant effects of Sr^{2+} in this animal relative to control were an increase in peak *dp/dt*, with no change in time to peak *dp/dt*; an increase in aortic flow and pressure; and a slight increase in duration of systole in spite of the increase in heart rate of 10 beats/min. With higher doses, as exemplified by the 150 ml figure, there was a drop in heart rate and peak *dp/dt*, and a more marked prolongation of ventricular systole.

occur at serum concentrations less than twice this level. However, in unanesthetized animals given $SrCl_2$ as described above, emesis regularly occurred at a serum [Sr] of 3–4 m*M*. Also the inotropic effect appears to decline quite rapidly as the ion is excreted and bound to tissue, thus lowering the serum concentration. These two factors make it unlikely that this inotropic agent would be of use clinically, in spite of its apparent low cardiac toxicity. However, further studies of its mechanism of action may provide insight into the relationship of excitation–contraction coupling and positive inotropism in cardiac muscle.

Summary. The hemodynamic effects of $SrCl_2$ given intravenously to intact dogs were studied. Sr^{2+} had a positive inotropic effect on the heart, manifested by a rise in peak *dp/dt*, peak velocity of contractile element (V_{CE}) and a fall in left ventricular end-diastolic pressure. This inotropic effect was not mediated by beta-adrenergic receptors, and was maximal at a serum [Sr] of 5–7 m*M*. The inotropic effect of Sr^{2+} was associated with an increase in the duration of contraction, and with little if any change in the time to peak *dp/dt*, and did not appear to be a simple "Ca^{2+}-like" effect. Sr^{2+} also caused a rise in peripheral resistance in dogs with pharmacological blockade of both alpha and beta-adrenergic receptors. These effects appear to be direct actions of the ion on cardiac and arteriolar muscle.

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Received Apr. 4, 1972. P.S.E.B.M., 1972, Vol. 141.