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## Editorial

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## Editorial

J. A. S. McGuigan

t has become dogma in cardiovascular Mg<sup>2+</sup>-research that sub-clinical  $Mg^{2+}$ -deficiency is at least a contributory factor to arteriosclerosis and related cardiovascular disease [1–3], that an infusion of Mg<sup>2+</sup> is beneficial after an infarct [4, 5] or during and after cardiac surgery [6] and can be used in the treatment of cardiac arrhythmias [7, 8]. However, finding concrete evidence for these assertions is at times, rather like trying to locate the legendary grey man of Ben Macdhui in the Cairngorms, who on being sighted, simply vanishes into the mists of the Scottish Highlands. Adding to this difficulty is that trying to justify support in order to provide such concrete evidence can often be countered with the reply: "Interesting, but the evidence is at presence insufficient to justify support." It is the famous "catch 22" from Joseph Heller [9]. However, as this issue of the "Journal of Clinical and Basic Cardiology" shows, concepts and ideas are changing. When putting together this issue of the Journal, I wanted to get away from the "Magnesium Dogma" and I specifically asked the authors to take a very critical approach. The papers are divided into three main groups namely, 1) basic science, 2) magnesium and cardiovascular disease and 3) cardiac surgery. The articles identify not only the major gaps in our knowledge of Mg<sup>2+</sup>-homeostasis and regulation but also importantly delineate the direction of future research.

### Papers

In the basic science group, my colleagues and I document in "Magnesium homeostasis in heart: a critical reappraisal" the abysmal state of our understanding of magnesium homeostasis in heart. Halestrap in his article "The mitochondrial permeability transition – a pore way for the heart to die" describes the importance this pore could have in reperfusion injury. Grunert and colleagues in their article "Intracoronary and intravenous magnesium does not reduce myocardial infarct size in a canine model of regional ischaemia and reperfusion" found that serum Mg levels similar to those used in clinical practice had no effect on the experimentally produced infarct size, even if the Mg was infused before recovery. This is in contrast to three other similar studies (see Grunert et al. for references) using MgSO<sub>4</sub>, which found a significant reduction in infarct size under very similar experimental conditions.

In the second group, magnesium and cardiac disease, there are four papers. Classen in "Magnesium L-aspartate hydrochloride: experimental and clinical data" makes out an excellent case for Mg-L-Aspartate hydrochloride to be used as an oral magnesium supplement. However, there are uncertainties with oral magnesium supplements as Vormann and Anke demonstrate in "Dietary magnesium: supply, requirements and recommendations. Results from duplicate and balance studies in man". In these balance studies, even when the subject's Mg intake was less than the recommended dose, supplementing the diet with 4 mmol (100 mg) Mg did not lead to a positive Mg balance over 7 days as the increased Mg was excreted either in the faeces and/or urine. Stühlinger discusses the use of intravenous and oral Mg in the treatment of arrhythmias in "Magnesium and cardiovascular disease". He also summarizes the results of several small clinical trials (of less than 100 in both placebo and test groups), which showed a positive outcome of oral magnesium in patients with proven coronary heart disease. However, Elwood and Pickering in "Magnesium and cardiovascular disease: a review of epidemiological evidence" concluded that the evidence of a correlation between magnesium intake and cardiovascular disease on the one hand, and magnesium supplementation and a reduction in the incidence of vascular disease and/or death on the other, is not conclusive.

In the third group there is one paper, "Magnesium and its role in cardiac surgical practice: a review". In this paper, Satur discusses the advantages of magnesium infusion in cardiac surgery, and tentatively concludes that increasing the plasma Mg concentration during and after cardiac surgery decreases postoperative morbidity, arrhythmias and increases cardiac performance.

### Conclusions

The fundamental problem in trying to understand the clinical use of magnesium is the lack of understanding of the physiology of magnesium in the heart. Because of this, it is difficult to propose specific mechanisms for the action of magnesium in deficiency, reperfusion and established cardiac disease. A better understanding of the basic  $Mg^{2+}$ -physiology in the heart would allow specific hypotheses to be tested directly. However, in heart, the areas of our lack of understanding have been identified, new methods are available and it is the combination of those two that makes future investigation of basic  $Mg^{2+}$ physiology in heart not only most opportune but essential.

Related to the lack of understanding of basic  $Mg^{2+}$ -physiology are two further problems. The first is the controversy over the results of infarct size in whole animal experiments between Grunert et al. (this issue), using Mg-aspartate, who found no decrease in infarct size, and the three other groups, using MgSO<sub>4</sub>, who did. The question now arises that it could be the aspartate anion that is having a negative effect on the heart and that this was the cause of the failure to see a reduction in infarct size. This problem has to be solved and a direct comparison between Mg-aspartate and MgSO<sub>4</sub> on infarct size is now essential, for this has important clinical ramifications. The second problem is to define the role of magnesium in the regulation of the mitochondrial permeability transition pore during reperfusion.

Small clinical trials are suggestive, but not always conclusive. Despite the cost and effort involved in large or multicentre placebo-controlled trials it would appear that such trials have now become necessary to establish the actual role of  $Mg^{2+}$  in cardiac surgery, supplementation in established cardiac disease and in the recovery from AMI. Serious consideration must now be given to organising carefully controlled clinical trials of adequate statistical power, to convincingly settle the argument concerning the use of  $Mg^{2+}$  in the treatment of cardiovascular disease.

Until these problems are solved, the sterile arguments concerning the relevance of  $Mg^{2+}$  as a therapeutic agent in cardiovascular disease will continue. If this issue of the "Journal of Clinical and Basic Cardiology" is to achieve anything in the field of magnesium research, it will be in not only having identified the main areas where understanding is lacking but also in proposing possible solutions to the relevant questions concerning the role of magnesium in therapeutics.

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