CARDIOVASCULAR MEDICINE

Effect of diabetes on serum potassium concentrations in acute coronary syndromes

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Objectives: To compare serum potassium concentrations in diabetic and non-diabetic patients in the early phase of acute coronary syndromes.

Background: Acute phase hypokalaemia occurs in response to adrenergic activation, which stimulates membrane bound sodium-potassium-ATPase and drives potassium into the cells. It is not known whether the hypokalaemia is attenuated in patients with diabetes because of the high prevalence of sympathetic nerve dysfunction.

Methods: Prospective cohort study of 2428 patients presenting with acute coronary syndromes. Patients were stratified by duration of chest pain, diabetic status, and pretreatment with β blockers.

Results: The mean (SD) serum potassium concentration was significantly higher in diabetic than in non-diabetic patients (4.3 (0.5) *v* 4.1 (0.5) mmol/l, $p < 0.0001$). Multivariate analysis identified diabetes as an independent predictor of a serum potassium concentration in the upper half of the distribution (odds ratio 1.66, 95% confidence interval 1.38 to 2.00). In patients presenting within 6 hours of symptom onset, there was a progressive increase in plasma potassium concentrations from 4.08 (0.46) mmol/l in patients presenting within 2 hours, to 4.20 (0.47) mmol/l in patients presenting between 2–4 hours, to 4.24 (0.52) mmol/l in patients presenting between 4–6 hours ($p = 0.0007$). This pattern of increasing serum potassium concentration with duration of chest pain was attenuated in patients with diabetes, particularly those with unstable angina. Similar attenuation occurred in patients pretreated with β blockers.

Conclusion: In acute coronary syndromes, patients with diabetes have significantly higher serum potassium concentrations and do not exhibit the early dip seen in non-diabetics. This may reflect sympathetic nerve dysfunction that commonly complicates diabetes.

Patients presenting with acute coronary syndromes are commonly hypokalaemic,[1–3] which may increase the risk of lethal ventricular arrhythmias.[4–6] Hypokalaemia can be regarded as an acute phase response to adrenergic activation, which stimulates membrane bound sodium-potassium-ATPase and drives potassium into the cells.[7–9] Experimentally, hypokalaemia can be induced in human volunteers by infusion of physiological concentrations of adrenaline but not isoproterenol.[10 11] The hypokalaemia is prevented by specific β_2 antagonists, identifying β_2 receptors in skeletal muscle as the likely target for this adrenergic response.[12]

Another potential mechanism of hypokalaemia in acute coronary syndromes is reactive hyperinsulinaemia in response to adrenergically driven increases in serum glucose.[13] Thus, pharmacological doses of insulin reduce serum potassium concentrations, an effect ascribed to insulin mediated uptake of potassium by muscle and liver.[14 15] In contrast, however, physiological changes in circulating insulin concentrations have very little effect on potassium in diabetic or non-diabetic patients.[16 17] This mechanism was discounted by Brown and colleagues[10] because in their study serum potassium concentration was reduced in response to adrenaline infusion during simultaneous reductions in serum insulin. Insulin increased only after the adrenaline infusion was discontinued, at a time when potassium concentrations were recovering.[10]

If hypokalaemia in acute coronary syndromes is driven principally by adrenergic mechanisms, attenuation would be expected in patients with diabetes due largely to the high prevalence of sympathetic nerve dysfunction associated with autonomic neuropathy.[18–22] To test this hypothesis, we prospectively recorded admission potassium concentrations and duration of symptoms in a large cohort of patients presenting with acute coronary syndromes, comparing time related changes in serum potassium concentrations in diabetic versus non-diabetic subgroups.

METHODS

Patient population

During a two year period from January 2000, 2542 patients with acute coronary syndromes were logged on to the coronary care databases of three east London hospitals. Of these, 2428 patients (95.5%) in whom admission serum potassium concentration was recorded constitute the study group. Only first admissions to the three hospitals with either myocardial infarction or unstable angina were included to avoid double counting. The discharge diagnosis was myocardial infarction in 987 patients (35.9% non-Q wave infarction) based on any two of the following criteria: (a) cardiac chest pain lasting at least 30 minutes; (b) ⩾ 0.1 mV ST elevation in at least one standard lead or ⩾ 0.2 mV ST elevation in two or more contiguous chest leads; (c) creatine kinase ⩾ 400 IU/l (upper limit of reference range 200 IU/l). A further 1441 patients were discharged with a diagnosis of unstable angina, all of whom fulfilled criteria for Braunwald class 3B: cardiac chest pain at rest within the preceding 48 hours not fulfilling criteria for myocardial infarction and not attributable to non-cardiac causes. Patients with class A (unstable symptoms attributable less to coronary disease than to other disorders such as severe anaemia, arrhythmias, left ventricular hypertrophic disease) and class C (unstable symptoms within two weeks of acute infarction) were excluded.[23]

Data collection

Baseline clinical characteristics including demographic, clinical, and biochemical data were collected prospectively by a

Table 1 Comparison between patients in the upper and lower halves of the distribution of plasma potassium concentration

	K+ ⩽4.2 mmol/l (n=1473)	K+ >4.2 mmol/l (n=955)	p Value
Age (years)	62 (13)	65 (13)	<0.0001
Plasma creatinine (μmmol/l)	105 (44)	120 (69)	<0.0001
Male sex	1003 (68.1%)	692 (72.5%)	0.02
Diabetes	337 (22.9%)	328 (34.3%)	<0.0001
Hypertension	731 (49.6%)	471 (49.3%)	NS
Smoking	497 (34.1%)	299 (31.6%)	NS
Admission drugs			
Aspirin	789 (53.8%)	531 (55.7%)	NS
ACE inhibitor	305 (20.8%)	245 (25.7%)	0.005
Diuretic	372 (25.4%)	177 (18.7%)	0.0001
β Blocker	365 (24.9%)	251 (26.3%)	NS
Statin	377 (25.8%)	265 (27.8%)	NS
Admission haemodynamics			
Heart rate (beats/min)	79 (20)	79 (20)	NS
Systolic blood pressure (mm Hg)	145 (29)	144 (29)	NS
Complications			
LVF	176 (12.0%)	163 (17.2%)	0.0004
Ventricular fibrillation	21 (1.4%)	23 (2.4%)	NS
Enzyme release and discharge diagnosis			
Peak CK (mmol/l)	610 (1034)	612 (1148)	NS
Acute myocardial infarction	595 (40.4%)	392 (41.0%)	NS
Unstable angina	878 (59.6%)	563 (59.0%)	NS

Data are numbers (percentages) or mean (SD). ACE, angiotensin converting enzyme. LVF, left ventricular failure.

dedicated cardiologist or research nurse and stored on a purpose built electronic database. The duration of pain before presentation at hospital was recorded, as were routine biochemistry parameters for blood samples obtained in the emergency department and all admission drugs, including β blockers. Diabetes was recorded in patients taking insulin or oral hypoglycaemic drugs or with dietary restriction. Hypertension was recorded in patients taking antihypertensive drugs. Ventricular arrhythmias (tachycardia, fibrillation) that occurred in the emergency department or during monitoring in the coronary care unit were also recorded.

Statistical analysis

Comparison of discrete variables was by χ^2 analysis and continuous variables by *t* testing. To evaluate their independent influence, variables significantly different ($p < 0.05$) in univariate analysis or believed to be of clinical or biological relevance were entered into a regression analysis using a multinomial logistical model. Improvements in model fit were based on comparison of likelihood ratios. Odds ratios are quoted together with 95% confidence intervals; means are accompanied by SD. Analysis of variance was used to test differences between potassium concentrations by duration of chest pain. Simple regression analysis was used to test correlations between continuous variables.

RESULTS

Of the 2428 patients with acute coronary syndromes, 987 (41%) had a discharge diagnosis of acute myocardial infarction. In patients with acute myocardial infarction, diabetes was recorded less frequently (23.2% *v* 30.3%, $p = 0.0001$) but markers of adrenergic stress including heart rate (81 (22) *v* 78 (19) beats/minute, $p = 0.0005$), admission glucose concentrations (9.6 (5.2) *v* 8.3 (4.5) mmol/l, $p < 0.0001$), and peak creatine kinase concentrations (1297 (1432) *v* 139 (125) mmol/l, $p < 0.0001$) were all significantly higher than in patients with unstable angina.

Admission serum potassium concentration: univariate predictors

Comparison between patients in the upper and lower halves of the potassium distribution (median 4.2 mmol/l) confirmed that those with a potassium concentration > 4.2 mmol/l were more commonly diabetic and tended to be older with a higher serum creatinine concentration (table 1). Pretreatment with angiotensin converting enzyme (ACE) inhibitors and diuretics was, respectively, more and less common when the admission potassium concentration was > 4.1 mmol/l.

Admission serum potassium concentration: multivariate predictors

In patients with diabetes, the odds of presenting with a serum potassium concentration in the upper half of the distribution (> 4.2 mmol/l) were 66% higher than in patients without diabetes. The odds increased by 1.6% per year with increasing age and by 0.6% per μmmol/l with increasing serum creatinine concentration. The odds were increased 33% by pretreatment

Table 2 Multivariate predictors of plasma potassium concentration in upper half of the distribution (>4.2 mmol/l)

	Odds ratio	95% CI	p Value
Age (years)	1.016	1.009 to 1.023	<0.0001
Diabetes	1.66	1.38 to 2.00	<0.0001
Serum creatinine (μmmol/l)	1.006	1.004 to 1.008	<0.0001
ACE inhibitor	1.33	1.07 to 1.64	0.009
Diuretic	0.49	0.39 to 0.61	<0.0001

Data are for 2399 patients for whom complete data were available.
CI, confidence interval.

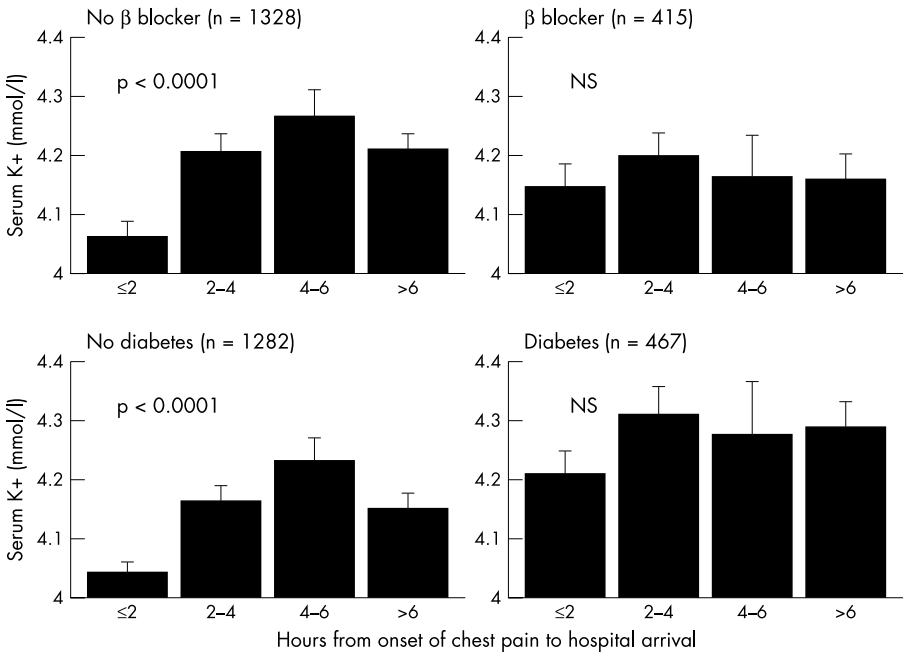

Figure 1 Serum potassium concentrations by duration of chest pain. Data are mean (SEM). Upper panels show the effects of pretreatment with β blockers in 1118 patients for whom complete data were available. Lower panels show effects of diabetes in 1124 patients for whom complete data were available.

with ACE inhibitors but were reduced 49% by pretreatment with diuretics (table 2).

Serum potassium concentration and duration of chest pain

The time from onset of chest pain to arrival at the emergency department was recorded in 1749 patients, 71% of whom arrived in the first 6 hours. Subgrouping the patients by duration of chest pain showed a progressive and highly significant increase in serum potassium concentrations rising from a low point of 4.08 (0.46) mmol/l in those arriving ⩽ 2 hours of the onset of symptoms, through 4.20 (0.47) mmol/l after 2–4 hours, to a peak of 4.24 (0.52) mmol/l in those arriving 4–6 hours after the onset of symptoms ($p < 0.0001$). This pattern of increasing admission potassium concentration with duration of chest pain was severely attenuated in patients with diabetes, in whom potassium concentrations at every time increment were substantially higher than in patients without diabetes (fig 1). Subgroup analysis showed that attenuation was confined to diabetic patients with unstable angina and was not seen in acute myocardial infarction, although for both groups diabetes was associated with higher potassium concentrations (table 3). The incidence of ventricular fibrillation was similar for diabetic (0.99%) and non-diabetic (2.02%) patients.

Serum potassium concentration, sympathetic blockade, and markers of stress

Among patients pretreated and not pretreated with β blockers, serum potassium concentrations were similar (4.2 (0.4) *v* 4.2 (0.5) mmol/l). However, pretreatment with β blockers attenuated the pattern of increasing serum potassium concentration with duration of chest pain (fig 1). Again, attenuation was seen most clearly for patients with unstable angina (table 3).

There were weak but significant negative correlations between serum potassium concentrations and markers of stress in non-diabetic, but not diabetic, patients who arrived ⩽ 2 hours after the onset of chest pain: heart rate ($r = -0.13$, $p = 0.003$), blood sugar ($r = -0.10$, $p = 0.04$), peak creating kinase ($r = -0.14$, $p = 0.002$).

Serum glucose concentration and duration of chest pain

In patients with diabetes, serum glucose concentrations were higher at every time increment than in patients without diabetes. Although there were significant differences according to symptom duration, the pattern of fluctuations was not clear (fig 2). Among patients without diabetes glucose concentrations remained stable, regardless of symptom duration.

DISCUSSION

Acute coronary syndromes provide a useful clinical model of adrenergic stress as reflected in many of the typical presenting features such as diaphoresis and tachycardia.[24 25] Hypokalaemia has also been attributed to this mechanism and our finding of lower serum potassium concentrations in patients presenting very early after the onset of chest pain is well

Table 3 Plasma potassium concentrations (mmol/l) by duration of chest pain

	⩽2 hours	2–4 hours	4–6 hours	6 hours	p Value
Unstable angina					
Non-diabetic (n=653)	4.08 (0.42)	4.11 (0.39)	4.27 (0.57)	4.14 (0.43)	0.01
Diabetic (n=288)	4.24 (0.49)	4.24 (0.41)	4.16 (0.58)	4.30 (0.50)	NS
No β blocker (n=635)	4.10 (0.43)	4.12 (0.41)	4.29 (0.61)	4.20 (0.47)	0.009
β Blocker (n=302)	4.18 (0.48)	4.20 (0.36)	4.14 (0.45)	4.18 (0.45)	NS
Myocardial infarction					
Non-diabetic (n=629)	4.0 (0.46)	4.22 (0.50)	4.19 (0.44)	4.18 (0.45)	<0.0001
Diabetic (n=179)	4.17 (0.51)	4.43 (0.58)	4.50 (0.50)	4.29 (0.56)	0.05
No β blocker (n=693)	4.03 (0.49)	4.28 (0.53)	4.25 (0.42)	4.23 (0.50)	<0.0001
β Blocker (n=113)	4.08 (0.38)	4.20 (0.49)	4.23 (0.62)	4.08 (0.33)	NS

Data are mean (SD).

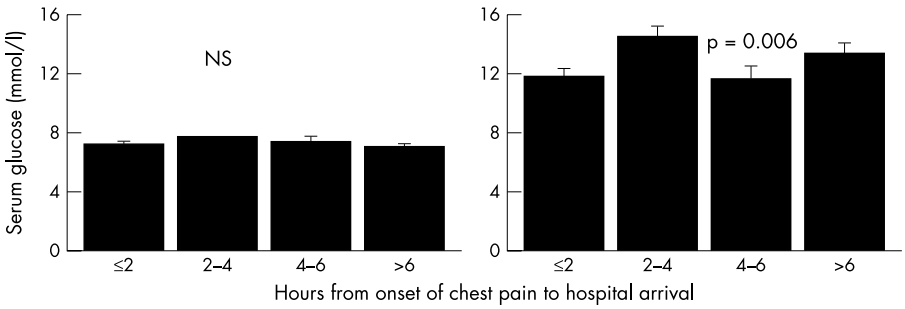

Figure 2 Serum glucose concentrations by duration of chest pain in 932 patients for whom complete data were available.

recognised.[1–3] Rapid recovery of serum potassium concentrations in the first six hours has also been documented by serial blood sampling in patients with acute myocardial infarction.[26] This is clearly analogous to our own finding of progressively increasing potassium concentrations in subgroups presenting later after the onset of symptoms.

The early recovery in serum potassium concentrations in patients presenting later after the onset of symptoms is most likely a response to sympathetic withdrawal allowing intracellular potassium to re-enter the circulation. Support for an adrenergic mechanism of increasing serum potassium concentration with later hospital presentation was provided by our novel observations in patients pretreated with β blockers. In this group the early dip in serum potassium concentrations and its later increase were attenuated, presumably because adrenergic stimulation of sodium-potassium-ATPase was blocked, reducing potassium flux across the cell membrane. Attenuation was seen most clearly in unstable angina and was less pronounced in acute myocardial infarction when the early dip in potassium and its later recovery were preserved, albeit with loss of significance. This may reflect the fact that adrenergic responses to coronary syndromes are related to the extent of myocardial injury[24] and are greater, therefore, in acute myocardial infarction, with the potential to overwhelm any effects that pretreatment with β blockers might have in modifying potassium flux across cell membranes.

Our finding of increased serum potassium concentrations in diabetic patients with acute coronary syndromes has not previously been reported, although hyperkalaemia is known to be relatively common in diabetic clinics,[27] reflecting the role of insulin in potassium homeostasis.[28] Also unreported is the independent effect of diabetes in attenuating the early dip in serum potassium concentration and its later recovery, an effect largely confined to unstable angina and not seen in acute myocardial infarction. In these respects, patients with diabetes behaved remarkably like patients pretreated with β blockers, making sympathetic nerve dysfunction the most plausible explanation for the effects on potassium. Again it is possible to speculate that the heightened adrenergic response to acute myocardial infarction overwhelmed the effect of diabetes in modifying serum potassium concentrations.

Further support for adrenergic mechanisms driving early changes in serum potassium concentrations in non-diabetic patients is provided by the negative correlations between serum potassium in the first two hours and various markers of adrenergic stress, including heart rate, acute phase glycaemia, and enzymatic markers of injury[24 29] These correlations were seen only in non-diabetic patients. Those with the greatest increases in heart rate, glucose, or creatine kinase tended to have the greatest reductions in serum potassium concentrations that were presumably less amenable to modification by sympathetic nerve dysfunction or β blockade. Insulin resistance may also have had a role in preventing the early dip in serum potassium in diabetes by attenuating intracellular ionic flux early after the onset of symptoms, although the experimental findings of Brown and colleagues indicate that insulin does not contribute significantly to adrenergically driven changes in serum potassium.[10] Certainly, our finding of stable blood glucose concentrations in non-diabetic patients during the first six hours after the onset of chest pain, when potassium concentrations were changing rapidly, suggests that adrenergic mechanisms were more important than insulin in driving potassium across the cell membrane.

Autonomic function was not measured in this study, and our mechanistic hypotheses about the effects of diabetes in modifying early changes in serum potassium concentrations can only be inferred from the effects of β blockers and correlations with indirect markers of adrenergic stress. Nevertheless, sympathetic nerve dysfunction is a common manifestation of autonomic neuropathy, which can be shown in up to 40% of randomly selected diabetic patients by using conventional reflex tests. A much larger proportion may have more subtle alterations of sympathetic pathways as determined by myocardial radiolabelled hydroxyephedrine uptake using positron emission tomography.[19–22] The association of diabetic autonomic neuropathy with a poor prognosis and sudden death is well established[30 31]; prolongation of the QT interval, exaggerated exertional ischaemia, and impairment of sympathetically mediated myocardial blood flow are possible mechanisms.[32–35] However, our finding of an independent association between diabetes and increased serum potassium concentration early after the onset of symptoms in acute coronary syndromes is unlikely to be detrimental and may be beneficial if it helps protect against acute phase ventricular arrhythmias. Thus, while diabetes may be associated with severe coronary syndromes, there are no data associating it with an increased incidence of ventricular arrhythmias.[36–39]

An important limitation of this study is the absence of serial potassium measurements. Thus, while it is clear from our data that serum potassium concentrations were increased in diabetic patients with acute coronary syndromes, the changes during the early hours after the onset of symptoms were deduced by grouping the patients by arrival time. Because numbers were large this deduction is almost certainly valid, and our findings are consistent with the work of previous investigators who have undertaken serial blood sampling in much smaller cohorts.[26] Additional limitations are the absence of data on type I and type II diabetes or the cardioselectivity of β blockers, neither of which were entered on our database.

In conclusion, patients with diabetes presenting with acute coronary syndromes had significantly higher serum potassium concentrations and did not exhibit the early dip seen in non-diabetic patients. Although other factors affecting serum potassium—particularly renal dysfunction, ACE inhibition, and diuretic treatment—were more prevalent in the diabetic group, this did not account for our observations and diabetes was retained as an independent predictor of increased serum potassium concentration in multivariate analysis. Relative insulin deficiency almost certainly accounted for the increased serum potassium concentrations in diabetic patients, but the absence of an early potassium dip in this group was also seen in patients taking β blockers and is more plausibly attributed to sympathetic nerve dysfunction.

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