Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2002; 5 (1), 67-73

Magnesium and Its Role in Cardiac Surgical Practice: A Review

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

Magnesium and Its Role in Cardiac Surgical Practice: A Review

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Magnesium is a coenzyme essential to numerous cellular processes and it modulates the electrical conduction of the heart and its contractility. Magnesium deficiency though often caused by cardiac surgery may not be readily diagnosed. Its metabolism may be deranged by effect of cardiopulmonary bypass, by increased excretion and by the secondary effects of the neuroendocrine response to surgery. These changes induce both cardiac symptoms evident as arrhythmias and reduced cardiac function, and neurological disturbances. Active management of magnesium metabolism can ameliorate many of the shifts in electrolyte balance and the resultant problems. In addition, magnesium may be administered as a pharmacological agent to inhibit the myocardial injury that arises during periods of ischaemia. It is the aim of this article to present the contemporary state of knowledge on this subject and to clarify some of its complexities that arise from apparently conflicting details. It is also intended to present the case for a more aggressive approach to be taken to the management of magnesium metabolism than is commonly adopted. *J Clin Basic Cardiol 2002; 5: 67–73.*

Key words: magnesium, cardiac surgery, physiology, cardioplegia, plasma

Magnesium has an essential role in numerous cellular processes and if its metabolism is disturbed it can have serious biological consequences. Discovery of the degree of its importance has had a long history from the time that Epsom Spa water, which had an embittered taste due to containing the sulphate of magnesium, was drunk in 1645 [1]. In 1808 Sir Humphrey Davy isolated the alkaline metal by electrolysis, a pioneering technique developed by himself which was also used to isolate sodium and potassium [2]. In 1869 Jolyet and Cahours reported the results of investigations undertaken to examine the biological properties of the sulphates of magnesium, potassium and sodium [3]. In this report the authors reported that 2–6 g administered intravenously to an 8 kg dog would cause neuromuscular blockade and paralysis without disturbing cardiac function. Jolyet and Cahours also provided an astute observation that magnesium may have anti-coagulant properties, a feature which is receiving greater attention in recent times. In the twentieth century magnesium was found to be an important co-enzyme to numerous intracellular enzymes, including those involved in energy production and utilisation. These enzymes include hexokinase that is active in the glycolytic pathway and myosin triphosphatase [4]. Adenosine triphosphate [ATP] is intimately bound to magnesium, thus the content of magnesium in tissues is closely related to the metabolic activity of that tissue [5, 6]. Brain, muscles and red blood cells contain decreasing quantities of magnesium and ATP respectively [7]. Within the heart the left ventricle contains the greatest quantity of magnesium and ATP per unit weight, whilst the right ventricle and atria contain descending quantities respectively [8, 9].

Magnesium is not a trace element but the fourth most abundant cation in the body, and the second, potassium being first, most abundant in the intracellular space. Physiological roles of Mg^{2+} include its action as a regulator of Ca^{2+}, K^{+} and Na^{+} transport channels and pumps in cell membranes [10]. It modulates the binding of calcium to the troponin complex during contraction, thus elevated cellular and extra-cellular content causes smooth muscle relaxation [11].

Intravenous administration of Mg^{2+} may cause an increase in cardiac output, left ventricular stroke volume, and coronary blood flow secondary to coronary artery vasodilatation, and systemic vasodilatation [12]. The degree of the changes in the cardiovascular status effected by the infusion of Mg^{2+} is related to both the concentration and the rate of infusion of Mg^{2+}, and cardiovascular changes may not be evident following the administration of lower doses [13]. Elevation of extra-cellular and intra-cellular Mg^{2+} content increases the resting membrane potential of myocytes, slows A-V conduction in the sino-atrial and atrioventricular node and increases depolarisation rate [14, 15]. Deranged Mg^{2+} metabolism, principally Mg^{2+} depletion, may therefore have serious consequences on the cardiovascular system, including reduced cardiac function, increasing diastolic stiffness and reduced systolic contraction, and potentiation of ventricular and atrial dysrhythmias [16]. Neurological dysfunction, including fits, can also be readily produced by depletion as witnessed in patients recovering after cardiac surgical procedures and those can be treated by replacement of Mg^{2+} [17].

Whilst the history of its discovery has been long, a clear understanding of the application of the knowledge of magnesium's role in clinical medicine, in particular cardiac surgery is only recent and still evolving. Holden and associates in 1972 reported that hypomagnesaemia was the most common preoperative electrolyte abnormality in patients undergoing cardiac surgical procedures and demonstrated marked changes in its plasma concentration after surgery [18]. Studies undertaken to investigate the patterns of change in Mg^{2+} metabolism that occur during and after cardiac surgery have revealed the patterns may be complex and dependant on numerous variables. There is now a wealth of evidence relating the essentiality of Mg^{2+} to the cardiovascular system which supports the need for regular and close manipulation of magnesium metabolism during and after cardiac surgery. However Mg^{2+} metabolism remains a complex, intertwining and sometimes an apparently conflicting subject that can make the assessment of a patient's requirements at any particular time difficult. It is the aim of this article to present a summary of the contemporary state of knowledge of this topic and to attempt to clarify some of its complexities.

Influences on Magnesium Metabolism During Cardiac Surgery

Patients requiring cardiac operations often demonstrate deranged Mg^{2+} metabolism at the time of presentation for surgical treatment. Hypomagnesaemia may be identified in 41 % of infants and children with congenital cardiac lesions and in

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18.2 % of adults requiring various operative procedures [19, 20]. This deficiency is commonly related to chronic treatment with frusemide. The subsequent undertaking of cardiac surgical procedures may cause rapid and acute changes in the Mg^{2+} status of these patients, the pattern of which is dependant on details of the individual surgical technique utilised. Thus the nature of the change in Mg^{2+} metabolism differs between patients treated by closed heart procedures and open heart procedures.

A closed heart operation is one that in the loosest definition refers to an operation on the heart or its blood vessels that does not require the support of cardiopulmonary bypass. Open heart procedures utilises cardiopulmonary bypass (CPB). The procedure of cardiopulmonary bypass requires that the fully anti-coagulated blood volume of a patient or animal is drained to an external circuit, previously primed with either an asanguinous or sanguinous solution. A pump returns the blood through an oxygenator to the patient at a rate sufficiently high enough to provide organ perfusion during the time of the operation when the heart is immobilised and operated upon. Open heart procedures are thus influenced by the fluid shifts induced by cardiopulmonary bypass prime, the inflammatory and metabolic response to cardiopulmonary bypass and by the varying techniques of perfusion and myocardial protection utilised during surgical procedures.

Closed Heart Operations

Closed heart operations are commonly required to provide palliation for complex congenital heart defects and correct other congenital defects. The principles of closed heart operations are also incorporated in the undertaking of "off-pump" coronary artery bypass graft surgery (CABG) [17, 21, 22]. The latter situation to my knowledge has not been investigated with regard to changes in Mg^{2+} metabolism.

Corrective operations for congenital pathologies include repair of coarctation of aorta, ligation of patent ductus arteriosus, and placement of an aorto-pulmonary shunt for complex cyanotic congenital lesions. Satur et al. reported that in a group of 35 children, hypomagnesaemia below a level of 0.6 mmol/l (normal being 0.7–1.2 mmol/l) was identified in 10 (28.6 %) of children postoperatively in the intensive care unit (ICU), and evidence of a significant decline by a value greater than 20 % of the baseline value on admission to the ICU affected 11 (34.4 %) [15]. Eight (20.5 %) children had atrial and ventricular ectopics, but the occurrence was not related to hypomagnesaemia. Neurological irritability occurred in 6 (18.8 %) of the group, five of whom had values below 0.6 mmol/l, but all 6 had experienced the decline in the plasma Mg^{2+} concentration of 20 %. Thus symptoms may be more closely related to the change in the Mg^{2+} concentration than to the absolute values alone. The Mg^{2+} depletion in this and other studies has been related to the use of frusemide [17, 19, 20].

At the time of publication in 1993 of the above study by Satur et al., patients in intensive care did not routinely have their serum Mg^{2+} concentrations monitored [17]. Recommendations were therefore made that the evaluation should be undertaken at least daily. Since this time, adult populations requiring intensive care have also been found to have a high incidence of Mg^{2+} deficiency. Of 117 patients who had received a variety of major general surgical procedures including lung resection and oesophagectomy, 61 % possessed a serum Mg^{2+} below 0.75 mmol/l at the time of admission into an intensive care unit [23]. In this study by Chernow at al., the presence of severe hypomagnesaemia, serum levels below 0.5 mmol/l, was found to be an independent predictor of mortality. Hypomagnesaemia was also reported to affect between 11 % and 59 % of children treated in ICUs after major surgery, and was related to chronic treatment with frusemide, glycosides and intravenous nutrition [24, 25]. Daily supplementation of enteral and parenteral fluids nutrition to provide a normal intake, rather than merely replacement when deficiency developed, in my experience, remains a recommendation that has not been widely incorporated into clinical practice.

Open Heart Operations

Provision of cardiopulmonary bypass for the undertaking of cardiac surgical procedures in children and adults causes marked changes in the serum and tissue Mg^{2+} content, and urinary excretion that continue into the days after surgery. The patterns of change are influenced by the techniques used to provided cardiopulmonary bypass and the types of solution used during surgery to arrest and protect the heart [26–29].

Coronary artery bypass grafting involves the suturing of conduits to coronary arteries beyond the sites of acquired occlusions or narrowings on the coronary arteries that prevent the myocardium from receiving an adequate blood supply. The conduits most commonly used are sections of the long saphenous vein obtained from the leg and the left internal mammary artery which lies within the chest adjacent to the breast bone. The surgery is commonly undertaken whilst the patient is supported by cardiopulmonary bypass and with the blood supply to the heart arrested and the heart immobile. The blood supply to the heart may be interrupted for short intervals of approximately 10 minutes whilst an individual conduit/coronary anastomosis is fashioned [26, 30]. The proximal end of the venous conduits is sewn to the aorta as the aorta arises from the heart and after the blood supply to the heart was re-established. The periods of ischaemia and reperfusion are used sequentially to fashion bypass grafts to an average of three vessels per patient, after which the patient is weaned from cardiopulmonary bypass. An alternate technique uses prolonged periods of ischaemia to fashion all required conduit/graft anastomoses synchronously, and is also used to enable cardiac valve replacement and the undertaking of numerous other complex operative procedures. Prolonged periods of ischaemia however, require the use of techniques, such as infusion of "cardioplegia" solutions and hypothermia that minimise oxygen utilisation, to prevent myocardial injury during the period of ischaemia [31–34].

Satur et al., reported a study in which a detailed examination of the changes in Mg^{2+} metabolism during and after CPB was performed [26]. The study utilised the simple clinical model of CABG in adults undertaken with the support of cardiopulmonary bypass, utilising intermittent short periods of myocardial ischaemia without cardioplegia to fashion coronary artery grafts. No extraneous Mg^{2+} was provided. Plasma, cardiac and skeletal muscle Mg^{2+} content were evaluated during surgery, and the plasma content and urinary excretion evaluated on the 1st and 5th post-operative days. The study discovered that 3 clinico-pathological patterns of change and Mg^{2+} deficiency had occurred. Some of the findings were not novel but the model was simple and comprehensive and has provided a good foundation upon which the findings of other investigators may be placed and discussed.

Basic Changes in Magnesium Metabolism During Cardiac Surgery [22]

Pattern 1 – Cardiopulmonary Bypass: Initiation of CPB in adults caused acute hypomagnesaemia secondary to haemodilution with a prime deplete of Mg^{2+}, the concentration of which was 0.25 mmol/l [22]. Total plasma Mg^{2+} concentration there-

fore decreased by 19 % from 0.79 mmol/l to 0.67 mmol/l. This level remained unchanged throughout surgery and until the time of admission into the intensive care unit.

Pattern 2 – Myocardial Ischaemia/Injury: Measurement of the content of Mg^{2+} in myocardial and skeletal muscle biopsies obtained before and after CPB demonstrated that during the period of CPB the skeletal muscle Mg^{2+} content was reduced by 2.9 % and cardiac muscle content by 13 %. These findings suggested that the CPB induced hypomagnesaemia also induced generalised total body cellular depletion and that the associated periods of myocardial ischaemia caused an additional depletion of cardiac Mg^{2+} content.

Pattern 3 – Postoperative Depletion: The reduced plasma Mg^{2+} concentration at the time of admission into the ICU remained unchanged throughout the period of surgery and until the first postoperative day. By the 5th postoperative day the plasma Mg^{2+} content had increased to a value 19.5 % above the preoperative value. Urinary excretion of Mg had mirrored the plasma changes and demonstrated a 47 % reduction from the preoperative value to that on the first postoperative day and subsequently increased to a value on the 5th postoperative day that was 25 % above preoperative values. In the light of the mirroring that urinary excretion of Mg^{2+} demonstrated in relation to plasma concentration, it was interpreted that the changes did not represent a physiological attempt to minimise excretion and conserve Mg^{2+}. It was, however, interpreted that postoperative depletion of the intracellular compartment was occurring and augmenting the extra-cellular compartment.

Depletion of Mg^{2+} during and after cardiac surgery has been associated with a depression of myocardial contractility and an enhanced potential for cardiac arrhythmias [28, 29]. Furthermore, many of these complications have been found to be preventable or reversible. The following discussion will utilise the model discussed above and expand on some areas to determine how the patterns of Mg^{2+} depletion may be influenced.

Pattern 1 – Cardiopulmonary Bypass

Haemodilution is the primary cause of hypomagnesaemia on CPB. Could this change be prevented and would its prevention prove to be beneficial [26–29]. Satur et al. [27], identified that the cardiopulmonary bypass prime was not the sole cause of hypomagnesaemia, but the administration of other intravenous fluids during anaesthesia before induction of CPB also caused depletion. Supplementation of all the fluids administered to a patient therefore would prevent depletion of serum Mg^{2+} and myocardial tissue Mg^{2+}. Furthermore, elevation of the plasma concentration to supra-normal values by administration of 16 mmol/l immediately before CPB appeared to have beneficial effects by raising the cardiac muscle Mg content above baseline. Supra-normal plasma Mg^{2+} concentrations also caused prolongation of the QT interval corrected for heart rate, and reduced the potential for dysrhythmias [27].

Administration of cardioplegia containing Mg^{2+} (12–16 mmol/l), St Thomas's Cardioplegia, has been shown to prevent the hypomagnesaemia of CPB and maintain the myocardial content [19, 29, 31]. Following the use of this Mg^{2+}protocol, 55 % of a single cardioplegia load is excreted on the first day, but the balance remains positive on the 1st and 2nd postoperative day [31]. Despite the early positive balance, Vyvyan et al., reported an incidence of hypomagnesaemia in 30 % of a group of 130 adult patients and Satur et al. reported an incidence 34 % of a group of 41 children postoperatively [32, 33]. In groups of patients that had routinely received Mg^{2+} supplemented cardioplegia the occurrence of arrhythmias, principally atrial or nodal tachycardia and ventricular ectopy, could not however, be related to the serum level of total or ionised Mg^{2+} [19, 33]. It has been assumed this discrepancy between symptoms and plasma concentrations arose because plasma Mg^{2+} concentrations poorly represent the changes in total body and intracellular content. As arrhythmias were a continuing problem however, with an incidence of 18 % and 41 % in the above studies, it has to be asked whether the addition of Mg^{2+} to cardioplegia was of benefit?

Pattern 2 – Myocardial Ischaemia/Injury

Mg^{2+} and Cardioplegia

Administration of cardioplegia containing Mg^{2+} as compared to Mg^{2+} free cardioplegia has been shown in experimental and clinical studies to provide protection against ischaemic myocardial injury and to reduce the incidence of postoperative arrhythmias [34–36]. Hearse and colleagues used a rat heart model to evaluate whether the addition of variable concentrations of Mg^{2+} sulphate to hyperkalaemic cardioplegia solution provided myocardial protection [34]. It was identified that the benefit proffered by the inclusion of Mg^{2+} in cardioplegic solutions possessed a dose/efficacy relationship, the optimum concentration of Mg^{2+} in this model being 16 mmol/l. It was identified that the aortic pressure generated after a period of myocardial ischaemia protected with Mg^{2+} and K^+ cardioplegia and reperfusion was 96 % of pre-test values as opposed to 76.5 % with K^+ cardioplegia alone. The protection provided by Mg^{2+} cardioplegia was further enhanced by the addition of topical hypothermia. Thus the benefit of Mg^{2+} in cardioplegia in protecting against ischaemic myocardial injury is over and above the protection provided by hyperkalaemic cardiac arrest and hypothermia alone or combined. This composition was subsequently utilised as St. Thomas Cardioplegia No 2, effectively improving the outcome of surgical procedures.

In the modern era of cold and warm blood cardioplegic techniques, potassium has often been used as the primary protective agent. The value of Mg^{2+} in these situations has therefore required re-examination. Brown et al., used a rat heart model of ischaemia to investigate the value of added Mg^{2+} to cold blood cardioplegia. After 90 minutes of ischaemia followed by reperfusion, hearts protected with Mg^{2+} cold blood cardioplegia, regained 99 % of ATP content and 104 % stroke work, as opposed to 76 % and 52 % respectively following Mg^{2+} free cardioplegia [37].

The protection afforded by Mg^{2+} supplementation in cardioplegia is however influenced by and related to the concentration of other cations and the maturity of the myocardium. Nakamura et al., tested the efficacy of crystalloid cardioplegia that contained various combinations of $MgCl_2$ and Ca^{2+} in a working rat heart model [38]. The concentrations of $MgCl_2$ were 1.2, 8.0 and 16.0 mmol/l combined with Ca^{2+} concentrations of 0.1, 0.3, 0.5, 1.0 and 2.5 mmol/l. Solutions containing 8 and 16 mmol/l $MgCl_2$ when combined with 1.0 mmol/l Ca^{2+} provided optimum protection, whilst concentrations of 0.5 mmol/l and lower resulted in a marked myocardial dysfunction that was not preventable by the addition of Mg^{2+}. It has been suggested that the latter was due to the effect of the calcium paradox.

Kronon et al., investigated the effectiveness of hypocalcaemic cardioplegia in providing protection for neonatal hearts [35, 39]. In two studies with swine neonatal hearts this group identified that with hypocalcaemic cardioplegia hearts suffered less injury following ischaemia than if a normocalcaemic solution had been used. In both studies addition of Mg^{2+} amel-

iorated the injury induced by ischaemia when normocalcaemic cardioplegic solutions were used, maintaining ATP content, and ventricular contractility. Results are however, conflicting on whether Mg^{2+} provided additional benefit to the use of hypocalcaemic solutions alone. In one study [35] no benefit was shown but in an exactly similar study, hypocalcaemic solutions did not prevent ischaemia, and Mg^{2+} prevented injury, though no difference was demonstrated between the use of 6 mmol/l or 12 mmol/l Mg^{2+} in the cardioplegia [39].

Myocardium rendered ischaemic experiences a rapid decrease in phosphocreatine levels, a slower reduction of ATP but an increase in phosphate content. These changes are associated with a rise in intracellular calcium, which if excessive causes ischaemic contracture and cell death [40]. The mechanism by which Mg^{2+} prevents myocardial injury during ischaemia is not fully identified. Factors that have been identified however, include a reduction in the rate of the degradation of high energy phosphates by the modulating action of Mg^{2+} on contractile proteins and at sarcolemmal sites. Secondly, during reperfusion after a period of ischaemia Mg^{2+} inhibits the calcium overload that normally accompanies reperfusion [40]. One of the mechanisms by which Mg^{2+} provides its protection against reperfusion injury is by blocking slow calcium channels thus inhibiting the influx of calcium, and preventing the secondary and destabilizing effect of increased calcium on mitochondrial membranes leading to reduced ATP production [see also Halestrap, this issue].

Senescent myocardium is more sensitive to the effect of ischaemia and experiences a 30 % more rapid rise in intracellular calcium content than mature myocardium [41, 42]. In a rabbit model in which senescent hearts were evaluated both K^+ and K^+-Mg^{2+} cardioplegia, 20 mmol/l of each, reduced the rate of degradation of high energy phosphates by equivalent quantities during normothermic ischaemia. In a similar model Faulk et al., demonstrated that senescent hearts subjected to global ischaemia without protection caused mitochondrial Ca^{2+} to increase by 166 % of control values [42]. K^+ cardioplegia reduced the increase to 143 % and Mg^{2+} and K^+-Mg^{2+} ameliorated the rise almost completely. In the same model, mRNA in the mature hearts was not affected by ischaemia, but senescent hearts experienced a decline in mRNA content of 50 % that is minimised though not prevented by Mg^{2+} cardioplegia. Tsukube et al., in another comparative study, demonstrated DNA fragmentation occurred during ischaemia in aged hearts but not mature hearts [41]. During global ischaemia nuclear fragmentation in the myocytes of senescent hearts increased from 7.3 % to 16.6 %. This was moderated by K^+ cardioplegia to 13.7 %, and both Mg^{2+} alone and K^+-Mg^{2+} cardioplegia reduced it to 9.3 % and 10.3 % respectively.

Pattern 3 – Postoperative Depletion

Hypomagnesaemia Induced by Cardiac Surgery

Hypomagnesaemia induced by cardiopulmonary bypass has been shown to potentiate postoperative morbidity. Aglio and associates reported that of 101 adult patients receiving open heart operations as many as 71 % of patients were hypomagnesaemic on the first day following surgery and this subgroup of patients suffered a significantly higher incidence of atrial dysrhythmias than the normomagnesaemic patients 31 % vs 10 % respectively [20]. In a study by England and associates, 100 patients randomised to receive 8 mmol of $MgCl_2$ or placebo immediately after bypass showed a reduction in hypomagnesaemia that followed administration of $MgCl_2$ and was accompanied by a reduced rate of ventricular ectopics from 34 % to 16 % and a reduced rate of supraventricular tachycardia from 37 % to 17 % was reported [29]. These changes were accompanied by a reduced need for ventilatory support greater than 24 hours from 30 % to 16 %.

Similar findings were reproduced in others clinical situations. In a randomised studied by Caspi et al., 98 patients who were treated by coronary artery bypass surgery were randomised to two groups [36]. 50 patients received 16 mmol/l of $MgSO_4$ during the period after induction of anaesthesia but prior to cardioplegic arrest of the heart, and a further 32 mmol/l after cessation of cardiopulmonary bypass. Cardiac arrest was induced with warm blood cardioplegia that contained 16 mmol/l Mg^{2+} and 30 mmol/l K^+ and was maintained with a cardioplegia containing 10 mmol/l K^+. 48 patients did not receive the supplementary Mg^{2+} before and after cardiac arrest. The group of patients receiving Mg^{2+} supplementation showed a significantly improved cardiac index 3.2 l/min/m^2 and left ventricular stoke work index 48 g/m/m^2 at 24 h as compared with 48 controls who exhibited values of 2.9 l/min/m^2 and 41 g/m/m^2 respectively. 2 patients receiving Mg^{2+} as opposed to 12 who did not receive Mg^{2+} required inotrope support for greater than 12 hours, and 1 patient as opposed to 12 suffered multiple ventricular ectopics requiring lidocaine.

The beneficial effect of preventing cardiac arrhythmias by the supplementation of plasma Mg^{2+} was again demonstrated in a randomised study which evaluated a group of children. In this study by Dorman et al., it was intended to study 100 children randomised to a control and study group, but the study was curtailed after 28 children, because of the marked difference between groups [28]. Children in the study group ($n = 13$) received 30 mg/kg of $MgSO_4$ immediately after CPB, and again a dose of 10 mg/kg to maintain normomagnesaemia, whilst controls ($n = 15$) received no additional Mg^{2+} after cardiopulmonary bypass. The control group exhibited a significantly higher incidence of arrhythmias, 27 % of junctional tachycardia, than the Mg^{2+} group who exhibited none, $p = 0.026$.

There therefore appears to be a clear relationship between the hypomagnesaemia that may occur early after cardiopulmonary bypass, and cardiac symptoms. Satur el al., also suggested that the changes in Mg^{2+} metabolism that cause hypermagnesaemia and intracellular depletion of Mg^{2+}, may also be related to cardiac symptoms [26]. This hypothesis was formulated because of the observation, that patients exhibited secondary hypermagnesaemia following a period of postoperative hypomagnesaemia that occurred early after cardiopulmonary bypass, when no Mg^{2+} was administered to the patients. This secondary hypermagnesaemia was considered to be the result of a depletion of intracellular Mg^{2+} stores resulting in an elevated extracellular Mg^{2+} concentration. It was suggested that these postoperative swings in the plasma content of Mg^{2+} were caused by the neurohormonal consequences of cardiac surgery [26].

Neurohormonal Effects of Cardiac Surgery

Cardiopulmonary bypass provides an intense stimulus to the neurohormonal system, in addition to the stimulus induced by the pain of surgery alone [43–46]. Plasma concentrations of both noradrenaline and adrenaline rise dramatically following the induction of cardiopulmonary bypass, the peak plasma concentrations reaching 5–10 fold the values of baseline concentrations. In these studies, the plasma noradrenaline concentrations rose from the baseline values of 50–200 pg/ml to 1000–2000 pg/ml measured one hour after the induction of cardiopulmonary bypass. The plasma adrenaline concentrations also rose from 20–100 pg/ml to values approximating

1000 pg/ml. These levels remained significantly elevated 24 hours after surgery.

Whilst secretion of catecholamine is a normal physiological response to stress the resultant physiological effects may not all be beneficial. Stimulation of myocardial adrenergic receptors induces an immediate increase in contractility and myocardial performance, resulting in improved cardiac output and systemic blood pressure [47, 48]. Caspi et al., however, showed that infusions of high doses of adrenaline to neonatal pigs, 2 μg/kg/min, caused a depletion in myocyte ATP, damaged diastolic myocyte function and caused disruption of the myocyte subcellular structure [49]. The infusion of adrenaline in this study elevated the baseline plasma concentrations from 45 pg/ml to 1200 pg/ml. The deleterious effects were inhibited by an infusion $MgSO_4$ that elevated the serum Mg^{2+} concentration to 1.9 mmol/l. Romani and Scarpa, and Amano and associates demonstrated the potentially deleterious effects of catecholamine stimulation and the benefit of inhibition of these effects by β-receptor blockade [46, 48]. Zdanowicz and Barletta also demonstrated in a model using cultured rat cardiomyocytes, that catecholamine stimulation caused a depletion of intracellular Mg^{2+} and K^+ that correlated with a reduced myocardial function and an increased incidence of irregular contraction and arrhythmias [50].

The deleterious effects of catecholamines bore a direct relationship to the dose administered. Studies have been reported in which human volunteers or patients receiving cardiac surgical treatment have been used to evaluate the effect of the infusions of catecholamine. These investigators reported that infusions of catecholamine at rates of between 0.01–0.1 μg/kg/min readily increased the cardiac output and the blood pressure of subjects, and also induce changes in the plasma Mg^{2+} concentration [13, 47]. Joborn et al., studied 6 adults during the infusion of adrenaline at a dose of 5 μg/kg and then 10 μg/kg for 30 minutes at each rate and demonstrated that the latter caused a more rapid change in Mg^{2+} metabolism than the former. 10 μg/kg caused an acute decrease in serum Mg^{2+} concentration from approximately 0.78 mmol/l to 0.65 mmol/l whilst the former caused a minimum change [47]. The onset of hypomagnesaemia could be prevented by the administration of propranolol. Interestingly in the same study, Joborn and associates showed that an infusion of noradrenaline did not induce the same changes confirming the hypothesis that β-stimulation was causing the effect.

The above discussion concerning the changes in plasma catecholamine concentrations that can occur during clinical and experimental studies, has revealed similarities between the two areas of study. Firstly, the serum levels of catecholamine achieved during cardiac surgical procedures are similar to those achieved in animal studies, in which it was demonstrated that an infusion of catecholamines could produce significant myocyte injury [13, 47–50]. Secondly, the intravenous infusion of catecholamine solutions caused acute changes in cellular and systemic metabolism of Mg^{2+} [13, 50]. These changes were themselves correlated with reduced myocardial function. In view of these findings, it may be concluded that there may be a degree of morbidity following cardiac surgery which is related to the associated catecholamine response, and to the administration of catecholamine, particularly in high doses. Moreover, it has been reported that the administration of β-adrenergic blockers, such as sotalol and propranolol prevent the myocyte Mg^{2+} depletion induced by catecholamines and provided clinical benefit [46–48, 51, 52].

Postoperative Morbidity and Cardiac Arrhythmias

The incidence of atrial and ventricular dysrhythmias complicating cardiac surgery has been reported in various studies to be between 25 % and 60 %. Ventricular arrhythmias occur less frequently than atrial arrhythmias, the latter being atrial fibrillation or atrial flutter (AF). The incidence of AF is related to age, with those patients below the age of 40 years of age, experiencing an incidence of below 3.7 %, and those patients above 70 years of age an incidence of 37.7 % [51, 52]. Others have reported on a relationship between the change in metabolic status of patients and postoperative symptoms. Kalman et al., found patients who developed postoperative AF possessed plasma concentrations of noradrenaline 62 % higher than those that remained in sinus rhythm [53].

Studies have been reported in which the post-operative morbidity of cardiac surgery had been reduced by positively manipulating Mg^{2+} metabolism. A number of studies investigated the benefit of administration of Mg^{2+} intravenously in the days following surgery [36, 54–56]. Infusions of between 50 mmol and 100 mmol administered over a period of 48 hours to 5 days caused the serum levels to rise only modestly to levels not exceeding 1.5 mmol/l, thus fears that these protocols may cause toxic levels were not confirmed. Nurozler et al., demonstrated a reduction in the incidence of AF from 20 % to 4 % occurred [56]. Caspi et al., demonstrated a reduction in the incidence of ventricular arrhythmias, mainly ectopics from 28% to 2%, but no significant difference in the incidence of atrial arrhythmias [36]. Fanning et al., however, demonstrated a marked reduction in incidence of AF from 28% to 14%, as did Colquhoun et al., from 37.5% to 16.7% [54, 55]. Fanning et al., and Caspi et al., also demonstrated a reduced need for inotropic support in the groups that received Mg^{2+} from 54 % to 35 % and 18 % to 4 % respectively [36, 55]. The reduced need for pressor administration was associated by a measured improvement in cardiac function and demonstrated that Mg^{2+} did not cause vasodilatation and haemodynamic instability.

Lazar et al., undertook a small randomised study incorporating a group of 30 patients that investigated the potential benefits of the administration of glucose-insulin and potassium (GIK) to patients after undertaking CABG [57]. They demonstrated that postoperative myocardial function was significantly improved and that the incidence of atrial fibrillation was reduced. Atrial fibrillation occurred in 13.3 % of the GIK group as compared to 53.3 % of controls. These pharmacological manipulations may act by enhancing the myocardial Mg^{2+} metabolism, preventing the depletion of intracellular Mg^{2+}.

Other studies have demonstrated a reduction in the rate of atrial fibrillation after cardiac surgery by the prophylactic administration of β adrenoceptor blocking agents. Pfisterer et al., demonstrated in a study of 255 patients a reduction in the rate of atrial fibrillation when sotalol was prescribed in a dose of 80 mg twice daily, from 46 % in controls to 26 % [58]. Suttorp and associates in a study of 429 patients divided into 4 groups, reported that use of sotalol resulted in a low incidence of postoperative atrial fibrillation. There was no significant difference between the use of a dose of sotalol of 40 mg three times daily and 80 mg three times daily[59]. Furthermore the same benefit was afforded by the non-selective β-adrenergic blocker propranolol.

Conclusion

The pattern of changes in Mg^{2+} metabolism that occur during and after cardiac surgery are complex. Hypomagnesaemia is a reliable indicator of the presence of depletion, but normomagnesaemia or even hypermagnesaemia does not exclude intracellular and total body Mg^{2+} depletion. These changes may arise as a direct result of surgical intervention in the form of cardiopulmonary bypass, administration of loop diuretics

and ischaemic cardiac arrest. They are also induced indirectly by a patient's own neurohormonal responses to cardiac surgery. The Mg^{2+} depletion that commonly occurs also causes a tangible increase in patient morbidity and hampers recovery following cardiac surgery. These changes in the patient's physiology may be modified and the secondary myocardial injury ameliorated by the techniques discussed above. Consideration should therefore, be given to the prevention of Mg^{2+} depletion, the replacement of Mg^{2+} losses, and therapeutic measures to inhibit myocardial injury.

In the evolving era of cardiac surgery, when more elderly patients are undergoing cardiac surgery, and the operations are not only more complex but also require longer periods of myocardial ischaemia, consideration should be given to utilising techniques that minimise operative risk. Risk stratification studies demonstrate that patients over 70 years of age experience an exponential rise in operative risk [60]. Thus whilst some patients, in particular younger adults with good ventricular function may tolerate most methods of protection well, others such as neonates and elderly patients do not posses the same reserve and are more prone to ischaemic injury. The evidence suggests that the cardioplegia administered to the elderly group of patients should include Mg^{2+}. However it is my opinion, that maximum risk reduction strategies should be applied to all age groups.

There is thus an increasing weight of evidence supporting the need to regulate Mg^{2+} metabolism before, during and after cardiac surgical procedures. While many of the studies provide convincing evidence that the administration of Mg^{2+} is beneficial, the size of the population of patients evaluated is in the studies relatively small. Some studies have examined whether the concerns that had been voiced regarding administration of Mg^{2+} in clinical situations were justified, and have demonstrated magnesium toxicity and potential cardiovascular or neurological complication do not readily occur. On the contrary, the balance of evidence suggests that a practice utilising the protocols discussed generally improves patient outcome and reduces morbidity.

There is now an urgent need to examine whether or not, the putative benefits of regulating Mg^{2+} metabolism during cardiac surgery, should be widely accepted and measures taken to adopt such protocols in standard clinical practice. To answer this question will however, require that larger studies that recruit multi-centre cooperation are undertaken.

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