SUMMARY OF CURRENT THERAPY

Relationship of Potassium to Cardiac Disease

JOHN J. SAMPSON, M.D., F.C.C.P.*
San Francisco, California

I. Historic Note

In 1878 and 1882, Ringer1,4 published his classic experiments on the effects of sodium, potassium and calcium on the isolated frog heart. A minimum concentration of sodium was essential in the solution bathing the heart for maintenance of any contraction. Calcium, in excessive concentration, increased the rate and force of contraction and excess potassium tended to slow the rate and contractile force, eventually stopping the heart in diastole. A balanced concentration of these ions was considered necessary for proper function.

Hering5 in 1903 terminated paroxysms of ventricular tachycardia and ventricular fibrillation in the dog heart by intravenous injection of a concentrated potassium chloride solution. Rothberger and Wintersberg,4 in 1911, obtained similar effects of potassium on atrial and ventricular ectopic beats and tachycardia.

Wiggers6 in 1930 first suggested the possible use of potassium to terminate the ventricular fibrillation of accidental electrocution in man, but the first actual therapeutic use in human cardiac arrhythmias was reported in the same year by Sampson and Anderson.6a, 6b Potassium had been used prior to this date chiefly as the iodide in treatment of syphilis and as a diuretic. Its poisonous effect on the heart, when retained in nephritic patients, was recognized by Smillie7 in 1915 and others. Oral doses of potassium chloride, as large as 12 and 15 gm. had been given to normal men by Norn8 and by Wilkins and Kramer9 with transient rises of serum K to approximately 7 mEq./L. and 8 mEq./L., without untoward effect. Sampson and Anderson6a then used KC1, potassium citrate and potassium acetate in oral doses, from 1.0 to 16 gm., the average dose being 5.0 gm., a 25 per cent aqueous solution, and KC1 intravenously in a 1.0 gm. dose in a 1 per cent solution, on atrial and ventricular tachycardias and ectopic beats in 42 patients with rheumatic, hypertensive and coronary heart diseases, and in 16 patients without evident organic heart disease.

Harrison and associates10 gave in 1930 the first known reports of the reduction of K concentration in the heart muscle of patients dying with heart failure. This suggested an explanation of the greater effectiveness of K on arrhythmias of patients with organic heart disease.

In the 50 per cent of the patients of Sampson and Anderson6a whose arrhythmias favorably responded to the potassium, were two patients with ventricular ectopic beats induced by overdosage with digitalis. This suggested that there may be a relation between myocardial depletion of potassium by the digitalis in toxic doses, as had been shown by Wood and Moe11 in 1938 and others, and the occurrence of arrhythmias. The uniform decrease of digitalis-induced ventricular ectopic beats by K therapy was reported by Sampson, Alberton and Kondo12 in 1943, and the use of potassium in the treatment of these arrhythmias recommended.

*Clinical Professor of Medicine, University of California and Senior Physician, Mount Zion Hospital.
The work of Lown, Levine and their associates since 1951, demonstrated the effect of lowered body potassium in the precipitation of serious cardiac arrhythmias, especially paroxysmal atrial tachycardia with A-V block, by sensitizing the myocardium to relatively smaller doses of digitalis, than generally inducing ventricular ectopic rhythms. Ventricular extrasystoles and ventricular tachycardia are more common in digitalis intoxication without K loss. The critical need for K therapy in the serious atrial arrhythmias was presented. However, a dilemma was occasionally presented when atrial arrhythmia such as atrial flutter would require more digitalis than previously given, rather than the antidote potassium. Friedberg and others have recommended use of 0.1 mg. acetyl strophantidin intravenously because of its brief action to indicate digitalis need by slowing of the rate of the ventricle.

II. Current Concepts of Potassium Therapy in Digitalis-Induced Arrhythmias.

With the present advances in molecular biology, a rationale is developing for the various clinical and physiologic actions of heart muscle. In 1952, intracellular potential studies were made by Hodgkin and Huxley on the squid giant nerve axone, and since then, Hoffman and others have investigated the myocardial fiber potentials by microelectrode puncture. This has led to increasing evidence in support of an ionic hypothesis for the myocardial action current, rhythmicity, excitability, conductivity and contractility. This ionic hypothesis assumes a resting potential within the fiber of about -90 mv. with a high K+ concentration, a threshold level of K+ concentration which when passed initiates depolarization, with Na+ entry into and K+ loss from the fiber as the potential quickly falls to 0 and overshoots to a positive potential. There is then a short, rapid phase of return, a plateau and a slower repolarization to the resting potential as K+ is regained and Na+ lost.

The transmembrane action potential curve of the muscle fiber indicates the timing and magnitude of certain fiber functions, especially rhythmicity and conduction (Hoffman and associates). The character of these potential curves after excitation, differ in various cardiac tissues. Thus, S-A and A-V nodal fibers exhibit a slow transmembrane potential rise, making for poor conduction and the rapid repolarization fall in diastole is associated with increased rhythmicity or excitability. The bundle of His and Purkinje fibers exhibit rapid rise with high conduction function and a slower descent in repolarization with poorer rhythmicity.

These potential variations are dependent not only on the normally high K+ and low Na+ concentration of the resting fiber, but also on the intracellular/extracellular gradient of K+ and Na+ and the forces moving Na+ and K+ across the cell boundaries. It is thus apparent why cell membrane Na+ and K+ gradients are often the determinants of certain functions. Increase in extracellular K+ concentration, or decrease in Na+ concentration, will decrease the transmembrane action potential by diminishing the inward flow of Na+ and the outward flow of K+, modify its time pattern and increase the fiber excitability. This may be exaggerated by previous depletion of intracellular K+ or acquisition of excess Na+.

Digitalis in toxic doses depresses the active transmembrane transport of Na+ (Caldwell and Keynes) and K+ and may block the entrance of K into many body cells, even in patients with general K depletion. This accounts for the abrupt rise in serum K when potassium is given rapidly, either orally or by vein, to treat ectopic rhythms induced by digitalis (Fisch, et al.). Lown, et al. These rises may paradoxically damage the contractile quality of the myocardium, and experimentally in dogs, increase the fatality rate of digitoxin poisoning. The clinical implication of these findings is to use K slowly, preferably not intravenously unless low serum K exists, and to follow the serum K levels when contemplating successive doses of K. Renal insufficiency may cause rapid and critical
elevation of serum K. Physical exercise may give transient, but unimportant elevations of serum K. Dangerous elevations of serum K may occur when adrenal corticosteroids or aldosterone secretion inhibitors are being given to a patient.

Toxic concentrations of digitalis glycosides (ouabain) were shown by Vassalle, Greenspan and Hoffman to induce extrasystoles more readily in the Purkinje fibers than in the ventricular muscle cell. Foci in the Purkinje system are probably the sources of the "ventricular" ectopic rhythms. The increased excitability presumably accompanied the rapid depolarization of the cell following decreased action potential and resting potential. The action of K in ouabain toxic arrhythmias was primarily to suppress the automaticity of the Purkinje fibers. Also, an initial action of K was to increase depolarization of the cell and relatively prolong the repolarization phase of the action potential curve. In fatal K poisoning, the diastolic standstill is the result of pacemaker and conduction suppression.

III. Potassium and Cellular Osmolarity

Since K is the major intracellular cation, the maintenance of its concentration as well as sodium, is required for osmolar balance with extracellular fluids and intact cell structure. In heart failure, K is lost, not only from the myocardium, but as much as one-third of the exchangeable body K may be depleted (de Deuchaisnes, et al). This loss occurs from inanition, diuretics and probably hypoxia with its effects on cellular metabolism. Potassium depletion is often not reflected in plasma K concentration, e.g. levels of 4.0 mEq./L., when exchangeable body K+ has been reduced over 25 per cent.

The lowered intracellular osmolarity has been suggested as a teleologic explanation (by Elkingston and Squires) for the "dilutional edema" of hypo-osmolar extracellular fluid often found in heart failure.

There is no doubt that as cardiac efficiency improves, increased amounts of potassium are retained by the body cells and the sodium concentration of the extra-
cellular fluid rises with excretion of water in excess of Na.

The value of K as a diuretic, as used for many years in cardiac dropsy, has been supported by the current administration to patients with intractable cardiac edema, of KCl in divided doses of 3 to 8 gm. daily. The precautions against initiating hypokalemia, as mentioned above, should be observed.

IV. Potassium and the Myocardial Contractility.

The continuing studies on the physico-chemical changes that enter into the contractile cycle of heart muscle fibers have shown that K plays an essential role. Potassium enters into the oxidative phosphorylation cycle with production of the major energy source, adenosine triphosphate. Potassium presumably increases the activity of the enzyme ATP-ase, entering the phase of muscular relaxation and of other enzyme systems. Its migration out of the cell following electrical excitation during systole has been mentioned, and its reentry with water during diastole is essential for restoration of the mechanical, as well as the electrical resting phase of the muscle.

These few paragraphs are presented to give some of the highlights in the development of the practical considerations of potassium's important relation to normal and diseased myocardial function. It is an artificial approach to cardiac function to single out this ion for isolated consideration, other than where striking deviations warrant it. Sodium, calcium and probably other cations, as well as the complex of other tissue constituents including enzymes are generally involved in the biologic reactions in which potassium seems to be the dominant element concerned, as was originally implied by Ringer.

REFERENCES


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BRONCHIAL OBSTRUCTION AND ASTHMATIC REACTION

Pulmonary congestion has great importance in the development of the asthmatic reaction. Bronchial obstruction also plays a fundamental role in its genesis while the importance of bronchospasm seems to be unclear. To obtain a favorable change in the clinical condition of the patient, it is necessary to improve one of these two factors (congestion or obstruction). Adrenalin has great influence on pul- monary blood volume. Steroids have a broader action and they influence both factors. There is no parallelism between pulmonary congestion and pul- monary dinstensibility.