Why is Postoperative Atrial Fibrillation Difficult to Prevent and Treat: Potential Roles of Unrecognized Magnesium Deficiency and Release of Ceramide and Platelet-Activating Factor

Research Article

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Abstract

Heart failure is a major cause of morbidity and mortality whose costs impose staggering health-care costs and often lengthy hospitalizations. Post-operative atrial fibrillation (POAF) represents a leading cause for heart failure, paricularly after cardiac and lung surgeries. Although PAOF is a common cardiac arrhythmia, it is impossible to predict. As the worldwide population is aging, the incidence and prevalence of PAOF is growing. Identifying mechanisms for PAOF is attracting a considerable amount of research with no agreement on the mechanism(s). Our research on the heart and cardiovascular system, over the past 50-plus years, leads us to believe that major causes of PAOF may be an underlying magnesium deficiency (MgD) coupled to a generation/ release of ceramides and platelet-activating factor (PAF). Herein, we review reasons behind our hypothesis and suggestions for testing its validity.

Keywords: PAF; Sphingolipids ; Heart Failure; Atherosclerosis; Inflammation.

Introduction

Post-operative atrial fibrillation (POAF) is the most prevalent complication after cardiac or lung surgery, occurring in about 20-50 percent of these patients [1-5]. This event often leads to increased morbidity, thromboembolisms, strokes and long-term mortality resulting in 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 [1-5]. According to a number of reports, the incidence of cerebral infarction and heart failure can increase two-four - fold after PAOF [1-5]. Added to this, are a number of growing autopsy studies which demonstrate that many of the PAOF patients, who have died, have considerable atherosclerotic plaques on the walls of the coronary vessels leading to the idea that inflammatory events probably play an important role in the PAOF syndrome [5]. POAF is usually managed by digoxin, calcium channel blockers, beta-blockers, quinidine, amiodarone, direct current cardioversion, catheter ablation inside the heart, or appropriate rate control techniques to restore rhythm to normal [1-5]. Although digoxin is often utilized, it can present direct risks for POAF patients and has been associated with increased hospitalizations and mortalities [6, 7]. Such data has raised serious concerns about use of digoxin, one of our oldest and most controversial drugs . Ever since 1935 [8], digoxin and cardiac glycosides have been known to deplete the human body and heart of magnesium (Mg) [for review, see [9]]. Several studies have suggested that use of intravenous magnesium sulfate may be better than either beta-blockers, calcium channel blockers, or amiodarone [1, 5, 10-12]. This concept is currently under investigation by several groups in the USA and Europe.

Why use intravenous Mg^{2+} ?

Mg is a co-factor for more than 500 enzymes, and is the second most abundant intracellular cation after potassium. It is vital in numerous physiological , cellular and biochemical functions necessary for life [for reviews, see [13-15]].

Approximately 35 years ago, our laboratory suggested a progressive, dietary deficiency and/or metabolic-induced loss of Mg from the body (and heart), particularly during development of coronary arteries, could lead to coronary arterial vasospasm, arrhythmias, and sudden-cardiac death [16, 17]. Ever since this work was published, a number of clinical studies have been done and published which support this hypothesis, at least in adults [18-23]. Disturbances in diet are known to produce inflammatory lesions, promote lipid deposition and accelerated growth, and transformation of the smooth muscle cells in the vascular walls [9, 13, 14, 24-28]. Reduction in dietary Mg intake has been demonstrated , experimentally, to result in atherogenesis, hypertension, cardiac dysfunctions, inflammations, and stroke of different types [9, 13-15, 29-33]; most of these phenomena usually being observed in patients scheduled for cardiac and lung surgeries. Hypermagnesemic diets have been shown to ameliorate atherogenesis, hypertension, cardiac dysfunctions, strokes and certain inflammatory conditions often found in patients scheduled for cardiac and lung surgeries [9, 13, 14, 24, 27-33]. In the Western World, dietary intake of Mg is subnormal, with shortfalls of between 65 and 225 mg of Mg/day, depending upon geographic region [9, 13-15, 30, 34, 35]. Newly compiled NHANES data indicate that approximately 65% of the American population is Mg deficient [36]. Low Mg content in drinking water, found in areas of soft water and Mg-poor soil, is associated with high incidences of ischemic heart disease (IHD), severe atherosclerosis, coronary vasospasm, hypertension, hyperlipidemia, and sudden-cardiac death [37- 44]. The myocardial level of Mg has consistently been observed to be lower in subjects dying from IHD and sudden-cardiac death in soft water areas [9, 13, 16, 17, 24, 39, 43].

Using sensitive, specific Mg^{2+}- ion electrodes, it has been shown that patients with IHD, patients scheduled for cardiac surgery or lung surgery, patients in cardiac failure, and patients with severe atherosclerosis exhibit significant depletion of serum/plasma and tissue levels of ionized, but not usually total Mg [15, 27, 33, 45-65]. Moreover, dietary deficiency of Mg, under very controlled laboratory conditions, in rats and rabbits has been shown to cause vascular remodeling concomitant with atherogenesis and hypertension (e.g., arteriolar wall hypertrophy and alterations in arterial wall matrices) of unknown origin [67-69].

Mg^{2+} modulates sphingolipid pathways in cardiac and vascular smooth muscle cells

Although Mg depletion has long been known to result in cellular Ca^{2+}-overload in cardiac and vascular smooth muscles (VSM) [70-73], and Mg can act as a natural Ca^{2+} channel blocker [71-73], recent studies indicate that Mg^{2+} modulates sphingolipid pathways in both cardiac and VSM cells [27, 43, 44, 74-86]. Ceramides are sphingolipids known to be released as a consequence of sphingomyelinase (SMase) acting on sphingomyelin (SM), a component of all cell membranes, or as a consequence of the activation of serine palmitoyl transferase 1 and 2 (SPT 1 and SPT 2) (a *de novo* synthetic pathway) [87]. Ceramides are now thought to play important roles in fundamental processes such as inflammation, angiogenesis, membrane-receptor functions, cell proliferation, microcirculatory functions, cell adhesion, immunogenic responses, excitation-contraction coupling events in smooth muscles, and cell death (i.e., apoptosis) [27, 43, 44, 74-92]. SPT 1 and SPT 2 are the rate-limiting enzymes in the biosynthesis of sphingolipids [87]. More than 25 years ago, it was first demonstrated that SPT activity was increased in aortas of rabbits fed a high-cholesterol diet [93]. A short time after these latter studies were published, two of us showed that dietary deficiency of Mg, in levels found commonly in Western World diets, vastly increased atherosclerotic plaque formations in rabbits fed high -cholesterol diets, whereas high dietary levels of Mg inhibited plaque formations [28]. SPT is a hetrodimer of 53-kDa SPT-1 and 63-kDa SPT-2 subunits [87], both of which are bound to the endoplasmic reticulum [94]. An upregulation of SPT has been hypothesized to play a role in apoptosis, cell death events taking place in atherogenesis [79, 95].

Recently, we reported that Mg deficient (MgD) diets given to rats for only 21 days results in upregulation of SMases (i.e., N-SMase, acid--SMase, and alkaline SMase), ceramide synthase, sphingomyelin synthase, SPT-1 and SPT-2 in a variety of cardiovascular tissues and cells as well decreased levels of SM and phosphatidylcholine (PC) [79-82, 84-86]. We also noted that MgD diets resulted in fragmentation of DNA [81, 86, 96], release/ generation of a number of cytokines (and chemokines) [84], a release of cytochrome C [80] and lactic acid dehydrogenase [82], an increased expression of apototic protease factor-1 [81, 84], an activation of caspase-3 (needed for cell death) [79], all hallmarks of atherogenesis. When specific inhibitors of the SMases and SPT-1 (and SPT-2) were utilized, in primary cell cultures of VSM cells (including those from coronary arteries), exposed to low Mg^{2+} environments, we noted an inhibition and release of ceramides, inhibition of DNA fragmentation, inhibition of release of cytochrome C from the mitochondria, reduced expression of protease factor-1, an inhibition of activation of caspase-3, a decreased release of lactic acid dehydrogenase from the heart, reduced lipid peroxidation of cardiac muscle cells, and attenuation of release/generation of cytokines and chemokines [79-82, 84-86, 96, 97]. Working with perfused rat hearts, our laboratories found that low Mg^{2+} environments caused decreased perfusion pressures, decreases in stroke volume, marked decreases in coronary arterial flows, decreases in cardiac output, generation of ceramides, reductions in cardiac cellular ATP, phosphocreatine and pH [98] and generation of reactive oxygen species [99]. We, thus, believe that , collectively, these new studies on hearts and coronary arteries 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 arterial (and coronary microcirculatory) ischemic changes, eventuating in inflammatory and atherogenic events producing atrial arrythmias and fibrillation.

During the performance of the foregoing *in-vivo* and *in-vitro* studies , using proton- nuclear magnetic resonance spectroscopy, we noted rapid formation of platelet-activating factor (PAF) and PAF-like lipid molecules [74].

Magnesium deficient environments lead to formation of PAF and its potential significance to atrial fibrillatory events

PAF is known to play major roles in inflammatory responses and atherogenesis [for reviews, see [100-102]]. In addition, PAF is known to affect the heart and cardiac muscle cells in numerous ways [for reviews, see [101, 102]]. For example, PAF can produce coronary arterial vasoconstriction, lower arterial blood pressure, increase coronary vascular resistance, release several lipid-like molecules from the heart, reduce cardiac output, decrease cardiac contractility, alter atrial and papillary muscle chronotropicity and membrane action potentials, as well as alter potassium currents in isolated cardiomyocytes [for reviews, see [101, 102, 103]]. All of these attributes of PAF's actions on the heart and coronary vascular tree certainly would be more than enough to cause profound atrial fibrillation. Moreover, a variety of the circulating blood formed elements (e.g., polymorph nuclear leukocytes, platelets, basophils, and macrophages) and endothelial cells can elaborate PAF [101, 102]. Recently, we have found that coronary, cerebral and aortic VSM cells can also elaborate and release PAF [103]. There are a growing number of reports that both PAF and ceramides may result in transformation of VSM cells from one phenotype to another, as is typically found in the atherosclerotic process [for reviews, see [103-106]]. A number of investigators employing intravital microscopy techniques, similar to those used in our laboratories [for review, see [103]] have demonstrated that PAF increased the number of white blood cells in the microvessels concomitant with intense vasoconstriction-spasms with increasing concentrations of the putative lipid mediator (i.e., PAF), less leukocyte rolling , and increased adherence of the leukocytes to the endothelial surfaces with increased vascular-capillary permeability [for review, see [103]]. Using open and closed chambers implanted in rodent cerebral cortex and skeletal muscles, we have observed similar phenomena [103]. Interestingly, we have reported that ceramides produce almost similar phenomena in a variety of microvascular beds when studied by high-resolution video microscopy [78, 103]. Collectively, these older and newer experimental studies could be used to advance our hypothesis that generation and release of both PAF and ceramides with underlying MgD states are more than likely involved in generation of atrial fibrillation after cardiac and lung surgery and may be major contributors in other types of patients presenting with atrial fibrillation.

Importance of Mg supplemented drinking water and beverages for heart health

Over the past two-plus decades, our laboratories have been investigating the utility of Mg-supplemented or naturally-occurring spring waters to avoid the pitfalls of dietary-and/or metabolically-induced MgD-states which affect heart health [e.g., see [79-82, 84-86, 96, 97]. Our results, so far, bolster the idea that water intake (e.g., from tap waters, well waters, bottled waters, beverages using tap/well/spring waters, or desalinated waters) in humans should contain at least 25-40 mg/liter/day of Mg^{2+} [107]. A number of experiments done in our labs indicate that most, if not all of the cardiovascular manifestations (i.e., decreased cardiac output, decreased coronary arterial flows, lipid peroxidation of cardiac muscle membranes, synthesis/release of toxic sphingolipids, cytokines and chemokines, mitochondrial release of cytochrome C, increased Ca^{2+} entry and overload,

apoptosis, etc) observed in hearts of experimental animals can be prevented or ameliorated when imbibing drinking waters with appropriate amounts of Mg^{2+} [79-82, 84-86, 96, 97]. We believe the latter inclusion in our diets should go a long-way towards the prevention and amelioration of heart arrthymias and fibrillations . Instituting such a daily regimen should also prevent a number of underlying risk factors for PAOF (e.g., drinking of alcoholic beverages, excessive smoking, and aging). Interestingly, on the basis of our work in animals, the World Health Organization has suggested people should consume drinking waters containing our recommended 25-40 mg/liter/day of Mg^{2+} [108]. It is our hope that a large scale appropriately-controlled clinical trial can be instituted in patients scheduled for cardiac and lung surgeries to test our hypothesis.

Future considerations

Although the exact underlying cause(s) of the high frequency of PAOF in patients scheduled for heart or lung surgeries remains to be determined, a number of animal models (in mice, goats, rabbits and dogs) have been utilized to gain insights into possible causes of atrial fibrillation (AF) [for reviews, see [2, 4, 5]]. A number of these models have employed knock-out and knock-down mice for several potential target genes . Several of these mouse AF models could be examined to determine if they are MgD (particularly decreased ionized Mg levels) and have excess PAF and ceramide synthesis and release as a test of our hypothesis. In addition, a clinical study should be undertaken to determine ionized Mg levels, ceramide levels, and PAF levels prior to and after cardiac and lung surgeries to examine any correlations between these parameters before (and after surgeries) to frequency of PAOF. Moreover, it would be prudent, we believe, to undertake clinical blinded- trials to determine whether pretreatment of patients, scheduled for cardiac or lung surgery, would benefit from pretreatment with selective blockers of ceramide generation/release and PAF generation/release along with administration of oral and intravenous Mg. Only time will tell whether these human and animal studies will prove to validate our hypothesis.

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51