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# Why Do Chemotherapeutic Drugs and Radiation Induce Cardiomyopathy and Cardiac Failure in Cancer Patients: Is This a Consequence of Unrecognized Hypomagnesemia and Release of Ceramides and Platelet-Activating Factor?

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# Why Do Chemotherapeutic Drugs and Radiation Induce Cardiomyopathy and Cardiac Failure in Cancer Patients: Is this a Consequence of Unrecognized Hypomagnesemia and Release of Ceramides and Platelet-Activating Factor?

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## Ever since the earliest

use of platinum –based drugs having been given to cancer patients, there has been recognition of an increased incidence of cardiac failure and cardiomyopathy [ see 1-3]. Radiation- based therapy, either alone or more likely combined with chemotherapeutic drugs, has also been associated with cardiac failure and cardiomyopathy [4-11]. Although a patient may want to accept temporary occurrence of cardiac and cardiovascular dysfunctions of various types (e.g., QT prolongation, left ventricular dysfunctions, arrhythmias, fibrillations[ e.g., atrial fibrillation-AF], coronary ischemia, coronary vasospasm, pulmonary hypertension, myocardial infarctions, elevation in arterial blood pressure, congestive heart failure, venous and arterial thrombo-embolism, diastolic or systolic dysfunctions, coronary arterial inflammations, pericardial disease, and/or accelerated atherogenesis, etc.) for a higher potential of a cancer cure, the risk for cardiac failure or cardiomyopathy increases with dosing of many platinum-based chemotherapeutic drugs(PBCDs), aminoglycosides like amphotericin B as well as anthracyclines(e.g., doxorubicin), and antimetabolite agents like 5-fluorouracil [1-11]. It should be pointed out that many of these cardiovascular events occur after prolonged PCBDs , amphotericin B, anthracyclines, alkaloids(e.g., vinblastine), anti-tumor antibiotics(e.g., bleomycin) , cyclophosphamide or radiation treatment. Even treatment with a variety of the newer anti-angiogenic drugs such as the antibodies like bevacizumab, sorafenib, and sunitinib have been associated with cardio-and cardiovascular toxicities similar to the PBCDs, anthracyclines, amphotericin B and cyclophosphamide [4-11]. More recently, use of the small-molecule tyrosine kinase inhibitors, multiple tyrosine kinase inhibitors, monoclonal antibodies to HERS2, as well as proteasome inhibitors (e.g., bortezomib, carfilzomib) have also been associated with increased incidences of cardio-toxicities [5-11]. Why, however, do these structurally, diverse chemotherapeutic drugs and radiation induce cardiac toxicity, unexplained coronary vasospasm, congestive heart failure, cardiomyopathy, and complete cardiac failure followed by death?

Almost four decades ago [13], two of us pointed out that there was a scattered number of clinical studies that were beginning to indicate that at least three of the chemotherapeutic drugs (i.e., cisplatin, vinbastine, and bleomycin) appeared to suggest that chemotherapeutic anticancer drugs may deplete the body of magnesium(Mg) [for references and review, see 1-3,12 ]. Ever since we suggested the potential danger of these drugs to the heart and cardiovascular system[13], a growing body of evidence has borne-out these initial dangers to cancer patients[e.g., for reviews see 4-11]. It appears from recent

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studies that cancer patients receiving cardiac transplants, who had taken chemotherapeutic drugs and/or radiation often showed unexplained, worsened depletion of Mg [for recent review, see 12]. How and why could depletion of body Mg stores, and Mg depletion from the heart and blood vessels, cause cardiac arrhythmias, elevated arterial blood pressure , prolonged QT intervals, coronary arterial vasospasm, myocardial ischemic events, myocardial infarctions, and sudden-cardiac death (SCD) ?

## Relationship of Mg to Cardiac Stabilization and Function, Hypertension, Cardiomyopathy, and Sudden-Cardiac Death

Over the past four decades, evidence has accumulated to indicate that daily dietary deficiency of Mg intake and/or errors in Mg metabolism pose serious risks for development of AF, hypertension, atherosclerosis, inflammation, endothelial cell dysfunctions, dysfunctions of cardiac bioenergetics, coronary arterial vasospasm, myocardial infarctions, coronary ischemic events, cardiomyopathy, cardiac failure, strokes and SCD[13-53], whereas higher than normal Mg intake is found to be associated with decreased or ameliorated AFs, myocardial infarctions, hypertension, strokes, and incidences of cardiomyopathies and SCD[16-33]. Moreover, there is a growing, scattered literature which suggests that cancer patients pretreated with Mg have less cardiotoxic events after chemo-or radiation treatment [2, 12]. Mg is a co-factor for more than 500 enzymes, and is the second most abundant intracellular cation after potassium and is a critical requirement for regulation of $Ca^{2+}$, $Na^{+}/K^{+}$ transport across all cell membranes [54]. It is vital in numerous physiological, cellular and biochemical reactions including carbohydrate, lipid, protein, DNA and RNA metabolism, membrane ion transport, among other pathways [19,22,27-33,36,37,42,46,49,51,52,54 ]. Several epidemiologic studies in North America and Europe have shown that people consuming Western-type diets are low in Mg content(i.e., 30-45 % of the RDA for Mg) [13,54-59]; most such studies in the USA show that 60-80% of Americans are consuming 185-235 mg/day of Mg [31,51,54-59]. In1900, in contrast, most Americans were consuming 450-550 mg/day of Mg [ 31,51 ]. Low Mg content of drinking water , found in areas of soft-water and Mg-poor soil, is associated with high incidences of ischemic heart disease(IHD), atherosclerosis, coronary ischemia, hypertension, and SCD [13-17,21,28,31,51,55,56]. The myocardial level of Mg has consistently been observed to be lower in subjects dying from IHD and SCD in soft-water areas than those subjects living in hard-water areas [14-17, 21,28,31,55, 56 ]. More than 45 years ago, two of us demonstrated that $Mg^{2+}$ behaves as a natural calcium channel blocker in both cardiac and vascular smooth muscle (VSM) cells [19, 60-65]. We also showed that Mg behaves as a natural statin drug as it can lower cholesterol and trigyceride levels as well as act as a powerful vasodilator in the microcirculation, on coronary arteries and arterioles, and as cardiac muscle relaxant [16-19,23,27-33,36,48,50,66-68; unpublished findings ]. Hypermagnesemic diets have been shown to ameliorate hypertension and atherogenesis as well as lower the incidences of arrhythmias and strokes [13, 20,28,31-33,44,49,51, 69-86 ].

## Use of $Mg^{2+}$ Ion-Selective Electrodes in Diseased Patients

Using sensitive and newly-designed specific $Mg^{2+}$-ion selective electrodes, our laboratories demonstrated that patients with hypertension, IHD, cardiac failure, ischemic and hemorrhagic strokes, blood loss, and atherogenesis exhibit significant reductions in plasma/serum/whole blood levels of ionized Mg [39, 40,51, 87-101]. Other experiments on cancer patients receiving a variety of the chemotherapeutic drugs mentioned, above, also demonstrate marked reductions in serum ionized Mg levels[for reviews, see 102]. We have shown that dietary deficiencies in Mg in rabbits and rats cause vascular remodeling(i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls) concomitant with atherogenesis, high blood pressure, and microvascular vessel vasospasm . Such events in cancer patients receiving the variety of chemotherapeutic drugs, discussed above, could easily account for cardiotoxic and cardiovascular disturbances seen with these drugs leading to cardiomyopathy , cardiac failure, and SCD.

## Low $[Mg^{2+}]_0$ Environments Result in Concentration-dependent Coronary Arterial Vasospasm, Increased Vascular Reactivity to Endogenous Vasoconstrictor Agents, and Dysfunctions of Cardiac Hemodynamics

Approximately 40 years ago, our group found that declining levels of extracellular $Mg^{2+}$($[Mg^{2+}]_0$) resulted in concentration-dependent constriction and vasospasm of small (<100 um in diameter), medium and large coronary arteries excised from dogs, sheep, baboons and rats . These

low $[Mg^{2+}]_0$-induced vasospasms could only be attenuated or inhibited with elevated concentrations of $Mg^{2+}$. In addition, we noted that low $[Mg^{2+}]_0$ levels enhanced vasoconstrictor responses to a variety of vasoactive and neurohumoral transmitters (e.g., angiotensin II, serotonin, norepinephrine, multiple peptides, etc.). We suggested, at that time, that low dietary levels of Mg could result in arrhythmias, IHD and SCD . Ever since these early studies were published, a number of clinical studies have been published which support our hypothesis . Using perfused , working rat hearts, we found that low levels of $Mg^{2+}$ result in reductions in coronary flows, reductions in cardiac output, reductions in stroke volume and peak systolic pressure development, reductions in myocardial intracellular $Mg^{2+}$ levels, reduction in myocardial levels of ATP, increased levels of inorganic phosphate, acidification of atrial and ventricular myocytes, $Ca^{2+}$ overload, and generation of powerful reactive oxygen and nitrogen species (e.g,$H_2O_2$, hypochlorite ions, hydroxyl ions, ferrylmyoglobin, etc.) . Taken together, such results, in themselves, could account for chemotherapeutic drug-induced AF, myocardial ischemia, coronary vasospasm, prolonged QT intervals, increased vascular tone and pressures, IHD, and SCD. But, added to these events are the multiple effects of low $[Mg^{2+}]_0$ on intravessel inflammatory dynamics such as leukocytic, monocyte and platelet sticking to endothelial cell walls, increased postcapillary changes in vascular permeability, vasoconstriction in the coronary microcirculation, increased release of cytokines and chemokines, release of antibodies of diverse types, and release of complement proteins.

## $Mg^{2+}$ Regulates Sphingolipid Pathways in Cardiac and Vascular Smooth Muscle Cells

Recent studies, from our laboratories, indicate that $Mg^{2+}$ can modulate sphingolipid pathways in both cardiac and vascular smooth muscle (VSM) cells . Ceramides are sphingolipids known to be released as a consequence of sphingomyelinases (SMases) acting on sphingomyelin(SM), a component of all extra- and intracellular 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) . Ceramides are now known to play important, and key, roles in fundamental pathophysiological processes such as inflammation, angiogenesis, atherogenesis, membrane-receptor functions, cell proliferation, microcirculatory functions, cell adhesion, immunogenic responses, excitation-contraction coupling events in cardiac and VSM cells, and cell death (i.e., apoptosis) . An upregulation of SPT 1 and SPT 2 has been hypothesized to play an important role in apoptosis cell death events taking place in atherogenesis . Such upregulation could be quite pivotal in producing plaques on the endothelium of coronary vessels leading to ischemic events , IHD, and SCD observed in cancer patients treated with diverse chemotherapeutic agents . Working with perfused rat hearts, we have noted incremental rises in ceramides as the $[Mg^{2+}]_0$ was reduced concomitant with decreases in stroke volume, increased levels of lactic acid dehydrogenase and creatine phosphokinase, increased lipid peroxidation of cardiac muscle cells, reduction of cardiac intracellular pH, and generation of reactive- oxygen and nitrogen species . Preliminary experiments , with perfused hearts given increasing doses of doxorubicin yield very similar results [ unpublished findings].

It is of considerable interest to note, here, that, experimentally, myocardial infarctions have recently been shown to be associated with rising levels of ceramides . In human subjects,it has been reported that stable angina pectoris, unstable angina pectoris, and acute myocardial infarction are also associated with rising levels of ceramides . In some of these patients, a clear elevation in SMases was observed along with a reduction in SM .

During the performance of our foregoing in vitro and in vivo low $[Mg^{2+}\}_0$ experiments, using proton-nuclear magnetic resonance spectroscopy, we noted a rapid formation of platelet-activating factor (PAF) and PAF-like lipid molecules.

## $Mg^{2+}$-Deficient Environments Lead to Formation of PAF and PAF-like Lipids: Potential Significance to Chemotherapeutic – induced Ischemic Cardiac Events

PAF is now known to play major roles in inflammatory responses, blood pressure and atherogenesis . In addition, PAF and PAF-like lipids are known to affect the heart and cardiac muscle cells in numerous ways For example, PAF can produce coronary arterial vasoconstriction, alter arterial blood pressure, increases 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. All of these attributes of PAF's actions on the myocardium and the coronary vascular tree would be more than enough to cause profound atrial and ventricular fibrillation, and SCD. Moreover, a variety of the circulating blood-formed elements (e.g., polymorph nuclear leukocytes, platelets, basophils, and macrophages) can elaborate PAF and PAF-like lipids. Recently, we have reported that coronary, cerebral and aortic vSM cells as well as atrial and ventricular cardiac myocytes can also elaborate PAF , particularly when the diverse cells are exposed to low $[Mg^{2+}]_0$ levels. A number of investigators employing intravital microscopy techniques, similar to those used in our laboratorieshave demonstrated that PAF increased the numbers of white blood cells in the microvessels concomitant with intense vasoconstriction-spasms with increasing concentrations of the putative lipid mediator (i.e., PAF), and less leukocyte rolling along the endothelial cell surfaces wth increased venular-postcapillary permeability Interestingly, we have found that ceramides can produce almost identical phenomena in a variety of microvascular beds, in vivo, when studied by high-resolution video microscopy . We believe rather firmly, that these older and newer experimental studies could be used to advance our hypothesis that generation and release of both PAF(and PAF-like lipids) and ceramides due, in large measure to chemotherapeutically- and diet-induced Mg-deficiency, are more than likely involved in generation of anti-cancer drug-induced cardiomyopathy, IHD, coronary vasospasm , and SCD.

## Importance of Dietary Mg Supplementation for Prevention and Amelioration of Chemotherapeutic Anti-Cancer Drug –induced Cardiomyopathy, Cardiac Failure and SCD

Over the past 30 years , our laboratories have been investigating the utility of using $Mg^{2+}$ ion-selective electrodes and Mg-supplemented or naturally-occurring Mg-enriched spring waters to avoid the pitfalls of dietary- and/or metabolically-induced Mg-deficient states which affect heart health . Our results, to date, with the $Mg^{2+}$-electrodes ( to accurately measure ionized Mg levels), bolster the idea that water intake(e.g., from tap waters, well waters, bottled waters, beverages using tap/well/spring waters, or distilled waters) in humans should contain at least 25-40 mg/liter/day of $Mg^{2+}$. A number of studies done in our labs indicate that most, if not all of the cardiovascular manifestations (i.e.,decreased cardiac output, decreased coronary flows, decreased myocardial contractility, lipid peroxidation of cardiac and coronary VSM cell membranes, synthesis/release of toxic ceramides , PAF, cytokines, and chemokines , as well as $Ca^{2+}$overload, myocardial acidification, loss of ATP, and apoptosis) observed in hearts of experimental animals fed low dietary Mg intake, can either be prevented or greatly ameliorated when the animals imbibe drinking waters with appropriate amounts of $Mg^{2+}$. We are convinced the latter inclusion in our diets and those of all cancer patients should go a long-way towards the prevention and amelioration of atrial and ventricular arrhythmias, decreased cardiac output and contractility, increased coronary vascular resistance, hypertension, and cardiac ischemic events leading to IHD and SCD. In this context, it is of particular interest to note that several clinical studies have shown some positive effects of Mg therapy( either prophylactic or orally administered) in several types of cancer patients treated with PBCDs.

## Conclusions

Although the exact cause(s) of PBCD-induced cardiomyopathy, cardiac failure and SCD in cancer patients is not known, $Mg^{2+}$-depletion is clearly observed in many of these treated subjects. Experimentally, low dietary intake of Mg or animals given PBCDs demonstrate most, if not all, of the pathophysiological cardiovascular effects observed in cancer patients given these antitumor drugs. Generation/ release of ceramides and PAF, as well as PAF-like lipids, appear to be critically-involved in the cardiovascular effects of Mg-deficiency and most likely in PBCD-indiuced cardiac manifestations in patients. In view of our data, and hypothesis, it would probably be prudent to undertake clinical trials to determine if antagonists of SMases, SPT 1 and SPT 2, as well as antagonists of PAF would, along with Mg supplementation, reduce markedly the incidence and severity of cardiac problems in patients treated with PBCDs.

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