



Magnesium & Potassium in Lone Atrial Fibrillation

By Patrick Chambers MD

Lone Atrial Fibrillation (LAF) is AF without discernible cardiovascular disease, e.g., without congestive heart failure, high blood pressure, prior cardiac surgery, rheumatic heart disease, etc. It has been associated with a number of diseases primarily involving organs other than the heart. These include seemingly widely disparate disorders such as hyperthyroidism, gastroesophageal reflux disease (GERD), dysautonomia (abnormality of autonomic nervous system), impaired glucose tolerance, etc. LAF involves a “defective substrate” and is triggered by an increase in sympathetic tone (adrenergically mediated LAF or AMAF) or an increase in parasympathetic tone (vagally mediated LAF or VMAF). The disorder is chronic in nature and may occur intermittently (paroxysmal) or be a constant companion (permanent).

The phrase “defective substrate” has become integral to any discussion of the cause of LAF. Organ candidates for this “substrate” include the heart, as well as kidney, adrenal gland, pancreas, GI tract and autonomic nervous system (ANS). This defect could involve an enzyme, a hormone or receptor site, a membrane pump, channel or exchanger, to name a few. It could be environmental, genetic or both. Magnesium (Mg) deficiency has emerged as a significant player in the etiology of LAF. This is not completely unexpected, since some 350 different enzymes(1) or about 80% of all enzymatic reactions in the body(2) rely on magnesium. Although much has been written on the role of Mg deficiency in other diseases, little has been devoted to LAF. Much is still unknown, e.g., why one individual with Mg deficiency manifests with insulin resistance and another with insulin hypersensitivity, is not clear. What is clear is that LAF is not caused by a single factor, but by the delicate interplay of many factors. Some of those due to Mg deficiency follow.

ROLE OF MAGNESIUM

Cell Membranes

One of the most important roles of Mg involves maintenance of the intracellular environment. It does this primarily by attaching to phospholipids in membranes (both of the cell and its organelles, such as mitochondria, sarcoplasmic reticulum...) to reduce their permeability and enhance their function (12). It is also a required cofactor in the various membrane ATP (energy requiring) pumps. The most important of these pumps is the Na/K pump. Others include Ca/Mg, K/H and Na/H pumps. In addition there are channels (such as Ca and Na) and exchangers (such as Na-Mg, Na-Ca and Na-H). Neither channels nor exchangers require ATP and are passive (rely on diffusion). Some of these are also adversely affected by Mg deficiency. For example, Mg is a Ca channel blocker and Mg deficiency leads to increased intracellular Ca via channel (and pump) because heart cells must maintain a Ca gradient of 25,000:1 (difference between extracellular and intracellular concentrations)(71).

Mg deficiency also results in dysfunction of the Na-Mg exchanger(56), leading to increased intracellular Na via exchanger (and pump) due to a Na gradient of 13:1(71). If there is insufficient Mg for adequate ATP, then the primarily extracellular cations sodium (Na) and calcium (Ca) tend to leak into the cells and the primarily intracellular cations potassium (K) and Mg tend to leak out. However, membrane leakiness in magnesium deficiency depends less on ATP related activity and more on the membrane stabilizing effects of magnesium phospholipid complexes(12). This leakiness disrupts proper gradients and cellular function. In addition Mg is an antioxidant and Mg deficiency allows accelerated free radical damage to cell membranes (lipid peroxidation), further compromising cellular cation (positive ion) homeostasis(3,24,32,60,61).

Maintenance of proper cationic (Na, K, Ca, Mg) gradients is especially critical for successful muscle contraction and nerve impulse transmission. In fact the earliest symptoms of magnesium deficiency are neuromuscular symptoms, e.g., muscle twitching (fasciculations), difficulty sleeping, difficulty swallowing. Accordingly, the list of disorders associated with Mg deficiency is top heavy with neuromuscular diseases, e.g., asthma (bronchial smooth muscle), migraines and eclampsia (vascular smooth muscle), leg cramps (skeletal muscle), LAF (cardiac muscle) and even chronic constipation (GI smooth muscle).

Mg and K

Like Mg, K inhibits free radical formation(4). In fact, there are a number of parallels between these two cations. Both are inextricably linked to specific anions (Na for K and Ca for Mg). Hyperkalemia (like hypermagnesemia) does not typically occur in patients with normal renal function. Aldosterone increases the secretion/excretion of both K and Mg(5). Successfully replenishing a K deficiency (like a Mg deficiency) in the presence of low intracellular Mg is difficult and takes months(6). Even in the presence of a normal serum K, reduced dietary K can be problematic, just as for Mg(4). K and Mg both can reduce high blood pressure(7). Fruits and vegetables are great sources for both minerals (mother was right). Both because K is so vital to cardiac function and because Mg is so vital to K utilization(33), any discussion of Mg and LAF is incomplete without inclusion of K.

Absorption and Excretion

In addition to passive diffusion there appears to be an ATP requiring mechanism for Mg absorption from the GI tract(8). Similarly, in the kidney in addition to passive diffusion there appears to be an additional active transport system for the reabsorption of Mg(9,10,12,19). In short, Mg via ATP is required for a portion of its own GI absorption and renal reabsorption(19). Likewise GI absorption of K is decreased and renal reabsorption decreased, if there is a Mg (and therefore ATP) shortage in GI and kidney cells respectively(14,19,56). Both absorption and reabsorption of K (and Mg) worsen with age(11). Some hormones, e.g., glucagon (produced in the pancreas) and calcitonin, stimulate renal reabsorption of Mg via cyclic AMP (cAMP), which requires the Mg dependent enzyme adenylate cyclase(90).

MAGNESIUM AND HORMONES

Homeostasis

Neither Mg nor K has good neurohormonal controls for either GI absorption or renal reabsorption to maintain proper balance (v parathormone, calcitonin and vitamin D for Ca, aldosterone and atrial natriuretic peptide (ANP) for Na)(35). However, insulin, parathormone (PTH) and Vitamin D do play a role in Mg homeostasis by increasing cellular uptake(13). The former is primarily associated with carbohydrates and the latter two with Ca, a Mg antagonist. A variety of other hormones have been implicated in urinary magnesium wasting. These include catecholamines, TSH (thyroid-stimulating hormone or thyrotropin), T3 (triiodothyronine), T4 (thyroxine) and calcitonin (produced in the thyroid

gland), glucocorticoids (affect glucose metabolism, especially cortisol) and mineralocorticoids (affect sodium metabolism, especially aldosterone), ADH (antidiuretic hormone from pituitary) and angiotensins (liver and lungs)(14,15,20,57). Catecholamines are produced by both the adrenal medulla (humoral) and sympathetic nerves (neurotransmitter). Corticoids (corticosteroids) are produced by the adrenal cortex. High dietary sodium and calcium may also result in urinary magnesium wasting(16).

Insulin

Insulin causes cellular uptake of Mg(12). Magnesium deficiency results in insulin resistance(13) as well as impaired insulin secretion(17,22,23). Furthermore, the most significant mechanism for urinary magnesium wasting is probably through glycosuria (glucose in the urine) secondary to impaired glucose tolerance(14,21,23,25). Insulin resistance appears to be due to defective tyrosine-kinase activity (requires Mg) at the insulin receptor level and increased intracellular calcium(18). This resistance mandates release of more insulin, causing more Mg (and K) to be transported from blood into cells. Intracellular Mg (and K) must then be maintained against a greater concentration. This gradient is about 40:1 for K and 3:1 for Mg (intracellular v. extracellular)(71). The concomitant urinary Mg wasting aggravates this further causing both additional membrane instability (decreased magnesium phospholipid complexes) and pump dysfunction (defective Ca/Mg ATPase and Na/K ATPase pumps), causing more Mg loss and more insulin resistance (see cAMP/cGMP discussion below).

Parathormone

The parathyroid gland in response to low serum magnesium or calcium releases PTH. PTH then increases GI absorption and renal reabsorption of Mg(12). However, adequate magnesium is required for parathyroid hormone synthesis and secretion(20). So this also is a kind of a hormonal catch 22 (Mg is required for the efficacy of one of its regulating hormones) similar to the electrolyte catch 22 (Mg is required for its own cellular uptake). Mg deficiency also causes end organ PTH resistance (serum Ca does not rise when PTH is increased in Mg deficient patients)(12,48,55,87).

Vitamin D

Intestinal absorption of magnesium and calcium is enhanced by Vitamin D(52). Mg absorption in Vitamin D deficiency is decreased(72). In addition serum concentration of 1,25 dihydroxy cholecalciferol (cholecalciferol = Vitamin D3) is low or low/normal in a magnesium deficient state and does not rise in response to a low calcium diet. This is because the formation of 1,25 dihydroxy cholecalciferol involves a magnesium dependent hydroxylase enzyme(12). Magnesium deficiency also results in end organ resistance to vitamin D and its metabolites(12). This is another hormonal catch 22. Vitamin D increases net absorption of Mg but to a lesser degree than for Ca (34,35). The subsequently elevated blood Ca may result in greater urinary Mg wasting(12).

Glucagon

Insulin and glucagon (and to a lesser extent catecholamines) counter regulate each other in maintaining glucose balance. Glucagon causes glycogenolysis (break down of glycogen) and gluconeogenesis (production of glucose) increasing blood glucose while insulin transports glucose (and K) into the cell decreasing blood glucose. Magnesium deficiency has been strongly associated with chronic fatigue syndrome (CFS)(106). Some have suggested that this may be because Mg is required for six of the nine enzymatic steps in glycolysis (breaking down glucose to produce energy, i.e., the opposite of gluconeogenesis)(91,95). Furthermore, cAMP via adenylate cyclase, a Mg dependent process, mediates glucagon receptor activity(105). Therefore, in order to effectively counterbalance insulin glucagon requires Mg.

Aldosterone and ANP

Mention aldosterone and most think renal Na reabsorption and renal K secretion/excretion. Few realize that aldosterone also causes urinary Mg wasting due to blood volume expansion and consequent greater delivery of sodium, calcium, and magnesium to the distal renal tubules(14). Magnesium deficiency enhances angiotensin-induced aldosterone synthesis (RAAS)(47). Indeed, there have been many articles written touting the antihypertensive qualities of Mg supplementation in those deficient. Magnesium deficiency causes hypertrophy of the juxtaglomerular apparatus (JGA), located in the kidney(36,37). This releases renin, which ultimately increases aldosterone, lowering serum Mg (and K). This, of course, again aggravates membrane permeability and pump function.

Aldosterone levels fluctuate diurnally—highest concentration being at 8 AM, lowest at 11 PM, in parallel to cortisol and ACTH rhythms(64). These levels increase with age. Aldosterone may be a major contributor to LAF, predominantly via the resultant increase in the intracellular Na/K ratio. Unfortunately, the deleterious effects of aldosterone and the RAAS do not end with Na/K. Recent research(41) has shown that the heart and endothelium both contain receptors for aldosterone and that this mineralocorticoid is responsible for left ventricular fibrosis, dilatation, and hypertrophy. Spironolactone, a K sparing diuretic, blocks many of the adverse effects of aldosterone but has some adverse side effects, including causing development of breasts in males and irregular menses in females. An exciting new diuretic called eplerenone(39) is similarly K sparing and cardioprotective, but without the side effects of spironolactone. Evidence has accumulated in recent years indicating that these K sparing drugs may also exert some Mg-sparing properties(51,52,59).

Atrial natriuretic peptide (ANP) is the hormonal antagonist of aldosterone. It causes renal reabsorption of K and excretion/secretion of Na. Congestive heart failure (CHF) and atrial fibrillation (AF) stimulate release of ANP from atrial cells via atrial muscle cell stretching that occurs at such times. ANP is also secreted during exercise(68). In fact, hypoxia is a potent stimulus for ANP(70). K and ATP (and Mg) mediate the release of ANP. Many believe that ANP is helpful in terminating episodes of AF by favorably rebalancing the intracellular Na/K ratio. It is also a Ca channel blocker(69).

Cyclic AMP/cGMP and Taurine

Cyclic AMP (cAMP) and cyclic GMP (cGMP) act as “second messengers” for certain hormones. They function as kind of localized intracellular hormones. Insulin and catecholamines function via receptors (beta) on target cell membranes, which involve cAMP. On the other hand, cholinergic receptor activity (predominantly the parasympathetic nervous system or PNS) involves cGMP. Adenylate cyclase (for cAMP production) requires Mg, whereas guanylate cyclase (for cGMP production) requires Ca(13). Consequently, in Mg deficiency the intracellular cAMP/cGMP ratio, normally between 10 and 100 to 1, is reversed(52). This may partially explain the insulin receptor resistance (low cAMP) seen in impaired glucose tolerance associated with Mg deficiency. cGMP also mediates the effects of ANP in target cells, i.e., enhanced natriuresis(31). This may be another reason why VMAF episodes (enhanced cholinergic receptor activity) and/or LAF episodes due to Mg deficiency, both associated with high cGMP, seem to revert to NSR (normal sinus rhythm) more spontaneously than do adrenergically mediated episodes(95).

Interestingly, hyperinsulinism tends to maintain this reduction in cAMP(13). Jean Durlach, M.D., Editor-in-Chief, *Magnesium Research*, President of the International Society for the Development of Research on Magnesium, and author of *Magnesium in Clinical Practice*, suggests that taurine may affect this turnaround (less cGMP and more cAMP). Catecholamines and insulin favor cellular influx of taurine. Taurine is a powerful membrane stabilizer. It also chelates Ca, a Mg antagonist, facilitates maintenance of intracellular K and opposes the undesirable cellular effects of insulin and catecholamines(13). Taurine plays an important role in Mg deficiency. Ingestion of monosodium glutamate (MSG) can lead to taurine deficiency, since glutamate competes with cysteine (required to make taurine) for cellular uptake(46).

Glutamate and Aspartate

Glutamate and aspartate are neurotransmitters. Specifically glutamate determines HR through the SA node. More glutamate translates to higher vagal tone. MSG is also a common trigger of AF and premature atrial complexes (PACs) for many LAFers(72). NMDA (N-Methyl-D-Aspartate) receptors are located on neurons and are associated with the Ca channel(42). When glutamate or aspartate (aspartame in NutraSweet is metabolized to aspartate) attaches to the NMDA receptor, it triggers the flow of sodium (Na) and calcium (Ca) ions into the neuron, and an outflow of potassium (K), firing the neuron. ATP pumps are required to return the ions and restore the resting state. The Ca channel is blocked by magnesium. This helps maintain membrane potentials near resting value. If the repolarized or resting state cannot be maintained, e.g., hypoglycemia, defective pump (as in Mg deficiency), then the neuron fires and the channels open. This pump failure gradually allows excessive calcium/sodium build up inside the cell, which is eventually lethal(43,44). Furthermore, ATP pumps are required not only to return the ions but also to remove the glutamate and return it to the neuron (neuronal reuptake). Glutamate is then converted into glutamine, another process that requires ATP. That is a total of three separate ATP and Mg requiring steps. Free radicals further impede this(45). Mg has a circadian excretory rhythm, with lower blood levels and higher excretion occurring at night(56,92)). During this period, extracellular Mg is at its diurnal nadir and vagal tone is at its zenith. Undoubtedly the compounding effects of concomitant Mg deficiency are a powerful stimulant for nighttime VMAF. Add the excitatory properties of glutamate to the recipe and the soil becomes very fertile for LAF. For these reasons, MSG and even mild gastroesophageal reflux disease (GERD) make dinner out a risky proposition for many LAFers, especially VMAFers (see discussion on GERD and postprandial reactive hypoglycemia below).

MAGNESIUM AND THE DEFECTIVE SUBSTRATE

Autonomic Nervous System

Mg is required for activity by the cholinesterase enzymes(13). One of these, acetyl cholinesterase degrades acetylcholine, the neurotransmitter substance for the PNS and for the first part of the sympathetic nervous system (SNS), specifically the nicotinic receptors of the SNS. In fact, deficiency of magnesium and excess calcium both increase the release of acetylcholine. Deficiency of either magnesium or calcium prolongs the effect of acetylcholine(58). Mg deficiency translates to enhanced vagal tone further augmented by too much or too little Ca.

Catecholamine-O-methyltransferase (COMT) and monoamine oxidase (MAO) catabolize (break down) norepinephrine (NE), the neurotransmitter for the rest of the SNS. However, unlike acetylcholine but like glutamate, neuronal reuptake of discharged norepinephrine is a major mechanism for terminating sympathetic neurotransmission (see glutamate discussion above). MAO catabolizes this NE, while COMT is more active in catabolizing extracellular circulating (humoral) catecholamines secreted by the adrenal gland(30). Both are part of the SNS. COMT requires Mg as a cofactor(28,29). Neuronal reuptake also requires ATP (and Mg). Low Mg translates to higher sympathetic tone(105). These enzymatic shortfalls might produce an exaggerated response of either the PNS or the SNS at transition or crossover points, a time when many VMAF episodes arise, e.g., lying down or bending over. The neurotransmitter substance or hormone secreted on each occasion is not degraded or removed, resulting in a prolonged over response. For example, cocaine blocks dopamine reuptake, leaving more dopamine in the synaptic cleft, which results in over stimulation of the D2 receptors (causing schizophrenic episodes)(106).

Sexual activity triggers some episodes for many afibbers(72). In addition to MAO breakdown of dopamine within neurons (neuronal reuptake) COMT breaks down circulating dopamine, an important hormone produced at this time. The dopamine no doubt triggers automaticity (associated with beta-1 receptors) in ectopic foci with a resulting increase in PACs (see EP discussion below)(107). The over responding vagus causes a shortening of the AERP. Mg deficiency in this scenario (independent of K) may be causative in bedtime episodes and even some more typically adrenergic episodes.

GERD

The “alkaline tide” precedes the start of any meal. This is caused by gastric cell secretion of H and Cl into the lumen for digestion of food and simultaneous extrusion of K and HCO₃ into the blood. This more alkaline blood causes bicarbonaturia (HCO₃ in urine) to lower this pH (blood pH is tightly controlled between 7.35 and 7.45). Unfortunately, K(54) as well as Mg(104) are cations lost in the urine (kaliuria and magnesuria respectively) along with the anion HCO₃. This lowers blood K, although not necessarily below lower limit of normal. Furthermore, there is evidence that high vagal tone may sustain basal gastric acid hypersecretion in some persons and temporary hypersecretion during stress in others(49). Some cases of GERD (gastroesophageal reflux disease) and non-ulcer dyspepsia (NUD) probably result in transiently low K via the constant steady alkaline state (in plasma) that accompanies the slightly hyperacidic state (in the stomach). The K/H pump also rectifies this increase in blood pH. H goes into the blood and K comes into the cells. Again this requires cardiac muscle cells to maintain their intracellular K concentration against a greater gradient. Also, greater concentration of K within renal tubule cells contributes to increased renal secretion of K into urine. Normally the concentration of K within heart muscle cells is 150 millimoles/liter (v. four mm/l outside the cell), a considerable gradient (almost 40:1) to maintain(9). Ingested protein stimulates more HCl secretion (and a stronger alkaline tide and greater kaliuria). Other suggested mechanisms for GERD related episodes of LAF include stimulation via irritation of the vagus nerve during episodes of reflux and/or gastric distention. Some VMAFers associate their episodes with GERD(72). Curiously, many of them prefer to sleep on their right side (right lateral decubitus position). Vagal tone is increased while in this position(67). This is because the heart is slightly higher (v. the left side position) relative to the carotid baroreceptor. This pressure receptor in the neck senses more hydrostatic pressure and signals the vagus nerve to increase tone (bad for a VMAFer). However, the preference may be because this position promotes gastric emptying (our stomachs pass their contents to the right and dump them into the duodenum) and possible relief for a GERDer.

Dysinsulinism

Those with impaired glucose metabolism hyper respond with insulin (produced by the beta cells of the pancreatic islets) to a carbohydrate meal (target cells are insulin resistant). The ensuing hypoglycemia (low blood glucose) stimulates release of glucagon (produced by alpha cells of the pancreatic islets) and catecholamines with consequent hyperglycemia (high blood glucose) with a kind of yo-yo effect(72). Catecholamines but especially glucagon stimulate glycogenolysis (breakdown of glycogen, the storage form of glucose) and gluconeogenesis (release of glucose from cells that store glycogen), most notably from the liver. Gluconeogenesis involves enolase and magnesium is required as a cofactor(91). In fact five of the other eight steps in gluconeogenesis also require Mg(94). It appears that Mg is critical to the proper function of glucagon and catecholamines in this area.

There is an epidemic of overweight/obesity in the Western world, especially here in America. Syndrome X (or Metabolic Syndrome = includes high blood pressure, obesity, diabetes, high blood insulin and triglyceride levels) represents the far end of the spectrum of this disorder of carbohydrate metabolism. Useful laboratory tests include serum hemoglobin A1C, which will detect large swings in blood glucose levels over the preceding three months. Fasting blood glucose and then an OGTT (oral glucose tolerance test) are the best tests to diagnose impaired glucose tolerance and diabetes mellitus. Mg deficiency plays an important role in this process (see insulin section above).

Postprandial (after a meal) reactive hypoglycemia (PRH) is defined as low blood sugar (less than 3.3 mmol = 60 gm/dl) concurrent with symptoms (dizziness, depression, sweating, weakness, hunger, anxiety)(82,83,89). LAF has recently been added to this list(84,85,86). Although the oral glucose tolerance test (OGTT) is not abnormal (88,89), a characteristic pattern is often seen in PRH. The release of insulin is sluggish and the insulin peak delayed with respect to the peak value for blood glucose(72,98,99). These flat curves are associated with excessive vagal tone(29,72,100). Instead of insulin resistance, as seen in diabetes, there is insulin hypersensitivity in 50 to 70% of those with PRH. In addition to insulin the body secretes other hormones, such as glucagon like peptide (GLP), from GI tract endocrine cells that stimulate insulin synthesis and secretion(96). GLP-1 levels in those with PRH average 10 times those of normals(89) and it is this hormone that is felt to be responsible for this

insulin hypersensitivity. However, this alone is insufficient for a diagnosis of PRH(89). Glucagon dysfunction is a necessary ingredient(97,98). Mg deficiency and its negative effect on gluconeogenesis (glucagon dysfunction) in combination with insulin hypersensitivity may well explain postprandial reactive hypoglycemia in some individuals (see glucagon section above). Furthermore, many with PRH are very lean or women with moderate lower body weight(89) with increased HDL cholesterol. These lean individuals with excessive vagal tone are precisely those that pursue endurance activities. VMAF is increased in endurance athletes (101). Studies comparing the effect of blood glucose on right and left atrial refractory periods reveal these to be shortest under hypoglycemia in the left atrium and longest under normo or hyperglycemia in the right atrium(102) (see EP discussion below). Triggering PACs in LAF typically arise in the left atrium(72,75).

Magnesium deficiency also causes release of catecholamines(12). Perhaps this is partially because Mg deficiency causes glucagon dysfunction, which stimulates catecholamine release to cover the glucose shortfall(89). Catecholamines stimulate release of fatty acids that complex with blood Mg, further aggravating the Mg shortfall(60,62,63). Insulin and catecholamines both cause intracellular migration of K and decrease serum K(12). Consequently, catecholamines (and insulin) cause a greater gradient, not only promoting steady leakage of cardiac muscle cell K to blood but also facilitating renal K excretion. Increased K within renal tubule cells stimulates more secretion of K into urine. Hypokalemia, hypoglycemia induced or otherwise, is highly arrhythmogenic.

Hyperthyroidism

Hypomagnesemia is a common problem in hyperthyroid patients. Thyroid hormones induce shifting of magnesium into the cells. Excessive levels of T3/T4 consequently cause urinary Mg wasting(13). This Mg deficiency again leads to low intracellular K (defective Na/K ATPase pump and unstable membrane), as evidenced by the fact that 14% of hyperthyroids have AF(26) and 10% have hypokalemic periodic paralysis(27).

Dehydration

Dehydration (via the renin angiotensin aldosterone system (RAAS)) stimulates release of aldosterone to reabsorb Na and with it water. In exchange, K is secreted/excreted, thereby lowering serum K. Aldosterone receptors are also present in colon and skin. In the distal colon, aldosterone enhances active Na absorption and K (and Mg) excretion/secretion (via pump and channel)(50). Exercise induced dehydration stimulates aldosterone release, causing increased loss of K and Mg in sweat(65,66). Excessive exercise also stimulates secretion of ADH, catecholamines, TSH, cortisol and aldosterone, all of which cause urinary Mg wasting(57) (see above).

Left-Handedness

Although we get the word sinister from the Latin word for left, most left-handers do not consider themselves defective. However, many left-handers have increased need of Mg. Digoxin is a steroidal glycoside often prescribed for those with LAF. It is a potent inhibitor of the Na/K pump and is contraindicated especially in those with VMAF(93,95). Curiously it also produced endogenously by the hypothalamus via the isoprenoid pathway(92). This causes an increase in intracellular Ca and a decrease in the functional availability of Mg. The resulting atrial conduction deficit, increased incidence of atrial fibrillation and stroke has been strongly associated with right hemisphere dominant (left-handed) individuals in whom the isoprenoid pathway is often up regulated (v. right-handers)(92).

ABNORMAL ELECTROPHYSIOLOGY OF LAF

How does Mg (and K) deficiency actually cause AF? Muscle cells (skeletal, smooth and cardiac) contract during depolarization (excitation phase) and relax during repolarization. During a portion of the relaxation phase, the cell is immune to further stimulation (refractory period)(75). AF requires a shortened atrial effective refractory period (AERP), enhanced atrial dispersion of refractoriness, slow conduction velocity and a trigger (increased PACs)(78). Dispersion of refractoriness is nothing more than a measure of how much variability in AERP exists between atrial muscle cells. Greater variability in AERP from cell to cell implies greater dispersion. The mechanism of AF is based on the now proven Moe wavelet theory (1959)(74), which requires both reentry and automaticity. Reentry occurs when the advancing wavefront of depolarization (and contraction) encounters refractory tissue in such a way that it reenters its own path, creating a wavelet (circular wave). The lack of AERP uniformity between cells can force some unusual paths of conduction (colorfully called circus movements), making creation of these wavelets or closed circuits a real possibility. Wavelets are described by the equation:

$$\text{wavelength} = (\text{conduction velocity}) \times (\text{AERP})(75,76).$$

Atrial conduction velocity (via normal pathway) is about 1m/s and AERP<50 ms results in AF 80% of the time. Therefore, a micro reentrant wavelet is something around 5 mm in circumference(73). In addition to reentry, there must be automaticity, whereby a single atrial focus fires repeatedly (PACs). The number of PACs is inversely proportional to intracellular K and Mg and directly proportional to intracellular Ca(80,81). The SA and AV nodes and the rest of the His Purkinje conduction system have innate pacemaking properties (automaticity). Catecholamines can cause automaticity in cells not so disposed (foci of ectopics)(76). Since PACs arise outside the normal conduction system of the heart, the impulse travels via an alternate less efficient pathway with slower conduction velocity. This further contributes to shortening of the wavelength and dispersion of refractoriness (see above equation). These simultaneously occurring conditions (PACs, slow velocity, shortened AERP and enhanced dispersion) lead to AF by fragmentation of the propagating wavefront of depolarization. Multiple reentrant wavelets (six wavelets or involvement of about 75% of atrial tissue constitute critical mass for sustaining AF)(73,76) are created. The dispersion of refractoriness allows the wavelets to meander around the atrium forming a moving barrier against any successful wave of contraction. Instead, additional wavelets are created from these unsuccessful attempts. Hence, there is no P wave, unlike in atrial flutter.

Autonomic tone (especially vagal but also sympathetic) can shorten AERP(75) and increase atrial dispersion. Hypokalemia and hypomagnesemia can also increase atrial dispersion(79). Inhomogeneous distribution of vagal nerve endings will increase dispersion of refractoriness(77). Atrial dispersion is also a function of atrial electrical remodeling (increased intracellular Ca)(76). Electrical remodeling causes loss of physiologic rate adaptation, i.e., the AERP fails to adapt to the heart rate, especially during bradycardia(74), when it should lengthen. There is also structural remodeling (increase in atrial size) as well as ultrastructural or contractile remodeling (76,77). When the conduction velocity increases, the wavelets begin to disappear or fuse because the advancing wavelet front of depolarization catches up to its trailing tail of refractory tissue. The wavelets are forced to enlarge or coalesce, but then they are more likely to bump into others, canceling themselves. At some point their numbers dip below critical mass and AF is terminated. Increasing sympathetic tone causes an increase in conduction velocity (dromotropism) (74). This latter is instrumental in terminating VMAF episodes.

MAGNESIUM THERAPY

Mg Water

In view of the growing problem of inadequate Mg intake, several Mg rich drinking waters have become quite popular. These are mineral waters or their approximations. They include Unique Water

(Australia, 120 mg Mg/liter), Noah's California Spring Water (120 mg Mg/liter) and Waller Water (developed by Erling Waller and containing 150 mg of Mg/liter). All have pHs well over 8 and have the potential to cause urinary K wasting, due to bicarbonaturia (see GERD discussion). This also causes urinary Mg loss(104). However, a generous squeeze from a fresh lemon addresses nicely not only this concern but also adds a touch of taste. Hexahydrated Mg is otherwise especially beneficial, because it provides more bioavailable Mg. This results in not only enhanced GI absorption but also more biologically active ionized Mg. If the concentrations of ionized magnesium falls 25 to 40 percent below normal—irrespective of the total amount of magnesium present—magnesium-dependent enzymes no longer function properly(1).

There are also some Mg preparations that dissolve in water (Natural Calm with magnesium citrate). Oral Mg supplementation in tablet form enjoys considerable popularity and success. Herbert Mansmann, M.D., Director of the Magnesium Research Laboratory at Thomas Jefferson Medical College, has developed an effective magnesium dosing regimen that exploits nighttime absorption(40). However, whichever route one chooses, the maximum tolerated dose (MTD) should be approached carefully. Once exceeded, the K and Mg loss in loose stool is regressive and may easily trigger a breakthrough episode of LAF. Many factors help or hinder Mg absorption and directly impact the efficacy of oral supplementation.

HEART RATE VARIABILITY (HRV)

Finally, heart rate variability (HRV) is a measure of the small variation in heart rate from beat to beat. It is a direct measure of autonomic tone and decreases with age. Elevated HRV implies greater vagal tone and has always been an independent prognosticator of longevity(108). Greater vagal tone translates to longer life, all else being equal. Perhaps the “defective substrate” of VMAF is nothing more than the combination of many years of poor diet, skipped meals and poor hydration along with excessive exercise in individuals already possessing a slow heart rate. But it's never too late to change. Increased dietary Mg and regular moderate exercise with plenty of hydration will increase ANP(38,53), the antialdosterone hormone. This will help flush out excess Na and oppose the deleterious effects of RAAS. It will enable glucagon to help moderate glucose levels and it will promote proper balance within the ANS. All this should help keep LAF at bay. Besides that you'll sleep better (more serotonin and melatonin) as well, because Mg is required for the synthesis of both(94).

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