Magnesium Metabolism in Hyperthyroidism[#]

TUMBA DISASHI, TAISUKE IWAOKA, JUNNOSUKE INOUE, SHOJIRO NAOMI,
YASUKO FUJIMOTO, TERUHISA UMEDA*, AND KIMIO TOMITA

Third Department of Internal Medicine, Kumamoto University School of Medicine, Kumamoto 860, and

*Institute of Hypertension and Endocrinology, Mitsui Ohmuta Hospital, Ohmuta 836, Japan

Abstract. Changes in magnesium metabolism, along with those in sodium, were investigated in 17 patients with Graves' disease (14 females and 3 males, mean $\pm$ SD, 44.8 $\pm$ 12.2 years) and their relationship to plasma levels of thyroid hormones were assessed before and after treatment. Each patient was studied in hyperthyroid state and euthyroid state after treatment with methimazole. Treatment with methimazole increased the magnesium concentration both in erythrocytes (2.00 $\pm$ 0.18 vs. 2.08 $\pm$ 0.24 mmol/l cells, P <0.05) and in serum (0.72 $\pm$ 0.12 vs. 0.84 $\pm$ 0.11 mmol/l, P <0.001) but both urinary output and fractional excretion of magnesium decreased significantly (P <0.05 and P <0.001, respectively). The erythrocyte sodium concentration decreased with treatment (10.7 $\pm$ 2.6 vs. 8.1 $\pm$ 1.1 mmol/l cells, P <0.001) but the serum sodium remained unchanged (140.9 $\pm$ 1.9 vs. 140.9 $\pm$ 2.1 mmol/l, NS). Urinary excretion of sodium also decreased with treatment (P <0.05), but only changes in indices of magnesium metabolism (decrease in renal fractional excretion, rise in serum level) correlated significantly with those of the thyroid functions with treatment. These observations clearly indicate that in Graves' disease, the magnitude of magnesium metabolism alteration is closely related to the extent of the increase in thyroid hormones in plasma.

Key words: Hyperthyroidism, Serum magnesium, Erythrocyte magnesium, Urinary magnesium, Sodium metabolism

(Endocrine Journal 43: 397–402, 1996)

MAGNESIUM is an essential mineral for human beings and participates in a variety of metabolic functions [1, 2]. The influence of thyroid hormones on magnesium homeostasis is well known [3], but not enough attention is paid to magnesium metabolism in hyperthyroidism. Firstly, serum magnesium in hyperthyroidism is often in the normal range for patients on an unrestricted diet. Secondly, conflicting results have been reported about the serum magnesium status in hyperthy-

roidism. Some investigators found that serum magnesium was unchanged in hyperthyroidism, but others found it to be reduced, with serum free magnesium being the most often lowered [4, 5]. Thirdly, the clinical relevance of magnesium deficiency in hyperthyroidism is not yet known. Magnesium administration was reported to improve symptoms in hyperthyroidism in a clinical study [6].

Thyroid hormones affect renal excretion and cellular transport of ions. Most of the studies of magnesium metabolism in hyperthyroidism did not concomitantly investigate cellular, plasma and urinary magnesium [7, 8], but this approach is important, for it gives a comprehensive explanation of changes in magnesium homeostasis during hyperthyroidism. To test the possibility that an increase in serum thyroid hormones may imply disturbances of magnesium metabolism in hyperthyroid patients, we therefore studied cellular,

Received: November 30, 1995

Accepted: April 4, 1996

Correspondence to: Dr. Tumba DISASHI, Third Department of Internal Medicine, Kumamoto University School of Medicine, 1–1–1 Honjo, Kumamoto 860, Japan

[#]The present article was presented in part at the 67th meeting of the Japan Endocrine Society, Nagasaki, Japan, June 1–3, 1994.

serum and renal changes in magnesium metabolism before and after treatment of hyperthyroidism, and analyzed their relationships with serum levels of thyroid hormones. In order to get a better understanding of these relationships, sodium metabolism, which has been more widely investigated in hyperthyroidism, was also studied.

Subjects and Methods

Patients

Seventeen patients, 14 females and 3 males, with hyperthyroidism due to Graves' disease (age range 20–71 years, mean age $\pm$ SD, 41.4 ± 12.8 years) were studied. The diagnosis was based on typical clinical findings, levels of serum thyroid hormones and TSH [9], and the presence of anti TSH-receptor antibodies. All the patients were treated with methimazole for 4.4 to 14.3 months (mean $\pm$ SD, 9.2 ± 4.2 months). None of them had been treated before for hyperthyroidism, had other medical problems, or was taking any drug known to affect magnesium or sodium metabolism. All patients gave informed consent to the study which was approved by the Ethical Committee of our institution.

Blood and urine sample collection

The study was performed in each patient before and after treatment. On a fasting morning, urine specimens were collected from 0930 h to 1230 h after a first miction with patients in the supine position. The patient took 150 ml water at 0900, 1000, 1100 and 1200 h to keep the urine flow constant; blood samples were drawn at 1100 h (the midpoint of the collection period) in three tubes: one tube with heparin for determination of erythrocyte magnesium and sodium, another one with no additive for determination of serum thyroid hormones (T_4 , T_3 , free T_4 and free T_3), TSH and anti TSH-receptor antibodies; a third one also with no additive for serum magnesium, sodium, creatinine and albumin determinations.

Measurements

Serum thyroid hormones (normal ranges: T_4 45–120 $\mu\text{g/l}$; T_3 0.7–2.1 $\mu\text{g/l}$; free T_4 7–17 ng/l; free T_3 2.7–5.5 ng/l) and anti TSH-receptor antibodies (nor-

mal <15% inhibition of ^{125}I iodine-TSH binding to the thyroid TSH receptor) were measured by radio-immunoassay and TSH was estimated by radioimmunoassay (normal range: 0.36–3.25 mU/l) with a detection limit of 0.06 mU/l with commercialized kits (Amersham, Tokyo, Japan).

To determine the intraerythrocyte magnesium and sodium concentrations, a 10 ml heparinized blood sample was centrifuged at 1,500 g for 10 min at 4 °C and the plasma and buffy coat were removed by aspiration. The erythrocytes were then washed three times at 4 °C with a buffer containing 150 mM choline chloride and 10 mM morpholinopropane sulfonic acid (MOPS) adjusted with 1.6 M tris (hydroxymethyl) aminomethane solution to pH 7.4 at 4 °C (modified from Smith) [10]. After washing, some of the erythrocyte pellet was set aside in order to measure in duplicate the hematocrit by a microcapillary method, and an aliquot of 0.1 ml was hemolyzed in 9.9 ml of distilled-deionized water. Erythrocyte ghosts in this lysate were discarded by centrifugation at 2,000 g for 15 min and kept frozen at -20°C until assayed for magnesium and sodium by atomic absorption spectrophotometry and flame photometry (Perkin-Elmer 403, Norwalk, Connecticut, USA), respectively.

Serum and urine samples for magnesium and sodium determinations were also kept frozen under the same conditions till assay by the same methods. Magnesium and sodium standard solutions were purchased from Wako Pure Chemical Industries, Ltd Japan.

Creatinine and albumin were determined with an automatic analyzer.

Calculation

The intraerythrocyte magnesium and sodium concentrations (mmol/l) were calculated after correcting for hematocrit.

Clearances of creatinine, magnesium and sodium (C_x , ml/min) were calculated with the formula:

$$C_x = \frac{U_x}{P_x} \times V \times \frac{1.48}{A}$$

where x is the substance of interest, U_x and P_x are urinary and plasma concentrations of x (mmol/l), V is the urine flow rate (ml/min) and A is the body surface area of each patient (m^2) with 1.48 (m^2) being the average for the Japanese population. Fractional excretion of magnesium or sodium (FE_x) was calculated as the clearance of the electro-

lyte divided by creatinine clearance.

Correction of the serum magnesium concentration as a function of the serum albumin concentration was performed according to Kroll and Elin [11] with the following equation:

$$\text{Mg}_c = \text{Mg}_t + 0.005 \times (40 - \text{Alb})$$

where Mg_c is the corrected magnesium concentration (mmol/l), Mg_t is the total serum magnesium concentration actually measured (mmol/l), and Alb is the serum albumin concentration (g/l).

Statistical analysis

Data are expressed as the mean $\pm$ SD unless otherwise stated. Mean values before and after treatment were compared by paired *t*-test and the relation between two variables was examined by Pearson's simple correlation analysis. The analyses were performed with Statview 512+I statistical software (Brain Power, Inc. 1986, Calabas, USA) running on an Apple Macintosh IIsi computer. Values of $P < 0.05$ were considered significant.

Results

Comparison of measured parameters before and after treatment

The biochemical and hormonal parameters before and after treatment with methimazole are summarized in Table 1. Before treatment, the serum levels of T_4 , T_3 , free T_4 and free T_3 were increased and serum TSH was suppressed. These values were all normalized after treatment. We also observed that the erythrocyte magnesium concentration significantly increased from 2.00 ± 0.18 to 2.08 ± 0.24 mmol/l cells ($n=17$, $P < 0.05$), whereas erythrocyte sodium concentration decreased from 10.4 ± 2.6 to 8.1 ± 1.1 mmol/l cells ($P < 0.001$). The serum level of magnesium rose significantly ($P < 0.001$) from 0.72 ± 0.12 to 0.84 ± 0.11 mmol/l (from 0.73 ± 0.12 to 0.84 ± 0.11 mmol/l after correction for serum albumin), but the three hour urinary magnesium excretion decreased from 0.38 ± 0.19 to 0.25 ± 0.23 mmol ($P < 0.001$) without a significant change in the urinary volume (450 ± 182 vs. 556 ± 172 ml/3 h, NS). The fractional magnesium excretion also decreased by one third from 2.92 ± 1.33 to $1.96 \pm 1.96\%$ ($P < 0.05$).

Table 1. The change in variables before and after treatment with methimazole in 17 patients with hyperthyroidism

	before	after
Thyroid function		
T_4 ($\mu\text{g/l}$)	184 ± 44	$68 \pm 27^{***}$
T_3 ($\mu\text{g/l}$)	3.6 ± 1.5	$1.0 \pm 0.4^{***}$
free T_4 (ng/l)	64 ± 34	$11 \pm 5^{***}$
free T_3 (ng/l)	15.9 ± 6.1	$4.2 \pm 1.5^{***}$
TSH (mU/l)	< 0.06	$1.62 \pm 1.37^{***}$
Erythrocyte		
Mg (mmol/l cells)	2.00 ± 0.18	$2.08 \pm 0.24^*$
Na (mmol/l cells)	10.7 ± 2.6	$8.1 \pm 1.1^{***}$
Erythrocyte: Serum		
Mg ratio	2.85 ± 0.57	$2.52 \pm 0.43^{**}$
Na ratio	0.08 ± 0.02	$0.06 \pm 0.01^{***}$
Serum		
Mg (mmol/l)	0.72 ± 0.12	$0.84 \pm 0.11^{***}$
Mg (mmol/l) [¶]	0.73 ± 0.12	$0.84 \pm 0.11^{***}$
Na (mmol/l)	140.9 ± 1.9	140.9 ± 2.1
Urine		
Mg (mmol/3 h)	0.38 ± 0.19	$0.25 \pm 0.23^{***}$
Na (mmol/3 h)	29.2 ± 8.2	$23.7 \pm 7.8^*$
Renal function		
C_{Cr} (ml/min)	105.3 ± 29.7	90.7 ± 27.9
C_{Mg} (ml/min)	2.97 ± 1.31	$1.62 \pm 1.38^{***}$
C_{Na} (ml/min)	1.15 ± 0.29	$0.92 \pm 0.31^*$
FE_{Mg} (%)	2.92 ± 1.33	$1.96 \pm 1.96^*$
FE_{Na} (%)	1.21 ± 0.56	1.11 ± 0.48

Data are expressed as the mean $\pm$ SD. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, vs. before treatment. [¶] Value corrected for low serum albumin according to Kroll and Elin.

There was no significant change in the serum sodium level (140.9 ± 1.9 vs. 140.9 ± 2.1 mmol/l), and urinary sodium excretion decreased significantly (29.2 ± 8.2 vs. 23.7 ± 7.8 mmol/3 h, $P < 0.05$), but fractional sodium excretion did not (FE_{Na} , 1.21 ± 0.56 vs. $1.11 \pm 0.48\%$, NS) when the patients became euthyroid. The erythrocyte to serum ratio decreased significantly from 2.85 ± 0.57 to 2.52 ± 0.43 ($P < 0.01$) for magnesium, and from 0.08 ± 0.02 to 0.06 ± 0.01 ($P < 0.001$) for sodium. Serum albumin increased significantly ($P < 0.001$) from 38.8 ± 3.1 to 42.1 ± 2.7 g/l.

Correlation analysis

The change in the serum magnesium concentration did not correlate with that of erythrocyte magnesium ($r=0.102$, NS), but, as shown in Fig. 1,

Fig. 1. Correlation between the change in the serum magnesium concentration and that in the fractional excretion of magnesium before and after treatment in 17 patients with hyperthyroidism.

Fig. 2. Correlation between the erythrocyte magnesium concentration and serum free T_3 concentration before treatment in 17 patients with hyperthyroidism.

Table 2. Simple correlation analyses of changes in variables before and after treatment with methimazole in 17 patients with hyperthyroidism

	Erythrocyte		Serum		Renal	
	ΔMg	ΔNa	ΔMg	ΔNa	$\Delta FEMg$	$\Delta FENa$
ΔT_3	-0.242	0.087	-0.640**	0.071	0.560*	-0.190
ΔT_4	0.108	0.419	-0.629**	0.030	0.584*	-0.110
$\Delta free T_3$	-0.111	0.084	-0.553*	0.030	0.577*	-0.341
$\Delta free T_4$	-0.127	0.225	-0.618**	0.170	0.506*	-0.279

* $P < 0.05$, ** $P < 0.01$.

it correlated with the change in fractional magnesium excretion ($r = -0.709$, $P < 0.01$), suggesting that the decrease in fractional magnesium excretion with treatment was associated with the increase in serum magnesium. Correlation analysis of the change of serum sodium and those of fractional sodium excretion or erythrocyte sodium ($r = 0.057$, NS) did not show any significance. As shown in Table 2, the decrease in serum thyroid hormones with treatment inversely correlated strongly and negatively with the change in serum magnesium (with ΔT_4 , $r = -0.629$, $P < 0.01$; with ΔT_3 , $r = -0.640$, $P < 0.01$) and positively with the decrease in FE_{Mg} (with ΔT_4 , $r = 0.584$, $P < 0.05$; with ΔT_3 , $r = 0.560$, $P < 0.05$), but not with the changes in similar variables for sodium metabolism.

For the pretreatment values of the studied variables, levels of serum thyroid hormones showed a significant inverse correlation with erythrocyte magnesium (with free T_3 , $r = -0.491$, $P < 0.05$, Fig. 2; with free T_4 , $r = -0.238$, NS) but not with erythrocyte so-

dium (with free T_3 , $r = 0.047$; with free T_4 , $r = 0.240$).

Discussion

The present study provides evidence for disturbances of magnesium metabolism in hyperthyroidism and shows their relations with the thyroid hormones. These alterations were improved with treatment.

Serum magnesium decreased in hyperthyroidism, as previously found by others [7, 12–14]. To determine the magnesium level, serum rather than plasma was used to avoid both magnesium contaminated anticoagulants and calcium chelating anticoagulants which also bind magnesium [15]. As reported by Ford *et al.* [14], we also observed that serum albumin increased when the patients became euthyroid, but this increase can not account entirely for that of serum magnesium. As reported also by Shibutani *et al.* [13], even after correction of serum magnesium for serum albumin according to Kroll et Elin [11], we still got significant lower levels of serum magnesium in hyperthyroidism as compared to the euthyroid levels. Moreover, Frizel *et al.* [5] demonstrated that free magnesium, rather than the bound fraction, mostly accounts for the lowered magnesium in the hyperthyroid state.

The decrease in serum magnesium is ascribed to the urinary loss. The kidney is a key organ for magnesium homeostasis. The capacity of the kidney to conserve magnesium is demonstrated in the case of dietary restriction [16, 17] or during lactation. Lactating women compensate for magnesium

secreted into breast milk by decreasing urinary magnesium losses [18]. Vitale *et al.* [3] showed that more magnesium was required for normal growth as thyroxine increased in the diet in animal experiments, and Tapley [19] demonstrated an immediate negative balance of magnesium after administration of L-triiodothyronine because of increased urinary output in human experiment. The increase in fractional magnesium excretion in our patients during hyperthyroidism shows that renal magnesium handling is disturbed in this condition. After treatment, the fall in the fractional magnesium excretion significantly correlated with the rise in serum magnesium. It is therefore speculated that the renal conservative capacity for magnesium will be more greatly reduced in more severe hyperthyroid conditions.

In previous investigations, a linear correlation between changes in parameters for thyroid function and magnesium metabolism could not be estimated because of the change in the assay method for thyroid function during the study [14]. In the present study, the change in thyroid hormone levels inversely correlated with that of the serum magnesium concentration, but not with that of the erythrocyte magnesium concentration. However, the initial erythrocyte magnesium concentration correlated inversely with that of thyroid hormones. The level of erythrocyte magnesium at the end of the treatment may be related to earlier plasma levels of thyroid hormones as reported for zinc elsewhere [20].

In hyperthyroid patients, both serum and erythrocyte magnesium concentrations were low at first, but increased significantly after treatment. This is contrary to the findings of Jones *et al.* [7] who got rather lower erythrocyte magnesium after treatment with propylthiouracil. That is probably because they utilized erythrocyte magnesium, a marker of a chronic magnesium status [21], in spite of their limited period (11 days) of observation. It is unlikely that this discrepancy is due to the difference in the antithyroid drug used.

We found a decrease in both the erythrocyte to serum sodium ratio and erythrocyte to serum magnesium ratio. This observation is in accordance with previous findings indicating that erythrocyte ion transport is altered in hyperthyroidism. Changes in sodium metabolism in hyperthyroidism have been discussed extensively by several groups [22–25]. Although their clinical significance is not

known, they indicate pathophysiological responses to high plasma thyroid levels. Urinary sodium excretion increased during hyperthyroidism. A concomitant increase in renal sodium clearance suggests changes in renal sodium handling, but we did not observe any significant change in the serum sodium level. Unlike magnesium, when total body sodium increases or decreases, the hormonal systems involved in the homeostatic control of plasma osmolality and sodium water balance adjust total body water proportionately to maintain a constant extracellular sodium concentration. Lower levels may occur in severe illness or poor dietary intake. On a controlled diet, Jones *et al.* [7] demonstrated a negative balance for sodium and magnesium in hyperthyroid patients. The amount of sodium and magnesium excreted in urine exceeds the amount reabsorbed. Some hyperthyroid patients have polyphagia. This does not entirely explain this high urinary sodium or magnesium excretion, but the high intake may delay the occurrence of severe deficiency.

Concerning the low erythrocyte magnesium concentration, Elin *et al.* [26] suggested that a slight magnesium deficiency, if prolonged, can cause a steep drop in erythrocyte magnesium content. Magnesium deficiency, as assessed by decreased magnesium in the blood or tissues, and cardiovascular disease are linked [27, 28]. In a recent review [29], none of the various circulating spasmogenic theories could satisfactorily account for coronary vasospasm in hyperthyroidism, and Miyagi *et al.* [30] had shown magnesium to suppress coronary spastic angina. Evidently the potential for decreased magnesium to enhance coronary or cardiac reactivity to vasoactive agonists [31, 32] deserves consideration in hyperthyroidism.

In a self-controlled study, we have demonstrated that the degree of magnesium metabolism alteration is closely related to the increase in circulating thyroid hormones in hyperthyroidism. Severe hyperthyroidism is likely to cause a serious decrease in body magnesium, especially in the case of a poor dietary intake.

Acknowledgments

We are indebted to Professor Dr. Tatsuo SATO for his helpful support.

References

- Burch G, Giles T (1977) The importance of magnesium deficiency in cardiovascular disease. *Am Heart J* 94: 649–657.
- Reinhart RA (1991) Clinical correlates of molecular and cellular actions of magnesium on the cardiovascular system. *Am Heart J* 121: 1513–1521.
- Vitale J, Hegsted D, Nakamura M, Connors P (1957) The effect of thyroxine on magnesium requirement. *J Biol Chem* 226: 597–601.
- Kleeman CR, Epstein FH, McKay D, Taborsky E (1958) Effects of hypo- and hyperthyroidism on the filterability of serum magnesium. *J Clin Endocrinol Metab* 18: 1111–1116.
- Frizel D, Malleson A, Marks V (1967) Plasma levels of ionized calcium and magnesium in thyroid disease. *Lancet* 1: 1360–1361.
- Hueber E (1939) Ueber die beeinflussung von hyperthyreosen durch magnesiumglutaminat. *Wien Klin Wochenschr* 52: 932.
- Jones J, Desper P, Shane S, Flink E (1966) Magnesium metabolism in hyperthyroidism and hypothyroidism. *J Clin Invest* 45: 891–900.
- Dolev E, Deuster PA, Solomon B, Trostmann UH, Wartofsky L, Burman KD (1988) Alterations in magnesium and zinc metabolism in thyroid disease. *Metabolism* 37: 61–67.
- Caldwell G, Kellett H, Gow S, Beckett G, Sweeting V, Seth J, Toft A (1985) A new strategy for thyroid function testing. *Lancet* 1: 1117–1119.
- Smith J, Price A, Williams R, Hentschel W, Sprowell W, Hunt S, Ash K (1982) A reproducible sodium-lithium countertransport assay: The outcome of changing key laboratory parameters. *Clin Chim Acta* 122: 327–335.
- Kroll M, Elin R (1985) Relationships between magnesium and protein concentrations in serum. *Clin Chem* 31: 244–246.
- Rizek J, Dimich A, Wallach S (1965) Plasma and erythrocyte magnesium in thyroid disease. *J Clin Endocrinol Metab* 25: 350–358.
- Shibutani Y, Yokota T, Iijima S, Fujioka A, Katsuno S, Sakamoto K (1989) Plasma and erythrocyte magnesium concentrations in thyroid disease: Relation to thyroid function and the duration of illness. *Jpn J Med* 28: 496–502.
- Ford H, Croke M, Murphy C (1989) Disturbances of calcium and magnesium metabolism occur in most hyperthyroid patients. *Clin Biochem* 22: 373–376.
- Elin R (1987) Assessment of magnesium status. *Clin Chem* 33: 1965–1970.
- Shils M (1969) Experimental production of magnesium deficiency. *Ann NY Acad Sci* 162: 847–855.
- Shafik I, Quamme G (1989) Early adaptation of renal magnesium reabsorption in response to magnesium restriction. *Am J Physiol* 257: F974–F977.
- Dengel J, Mangels A, Moser-Veillon P (1994) Magnesium homeostasis: Conservation mechanism in lactating women consuming a controlled-magnesium diet. *Am J Clin Nutr* 59: 990–994.
- Tapley D (1955) Magnesium balance in myxedematous patients treated with triiodothyronine. *Bull Johns Hopkins Hosp* 96: 274–278.
- Yoshida K, Kiso Y, Watanabe T, Kaise K, Kaise N, Itagaki Y, Yamamoto M, Sakurada T, Yoshinaga K (1990) Erythrocyte zinc in hyperthyroidism: Reflection of integrated thyroid hormone levels over the previous few months. *Metabolism* 39: 182–186.
- White J, Campbell R (1993) Magnesium and diabetes: A review. *Ann Pharmacother* 27: 775–780.
- Bradley S, Stéphan F, Coelho J, Réville P (1974) The thyroid and the kidney. *Kidney Int* 6: 346–365.
- Cole C, Waddell R (1976) Alteration in intracellular sodium concentration and ouabain-sensitive ATPase in erythrocytes from hyperthyroid patients. *J Clin Endocrinol Metab* 42: 1056–1063.
- Gless K, Sütterlin U, Schaz K, Schütz V, Hunstein W (1986) Intracellular sodium concentration and transport in red cells in essential hypertension, hyperthyroidism, pregnancy and hypokalemia. *Clin Physiol Biochem* 4: 199–209.
- Ford H, Lim W, Chisnall W, Pearce J (1989) Renal function and electrolyte levels in hyperthyroidism: Urinary protein excretion and the plasma concentrations of urea, creatinine, uric acid, hydrogen ion and electrolytes. *Clin Endocrinol* 30: 293–301.
- Elin J, Armstrong W, Singer L (1971) Body fluid electrolyte composition of chronically magnesium-deficient and control rats. *Am J Physiol* 220: 543–548.
- Chipperfield B, Chipperfield J (1973) Heart-muscle magnesium, potassium, and zinc concentrations after sudden death from heart-disease. *Lancet* 2: 293–296.
- Altura B, Altura B, Gebrewold A, Ising H, Günther T (1992) Noise-induced hypertension and magnesium in rats: Relationship to microcirculation and calcium. *J Appl Physiol* 72: 194–202.
- Moliterno D, DeBold C, Robertson R (1992) Case report: Coronary vasospasm—Relation to the hyperthyroid state. *Am J Med Sci* 304: 38–42.
- Miyagi H, Yasue H, Okumura K, Ogawa H, Goto K, Oshima S (1989) Effect of magnesium on anginal attack induced by hyperventilation in patients with variant angina. *Circulation* 79: 597–602.
- Kimura T, Yasue H, Sakaino N, Rokutanda M, Jougasaki M, Araki H (1989) Effects of magnesium on the tone of isolated human coronary arteries. Comparison with diltiazem and nitroglycerin. *Circulation* 79: 1118–1124.
- Bean B, Varghese P (1994) Role of dietary magnesium deficiency in the pressor and arrhythmogenic response to epinephrine in the intact dog. *Am Heart J* 127: 96–102.