Coronary sinus pH during percutaneous transluminal coronary angioplasty: early development of acidosis during myocardial ischaemia in man

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SUMMARY Coronary sinus pH was measured continuously in eight patients undergoing angioplasty to the left anterior descending coronary artery. A catheter tip pH sensitive electrode with a response time of less than 300 ms and an output ≥ 57 mV/pH unit was placed high in the coronary sinus. Recordings were obtained during a total of 24 balloon occlusions of the left anterior descending coronary artery varying in duration from 5 to 45 s. Continuous 12 lead surface electrocardiograms were recorded. During or after balloon inflation of ≤ 12 s ($n = 4$) there was no change in coronary sinus pH or the electrocardiogram. During balloon inflation of ≥ 15 s ($n = 20$) coronary sinus pH was unaltered but between 4 and 6 s after balloon deflation coronary sinus pH fell transiently by between 0.010 and 0.120 pH units before returning to the control value within 65 s. Ischaemic changes were seen on the electrocardiogram during 15 balloon occlusions. In individual patients the peak fall in coronary sinus pH was related to the duration of occlusion of the left anterior descending coronary artery. A rise in coronary sinus pH (alkalosis) was never seen.

In man acidosis occurs in the myocardium after short periods (≥ 12 s) of ischaemia. The fall of pH precedes ischaemic changes on the surface electrocardiogram and occurs concurrently with the earliest reported changes in contractile function.

The cause of the early decline in contractile function during myocardial ischaemia is not well understood but is almost certainly multifactorial.¹ Although the tissue content² of high energy phosphates, in particular creatine phosphate, is reduced, the magnitude of the fall in the free energy change of ATP hydrolysis is insufficient to depress contractility until several minutes of ischaemia have elapsed.³ Alternative mechanisms have been proposed and some of these relate not to the lack of oxygen and substrate supply that occurs during ischaemia but to the retention of the products of metabolism, notably phosphate⁴⁻⁶ and hydrogen ions (acidosis).⁷⁻⁹

Acidosis is known to depress the contractile function of the heart¹⁰⁻¹² and has been put forward as a

mechanism for the loss of function early after the onset of myocardial ischaemia.^{7,9} This hypothesis has been disputed^{13,14} partly because the mechanism for the occurrence of an acidosis is uncertain and partly because of difficulties in quantifying the severity and rate of onset of acidosis in ischaemia. Under some experimental conditions acidosis and contractile failure were dissociated.^{13,14} Early during hypoxia and ischaemia an alkalosis was reported.^{15,16} If the retention of hydrogen ions and subsequent intracellular acidosis is an important cause of contractile dysfunction, then it is necessary to show that the acidosis is both sufficiently large and rapid in onset to account for at least part of the early decline in contractility.

Percutaneous transluminal coronary angioplasty provides a unique opportunity to study the early ionic changes during myocardial ischaemia in man and thus allow a comparison with results previously obtained during transient coronary occlusion in animals. This study was designed to determine the time

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Accepted for publication 26 March 1987

of onset and severity of acidosis in the human myocardium during acute myocardial ischaemia. We have continuously measured changes in coronary sinus pH during repeated episodes of balloon occlusion of the left anterior descending coronary artery using rapidly responding pH sensitive electrodes.

Patients and methods

We studied eight patients (5 men, 3 women; aged 44–71, mean 53 years) with effort related angina pectoris who were already scheduled for routine percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. Patients with a recent myocardial infarction or chest pain at rest were excluded. All patients developed chest pain and significant ST segment depression (≥ 1 mm planar or downsloping 80 ms after the J point) during treadmill exercise by a modified Bruce protocol. All were in sinus rhythm with no conduction abnormalities or evidence of other cardiac abnormality apart from ischaemic heart disease. No patients were taking digoxin or antiarrhythmic medication. All patients were receiving nifedipine 10 mg three times daily but no other antianginal medication had been prescribed for at least 24 hours. Five patients had left anterior descending coronary artery disease only, one had additional left circumflex disease, and two had three vessel disease. Written informed consent was obtained in all cases and the study was approved by the ethics committee of the National Heart and Chest Hospitals.

pH ELECTRODES

Intravascular pH monitoring at any site other than a peripheral vein or artery requires an electrode at the tip of a flexible catheter which can be inserted into a vessel and left in situ. The construction and use of pH¹⁷ and potassium¹⁸ sensitive electrodes suitable for intravascular recording have been described. The pH sensitive ligand tridodecylamine (Fluka AG, Switzerland) was used in these experiments rather than OCPH (*p*-octydecyloxy *m*-chlorophenyl hydrazone mesoxalonitrile), which was used in our earlier studies.^{17 19 20} The electrode was inserted through a standard cardiac catheter (8 French thin-walled Cournand, USCI, USA). At the proximal end the electrode passed through a sliding adapter with a side arm (SFLL PCF MLL RA45°, Cook, UK). The space in the catheter around the electrode was filled with a heparinised saline solution and a calomel reference electrode (K4112, Radiometer, Sweden) was connected through a T-piece to the side arm of the adapter. The column of saline surrounding the pH electrode within the cardiac cath-

eter thus acted as a salt bridge to connect the reference electrode to the bloodstream and it also provided coaxial electrical screening for the pH electrode.

The potential difference between the silver/silver chloride wire within the pH electrode and the calomel electrode was measured by a high impedance input amplifier (LF 352D National Semiconductor, Japan). The signal was passed through an optical isolator (3650 HG Burr Brown, Arizona, USA), to prevent leakage currents running to earth through the intravascular electrode, and through a 2 Hz filter. It was displayed on a pen recorder and recorded on magnetic tape.

The membrane resistance was $10^9 \Omega$. The pH response of the electrodes was linear between pH 6.5 and 8.0 and the output at 37°C was between 57 and 59 mV/pH unit. The response time was less than 300 ms. The electrode was unresponsive to flow, blood pressure, PO_2 , or osmolality (100–400 mmol/l). There was no cross sensitivity to Na^+ (100–200 mmol/l), K^+ (0–10 mmol/l), Ca^{2+} (0–10 mmol/l), or Mg^{2+} (0–10 mmol/l). It was not affected by changing the bicarbonate concentration (10–50 mmol/l) or carbon dioxide tension (20–100 mm Hg) at constant pH. The electrode stabilised in vivo in less than 15 minutes, and thereafter the drift was less than 0.005 pH units/hour. The electrode could detect changes as small as 0.005 pH units.

The electrodes were sterilised by immersion in an aqueous glutaraldehyde solution for one hour. The function of the electrodes was not affected by this process. Electrodes were calibrated before and after the entire procedure. Results were only accepted if there was no change in calibration. This procedure lead to the rejection of results in only one patient. Blood samples were obtained for determination of the absolute value of pH from the coronary sinus before insertion of the electrode into the catheter and at the end of the procedure.

STUDY PROTOCOL

One hour after premedication with lorazepam (1–2 mg orally) the Cournand catheter was inserted into the left subclavian vein and positioned in the coronary sinus just proximal to the great cardiac vein. The position was checked by the injection of contrast medium (Omnipaque 300, Nycomed (UK)). A pH electrode was introduced through the lumen of this catheter until the tip protruded 1 cm from the end of the catheter. The output from the electrode was allowed to stabilise for at least 20 minutes before angioplasty. pH was recorded continuously together with a standard 12 lead electrocardiogram until the end of the procedure.

Percutaneous transluminal angioplasty was per-

formed from the right femoral artery with coronary guiding catheters and Simpson-Roberts coronary balloon dilatation catheters from Advanced Cardiovascular Systems Inc., California, USA. The number of balloon inflations required to dilate the vessel varied between 2 and 5 (mean (SEM) 3.0 (0.5)). Inflation lasted from 8 to 45 s (mean (SEM) 24.8 (2.8) s). Clinical considerations alone determined the number and duration of balloon inflations.

Results

PH CHANGES IN BLOOD FROM THE CORONARY SINUS

Figure 1 shows a recording of changes in coronary sinus pH during three successive balloon inflations. No change in coronary sinus pH was seen during the period of occlusion of the anterior descending coronary artery by the inflated balloon. When blood flow was restored by deflation of the balloon there was a transient fall in coronary sinus pH after a delay of 4–6 s. In one coronary occlusion (the second inflation in fig 1), where balloon inflation was initiated before the signal had returned to the baseline, the blood pH continued to return to the baseline during the early part of the inflation, indicating that some blood flow was present in the great cardiac vein during the period that the left anterior descending coronary artery was occluded (fig 1).

The peak pH change in an individual patient was related to the duration of coronary artery occlusion (fig 2). Four patients had an episode of coronary artery occlusion lasting < 12 s. Coronary sinus blood pH did not fall after these short episodes of coronary artery occlusion (fig 3). pH fell after all other episodes (all ≥ 15 s) of occlusion (fig 3). The maximum change in coronary sinus blood pH was 0.120 pH units. Coronary sinus pH returned to control values within 65 s. The fall in pH seen in the eight patients

was wide (fig 3). No rise of pH (alkalosis) was observed after any episode of coronary artery occlusion. A small (0.020 pH units) transient fall in pH was seen after injection of contrast medium (Omnipaque 300, Nycomed (UK) (pH 7.2)) into the left coronary artery (fig 1).

ELECTROCARDIOGRAPHIC CHANGES

ST segment elevation was > 1 mm in at least one precordial lead during 15 balloon inflations, all lasting more than 20 s (fig 3). Ischaemic electrocardiographic changes did not occur during the four balloon inflations lasting ≤ 12 s after which no pH change occurred. Five balloon occlusions of the coronary artery which were followed by a fall in coronary sinus pH were not accompanied by electrocardiographic changes. Heart rate did not change significantly from the control value during or after occlusion of the vessel.

Discussion

Percutaneous transluminal coronary angioplasty provides the opportunity to study the early metabolic and physiological effects of coronary occlusion in man. The results of this study show that in the human myocardium acidosis develops after 12 to 15 s of coronary occlusion. Measurements were made with fast responding catheter tip pH electrodes which would detect changes of pH that might be missed by conventional sampling techniques. The electrode is stable, can detect pH changes of less than 0.005 pH units, and is free from cross sensitivity to other ions.

The pH of coronary sinus blood did not change during coronary occlusion. The concentration of hydrogen ions in the coronary sinus blood rose transiently when the blood flow was restored. This is attributable to washout of hydrogen ions generated

Fig 1 Continuous recording of coronary sinus pH during three consecutive balloon occlusions of the left anterior descending coronary artery and one injection of contrast into the left coronary artery. Coronary sinus pH did not fall during balloon inflation but fell transiently 4 to 6 s after balloon deflation. Passage of contrast medium through the coronary circulation caused an abrupt transient fall in pH.

Fig 2 Relation between the peak fall in coronary sinus pH and the duration of balloon occlusion of the left anterior descending coronary artery in one patient

within the ischaemic tissue. Reduced arterial flow in the ischaemic area causes the retention of the end products of anaerobic metabolism in the tissue and such metabolites are removed from the myocardium when flow is restored. The small quantity of metabolites that might diffuse out from the edge of the ischaemic tissue during the period of ischaemia will be diluted by the coronary venous effluent from non-ischaemic myocardium, and the magnitude of any such change must either be too small to be detected or must be absent. The catheter was placed high in the coronary sinus so as to sense blood from the area of myocardium subserved by the occluded anterior descending coronary artery. Figure 1 shows there can be residual flow in the distal great cardiac vein during occlusion of the left anterior descending coronary artery; on the second inflation (initiated before the signal had returned to baseline) blood pH continued to return to the baseline value during the early part of the occlusion. The mechanism underlying this is unclear but it is probably related to hydrogen ions being washed out of the local coronary veins and great cardiac vein by blood flowing into them from the non-ischaemic area. It is unlikely to be due to a flow of blood from the ischaemic area, otherwise we would have observed a fall in pH during the latter part of balloon inflation.

After deflation of the balloon and hence restoration of blood flow, the coronary sinus pH fell after a delay of 4–6 s. The delay is due partly to the time required for collapse of the balloon and partly to the time taken by the hydrogen ions to diffuse from the intracellular and extracellular spaces into the blood and for the blood to reach the pH electrode. A similar delay has been reported in the dog.¹⁹ Consistent

with our findings others have reported a rise in the concentration of lactate in coronary sinus on balloon deflation after angioplasty.²⁰ Heart rate did not change during balloon inflation, so the observed change in pH was due to myocardial ischaemia induced by coronary artery occlusion and was not the result of an increase in heart rate causing ischaemia. Previous work has shown that ischaemia caused by atrial pacing in man is associated with a minor degree of acidosis during the pacing test and a washout of hydrogen ions immediately the test is stopped.²¹

The implications of these results depend on the validity of coronary sinus pH as an indirect indicator of changes in intracellular pH. We have continuously measured coronary sinus pH in this study and this avoids the errors that are introduced by sampling techniques. The time at which blood samples are taken after balloon deflation will have a profound effect on the magnitude of the pH changes, as fig 1 shows. Earlier studies have used changes in coronary sinus lactate as a marker of ischaemia but, unlike pH, lactate cannot be measured continuously and so is subject to the considerable errors that sampling introduces. It is not possible, without continuous measurement of regional coronary flow and coronary sinus blood flow and knowledge of the degree of mixing of blood from ischaemic myocardium with that from non-ischaemic myocardium, to calculate the precise quantity of hydrogen ions lost from a given amount of ischaemic myocardial tissue. These variables were not measured in this study. Blood in the coronary sinus will be subject to some dilution of hydrogen ions because blood from the ischaemic area will have mixed with that from the non-ischaemic

Fig 3 Peak coronary sinus pH changes after all balloon occlusions of the left anterior descending coronary artery. No change in pH occurred after balloon occlusion of < 12 s.

area, and any measured change in blood pH will necessarily be smaller than that present in the extracellular space of the ischaemic myocardium. We attempted to minimise these effects by placing the electrode high in the coronary sinus just proximal to the great cardiac vein. Furthermore, hydrogen ions are buffered by tissue buffer systems and by blood.

The magnitude of the pH changes that we have observed varied widely between patients. This can be explained in terms of the extent and severity of myocardial ischaemia and the magnitude of the collateral flow and flow through the reperfused native circulation. In individual patients the magnitude of the fall in coronary sinus pH was related to the duration of ischaemia (fig 2). The observed fall of pH in blood in the coronary sinus is likely to indicate the minimum change of intracellular pH. Cobbe *et al* have shown that in the dog the maximum fall of coronary sinus pH occurred 20 to 30 s after reperfusion and approximated to the maximum fall of tissue pH which also occurred 20–30 s after reperfusion.¹⁹

Our findings are consistent with those in animal experiments. Studies in dogs have shown that a fall in the pH of coronary sinus blood falls after coronary occlusions lasting >20 s.¹⁹ Other workers using intracellular dyes²² and rapidly responding extracellular pH electrodes⁹ have reported a fall in pH within 5 s.

An important question is whether the changes in pH are large enough to cause contractile dysfunction. Cobbe and Poole-Wilson found that in the rabbit heart a fall in tissue pH of 0.03 units could contribute to a substantial fall (>30%) in muscle tension.⁹ The changes in coronary sinus pH in the present study (fig 3) ranged from 0.015 to 0.075 pH units after balloon occlusions of between 17 and 20 s and from 0.025 to 0.120 pH units after balloon occlusions of between 25 and 45 s. If we assume that the peak fall in coronary sinus pH is similar to the peak fall in tissue pH,¹⁹ then the magnitude of the fall in pH would be sufficient to cause important contractile dysfunction.^{13 8 9 12}

Ventricular function has previously been assessed during coronary angioplasty.^{21 23} After coronary occlusion the myocardium contracts normally for at least four beats. There is sufficient oxygen in the blood and myoglobin to provide the energy for at least two beats and after this anaerobic metabolism is stimulated. Impaired contractility can be detected between the fifth and twentieth beat. The exact time of these changes will vary from patient to patient and will depend on many factors. The duration of the monophasic action potential in man has also been reported to change after about 10 beats.²⁴ We have already shown that potassium is lost from the myo-

cardium after approximately 12 beats.¹⁸ Thus acidosis and potassium loss in man appear at the same time as the earliest changes in the configuration of the action potential and in contractile function.

The mechanism for the development of an acidosis is complex. The conversion of creatine phosphate to creatine consumes hydrogen ions and would be expected to cause an alkalosis. Under some experimental conditions this has been reported.^{15 16} The breakdown of adenosine triphosphate (ATP) generates hydrogen ions but ATP is not greatly reduced early in ischaemia.²³ The major mechanism for the early appearance of acidosis is stimulation of glycogenolysis.²⁵

These studies show that in the human heart acidosis develops early after the onset of ischaemia and is of sufficient magnitude to contribute to the decline of contractility.

We are indebted to the British Heart Foundation for their support.

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