Sudden Cardiac Death in Infants, Children and Young Adults: Possible Roles of Dietary Magnesium Intake and Generation of Platelet-Activating Factor in Coronary Arteries

Altura BM[1-6]*, Li W[1], Zhang A[1], Zheng T[1], Shah NC[1,5], Shah GJ[1], Yang ZW[1], Perez-Albela JL[7] and Altura BT[1-6]

[1]*Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[2]*Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[3]*Center for Cardiovascular and Muscle Research, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[4]*The School of Graduate Studies in Molecular and Cellular Science, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[5]*Bio-Defense Systems, Inc, Rockville Center, New York, USA*

[6]*Orient Biomedica, Estero, Florida, USA*

[7]*Instituto Bien Salud, Lima, Peru*

*Corresponding author: Altura BM, Department of Physiology, Pharmacology & Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York 11203, USA, Tel: 718-270-2194; **E-mail:** baltura@downstate.edu

Abstract

Magnesium (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 and systems necessary for life. Approximately 35 years ago, our laboratory suggested that a progressive, dietary deficiency and/or metabolic induced loss of Mg from the body, beginning early in life, particularly during development of the coronary arteries, could lead to coronary arterial vasospasm, ischemic heart disease, and sudden-cardiac death (SCD). Herein, we review evidence for a brand-new, novel hypothesis which combines knowledge suggesting a combined role for hypomagnesemia and platelet-activating factor (PAF) which may provide insights into unexplained SCD in infants, children, and young adults. This review documents what takes place in the cardiovascular system when the body and its tissues are subjected to lower than normal dietary Mg intake, and also provides new evidence for a series of heretofore unknown actions of PAF that are most likely involved and/or trigger coronary arterial vasospasm in the presence of low concentrations of ionized Mg levels. The roles of vascular remodeling, NF-κB and proto-oncogenes are considered to play major roles in this hypothesis.

Keywords: Magnesium deficiency; SIDS; Atherogenesis; Nuclear factor-κB; Proto-oncogenes; Coronary vasospasm; Cardiovascular diseases; PAF

Introduction

Approximately 35 years ago our laboratory suggested that a progressive, dietary deficiency and/or a metabolic-induced loss of magnesium (Mg) from the body beginning early in life, particularly during development of the coronary arteries, could lead to coronary arterial vasospasm, ischemic heart disease, and sudden cardiac death (SCD) [1,2]. Ever since this work was published, a number of clinical studies have been done and published which support this hypothesis, at least in adults [3-10]. However, little or no studies have been published to either confirm or deny this hypothesis in either infants or young children.

Autopsies of children, who have died as a consequence of accidents, have often demonstrated early signs of atherogenesis (e.g., fatty streaks on the walls of the aorta and carotid arteries in young children as early as six years of age) [11]. It should be noted that atherosclerosis is the number-one cause of premature death in developing countries, including the United States and plays a major role in etiology of hypertension and strokes.

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 [11-16]. Reduction in dietary Mg intake has been demonstrated, experimentally, to result in hypertension [17-20], atherogenesis [15,21-27], and stroke [15,27-34]. Hypermagnesemic diets have been shown to ameliorate hypertension, atherogenesis, stroke and certain inflammatory responses [34-41]. 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 [42,43]. Newly compiled USA NHANES data indicate that approximately 65% of the American population is Mg deficient [44]. Several epidemiologic studies in North America and Europe have shown that children and adults consuming Western-type diets are low in Mg content as are pregnant women (i.e., 30-50% of the RDA for these populations) [42-44].

Low Ionized Mg measurements in Serum: Relationship to Ischemic Heart Disease and Vascular Remodeling

Using sensitive, specific Mg^{2+} - ion selective electrodes, it has been shown that patients with ischemic heart disease, essential hypertension, renal-diseased induced hypertension, and strokes exhibit significant depletion of serum and cellular ionized Mg^{2+}, the physiologically-active Mg [14,25,29-32,45-54]. In addition, we have shown that pregnant women with gestational diabetes, preeclampsia, and difficult labors also demonstrate depletion of serum as well as cellular levels of ionized Mg^{2+} [48,49,52-54]. Such low levels of ionized Mg, when mimicked *in vitro*, result in spasms of peripheral, coronary, placental, neonatal, and cerebral vascular smooth muscle (VSM) cells, rapid cellular influx and intracellular release of free Ca^{2+}, well as increasing vascular reactivity to numerous neurogenic and humoral molecules [2-4,14,19,25-31,55-62]. Dietary deficiency of Mg in rats has been shown to not only cause hypertension [17,20], but to also cause vascular remodeling (i.e., arteriolar wall hypertrophy of unknown origin), rarefaction of capillaries (known itself to result in hypertension) [18], stiffening of arterial walls [20], as well as release of cytokines and chemokines (involved in inflammatory and atherogenic responses) [63-65].

Magnesium Deficiency Results in Activation of NF-κB and Proto-Oncogenes

The nuclear factor-kappa B (NF-κB) and proto-oncogenes (e.g., c-fos, c-jun) are two major regulators of growth, differentiation, cell migration, and cell death (e.g., apoptosis) [66-69]. NF-κB is a transcription factor and a pleiotropic regulator of numerous genes involved in inflammatory responses, hypertension, and atherogenesis [12,66,67,69]. Both NF-κB and the proto-oncogenes are thought to be pivotal in numerous vascular disease processes such as inflammation, atherogenesis, hypertension, and ischemic heart disease [12,66,67,69]. It is, however, not clear as to what initiates expression of these molecular and cellular events, particularly with respect to how Mg deficiency impacts on these vascular events and how low Mg causes (or predisposes to) hypertension, intense vasospasm, inflammation, stroke-like events, cardiac failure , and SCD. Experiments performed *in-vitro* and *in-vivo* on cells and living animals have demonstrated that short-term magnesium deficiency (MgD) results in formation/activation of NF-κB and the proto-oncogenes in cardiovascular tissues and VSM cells [14,25,26,64,65,70].

Sudden Cardiac Death is a Growing World-wide Problem

Sudden infant death syndrome (SIDS) has become a significant problem without an agreed-upon pathological mechanism(s) [71-76]. Explanations run the gamut from hypoxia, gene mutations, cardiac conduction abnormalities, inherited channelopathies, unknown infections, diaphragmatic dysfunctions, central hypoventillation, susceptibility to ventricular arrhythmias, etc.. Pediatric sudden cardiac arrest likewise seems, for the most part, to be a growing problem around the world with little in the way of an acceptable pathogenic mechanism(s) [71-76]. SCD accounts for approximately 20% of nearly all deaths in Western countries with multiple possible, but little agreed-upon explanations. SCD in the young (<35 yrs of age) has a structural/genetic basis in only about 20% of all cases in the Western World. In most of these SCD cases, there is no structural/pathological evidence for any heart abnormalities on autopsies [71-76].

Studies of Isolated Adult Mammalian and Human Coronary Arteries as well as Neonatal Piglet Coronary Arteries demonstrate Intense Vasospasm on Reduction in Extracellular Mg

Approximately 35 years ago, our laboratories reported that mammalian coronary arteries from neonates as well as adults (including those obtained from humans) demonstrate intense vasospasm as extracellular Mg^{2+} ($[Mg^{2+}]_0$) concentrations are lowered progressively in *in-vitro* studies; the lower the reduction in $[Mg^{2+}]_0$, and the smaller the coronary arterial vessel, the more intense the coronary arterial vasospasm [2-4,14,25-31,55-62]. No vasodilator, including Ca^{2+} channel blockers can effectively alleviate these intense coronary vasospasms. These contractile actions of low Mg^{2+} are potentiated in the presence of neurohumoral and circulating vasoconstrictor agents, such as angiotensin II, vasopressin, serotonin, norepinephrine, and a variety of pressor peptides. Coronary arterial vessels, particularly small ones (<100 μm in diameter) obtained from neonatal piglets are exquisitely sensitive to low $[Mg^{2+}]_0$ levels. On the basis of our studies on the neonatal piglet coronaries, we suggested almost 20 years ago, that low $[Mg]_0$ could play an important role in SIDS and SCD [77]. Collectively, such findings lead us to conclude that low dietary Mg levels in pregnant women, infants and children must be taken into consideration as a major underlying mechanism for unexplained SCD in infants, children and young adults.

Low Serum Ionized Magnesium Levels found in Infants and Children in the USA

In view of the above evidence and hypothesis, it is of considerable interest to point out, here, that several studies, including those done in our laboratories, have been published which indicate that infants and children in the USA demonstrate a much higher percentage of abnormally lowered serum total and ionized Mg levels when compared to adults 35-60 years of age [14,45,48,49,78-81]. Moreover, our studies on infants, children and pregnant women have shown a high percentage of abnormally low serum ionized Mg levels as well [14,52-54,82-84]. Taken together, we believe such clinical studies, collectively, provide substantial evidence for our hypothesis that unexplained SCD in infants and children possibly is due, in large measure, to abnormally low serum as well as low VSM and cardiac myocyte Mg^{2+} levels. With respect to the latter, we have shown, working with perfused rat hearts, that even short-term MgD results in reductions in a variety of hemodynamic functions, i.e., cardiac output, coronary flows, stroke volume, developed pressures, and cellular high-energy phosphate levels with concomitant Ca^{2+} overload [85]. In 1996, we demonstrated on hearts excised from rats given low Mg diets that Mg depletion impairs carbohydrate metabolism and lipid metabolism and results in cardiac calcium overload [86]. We showed more than 40 years ago that Mg^{2+} blocks the entry and intracellular release of Ca^{2+} from both VSM and cardiac myocytes [55,57,59,86-88]. This together with the adverse effects on both cardiac hemodynamics and energy production (and utilization) would perforce seriously compromise young hearts and result in SCD.

Is Genesis and Release of Platelet-Activating Factor (PAF) the Major Downstream Signal for induction of Coronary Arterial Vasospasm seen in Low Mg Environments?

Approximately 18 years ago, we reported that reduction of extracellular Mg^{2+} levels resulted in generation of variety PAF-like lipids, as seen with proton nuclear magnetic resonance spectroscopy [87]. At that time, we suggested that one or more of these PAF-like molecules may be an initiator of low Mg^{2+}-induced arterial vasopasm and atherogenesis [87]. Over the intervening two decades, we have found that peripheral, cerebral and coronary arterial vessels, including neonatal coronaries, undergo contraction in the presence of low concentrations (<10^{-6} M) of PAF by acting on specific VSM membrane PAF receptors [88]. Moreover, the intense arterial vasospasms observed as $[Mg^{2+}]_0$ is lowered can be dramatically attenuated in the presence of specific PAF- membrane receptor blocking drugs [88]. In addition, our new findings indicate that as $[Mg^{2+}]_0$ is lowered, a rapid (within seconds) generation and release

of PAF is observed in the cultured VSM cells, including those obtained from neonatal piglets [88]. PAF is now thought to be an important, maybe critical, molecule in etiology of inflammatory conditions and atherosclerosis [89-91]. We thus believe that our new findings suggest major roles for MgD and PAF formation (and PAF-like lipids) in the cardiovascular manifestations of MgD, inflammation, atherogenesis, and SCD in children.

Approximately 40 years ago, Russell Ross and colleagues [92] advanced the hypothesis that atherosclerosis is an inflammatory disease brought about by injury to the endothelial surfaces of blood vessels in the macro- and microcirculations. The hypothesis stated that different forms of injury (including hypoxia and ischemia) will result in numerous dysfunctions in the homeostatic properties of the blood vessels and the underlying vascular smooth muscle cells, e.g., adhesiveness of leukocytes and/or platelets, formation/release of cytokines/chemokines and growth factors; all of these entities needed for atherogenesis are produced in MgD states. We believe low $[Mg^{2+}]_0$ environments act as triggers to induce local hypoxic and ischemic events within the macro- and microcirculations to initiate inflammatory-atherosclerotic sites via initial generation and release of Ca^{2+} and PAF. These events could be expected to take place in developing fetuses in-utero and after birth. Since most diets consumed in the Western World are deficient in Mg by as much as 65% below the RDAs for adults, infants and the young, such circumstances would perforce result in inflammatory conditions, vasospams, atherogenesis, and SCD.

Conclusions

This article reviews the evidence for a brand-new, novel hypothesis which combines evidence suggesting a combined role for hypomagnesemia and PAF which may provide insights into unexplained SCD in infants, children, and young adults. This report not only documents what takes place in the cardiovascular system when the body and its tissues are subjected to lower than normal dietary Mg intake, but provides new evidence for a series of heretofore unknown actions of PAF that are most likely involved and/or trigger arterial vasospasm in the presence of low $[Mg^{2+}]_0$ and probably is a major trigger for unexplained SCD.

References

1. Altura BM (1979) Sudden-death ischemic heart disease and dietary magnesium intake: Is the target site coronary vascular smooth muscle? Med Hypotheses 5: 843-848.

2. Turlapaty PMDV, Altura BM (1980) Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. Science 208: 198-200.

3. Altura BM, Altura BT, Carella A (1981) Hypomagnesemia and vasoconstriction: possible relationship to etiology of sudden death ischemic heart disease and hypertensive vascular disease. Artery 9: 212-231.

4. Altura BM, Altura BT (1981) Role of magnesium ions in contractility of blood vessels and skeletal muscles. Magnesium Bull 3: 102-114.

5. Kimura T, Yasue H, Sakaino N, Rokutanda M, Jougasaki M, et al. (1989) Effects of magnesium on the tone of isolated human coronary arteries. Circulation 79: 1118-1124.

6. Goto K, Yasue H, Okumura K (1990) Magnesium deficiency detected by intravenous loading test in variant angina pectoris. Am J Cardiol 65: 709-712.

7. Simko F (1994) Pathophysiological aspects of the protective effect of magnesium in myocardial infarction. Acta Med Hung 50: 55-64.

8. Satake K, Lee JD, Shinizu H, Ueda T, Nakamura T (1996) Relation between severity of magnesium deficiency and frequency of anginal attacks in men with variant angina. J Am Coll Cardiol 28: 897-902.

9. Sueda S, Fukuda H, Watanabe K (2001) Magnesium deficiency in patients with recent myocardial infarction and provoked coronary artery spasm. Jap Circ J 65: 643-648.

10. Minato N, Katayama Y, Sakaguchi M, Itoh M (2006) Perioperative coronary artery spasm in off-pump coronary bypass grafting and its possible relation with perioperative hypomagnesemia. Ann Thorac Cardiovasc Surg 12: 32-36.

11. Berenson GS, Srinivassan SR, Bao W, Newman WP, Tracey RE, et al. (1998) Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 338: 1650-1656.

12. Kumar V, Abbas K, Fasuto N, Aster JC (2010) Robbins and Cotran Pathologic Basis of Disease. 8th Edition Elsevier, New York, USA.

13. Seelig MS (1980) Magnesium in the Pathogenesis of Disease. Plenum, New York, USA.

14. Altura BM, Altura BT (2007) Magnesium: forgotten mineral in cardiovascular biology and angiogenesis. In: Nishizawa N, Morii H, Durlach J (eds) New Perspectives in Magnesium Research, Springer, London, UK.

15. Seelig MS, Rosanoff A (2003) The Magnesium Factor. The Penguin Group, New York, USA.

16. Dean C (2014) The Magnesium Miracle. 3rd Edition, Ballantine Books, New York, USA.

17. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T (1984) Magnesium deficiency and hypertension: correlation between magnesium deficiency diets and microcirculatory changes in situ. Science 223: 1315-1317.

18. Altura BM, Altura BT, Gebrewold A, Gunther T, Ising H (1992) Noise-induced hypertension and magnesium: relationship to microcirculation and calcium. J Appl Physiol 72: 194-202.

19. Altura BM, Altura BT (1978) Magnesium and vascular tone and reactivity. Blood Vessels 15: 5-16.

20. Laurant P, Hayoz D, Brunner HR, Berthelot A (1999) Effect of magnesium deficiency on blood pressure and mechanical properties of rat carotid artery. Hypertension 33: 1105-1110.

21. Altura BT, Brust M, Bloom S, Barbour RL, Stempak JG, et al. (1990) Magnesium deficiency modulates blood lipid levels and atherogenesis. Proc Natl Acad Sci U S A 87: 1840-1844.

22. Ouchi Y, Tabata RE, Stegiopoulos K, Hatori A, Orimo H (1990) Effect of dietary magnesium on development of atherosclerosis in cholesterol-fed rabbits. Arteriosclerosis 10: 732-737.

23. Maier JA (2003) Low magnesium and atherosclerosis: an evidence-based link. Mol Aspects Med 24: 137-146.

24. Ravn HB, Korsholm TL, Falk E (2001) Oral magnesium supplementation induces favorable antiatherogenic changes in ApoE-deficient mice. Arterioscler Thromb Vasc Biol 21: 858-862.

25. Altura BM, Altura BT (1995) Magnesium and cardiovascular risk factors and atherogenesis. Cell Mol Biol Res 41: 347-359.

26. Altura BM, Kostellow AB, Zhang A, Li W, Morrill GA, et al. (2003) Expression of the nuclear factor-kB and proto-oncogenes c-fos and c-jun are induced by low extracellular Mg^{2+} in aortic and cerebral vascular smooth muscle cells: possible links to hypertension, atherogenesis, and stroke. Am J Hypertens 16: 701-707.

27. Altura BT, Altura BM (1982) The role of magnesium in etiology of strokes and cerebrovasospasm. Magnesium 1: 277-291.

28. Altura BM, Altura BT (1994) Role of magnesium in alcohol-induced hypertension and strokes as probed by *in vivo* television microscopy, digital image microscopy, optical spectroscopy and a unique magnesium ion-selective electrode. Alcohol Clin Exp Res 18: 1057-1068.

29. Altura BM, Altura BT (1995) Magnesium in cardiovascular biology. Sci Am Sci Med 2: 28-37.

30. Altura BT, Memon ZS, Zhang A, Cheng TP-O, Silverman R, et al. (1997) Low levels of serum ionized magnesium are found in stroke patients early after stroke which results in rapid elevation in cytosolic free calcium and spasm in cerebral vascular smooth muscle cells. Neurosci Lett 230: 37-40.

31. Altura BM, Altura BT (1996) Role of magnesium in pathophysiological processes and the clinical utility of magnesium ion selective electrodes. Scand J Clin Lab Invest Suppl 224: 211-234.

32. Altura BM, Altura BT (1999) Association of alcohol in brain injury, headaches, and stroke with brain-tissue and serum levels of ionized magnesium: a review of recent findings and mechanisms of action. Alcohol 19: 119-130.

33. Touyz RM (2003) Role of magnesium in the pathogenesis of hypertension. Mol Aspects Med 24: 107-136.

34. Vink R, Cook NL, van den Heuvel C (2009) Magnesium in acute and chronic brain injury: an update. Magnes Res 22: 158-162.

35. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A (2000) Magnesium, an update on physiological, clinical and analytical aspects. Clin Chim Acta 294: 1-26.

36. Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, et al. (2000) Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation 102: 2353-2358.

37. Turgut F, Kanaby M, Metin R, Uz E, Akcay A, et al. (2008) Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis. Int Urol Nephrol 40: 1075-1082.

38. Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Ramirez-Kitchen CM, et al. (2012) Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. J Immunol 188: 6338-6346.

39. Blitz M, Blitz S, Hughes R, Diner B, Beasley R, et al. (2005) Aerosolized magnesium sulfate for acute asthma: a systematic review. Chest 128: 337-344.

40. Kh R, Khullar M, Kashyap M, Pandhi P, Uppal R (2000) Effect of magnesium supplementation on blood pressure, platelet aggregation and calcium handling in deoxycorticosterone acetate induced hypertension in rats. J Hypertens 18: 919-926.

41. King DE, Mainous AG 3rd, Geesey ME, Woolson RF (2005) Dietary magnesium and C-reactive protein levels. J Am Coll Nutr 24: 166-171.

42. Ford ES, Mokdad AH (2003) Dietary magnesium intake in a national sample of US adults. J Nutr 121: 2879-2882.

43. Mosfegh A, Goldman J, Abula J, Rhodes D, La Comb R (2009) What We Eat in America. NHANES 2005-2006: Usual Intakes from Food and Water compared to 1997 Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium. U.S. Department of Agricultural Research, Washington, DC, USA.

44. NHANES 2009-2012 (2016) Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium. U.S. Department of Agricultural Research, Washington, DC, USA.

45. Altura BT, Altura BM (1991) Measurement of ionized magnesium in whole blood, plasma and serum with a new ion-selective electrode in healthy and diseased human subjects. Magnes Trace Elem 10: 90-98.

46. Markell MS, Altura BT, Barbour RL, Altura BM (1993) Ionized and total magnesium levels in cyclosporine-treated renal transplant recipients: relationship with cholesterol and cyclosporin levels. Clin Sci 85: 315-318.

47. Markell MS, Altura BT, Sarn Y, Delano BG, Hudo O, et al. (1993) Deficiency of serum ionized magnesium in patients receiving hemodialysis or peritoneal dialysis. ASAIO J 39: M801-M804.

48. Handwerker SM, Altura BT, Royo B, Altura BM (1993) Ionized magnesium and calcium levels in cord serum of pregnant women with transient hypertension. Am J Hypertens 6: 542-545.

49. Altura BM, Lewenstam A (1994) Unique magnesium ion-selective electrodes. Scand J Clin Lab Invest 54: 1-100.

50. Resnick LM, Bardicef D, Altura BT, Alderman MH, Altura BM (1997) Serum ionized magnesium: relationship to blood pressure and racial factors. Am J Hypertens 10: 1420-1424.

51. Resnick LM, Altura BT, Gupta RK, Laragh JH, Alderman MH, et al. (1993) Intracellular and extracellular magnesium depletion in type-2 diabetes (non-insulin-dependent) diabetes mellitus. Diabetologia 36: 767-770.

52. Handwerker SM, Altura BT, Jones KY, Altura BM (1995) Maternal-fetal transfer of ionized serum magnesium during stress of labor and delivery. J Am Coll Nutr 14: 376-381.

53. Bardicef M, Bardicef O, Sorokin Y, Altura BM, Altura BT, et al. (1996) Extracellular and intracellular magnesium depletion in pregnancy and gestational diabetes. Am J Obstet Gymecol 172: 1009-1013.

54. Handwerker SM, Altura BT, Altura BM (1996) Serum ionized magnesium and other electrolytes in the antenatal period of human pregnancy. J Am Coll Nutr 15: 36-43.

55. Altura BM, Altura BT (1981) Magnesium modulates calcium entry in vascular smooth muscle. In: Onishi T, Endo M (Eds) The Mechanisms of Gated Calcium Transport Across Biological Membranes. Academic Press, New York, USA.

56. Altura BT, Altura BM (1980) Withdrawal of magnesium causes vasospasm while elevated magnesium produces relaxation of tone in cerebral arteries. Neurosci Lett 20: 323-327.

57. Zhang A, Cheng TP-O, Altura BM (1992) Magnesium regulates intracellular free calcium contraction and cell geometry in vascular smooth muscle cells. Biochim Biophys Acta 1134: 25-29.

58. Altura BM, Altura BT, Carella A (1983) Magnesium deficiency-induced spasms of umbilical vessels: relation to preeclampsia, hypertension, growth retardation. Science 221: 376-378.

59. Altura BM, Altura BT (1974) Magnesium and contraction of arterial smooth muscle. Microvasc Res 7: 145-155.

60. Yang ZW, Wang J, Altura BT, Altura BM (2000) Extracellular magnesium deficiency induces contraction of arterial muscle: role of PI3 kinases and MAPK signaling pathways. Pflugers Arch 439: 240-247.

61. Yang ZW, Wang J, Zheng T, Altura BT, Altura BM (2000) Low [Mg(2+)] (o) induces contraction and [Ca(2+)](i) rises in cerebral arteries: roles of ca(2+), PKC, and PI3. Am J Physiol Heart Circ Physiol 279: H2898-H2907.

62. Yang ZW, Wang J, Zheng T, Altura BT, Altura BM (2000) Low [Mg(2+)] (o) induces contraction of cerebral arteries: roles of tyrosine and mitogen-activated protein kinases. Am J Physiol Heart Circ Physiol 279: H185-H194.

63. Malpeuch-Brugere C, Nowacki W, Daveau M, Gueux E, Linard E, et al. (2000) Inflammatory response following acute magnesium deficiency in the rat. Biochim Biophys Acta 1501: 91-98.

64. Altura BM, Shah NC, Shah G, Zhang A, Li W, et al. (2012) Short-term magnesium deficiency upregulates ceramide synthase in cardiovascular tissues and cells: cross-talk among cytokines, Mg^{2+}, NF-κB and de novo ceramide. Am J Physiol Heart Circ Physiol 302: H319-H332.

65. Altura BM, Shah NC, Shah GJ, Zhang A, Li W, et al. (2014) Short-term Mg deficiency upregulates protein kinase C isoforms in cardiovascular tissues and cells: relation to NF-κB, cytokines, ceramide salvage sphingolipid pathway and PKC-zeta: hypothesis and review. Int J Clin Exp Med 7: 1-21.

66. Barnes PJ, Karin M (1997) Nuclear factor-κB-A pivotal transcription factor in chronic inflammatory disease. N Engl J Med 336: 1066-1071.

67. Baeuerle PA, Baltimore D (1996) NF-kappa B: ten years after. Cell 87: 13-20.

68. Ransone LJ, Verma IM (1990) Nuclear proto-oncogenes fos and jun. Ann Rev Cell Biol 6: 539-557.

69. Hayden MS, Ghossh S (2011) NF-κB in immunology. Cell Res 21: 233-244.

70. Altura BM, Gebrewold A, Zhang A, Altura BT (2003) Low extracellular magnesium ions induces lipid peroxidation and activation of nuclear factor kappa B in canine cerebral vascular smooth muscle: possible relation to traumatic brain injury and strokes. Neurosci Lett 341: 189-192.

71. Doolan A, Langios N, Semsarian C (2004) Causes of sudden cardiac death in young Australians. Med J Aust 180: 110-112.

72. Winkel BG (2012) Sudden cardiac death in young Danes. Dan Med J 59: B4403.

73. American Academy of Pediatrics (2012) Pediatric sudden cardiac arrest. Pediatr 129: e1094-e1102.

74. Neary MT, Breckenridge RA (2013) Hypoxia at the heart of sudden infant death syndrome. Pediatr Res 74: 376-379.

75. George Jr AL (2013) Molecular and genetic basis of sudden cardiac death. J Clin Invest 123: 75-83.

76. Capucci A (2007) Sudden Cardiac Death. N Engl J Med 357: 834-835.

77. Altura BM, Zhang A, Altura BT (1997) Exposure of piglet coronary arterial cells to low concentrations of Mg^{2+} found in blood of ischemic heart disease patients result in rapid elevation of cytosolic Ca^{2+}: relevance to sudden infant death syndrome. Eur J Pharmacol 338: R7-R9.

78. Bronner CW, Stidham GL, Westenkirchner DF, Tolley EA (1990) Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients. Crit Care Med 18: 921-928.

79. Cook LA, Mimouni FB (1997) Whole blood ionized magnesium in the healthy neonate. J Am Coll Nutr 16: 181-183.

80. Maggioni A, Orzalesi M, Mimouni FB (1998) Intravenous correction of neonatal hypomagnesemia: Effect of ionized magnesium. J Pediatr 132: 652-655.

81. Fiser RT, Torres Jr A, Butch AW, Valentine JL (1998) Ionized magnesium concentrations in critically ill children. Crit Care Med 26: 2048-2052.

82. Marcus J, Altura BT, Altura BM (2001) Serum ionized magnesium in pediatric post-traumatic patients. J Pediatr 139: 459-462.

83. Marcus J, Valencia GB, Altura BT, Cracco RQ, Jean-Baptiste D, et al. (1998) Serum ionized magnesium in premature and term infants. Pediatr Neurol 18: 311-314.

84. Altura BM, Altura BT (1997) Serum ionized Mg^{2+} in the antenatal and perinatal period. In: Ronald Smetana (eds) Advances in Magnesium Research: 1, John Libbey & Company Ltd., London, UK.

85. Altura BM, Barbour RL, Dowd TL, Wu F, Altura BT, et al. (2003) Low extracellular magnesium induces intracellular free Mg deficits, ischemia, depletion of high-energy phosphates and cardiac failure in intact working rat hearts: a 31P-NMR study. Biochim Biophys Acta 1182: 329-332.

86. Altura BM, Gebrewold A, Altura BT, Brautbar N (1996) Magnesium depletion impairs carbohydrate and lipid metabolism and cardiac bioenergetics and raises myocardial calcium content *in vivo*: relationships to etiology of cardiac diseases. Biochem Molecular Biol Int 40: 1183-1190.

87. Morrill GA, Gupta RK, Kostellow AB, Ma GY, Zhang A, et al. (1997) Mg^{2+} modulates membrane lipids in vascular smooth muscle: a link to atherogenesis. FEBS Lett 408: 191-194.

88. Altura BM, Li W, Zhang A, Zheng T, Yang ZW, et al. (2016) Expression of PAF is iduced by low extracellular Mg^{2+} in aortic, cerebral and piglet coronary arterial vascular smooth muscle cells; cross talk with ceramide production, DNA, nuclear factor -κB and proto-oncogenes: possible links to inflammation, atherogenesis, hypertension, sudden cardiac death in children and infants and aging: hypothesis and review. International Journal of Cardiology and Research.

89. Nigam S, Kunkel G, Prescott SM (1996) Platelet-Activating Factor and Related Lipid Mediators 2. Plenum Press, New York, USA.

90. Prescott SM, Zimmerman GA, Stafforini DM, McIntyre TM (2000) Platelet-activating factor and related lipid mediators. Annu Rev Biochem 69: 419-445.

91. Montrucchio G, Alloatti G, Camussi G (2000) Role of platelet-activating factor in cardiovascular pathophysiology. Physiol Rev 80: 1669-1699.

92. Ross R (1999) Atherosclerosis-An inflammatory disease. N Engl J Med 340: 115-126.