Potassium Depletion and Diastolic Dysfunction

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Changes in extracellular potassium concentration affect nearly all aspects of myocardial function. Reductions in potassium concentration alter the resting membrane potential, membrane conductance for sodium and potassium, repolarization time, relative refractory time, and conduction velocity. The arrhythmogenic consequences of these effects of potassium depletion are well recognized by the medical community. However, the potential influence of hypokalemia on mechanical function of the heart has not been as thoroughly appreciated.

More than 10 years ago, Fitzovich et al.1,2 analyzed changes in left ventricular mechanical function of dogs who were either potassium replete or moderately depleted as a result of 7 days of low-potassium intake together with a high-sodium intake and thiazide diuretics. The depleted dogs had a mean plasma potassium concentration of 3.2 mmol/L. The investigators observed in the depleted dogs significant impairment of both systolic and diastolic function, with the most striking effect noted in peak rate of ventricular filling, reduced by ≈49% during acute elevation of preload. The same group extended the study to normal volunteers age 22 to 30 years whose cardiac mechanical function was studied noninvasively by echo and Doppler techniques.2,3 Compared with the potassium replete state, during potassium depletion (plasma potassium reduced by 1.0 mmol/L), the peak rate of ventricular filling was reduced by 14%.

The study of the effect of potassium depletion on diastolic function in hypertensive rats by Matsui et al.4 described in the accompanying article has added significantly to the understanding of the mechanism of the actions of potassium to affect relaxation and filling of the ventricle. The analysis in Dahl salt-sensitive rats compared ventricular relaxation in animals on normal and high levels of NaCl intake (which produces moderate potassium depletion and hypertension in this model) with or without potassium supplementation. High-sodium intake resulted in significant reductions in the rate of active relaxation of the ventricle, as assessed by the deceleration time of peak early diastolic left ventricular filling obtained from Doppler-measured transmural inflow, the slope of the pressure curve, and the time constant of the isovolumic relaxation phase, variables known to be associated with diastolic function and active relaxation of the ventricle. In contrast, the animals receiving potassium supplementation preserved normal diastolic function, although arterial pressure remained at hypertensive levels. Matsui et al.4 also analyzed reduced nicotinamide-adenine dinucleotide phosphate oxidase activity and reactive oxygen species (ROS) formation in myocardial tissue, finding that the tissue from the high-salt Dahl rats with impaired diastolic function produced more ROS than that of the rats on normal NaCl intake. Especially interesting was the finding that potassium supplementation that preserved diastolic function also reduced the ROS formation to the normal NaCl control level. Furthermore, they observed a protective effect on diastolic function in high-sodium rats given the ROS scavenger 4-hydroxy-2,2,6,6-tetramethyl-piperidine-N-oxyl. On the basis of the protection afforded by both potassium and 4-hydroxy-2,2,6,6-tetramethyl-piperidine-N-oxyl with reductions in reduced nicotinamide-adenine dinucleotide phosphate oxidase activity, they propose an attractive hypothesis that excess ROS formation may be causally related to the impairment of diastolic function seen in the Dahl rats on a high-sodium chloride intake. The finding reported by MacCarthy et al.5 in the aortic banding pressure overload model of heart failure supports this proposal; they found that impaired left ventricular relaxation was improved effectively by antioxidant treatment with vitamin C or deferoxamine. Support for a proposed relationship between potassium depletion and elevated ROS levels can be derived from the in vitro study by McCabe et al.,6 finding a strong, consistent stimulatory effect of decreasing potassium concentration over a range from 7 to 3 mmol/L on ROS formation from endothelial and vascular smooth muscle cell lines and human white blood cells. Excessive ROS levels could affect active relaxation by irreversible direct oxidation of the thiol residue of the sarcoplasmic reticular calcium uptake pump7 or by impairment of the physiological phosphorylation of phospholamban.8 Active relaxation is believed to be associated with removal of calcium ions from the cytoplasm, either by transporting the ions to the extracellular fluid or into the sarcoplasmic reticulum by the sarcoplasmic reticular calcium uptake pump. Therefore, the linkage proposed by Matsui et al.4 among potassium depletion–induced excess ROS formation, inhibition of sarcoplasmic calcium uptake by ROS, and diastolic dysfunction is worthy of serious consideration.

The relationship of moderate potassium depletion to diastolic dysfunction is important for several reasons. First, active relaxation and diastolic function are impaired before contraction abnormalities become apparent in several types of cardiac pathology including those associated with hypertension, diabetes mellitus, and in forms of hypertrophic and ischemic cardiomyopathy. In many such patients, hemody-
Dynamic abnormalities resulting in the clinical picture of heart failure are not because of derangements of systolic function, particularly in the early stages of the disease. Instead, the functional defect may be due to active relaxation abnormalities. Second, several patient groups with demonstrated high-risk levels for developing cardiac failure because of diastolic dysfunction are also at risk of developing moderate hypokalemia: the elderly, because of poor nutrition; the hypertensive, because of diuretic therapy; and blacks, possibly because of dietary choices. In these large patient populations doubly at risk of developing diastolic impairment, attention to maintenance of normal potassium status may be warranted, particularly considering that diastolic dysfunction in heart failure is considered to be a predictor of poor prognosis, and few effective treatment options are available.

Third, the proposed link between potassium depletion and diastolic dysfunction suggests the possibility that the hypertensive, the diabetic, and those patients with left ventricular hypertrophy with or without signs of failure, because they all are likely to have a degree of diastolic dysfunction, will be sensitive to the deleterious effects of even moderate hypokalemia.

The study by Matsui et al and the hypothesis that they propose have special relevance to a large patient population. Although the clinical significance of the proposal and its implications remain to be evaluated, the investigations required to do so should be straightforward and could be completed in the near future.

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References
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