The Effects of Infusion of Calcium and Magnesium Ions on the Cardiovascular System in Man

Kiyoo MORI, M.D.

SUMMARY

The effects of Ca^{++} and Mg^{++} infusion on the cardiovascular system were studied in 96 normotensive subjects and 85 hypertensive patients. The results obtained were as follows:

(1) The effects of Ca^{++} infusion on the systolic time intervals were characterized by the shortening of QS_2I , PEPI, and ICT, and increase in ET/PEP. The responses of the systemic hemodynamics were elevation of mean blood pressure and increase in cardiac index and stroke index. The heart rate was not altered.

(2) These results support that Ca^{++} has a positive inotropic action and increases the left ventricular performance.

(3) The effects of Mg^{++} infusion on the systolic time intervals were characterized by the prolongation of QS_2I , PEPI, and ICT. The responses of systemic hemodynamics were elevation of mean blood pressure and increase in heart rate. The ET/PEP and cardiac index tended to decrease, but these changes were not significant.

(4) From these results it is suggested that Mg^{++} depresses myocardial contractility and has a positive chronotropic action.

(5) There were no significant differences in the systolic time intervals and hemodynamic responses to the infusion of Ca^{++} and Mg^{++} between normotensives and hypertensives.

Additional Indexing Words:

Divalent cation Systolic time intervals Systemic hemodynamics
Hypertension

THE influence of divalent cations on the heart and vascular smooth muscle has been studied by several investigators.¹⁾⁻⁴⁾ It is well known that excitation-contraction coupling in heart muscle cell depends upon an inward displacement of Ca^{++} from the extracellular to the intracellular phase.⁵⁾ Baston and Makay showed that the contracture tension of superfused ventricle of helix aspersa could be altered by varying the Ca^{++} and Mg^{++} concentrations of perfusion medium.⁶⁾ The tension was decreased immediately after the level of Ca^{++} was lowered while increased after the level of Mg^{++} was lowered.

From the Second Department of Internal Medicine, Kanazawa University, Kanazawa, Japan.
Present address and address for reprints: Kiyoo Mori, M.D., Department of Internal Medicine, Ishikawa Prefectural Central Hospital, 153 Minami-shinbomachi, Kanazawa 920, Japan.

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On the other hand, Hoffman and Suckling found that an excess and deficiency of magnesium had little effect on the action potential of papillary muscles of dog as far as calcium concentration was normal.⁷⁾

From the standpoint of the significance of sarcoplasmic reticulum in the pathogenesis of hypertension, Aoki urged that the Ca⁺⁺ binding of isolated sarcoplasmic reticulum was lower in the aorta of spontaneously hypertensive rat.⁸⁾ Another clinical study indicated that the exchangeable magnesium and serum magnesium levels were decreased in hypertensive man as compared with normotensive man.⁹⁾

However, there are few available reports concerning the role of these divalent cations on the cardiac function and systemic hemodynamics. The purpose of the present study, therefore, was to evaluate the effects of intravenous infusion of Ca⁺⁺ and Mg⁺⁺ on the cardiovascular system in man, and secondarily to compare the cardiovascular responses to intravenous infusion of Ca⁺⁺ and Mg⁺⁺ between normotensive controls and hypertensive patients.

MATERIALS AND METHODS

The normotensive subjects were volunteers who had no evidence of heart, lung, renal, blood, and metabolic diseases. The hypertensive patients were defined as subjects who had blood pressure persistently higher than 150 / 90 mmHg without secondary hypertension, heart failure, histories of renal disease, myocardial infarction, and cerebrovascular accident. At least 10 days prior to the study the drugs were discontinued, and these studies were performed without premedication in a quiet laboratory. The left ventricular systolic time intervals were obtained by non-invasive technique using carotid artery tracing and the hemodynamic studies were done by dye-dilution method before and immediately after intravenous infusion of 0.2 mEq/Kg of Ca⁺⁺ (Ca-*l*-Asparate) over 5 min or 0.1 mEq/Kg of Mg⁺⁺ (Mg-*l*-Asparate) over 5 min. With respect to the study of Ca⁺⁺, the systolic time intervals were measured in 21 normotensive subjects (mean age 42; range 26–68 years) and 17 hypertensive patients (mean age 47; range 20–70 years), and the hemodynamic observations were made in 26 normotensive subjects (mean age 42; range 16–78 years) and 25 hypertensive patients (mean age 47; range 23–69 years). With respect to the study of Mg⁺⁺, the systolic time intervals were measured in 22 normotensive subjects (mean age 41; 16–68 years) and 21 hypertensive patients (mean age 39; 16–62 years), and the hemodynamic observations were made in 26 normotensive subjects (mean age 46; 24–74 years) and 22 hypertensive patients (mean age 49; 24–68 years).

For the carotid pulse recording a Fukuda TY 302 transducer was used. Simultaneous ECG (Lead II), phonocardiogram and carotid pulse tracing were recorded in supine position at a paper speed of 100 mm/sec on a Siemens-Elcoma Mingograph No. 82 8 channel recorder with the method of Weissler, Harris, and Schoenfeld.¹⁰⁾ The total electromechanical systole (QS₂), left ventricular ejection time (ET), pre-ejection period (PEP), isovolumic contraction time (ICT), and ratio of ejection

time to the preejection period (ET/PEP) were measured, using the averages of 5 technically adequate consecutive beats, and were corrected for heart rate to give the respective indexes QS₂I, ETI, and PEPI. Cardiac output was determined by dye-dilution method using Water's D-400 earpiece densitometer. A 19-gauge 300 mm polyethylene catheter was inserted percutaneously into right antecubital vein. Following the injection of indocyanine green (10 mg) with flash of 10 ml of saline into central vein, dilution curve were inscribed on a National pen recorder VP 2654. About 3 min after the injection, blood samples for calibration were withdrawn from another antecubital vein. The area under each dye curve was measured by planimetry and the cardiac output was calculated by the Stewart-Hamilton principle.¹¹⁾ Hemodynamic parameters were calculated according to the previous report.¹²⁾

RESULTS

Following the infusion of Ca⁺⁺, plasma Ca⁺⁺ concentration was elevated by an average of 0.59 ± 0.28 (S.D.) mEq/L and following the infusion of Mg⁺⁺, plasma Mg⁺⁺ concentration was elevated by an average of 0.69 ± 0.38 (S.D.) mEq/L. The infusion of Ca⁺⁺ and Mg⁺⁺ did not affect other plasma electrolyte concentrations.

I. Comparison of the control values in systolic time intervals and hemodynamics between normotensives and hypertensives (Tables I-IV)

There were no differences in systolic time intervals, heart rate, cardiac index, and stroke index between normotensives and hypertensives. The hyper-

Table I. Effects of Ca⁺⁺ Infusion on Systolic Time Intervals

Ca ⁺⁺ infusion		Control $\pm$ S.D.	P (vs. NT)	After infusion $\pm$ S.D.	Change $\pm$ S.D.	p (vs. control)
QS ₂ I msec	NT	525 $\pm$ 10.7		518 $\pm$ 13.9	-8 $\pm$ 7.7	0.001
	HT	520 $\pm$ 15.7	ns	511 $\pm$ 17.8	-8 $\pm$ 9.6	0.005
ETI msec	NT	401 $\pm$ 25.8		398 $\pm$ 26.3	-2 $\pm$ 5.5	0.10
	HT	391 $\pm$ 17.1	ns	391 $\pm$ 18.0	-0 $\pm$ 5.7	ns
PEPI msec	NT	121 $\pm$ 13.2		115 $\pm$ 14.0	-6 $\pm$ 5.7	0.001
	HT	126 $\pm$ 13.0	ns	119 $\pm$ 13.9	-7 $\pm$ 7.6	0.005
ICT msec	NT	43 $\pm$ 13.8		41 $\pm$ 13.8	-3 $\pm$ 6.5	0.05
	HT	49 $\pm$ 13.6	ns	44 $\pm$ 18.0	-5 $\pm$ 9.0	0.05
ET/PEP	NT	3.117 $\pm$ 0.521		3.330 $\pm$ 0.656	+0.214 $\pm$ 0.275	0.005
	HT	2.825 $\pm$ 0.483	ns	3.126 $\pm$ 0.711	+0.229 $\pm$ 0.278	0.005

Each value represents the mean $\pm$ 1 S.D.

Twenty-one normotensives and 17 hypertensives were studied.

Abbreviations: NT=normotensive subject; HT=hypertensive patient; ns=not significant.

Table II. Effects of Ca⁺⁺ Infusion on Systemic Hemodynamics

Ca ⁺⁺ infusion		Control±S.D.	P (vs. NT)	After infusion±S.D.	Change±S.D.	p (vs. control)
HR beats/min	NT	67± 8.6	ns	68± 11.6	+2± 8.2	ns
	HT	68± 12.6		69± 14.0	+1± 6.2	ns
MBP mmHg	NT	87± 9.1	0.001	93± 11.6	+6± 7.6	0.001
	HT	113± 9.8		122± 12.7	+9± 9.0	0.001
CI L/min/M ²	NT	3.9 ± 1.01	ns	4.7 ± 1.40	+0.8 ± 0.24	0.001
	HT	4.0 ± 1.23		4.6 ± 1.31	+0.6 ± 0.62	0.005
SI ml/beat/M ²	NT	60± 16.4	ns	70± 20.7	+10± 12.9	0.001
	HT	59± 15.0		68± 18.1	+8± 9.4	0.001
TPRI dyn·sec· cm ⁻⁵ ·M ²	NT	1876±479.1	0.01	1702±501.4	-173±301.9	0.01
	HT	2395±693.1		2277±714.6	-139±341.6	ns
LVWI Kg·M/M ²	NT	4.69± 1.31	0.01	5.97± 1.69	+1.28± 1.02	0.001
	HT	6.10± 1.86		7.83± 1.93	+1.29± 1.11	0.005

Each value represents the mean±1 S.D.

Twenty-seven normotensives and 25 hypertensives were studied.

Abbreviations: See Table I. HR=heart rate; MBP=mean blood pressure; CI=cardiac index; SI=stroke index; TPRI=total peripheral resistance index; LVWI=left ventricular work index.

Table III. Effects of Mg⁺⁺ Infusion on Systolic Time Intervals

Mg ⁺⁺ infusion		Control±S.D.	P (vs. NT)	After infusion±S.D.	Change±S.D.	p (vs. control)
QS ₂ I msec	NT	525±21.8	ns	532±21.5	+7±11.0	0.05
	HT	523±21.2		529±22.8	+6±11.1	0.05
ETI msec	NT	402±18.8	ns	406±12.5	+4± 9.2	0.1
	HT	390±18.3		392±17.3	+3± 9.0	ns
PEPI msec	NT	123±12.1	ns	126±12.8	+3± 5.0	0.01
	HT	134±22.8		137±22.3	+4± 5.9	0.01
ICT msec	NT	40±14.1	ns	43±13.5	+3± 4.7	0.05
	HT	46±13.6		51±15.6	+6± 7.8	0.05
ET/PEP	NT	3.079± 0.455	ns	3.019± 0.470	-0.061± 0.196	ns
	HT	2.762± 0.761		2.570± 0.629	-0.129± 0.361	ns

Each value represents the mean±1 S.D.

Twenty-two normotensives and 21 hypertensives were studied.

Abbreviations: See Table I.

Table IV. Effects of Mg^{++} Infusion on the Systemic Hemodynamics

Mg^{++} infusion		Control $\pm$ S.D.		P (vs. NT)	After infusion $\pm$ S.D.		Change $\pm$ S.D.	P (vs. control)
HR beats/min	NT	64 $\pm$	9.0	ns	70 $\pm$	11.7	+6 $\pm$ 5.2	0.001
	HT	68 $\pm$	9.1		72 $\pm$	11.6	+5 $\pm$ 7.3	0.01
MBP mmHg	NT	87 $\pm$	9.4	0.001	92 $\pm$	13.4	+5 $\pm$ 8.8	0.05
	HT	121 $\pm$	13.2		125 $\pm$	15.0	+4 $\pm$ 6.3	0.01
CI L/min/M ²	NT	4.0 $\pm$	1.33	ns	3.9 $\pm$	1.69	-0.0 $\pm$ 1.01	ns
	HT	3.9 $\pm$	1.85		3.8 $\pm$	1.73	-0.1 $\pm$ 0.85	ns
SI ml/beat/M ²	NT	63 $\pm$	19.0	ns	56 $\pm$	18.6	-8 $\pm$ 14.3	0.05
	HT	58 $\pm$	25.6		53 $\pm$	20.9	-6 $\pm$ 12.6	0.1
TPRI dyn $\cdot$ sec. cm ⁻⁵ ·M ²	NT	1878 $\pm$	660.4	0.01	2071 $\pm$	878.3	+193 $\pm$ 588.2	ns
	HT	2831 $\pm$	1123.1		3040 $\pm$	1246.2	+253 $\pm$ 631.7	0.1
LVWI Kg $\cdot$ M/M ²	NT	4.80 $\pm$	1.50	0.01	5.00 $\pm$	2.00	+0.25 $\pm$ 1.39	ns
	HT	6.55 $\pm$	3.14		6.42 $\pm$	2.88	-0.13 $\pm$ 1.37	ns

Each value represents the mean $\pm$ 1 S.D.

Twenty-six normotensives and 22 hypertensives were studied.

Abbreviations: See Table II.

tensive patients in this study had compensated left ventricular performance, and systolic time intervals, cardiac index, and stroke index remained within normal limits.

II. Ca^{++} infusion

1. Effects of Ca^{++} infusion on systolic time intervals

There was significant shortening of QS_2I , PEPI, and ICT in normotensives and hypertensives (Table I and Fig. 1). ET/PEP increased significantly, but ETI was not altered in both groups.

2). Effects of Ca^{++} infusion on hemodynamics

The heart rate was not altered, but mean blood pressure, cardiac index, and stroke index increased significantly in normotensives and hypertensives (Table II and Fig. 2). The total peripheral resistance index decreased significantly in normotensives, but not in hypertensives.

However, there were no significant differences in systolic time intervals and hemodynamic parameters between normotensives and hypertensives.

III. Mg^{++} infusion

1. Effects of Mg^{++} infusion on systolic time intervals

There was significant prolongation of QS_2I , PEPI, and ICT in normotensives and hypertensives (Table III and Fig. 1). ET/PEP tended to decrease and ETI tended to be prolonged in both groups, but these changes

Fig. 1. Effects of Ca^{++} and Mg^{++} infusion on the systolic time intervals. Each parameter is expressed as changes from the control levels.

Fig. 2. Effects of Ca^{++} and Mg^{++} infusion on systemic hemodynamics. Each parameter is expressed as change from the control level.

were not significant.

2. Effects of Mg^{++} infusion on the hemodynamics

The heart rate increased in normotensives and hypertensives (Table IV and Fig. 2). These changes were small, but statistically significant. The mean blood pressure rose significantly in normotensives and hypertensives. The cardiac index was not altered, and total peripheral resistance index tended to increase in both groups.

The response to Mg^{++} infusion in hypertensives was similar to that in normotensives.

DISCUSSION

It is known that Ca^{++} plays an important role in the muscle contraction, but the precise mechanisms have not been elucidated. There is general agreement that the transition from the resting to the active state in heart muscle

cells depends upon the increase in intracellular availability of Ca^{++} , which comes from the internal stores of sarcoplasmic reticulum or extracellular medium.¹³⁾⁻¹⁵⁾ Drugs such as catecholamines, cardiac glycosides, and verapamil alter the cardiac contractility by increasing or decreasing the amount of Ca^{++} which becomes available for participation in the events associated with excitation-contraction coupling.¹⁶⁾⁻¹⁸⁾ Previous *in vitro* studies^{3), 6), 19), 20)} showed that the contractile force of cardiac and smooth muscle was directly influenced by changes in external Ca^{++} concentration. On the other hand, the effect of Mg^{++} may be little as compared with the effect of Ca^{++} , because there were no demonstrable effects of Mg^{++} on the myogram of papillary muscle strips with omission of Mg^{++} or a 10-fold increase of Mg^{++} concentration,²¹⁾ and also a slight decrease in contractility of isolated guinea pig heart was found with an increase of Mg^{++} from 0 to 4.5 mM/L.²²⁾

In the present study, ETI, QS_2I , PEPI, and ICT are deemed as representatives of cardiac contractility,²³⁾⁻²⁵⁾ stroke volume, cardiac output, and ET/PEP as representatives of the pump function of heart,^{23), 26)} heart rate as a representative of chronotropic effect, and total peripheral resistance as a representative of peripheral arterial condition. In this study, despite the small elevation of plasma Ca^{++} and Mg^{++} concentrations, many significant effects of these cations were observed. Although some workers^{8), 9)} have stated calcium and magnesium might involve in the development of hypertension, the author could not find the difference in the response to infusion of Ca^{++} and Mg^{++} between normotensives and hypertensives.

Administration of Ca^{++} was followed by prompt abbreviation in systolic time intervals. Weissler and Schoenfeld demonstrated that the changes in PEPI and ETI induced by digitalis correlated significantly with each of the hemodynamic responses (cardiac output, stroke volume).²⁷⁾ Increased ET/PEP, shortened PEP and ICT, and increased cardiac index and stroke index produced by Ca^{++} infusion were thought to be the result of increased performance of cardiac muscle.

Somjen and Baskerville demonstrated that administration of Ca^{++} caused the increase of basal rhythm of heart *in situ*.¹⁾ Toda and West showed that the negative chronotropic response of isolated atrium of rabbit to vagal stimulation had increased exponentially with increase of concentration of Ca^{++} in the experimental solution.²⁸⁾ In this study stroke index increased significantly after infusion of Ca^{++} , under which the heart rate might be expected to decrease because of the inverted relationship between heart rate and stroke volume,^{10), 25)} and negative chronotropic effect of Ca^{++} , but there was no change in the heart rate. It is suggested that the release of catecholamines might prevent the decrease in heart rate.¹⁾

The infusion of Mg⁺⁺ showed the opposite effects to the infusion of Ca⁺⁺ on systolic time intervals. The significant prolongation of PEPI and ICT appeared, ETI tended to be lengthened and ET/PEP tended to decrease. The systolic time intervals are influenced by multiple factors, such as ventricular volume, preload, afterload, contractility, and neurohumoral activity.^{27),29),30)} There are some controversies concerning the effect of acutely increased afterload on systolic time intervals. Wigger noted, using a dog preparation, a slightly decreased ejection time with the increase in aortic pressure.³¹⁾ Harris and co-workers showed that acute pharmacologic vasoconstriction prolonged PEP through reflex stimulation of vagal efferents to the heart.³²⁾ On the other hand, it was reported that ejection time was increased and ICT was shortened by constriction of aorta.³³⁾ Altire suggested that Mg⁺⁺ increased the affinity of vasopressin for its receptor on blood vessels.³⁴⁾ In the present hemodynamic study total peripheral resistance index tended to increase, while the changes of systolic time intervals might be affected by a little increase in peripheral arterial resistance, but these intervals could be altered mainly by the depressant action on myocardial contractility.^{21),22)} These findings agreed with other studies. Santurbuny and Farah demonstrated using the heart-lung preparations that increase of magnesium concentration in serum diminished the systemic output,³⁵⁾ and another group observed the cardiac output of dog decreased with increase of magnesium concentration.³⁶⁾

Smith and co-workers have noted the development of tachycardia with elevations of plasma magnesium concentration to 5 mEq/L, but bradycardia at higher magnesium concentration.³⁷⁾ Several investigators confirmed that a depressant action on rhythm and conduction and a transient tachycardia at a small elevation of magnesium concentration were explained by the fall of blood pressure.³⁷⁾⁻³⁹⁾ The fall of blood pressure was explained by decreased cardiac output or vasodilatation produced by magnesium, but in this study heart rate was increased and blood pressure elevated. These observations are consistent with the experiments of Somjen and co-workers,³⁸⁾ and Toda and West showed that Mg⁺⁺ diminished the negative chronotropic effect of vagal stimulation in isolated atria of rabbit.²⁸⁾ The stroke volume follows an inverse linear relationship with heart rate. In this study heart rate increased and cardiac index tended to decrease. Decrease of stroke index may be not only due to the effect of increase of heart rate, but also negative inotropic action of Mg⁺⁺.

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