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Letter to the Editor

Does Magnesium Supplementation Have any Role in Acute Myocardial Infarction? No

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Dear Sir,

In the wake of ISIS 4 [1], it will be difficult for even the most enthusiastic proponents of magnesium supplementation in acute myocardial infarction (AMI) not to question the basis of their investigative premise. The statistically nonsignificant 6% (SD 3) proportional increase in the odds of death during the first 5 weeks following 24-hour intravenous magnesium is completely discordant with previous results [1]. Will we be prepared to look *beyond* methodological limitations of trials [2] as well as meta-analyses [3] to reconsider the biological role of extracellular magnesium depletion? As the second most abundant cation in the intracellular fluid, the potential for magnesium to *indirectly* influence muscle and myocardial function is substantial. The assumption that magnesium depletion is overall inimical to cardiovascular function is debatable.

Every biochemical aberration should not be regarded as pathological; several such changes are adaptive. Profound autonomic nervous system alternations are the rule in AMI. The exact role of autonomic aberrations, and therefore the biological role of magnesium, cannot be understood without teleological considerations [4–6]. Magnesium *opposes* release of catecholamines from the adrenal gland [7]. While ischemia induces ATP depletion (and free intracellular magnesium *rises*), thereby downgrading myocyte metabolism (and contractility) in the face of diminished substrate, extracellular magnesium depletion in AMI [8] probably sets the stage for *appropriate* augmentation of adaptive inotropic and chronotropic sympathoadrenal catecholamine release in the face of a life-threatening excruciatingly painful condition. The overall biological precision of adaptive mechanisms is, however, limited and simplistic, for example, adaptive fluid retention may precipitate pulmonary venous congestion in left heart failure. The predisposition to potentially fatal arrhythmia during hypomagnesemia could be regarded as an unfortunate concomitant side effect of an otherwise useful *physiological* sympathoadrenal discharge.

The potential benefits of magnesium therapy in AMI do not extend beyond modulating thrombosis [7], reperfusion injury, and potassium-shift related ischemic arrhythmias [9]. Unlike prompt antiplatelet and fibrinolytic therapy [1], the modulation by magnesium of the primary pathogenetic event in AMI is at best uncertain. The pathogenetic role of oxygen radicals in general [10], as well as in the mediation of myocardial reperfusion injury, is dubious [11]. Modulation of the effects of oxygen radicals by magnesium in AMI [7] is speculative. Such therapy, nevertheless, reverses a *systemic* adaptive teleological response that offers circulatory support. Furthermore, ionic calcium is a principal mediator of the inotropic state of the heart. Magnesium opposes calcium entry and competes with it for binding to troponin C [8]. Magnesium repletion in a state of intracellular magnesium excess amounts to a double inotropic jeopardy, which, in turn, might critically compromise *myocardial contractility* (pump function) during severe ischemic insult, a situation that is very unlikely to provide an *overall* cardiopulmonary protection. The analogy of magnesium with other vasodilators is not straightforward. Any salutary vasodilator influence of magnesium [1] is counteracted by its negative influence on pump function. Magnesium supplementation is associated with significant excess occurrence of bradycardia, hypotension, heart failure, cardiogenic shock, and deaths attributed to cardiogenic shock during or just after the infusion period [1], an unsurprising outcome of attenuation of both systemic and local cardiovascular *protective* influences. In effect, magnesium supplementation in AMI amounts to infusion of a myocardial depressant in a clinical situation where optimal or supraoptimal functioning of residual myocardium is vital—an approach that defies common sense. Whereas the negative role of magnesium supplementation may not be evinced in lesser degrees of pump dysfunction, it will be frankly manifest in cases with moderate to severe mechanical dysfunction, in which situation any role for magnesium supplementation should be inconceivable.

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In clincially significant pump dysfunction, the theoretical benefit of modulating calcium-overload–mediated reperfusion injury through magnesium supplementation [9] is, therefore, simply an academic exercise.

Magnesium deficiency in the general population (12.5%–20%), hospitalized patients, hypertension, migraine, premenstrual syndrome, pancreatitis, therapeutic hyperthermia, extensive burns, profuse sweating, chronic diuresis, and other diverse conditions [12,13] underscores the *nonspecific* nature of the "deficiency." Moreover, most cases of hypomagnesemia can be managed by measures directed at the underlying etiology *without* administration of magnesium [13]. Also, studies of magnesium in AMI with negative results may have suffered publication bias [2,3]. Researchers (and reviewers) may disbelieve their own data in order to sustain a preconception. Realistically, acute magnesium repletion in clinical states of deficiency has not found an established therapeutic role in *any* entity. Finally, magnesium depletion in the elderly, or in those with heart failure, should not be viewed as a state of deficiency but as an active physiological adaptation designed to optimize pump function. The decrease in functional reserve capacity of the aging heart places it at a mechanical disadvantage. The suggestion for magnesium repletion in AMI such cases [8] with already compromised latent or overt myocardial pump function is a high-risk *illogical* research strategy. Routine use of magnesium clearly has no role in the therapy of AMI [1,2]. *More importantly, the grounds for seeking further research evidence [2] are extremely tenuous.*

Research is rarely (never?) an activity free of ideological roots. There is no such thing as "purely objective" observation [14]. Propagators of hypotheses are never wrong, or they do not admit it, preferring to wriggle on at the end of the hook [15]. Investigative philosophic commitment carries with it a conceptually limiting bias [5] that constitutes a form of irrational skepticism [16]. Do no harm—the principle of beneficence and nonmaleficence—is the least controversial guiding principle for clinicians [17]. The study of experimental magnesium supplementation in myocardial infarction has been initiated with insufficient conceptual groundwork. Consequently, we *cannot* be working in the best interests of our patients. At the cutting edge of research, matters are nebulous to all [6], including researchers, reviewers, and ethical committees. The perennial guide in ethical debates is the cardinal principle of mutual and/or reciprocal expectation [6]. *The single most important ethical consideration for investigators and ethical committees is whether in similar circumstances they would themselves be prepared to accept similar medication.* If this negative teleolgical aspect of magnesium supplementation had been conceptually explored, I believe that no cardiologist or ethicist would have ever approved of such experimentation.

Scientific data not put to the sword of logical rationalization run the risk of being labeled as hype, hope, or worse [18]. Researchers owe it to themselves, to their discipline, and above all to their patients to keep in perspective the negative potential of magnesium supplementation in the maintenance of cardiovascular integrity—*a hitherto completely ignored aspect*—and to reevaluate the validity of the premises that started this investigative trend, rather than to envisage further trials. The perception of this conceptual difference is essential to maintain ourselves on the slippery slope of insight [6] and to balance the excitement of event management [19]. The widely embraced current paradigm that has persisted uncertainly since the last two decades [2] is unwarranted. *The subtleties of cellular level homeostasis must be comprehended in order to rationalize therapy.* Such insight will not devolve from meta-analysis, an exciting in-vogue form of artificial intelligence that seeks to reconstruct the whole through montage of several clinical efforts. Meta-analysis, like statistical sophistication [5], is yet another mathematical mode to seek or force consensus in the state of biological confusion. Even at a research level, scientists are not justified to continue to embrace irrational skepticism over basic and pragmatic logic, especially when lives are clearly at stake. Further experimentation with magnesium supplementation in AMI is clearly unethical. What could be more tragic than a steadfast refusal to learn from our patients?

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