Potassium Depletion and Cardiac Hypertrophy

How Does It Work?

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For a number of years, many clinicians have believed that potassium depletion should be avoided in the treatment of hypertension, and that potassium supplementation might be advantageous in such patients. The Dietary Approaches to Stop Hypertension (DASH) diet, a diet that is low in sodium and replete with potassium, is now being recommended as a standard lifestyle modification for patients with hypertension or other cardiovascular risk factors. Cardiac hypertrophy is a well-known complication of hypertension that is believed to have substantial consequences in afflicted patients. However, the interactions between potassium supplementation, blood pressure, and cardiac hypertrophy are still incompletely understood.

In this issue of Hypertension, Dr Burnier’s laboratory reports that potassium supplementation ameliorates both renal and cardiac hypertrophy in both 1 and 2 renin-gene mice given deoxycorticosterone acetate (DOCA) and sodium supplementation. Furthermore, these scientists are able to dissociate the effects of potassium supplementation on blood pressure from the effects on organ hypertrophy. Specifically, these authors demonstrated that whereas potassium supplementation did lower blood pressure in the 2-renin gene mice that developed substantial hypertension with DOCA and sodium supplementation, it did not significantly affect blood pressure in the normotensive 1-renin gene mouse that also developed cardiac and renal hypertrophy, the former to a lesser degree than seen in the 2-renin gene model supplemented with DOCA and sodium. We should note that the authors chose to effect potassium replacement by using potassium chloride rather than combining potassium with other anions. It is clear that combining potassium with anions that generate base may have substantial advantages over potassium chloride in a number of clinical settings. However, as the experimental model used by the Burnier group was also complicated by metabolic alkalosis, the use of potassium chloride was quite reasonable.

As stated above, Burnier and colleagues found that potassium supplementation attenuated both cardiac and renal hypertrophy in the 1- and 2-renin gene animals given DOCA and sodium. Frankly, the effects of potassium supplementation on the observed renal hypertrophy were fairly predictable. It has been known for many years that hypokalemia induces substantial renal hypertrophy, and this hypertrophy occurs largely in the proximal tubule and has been ascribed to the increased ammoniagenesis that is stimulated by a reduced serum potassium concentration. Although the authors noted that potassium repletion did not ameliorate the renal hypertrophy as much as the cardiac hypertrophy in their models, this is likely because of the direct effects of other hormones activated in their model, a point discussed by the authors. However, the profound effects of potassium supplementation to ameliorate cardiac hypertrophy in the 2 models are not so easily explained and will generate considerable excitement.

This potentially important article clearly demonstrates that potassium repletion may, independent of blood pressure changes, ameliorate cardiac hypertrophy. Now the important question is “how does it do this?” To answer this question, one would logically pose the question how reduced potassium concentration might cause cardiac hypertrophy in the first place. Unfortunately, this question is not as simple as it seems for several reasons. First and foremost, hypokalemia alone does not appear to cause cardiac hypertrophy in a consistent manner. We have observed that dietary potassium depletion in the rat does not produce cardiac hypertrophy by itself, but it does potentiate cardiac hypertrophy induced by aortic constriction. It may be that in the current article, hypokalemia potentiates any number of other potential hypertrophic stimuli present in the 1-renin mineralocorticoid and sodium-supplemented model. Certainly this model with its attendant activation of the renin-angiotensin-aldosterone system, exogenous mineralocorticoid and extracellular volume expansion is replete with potential explanations for cardiac hypertrophy, even in the absence of hypertension. If one accepts the concept that many of these pathways toward cardiac hypertrophy involve alterations in calcium cycling, it is quite clear that the hypokalemia induced by DOCA and sodium supplementation could enhance or accelerate the hypertrophic response in this model.

An additional pathway toward cardiac hypertrophy deserves some discussion. Recent work from several laboratories has established that signal transduction through the Na/K-ATPase, a process known to involve caveolae, Src activation, reactive oxygen species generation, and ultimately activation of extracellular signal regulated kinase, may be important in a number of processes including cardiac hypertrophy. We believe that this signal transduction is induced by circulating cardiotonic steroids, also known as digitalis-like substances. As it is clear that the effects of cardiotonic steroids are magnified in settings where extracellular potassium is reduced, we would argue that the observ-
vations of the Burnier laboratory are consistent with a molecular antagonism of circulating cardiotonic steroids by the increased plasma potassium that resulted from potassium supplementation. Moreover, it is likely that the circulating concentrations of these cardiotonic steroids would likely be higher because of the sodium loading used. It is unfortunate that the authors of this article did not measure the concentrations of these cardiotonic steroids or discuss this possibility in their manuscript.

This point aside, it appears that the Burnier group has made an interesting and potentially important contribution to our understanding of potassium in the setting of hypertension. It is particularly interesting in view of the results of the Randomized ALdactone Evaluation Study (RALES) study, which demonstrated a marked advantage for patients with congestive heart failure to receive spironolactone in addition to their other medications. As one reviews the RALES study, it is clear that the spironolactone-supplemented patients did have statistically higher serum potassium values. This would lead one to speculate that some of the beneficial effect of spironolactone may be attributable to this higher serum potassium. However, before recommending aggressive potassium supplementation in all patients at risk for cardiac hypertrophy, one must consider the recent report from Canada demonstrating increases in hyperkalemia and sudden death in heart failure patients treated with spironolactone. This disclaimer aside, the Burnier article furnishes additional basic science justification for the DASH diet, and opens up a new area for subsequent investigations.

References
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