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MYOCARDIAL LOSS OF FUNCTIONAL MAGNESIUM

II. IN CARDIOMYOPATHIES OF DIVERSE ETIOLOGY

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In his concluding remarks to the conference on the relationship of experimental "metabolic" cardiomyopathies to human-heart diseases (54), Bajusz (3) brought into focus the findings that point towards the probability that underlying almost all types of cardiac necrosis is mitochondrial disorganization. He pointed out that, with the exception of the cardiomyopathy of K deficiency, mitochondrial failure plays an important role in causing the muscle cell to enter a stage of irreversible injury. Bajusz (3) further emphasized that no longer tenable is the earlier belief that losses of K and Mg from the myocardial cells and the uptake of Na and Ca are merely secondary consequences of cellular necrosis.

That both cations are vitally involved in the maintenance of functional and structural integrity of the myocardium is indicated by the cardiac necrosis that develops in animals that are nutritionally depleted of one or both (5). Selye and his co-workers (66) showed, long ago, that deficiency of each of these cations intensifies the necrotizing effect of diverse cardiotoxic agents and that their administration protects against these influences. It should be noted, however, that the first reported application of Mg salts in cardiotoxicity was the use by Hueber and Lehr (28) of each of several Mg preparations to treat and protect against aconitine-poisoning. Mishra (48) showed that Mg-deficient rats had less numerous cardiac mitochondria than did control rats. He postulated that similar mitochondrial abnormalities, possibly caused by loss of myocardial Mg and K, might be responsible for the functional and structural disturbances seen in the electrolyte steroid cardiac necrosis (ESCN). DuRuisseau and Mori (17) found that, in the ESCN model, the loss of Mg from the heart was significant, whereas there was no loss of cardiac K (table I). Associated with the drop to half the level of Mg seen in hearts of control rats, there were significant increases in Na, Ca, and PO_4.

Lehr and Krukowski (38), considering the mechanism by which corticosteroid in combination with NaH_2PO_4 causes myocardial necrosis, proposed that depletion of myocardial Mg might have at least equal, if not greater, pathogenic significance than depletion of myocardial K. Their observation that parathyroidectomy intensified cardiac susceptibility to NaH_2PO_4 loads (38, 40) is of particular interest, in view of Kimmich and Rasmussen's (34) demonstration that

Table I

Cardiac Electrolytes in the ESCN Model (9-Day Study)

	Mg	K	Na	Ca	PO_4	Cardiac necrosis
			mEq/kg			
Control	30.4	78.4	55.1	22.5	59.0	0
NaH_2PO_4 (2 mM orally, b.i.d.)	32.5	83.5	59.5	31.2	59.6	0
Me-Cl-Col-AC* (100 μg subcutaneously)	23.2	80.5	58.9	33.2	62.3	0
NaH_2PO_4 (orally) + MeCl-Col-AC* (subcutaneously)	15.0	81.1	69.0	35.1	68.0	Present

* Corticosteroid with mineralo- and glucocorticoid activities.
$p = < 0.05$ developed. Adapted from DuRuisseau and Mori (17).

parathyroid hormone plays a role in the transport of Mg as well as of inorganic PO_4 into the mitochondria. The subsequent studies by Lehr and his associates (36, 37, 39) provided direct evidence that PO_4-loaded, parathyroidectomized rats lost myocardial Mg to a much greater extent than K, and gained Na (table II). Prevention of the parathyroid-depletion effect by administration of parathyroid extract to parathyroidectomized rats resulted in only a slight decrease of cardiac Mg from control levels but in a further rise in PO_4. This observation raises the question as to whether all of that Mg was necessarily functional or whether some may have been in association with the elevated inorganic PO_4.

Table II

Cardiac Electrolytes in the Parathyroidectomized PO_4-Loaded Model of Cardiac Necrosis

	Mg	K	Na	Ca	PO_4	Cardiac necrosis
			mEq/kg wet wt.			
Controls	19.1	83.6	44.1	2.8	57.6	0
PT_X* only	19.7	83.8	43.1	2.9	58.4	
NaH_2PO_4 only	19.2	82.1	42.4	3.5	61.1	0
PT_X + NaH_2PO_4	15.7	81.3	49.0	3.2	53.	100%
PT_X + NaH_2PO_4 + PTE†	18.4	82.9	43.8	3.2	61.4	0

* PT_X = parathyroidectomized.
† PTE = parathyroid extract.
Adapted from Lehr (37).

Table III

Cardiac Electrolytes in the Isoproterenol Model of Cardiac Necrosis

	Time after injection	Mg	K	Na	Ca	PO_4	Cardiac necrosis
	h	*mEq/kg wet wt.*					
Controls		19.2	83.6	44.1	2.8	57.6	0
Isopro-	3	17.0	83.0	42.4	3.8	53.9	0
terenol	7	16.3	83.0	47.1	4.8	53.6	60%
	24	15.6	81.3	53.0	4.3	48.1	100%

Adapted from Lehr (37).

Both in the parathyroidectomized PO_4-loaded model and in the isoproterenol model of cardiac necrosis, Lehr and Krukowski (37, 39) found the K loss to be apparently subordinate to the Mg loss (table III). In the isoproterenol model, a time sequence study revealed that the Mg loss occurred earlier than did the K loss and was greater in degree. The prompt uptake of Ca in the hearts of isoproterenol-treated rats may be explained by the work of Grossman and Furchgott (20), who showed that catecholamine (norepinephrine) causes significant increases in the exchange of Ca by the isolated guinea-pig auricle. This effect was associated with the positive inotrophic effect of norepinephrine, which may be mediated by the effect of intracellular Ca in the mechanism of muscle contraction.

Table IV

Myocardial Electrolytes in Hamsters of the Cardiomyopathic (BIO 14.6) Strain and an Unrelated (LSH) Strain

Group	Strain	Age (days) Mean	Range	Myocardial electrolytes* (mg/100 g dry wt.) Ca	Mg	K	Na
1a	Control (LSH)	29	23–33	12.1 ± 0.51	115 ± 2.33	1535 ± 16	421 ± 13
1b	Cardiomyopathic (BIO 14.6)			17.2 ± 0.46	73 ± 0.80	1575 ± 23	419 ± 11
2a	Control (LSH)	62	56–71	14.6 ± 0.44	109 ± 0.98	1496 ± 20	342 ± 2
2b	Cardiomyopathic (BIO 14.6)			215.2 ± 33.90	109 ± 1.25	1422 ±	479 ± 15

* Lower two-thirds of both ventricles. Values represent mean ± standard error. From Bajusz and Lossnitzer (6).

Table V

Serum Electrolytes in Hamsters of the Cardiomyopathic (BIO 14.6) Strain and an Unrelated (LSH) Strain

Group	Strain	Age (days) Mean	Range	Serum electrolytes* (mg %) Ca	Mg	K	Na
1a	Control (LSH)	29	23–33	9.4 ± 0.40	3.2 ± 0.32	16.3 ± 0.49	309 ± 4.8
1b	Cardiomyopathic (BIO 14.6)			12.0 ± 0.45	4.1 ± 0.19	15.4 ± 0.65	303 ± 2.6
2a	Control (LSH)	62	56–71	10.1 ± 0.37	3.4 ± 0.15	13.8 ± 0.22	316 ± 4.5
2b	Cardiomyopathic (BIO 14.6)			10.2 ± 0.31	3.5 ± 0.15	13.9 ± 0.34	307 ± 6.3

* Mean ± standard error. From Bajusz and Lossnitzer (6).

The cardiomyopathic BIO 14.6 strain of Syrian hamsters has been shown by Bajusz and Lossnitzer (6) also to exhibit decreased myocardial Mg during the prenecrotic phase, at 23–33 days of life (table IV). The fact that the myocardial Mg had returned to normal levels at 56–71 days, at which time the hamsters presented calcifying myocardial lesions, further suggests that not all of the myocardial Mg was functional. The elevation of serum Mg (table V) at the time that myocardial Mg was depressed indicates that serum Mg levels cannot be relied upon as an index of cellular levels. The demonstration by Angelakos (2) that myocardial norepinephrine levels are elevated (table VI) at about the same age as the drop in myocardial Mg was seen, is an indirect indication of the Mg-tissue-depleting effect of catecholamine.

Raab (58) recently evaluated the interrelationships of the increased metabolic

Table VI

Heart Norepinephrine (Means of Determinations in 6 Pools, 5 Hearts/Pool)

Age (days)	NE μg/g Controls	Dystrophic	NE μg/heart Controls	Dystrophic
35	0.99	1.18*	0.18	0.20
55	1.03	1.28*	0.23	0.27*
85	1.08	1.12	0.30	0.33
105	1.08	0.93	0.33	0.32
120	1.68	0.47*	0.43	0.26*

* Significantly different from the controls ($p < 0.05$). From Angelakos (2).

demands on the heart caused by catecholamine in the light of the myocardial electrolyte derangement seen in what he terms "dysionic cardiopathy" or "pluricausal," so-called coronary heart disease. He pointed out interrelationships of the neurohormonal axis with cardiac metabolic dysfunctions in which a cardiac deficit of Mg, as well as of K, has been shown to play an important role.

Additional to the foregoing examples of drug-induced prenecrotic losses of myocardial Mg, Hochrein *et al.* (26) demonstrated that digitalis or phenylbutazone intoxication of guinea pigs caused substantial drops in intracellular myocardial Mg, as did hypoxia, overload, or hyperkalemia. They concluded that Mg^{++} occupies a central position in the structure and metabolism of myocardial cells.

Myocardial loss of Mg has also been reported in the infarcted area of the heart, subsequent to experimental ligation of a coronary artery (15, 30), and in patients who died suddenly of myocardial infarction (29, 58). Cummings (15) reported that the Mg content of the infarcted left ventricle of dogs, whose left anterior descending coronary artery had been ligated 11 h before sacrifice, was 1.18 mEq/100 g wet weight, as compared with 2.30 for the left ventricle of control, sham-operated dogs. Even the noninfarcted ventricle showed a lower than control level of Mg (2.11 *vs* 2.26), possibly as a consequence of the stress. The drop in myocardial K of the infarcted segment was much more profound (4.5 *vs* 8.5 mEq/100g). The analysis by Iseri *et al.* (29) of infarcted and noninfarcted segments of hearts from patients who had died of myocardial infarction similarly showed lower than normal Mg levels in both segments (table VII). A much greater loss was seen in the infarcted area. Raab (58) recently reported significantly diminished Mg and K and elevated Na contents, even of the structurally noninvolved parts of heart muscle obtained from patients who had died of an infarction within several hours to several days.

Table VII

Cardiac Electrolytes: Clinical Myocardial Infarction

	Mg	K	Na	P
	mEq/100 mg wet tissue (mean values)			
Heart muscle (patients who died of other causes than heart disease)	0.45	8.32	4.96	3.88
Acute myocardial infarction				
Non-infarcted segment	0.30	5.91	6.68	3.23
Infarcted segment	0.22	4.19	8.11	2.32

Adapted from Iseri *et al.* (29).

As indicated by Lehr and his associates (36, 37, 39) in their isoproterenol studies, and by Hochrein *et al.* (26) in their asphyxia study, the loss of Mg from the heart was greatest shortly after the insult. The loss of K from the isoproterenol-damaged heart was delayed. A 6 h delay before 50% of myocardial K was lost from infarcted dog hearts had been reported in 1957 and 1964 by Jennings *et al.* (31, 33) as attributable to the time taken for failure of the energy-producing mechanisms involved in maintaining intracellular K. In 1969 (30, 32), these investigators reaffirmed the observation, supporting it with electron microscopic findings. Their data indicate that the myocardial cellular injury was reversible after 15–18 min of ischemia, but that cells were irreversibly damaged after 40 min (32). The authors commented that the spatial disorganization and/or inactivation of the mitochondrial enzymes were associated with loss of essential cofactors and maldistribution of essential anions and cations within the mitochondrion. These changes were reflected ultramicroscopically by sarcolemmal and mitochondrial disruption.

That the aging process and long-continued stress situations may be associated with decreases in myocardial Mg, and that such losses may predispose to impaired resistance to other cardiopathic agents, is suggested by the work of Mori and DuRuisseau (51) and Raab *et al.* (59). The former authors reported a substantial drop in myocardial Mg and a lesser drop in K as the rats aged (table VIII). They attributed the decrease in Ca seen in the aged animals to the loss of nucleic acids, to which both Ca and Mg are closely linked. The decrease in Na was attributed largely to the shrinking of extracellular phase. Raab *et al.* (59) demonstrated decreases in both myocardial Mg and K with increasing duration of isolation (table IX). They showed that the rats kept in isolation were, in fact, more susceptible to the cardiotoxic effect of epinephrine.

That the K loss by Mg-deficient isolated mitochondria is relevant to the intact animal or man is indicated by Mg-deficiency studies in animals from which tissue analyses were made, and in human subjects undergoing metabolic balance determinations. A decrease in muscle K in Mg-depleted animals was first demonstrated in 1951 by Cotlove *et al.* (12); in that study, the serum K

Table VIII

Cardiac Electrolytes in Aging Rats

Age	Mg	K	Na	Ca	P
mo.	*mEq/kg dry, fat-free tissue*				*mM*
0.9–1.2	86.4	385	230	41.2	335
1.5–2.0	82.7	396	247	30.7	344
10–12	68.8	389	190	25.5	348
34–36	47.4	355	112	21.2	339

Adapted from Mori and DuRuisseau (51).

Table IX

Cardiac Electrolytes in Isolated Rats

	Mg	K	Na	Ca
	mg/100 g wet wt.			
Control rats (in colony)	25.4	342	81	5.0
4 Months isolation	23.9	309	79	5.5
14 Months isolation	22.6	298	102	5.7
2 Weeks in colony (after 14 months isolation)	25.4	314	93	No data

Adapted from Raab *et al.* (59).

remained unaffected. Many subsequent investigations have shown substantial drops of muscle Mg and K, and often also of serum Mg and K (22, 35, 42–45, 68–71, 76, 80, 81, 84–90); in most instances, elevated Na levels were reported (22, 42–45, 68, 84, 88–90). Human metabolic studies with subjects on Mg-deficient diets have provided proof that Mg loss is followed by K loss; in the longer term studies, hypokalemia developed, and this could not be corrected until the Mg was repleted (16, 19, 72–74). In several instances, ECG changes of hypokalemia were recorded as the period of Mg-deficiency lengthened (16, 72, 74).

Despite the substantial laboratory evidence that Mg loss is incompatible with the maintenance of cardiac integrity and function, be it of the isolated cardiac mitochondria, or of the heart in the intact animal, it has been difficult to provide convincing evidence that these findings are relevant to clinical cardiovascular disease. It has been widely assumed that the Mg intake is adequate in the Occident, where cardiovascular disease is a major cause of death. However, a 1964 review (64) of Mg balance data obtained from studies throughout the world indicates that the Occidental diet delivers substantially less Mg than does the Oriental diet (fig. 1). On diets that delivered amounts of Mg found in the typical American diet (daily Mg intake of 4–5.9 mg/kg), young men often showed negative Mg balance; young women tended to stay in balance at such intakes. On diets delivering as much as has been reported from Oriental studies (6–10 mg/kg/d), the test subjects stored Mg.

Perhaps it is an underlying suboptimal intake of Mg that contributes to the greater incidence of cardiac deaths in soft water areas as compared with the incidence in hard water areas (1, 4, 7, 13, 14, 52, 63, 78). Crawford and Crawford (14) found that young accident victims from a soft-water area (Glasgow), where myocardial disease develops early and is more lethal than it is in a hard-water area (London), had much lower concentrations of coronary Mg (fig. 2). The authors attributed the greater incidence of high coronary Mg levels

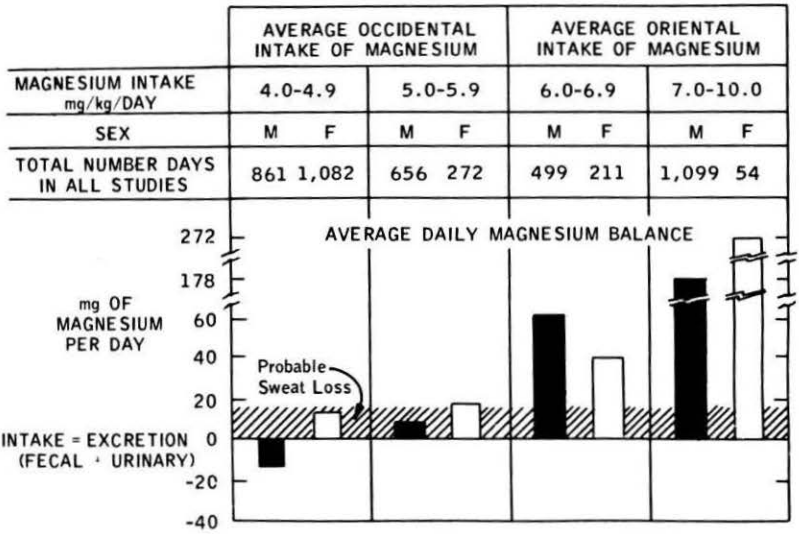

Fig. 1 Influence of sex on magnesium balance at different intakes of magnesium. Adapted from Seelig (64).

Fig. 2 Coronary magnesium in accident cases. From Crawford and Crawford (14).

in older men from the hard-water group to the deposition of minerals in established lesions.

Manifestly, variations in the amount of Mg in the diet cannot be the sole explanation of clinical heart disease. Quite apart from the hormonal and drug insults that have cardiomyopathic potential, we ingest nutrients that increase Mg requirements. High protein intakes have long been known to increase Mg requirements and to intensify Mg deficiency (10, 11, 18, 47, 82) as have high Ca and/or PO_4 intakes (9, 11, 27, 41, 46, 49, 50, 53, 55–57, 62, 77). High cholesterol intake has also been shown to increase the Mg requirement (24, 25, 49, 79, 82). Vitamin D and its analogue, dihydrotachysterol, have long been known to cause cardiac necrosis in experimental animals (for reviews, see 5, 66, 67). Vitamin D excess, or hyper-reactivity to vitamin D, has more recently been implicated in supravalvular aortic stenosis and myocardial necrosis in infants and children (for reviews, see 8, 65). It is thus provocative: (1) that toxic doses of vitamin D have been shown to cause Mg loss and/or hypomagnesemia in laboratory animals (21, 23, 60, 75, 83, 84, 90); and (2) that 5-fold higher than normal Mg intakes have protected against cardionecrosis caused by feeding rats a diet that was rich in vitamin D, as well as in Ca, PO_4, and protein (61).

SUMMARY

A number of diverse cardiopathic agents, including hormones, ischemia, stress, aging, and nutritional imbalances, have been shown to cause decreased myocardial Mg and mitochondrial disruption. Dietary Mg-deficiency intensifies the cardiotoxicity of many such agents. Mg is necessary for the integrity of the mitochondrial system, which is responsible for the maintenance of cellular K as well as for the metabolic processes. Depletion of cardiac Mg may be contributed to by disease, drugs, or diet. This may be a pivotal factor in the "pluricausal" cardiomyopathies.

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