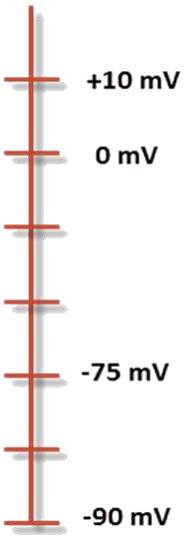
Why Am I Giving Calcium for Hyperkalemia?

If you are reading this monograph, it's perhaps because you have had to manage a patient with a dangerously high potassium level – possibly on several occasions. When confronted with such a patient who has an ECG that shows significantly widened QRS complexes, we reach for the calcium chloride or calcium gluconate. After giving one or two amps*, the QRS interval begins to narrow and takes on a more normal appearance.

But ***why are we giving the calcium*** and ***how is it able to do this***? If you try looking this up, you are not likely to find anything other than the fact that calcium helps manage hyperkalemia and is involved – *somehow* – with "moving" the threshold potential. To understand why calcium is indicated in this condition, we need to review a little about action potentials and also how K^+ exerts its effect on the myocardium.



This scale on the left depicts values for the resting transmembrane potential. As we move toward zero, the resting potential *decreases* since there is *less difference in the K^+ concentrations between the inside and the outside of the cell* (I'll repeat this numerous times in this monograph). Since we are normally in negative territory (-90 mV), a decrease in resting membrane potential means we are moving *UP the scale – not DOWN the scale!* This is where everyone gets very confused. Just remember that the term "membrane potential" is really an abbreviation of the actual term, *membrane potential* ***<u>difference</u>****!* Therefore, the resting membrane potential ***decreases (depolarizes) whenever it moves closer to ZERO*** ("**0 mV**" on the scale).

The normal working myocyte has a resting transmembrane potential of around -90 mV. This is maintained primarily by K^+ ions. K^+ is the only major ion that can freely pass back and forth through the cell membrane (sarcolemma) without having to be transported or ushered in depending on certain phenomena (depolarization, for instance). Na^+ and Ca^{++} do not have this ability. Because there are some large negatively-charged ions trapped in the cell, their electrostatic force draws in very large amounts of K^+ in an attempt to achieve neutrality. However, once the transmembrane potential reaches -90 mV, the osmotic force generated by the remaining extracellular K^+ (or, more precisely, the lack thereof) achieves enough strength to resist any further attraction by the large negatively-charge sulfates and phosphates. This results in a large concentration of K^+ ions INSIDE the cell and a much smaller concentration OUTSIDE the cell (a 50:1 ratio).

As for *depolarization*, when the depolarizing impulse from an adjacent cell arrives, it causes enough Na^+ channels to open *simultaneously* to create an *action potential* – which, in turn, causes the rest of the Na^+ channels to open, allowing the sudden, rapid and quite massive influx of Na^+ ions into the cell. So far, so good. Everything appears to be working normally. But let's see what happens when the extracellular K+ level begins to rise.

First, a brief word about the Na+ channels themselves: you must understand that Na+ channels open because of *depolarization* of the cell. A small or slight depolarization may open a few Na+ channels but that won't do anything. *There must be enough Na+ channels opened* ***<u>simultaneously</u>*** *to create enough depolarization to cause the opening of all the remaining Na+ channels*. Therefore, the arriving impulse must be *strong enough* (manifested by the *height of Phase 0*) to achieve the "threshold" potential and it must do so *rapidly enough* (manifested by the *slope of Phase 0*) to assure the *simultaneous activation* of the "threshold" number of Na+ channels. One other thing you must understand: the Na+ channels are only open for a msec or so and then they

slam shut! At this point they are essentially *locked* and *the only thing that can unlock them is repolarization*. Repolarization does not "re-open" the Na^+ channels; it only "unlocks" them making them available to re-open with the next depolarization. Now if the elevated extracellular K+ level continues to cause a baseline depolarization, repolarization is going to be less and less effective because the baseline resting transmembrane potential will be less and less negative. More and more of those Na+ channels are going to remain shut and locked!

What effect does an increase in extracellular K^+ have on the cell? As the extracellular K^+ begins to rise, there is less voltage difference between the inside and outside of the cell (reduction of resting transmembrane potential). This constitutes *depolarization*, though not the type of depolarization that triggers an action potential like an arriving impulse. As this *slower* depolarization continues, the resting transmembrane potential gradually *decreases*. This causes some Na^+ channels to open and shut but there are never enough Na+ channels open simultaneously to sustain an action potential and thus open the rest of the Na^+ channels. So the transmembrane resting potential gradually decreases and fewer and fewer Na^+ channels remain open. As the impulses continue to arrive, there are fewer and fewer Na+ channels available for this massive influx of Na^+ to pass through. It begins to take each action potential longer and longer and soon significantly fewer Na^+ ions are entering the cell during the action potential. This causes the QRS (which represents Phase 0 of the action potential on the ECG) to widen and the maximum voltage to decrease. As the extracellular K^+ level rises even more, there comes a point when there are simply too few Na^+ channels available to initiate an action potential. This is how hyperkalemia kills!

In the beginning – when the resting transmembrane potential has decreased *just a small amount*, the myocytes become "irritable." It now takes less stimulation to cause an action potential and some ectopy may occur. This is because the resting transmembrane potential – by decreasing slightly – has moved closer to the threshold potential (around -70 mV) yet there are still sufficient Na^+ channels remaining to be activated. This can predispose to increased ectopy since it takes less depolarization now to trigger an action potential.

But this "irritability" is short-lived. As the K^+ level rises further, it inactivates too many Na^+ channels to allow for an effective action potential. It is at this point that we see the QRS interval on the ECG begin to widen and start to take on a sine wave appearance. Also, by this time the atria have become paralyzed and there are no more P waves. The ventricles are still functioning because the conducting system is more resistant to the effects of hyperkalemia and the ventricles are now activated by *sinoventricular conduction*.

Please note that I am NOT relating any of these changes to a specific serum K^+ ***level. I feel that the patient is in danger whenever <u>any</u> ECG manifestations of hyperkalemia begin to appear***. Remember that *prolongation of the P wave and the PR interval* are both manifestations of hyperkalemia! Obviously, neither is very specific, but *if you have reason to suspect hyperkalemia* and *these findings are present*, *be extremely vigilant!*

So now you want to give Ca^{++} intravenously to improve the situation. Excellent decision… but WHY are you giving it? *What do you intend for it to do?*

We know that at this point the rising K^+ level has inactivated a large number of Na^+ channels. This is because the resting transmembrane potential has depolarized to a point so close to the threshold potential that there are not enough Na^+ channels left to function effectively. We need to create some more space between the resting transmembrane potential and the threshold potential which will allow more Na^+ channels to be available. There are – theoretically – two ways to go about this: first, we could *reduce* the threshold potential (i.e., depolarize it even further moving it closer to zero) or second, we could *increase* the resting transmembrane potential (i.e., move it further away from zero). The second option is the only feasible one.

If we *increase* the resting transmembrane potential, we could move it closer to -90 mV (where it should normally be) which would allow more Na^+ channels to be available for activation. But to do this, we are going to have to increase the voltage difference between the inside and the outside of the cell. We are going to have to use an ion in which the concentration outside the cell will be much higher than inside and – importantly - there cannot be the same mobility as the K^+ to move inside the cell. And it especially should not be involved with any transports or exchanges involving K^+! Obviously, K^+ is out! How about Na^+? Care to give a couple of amps of 3% NaCl to the patient IV? *Not a good idea!* Besides, Na^+ exchanges with K^+; giving extra Na+ might stimulate more K+ to be excreted from the cell and increase the extracellular K^+ even more. Also, many (if not *most*) patients with hyperkalemia have very reduced renal function and a large Na^+ load could acutely worsen an already very dire situation. How about calcium? There is a very small amount of Ca^{++} inside the cell compared to its extracellular concentration (while intracellular K^+ is 50 times greater than extracellular K^+, extracellular Ca^{++} is about 12,000 times the intracellular Ca^{++}). And we can give a lot of it without doing any immediate harm to the patient. Its downside, however, is that – while the cell membrane is not as freely permeable to Ca^{++} as it is to K^+ - Ca^{++} <u>*can*</u> be transported inside the cell and there <u>*are*</u> Ca^{++} channels that will admit the Ca^{++} at regular (and frequent) intervals. Therefore, while Ca^{++} can certainly help us restore stability to the cell, *that effect isn't going to last very long*. However, it will buy us some time to initiate other K^+-reducing measures.

We give a couple of amps of Ca^{++} gluconate and what happens? We have suddenly increased the resting transmembrane potential and it returns closer to -90 mV, thus putting some distance between it and the threshold potential. Now, when the action potential arrives, it finds more Na^+ channels available to open and the action potential begins to look more normal. The QRS intervals begin to narrow and appear more recognizable.

You may feel that there is a *paradox* here: we increased the resting transmembrane potential by adding more positive ions (Ca^{++}) to the extracellular milieu in order to increase (move away from zero) the difference between the resting transmembrane potential and the threshold potential. But isn't hyperkalemia doing the *same thing* and yet getting the *opposite effect*? To understand the answer to this conundrum, you must realize three points…

First, potassium is the only one of the major ions involved in repolarization and depolarization that can move relatively freely back and forth across the sarcolemma (cell membrane). Because of this, under normal circumstances, K^+ is the controlling factor in the determination of the resting transmembrane potential. The normal resting transmembrane potential of the working myocyte is -90 mV which is only 6 mV away from the equilibrium potential of K^+.

Second, when the level of extracellular potassium *increases*, it is increasing across from a much larger intracellular concentration. Thus, the difference in voltage between the inside of the cell and the outside of the cell (the resting transmembrane potential) *decreases* and a *gradual depolarization* occurs.

Third, by *acutely* adding Ca^{++} to the extracellular fluid, we are giving more positive ions to an extracellular concentration that already has a much, much larger concentration of ions than its intracellular concentration. We have essentially taken control of the resting membrane potential away from K^+, at least momentarily.

But a person can have hypercalcemia as well without giving extra calcium. Should we see the same effect then? Maybe – to some extent – but not like when we give it intravenously to treat hyperkalemia. And remember also, naturally-occurring hypercalcemia typically occurs in people with otherwise normal (or very *near* normal) serum potassium levels.

*$CaCl_2$ has 3 times the ionic equivalence of Ca^{++} gluconate. Check references for recommended doses.