Continuous Intravascular Monitoring of Epinephrine-induced Changes in Plasma Potassium


Ion-selective electrode catheters were used for continuous monitoring of epinephrine-induced changes in plasma potassium in different parts of the circulation of anesthetized greyhounds. Bolus injections and continuous infusions of epinephrine produced dose-related changes consisting of an initial transient increase followed by a decrease to levels below control. The latter part of the response was relatively short-lived in the case of bolus injections, but when the epinephrine was administered by continuous infusion, a progressive fall was maintained for the duration of the infusion. During the period when potassium levels were undergoing an acute change, marked differences were seen between concentrations in different parts of the circulation. Further studies are needed to delineate the incidence and extent of similar changes in humans, and their significance in producing dangerous dysrhythmias. (Key words: Ionic potassium. Measurement techniques: Ion-selective electrode. Monitoring: potassium. Sympathetic nervous system: catecholamines, epinephrine.)

Following the initial observations of Bachromejew (1932) and D'Silva (1934), it has been well-documented that in the experimental animal, epinephrine produces an initial transient increase in plasma potassium concentration followed by a more prolonged decrease to a level below control. The initial increase is the result of a release of potassium from the liver, and both liver and skeletal muscle have been implicated in the uptake that results in the subsequent decrease. Furthermore, it has been suggested that the release of potassium from the liver is the result of interaction between the α- and β-receptor-mediated effects of epinephrine while the subsequent uptake is mediated predominantly by β-receptors.

It is difficult to follow such transient changes and also, to evaluate the contribution from various parts of the body to the overall alterations using intermittent sampling. Changes may be missed because of inappropriate timing of the samples, and it is not possible to detect trends early or to accurately follow the time course of any change. These limitations can now be overcome by using fast-responding potassium-selective electrode catheters which are suitable for continuous intravascular monitoring. Treasure has demonstrated the convenience of using multiple electrode catheter recordings in following the changes in plasma potassium induced by bolus injections of epinephrine in the anesthetized cat. We report here the results of a more detailed study to delineate the time course and extent of changes in plasma potassium in four separate sites in the circulation of the anesthetized greyhound following varying doses of bolus injections and continuous infusions of epinephrine.

Materials and Method

Potassium-selective Electrode Catheters

Plasma potassium was monitored with electrode catheters similar in design to those used in earlier studies (fig 1). The electrode consists of a length of polyvinyl chloride tubing (outside diameter 1 mm) with the potassium-selective membrane supported by a porous ceramic plug at the end which is placed in the bloodstream. The tubing contains an internal silver/silver chloride reference electrode and is filled with 100 mM KCl solution. The membrane separates the blood from this solution, and the potential difference developed across it bears a logarithmic relationship to the plasma potassium ion activity. In a previous paper, the relationship between activity measured by these electrodes and the concentration measured by flame photometry has been established, and for practical purposes can be considered linear. After logarithmic conversion, the voltages recorded from the electrode catheters can therefore be interpreted in terms of plasma potassium concentration in millimoles per liter.

The electrode is inserted into the bloodstream by passing it down an outer catheter until its tip is just protruding. The outer catheter is filled with Hartmann's solution which forms a salt bridge connecting the blood to an external silver/silver chloride reference electrode via a 3-way tap. The provision of the latter allows blood

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samples to be withdrawn via the outer catheter for calibration purposes. The internal and external reference electrodes are connected to a high-input impedance telemeter and the signals from this received by a car radio. The speaker output from the radio is decoded and displayed as a continuous record on an ultraviolet recording oscillograph (SE 2005).

Animal Experiments

Six greyhounds weighing 21–26 kg were anesthetized with sodium pentobarbitone. The animals were then intubated with a cuffed endotracheal tube and artificially ventilated with air (Palmer “Ideal” Respiratory Pump). Airway CO₂ was monitored during the course of the experiments (Beckman L/B2 infrared CO₂ analyzer) and ventilator settings adjusted to give an end-tidal CO₂ of approximately 5%. No muscle relaxants were used. Arterial blood pressure was continuously recorded via a cannula inserted in the left femoral artery; another cannula was introduced into the left jugular vein for the administration of drugs. Four potassium electrode catheters were then introduced percutaneously into the following sites: 1) thoracic inferior vena cava (above entry of hepatic veins) via the right femoral vein (TIVC); 2) abdominal aorta via the right femoral artery (AORTA); 3) abdominal inferior vena cava (below entry of hepatic veins) via the left femoral vein (AIVC); and 4) superior vena cava via the right jugular vein (SVC).

All the electrode catheters were inserted until the tips were judged to be located in the chosen sites as estimated from measured marks on the catheters. The positions were subsequently confirmed by postmortem examination of the animals. The electrodes used were calibrated before and after each experiment by dipping them into standard solutions of 2, 4, and 8 mmol·l⁻¹ KCl (in 150 mmol·l⁻¹ NaCl). A typical calibration sequence is shown in figure 2. According to the Nernst equation, at room temperature (20°C), the potential difference across the membrane should change by ±17.5 mV for a doubling or halving of the external (sample) potassium concentration. Electrodes that exhibited less than 90% of the theoretical Nernstian response or showed excessive drift were rejected. Following placement of the catheters, the animals were anticoagulated with heparin (400 IU·kg⁻¹).

The responses to epinephrine given as bolus injections (1.0 μg·kg⁻¹; 2.0 μg·kg⁻¹) and continuous infusions (0.1 μg·kg⁻¹·min⁻¹; 1.0 μg·kg⁻¹·min⁻¹) were then recorded. All dosages were administered via the cannula.
Blood samples were taken up the outer catheters before each dose of epinephrine and analyzed using an in vitro ion-selective electrode. The potassium concentrations of these were then related to the voltages recorded from the in vivo electrodes at the time of sampling, and in this way, it was possible to derive the subsequent plasma concentrations from the voltage changes which occurred.

**Results**

These are summarized in tables 1 and 2, and representative traces are shown in figures 3–6. Bolus injections of epinephrine produced dose-related changes consisting of an initial increase followed by decrease to levels below control in the four monitored sites. The dominant role of the liver in producing these effects is reflected in the large changes seen in the TIVC compared with those in the other sites.

Continuous infusion of epinephrine resulted in a similar biphasic response. Much smaller changes were observed following infusion of 0.1 μg·kg⁻¹·min⁻¹ compared with 1.0 μg·kg⁻¹·min⁻¹, but the general pattern of response was similar. The most striking feature of the effect of continuous infusion was the continuing decrease in plasma potassium levels as the infusion progressed. Small differences were observed in the levels in the four monitored sites as they decreased during the infusions, but no definite conclusion can be reached regarding the relative contributions of the liver and the peripheral tissues in the absence of corresponding flow measurements. Renal excretion does not appear to play a major role in producing the decrease since studies have shown that this is decreased during epinephrine infusions.

**Discussion**

The use of in vivo electrodes to obtain simultaneous continuous recordings from several sites in this study has brought to light two features that merit further discussion. First, the recordings show that the potassium-releasing effects of epinephrine on the liver are manifest within one circulation time, and are also relatively short-lived. Thus, following a bolus injection of 1.0 μg·kg⁻¹, an increase in the TIVC plasma potassium was observed within 12.1 ± 0.5 s, the peak occurred at 36.0 ± 4.5 s, and the response had passed on to the hypokalemic phase within 1.6 ± 0.1 min. The rapidity of changes such as these highlight the difficulties of accurate delineation of the response when intermittent sampling techniques are used. The second point to note is that marked differences may exist between the plasma potassium concentrations in different parts of the circulation. This is particularly so during the hyperkalemic part of the response where rises recorded in the AIVC and SVC were minor com-
### Table 1. Changes (Means ± SEM) in Plasma Potassium Concentrations in Response to Bolus Injections of Epinephrine

<table>
<thead>
<tr>
<th>Site at Different Dose (μg · kg⁻¹)</th>
<th>Plasma K⁺ (mmol·L⁻¹)</th>
<th>Injection-Response Time (s)</th>
<th>Injection-Response Time (min)</th>
<th>Injection-Maximum Time (s)</th>
<th>Injection-Minimum Time (min)</th>
<th>Duration of Hyperkalemic Phase (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Maximum</td>
<td>Minimum</td>
<td>5 min</td>
<td>15 min</td>
<td>Control</td>
</tr>
<tr>
<td>2.0 TIVC</td>
<td>3.6 ± 0.1</td>
<td>8.0 ± 1.0*</td>
<td>2.6 ± 0.2*</td>
<td>2.9 ± 0.2*</td>
<td>3.2 ± 0.1</td>
<td>13.4 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>AIVC</td>
<td>3.5 ± 0.1</td>
<td>4.5 ± 0.3*</td>
<td>3.1 ± 0.1*</td>
<td>3.2 ± 0.1*</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>AORTA</td>
<td>3.5 ± 0.1</td>
<td>6.2 ± 0.5*</td>
<td>2.8 ± 0.1*</td>
<td>3.0 ± 0.1*</td>
<td>3.0 ± 0.1*</td>
</tr>
<tr>
<td></td>
<td>SVC</td>
<td>3.7 ± 0.1</td>
<td>4.5 ± 0.4</td>
<td>3.1 ± 0.1*</td>
<td>3.2 ± 0.1*</td>
<td>3.3 ± 0.1*</td>
</tr>
<tr>
<td>1.0 TIVC</td>
<td>3.5 ± 0.1</td>
<td>6.2 ± 0.4*</td>
<td>2.6 ± 0.1*</td>
<td>2.7 ± 0.1*</td>
<td>3.2 ± 0.1</td>
<td>12.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>AIVC</td>
<td>3.6 ± 0.1</td>
<td>4.3 ± 0.2*</td>
<td>3.1 ± 0.1*</td>
<td>3.2 ± 0.1*</td>
<td>3.5 ± 0.1*</td>
</tr>
<tr>
<td></td>
<td>AORTA</td>
<td>3.5 ± 0.1</td>
<td>5.2 ± 0.4*</td>
<td>2.9 ± 0.1*</td>
<td>2.9 ± 0.1*</td>
<td>3.1 ± 0.1*</td>
</tr>
<tr>
<td></td>
<td>SVC</td>
<td>3.7 ± 0.2</td>
<td>4.2 ± 0.2*</td>
<td>3.2 ± 0.2*</td>
<td>3.3 ± 0.1*</td>
<td>3.4 ± 0.3</td>
</tr>
</tbody>
</table>

The number of tracings analyzed for each site and dose were above control values. Hyperkalemic phase describes that part of the response where levels were above control values. *P < 0.05 on paired t testing with the corresponding control value.

### Table 2. Changes in Plasma Potassium Concentrations (Means ± SEM) in Response to Continuous Infusion of Epinephrine at the Rate of 1.0 μg · kg⁻¹ · min⁻¹ (for 15–23 min) and 0.1 μg · kg⁻¹ · min⁻¹ (for 15 min)

<table>
<thead>
<tr>
<th>Site at Different Dose (μg · kg⁻¹ · min⁻¹)</th>
<th>Plasma K⁺ (mmol·L⁻¹)</th>
<th>Injection-Response Time (s)</th>
<th>Injection-Maximum Time (min)</th>
<th>Duration of Hyperkalemic Phase (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Maximum</td>
<td>15 Min after Starting Infusion</td>
<td>15 Min after Stopping Infusion</td>
</tr>
<tr>
<td>1.0 TIVC</td>
<td>3.6 ± 0.1</td>
<td>7.1 ± 0.5*</td>
<td>2.1 ± 0.1*</td>
<td>2.6 ± 0.2*</td>
</tr>
<tr>
<td></td>
<td>AIVC</td>
<td>3.6 ± 0.2</td>
<td>4.0 ± 0.2*</td>
<td>2.3 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>AORTA</td>
<td>3.5 ± 0.1</td>
<td>5.2 ± 0.3*</td>
<td>2.3 ± 0.2*</td>
</tr>
<tr>
<td></td>
<td>SVC</td>
<td>3.7 ± 0.1</td>
<td>3.9 ± 0.2</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>0.1 TIVC</td>
<td>3.3 ± 0.1</td>
<td>3.5 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>AIVC</td>
<td>3.4 ± 0.1</td>
<td>3.4 ± 0.1</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>AORTA</td>
<td>3.3 ± 0.1</td>
<td>3.4 ± 0.2</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>SVC</td>
<td>3.4 ± 0.1</td>
<td>3.5 ± 0.1</td>
<td>3.0 ± 0.1</td>
</tr>
</tbody>
</table>

The number of tracings analyzed for each site and dose were above control values. Hyperkalemic phase describes that part of the response where levels were above control values. *P < 0.05 on paired t testing with the corresponding control value.
pared with those seen in the TIVC and AORTA. This demonstrates clearly the limitations of studies in which measurements were made solely on peripheral venous samples.

Our experiments were performed on dogs and the question arises as to whether or not similar changes might be expected in humans. There is general agreement in the literature that epinephrine does cause a decrease in plasma potassium in humans\(^\text{16-21}\); and it has also been shown that this can be abolished by \(\beta\)-blockade.\(^\text{22}\) The hyperkalemic part of the response, however, has not been so well-documented. There is only one study\(^\text{23}\) showing a consistent small early increase in plasma potassium, while in two others,\(^\text{17,20}\) small increases were observed in only a small minority of the subjects studied. No increases were recorded by several other workers.\(^\text{14,16,18,19,22}\) Examination of the methodology in these studies revealed that the epinephrine had not always been administered intravenously (intramuscular or subcutaneous routes having been used instead); the times at which the first sample was taken varied from 0.5–15 min; and analyses had usually been performed on peripheral venous samples.

The discrepancies in the above results are not entirely unexpected since the tracings from our animal experiments have clearly demonstrated first that the response is dose-related, second that the hyperkalemic phase is transient, and third that plasma potassium in the SVC (and therefore by inference, the peripheral arm veins) does not accurately reflect the changes in the arterial circulation. Definitive proof will ultimately depend on hepatic venous, thoracic inferior vena cava, or arterial monitoring, but until such studies are available, we feel that there is reasonable evidence to suggest that epinephrine will produce a broadly similar response in humans as in the dog.

It is generally considered that significant dysrhythmias may result if plasma potassium is abnormally high or low.\(^\text{24}\) The results from this study indicate that rapid and profound changes in plasma potassium may occur in the arterial circulation when epinephrine is administered. The bolus doses which were found to produce significant changes (1.0 and 2.0 \(\mu\)g \(\cdot\) kg\(^{-1}\)) are well within the range used in cardiopulmonary resuscitation in humans (where doses in excess of 10 \(\mu\)g \(\cdot\) kg\(^{-1}\) are often used), but as far as we are aware, there has been little discussion of their implications with regard to the management of the dysrhythmias which are a frequent complication in these circumstances. Insofar as the effects of continuous infusions are concerned, although the changes observed with the smaller dose in the first 15 min were minor, the trend was for plasma levels to fall, and it is

**Fig. 5.** Response to 1.0 \(\mu\)g \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\) epinephrine infusion administered via the left jugular vein. Infusion was started at arrow A and terminated at arrow B. 1 = TIVC; 2 = AORTA; 3 = AIVC; 4 = SVC.
possible that prolonged administration in critically ill patients may be accompanied by potentially dangerous hypokalemia. Further studies are needed to delineate the incidence and extent of epinephrine-induced changes in plasma potassium and their significance in producing dangerous dysrhythmias.

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