

Effect of Magnesium on Anginal Attack Induced by Hyperventilation in Patients With Variant Angina

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To examine whether or not magnesium suppresses coronary spasm, the effect of magnesium infusion on anginal attacks induced by hyperventilation was studied in 20 patients with variant angina. In all patients, anginal attacks associated with ischemic ST segment changes on the electrocardiogram were repeatedly induced by hyperventilation. The study was performed in the early morning successively for 3 days. On days 1 and 3 (control studies), 50 minutes before the hyperventilation test, a 5% glucose solution was infused as a placebo. On day 2 (magnesium study), 50 minutes before the hyperventilation test, magnesium sulfate (0.27 mM/kg body wt) was infused during a 20-minute period. During the control studies, anginal attack was induced by hyperventilation in all 20 patients, whereas during the magnesium study, anginal attack was induced by hyperventilation in only six (30%) of the 20 patients ($p < 0.001$ vs. control studies). The changes in arterial blood pH and PCO_2 caused by hyperventilation were not significant between the control study and the magnesium study. Mean serum magnesium concentration increased from 2.2 ± 0.2 to 6.0 ± 0.5 mg/dl immediately after infusing magnesium and was 4.5 ± 0.6 mg/dl before the hyperventilation test during the magnesium study. We conclude that magnesium suppresses anginal attacks induced by hyperventilation in patients with variant angina. (*Circulation* 1989;79:597-602)

Previous studies have shown that variant angina is caused by spasm of a large coronary artery,¹⁻⁴ and hyperventilation has been used to induce coronary spasm in patients with variant angina.⁵⁻⁷ Although the precise mechanism whereby hyperventilation induces coronary spasm is still unclear, alkalosis caused by hyperventilation may increase intracellular calcium ion, which results in contraction of the coronary vascular smooth muscle.^{5,8,9}

The role of magnesium in cardiac disease was recently reviewed.¹⁰⁻¹³ Experimental studies in vitro have shown that depletion of magnesium from the superfusate medium potentiates contractile responses of small and large coronary arteries to various stimuli.¹⁴ Magnesium also may be a physiologic calcium antagonist and thus may prevent the contraction of the vascular smooth muscle.¹³⁻¹⁵ How-

ever, to date, no clinical study concerning the effect of magnesium on coronary spasm has been performed. In this study, we examined the effect of magnesium on anginal attack induced by hyperventilation in patients with variant angina.

Methods

Patients

Twenty-seven consecutive patients with variant angina were studied by inducing anginal attack with hyperventilation. All had spontaneous attacks associated with ST segment elevation on the electrocardiogram. In 20 patients, anginal attacks associated with ST segment changes on the electrocardiogram were repeatedly induced by hyperventilation. These 20 patients (19 men and 1 woman; age range, 45-72 years; mean age, 61 years) were included in this study (Table 1). Coronary angiography was performed in 19 of the 20 patients, and in all patients, coronary spasm, defined as total or subtotal coronary occlusion associated with chest pain and ischemic ST segment changes, was induced by intracoronary injection of acetylcholine¹⁶⁻¹⁸ in the artery or arteries predicted to be responsible for spontaneous attacks based on the ST segment elevation on the electrocardiogram (Table 1). None of the

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TABLE 1. Clinical Characteristics of Patients With Variant Angina

Patient	Age	Sex	ST segment elevation during spontaneous attack	Coronary arteriography					
				Spasm induced by acetylcholine			% Stenosis after nitroglycerin		
				LAD	LCx	RCA	LAD	LCx	RCA
1	72	M	II,III,aV _F	+	-	+	25	75	75
2	72	M	V ₁₋₃ , aV _L	+	-	+	50	N	25
3	57	M	II,III,aV _F	+	-	+	N	N	N
4	65	M	II,III,aV _F	-	-	+	75	N	N
5	68	M	II,III,aV _F or V ₁₋₄	+	+	+	25	N	N
6	48	M	V ₁₋₄ , aV _L	+	-	-	N	N	N
7	60	M	II,III,aV _F	-	-	+	N	N	90
8	69	M	II,III,aV _F	+	-	+	N	N	N
9	69	M	II,III,aV _F or V ₁₋₄	+	-	+	N	N	N
10	64	M	II,III,aV _F or V ₁₋₃	+	-	+	N	N	N
11	61	M	V ₁₋₅	+	-	-	50	N	N
12	53	M	V ₁₋₅ , I, aV _L	+	+	+	50	25	25
13	56	M	II,III,aV _F , V ₄₋₆	+	-	+	N	N	N
14	63	F	V ₄₋₆	+	-	-	N	N	N
15	64	M	II,III,aV _F	+	-	+	N	N	N
16	60	M	V ₂₋₆ , I, aV _L	+	-	-	N	N	N
17	60	M	II,III,aV _F	-	-	+	N	N	90
18	67	M	II,III,aV _F , V ₅₋₆
19	56	M	V ₁₋₅	+	-	+	N	N	N
20	45	M	II,III,aV _F , V _I	+	-	+	N	N	N

LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; N, normal or <25% stenosis; +, occurrence of coronary spasm; -, no occurrence of coronary spasm.

patients had previous myocardial infarction, heart failure, or renal failure. All medication was stopped at least 2 days before the study except nitroglycerin, which was stopped 2 hours before the study. Written, informed consent was obtained from each patient.

Study Protocol

The hyperventilation test was performed in the early morning (from 6:00 AM to 8:00 AM) successfully for 3 days because anginal attack is more easily induced in the early morning in patients with variant angina.¹⁹ Three lead electrocardiogram consisting of V₃, V₅, and aV_F were continuously monitored on an oscilloscope (Case II, Marquette) during the study. Blood pressure was measured with a cuff sphygmomanometer at appropriate intervals. On days 1 and 3 (control studies), 50 minutes before the hyperventilation test, 100 ml 5% glucose solution was infused for 20 minutes as a placebo. On day 2 (magnesium study), 50 minutes before the hyperventilation test, magnesium sulfate (0.27 mM/kg body wt) dissolved in 100 ml isotonic glucose solution was infused for 20 minutes. The patients were unaware of whether intravenous glucose or intravenous magnesium was administered. After a 12 lead electrocardiogram was recorded, the patients were asked to perform the hyperventilation test, in which they vigorously hyperventilated for 6 minutes.^{5,7} If chest pain or ischemic ST segment changes on the electrocardiogram appeared during

hyperventilation, the test was terminated immediately. Twelve lead electrocardiograms were recorded at 1-minute intervals or more often during and after the hyperventilation test. Sublingual nitroglycerin (0.3 mg) was administered when the attack was induced. The degree of ST segment shift was measured at a point 80 msec after the nadir of the S wave. The hyperventilation test was considered positive if ischemic ST segment changes were induced by hyperventilation.

Blood samples for measuring serum magnesium, calcium, and phosphorus concentrations were taken before and after infusion of placebo or magnesium solution and before and after hyperventilation. Blood samples were also taken when the attack was induced by hyperventilation. Arterial blood samples for pH and gas analysis were also taken before and after the hyperventilation test. Serum magnesium concentration was determined by atomic absorption spectrophotometry (Model 403, Perkin-Elmer). Serum calcium and phosphorus concentrations were determined with autoanalyser (SMAC-1, Technicon). Arterial blood pH and gas were measured with an autoanalyser (ABL-2, Radiometer).

During the 3-day study period, a diary of anginal attacks was maintained by all patients. Also, the oscillographic electrocardiographic monitoring was performed continuously in all patients during the same period. The number of spontaneous ischemic

TABLE 2. Hyperventilation-Induced Anginal Attack and Disease Activity

Patient	Day 1		Day 2		Day 3		Spontaneous angina during study period (n)
	ST segment deviation	Maximum ST deviation (mV)	ST segment deviation	Maximum ST deviation (mV)	ST segment deviation	Maximum ST deviation (mV)	
1	II,III,aV _F ,V ₁	↑ 0.44	No Attack		II,III,aV _F ,V ₁	↑ 0.45	3
2	V ₁₋₄ ,aV _L	↑ 0.14	No Attack		V ₁₋₄ ,aV _L	↑ 0.37	4
3	II,III,aV _F	↑ 0.33	No Attack		II,III,aV _F	↑ 0.45	7
4	II,III,aV _F	↑ 0.10	No Attack		II,III,aV _F	↑ 0.10	1
5	II,III,aV _F ,V ₂₋₆	↓ -0.20	No Attack		II,III,aV _F	↑ 0.30	6
6	V ₁₋₄ ,aV _L	↑ 0.24	No Attack		V ₁₋₄	↑ 0.15	0
7	II,III,aV _F	↑ 0.10	No Attack		II,III,aV _F	↑ 0.10	0
8	II,III,aV _F	↑ 0.15	No Attack		II,III,aV _F	↑ 0.15	1
9	II,III,aV _F ,V ₃₋₆	↓ -0.15	No Attack		II,III,aV _F ,V ₃₋₆	↓ -0.15	1
10	II,III,aV _F ,V ₁₋₃	↑ 0.28	No Attack		II,III,aV _F ,V ₁₋₃	↑ 0.30	4
11	V ₁₋₆	↑ 0.30	No Attack		V ₂₋₆	↓ -0.20	0
12	V ₁₋₅ ,I,aV _L	↑ 0.37	No Attack		V ₁₋₆ ,I,aV _L	↑ 0.45	2
13	II,III,aV _F ,V ₂₋₅	↓ -0.25	No Attack		II,III,aV _F ,V ₂₋₅	↓ -0.20	4
14	V ₂₋₆	↓ -0.15	No Attack		V ₂₋₆	↓ -0.14	2
15	II,III,aV _F ,V ₆	↑ 0.36	II,III,aV _F	↑ 0.18	II,III,aV _F	↑ 0.25	15
16	V ₂₋₆ ,I,aV _L	↑ 0.80	V ₂₋₆ ,I,aV _L	↑ 0.61	V ₂₋₆ ,I,aV _L	↑ 0.70	2
17	II,III,aV _F	↑ 0.14	II,III,aV _F	↑ 0.36	II,III,aV _F	↑ 0.20	28
18	II,III,aV _F ,V ₅₋₆	↑ 0.30	II,III,aV _F	↑ 0.49	II,III,aV _F	↑ 0.30	8
19	V ₁₋₆ ,I,aV _L	↑ 1.50	V ₁₋₆ ,I	↑ 0.54	V ₁₋₆ ,I,aV _L	↑ 0.81	14
20	II,III,aV _F ,V _{1,4-6}	↑ 0.78	II,III,aV _F ,V ₁	↑ 0.31	II,III,aV _F ,V _{1,5,6}	↑ 0.71	21

episodes indicated by anginal attack or ST segment elevation was counted.

Data are shown as mean ± SD. Normally distributed data were compared by analysis of variance and Student's paired *t* test with Bonferroni's correction, and data not normally distributed were compared by Wilcoxon's signed rank test.²⁰ The incidence of hyperventilation-induced attack between groups was compared with Fisher's exact test.

Results

Most patients experienced mild lightheadedness and numbness of the hands, feet, and lips, which began after 2–3 minutes and continued throughout the hyperventilation test.

Anginal Attack Induced by Hyperventilation

In the 20 patients, during control studies on days 1 and 3, the anginal attack was induced by hyperventilation. All patients had anginal pain during the attack. In two patients, the attack occurred during hyperventilation, and in the remaining 18, it occurred a mean of 4 minutes (range, 30 seconds to 7 minutes) after hyperventilation. Of the 40 episodes of hyperventilation-induced attacks in the study, 32 were associated with ST segment elevation on the electrocardiogram, and the remaining eight were associated with ST segment depression (Table 2). None of the eight episodes associated with ST segment depression was preceded by an increase in the rate-pressure product, which is considered to be an index of myocardial oxygen consumption. Fifteen patients had attacks associated with ST seg-

ment elevation on days 1 and 3, three patients had attacks associated with ST segment depression on days 1 and 3, and two patients had attacks associated with ST segment elevation on one of two days and ST segment depression on the other day.

Effects of Magnesium Infusion on Hemodynamic Output and Serum Electrolyte Levels

Effects of magnesium infusion on hemodynamic output and serum electrolyte levels are shown in Table 3. Infusion of magnesium sulfate did not change heart rate in any patients. Although heart rate significantly increased immediately after hyperventilation (from 60 ± 11 to 70 ± 12 beats/min, $p < 0.05$), the change was similar to that during the control study (from 60 ± 10 to 69 ± 13 beats/min, $p < 0.05$; $p = \text{NS}$ vs. the magnesium study). Neither systolic nor diastolic blood pressure changed after infusion of magnesium sulfate. Neither changed after hyperventilation during the control and magnesium studies.

All patients experienced a transient flush of face during magnesium infusion, but none had muscle weakness and hypotension during and after the infusion.

Serum magnesium concentration increased from 2.2 ± 0.2 to 6.0 ± 0.5 mg/dl immediately after the infusion of magnesium solution. Serum magnesium concentrations immediately before and immediately after hyperventilation were 4.5 ± 0.6 and 4.4 ± 0.5 mg/dl, respectively. During the control study, however, serum magnesium concentration did not change after the infusion of the placebo or after hyperventilation.

TABLE 3. Hemodynamic Output and Electrolyte Levels of Patients With Variant Angina

	Control					Magnesium				
	Before infusion	After infusion	Before hyper-ventilation	After hyper-ventilation	Attack	Before infusion	After infusion	Before hyper-ventilation	After hyper-ventilation	Attack (n=6)
Heart rate (beats/min)	58±8	59±8	60±10	69±13*	61±11	59±10	62±10	60±11	70±12*	61±10
Systolic blood pressure (mm Hg)	126±16	126±16	128±20	126±20	128±20	124±14	124±13	126±16	123±17	129±21
Diastolic blood pressure (mm Hg)	72±8	73±8	74±9	75±9	74±12	71±10	72±10	71±11	74±12	75±10
Serum magnesium concentration (mg/dl)	2.2±0.2	2.1±0.2	2.2±0.2	2.2±0.2	2.2±0.3	2.2±0.2	6.0±0.5†	4.5±0.6†	4.4±0.5†	4.3±0.4†
Serum calcium concentration (mg/dl)	9.0±0.3	9.0±0.4	9.0±0.4	9.1±0.4*	9.1±0.3*	8.9±0.3	8.8±0.4*	8.9±0.4	9.1±0.4*	9.1±0.5
Serum phosphorus concentration (mg/dl)	3.4±0.6	3.3±0.5*	3.3±0.5*	3.0±0.5†	3.0±0.4†	3.4±0.6	3.2±0.6*	3.2±0.5*	2.9±0.5†	2.8±0.6*

Control, control study (day 1); Magnesium, magnesium study (day 2).

* $p < 0.05$; † $p < 0.01$.

Serum magnesium concentration at the time of the attack was not different from the baseline value.

Serum calcium concentration increased slightly, but significantly, after hyperventilation during the control and magnesium studies. However, the degree of changes was not different in serum calcium concentration between the control and magnesium studies.

Serum phosphorus concentration decreased significantly after the glucose infusion during the control and magnesium studies. It also decreased significantly after hyperventilation in the control and magnesium studies. However, the degree of changes was not different in serum phosphorus concentration between the control and magnesium studies.

Effect of Magnesium on Anginal Attack Induced by Hyperventilation

After hyperventilation, arterial blood pH increased from 7.40 ± 0.02 to 7.61 ± 0.05 during the control study (day 1) and from 7.39 ± 0.02 to 7.60 ± 0.05

during the magnesium study (day 2), and arterial blood PCO_2 decreased from 41.3 ± 3.8 to 21.5 ± 3.4 mm Hg during the control study and from 42.6 ± 2.7 to 22.6 ± 3.6 mm Hg during the magnesium study (Table 4). The degree of changes was not significant in arterial blood pH and PCO_2 after hyperventilation between the control and magnesium studies.

The attack was not induced by hyperventilation in 14 (70%) of the 20 patients after intravenous administration of magnesium sulfate ($p < 0.001$ vs. the control study).

Figure 1 shows the representative patient (patient 3). The attack associated with ST segment elevation in leads II and III on the electrocardiogram appeared immediately after hyperventilation on day 1. After magnesium infusion on day 2, however, neither chest pain nor ST segment change on the electrocardiogram occurred after hyperventilation. Arterial blood pH rose from 7.40 to 7.60 on day 1 and from 7.39 to 7.59 on day 2. Arterial blood PCO_2 decreased from 42.8 to 22.1 mm Hg on day 1 and from 42.0 to 23.1 mm Hg on day 2. Serum magnesium concentration was 2.2 mg/dl before hyperventilation on day 1 and 4.5 mg/dl before hyperventilation on day 2.

In six patients, hyperventilation-induced attack was not prevented by magnesium infusion. All episodes in these patients occurred after hyperventilation (mean, 5 minutes after hyperventilation) and were associated with ST segment elevation. In these six patients, the mean maximal ST segment elevation during the anginal attack after magnesium infusion was 0.42 ± 0.15 mV, whereas elevation during the control study on day 1 was 0.65 ± 0.45 mV ($p = NS$).

Factors Affecting Anginal Attack Induced by Hyperventilation During Magnesium Study

There was no difference in age, sex, and organic coronary stenosis and baseline serum magnesium,

TABLE 4. Changes in Arterial Blood pH and Gases in Patients With Variant Angina

		Before hyperventilation		After hyperventilation
pH	Control	7.40 ± 0.02	*	7.61 ± 0.05
	Magnesium	NS		NS
PCO_2 (mm Hg)	Control	41.3 ± 3.8	*	21.5 ± 3.4
	Magnesium	NS		NS
PO_2 (mm Hg)	Control	92.1 ± 13.7	*	127.2 ± 13.7
	Magnesium	NS		NS

Control, control study (day 1); Magnesium, magnesium study (day 2).

* $p < 0.01$.

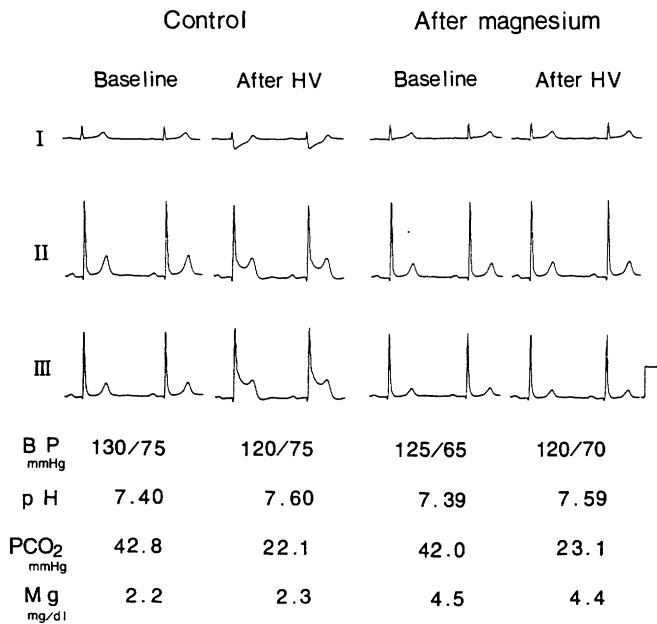


FIGURE 1. Tracings of three leads (I, II, and III) of the electrocardiogram and measures of blood pressure (BP), arterial pH and PCO₂, and serum magnesium (Mg) concentration before and after hyperventilation (HV) on days 1 and 2 in patient 3. ST segment elevation in leads II and III appeared after hyperventilation on day 1, whereas neither chest pain nor ST segment deviation was induced by hyperventilation after magnesium infusion on day 2.

calcium, and phosphorus concentrations between the patients in whom hyperventilation-induced attacks were suppressed by magnesium and the patients in whom the attacks were not suppressed. However, there was a significant difference in disease activity, which was defined as the total number of spontaneous ischemic episodes and nitroglycerin tablets consumed during the study period (3 days), between the two groups of patients. The number of spontaneous attacks was 3 ± 2 in patients in whom hyperventilation-induced attack was suppressed by magnesium, whereas it was 15 ± 8 in patients in whom the attack was not suppressed ($p < 0.01$). The number of nitroglycerin tablets consumed was 2 ± 2 in the former patients, whereas it was 15 ± 15 in the latter patients ($p < 0.01$). Thus, disease activity was higher in patients whose attacks were not suppressed by magnesium than in those whose attacks were suppressed by magnesium.

Discussion

Experimentally, when the extracellular magnesium concentration is low, the basal tension of the isolated canine coronary artery is increased and its contractile response to vasoconstrictive agents such as norepinephrine is potentiated, whereas when the magnesium concentration is high, the basal tension of the artery is decreased, and the response to constrictive agonists is depressed.¹⁴ Thus, physiologic effects of magnesium are antagonistic to those of calcium, and magnesium deficiency may produce coronary artery spasm. Magnesium may be a naturally occurring antagonist to calcium in the vascular system.¹³⁻¹⁵ Despite these experimental observations, few clinical studies have been done concerning the effects of magnesium on coronary arterial tension, and whether or not magnesium suppresses coronary spasm is not clear. To our knowledge, the

present study is the first systematic investigation of the effect of magnesium on coronary spastic angina.

In the present study, the effect of intravenous administration of magnesium on induced coronary spasm was evaluated in patients with variant angina. A hyperventilation test was used to induce coronary spasm. In the 20 patients, anginal attacks associated with ischemic ST segment changes (ST segment elevation occurred in most patients) were induced on days 1 and 3 (during control studies) during and after hyperventilation. Furthermore, the rate-pressure product, an index of myocardial oxygen consumption, did not increase in any of the patients immediately before the attack. Thus, the attack due to coronary spasm was reproducibly induced by hyperventilation in these patients, and it was possible to evaluate the effect of magnesium on inducing coronary spasm. The degree of hyperventilation necessary to induce coronary spasm was not different between the control study and the magnesium study as indicated by the same degree of changes in arterial blood pH and PCO₂ and serum calcium and phosphorus concentrations. Nevertheless, the incidence of the attacks induced by hyperventilation during the magnesium study was significantly lower than that during the control study. These results strongly suggest that magnesium suppresses coronary spasm in patients with variant angina.

Serum phosphorus concentrations decreased after glucose infusion and after hyperventilation in the control and magnesium studies. This was probably due to a shift of phosphorus from blood to cells as a result of glucose administration or increased glycolytic activity accompanying hyperventilation.²¹ Previous studies have shown that serum total calcium concentration remains unchanged, whereas serum calcium ion level decreases in acute respiratory

alkalosis.^{21,22} In the present study, a slight increment in serum total calcium concentration occurred after hyperventilation. The reason for this is unclear.

Coronary spasm is now widely accepted as having an important role in the pathogenesis of not only variant angina but also of other forms of ischemic heart disease, including some forms of unstable angina and acute myocardial infarction.^{19,23-27} The present study indicates that intravenous magnesium may be useful for the treatment of coronary spasm.

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