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Continuous coronary sinus and arterial pH monitoring during pacing-induced ischaemia in coronary artery disease

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SUMMARY Catheter tip pH electrodes were used for continuous recording of coronary sinus and arterial pH during atrial pacing in 20 patients undergoing coronary arteriography for chest pain. An ischaemic response to atrial pacing was identified by the onset of angina and/or electrocardiographic abnormalities. Technically satisfactory coronary sinus recordings were obtained in 18 patients. Mean coronary sinus pH at the peak pacing rate fell by 0·021±0·006 units (n=9) in the ischaemic group, while there was no significant change in the non-ischaemic group. A larger fall in coronary sinus pH (−0·052±0·009) was found in the ischaemic group in the 30 seconds *after* the end of atrial pacing, the maximum change occurring after 16·1±1·5 seconds. A maximum fall of coronary sinus pH>0·02 units identified patients with an ischaemic response. Changes in arterial pH did not account for these results. The sensitivity of coronary sinus pH recording for the detection of ischaemic heart disease is enhanced by sampling during the "washout" phase after the end of pacing.

Although atrial pacing has been widely used clinically in biochemical studies of myocardial ischaemia,[1,2] many reports have indicated a poor correlation between changes in coronary sinus lactate concentration and the development of angina pectoris or ischaemic electrocardiographic abnormalities.[3,4] Recent studies of regional coronary flow during pacing-induced ischaemia may explain the small changes in lactate concentrations which often occur. In an area of myocardium distal to a critical coronary stenosis, not only is there no *increase* in coronary blood flow to meet the increased metabolic demands induced by tachycardia, but there is an absolute *fall* in coronary flow.[5,6] Reduced arterial flow in an ischaemic area causes retention of the end product of anaerobic metabolism in the tissue, and such metabolites as are washed out will be considerably diluted by the increased coronary venous effluent from non-ischaemic myocardium. At the end of pacing the increased flow through the non-ischaemic myocardium falls to normal within seconds[7] and there is a rapid increase in flow to the ischaemic area.[6] A "washout" of metabolites coupled with reduced dilution by non-ischaemic venous effluent may result in larger changes in coronary sinus metabolite concentration in the first few minutes after cessation of atrial pacing.

Continuous measurement of coronary sinus lactate is not possible, and we have therefore used specially designed catheter tip pH electrodes[8] to record arterial and coronary sinus pH continuously during and after atrial pacing. The hydrogen ion is of particular interest since tissue acidosis is a possible cause of reduced myocardial contractility in acute ischaemia.[9]

Methods and subjects

PH ELECTRODES

The construction and evaluation of the catheter tip pH electrodes have been described in detail.[8] The pH electrode is mounted on the tip of a fine polyethylene tube, which can pass through the lumen of an 8 French gauge Cournand catheter. The electrodes were sterilised in aqueous glutaraldehyde and were calibrated before and after all studies to ensure no loss of function had occurred.

Twenty patients with effort related chest pain

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already scheduled for routine coronary arteriography were studied. There were 17 men and three women. The age range was 37 to 63 years. Patients with recent myocardial infarction, rest pain in the previous week, arrhythmias, or bundle-block were excluded. Informed written consent was obtained in all cases. Sixteen of the patients underwent a treadmill exercise test with 12 lead electrocardiographic recording before catheterisation.[10] The leads in which abnormalities occurred were noted.

PROCEDURE OF PACING TEST

After an overnight fast, the patients were premedicated with diazepam 10 mg intramuscularly. Beta-blockers and calcium antagonists were withdrawn the day before catheterisation, and no patient was taking digitalis. The coronary sinus was cannulated from a left antecubital vein, and the tip of the catheter sited halfway between the coronary sinus ostium and the left heart border. Cannulation was confirmed by injecting radiographic contrast down the Cournand catheter around the pH electrode. The pH electrode tip was then gently advanced 1 cm out of the distal end of the Cournard catheter. The reference electrode (Radiometer, Copenhagen, K4112) was connected to the line flushing the Cournard catheter with heparinised saline. The output of the pH electrode was allowed to stabilise.

A second operator performed a right brachial arterial and venous cutdown to introduce a NIH catheter to the left ventricle and a bipolar pacing electrode to the high right atrium. The patients were heparinised (100 units/kg) after catheter insertion. In nine patients, after baseline left ventricular pressures had been obtained, the NIH catheter was replaced by a second Cournand pH electrode catheter. The tip of this electrode was sited in the right axillary artery distal to the origins of the carotid and vetebral arteries. A pressurised flushing system (Intraflo, Sorenson Research, Salt Lake City, USA) was used for the arterial pH electrode, and a separate reference electrode connected. The amplifiers for the arterial and coronary sinus pH electrodes were operated in differential mode, and were "earthed" to the patient's right leg.

Atrial pacing began when baseline pressure and electrocardiograms had been recorded, and the outputs from the coronary sinus and arterial pH electrodes were stable. Left ventricular pressure, electrocardiogram (leads I, II, V5), and pH were recorded continuously. Atrial pacing started at 90/min. The rate was increased by 10 beats/min at one minute intervals up to a maximum rate of 180 beats/min, or the highest rate at which 1:1 atrioventricular conduction continued. If the patient complained of angina pectoris, or the electrocardiogram showed ST segment depression of 2 mm or more, pacing was discontinued after the one minute at that rate had been completed. After cessation of pacing, pH, pressure, and electrocardiogram were recorded for a further three minutes. At the end of the pH recording, the position of the electrode was checked once more by the injection of radiographic contrast. Left ventriculography and coronary arteriography were then performed.

The changes of arterial and coronary sinus pH from the values at the onset of pacing were measured. Results were expressed as mean±one standard error of the mean, and analysed by Student's t test or the χ^2 test.

Results

CLINICAL RESPONSE TO PACING

Atrial pacing studies were performed on 20 patients. Two groups were defined by the clinical and electrocardiographic response to pacing.

(1) *Non-ischaemic group* (n=10)

Four patients had normal coronary arteries or <50% reduction in vessel diameter on coronary angiography. All had negative exercise tests and, apart from one patient with atypical chest pain before pacing, there was no angina or electrocardiographic abnormality during or after the pacing test.

Significant coronary artery disease (>50% stenosis in one or more vessels) but no angina or electrocardiographic abnormalities on pacing were present in five patients. Three of these patients underwent an exercise test, and developed angina and diagnostic ST segment depression. None of the patients could be paced at a rate adequate to induce angina owing to the development of atrioventricular block. The failure to induce ischaemia in these patients is consistent with previous studies which showed that significantly higher heart rates are necessary to produce angina by pacing than by exercise.[11]

One patient had severe right coronary artery disease and a normal left coronary artery. The venous effluent from the ischaemic area was shown on coronary arteriography to enter the coronary sinus close to its ostium, and therefore acid efflux could not be recorded by our technique.

These 10 patients comprised a "non-ischaemic group" in terms of the response to atrial pacing.

(2) *Ischaemic group* (n=10)

Ten patients had significant left coronary disease with pacing-induced angina and/or diagnostic ST segment depression on the electrocardiogram. Nine of these patients underwent exercise testing. All developed angina, with diagnostic electrocardiographic abnor-

malities in eight out of nine. These patients comprised an "ischaemic" group.

CHANGES IN CORONARY SINUS AND ARTERIAL PH

Of the 20 patients studied, 11 had coronary sinus pH recording alone, and in nine simultaneous arterial and coronary sinus recording was attempted. Simultaneous recording proved to be technically more difficult as a result of electronic interference. Of the nine simultaneous tracings, two coronary sinus and one arterial tracing were rejected as technically unsatisfactory, leaving a total of 18 coronary sinus and eight arterial tracings for analysis, divided equally between the ischeamic and non-ischaemic groups.

The coronary sinus pH tracings from two patients, one with an ischaemic response to pacing and one without angina or electrocardiographic abnormalities, are illustrated in Fig. 1. Fig. 2 shows the pooled data for the coronary sinus pH response in the two groups. The pH changes before pacing, in the last 120 seconds before the end of pacing, and the 180 seconds after restoration of sinus rhythm are shown. During pacing there was a fall in coronary sinus pH in the ischaemic group (that is an acidosis) which reached $-0{\cdot}021\pm0{\cdot}006$ pH units (n=9) ($p<0{\cdot}01$) at the end of pacing, and was significantly different ($p<0{\cdot}005$) from the mean value in the non-ischaemic group ($+0{\cdot}007\pm0{\cdot}005$ pH units, n=9). After pacing, no significant change in coronary sinus pH occurred in the non-ischaemic group, while in the ischaemic group mean pH fell in the first 10 seconds from $-0{\cdot}021\pm0{\cdot}006$ to $-0{\cdot}039\pm0{\cdot}006$ ($p<0{\cdot}001$, paired t test). The mean maximum change in the ischaemic group was $-0{\cdot}052\pm0{\cdot}009$ which was significantly greater than the value obtained at the moment pacing ended ($-0{\cdot}021\pm0{\cdot}006$, $p<0{\cdot}001$, see Fig. 4). The maximum fall in coronary sinus pH occurred at slightly different times in the 30 seconds after pacing was terminated (mean $16{\cdot}1\pm1{\cdot}5$ seconds from the end of pacing). Coronary sinus pH in the ischaemic group returned gradually towards control in the 180 seconds after pacing, while no further change occurred in the non-ischaemic group (Fig. 2).

In Fig. 3 is shown the coronary sinus pH response in the ischaemic group (n=9), together with the simultaneous arterial pH recordings (n=4). The changes in coronary sinus pH cannot be explained on the basis of a parallel change in arterial pH. A slight arterial alkalosis developed with the onset of ischaemia, presumably because of hyperventilation.

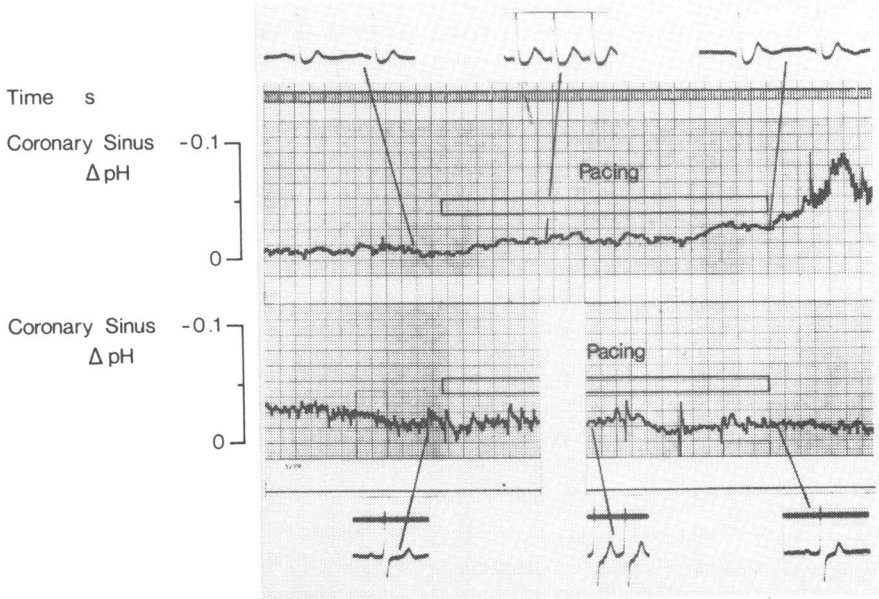

Fig. 1 *Continuous coronary sinus pH recordings from two patients before, during, and after atrial pacing. Upward deflection indicates acidosis.* Upper: *a typical ischaemic response in a patient who developed angina and ST depression after two minutes pacing. A small fall in coronary sinus pH occurred during pacing, but a much larger fall was demonstrated after cessation of pacing. The maximum fall occurred 25 seconds after the end of pacing.* Lower: *the patient was paced at incremental rates up to 170/min with no angina or electrocardiographic abnormalities. The tracing is interrupted and shows the first 30 seconds and last 60 seconds of pacing, with pre- and post-pacing recording of pH. No change in coronary sinus pH occurred during or after pacing.*

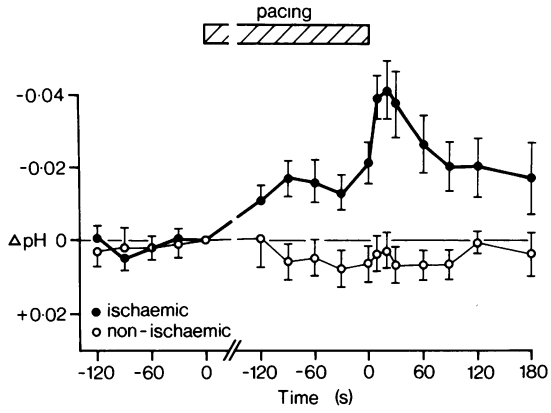

Fig. 2 *Mean change in coronary sinus pH for 120 seconds before the onset of pacing, the last 120 seconds of pacing, and 180 seconds after the end of pacing, in the ischaemic and non-ischaemic groups. Results are expressed as changes in pH from the value at the onset of pacing, upward deflection indicating increasing hydrogen ion concentration (fall in pH). In the ischaemic group, a significant coronary sinus acidosis occurred during pacing, but the maximum change was seen 20 seconds after the end of pacing. No acidosis occurred in the non-ischaemic group (n=9 each group).*

This resulted in a widening of the mean arteriocoronary sinus pH difference by 0·04 pH units at the end of pacing and by 0·06 units, 20 seconds later. It should be emphasised that no significant change in arterial pH occurred in the 60 seconds after pacing, indicating that the prompt fall in coronary sinus pH after pacing must be the result of efflux of hydrogen ions from the myocardium rather than any arterial pH change. Arterial pH in the non-ischaemic group did not differ from the control value before, during, or after pacing.

The individual values for coronary sinus pH at the end of pacing were compared with the most acidic value obtained in the first 30 seconds after pacing in both the ischaemic and non-ischaemic group (Fig. 4). At no time did coronary sinus pH in the non-ischaemic group fall by greater than 0·02 units below the value at the onset of pacing. At the moment pacing ended, five out of nine patients in the ischaemic group already had changes greater than −0·02 in coronary sinus pH. All but one patient in the ischaemic group subsequently showed a maximum fall of greater than 0·02 units in the 30 seconds after switchoff. Apart from this one patient a positive pH response (maximum change −0·02 units) discriminated between patients with and without myocardial ischaemia as assessed from the electrocardiogram and the onset of chest pain ($\chi^2=11{\cdot}4$, $p<0{\cdot}001$ for all patients). The discrimination was greatly improved by using the maximum fall in pH in the 30 seconds after pacing, rather than the value at the end of the pacing period.

Discussion

The results presented above show that pH recording from the arteries and coronary sinus of man is technically feasible with catheter tip electrodes. Continuous recording of pH permits identification of rapidly occurring changes in hydrogen ion concentration which would be missed by conventional sampling techniques. We have verified that acidosis does develop in the ischaemic myocardium of man and that a more pronounced change in coronary sinus pH occurs immediately *after* the end of pacing than *during* pacing itself. Tissue acidosis in the myocardium is an important cause of contractile failure during ischaemia.[9]

In the presence of normal coronary arteries, pacing-induced tachycardia results in an increase in myocardial oxygen and substrate demand which is balanced by a parallel increase in coronary flow.[12, 13] This increase must occur as a result of vasodilatation, since the diastolic pressure/time index steadily falls with increasing heart rate.[14] Even at very rapid heart rates, however, the capacity for vasodilatation is not exhausted[15] and no evidence of subendocardial ischaemia is found.[16]

In the presence of coronary artery stenosis, the capacity for distal vasodilatation may initially allow a small increase in coronary flow through a stenosis. As

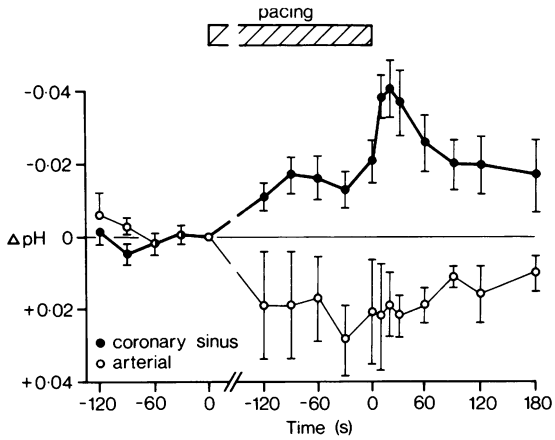

Fig. 3 *Mean changes in arterial and coronary sinus pH in the ischaemic group before, during, and after atrial pacing. A mild alkalosis developed in the arterial blood, which in conjunction with the coronary sinus acidosis produced an increase in arteriovenous pH difference. No significant change in arterial pH occurred after the end of pacing in contrast to the rapid fall in coronary sinus pH. n=9 coronary sinus tracings, n=4 arterial changes.*

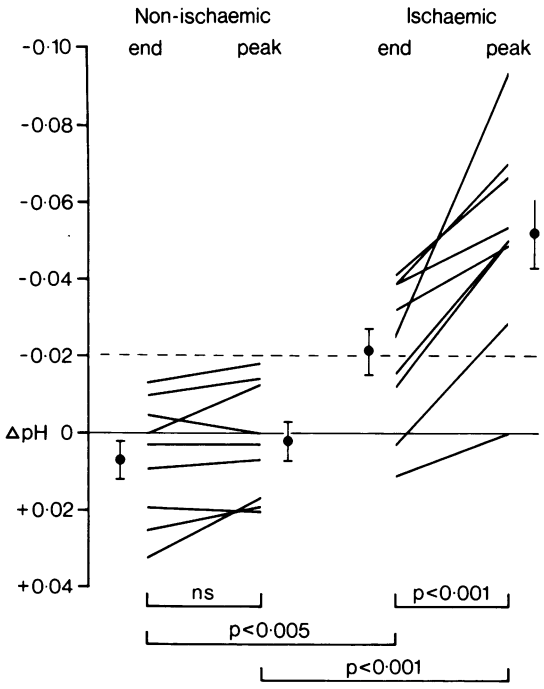

Fig. 4 *Individual values for change in coronary sinus pH at the end of pacing (end) compared with the maximum change occurring in the 30 seconds after the end of pacing (peak). Zero refers to the coronary sinus pH at the start of pacing, and values are expressed as changes from this level, upwards indicating acidosis. Though mean pH in the ischaemic group at the end of pacing is significantly more acidic than in the non-ischaemic group ($p<0·005$) there is some overlap. The difference between the peak values, however, is highly significant ($p<0·001$) and only one value overlaps the dividing line of −0·02 units.*

the heart rate increases, however, distal vasodilatation becomes maximal, and then coronary flow through the stenosis becomes directly proportional to the diastolic pressure/time index, which falls with increasing heart rate. There is also some evidence that coronary vasoconstriction may occur as a result of thromboxane release.[17] Thus, absolute reductions in coronary flow distal to a stenosis may occur[5,6] affecting principally the subendocardium.[18]

Such a reduction in coronary flow in the presence of increased metabolic and oxygen demands results in ischaemia. Tissue accumulation of the end products of anaerobic metabolism such as lactate and hydrogen ion may be expected as a result of increased production and decreased washout. Even such a freely diffusible gas as carbon dioxide is found to be retained in the myocardium during pacing-induced ischaemia.[19] Although there is undoubtedly efflux of some small proportion of metabolites from the ischaemic area, the effluent is diluted by the increased venous effluent from non-ischaemic myocardium, so that the concentration of metabolites in venous blood changes relatively little during the period of ischaemia.

At the end of pacing, coronary flow to the non-ischaemic myocardium falls to control within six seconds[7] while the flow to the ischaemic area increases back to normal within three to five minutes.[6] The ischaemic area is "reperfused" and its retained metabolites washed out at a time when the dilution from non-ischaemic venous effluent is lessening.

It is not possible to estimate from our data whether the "washout" from the ischaemic area or the reduction in dilution by non-ischaemic effluent is more significant in causing the fall in coronary sinus pH after the end of pacing. A significant fall in coronary sinus pH did of course occur during pacing, indicating that there must have been efflux of hydrogen ions from the ischaemic area. This efflux was demonstrable despite the development of a mild arterial alkalosis which would result in an underestimation of coronary sinus acidosis. The results in the non-ischaemic group indicate the absence of excess acid efflux from non-ischaemic myocardium during the pacing test.

Our results with a continuous recording technique provide evidence of a fall in coronary sinus pH during ischaemia which becomes maximal in the 30 seconds after switchoff. Coronary sinus pH recording is technically difficult, and the construction of the electrodes time consuming, so that we do not at present foresee its widespread use. It seems likely, however, that the efflux of lactate into the coronary sinus will have a similar pattern to that of the hydrogen ion.[18] The sensitivity and specificity of coronary sinus lactate measurement during pacing in providing biochemical evidence of myocardial ischaemia in man may be considerably enhanced by sampling frequently during the first 30 seconds after the end of pacing.

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