



## Is the High Frequency of Postoperative Atrial Fibrillation after Cardiac and Lung Surgeries Related to Hypomagnesemia and Releases of Ceramides and Platelet-Activating Factor?

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### Editorial

There is a growing incidence (20-50%) of Post-Operative Atrial Fibrillation (POAF) after cardiac and lung surgeries around the globe [1,2]. These events often result in increased morbidity, thromboembolisms, strokes, and long-term mortality causing recurring hospitalizations and increased costs. Often the cause(s) of POAF is not known. Age, previous history of Atrial Fibrillation (AF), hypertension, diabetes, myocardial infarction, valvular heart disease, left ventricular hypertrophy, obesity, excessive drinking of alcohol and excessive smoking present great risk factors for development of POAF [1,2]. According to a number of autopsy reports, the incidence of considerable atherosclerotic plaques on the walls of the coronary blood vessels is very significant leading to the idea that inflammatory events, over years, play an important role in the PAOF syndrome. Several studies have suggested that use of intravenous magnesium (Mg) may yield better beneficial results than either beta-blockers, calcium channel blockers, digoxin and cardiac glycosides, or amiodarone [1,3,4].

Mg is a co-factor for more than 500 enzymes, and is the second most abundant intracellular cation after potassium. It is pivotal in numerous pathophysiological, cellular, and biochemical functions necessary for life [5-7].

Approximately 40 years ago, our laboratories suggested a progressive, dietary deficiency and/or metabolically-induced loss of Mg from the body (and heart), particularly the coronary vascular tree, could lead to coronary arterial spasms, arrhythmias, and sudden-cardiac death (SCD) [8,9]. Ever since we published these works, a number of clinical studies have been done which support our hypothesis, at least in adults, irrespective of gender [10]. It is well-known that disturbances in diet can produce inflammatory lesions, promote lipid deposition and accelerated growth, and transformation of the smooth muscle cells in the vascular walls [11]. Our group, over a period of many years, has demonstrated, experimentally, that reduction in dietary intake of Mg can result in hypertension, atherogenesis on coronary and peripheral blood vessels, cardiac dysfunctions, inflammations and strokes of diverse types [10,12-14]; most of these phenomena being observed in patients scheduled for cardiac and lung surgeries [1-4].

In the Western World, dietary intake of Mg is subnormal, with short falls of between 65 and 225 mg of Mg/day, depending upon geographic region [5,6,8,10,13]. However, in the elderly population, those being the greater population needing cardiac and lung surgeries, the shortfalls in daily Mg intake often approach 100-275 mg of Mg/day. Newly compiled NHANES data indicate that 65% of the American population is Mg deficient. Added to this, one must recognize that most drinking waters are low in Mg, particularly in soft-water areas, and that many geographic areas have Mg-poor soil contents. Most of the soft-water and Mg-poor soil contents of Mg are associated with high incidences of Ischemic Heart Disease (IHD), severe atherosclerosis, coronary vasospasm,

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hypertension, hyperlipidemia, and SCD [5-7,10]. The myocardial level of Mg, where autopsy data is available, has consistently been observed to be significantly lower in subjects dying from IHD and SCD, particularly in soft-water and Mg poor-soil regions around the globe [5,6,8,10].

Over the past two decades, our laboratories have helped to pioneer the development and use of sensitive, specific  $Mg^{2+}$ -ion electrodes [14,15]. Use of these  $Mg^{2+}$ -specific electrodes by our group has revealed that patients with IHD, and scheduled for cardiac surgery or lung surgery, as well patients in cardiac failure, and patients with severe atherosclerosis exhibit significant depletion of serum/plasma/whole blood levels of  $Mg^{2+}$ , but not necessarily total serum/plasma Mg [13-15]. In addition, we have shown that controlled dietary deficiency of Mg in laboratory rats and rabbits cause vascular remodeling concomitant with multiple areas of inflammation, atherogenesis, apoptosis, and hypertension( e.g., arteriolar wall hypertrophy and alterations in arterial wall matrices) of unknown origin [10].

Using a variety of new physical, biochemical, and biophysical techniques, our laboratories have recently found that Mg deficiency in intact animals and in isolated vascular smooth muscle (VSM) cells (subjected to primary cell culture) demonstrate an upregulation of all five major enzymatic pathways leading to synthesis and release of ceramides and other sphingolipid molecules in cardiac and VSM cells [10,13,16,17]. Ceramides and several other sphingolipid molecules are now known to be pivotal in fundamental processes such as inflammation, apoptosis, angiogenesis, atherosclerosis, excitation-contraction coupling events in VSM cells, cell adhesion events, immunogenic events, membrane-receptor functions, and microcirculatory functions [13,16,17]. Besides the findings that Mg-Deficient Diets (MgDD) lead to synthesis and release of ceramides coupled to increased levels of calcium [10,13,16,17], we found that MgDD result in upregulation of a variety of cytokines, chemokines, proto-oncogenes, generation of a number of reactive oxygen- and nitrogen-species, upregulation of protein kinases of diverse types, activation of caspases, activation of nuclear factor-kB (NF-kB), mitochondrial release of cytochrome C, release of mitochondrial protease factor-1, alterations in a number of cellular phospholipids, DNA oxidation and fragmentation, lipid peroxidation, and downregulation of telomerases [10,13,16,17]. All of these events are now known to play important roles in cardiovascular atherogenesis, inflammation, morbidity and mortality; Mg deficiency being able to cause and promote these entire cellular and biochemical events. It is important to note, here, that we have found use of specific inhibitors of ceramide release and synthesis either prevented or greatly ameliorated the cellular, biochemical and molecular changes indicated in the above in MgD animals, tissues, and cells [10,13,16,17].

It is our belief that, collectively, these new studies on hearts, coronary arteries and peripheral blood vessels from animals on MgD diets support our hypothesis that generation and release of ceramides are pivotal molecules in the initiation of cellular and molecular events leading to coronary (and coronary microcirculatory) ischemic changes eventuating in inflammatory and atherogenic events producing atrial arrhythmias and fibrillation. However, many of these events, on the basis of recent studies in our laboratories, appear to be dependent upon the rapid synthesis of another molecule, viz., platelet-activating factor (PAF) [10].

In 1997, using proton -nuclear magnetic resonance spectroscopy

we noted rapid formation of PAF and other PAF-like molecules in VSM cells in culture [18]. PAF is known to play important roles in inflammatory events and atherogenesis [19]. PAF has been demonstrated to affect the heart and cardiac muscle cells in diverse ways [19]. For example, PAF is known to induce coronary vasoconstriction, reduce arterial blood pressure, increase coronary vascular resistance, decrease stroke volume, reduce cardiac output, decrease cardiac contractility, alter cardiac atrial and papillary chronotropicity and membrane potentials, as well as alter potassium currents in isolated cardiomyocytes [19]. In addition, PAF can release a variety of vasoactive lipids from the myocardium [19]. Obviously, all of these attributes of PAF's actions on the heart, in themselves, could be more than enough to promote profound atrial fibrillation. It must also be remembered that PAF is known to be elaborated by a variety of circulating blood formed elements such as polymorphonuclear leukocytes, platelets, basophils, and macrophages as well as endothelial cells [19]. Importantly, we have recently demonstrated that Mg deficiency results in elaboration and release of PAF from coronary, cerebral, and peripheral VSM cells [10]. In addition, we have found that initiation of PAF release from these VSM cells results in synthesis and release of ceramides [10]. In addition, there are a growing number of reports that indicate that both PAF and ceramides can induce transformation of VSM cells from contractile cells to synthetic, non-contractile cells which elaborate a variety of growth factors, as observed in the atherogenic process [10,19]. In this context, our group has clearly demonstrated that MgDD in rabbits and rats can result in atherogenesis with adherence of leukocytes, platelets, and macrophages on the vascular walls [20]. Concomitant with these actions, using intravital study of the lung, muscle, and cutaneous microvessels, we have recently reported that increasing concentrations of PAF will result in intense leukocyte rolling, increased adherence of leukocytes and platelets to the endothelial surfaces of the postcapillary microvessels along with vasoconstriction and increases in permeability of the postcapillary microvessels [12, unpublished findings]. Interestingly, we have reported that introduction of several different ceramides causes similar events to take place in these microvascular beds, as observed *in-vivo* by high-power, quantitative TV-microscopy [10]. Collectively, it is our belief that these new studies could be used to advance our hypothesis that generation and release of both PAF and ceramides in the presence of an underlying Mg deficiency are more than likely involved in generation of atrial fibrillation after cardiac and lung surgery and are, most likely, major contributors in other types of patients presenting with atrial fibrillation.

In view of the above, we are of the belief that a clinical trial study should be initiated to determine ionized Mg levels, ceramide levels, and PAF levels prior to and after cardiac and lung surgeries in order to demonstrate any possible correlations between these parameters before (and after surgeries) to frequency of PAOF. It might also be prudent to initiate a clinical trial to determine whether patients scheduled for cardiac and lung surgeries would benefit from pretreatment with selective blockers of ceramide generation/ release and PAF generation/release along with administration of intravenous Mg.

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