



Diurnal Rhythm of Potassium

By Patrick Chambers MD

Introduction

There has been a GREAT deal of BB (Bulletin Board) discussion about potassium. Such discussion has been devoted not only to its importance in general but also specifically to AF. There have been many anecdotal stories testifying to the latter. On the other hand, I'm sure there are many LAFers that are unable to detect any appreciable benefit from potassium supplementation. Perhaps there is an explanation for this.

Although discussion has focused mainly on intake, there has also been some discussion about urinary loss. However, there has been NO discussion of what happens in between intake and urinary excretion/secretion of potassium. That is the topic of this post. I apologize in advance, if this strikes many as too technical. I've omitted some of the references to make it less overwhelming. It may not be important for you to know the why of it, but for me discouraging the unwelcome visitor is easier, if I understand why he comes. If you wish, just skip to the last paragraph.

Background Information

I initially assumed that because blood potassium is so intimately associated with aldosterone, it's diurnal rhythm would follow that of aldosterone (and ACTH/cortisol). But such is not the case.

The diurnal rhythm of aldosterone secretion in healthy individuals parallels that of cortisol and is ACTH dependent. The lowest values are observed from midnight to 4AM. Values peak in the morning around 8AM after which there is a gradual decline throughout the day (assuming a normal sleep-wake cycle). Furthermore, cortisol and ACTH are not always secreted uniformly throughout the day. Episodic spikes can occur when the body is stressed. In humans urinary potassium excretion peaks in the early morning between 0530 and 0730 with a minimum at night from 2100 to 0530. Therefore, the diurnal rhythm of urinary potassium excretion seems to be controlled by the diurnal rhythm of cortisol and/or aldosterone. Not so for blood potassium.

While researching an article on Magnesium and Potassium in LAF

<http://www.afibbers.org/conference/PCMagnesium.pdf>

I stumbled onto an excellent article entitled "Importance of Potassium in Cardiovascular Disease" at

<http://www.medscape.com/viewarticle/438088>

In fact I was so impressed with its progressive views on potassium (their well supported position that hypokalemia is more problematic than hyperkalemia flies in the face of mainstream medicine dogma) that I listed some of these in an 11/29/02 post on the BB. I either missed or just plain forgot (more likely) a reference in that article indicating that plasma potassium follows a diurnal rhythm with a peak at noon and a trough at midnight with an average peak-to-trough difference of 0.62 ± 0.05 mmol/L. In other words blood potassium is lowest when aldosterone secretion is lowest and blood potassium climbs as blood aldosterone/cortisol are peaking.

Because a one mmole reduction in blood potassium generally implies the net loss of 300 mmoles of potassium from the body, it would require over 7 gm of potassium to replenish that lost between its blood concentration peak and its trough.

According to one study, the frequency of hypokalemia (potassium less than or equal to 3.0 mmol/L) is related to the time at which the blood potassium is measured. Not many blood samples for evaluation of potassium are drawn in the evening, especially around midnight (its diurnal nadir).

There is a net flux of potassium from intracellular fluid to extracellular fluid (mainly blood) in the morning and a reverse net flux later in the day. The net fluxes between these two compartments counterbalance the diurnal rhythm in urinary potassium excretion. The flux appears to be driven by osmotic pressure.

Hans brought to my attention another article by Dr Allan Struthers ("What Is the Optimum Serum Potassium Level in Cardiovascular Patients?" - 2004) in which he states that potassium supplementation is pretty useless at least in heart failure patients in the absence of an aldosterone antagonist, e.g., spironolactone or eplerenone. "A serum potassium increase of 0.25 mmol/L elevates serum aldosterone concentrations by 50% or 100%." Virtually 100% of ingested potassium is absorbed and, at least initially, distributed in the blood (total blood volume is about 5 liters). Therefore, just over 1 mmole or about 50 mg of ingested potassium should result in a 50-100% increase in aldosterone.

I'm not sure that I buy this statement completely for normals. In one study of 150 normals 60 mmoles of supplemental potassium daily (about 2.4 gm) increased urinary potassium excretion by only 20.6 mmoles/24h (about 0.8 gm). This potassium supplementation was not accompanied by an aldosterone blocker.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11446724

In another study of eight patients with long QT syndrome the equivalent of 250 mg of spironolactone and 9 gm of supplemental potassium daily (70 kg person) increased blood potassium from 4.0 to 5.2 mmoles/L. Four weeks of this therapy resulted in no serious complications.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14642687

So, although the addition of an aldosterone antagonist may not be necessary, it certainly is effective and does not seem to pose excessive risk. "Clinicians can be comforted by the fact that hyperkalemia does not typically occur in patients with normal renal status, because large potassium loads are efficiently and rapidly excreted." Dr. Michael Lam (www.lammd.com) on p. 246 of his book *How to Stay Young and Live Longer* indicates 15gm daily potassium as safe in a healthy adult. However, although I'm a physician, I'm not your physician and this is not a blank endorsement of the above combination.

Furthermore, these aldosterone antagonists (potassium sparing diuretics) appear to be more effective in increasing blood potassium in the morning and ineffective in the evening. This latter finding is certainly consistent with the diurnal rhythm of aldosterone. It's hard to block aldosterone, if it's not being secreted (evening). Furthermore, angiotensin converting enzyme inhibitors (ACEIs) decrease urinary potassium excretion but do not affect either blood potassium level or its diurnal rhythm. This is also predictable given the fact that changes in blood potassium directly stimulate aldosterone secretion without the renin angiotensin system (RAS). And ACTH, responsible for the diurnal rhythm, also works independently of the RAS.

Other tidbits – Simultaneous supplementation of magnesium with potassium and an aldosterone antagonist increases cellular uptake of both potassium and magnesium. Urinary excretion of potassium increases during fasting (ACTH stimulates aldosterone secretion). Blood magnesium peaks around 0330 and reaches its lowest point around 1530. Its diurnal variation is greater than that of blood potassium.

Discussion

The discordance between the diurnal rhythm of blood potassium and aldosterone is both contradictory and perplexing, at least to me. What is driving the drop in blood potassium? A partial answer may be insulin. Other hormones may be involved. For example, TSH (thyroid stimulating hormone) has a diurnal rhythm and peaks at 11PM.

Blood potassium values decrease postprandially because of insulin released in response to an ingested carbohydrate load. Blood potassium after our largest meal of the day (dinner in America) slowly declines due to insulin (and the absence of any additional dietary potassium). It continues to fall and eventually troughs around midnight. Because the cell membrane of the heart is HIGHLY permeable to potassium ions (there are many passive potassium channels), it would seem that this slow decline in blood potassium causes slow leakage of potassium from within cardiac cells due to the growing concentration gradient (difference between inside and outside). This situation is not rectified until breakfast, underscoring the fact that it is indeed the most important meal of the day.

This intracellular potassium scenario would certainly explain the at risk period (late PM/early AM) for most with vagally mediated episodes. Insulin appears to be incriminated in such individuals. This effect would be accentuated with a larger meal. Potassium supplementation in the evening would seem to be a good idea for VMAFers especially. Addition of an aldosterone antagonist would improve not only intracellular potassium but also intracellular magnesium as well. In ALAF aldosterone/catecholamines and not insulin seem to be the culprit hormones. Insulin and catecholamines both stimulate simultaneous cellular uptake of glucose and potassium (see below). This insulin induced uptake occurs primarily in fat, liver and muscle, including cardiac muscle. However, cardiac muscle (v. skeletal muscle) is relatively less dependent on glucose generated ATP and relatively more dependent on oxygen generated ATP. This latter process occurs in the mitochondria and is called cellular respiration. Heart muscle cells have the greatest concentration of mitochondria at about 5,000 per cell (v. 50 for skeletal muscle). This is one reason why CoenzymeQ10 (protects mitochondria from oxidative damage) deficiency associated with statin therapy is causing an epidemic of heart failure.

Furthermore, aerobic training is associated with enhanced insulin sensitivity in skeletal muscle but diminished insulin-stimulated glucose uptake in the heart. Aging further diminishes this insulin sensitivity in the heart. Therefore, compared to skeletal muscle glucose and potassium uptake by the heart is relatively less, causing the potassium concentration gradient for the heart to be relatively more problematic than for skeletal muscle. So, at least in the physically fit and the elderly, potassium is more likely to leak from heart cells. This may be why low blood potassium appears to affect cardiac muscle more than skeletal muscle, smooth muscle, liver or fat cells.

Obviously aldosterone/catecholamines can aggravate VMAF and insulin can do the same for ALAF. That's why we have a mixed category.

IMHO the common denominator linking VMAF and ALAF (adrenergic lone atrial fibrillation) appears to be potassium, at least in part. I think P cells are the other part. P cells provide the arrhythmogenic substrate, hypokalemia provides the PACs (and PVCs) or trigger factor and autonomic tone provides the rest. These would fulfill Coumel's three required ingredients for AF. Autonomic tone and hypokalemia both cause shortening of the atrial effective refractory period (AERP). The Bordeaux Group has clearly shown that the PVs in those with paroxysmal AF provide a much more arrhythmogenic substrate via markedly shorter AERP than PVs in controls (see previous CR topic discussion). In the March 2004 AFIB Report Hans reported an article from the Cleveland Clinic stating that P cells, normally found only in nodal tissue (SA node, AV node), were found in 5/5 with AF and in 0/5 controls without AF. I think these P cells become damaged, because it takes many years for LAF to develop. Otherwise, we'd have LAF from birth. And, of course, the success of PVI for AF certainly supports this interpretation.

My own personal experience with LAF episodes suggests that vagal tone and low potassium work in concert. My 9AM potassium values are usually right around 4.5. That would put me well under 4 during the night. The simultaneous appearance of high vagal tone and low potassium would accentuate the shortening of AERP. This would conveniently explain my typical middle of the night episodes.

However, during the late morning or afternoon I've had occasional episodes (less than 10% of the total) that appear to be related to possible dehydration and/or hypoglycemia. Both of these stimulate not only catecholamine but also ACTH and aldosterone release (as does physical or emotional stress). Oftentimes I've had just a pastry for breakfast. Talk about an open invitation to an insulin surge. My HR is usually over 70 with low vagal tone at the time, but the episode is nonetheless triggered by a vagal maneuver. Presumably the insulin and fasting state induce the hypoglycemia. According to one study, AERP is shortest under hypoglycemia (v. hyperglycemia) in the left atrium (v. the right atrium). The hypoglycemia induced catecholamine secretion (for gluconeogenesis, i.e., glucose is produced by the liver to address the hypoglycemia) may cause additional shortening of the AERP. It achieves this through the potassium channels. A greater potassium gradient would presumably augment this shortening.

On very rare occasions I've triggered an episode by a short sprint. Here again, the timing of the episodes in the late afternoon before dinner suggests hypoglycemia and catecholamine activity. In fact the catecholamine surge that occurs causes a rapid, transient transcellular shift of potassium, resulting in a short-lived but dramatic fall in blood potassium of approximately 0.5-0.6 mmol/L, depending on the magnitude of the effort. Although these shifts are evanescent and readily reversible, the transient drop in blood potassium triggers PACs (and PVCs) and sometimes AF.

I've also had episodes that are postprandial, but only in the evening (presumably because there is more reinforcing vagal tone at this time). Initially I thought this was due primarily to the alkaline tide associated with a meal and subsequent urinary potassium loss. Then I thought that it was due to the effect of insulin and loss of cardiac intracellular potassium due to the increased concentration gradient. Then I thought I might have a mild problem with gastroesophageal reflux (GERD)/lower esophageal sphincter (LES). GERD is increased in athletes, especially in those that run, which I do. However, now I'm inclined to think that evening meals with poor K/glucose and K/Na ratios are the primary problem. I once thought that seafood (lots of salt) at dinner was a trigger. Looking back on such episodes, these meals were often low on the veggies and high on the simple carbs (love my desserts).

My present view of my flavor of LAF is that:

Late evening or early morning episodes – probably vagally induced and low potassium related (diurnal nadir)

Late morning or afternoon episodes – probably physical stress/dehydration/hypoglycemia and low potassium related (insufficient potassium intake and excess potassium loss)

Early evening episodes – especially low potassium related, aggravated by an imprudent dinner (see above)

Undoubtedly the majority of you are different. But if you look closely at your personal particulars, perhaps there is a common thread.

Like James D, I've become less inclined to differentiate adrenergic from vagally induced. Both arms of the ANS cause shortening of the AERP. So does low blood potassium. So either arm in combination with low potassium can trigger an episode.

Hans went from typical stress related adrenergic AF to typical vagally mediated AF, when he briefly took spironolactone, which has a vagotonic effect (in addition to being a potassium sparing diuretic). So, it seems that LAF can appear anywhere along the spectrum of autonomic tone. And remember, Hans always ran right at the lower limit of normal with his blood potassium. And his aldosterone, a vagolytic, and cortisol were always elevated (both aldosterone and cortisol bind to mineralocorticoid receptors, i.e., cause urinary loss of potassium). Furthermore, although there was never much change in his blood potassium (3.5 – 3.7 mmol/L). His urinary potassium (and magnesium) excretion continued to escalate, as he approached the next episode. Obviously there was continual leakage of potassium from the intracellular compartment to maintain the constant blood potassium concentration in the face of escalating urinary loss.

Many LAFers have commented on what seems to be a repeating periodicity to their episodes. It seems that the length of my episodes were directly proportional to the time interval before the next episode. Others, including myself, have speculated that the answer to both of these observations may lie with ANP (atrial natriuretic peptide). This is secreted during episodes via a mechanism that involves atrial cell stretch. It is an aldosterone antagonist. Perhaps during the episode there is a repletion of intracellular potassium. Perhaps when sufficiently repleted, the episode terminates. Perhaps after termination subsequent life style and diet combine to slowly deplete these intracellular potassium stores until some threshold value is breached and another episode is triggered.

Another interesting question is why proton pump inhibitors (PPI) not only relieve GERD but also appear to relieve AF. Is it only because there is less irritation of the lower esophagus (and less vagal stimulation)? Or is it also because of an improvement in potassium balance? Gastric acid production is a two step process. First, gastric parietal cells secrete KCl into the lumen. Then the gastric cell H⁺/K⁺ pump goes into action and the end result is HCl in the lumen. This latter is the proton pump, because H⁺ is no more than a proton. By inhibiting it less H⁺ is lost in the gastric juice. Less potassium is lost in the urine, because the blood is less alkaline (since the gastric fluid is less acidic). Who knows what the critical factor is? Perhaps Dean can provide some insight.

I think Jackie has hit upon the proper regimen in taking bedtime complex carbohydrates and supplemental potassium. Better listen closely to that girl. And, Jackie, I must thank you again for that tip from your nutritional pioneer and chiropractor Royal Lee, who said "if you can feel your heart beating at night when lying in bed, you are deficient in potassium". This undoubtedly is due to the mild BP elevating effects of low blood potassium. The heart has to work just a little harder, enough to make you aware of its beating, when all else is quiet. Because the insulin induced drop in blood potassium that occurs after a carbohydrate meal is caused by osmosis (entry of glucose into a cell brings water with it, thereby decreasing the concentration of intracellular potassium, thereby stimulating the Na⁺/K⁺ pump to increase intracellular potassium, thereby lowering blood potassium), it would seem prudent to always ingest potassium with your carbohydrates. MW of glucose is 174 and the MW of

potassium is 39, which is a 4.5 to 1 ratio. Perhaps 5 to 1 might be a good ratio for dietary simple sugars to potassium, especially for between meal snacks (if you must). As Jackie has pointed out, KCl can cause gastric irritation, at least if taken on an empty stomach. You should never let a meal go by without potassium supplementation thereby exploiting its buffering effect in this regard.

I heartily agree with the general recommendation to shift from simple to complex carbohydrates in our diets. I used to think this advice was better directed at those that struggle with their weight. However, given my problems with episodes being triggered when I skip or delay meals, I think thin people can also benefit from it. Eat properly and don't skip meals. Graze rather than gorge. Earlier is better than later.

I've been experimenting with spironolactone off and on for over two years. It peaks in blood in about 2 hours with a 10-20 hour half life. I started with just 25mg per day and slowly increased the dose. Initially I didn't supplement with potassium, but soon started supplementing a small amount. Then I tried increasing the dosage of spironolactone. Then I'd withdraw spironolactone or potassium, reintiate, etc., and gauge the effect on episodes. Although I consider myself adventurous, I don't take chances needlessly. I'm presently experimenting with a total daily dose of 100mg spironolactone divided between AM and PM. In the PM I accentuate the potassium supplementation (1.5 - 2.5 gm per day in 300mg pulses throughout the day), because it is during this time frame that blood aldosterone level is lowest. Might as well stimulate the production of more aldosterone via potassium supplementation. Then at least the PM spironolactone has some aldosterone to block. Accentuating the afternoon magnesium supplementation (I prefer neutralized aqueous magnesium AKA Waller water throughout the day) gives even more bang for the buck, since spironolactone conserves magnesium as well as potassium. This is precisely the time when magnesium absorption should be greatest, since blood magnesium is lowest at 1530. Although my PACs are better controlled with this approach, the experiment is ongoing, at least until I either sprout tits (gynecomastia) or require Viagra (impotence), both reportedly adverse effects of spironolactone. Increased vagal tone continues to be my main trigger and disopyramide continues to deflect that problem. Furthermore, I think good potassium balance potentiates the disopyramide. This is certainly consistent with the fact that disopyramide is both a sodium and a potassium channel blocker. If the potassium gradient is less, then fewer potassium channels have to be blocked.

One brief word on Waller water. This is an aqueous magnesium preparation divined by our own Erling Waller. He was one of the first to realize that many LAFers owe their malady to magnesium deficiency, at least in part, since it is inextricably entwined with maintenance of intracellular potassium. He created the recipe (soda water and milk of magnesia), which can be found at www.afibbers.org/Wallerwater.htm
Thank you, Erling.

In a previous post on the BB I suggested that a portable potassium meter might be a very useful item for an LAFer. Horiba and Hoskin Scientific make good ones, but they are not quite ready for prime time, at least not in humans. I recently purchased an Omron BP monitor (less than \$50 at Costco) and have found that relative evening BP (slightly higher systolic than normal) and/or the presence of PACs when lying on my right side (see previous CR topic) both provide feedback on probable intracellular potassium. Being on top of my daily potassium supplementation definitely decreases my evening PACs and BP. Although this is only an indirect approach at best, it presumably helps prevent PM AF.

Conclusion

You can't directly control the arrhythmogenic substrate (PVs) except through PVI. You can't effectively control vagal or sympathetic tone except through meds. That leaves low potassium. The long and the short of this post is that if you want to get serious about controlling your episodes, then you must get serious about your potassium intake. You must address not only how much you ingest but when you ingest it. Either avoid those situations that assault your internal potassium balance (stress,

hypoglycemia, dehydration, ...) or increase your daily potassium (and magnesium) intake with appropriately time targeted supplementation. Although food sources are best, they are much less convenient and intake is less quantifiable. And then there's the glycemic load problem they pose. Presently there is great resistance within mainstream medicine to combining potassium supplementation with an aldosterone blocker. Hyperkalemia and life threatening ventricular arrhythmias are of great concern. However, with the pioneering work of Drs. Struthers, MacDonald and others this overemphasized concern may soon take a back seat to a rational combination regimen. In my view it is quite plausible that this LAF epidemic might disappear entirely if such an aggressive regimen were pursued by those afflicted. The study that needs to be done is one similar to the above referenced one on LQTS (long QT syndrome), but on LAF patients instead. But until then please remember my above disclaimer and make sure you have good renal function. In fact I'm due to have some lab work done this week to monitor my blood potassium.

I sincerely hope you find this information useful.

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