SOME THOUGHTS ON SUDDEN CARDIAC DEATH – PART II

INTRODUCTION

In part I of this series, I reviewed two papers that make it unmistakably clear that optimal potassium intake and metabolism are very crucial and very under-appreciated factors that need to be considered in relation to a health care tragedy that continues to take people, both young and old, away from the friends and relatives who love them most, all too often and very unexpectedly: sudden cardiac death. Unfortunately, when a relatively unknown issue in the health care community is only addressed by a small amount of papers, many in the health care community may not give this issue the attention it deserves.

Therefore, in part II of this series I would like to review several more papers affirming that optimal potassium intake and metabolism is not just a quality of life issue like so many other products we sell. Rather, for many, it truly can be an issue of life or death.

MORE RESEARCH ON ELECTROLYTE STATUS & CARDIAC DYSFUNCTION

The first paper I would like to review carries a title that is certainly in line with the statement I made above, “Electrolyte abnormalities underlying lethal and ventricular arrhythmias.” The first quote I would like to present from this paper by Leonard Gettes (1) emphasizes the importance of optimal electrolyte physiology for cardiac health:

“…there is general agreement that alterations in extracellular potassium induce electrophysiological changes and arrhythmias, that alterations in extracellular magnesium may be arrhythmogenic, and that changes in intracellular calcium cause electrophysiological changes that are arrhythmogenic.”

The next quote makes it clear that administration of these electrolytes, particularly potassium and magnesium, can have a powerful impact in altering the detrimental scenario described in the above quote:

“There are clear associations of certain disease states to the above ionic changes and to the appearances of potentially lethal arrhythmias, and there is clear evidence that the administration of certain ions, particularly potassium and magnesium salts, may reverse or prevent potentially lethal arrhythmias even in the absence of documented abnormalities in the extracellular concentrations of these ions.”

Therefore, as I suggested in part I, even if serum potassium and magnesium are within traditional “normal” ranges, it still may be wise to supplement if the overall clinical picture suggests there may be a concern that less than optimal potassium and magnesium status exists.

The next few quotes presented below focus specifically on potassium. The first affirms what was stated in part I concerning how potassium status can adversely affect cardiac function:

“A decrease in extracellular potassium is a well-recognized cause of lethal and potentially lethal arrhythmias. Such a decrease hyperpolarizes the resting membrane and causes an increase in pacemaker activity in Purkinje cells, shortens plateau duration in ventricular fibers, prolongs the phase of rapid repolarization, and my increase the dispersion of the recovery of excitability.”

The next quote makes an interesting comparison between decreases in extracellular potassium and drugs often used in the treatment of cardiovascular disease (CVD):

“Many of the electrophysiological effects of a decrease in extracellular potassium on pacemaker activity and repolarization are
identical to those induced by the digitalis glycosides and by the $\beta$-adrenergic sympathetic agonists. It is not surprising therefore, that the combination of these factors would be associated with an increased incidence of cardiac arrhythmias.”

The next quote makes it clear that low potassium levels can lead to arrhythmias even in patients who have no evidence of heart disease and are not receiving digitalis:

“In humans, there are multiple well-documented episodes of supraventricular and ventricular arrhythmias occurring in hypopotassemic patients who do not have obvious underlying heart disease and who are not receiving digitalis therapy.”

Of even greater concern in relation to decreased potassium levels and potentially lethal cardiac events are the many hypertensive patients who utilize diuretic therapy:

“There are several discrete situations in which lethal ventricular arrhythmias have been shown to be related to and possibly caused by hypopotassemia. Several studies have documented that the ventricular arrhythmias occurring in hypertensive patients receiving thiazide and loop diuretics, are the result of hypopotassemia, which becomes more profound as the duration of therapy and the dose of diuretic therapy increases. Indeed, there has been speculation that the increased risk of death in hypertensive patients receiving thiazide diuretics, such as reported in the Multiple Risk Factor Intervention Trial (MRFIT), was the result of hypopotassemia and possibly hypomagnesemia.”

Interestingly, when the above mentioned combination exists, addition of a third component which we generally view quite positively could have dire consequences:

“It has been shown that the increase in ectopy associated with the development of hypopotassemia after the onset of thiazide therapy in hypertensive patients is worsened by exercise, suggesting a synergism between the hypopotassemia and the increase in $\beta$-adrenergic sympathetic effect induced by both static and dynamic exercise.”

Therefore, as I hope you can see, for patients who may have pre-existing low potassium due to poor dietary intake, when they are placed on thiazide diuretics, stressful situations that stimulate an adrenal response can be particularly worrisome concerning potentially lethal cardiac events.

Concerning the above scenario, what specific level of serum potassium is most highly correlated with adverse events? As you may recall from part I of this series, it was pointed out, based on the paper by Macdonald et al (2) that ideal levels of serum potassium are between 4.5 and 5.0 mmol/l. Reinforcing this correlation is data discussed in the quote below that demonstrates, when this group of patients reaches the generally accepted low-end cut-off for serum potassium, cardiac risk is significant:

“It has been clearly established in these studies that the incidence of ventricular tachycardia and ventricular fibrillation is greater in patients with hypopotassemia (potassium $<3.5$ mM) than in those with normal serum potassium levels (potassium $>3.5$ mM) and that the risk of arrhythmia increases as the degree of hypopotassemia becomes more pronounced. This occurs whether or not the patient was receiving diuretic agents before the infarction.”

Of course, your reply to the above quote may be that, my patient does not fall into this risk category because the last blood test demonstrated a serum potassium significantly above 3.5 mmol/l. Does this mean your patient has no need to worry about a cardiac crisis event related to low potassium levels? Not necessarily. Why? Just because serum potassium levels are optimal at the time blood was drawn for the blood test does not mean they stay optimal all day. For, Gettes (1) points out any stressful situation that leads to $\beta$-adrenergic stimulation can cause an increase in intracellular potassium which can, in turn, lead to a corresponding decrease in serum levels. Are there other scenarios that might lead to an increase in intracellular potassium and a decrease in serum potassium to such an extent that a cardiac crisis is likely? As I pointed out in part I of this series and will discuss more in subsequent installments, ingesting significant amounts of carbohydrate after several hours of not eating (generally known as refeeding syndrome), is well documented to lead to often substantial drops in serum potassium with potentially tragic outcomes.

What other clinical scenarios might lend themselves low potassium and lethal cardiac arrhythmias? As noted by Gettes (1), one is similar to what I mentioned above in relation to refeeding syndrome:

“There are several other clinical settings in which lethal cardiac arrhythmias are
believed due, at least in part, to hypopotassemia. These include the arrhythmias associated with acute starvation due to anorexia nervosa, bulimia, or excessive dieting and the arrhythmias occurring in patients with heart failure, particularly those receiving thiazide and loop diuretics. The arrhythmias occurring during acute alcoholic toxicity and withdrawal and the arrhythmias occurring after surgery, particularly cardiac surgery, may also be due, at least in part, to hypopotassemia.”

**What about magnesium?**

As I mentioned in part I of this series, magnesium is an essential part of this story and will be discussed in great detail in subsequent installments. However, before leaving the Gettes (1) paper I would like to share his comments on the potassium/magnesium connection in relation to cardiac arrhythmias:

“In many of the situations in which hypopotassemia is present, it is believed that hypomagnesemia or magnesium depletion even in the absence of hypomagnesemia may coexist and may contribute to the genesis of the associated arrhythmias.”

The author continues:

“…several observations have promoted increasing enthusiasm for the concept that abnormalities in extracellular and intracellular magnesium may contribute significantly to the genesis of lethal cardiac arrhythmias, particularly in patients with hypertension or heart failure who have received thiazide and loop diuretic drugs, in patients experiencing acute alcohol intoxication or withdrawal and possibly in patients with acute ischemia. The overlap with hypopotassemia related arrhythmias in these groups is obvious.”

Gettes (1) then makes a major point that is extremely important from a clinical management standpoint. Addressing both arrhythmias and hypopotassemia requires more than just supplemental potassium:

“The evidence supporting a causal role for hypomagnesemia and arrhythmias is as follows: 1) There are isolated occurrences of ventricular tachycardia, particularly of the torsade de pointes variety, occurring in the absence of abnormalities other than hypomagnesemia. These arrhythmias frequently respond to intravenous magnesium therapy. 2) Hypokalemia in patients receiving long-term diuretic therapy and the associated ventricular arrhythmias often require magnesium as well as potassium replacement before either the hypopotassemia or the arrhythmia is reversed. 3) The arrhythmias appearing in hypertensive patients treated with thiazide and loop diuretics correlate not only to the degree of hypopotassemia but also the serum magnesium concentration and best of all to the product of the change in the magnesium and potassium extracellular concentrations. 4) Therapy with magnesium salts has proven effective in the treatment of supraventricular and ventricular tachyarrhythmias occurring in the absence as well as in the presence of digitalis and torsade de pointes induced by type I antiarrhythmic drugs. 5) There is a possible relation between hypomagnesemia and arrhythmias in the setting of acute myocardial infarction, and there are reports that prophylactic therapy with magnesium salts lessens the incidence of ventricular arrhythmias and death in the first 24 hours after an infarction.”

**Can magnesium and potassium supplementation be effective in the absence of deficiency?**

All discussion up to this point suggested that potassium and magnesium supplementation is effective with arrhythmias only when a pre-existing deficiency exists. According to Gettes (1), this is not necessarily true:

“It must be kept in mind that the ability to treat an arrhythmia with an electrolyte solution does not necessarily indicate that the arrhythmia was the result of a deficiency in that electrolyte.”

The author continues:

“…increasing extracellular magnesium induces electrophysiological changes that may be antiarrhythmic. Similarly, the administration of potassium salts has clinically relevant antiarrhythmic effects even in the absence of hypopotassemia or digitalis excess.”

With this in mind, Gettes (1) states:

“Thus, the ability of prophylactically administered potassium or magnesium salts to impact on the frequency of an arrhythmia in any clinical setting should
not be taken as proof that the arrhythmias were caused by hypomagnesemia or hypopotassemia.”

Thus, Gettes (1) makes it clear that potassium and magnesium deficiency is clearly associated with arrhythmias. However, even if overt deficiency cannot be demonstrated, it may be prudent to still consider the use of supplemental potassium and magnesium in this instance.

**More research on potassium status with use of antihypertensive therapy**

As was mentioned in the paper discussed above by Gettes (1), use of antihypertensive drugs, which is becoming increasingly commonplace today, has a profound impact on potassium metabolism. Furthermore, as was also mentioned by Gettes (1), the impact of antihypertensive drugs on potassium metabolism can often have tragic consequences. Therefore, I would now like to review additional papers that examine this clinically crucial drug-nutrient interaction. The first paper I would like to review is “Antihypertensive therapy and its effects on potassium homeostasis” by Domenic Sica (3). To fully appreciate the impact of antihypertensive drugs on potassium metabolism, the author begins the paper by pointing out a basic but very important aspect of potassium physiology that I mentioned above. Serum potassium levels do not remain static throughout the day. Rather, they can rise or fall based on the impact of several factors. One of these factors is insulin. Sica (3) states:

“…serum K⁺ values transiently decrease after meals as the result of insulin stimulating an intracellular flux of K⁺.”

With the above in mind, the author states:

“Internal K⁺ balance in large measure relates to factors that encourage the intracellular migration of K⁺ such as insulin and β-adrenergic stimulation (mainly a β₂-adrenergic effect). Conversely, a lack of insulin and β-adrenergic blockade can be expected to have the opposite effect on the cellular translocation of K⁺. In this regard, the total body K⁺ content of a 70-kg adult is approximately 4000 mmol. The large majority of body K⁺ resides intracellularly, with about 60 mmol (<2%) of total body K⁺ located extracellularly. As such, since the quantity of K⁺ located outside of cells is so small, slight shifts one way or the other can result in significant changes in serum K⁺ values.”

With the above in mind, it is also interesting to note that exercise can actually raise serum potassium levels:

“Vigorous physical exercise is normally accompanied by transient hyperkalemia…”

Therefore, when we see shifts in serum potassium levels, these shifts do not necessarily reflect dietary potassium intake or whole-body status. Rather what we are seeing very often is redistribution. This is particularly true if serum potassium levels are high or high normal. Sica (3) comments:

“All forms of redistributional hyperkalemia, including those that are medication-related, evolve independent of the underlying state of total body K⁺ balance. Therefore, laboratory values obtained during such situations cannot be used to accurately gauge whether a true total body excess of K⁺ exists or, in the instance of a mixed picture – a patient with a known basis for K⁺ excess and the presence of factors associated with redistribution – to establish the true level of the excess.”

Redistributional hyperkalemia is a particularly important issue with the use of β-blockers:

“The duration of β-blocker-related redistributional hyperkalemia can be fairly prolonged.”

How do antihypertensive drugs alter potassium status? Primarily via their impact on renal function:

“Alterations in systemic K⁺ balance attributable to antihypertensive medications most typically occur on a renal basis. This is the case for several drug classes, including K⁺-wasting and K⁺-sparking diuretics as well as angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs).”

**K⁺-wasting diuretics and hypokalemia**

As I have mentioned repeatedly, the serum potassium level seen on a fasting serum test that presents no concern may not provide a reliable indicator of what might happen to the serum potassium levels when the patient is undergoing the routine stressors encountered during the course of daily living. This is of particular concern if the patient is ingesting K⁺-sparing diuretics. Sica (3) states:

“The typically mildly lowered serum K⁺ values observed with diuretic therapy serves as a starting point for more
significant hypokalemia if epinephrine-mediated transcellular shifts of K⁺ are interposed, as occurs during acute illness. Therein lies the major risk of diuretic-related hypokalemia, particularly when conditions that sensitize the myocardium to arrhythmias such as left ventricular hypertrophy, heart failure, and/or myocardial ischemia are present.”

For me, this quote makes a major clinical point that, if we truly keep it in mind when encountering certain patients, we may prevent an imminent health crisis. When we encounter patients with ongoing cardiac dysfunction who chronically use K⁺-wasting diuretics, it is easy to be lulled into a false sense of security by a fasting serum potassium level that is above 3.5 mmol/l. As was mentioned in part I of this series, this is a potentially tragic mistake. Why? As stated in the above quote, the daily stresses of life could easily drop serum potassium levels to a “straw that breaks the camel’s back” threshold where a stabilized, moderate risk cardiac patient becomes an acute crisis patient literally “in the blink of an eye.”

The next quote I would like to feature from the Sica (3) paper makes an important point about the risks of increased dosages of K⁺-sparing diuretics:

“….the odds ratios for sudden cardiac death with thiazide monotherapy rise as doses increase from 25 to 100 mg/d.”

Equally important is that, at higher doses, potassium supplementation has little impact on the cardiac risk levels:

“The addition of K⁺ supplements to a thiazide-type diuretic appear to have little effect on the risk of sudden cardiac death.”

Fortunately, the addition of a K⁺-sparing diuretic does have a positive impact:

“Alternatively, the risk of sudden cardiac death was substantially reduced in patients receiving a thiazide and K⁺-sparing diuretic in combination.”

What about the K⁺-sparing diuretics?

As was noted above, these diuretics will increase serum potassium levels:

“All aldosterone receptor antagonists (ARAs) increase serum K⁺ levels in a dose-dependent manner.”

Given that both hyperkalemia and hypokalemia can have an adverse impact on cardiac function, it is important to be aware of the type of diuretic your patient may be using when considering potassium supplementation. For, when your patient is using a K⁺-wasting diuretic, potassium supplementation presents little concern concerning an adverse impact. Conversely, if your patient is using a K⁺-sparing diuretic, use of potassium supplementation must be considered cautiously, ideally being instituted only with continuous monitoring of serum potassium levels.

ACE inhibitors and ARBs

These antihypertensive drugs can raise serum potassium levels. However increases are generally minimal with ACE-inhibitors and ARBs:

“Hyperkalemia is an ACE inhibitor- and ARB-associated side effect that has a clear physiologic basis, as is the case for ARAs. ACE inhibitors and ARBs will increase the serum K⁺ value in virtually all treated subjects, but only to a degree (0.1-0.2 mEq/L) that is barely discernable clinically.”

Given the low level of risk, when should serum potassium levels be monitored when patients are receiving ACE-inhibitors? Sica (3) comments:

“The frequency with which serum K⁺ values should be monitored in an ACE inhibitor-treated patient should be based on pretherapy K⁺ values, the level of renal function, the presence of diabetes, whether concomitant medications are being given that might influence systemic K⁺ balance, and past occurrences of hyperkalemia.”

Next Sica (3) comments on the use of potassium supplements:

“Potassium supplements, K⁺-sparing diuretics, and salt substitutes (≈60 mmol/tsp of potassium chloride) increase the probability of developing hyperkalemia if combined with an ACE inhibitor or an ARB.”

(60 mmol of potassium is approximately 2400 mg)

What about nonsteroidal anti-inflammatory drugs (NSAIDS)?

“Nonsteroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase inhibitors also can exaggerate the risk in serum K⁺ seen with either an ACE inhibitor or an ARB by reducing aldosterone concentrations and thereby decreasing K⁺ excretion.”

Sica (3) concludes his paper by making it clear that, with the exception of non-potassium-sparing diuretics, most anti-hypertensive drugs carry a risk
for the creation of hyperkalemia. In turn, concerning supplementation, the author states:

“Limiting the use of K+ supplements in anticipation of a rise in K+ values with these therapies is an important consideration. Weekly or biweekly determinations of serum K+ values are advisable until a patient is stabilized on a regimen comprised of an ACE inhibitor/ARB and an ARA. Once stabilized, serum K+ values can be obtained less frequently, but still need to be obtained regularly.”

Still more concern about non-potassium sparing diuretics

Before leaving the subject of antihypertensives, potassium, and sudden cardiac death, I wanted to present still one more quote that affirms the need to pay attention to an issue that I, as I mentioned, is not getting the attention it deserves. In “Hypokalemia and sudden cardiac death – lessons from implantable cardioverter defibrillators” by Maeder et al (4), the following is stated:

“Non-potassium-sparing diuretics – that is, loop and thiazide diuretics – form a cornerstone in the treatment of patients with hypertension and congestive heart failure. Although this therapy is very efficacious with respect to blood pressure reduction and relief of oedema and pulmonary congestion, it can be associated with significant hypokalemia, which in turn increases cardiac excitability and thus the risk for ventricular arrhythmia.”

Potassium and atrial fibrillation

While much of the published literature on the relationship between potassium and sudden cardiac death addresses ventricular arrhythmias, papers also exist that discuss the relationship between potassium and another significant area of cardiac dysfunction – atrial fibrillation. While atrial fibrillation may present a lower risk in terms of sudden death, it, nevertheless, presents a major concern, as stated by Krijthe et al (5) in their paper “Serum potassium levels and the risk of atrial fibrillation:”

“Atrial fibrillation is the most common sustained arrhythmia in the elderly. Atrial fibrillation is associated with a 3 to 5 times higher risk of stroke, and with a higher risk of heart failure, cardiac mortality, and total mortality. Serum potassium, especially hypokalemia (<3.5 mmol/l), is suggested to be associated with a higher risk of cardiovascular disease, especially ventricular arrhythmias and cardiac arrest.”

The authors continue:

“Clinical studies showed that lower serum potassium levels were associated with a higher perioperative risk of atrial fibrillation.”

Because other studies failed to demonstrate this connection, Krijthe et al (5) conducted a study of 4059 participants of what is known as The Rotterdam Study who had no atrial fibrillation at baseline and for whom baseline levels of serum potassium were measured. What were the results? The authors state:

“In this study, low levels of serum potassium were associated with a higher risk of atrial fibrillation. This association was independent of several potential confounders. We found that hypokalemia (<3.5 mmol/l) was associated with an increased risk of atrial fibrillation in comparison to normokalemia. Also, participants in the lowest quintile of serum potassium (3.85 mmol/l) were associated with a higher risk compared to the median quintile.”

As you might expect from preceding discussions in this newsletter, this study would consider the impact of non-potassium sparing diuretics. In the quote that follows, Krijthe et al (5) comment on this association, using the term “high-ceiling diuretics:”

“…we found that the association of low serum potassium with the risk of atrial fibrillation might be modified by the use of high-ceiling diuretics. High-ceiling diuretics can cause hypokalemia, thereby they might amplify the risk of atrial fibrillation in participants that are at lower levels of serum potassium.”

The last quote I would like to feature from this study presents a hypothesis as to why alterations in serum potassium levels might lead to atrial fibrillation:

“The most likely mechanism through which serum potassium leads to an increased risk of atrial fibrillation is by the influence of potassium on the cell membrane potential. It is proposed that a low serum potassium level causes cellular hyperpolarity, increases resting potential and hastens depolarization.”

Potassium and stroke
As was mentioned in the Krijthe et al (5) study, atrial fibrillation significantly increases the risk for stroke. With this in mind, could increases in potassium intake have a positive impact on stroke incidence? I found three studies that strongly suggested the answer is yes. First, in the study entitled “Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies” by Larsson et al (6) the following is stated:

“Ten independent prospective studies, with a total of 8695 stroke cases and 268,276 participants, were included in the meta-analysis. We observed a statistically significant inverse association between potassium intake and risk of stroke. For every 1000-mg/day increase in potassium intake, the risk of stroke decreased by 11%.”

Next, a study by Seth et al (7) pointed out the following:

“Mean dietary potassium intake was 2611 mg/d. Highest quartile of potassium intake was associated with lower incidence of ischemic and hemorrhagic stroke and total mortality.”

Finally, in a more recent meta-analysis entitled “Potassium-rich diet and risk of stroke: Updated meta-analysis” by D’Elia et al (8) the following was reported:

“In the pooled analysis of 12 studies…greater K intake (average weighted difference: 1.5 g or 38.5 mmol/day) was significantly associated with lower risk of stroke.”

Furthermore:

“In addition, the dose-response analysis showed that for every 1 g/day (25.6 mmol/day) increase in K intake there was a 10% reduction in stroke risk.”

The last paragraph from the D’Elia et al (7) paper makes it graphically clear how important it is that we pay close attention to the relationship between potassium and stroke:

“The World Heart Federation reported over 5.5 million deaths a year from stroke worldwide. Given these data and the results of this updated meta-analysis, an increase in population dietary K intake of 1.5 g/day (or 38.5 mmol/day) could avert over one million deaths from stroke per year on a worldwide scale and is expected to produce overall health benefits by reducing the impact of consequent disabilities. Unfortunately, the average K intake is still far lower than the recommended Adequate Intakes in most populations. Therefore, efforts should be made to favor K consumption, mainly by increase in fruit and vegetable consumption, as recommended by national guidelines for healthy nutrition in the general population and by guidelines for CVD prevention and treatment.”

**FINAL THOUGHTS FOR PART II**

As I hope you can see, potassium metabolism plays a major role not only in sudden cardiac death but in some of the most vexing cardiovascular concerns challenging our country today. In particular, I hope you took special note of the research on potassium and stroke, a relationship that I strongly feel is greatly under appreciated. Given the ever increasing prevalence rates of stroke and given the level of long term hardship and loss of quality of life that all too often accompanies a stroke, I sincerely hope that if you have not already done so, you will start to address potassium status, either through diet, supplementation, or both, with every patient who has a risk for stroke or already has a history.

In part III of this series, I will examine in depth two of the most important and misunderstood aspects of potassium metabolism and its relation to sudden cardiac death and the other cardiovascular issues I have discussed. First, as I mentioned previously, the idea that serum potassium levels stay static throughout the day is a complete fantasy. Therefore, a first-morning, fasting serum potassium level that is optimal can give a very false sense of security. For, a potentially catastrophic drop in serum potassium for only a few minutes a day may be, to use a bad pun, only a “heartbeat away” for many patients. The second important and misunderstood aspect of potassium metabolism I will address is the forces that determine serum potassium at any point in time. Many if not most in the nutritional community believe incorrectly that levels of serum potassium are purely issues of potassium intake and absorption. While this is important, as I have been suggesting throughout this series, there are other factors, many of which include seemingly unrelated dietary constituents that can dramatically and suddenly lower serum potassium levels for a short time. While I realize that this lowering for a short time many not be clinically significant for many patients, for others it may be, very literally, the difference between life and death.

(references, over)
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