Effect of Hypercapnia on Myocardial Potassium Movement in the Dog

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ABSTRACT
This investigation tested the hypothesis that uptake of potassium during respiratory acidosis is secondary to the increased catecholamine activity which accompanies hypercapnia. The plasma K+ concentration of simultaneously drawn arterial and coronary sinus blood samples from dogs was determined under three conditions: (1) hypercapnia (25% CO2, 75% O2), (2) normocapnia (25% N2, 75% O2) + propranolol (a beta-receptor blocker), and (3) hypercapnia + propranolol. The change during hypercapnia from uptake of K+ to loss of K+ after administration of propranolol (0.05 mg/kg, iv) was statistically significant. However, the administration of propranolol during normocapnia had no effect on myocardial K+ movement. Changes in heart rate and myocardial contractility did not explain the change in myocardial K+ movement during hypercapnia following the administration of propranolol. These data suggest that uptake of K+ is secondary to the increased catecholamine activity which accompanies hypercapnia.

KEY WORDS
respiratory acidosis heart potassium propranolol catecholamine beta-receptor blockade

The purpose of this investigation was to study the uptake of potassium by the myocardium during respiratory acidosis (1-4). The mechanism of this movement is not clearly understood. One explanation suggests that hydrogen ions (H+) and potassium ions (K+) exchange mole for mole between cells and extracellular fluid during respiratory acid-base disturbances (5). This theory is based on the suggestion that cardiac muscle may not be well buffered (6). Thus, during respiratory acidosis, elevated Pao2 will cause a relatively greater increase in [H+] inside the myocardial cell than it will outside. This proposed simple exchange of H+ for K+ would, therefore, result in a net uptake of K+ by the cardiac muscle cells. This theory can be seriously questioned because recent studies have shown that the buffer capacity of cardiac muscle is greater than that of both extracellular fluid and skeletal muscle (7).

Fenn and co-workers (8, 9) advanced the hypothesis that the ratio of intracellular potassium concentration ([K+]i) to extracellular potassium concentration ([K+]e) changes in the same direction as the ratio of intracellular hydrogen ion concentration ([H+]i) to extracellular hydrogen ion concentration ([H+]e). Brown and Gott (10) have shown that this theory correctly predicts the observed loss of K+ from skeletal muscle during respiratory and metabolic acidosis. They point out that if this mechanism is to account for the uptake of K+ by the myocardium during respiratory acidosis, then "cardiac tissue must be less well buffered than blood by a factor greater than the initial ratio of [H+]i/[H+]e, where [H+]i is the intracellular hydrogen ion concentration of cardiac tissue." However, Clancy and Brown (7) showed that the buffer capacity of cardiac muscle is greater than the buffer capacity of skeletal muscle. Thus, it is questionable if this theory can explain the uptake of K+ by the myocardium during respiratory acidosis.
Several authors have reported that hypercapnia leads to an increased level of circulating catecholamines (11–14). As an alternative proposal, this investigation will test the hypothesis that uptake of K\(^+\) by the myocardium during respiratory acidosis is secondary to stimulation of beta receptors by this increase in catecholamine concentration. A sympathoadrenal release of catecholamines has been recognized as an important factor in the adaptation of the cardiovascular system to sudden increases in PCO\(_2\) (15). In 1962 Stafford (16) reported that epinephrine caused an uptake of K\(^+\) by isolated rabbit auricles. This uptake of K\(^+\) could be blocked by dichlorisoprenoline (a beta-receptor blocker) but not by phenoxybenzamine (an alpha-receptor blocker). In 1968 Cingolani et al. found that catecholamines produced K\(^+\) uptake in isolated perfused hearts and that this uptake was blocked by propranolol (17). This hypothesis is supported by recent work in this laboratory (18) in which rats were depleted of catecholamines by administration of reserpine. Isolated heart preparations from these animals lost K\(^+\) during respiratory acidosis. This hypothesis was tested by studying the effect of propranolol on myocardial K\(^+\) movement during hypercapnia. If uptake of K\(^+\) by the myocardium during respiratory acidosis is secondary to stimulation of beta receptors by catecholamines, then the administration of propranolol should prevent the uptake.

**Methods**

Mongrel dogs (15–20 kg) were anesthetized with 30 mg/kg, iv, of sodium pentobarbital. The dogs were intubated and ventilated with a positive-pressure respirator. Throughout the entire experimental procedure, they breathed either the control gas mixture consisting of 75% O\(_2\)-25% N\(_2\) or the test gas mixture of 75% O\(_2\)-25% CO\(_2\). Cannulas were placed in the right and left femoral arteries to obtain arterial blood samples and measure blood pressure and in the right femoral vein to allow administration of drugs. The pH of anaerobically drawn arterial blood was intermittently measured at 37°C with a thermostatically controlled pH microelectrode. The heart was exposed by either a midsternal or a right lateral incision. The sinoatrial node was blocked with an injection of 95% ethanol, electrodes were attached to the right auricle, and the heart was paced at approximately 140 beats/min with an external electronic stimulator. A cannula, passing through the right external jugular vein, was placed in the coronary sinus. The placement of this cannula was periodically checked by palpation during the experiment and by examination at autopsy. In some of the experiments, a cannula for measurement of left ventricular pressure was passed through an incision in the left auricle into the left ventricle. The dogs were then given 10,000–20,000 units of sodium heparin to prevent blood clotting. All blood samples were immediately centrifuged, the plasma was decanted, and the [K\(^+\)] was determined on an Instrumentation Laboratory flame photometer.

In this study, K\(^+\)\(_{\text{A—V}}\) will represent myocardial K\(^+\) movement, the arterial plasma [K\(^+\)] minus the coronary sinus [K\(^+\)]. Thus a positive K\(^+\)\(_{\text{A—V}}\) indicates an uptake of K\(^+\) by the heart, and a negative K\(^+\)\(_{\text{A—V}}\) indicates a loss. Three groups of experiments were carried out to evaluate myocardial K\(^+\) movement. In the 16 dogs of group 1, simultaneous arterial and coronary sinus blood samples were drawn at 10-minute intervals for 80 minutes. After a 20-minute control period breathing the control gas mixture, the dogs were switched to the test gas mixture. In 6 randomly selected dogs, propranolol (0.05 mg/kg, iv) was given after 20 minutes of ventilation with the test gas mixture. In the 6 dogs of group 2, the effect of an intravenous dose of propranolol (0.05 mg/kg) on K\(^+\)\(_{\text{A—V}}\) during ventilation with the control gas mixture was studied. Samples were collected as in group 1. In group 3, the completeness of beta-receptor blockade by propranolol was tested. Heart rate and intraventricular pressure response to 8 μg of intravenously administered isoproterenol were observed before and after intravenous administration of 0.05 mg/kg of propranolol in an unpaced preparation in which the sinoatrial node was not blocked by injection of alcohol.

**Results**

The results from the experiments on group 1 (hypercapnia) are shown in Figure 1. During the control period, the average pH was 7.35 and the K\(^+\)\(_{\text{A—V}}\) was slightly negative, indicating a loss of K\(^+\) from the myocardium. After 20 minutes of control ventilation, the dogs were switched to the test gas. The pH fell to 6.80 and the K\(^+\)\(_{\text{A—V}}\) became positive and remained positive in the dogs not given propranolol. However, in the six dogs treated with

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propranolol, $K^{+}_{A-V}$ became negative immediately after administration of the drug. Analysis of variance (19) showed that $K^{+}_{A-V}$ after administration of propranolol was significantly different ($P < 0.01$) from the corresponding $K^{+}_{A-V}$ of dogs not receiving the drug.

$K^{+}_{A-V}$ during the experiments on group 2 (normocapnia + propranolol) is shown in Figure 2. Again during the control period $K^{+}_{A-V}$ was slightly negative and pH was 7.38. After the administration of propranolol (0.05 mg/kg, iv), $K^{+}_{A-V}$ fluctuated about zero. A two way analysis of variance (20) did not show a difference between the $K^{+}_{A-V}$ values before and after propranolol in group 2 ($P > 0.25$). This demonstrates that propranolol has no effect on $K^{+}_{A-V}$ during normocapnia.

Figure 3 illustrates the effectiveness of beta-receptor blockade by 0.05 mg/kg of propranolol and the effect of this drug on left ventricular pressure in an un paced heart (group 3). An intravenous injection of 5 ml of saline had no effect on heart rate, peak left ventricular pressure, or left ventricular diastolic pressure. An injection of 8 $\mu$g of isoproterenol, a sympathomimetic which interacts with beta-receptors, in 5 ml of saline produced a marked increase in the heart rate from 176 to 204 beats/min, an increase in peak left ventricular pressure, and a decrease in left ventricular diastolic pressure. After the effect of isoproterenol had dissipated, propranolol, 0.05 mg/kg, was given intravenously. This had no effect on peak left ventricular pressure, left ventricular diastolic pressure, or heart rate. Isoproterenol (8 $\mu$g) was again injected and the characteristic effects expected when beta-receptors are stimulated—increased peak left ventricular pressure, decreased left ventricular diastolic pressure, and increased heart rate—were not observed. This indicates that 0.05 mg/kg of propranolol is an effective dose to produce beta-receptor blockade.
Figure 4 shows the simultaneous arterial $[K^+]_A$ and coronary sinus $[K^+]_V$ in a typical experiment in a dog from group 1 which received propranolol. After switching from the control gas mixture to the test mixture, the arterial plasma $[K^+]_A$ gradually increased. It was not affected by the administration of propranolol. The positive $K^+_{A-V}$ that occurred after switching from the control to the test gas mixture resulted from a decrease in coronary sinus plasma $[K^+]_V$ and not from an increase in arterial plasma $[K^+]_A$. Similarly, the negative $K^+_{A-V}$ following the administration of propranolol resulted from an increase in the coronary sinus plasma $[K^+]_V$ and not from a decrease in arterial plasma $[K^+]_A$. This shows that the changes in $K^+_{A-V}$ are representative of myocardial $K^+$ uptake or loss.

**Discussion**

The experiments in group 1 show that hypercapnia is associated with an uptake of $K^+$ by the myocardium and that this uptake is not present after the administration of propranolol (Fig. 1). The results from group 2 indicate that the administration of propranolol to a normocapnic dog has no significant effect on $K^+_{A-V}$ (Fig. 2). We do not feel that simultaneous flow measurements were required because with each intervention there was either no change in $K^+_{A-V}$ (group 2) or a reversal in the direction of $K^+_{A-V}$ (group 1).

These results are consistent with the hypothesis that the uptake of $K^+$ during hypercapnia is secondary to the increased stimulation of beta-receptors by catecholamines. Other possible causes of changes in $K^+_{A-V}$ in the dogs in group 1 after administration of propranolol must also be considered.

The first of these possible causes is an increase in the arterial plasma potassium concentration ($[K^+]_A$). A rapid change in $[K^+]_A$ might give a spurious change in $K^+_{A-V}$. For example, if $[K^+]_A$ rose rapidly, the simultaneous coronary sinus plasma potassium concentration ($[K^+]_V$) would not be as high. Thus, the $K^+_{A-V}$ would be positive. Figure 4 shows that this is not the case. Although $[K^+]_A$ rises throughout the experiment, there are no rapid changes. Even when $[K^+]_A$ is rising most rapidly, it is only increasing at the rate of 0.05 mEq liter$^{-1}$ min$^{-1}$. The changes in $K^+_{A-V}$ clearly result from a change in $[K^+]_V$. When the dogs were switched from the control gas mixture to the test mixture $[K^+]_V$ fell, indicating an uptake of $K^+$ by the myocardium. Conversely, after propranolol was administered the rapid increase in $[K^+]_V$ indicates that the myocardium is losing $K^+$.

A second possible explanation of the change in $K^+_{A-V}$ after administration of propranolol in the dogs of group 1 might be based on past research which correlated changes in various cardiovascular parameters with myocardial $K^+$ movements. Sarnoff (21) has shown that increased heart rate and increased aortic pressure are associated with a loss of $K^+$ from the heart. This cannot explain the $K^+$ loss following propranolol administration in group 1, because heart rate was held constant by electrical pacing and peak left ventricular pressure, an indication of aortic pressure, decreased. Further investigations into the relationship of hemodynamic changes and myocardial $K^+$ flux by Gilmore and Gerlings (22) showed that an increase in peak left ventricular pressure in an isovolumic heart, and thus presumably an increase in wall tension, is associated with a loss of $K^+$ from the heart.
In our experiments, we were unable to control either the peak left ventricular pressure or the volume of the heart because of the nature of the preparation. However, we did measure peak left ventricular pressure and can estimate left ventricular size by using data of Wildenthal et al. (23, 24), which showed that left ventricular end-diastolic pressure, which we measured, gives a reasonable estimate of left ventricular size. Based on these data, in those dogs in group 1 which received propranolol, there was a slight increase in left ventricular volume, but there was also a decrease in peak left ventricular pressure after administration of propranolol. Thus there was probably only a slight, if any, increase in wall tension. In contrast, Gilmore and Gerlings (22) increased the tension of the myocardial wall by increasing peak left ventricular pressure from 50-150% of the base-line peak pressure. Presumably this increased the wall tension in their isovolumic preparation by a proportional amount. We seriously doubt that the small increase in wall tension which occurred in our dogs after the administration of propranolol can explain the negative K⁺ A→V.

A second argument against a change in wall tension explaining the negative K⁺ A→V in the dogs in group 1 which received propranolol is based on observations made after switching from the control gas mixture to the test mixture. This sudden increase in Pco₂ had no effect on left ventricular volume but did increase peak left ventricular pressure and thus presumably wall tension. Yet in the face of this increased wall tension, there was a positive K⁺ A→V.

The K⁺ loss in group 1 after administration of propranolol does not appear to be explained on the basis of hemodynamic alterations or changes in [K⁺] A. Thus, although it may not be the sole determinant, the uptake of K⁺ by the myocardium during respiratory acidosis appears to be largely dependent on stimulation of beta-receptors by the increased catecholamines present during hypercapnia.

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References


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