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Influence of Calcium Ions upon Energy Metabolism of the Mammalian Heart.*

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Certain of the cardiac actions of calcium are well known. Numerous experiments have demonstrated an increase in the mechanical energy liberated by the heart under the influence of calcium. The literature on the effects of this ion upon the heart has been reviewed recently by Berliner.[1] We have studied the changes in energy liberation and distribution which permit, at a given diastolic volume, an increased work output of the heart under these conditions.

The methods we have employed permit measurement of the oxygen consumption of the heart and eliminate possibility of error due to changes in the elasticity of the lungs inherent in the earlier methods.[2] The arrangement of apparatus (Fig. 1) is essentially that of

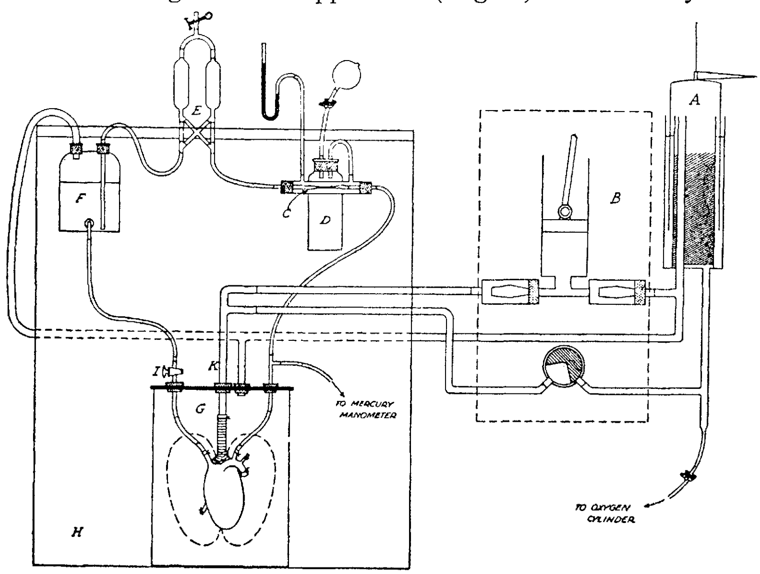

FIG. 1.
A—oxygen spirometer, B—respiration pump, C—artificial resistance, D—pressure bottle, E—stromuhr, F—venous reservoir, G—glass jar, actually horizontal, H—constant temperature bath, I—stopcock for adjustment of venous return, K—tracheal cannula.

* Aided by grant 282 from the Committee on Scientific Research of the American Medical Association.

[1] Berliner, *Am. Heart J.*, 1933, **8**, 548.

[2] Starling and Visscher, *J. Physiol.*, 1927, **62**, 243.

the usual heart-lung preparation in an entirely closed system. After the artificial circulation has been established, the heart and lungs are freed from the body of the dog and encased in an airtight glass jar, which is then connected with large rubber tubing to the oxygen spirometer and the venous reservoir, and lowered into a constant temperature bath adjusted to 37.5°. Under these conditions there is a continuity of the entire air content of the system with automatic compensation for changes in the volume of the heart and lungs. When the ventricular volume was recorded, a cardiometer, clamped rigidly in place, and communicating with a large tambour was also included in the glass chamber.

After a control period of approximately an hour calcium chloride or calcium gluconate was introduced into the venous reservoir. In the first 3 experiments of Table Ia, the experiments of Table Ib, and the first 2 experiments under "d" 1 cc. of 20% calcium chloride was injected. In experiments marked "c" ½ cc. of 20% calcium chloride was used. In the third experiment of the "d" group 1.5 cc. of 20% calcium gluconate (calglucon, Sandoz)† was given. In the fourth experiment of the "a" group and in the experiments of Table II 2 cc. of 20% calcium gluconate was injected. The blood volume of the system varied between the approximate limits, 900 cc. to 1200 cc. Oxygen consumption, arterial pressure, and, in some experiments, heart volume were recorded continuously. Volume out-

TABLE I.
Effect of calcium on energy exchanges in the heart.

Exp.	Oxygen cons. cal./min. Control	Oxygen cons. cal./min. After Ca	Volume output cc./min. Control	Volume output cc./min. After Ca	Efficiency % Control	Efficiency % After Ca	Inc. efficiency %	
3/27/33	39.4	40.6	468	500	3.84	4.11	7.0	(a)
3/28/33	58.6	57.0	385	385	2.15	2.21	2.8	(a)
3/29/33	60.1	55.9	326	326	2.19	2.35	7.3	(a)
2/16/34	81.6	79.6	382	400	1.29	1.41	9.3	(a)
1/19/33	71.9	71.9	400	732	2.09	4.07	95.	(b)
1/27/33	46.6	43.9	366	385	2.89	3.25	12.	(b)
1/28/33	54.1	54.9	357	577	2.33	3.82	64.	(b)
2/21/33	83.4	83.4	366	484	1.62	2.24	38.	(b)
6/1/33	48.7	43.1	353	423	2.62	3.62	38.	(c)
6/3/33	36.6	46.7	333	739	2.81	5.71	103.	(c)
2/27/33	78.1	72.6	492	541	2.30	2.77	20.	(d)
3/25/33	46.2	37.0	366	380	2.89	3.75	30.	(d)
5/4/34	74.2	78.6	462	1000	1.99	5.35	169.	(d)

(a) In the fresh heart.
(b) Following injection of parathormone.
(c) Following injection of ethyl alcohol.
(d) Spontaneously hypodynamic heart.

† We desire to thank the Sandoz Company for their courtesy in supplying us with this material.

TABLE II.
Effect of Calcium on Energy Liberation and Efficiency of Hypodynamic Heart at Approximately Constant Diastolic Volume.

Exp.	Diastolic vol.change due to Ca cc.	Oxygen cons. cal./min. Control	Oxygen cons. cal./min. After Ca	% inc. in O_2 cons. corrected	Efficiency % Control	Efficiency % After Ca	% inc. efficiency corrected
4/6/34	— .2	32.9	45.3	47	4.52	7.97	65
4/13/34	—1.1	45.4	55.6	28	2.80	5.42	85

put and rate were determined at frequent intervals. Averages are given in the tables.

The estimated efficiencies are based on the external work of the heart only and include an error due to the metabolism of the lungs. They therefore express the external efficiency of the preparation rather than the efficiency of the heart muscle. However, since we are interested in changes in efficiency rather than absolute values, lung metabolism introduces no significant error unless the consumption of oxygen varies considerably. In the last columns of Table II this source of error is roughly corrected by subtracting 20% of the oxygen consumption value for the control period. Since calcium dilates the coronary vessels (Mancke,[3] Hochrein[4]), measurement of changes in external output will not exaggerate but rather minimize changes in the total output. The external efficiency changes observed thus seem to represent real increases in muscular efficiency.

In all our experiments, except one in which no change was observed, calcium produced a slight increase in the heart rate. The average value of this increase was about 6%.

While the increase in frequency and the tonic effect of calcium upon the heart volume are seemingly independent of the previous treatment of the heart, the changes in cardiac output and efficiency due to calcium depend on the condition of the preparation at the time of injection. Fresh preparations respond to calcium with little or no increase in cardiac output and a hardly significant increase in efficiency (Table Ia). In hypodynamic preparations, however, injection of calcium is followed by a definite increase in cardiac output and efficiency (Table Ib, c, d). The beneficial effects are of relatively long duration, although the exact length of time cannot be adequately studied in this preparation because of the continuous spontaneous dilatation. The figures recorded in the tables are based upon the initial 10 or 15 minute period of maximum change in the variables studied.

[3] Mancke, *Arch. exp. Path. Pharm.*, 1930, **149**, 67.

[4] Hochrein, *Klin. Wchnschr.*, 1931, **10**, 1705.

In the experiments of Table II the diastolic volume was maintained nearly constant by adjustment of the venous inflow. In both experiments the injection of calcium was followed by a definite rise in total energy liberation measured as oxygen consumption, as well as a marked increase in efficiency. It appears from the observations of Starling and Visscher[2] that the increase in rate cannot account for more than a 10% increase in oxygen consumption in these experiments. There is therefore a definite increase in oxygen usage which is independent of the rate.

Summary. At a given initial fiber length the mechanical energy of contraction of the heart is increased under the influence of calcium. This is due not only to an increase in the fraction of the total energy liberated which is converted into useful work but also to an increased total energy liberation. The increase in efficiency occurring with administration of small doses of calcium salts indicates that the effect is a beneficial one, and might be of importance in contributing to the therapeutic effect of calcium in cardiac disease.

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Bromide Control of Experimental Convulsions.

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Since Locock[1] reported the successful use of bromides in several cases of epilepsy, this drug has been used extensively in the treatment of this disease. When these patients have been so treated, it has been noted that the concentration of the bromide ion in the blood is not always related to the amount of the drug administered; or is this concentration parallel to the clinical course, either in regard to the control of the convulsions or to the development of bromide intoxication.

Since the amount of bromide in the blood necessary to prevent epileptic convulsions in man varies, a determination of the concentration necessary to prevent experimentally produced convulsions in rabbits was made. The convulsions were induced by the intravenous injection of 2% thujone in 6% gum acacia, using 0.15 cc. per pound body weight. Seizures always followed such a dose, providing the

[1] Locock, Sir C., *London Lancet*, 1857, **1**, 528.