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CARDIAC EFFECTS OF SALBUTAMOL-INDUCED HYPOKALAEMIA IN THE CONSCIOUS DOG

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SUMMARY

1. Infusion of salbutamol (3.0 μg/min after a bolus injection of 100 μg) produced hypokalaemia in conscious dogs.

2. Measurement of arterial and coronary sinus potassium differences revealed no significant potassium loss from the heart with established hypokalaemia.

3. Shortly after the initial salbutamol bolus and before steady-state hypokalaemia had been achieved during salbutamol infusion, a prolongation of QT_c occurred; this corresponded to a significant myocardial potassium loss of −0.12 mmol/l plasma.

4. Urinary electrolyte excretions indicated that the hypokalaemia was not due to urinary potassium loss.

5. It was deduced that potassium had moved intracellularly. No change in hydrogen ion status occurred to account for this. Pronounced rises in plasma insulin immunoreactivities during salbutamol infusions suggested this as one mechanism for potassium shifts.

Key words: **β_2-adrenoceptor agonists, cardiac metabolism, electrocardiograph, insulin, potassium, salbutamol, urine output.**

INTRODUCTION

It has been recognized for a number of years that catecholamines can induce changes in serum potassium concentration (D'Silva, 1936; Todd, Vick & Turlington, 1968). Adrenaline causes a transient hyperkalaemia, attributed to hepatic glycogenolysis (D'Silva, 1934; Craig, 1965), followed by hypokalaemia, which depends on an intact pancreas (D'Silva, 1934). Insulin has been suggested as the mediator of catecholamine-induced hypokalaemia (D'Silva, 1934; Fahmy, 1976). It does appear, however, that β-adrenoceptors mediate the hypo-

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kalaemic actions of adrenaline and isoprenaline since β blockade of these receptors prevents their effect (Massara, Tripodina & Rotunno, 1970; Costin & Skinner, 1971; Todd & Vick, 1971; Malt, 1971). This role of β-adrenoceptors could be at the level of the pancreatic β cell or at the tissue level, where potassium flux has been altered. There is evidence that β-adrenoceptor agonists increase cation fluxes (Greengard, 1976), especially in avian red cells (Riddick, Kregenow & Orloff, 1971; Kregenow, 1973; Gardner *et al.*, 1973) and in cardiac pacemaker cells (Brady, 1974).

Now that β-adrenoceptors are recognized to be of two types, β_1 and β_2, it has been of interest to consider whether one or the other of these receptors is responsible for catecholamine-induced hypokalaemia. Recent work in man indicates that β_1-adrenoceptor blockade with metoprolol leads to an increase in serum potassium (Waal-Manning, 1976) and β_2-adrenoceptor stimulation with salbutamol leads to hypokalaemia (Leitch *et al.*, 1976; Neville *et al.*, 1977), so that both receptors may be involved. We have assessed the hypokalaemic response to salbutamol in the conscious dog and the possible causative mechanisms for the hypokalaemia.

It has been suggested that catecholamines cause the myocardial uptake of potassium (Cingolani *et al.*, 1968; Borasio & Vasalle, 1974). If this effect of catecholamines were direct, a β_2-adrenoceptor agonist might not have such an effect on the heart with its dominant β_1-adrenoceptor population. If the effect were indirect, stimulation of myocardial potassium uptake by salbutamol might still occur. If the heart were spared a direct or indirect effect of salbutamol, to stimulate potassium uptake, the induction of hypokalaemia could lead to myocardial potassium loss which could be of importance in terms of arrhythmogenesis. We have examined the myocardial handling of potassium in dogs administered salbutamol parenterally.

METHODS

The effects of salbutamol (Ventolin®, Allen & Hanburys) were studied in two groups of male mongrel dogs with body weights from 18 to 25 kg. Myocardial potassium balance and electrocardiographic intervals were assessed in one group, and urinary electrolyte excretion was assessed in the other group. The volumes of associated blood collections in each group were thus minimized.

Catheters were inserted into the aorta (through the common carotid or femoral artery) and a central vein (through the internal jugular or femoral vein), and coronary venous catheters, made of vinyl, were implanted 3-24 days prior to the study. The coronary venous catheter was introduced into the coronary sinus on the dorsal aspect of the heart, about 2.0 cm from its ostium through a right thoracotomy, and secured in place with a purse-string suture. A suture between two catheter collars about 2.0 mm apart on the epicardium prevented the catheter from slipping out of the coronary sinus. Catheter patency was maintained by daily flushes of sterile 0.17 mol/l sodium chloride and each catheter line was filled with sodium heparin (1000 u/ml).

The dogs were studied the morning after an overnight fast. Drinking water was not restricted during the fast. They stood in a loose harness for the duration of each study. An electrocardiograph was recorded on standard limb leads with a Grass polygraph (model 7), with a chart speed of 25 mm/s and a deflection of 1.0 mV/cm.

In one group of dogs, arterial blood was taken for determination of pH and P_{CO_2} with an Eel-Corning model 165 mark I blood-gas analyser and total plasma CO_2 was calculated by an

automated method (Skeggs & Hochstragger, 1964); whole blood lactate was measured enzymatically (Calbiochem, 1976), whole blood glucose was measured with a glucose oxidase electrode system (Clark, 1971) and plasma insulin was measured by a double antibody radioimmunoassay based on that of Hales & Randle (1963). Simultaneous arterial and coronary sinus blood samples were drawn for electrolyte determination by automated methods (Wootton, 1974).

In the other group of dogs, urine collections were made with the aid of a urinary catheter. Arterial blood was collected into ice for the determination of plasma sodium and potassium (Wootton, 1974), and of plasma vasopressin by radioimmunoassay (Pullan *et al.*, 1976). Not more than 10% of the blood volume was removed over the 2 h of study (Courtice, 1943). Urinary electrolytes were determined by the automated methods referred to above.

Salbutamol was given as a 100 μg bolus followed by a constant infusion of 3.0 μg/min. The bolus was given to allow a steady state to be reached earlier with the infusion. A Harvard infusion pump was used to deliver the salbutamol solution at 0.19 ml/min. At the commencement of the study the heparin solution was aspirated from the catheters; the catheters were flushed with 17 mmol/l sodium citrate as anticoagulant in 0.17 mol/l sodium chloride.

RESULTS

There were significant falls in the plasma potassium concentration during salbutamol infusion in both groups of dogs (Tables 1 and 2). There was no associated change in plasma sodium concentration (Table 2).

Table 1. Effect of salbutamol infusion on myocardial handling of potassium and on electrocardiographic intervals (mean results from 5 days)

			During infusion			
	Pre-infusion		5 min		60 min	
Parameter	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.
Potassium (mmol/l)						
Arterial plasma concentration	4.4	0.1			3.5	0.2*
Arterial–coronary sinus difference	−0.1	0.1			−0.1	0.1†
Heart rate (beats/min)	106	5.0	149	9.0‡	165	9.0§
QT_c (s)	0.29	0.1	0.35	0.02‡	0.32	0.02†

*$P < 0.001$. †Not significant. ‡$P < 0.05$. §$P < 0.01$. Significances of differences from pre-infusion values, assessed by paired *t*-test. QT_c: the electrocardiogram interval QT corrected for heart rate.

There was no significant change in potassium concentration across the coronary circulation prior to salbutamol infusion (Table 1). Despite a fall in plasma potassium from 4.4 to 3.5 mmol/l, no arterial–coronary sinus difference in plasma potassium was evident at 60 min after commencement of salbutamol infusion (Table 1).

Table 2. Effect of salbutamol infusion on electrolyte status, urinary volume and plasma vasopressin concentration (mean results from five dogs)

	Plasma electrolytes (mmol/l)				Urine electrolytes (mmol/l)				Urine volume (ml/h)		Plasma vasopressin (pmol/l)	
	Na^+		K^+		Na^+		K^+					
Time	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.
Pre-infusion												
−60 min	147	1.0	4.1	0.2							2.6	0.5
0 min	148	1.0	4.1	0.1	2.1	0.8	1.2	0.4	14	1.0	2.5	0.5
During infusion												
20 min	147	1.0*	3.3	0.2†							3.9	0.8*
40 min	148	1.0*	3.1	0.1†							5.6	1.6*
60 min	148	1.0*	3.2	0.1†	0.7	0.2‡	0.4	0.1*	9	1.0*	5.1	2.1*

* Not significant. † $P < 0.001$. ‡ $P < 0.01$. Significances of differences from pre-infusion values, assessed by the paired t-test.

Heart rate rose progressively during salbutamol infusion (Table 1). The QT interval measured from standard lead II of the ECG was corrected for rate according to Bazett's formula where $QT_c = QT/\sqrt{(\text{cycle length})}$.

5 min after commencement of salbutamol, QT_c was significantly prolonged, but there was no significant prolongation at 60 min (Table 1).

An additional dog had arterial–coronary sinus potassium differences examined in more detail on three occasions separated by 1 week intervals (Fig. 1). At 5 min after the commencement of salbutamol infusion, there was a significant release of potassium from the heart of 0.12 mmol/l.

Urinary sodium output fell significantly during salbutamol infusion (Table 2). Although urinary potassium excretion was closely related to urinary sodium excretion (Fig. 2), and

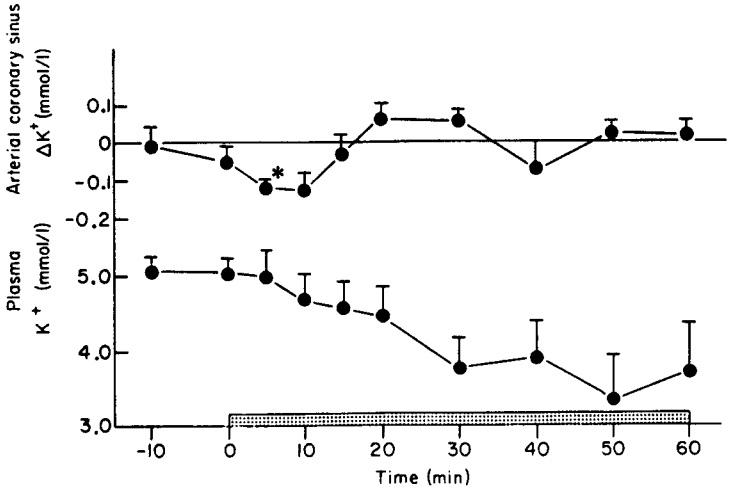

Fig. 1. Effect of salbutamol infusion for 1 h on arterial plasma potassium concentration and on arterial–coronary sinus differences in potassium concentration. Mean and standard error bars are shown. $*P < 0.01$. (▨) Salbutamol.

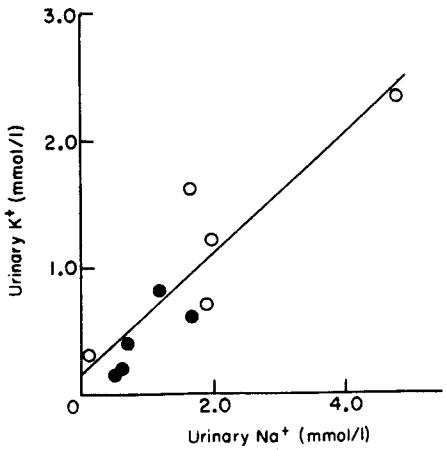

Fig. 2. Relationship between urinary sodium and urinary potassium excretions in conscious dogs. Control (○); dogs with salbutamol (●). $P < 0.001$; $r = 0.93$.

urinary potassium excretion fell in each dog, the fall in urinary potassium excretion did not reach statistical significance (Table 2). Both urinary sodium excretion ($r = 0.86$, $P < 0.01$) and urinary potassium excretion ($r = 0.89$, $P < 0.01$) were significantly related to urinary volume, which tended to fall during the salbutamol infusion (Table 2). However, when partial correlation analysis was used to eliminate the influence of urinary volume on the relationship between urinary sodium and urinary potassium excretions, these two excretions remained significantly related (the partial correlation coefficient was 0.72, $P < 0.05$).

The possibility that antidiuretic hormone (vasopressin) influenced urinary sodium and potassium outputs was assessed by measurement of plasma vasopressin immunoreactivity in arterial blood (Table 2). A tendency for vasopressin to rise during salbutamol infusion did not reach statistical significance.

No alteration in arterial pH accompanied the fall in plasma potassium (Table 3). The pH of the arterial blood remained constant, although there was a lower total plasma CO_2 content during salbutamol infusion (Table 3). In association with the fall in total plasma CO_2, lactate tended to rise (Table 3).

Table 3. The effect of salbutamol on acid-base status (mean results from the same groups of dogs as in Table 1)

	pH			P_{CO_2} (mmHg)			Total plasma CO_2 (mmol/l)			Blood lactate (mmol/l)		
Time	Mean	s.e.m.	*n*	Mean	s.e.m.	*n*	Mean	s.e.m.	*n*	Mean	s.e.m.	*n*
Pre-infusion	7.38	0.03	4	32	1.0	4	21	2.0	5	0.4	0.0	4
During infusion	7.38	0.03*	4	22	4.0*	4	18	2.0†	5	3.8	1.3*	4

* Not significant. † $P < 0.05$. Significances of differences from pre-infusion values, assessed by the paired *t*-test.

There was a pronounced rise in plasma insulin immunoreactivity following the administration of salbutamol (Table 4). Associated with this was a modest rise in blood glucose (Table 4). The insulin : glucose ratio rose from 25 prior to infusion to 273 at 20 min after commencement of salbutamol, 150 at 40 min and 108 at 60 min. This suggests that most of the effect of salbutamol on insulin secretion has not been mediated by an increase in blood glucose.

Table 4. Effect of salbutamol infusion on plasma insulin immunoreactivity and blood glucose concentration (mean results from the same group of dogs as in Table 1)

			During infusion					
	Pre-infusion		20 min		40 min		60 min	
	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.	Mean	s.e.m.
Insulin (pmol/l)	87	12	1583	378*	766	219*	517	192†
Glucose (mmol/l)	3.5	0.2	5.8	0.5‡	5.1	0.5‡	4.8	0.5*

* $P < 0.05$. † Not significant. ‡ $P < 0.01$. Significances of differences from pre-infusion values, assessed by the paired *t*-test.

DISCUSSION

The fall in plasma potassium concentration observed with salbutamol infusion in dogs confirms recent reports that salbutamol induces hypokalaemia in man (Leitch *et al.*, 1976; Neville *et al.*, 1977). This is also consistent with the effects on potassium previously described with other sympathomimetic agents (D'Silva, 1934, 1936; Todd *et al.*, 1968; Todd & Vick, 1971).

There was no evidence for increased urinary loss of potassium during salbutamol infusion. In fact, as urinary sodium excretion fell with salbutamol infusion, so also did urinary potassium excretion. The constant urinary sodium:potassium ratio suggests that there has been no or little change in mineralocorticoid activity during salbutamol infusion. Levi, Coburn & Kleeman (1976) have implied that a fall in urinary sodium and potassium excretion during β-adrenoceptor stimulation in man is in part due to increased secretion of plasma vasopressin and a decrease in urinary volume. In the present study, the falls in urinary electrolyte excretion were not dependent on a decrease in urinary volume. A rise in plasma vasopressin concentration in the dog had also been claimed to lead to increases in urinary sodium and potassium excretion (Buckalew & Dimond, 1976). Such increases in electrolyte excretion have not occurred in our study, despite the tendency for plasma vasopressin to rise during salbutamol infusion.

As no external potassium loss occurred, salbutamol-induced hypokalaemia must be due to internal shifts of potassium from the extracellular to the intracellular compartment. Studies have suggested that catecholamines cause a shift of potassium into skeletal muscle (Marenzi & Gerschmann, 1936; Stickney, 1941; Ellis, 1956; Vick, Todd & Leudke, 1972). An increased movement of potassium into the liver may also occur under the influence of sympathomimetic agents (Marenzi & Gerschmann, 1936; Brewer, 1939).

In these studies, salbutamol induced a rise in plasma insulin and a fall in plasma potassium concentration. This suggests that the rise in insulin may, at least in part, be responsible for the hypokalaemia by way of transferring potassium from the extracellular to the intracellular compartment. Inasmuch as ions modify insulin secretion, hypokalaemia in turn may have decreased insulin secretion (Table 4) (Dean & Matthews, 1970). However, the fact that adrenalin decreases plasma insulin (Williams & Porte, 1974) and plasma potassium concentration (D'Silva, 1934, 1936; Todd *et al.*, 1968), makes it possible that the β_2-adrenoceptor stimulant salbutamol may affect potassium status other than by affecting insulin secretion.

The transient prolongation of the QT_c interval that occurred 5 min after commencement of salbutamol infusion corresponded to the period when a significant release of potassium from the heart (0.12 mmol/l) could be detected. This contrasts with changes of the order of 0.4 mmol/l when ischaemia (Opie *et al.*, 1973) or cardiac glycosides induce potassium loss (Seller, 1976), or when glucagon induces potassium uptake (Bianco *et al.*, 1971). The question arises as to why these cardiac effects of salbutamol should be transient. One possibility is that salbutamol initially induced excessive cardiac glycogenolysis and potassium release (Cori & Welch, 1941). After the bolus, salbutamol may have reached high blood levels when effects due to stimulation of cardiac β-receptors could have become manifest. The effect did not appear to depend on the plasma potassium concentration, since the onset of hypokalaemia did not occur until later. It is possible that the tendency for myocardial potassium loss was offset by an increase in plasma insulin and blood glucose, with stimulation of myocardial potassium uptake. It is less likely that a direct effect of salbutamol on the myocardium prevented further potassium loss.

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