

Haemodynamic observations during percutaneous transluminal coronary angioplasty in the presence of synchronised diastolic coronary sinus retroperfusion

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SUMMARY Animal studies have demonstrated that synchronised coronary sinus retroperfusion with arterial blood can provide effective perfusion of ischaemic myocardium. Preliminary clinical studies have shown that the technique can also be used with safety in human beings, and in the present study its effectiveness was assessed in three patients undergoing repeated coronary artery occlusions during percutaneous transluminal coronary angioplasty. Arterial blood was removed via an 8F catheter positioned in the femoral artery and delivered by a retroperfusion pumping system to a 7F retroperfusion balloon catheter positioned in the anterior cardiac vein. Ischaemia-related indices were monitored both before and during coronary sinus retroperfusion. These indices included high fidelity left ventricular pressure recordings and pressure derived indices (including velocities of isovolumic contraction and relaxation), as well as electrocardiographic changes and symptoms. Analysis of these variables showed that the ischaemic changes induced during coronary artery occlusion were not prevented by this type of coronary sinus retroperfusion. There was no major complication in any of the patients.

It may be that adaptation of the technique or the use of alternative end points will establish a benefit, but further modifications of the delivery system are necessary for effective clinical use.

The effective preservation of acutely ischaemic myocardium remains an elusive goal. Coronary sinus retroperfusion has been put forward as a practical technique for providing temporary support of jeopardised myocardium. The concept was originally tested in the clinical setting by Beck *et al* in the 1940s with disappointing results.¹ They used an aorta-to-coronary-sinus anastomosis with an artificially increased coronary sinus outflow resistance to shunt a proportion of the blood retrogradely. The increase in venous pressure, however, led to myocardial engorgement and eventual myocardial failure. In 1976 Meerbaum *et al*² introduced a synchronised delivery system that limited the delivery of arterial blood to the coronary sinus to diastole, thereby overcoming some of the original complications associated with the continuous increase in pressure in

the coronary venous system. This technique was effective and safe in animal studies,³ and improved myocardial salvage, myocardial perfusion, and indices related to ischaemia.⁴⁻⁶ Although there is broad agreement on the safety of the procedure not all of the animal studies showed an improvement in myocardial perfusion.^{7,8}

Clinical studies confirmed the safety of the procedure in human beings, and suggested that it may be useful in unstable angina and during percutaneous transluminal coronary angioplasty.^{9,10} Recently Gore *et al* reported the experience of retroperfusion in five patients with acute ischaemia.¹¹ The procedure had no adverse effects and despite clinically encouraging results there was little objective evidence to support its effectiveness. We therefore conducted a pilot study in three patients to determine whether synchronised coronary sinus retroperfusion prevented transient loss of myocardial function, as assessed by central haemodynamic indices, during repeated occlusion of the coronary artery in percutaneous transluminal coronary angioplasty.

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Patients and methods

PATIENT SELECTION

We studied three patients who had easily provoked angina, a lesion of the proximal left anterior descending artery with a large area of potentially ischaemic myocardium, normal left ventricular anterior wall motion, and no angiographically demonstrable collateral supply to the potentially ischaemic area.

RETROPERFUSION SYSTEM

Oxygenated blood was delivered by a size 7 Fr single lumen, Nycore, retroperfusion catheter (USCI Division of Bard Inc. Billerica, MA, USA), 90 cm in length, and with a lumen diameter of 0.56 mm. This catheter consists of a balloon (maximal inflation diameter 10 mm) positioned close to the tip of the catheter that communicates with the central lumen of the catheter via a number of small holes. Thus when blood is pumped through the catheter, the increase in intraluminal pressure producing the flow through the catheter also causes the balloon to inflate, which in turn leads to occlusion of the coronary sinus lumen, thereby directing the delivered blood retrogradely (fig 1a). When flow ceases during systole, intraluminal pressure falls, the balloon deflates, and normal forward coronary sinus flow is resumed.

The tip of the catheter was positioned in the great cardiac vein, under fluoroscopic control with the aid of a 0.018 inch (Advanced Catheter Systems) high torque guide wire, and the position was verified by injection of contrast. Arterial blood was delivered to the catheter via a USCI synchronised retroperfusion system, model EC-I. Blood was removed with a special multihole catheter (8F, 40 cm (USCI)) introduced to the distal aorta via the femoral artery. There were three parts to the retroperfusion system: (a) a linear, constant force pump with a variable stroke volume; (b) a Hewlett Packard 7834 monitor to display selective electrocardiographic signals as well as perfusion and aortic pressures; (c) a pump control device that allowed the onset and duration of the pump stroke to be adjusted in relation to the triggering R wave. In addition, it allowed the volume of blood delivered per minute to be controlled independently of the heart rate.

HAEMODYNAMIC AND ELECTROCARDIOGRAPHIC MONITORING

Left ventricular pressure was measured by a Millar micromanometer catheter and digitised at 250 samples per second. A beat to beat computer program was used to analyse, display, and store the pressure signals for off line analysis. Peak left ventricular pressure, left ventricular end diastolic pressure, peak negative dP/dt , peak positive dP/dt , and the relation

between dP/dt /pressure and pressure linearly extrapolated to pressure 0 (V_{max}) (where V_{max} is the maximal velocity) were computed for each measured beat. $\tau_{1,}$ the time constant for the first 40 ms, taken from the bi-exponential model of the isovolumic relaxation period was also recorded. The definition of the pressure derived indices and their method of determination have been described elsewhere.¹²⁻¹⁴

Electrocardiograms from leads I, II, and V3 were recorded throughout the procedure and in addition an intracoronary electrocardiogram was recorded from the intraluminal balloon guide wire in one of the patients. The ST changes are expressed in mV and were recorded from the lead showing the maximal change in ST segment during occlusions, measured from the isoelectric line (P-Q interval) 0.08 seconds after the J point.

PROTOCOL

The protocol was approved by the ethics committee of the Thoraxcenter. The data were collected according to the guidelines of the Food and Drugs Administration of the United States and the procedures were performed with the technical assistance of representatives from the industry. Patients gave their informed consent to the study.

A pacing wire was positioned in the right atrium, and coronary angiography and left ventriculography were performed. The catheter for monitoring pressure was then positioned in the left ventricle and the retroperfusion catheter was inserted into the coronary sinus. The catheter for dilating the coronary artery was then introduced and the lesion was crossed. Two control dilatations were performed with haemodynamic monitoring before retroperfusion was started. This was started at an initial measured flow rate of 50 ml/min, increasing by 20 ml/min, up to 150 ml/min. Retroperfusion was then continued for 20 minutes. The extent of retroperfusion was assessed visually by direct hand injection of contrast (fig 1b). Two further investigational balloon dilatations were then performed.

Case reports

Patient 1—A 67 year old woman was admitted with chest pain at rest, which continued despite administration of intravenous isosorbide dinitrate. Coronary angiography showed an isolated severe proximal stenosis in the left anterior descending artery and she was therefore transferred to the Thoraxcenter for an immediate angioplasty. The retroperfusion catheter was satisfactorily positioned via the right femoral vein. Four balloon dilatations were performed at 10 atmospheres each—two before retroperfusion and

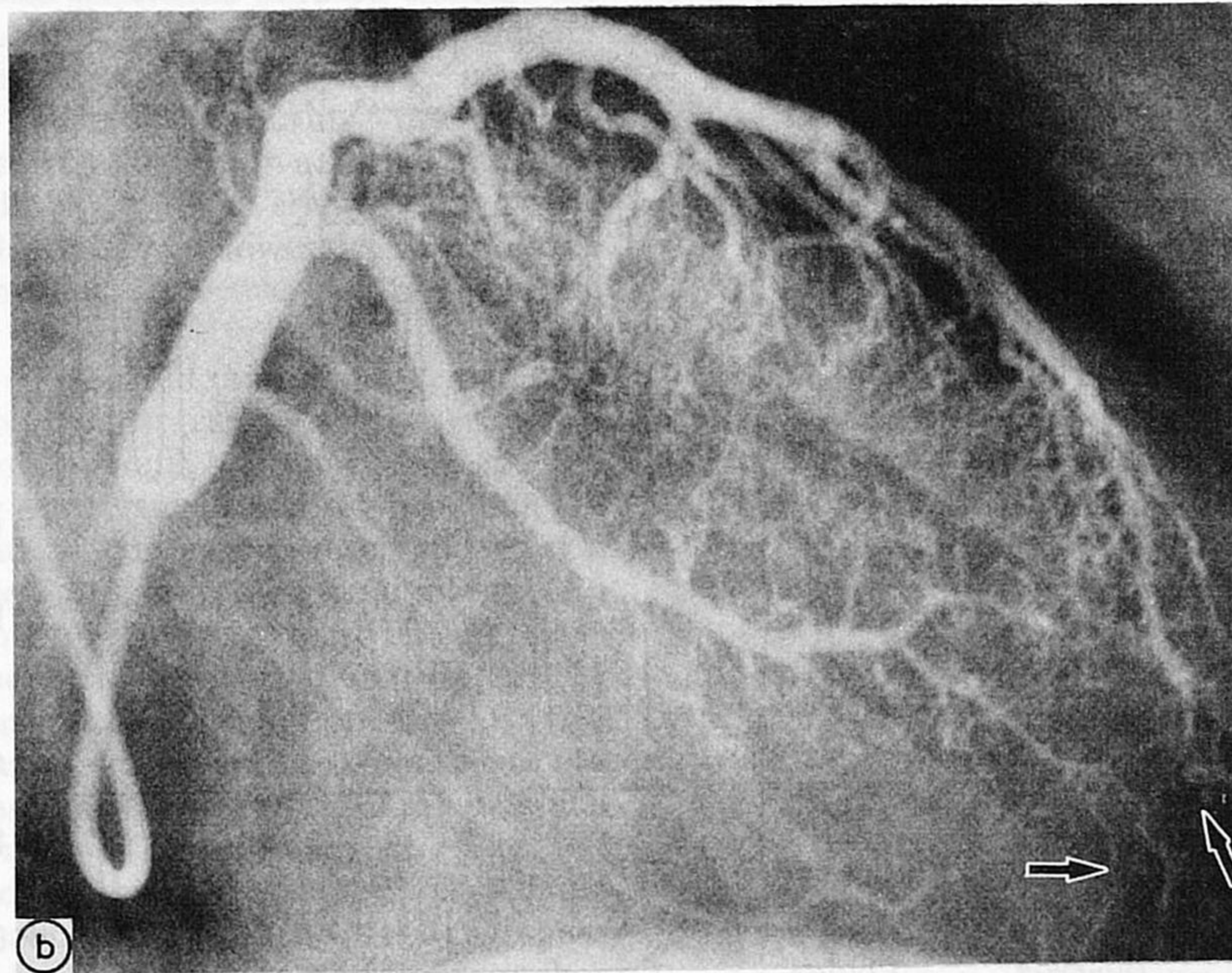
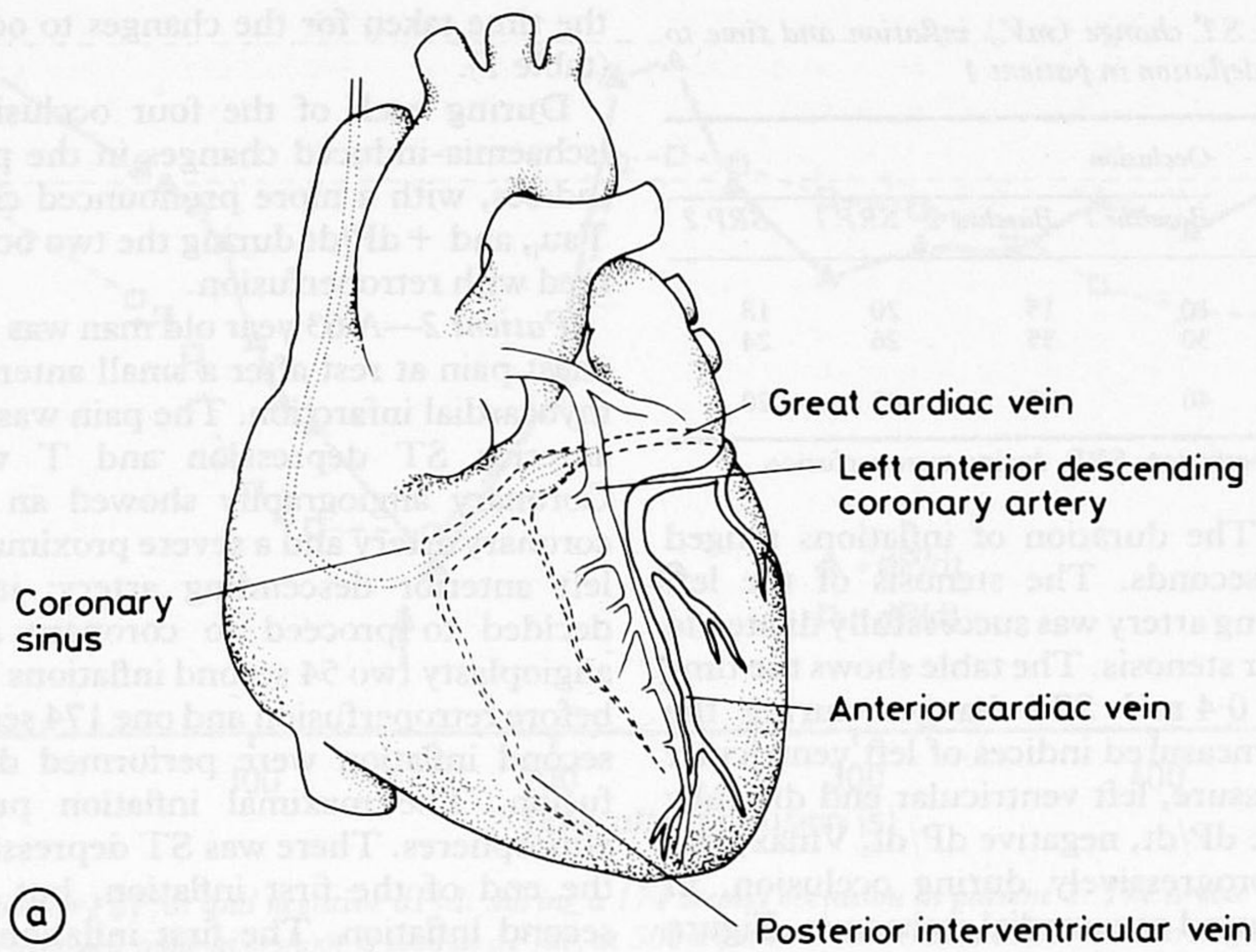


Fig 1 (a) Diagram showing the retroperfusion catheter positioned in the great cardiac vein. (b) Single frame angiogram showing the retroperfusion catheter positioned in the great cardiac vein. The anterior cardiac vein is clearly delineated by hand injection of contrast. This produces a myocardial blush and shows the venous to venous collateral circulation (arrows).

Table Time(s) to ST change (mV) inflation and time to normalisation after deflation in patient 1

	Occlusion			
	Baseline 1	Baseline 2	SRP 1	SRP 2
Time to:				
0.2 mV	10	15	20	18
0.4 mV	30	35	26	24
Normalisation (after deflation)	40	30	45	20

Baseline, before retroperfusion; SRP, during retroperfusion.

two afterwards. The duration of inflations ranged from 45 to 52 seconds. The stenosis of the left anterior descending artery was successfully dilated to a < 50% diameter stenosis. The table shows the time to 0.2 mV and 0.4 mV ST changes during the occlusions. The measured indices of left ventricular peak systolic pressure, left ventricular end diastolic pressure, positive dP/dt, negative dP/dt, Vmax, and Tau₁, changed progressively during occlusion, in keeping with induced myocardial ischaemia. Figure 2 shows the electrocardiogram, left ventricular pressure, and retroperfusion flow recordings at the end of each occlusion compared with the baseline recordings. At the end of each occlusion there was 0.4 mV of ST elevation; there was considerable variability in

the time taken for the changes to occur and resolve (table 1).

During each of the four occlusions there were ischaemia-induced changes in the pressure derived indices, with a more pronounced change in Vmax, Tau₁, and +dP/dt during the two occlusions performed with retroperfusion.

Patient 2—A 63 year old man was readmitted with chest pain at rest after a small anterior non-Q wave myocardial infarction. The pain was associated with anterior ST depression and T wave inversion. Coronary angiography showed an occluded right coronary artery and a severe proximal stenosis in the left anterior descending artery; it was therefore decided to proceed to coronary angioplasty. At angioplasty two 54 second inflations were performed before retroperfusion and one 174 second and one 54 second inflation were performed during retroperfusion. The maximal inflation pressure was 10 atmospheres. There was ST depression of 0.1 mV at the end of the first inflation, but not during the second inflation. The first inflation with retroperfusion was increased to 174 seconds, with the patient complaining of mild pain shortly after 30 seconds. There was no progression to severe chest pain during the procedure and only slow progression in ST change—0.1 mV at 70 s and 0.2 mV at 140 seconds.

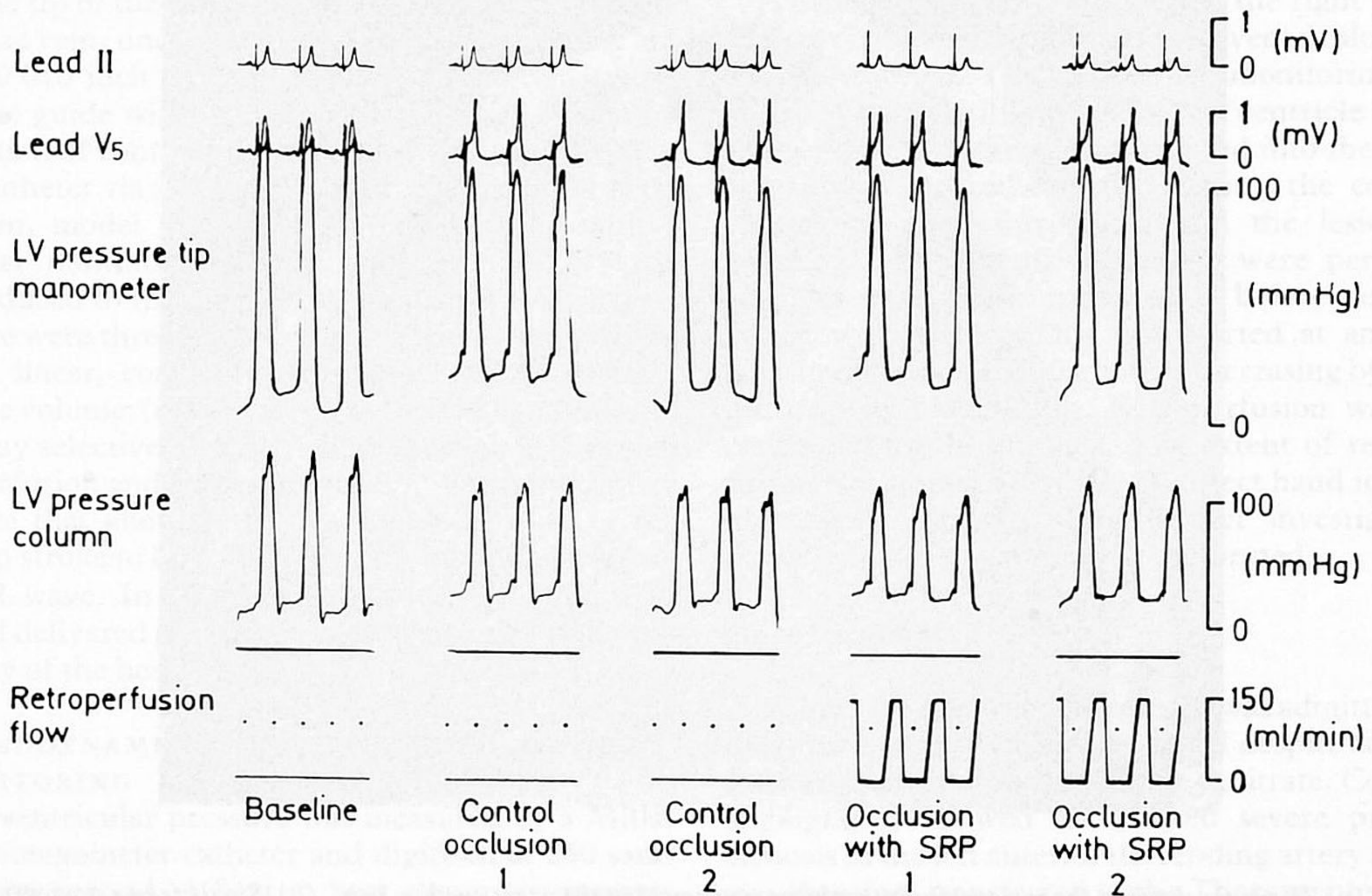


Fig 2 Left ventricular pressure and surface electrocardiograms in patient 1 before the first occlusion, at the end of the two controlled occlusions, and at the end of the two occlusions with synchronised retroperfusion (SRP). The retroperfusion flow tracing (b) shows the magnitude of the flow and the timing in relation to the cardiac cycle. The ST changes in lead V5 and the changes in left ventricular pressure were similar for the four occlusions.

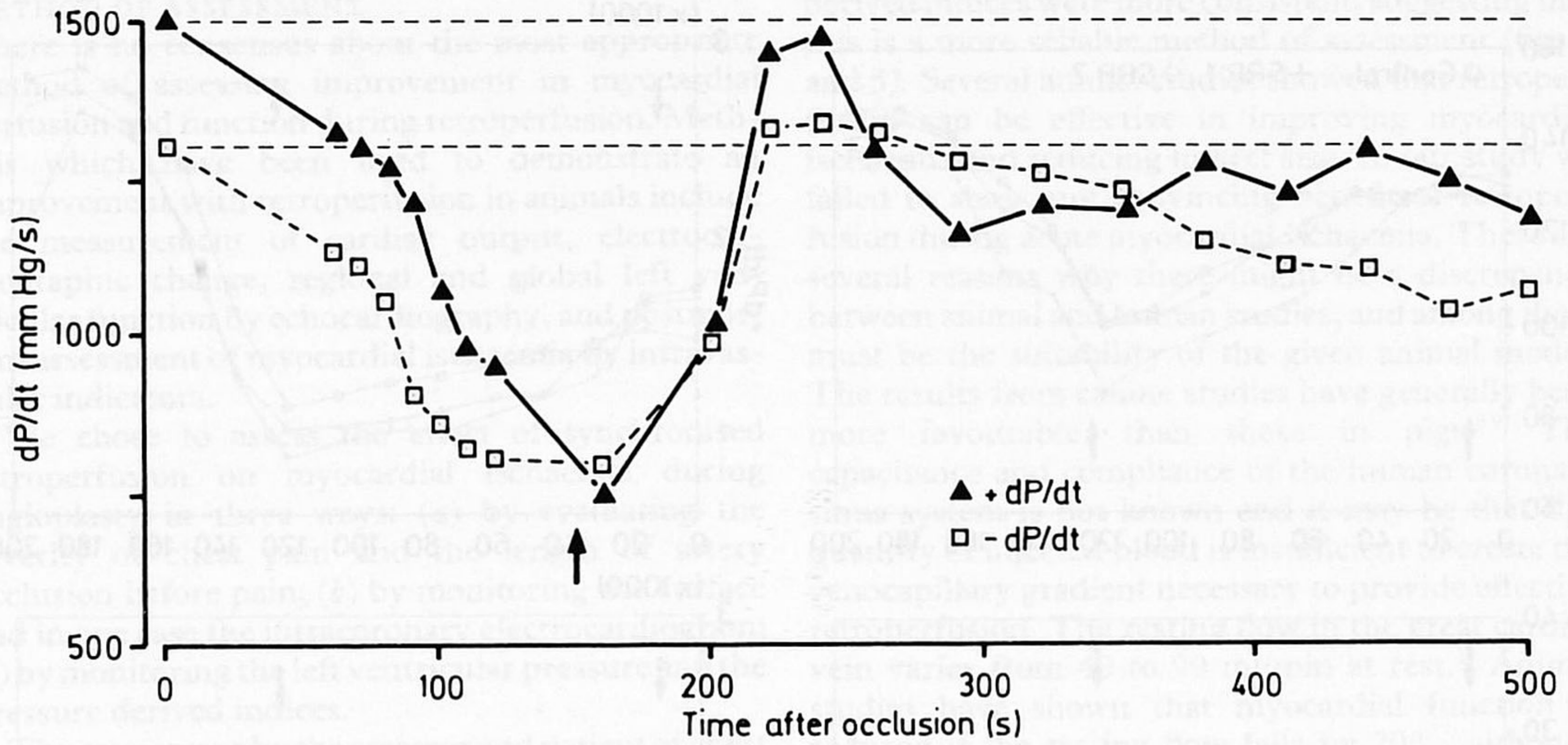


Fig 3 Values of positive dP/dt and negative dP/dt during a 174 second occlusion in patient 2. The arrow shows the point of balloon deflation. Although some overshoot is seen in dP/dt , at 500 s both values remain below the starting value, suggesting some persisting depression of myocardial function.

These changes resolved within 30 seconds of deflation. Figure 3 shows changes in $+dP/dt$ and $-dP/dt$. Again the expected ischaemia-induced changes are clearly present. Although there was an "overshoot" in the $+dP/dt$ on reperfusion, the change is not as pronounced as that seen during the shorter occlusions in patient 3 (fig 5b). In addition, the post-occlusion recordings (at 500 s) showed that all the pressure derived indices were lower than the baseline values, suggesting delayed recovery of the ischaemic myocardium.

Patient 3—A 64 year old man developed pain on minimal exertion and at rest when provoked by emotional or cold stimuli. Coronary angiography showed a single severe stenosis in the proximal left anterior descending coronary artery, and it was therefore decided to proceed to angioplasty. An initial inflation of 56 seconds produced no symptoms and therefore the inflation time was increased to 115 seconds without retroperfusion followed by two inflations with retroperfusion of 123 seconds and 116 seconds. All dilatations were performed at a maximal inflation pressure of 12 atmospheres. The left anterior descending lesion was successfully dilated without complications. The severity of the chest pain was categorised by the patient as mild, moderate, or severe on an analogue scale. Figure 4 shows the analogue scores and the degree of ST change during and immediately after balloon inflations. During all three occlusions there was a gradual decrease in left ventricular peak systolic pressure and an increase in end diastolic pressure, with no difference between

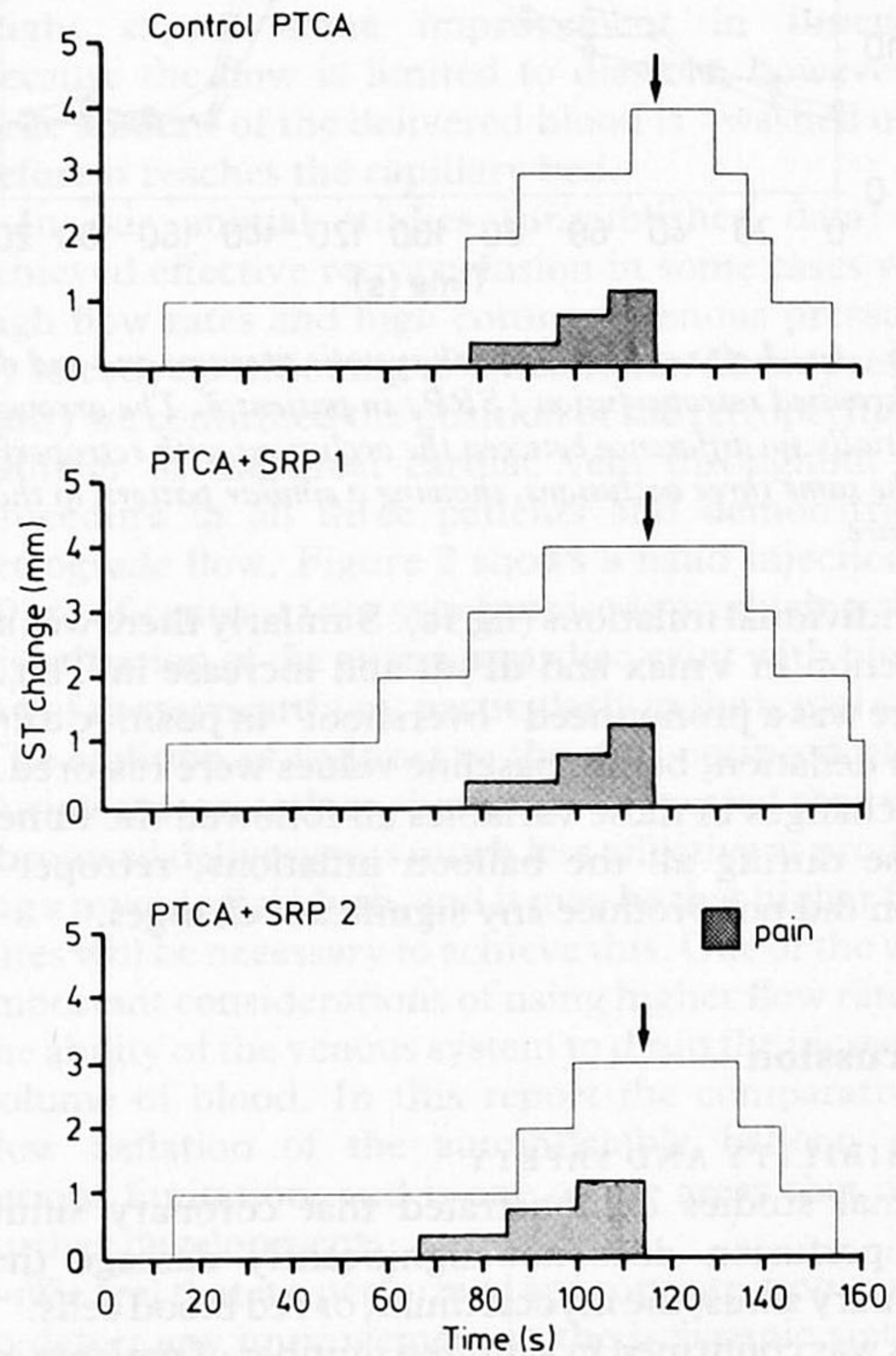


Fig 4 Time to given ST change and degree of chest pain during three occlusions in patient 3, one without and two with synchronised retroperfusion (SRP). The three steps on the pain scale correspond to mild, moderate, and severe chest pain respectively.

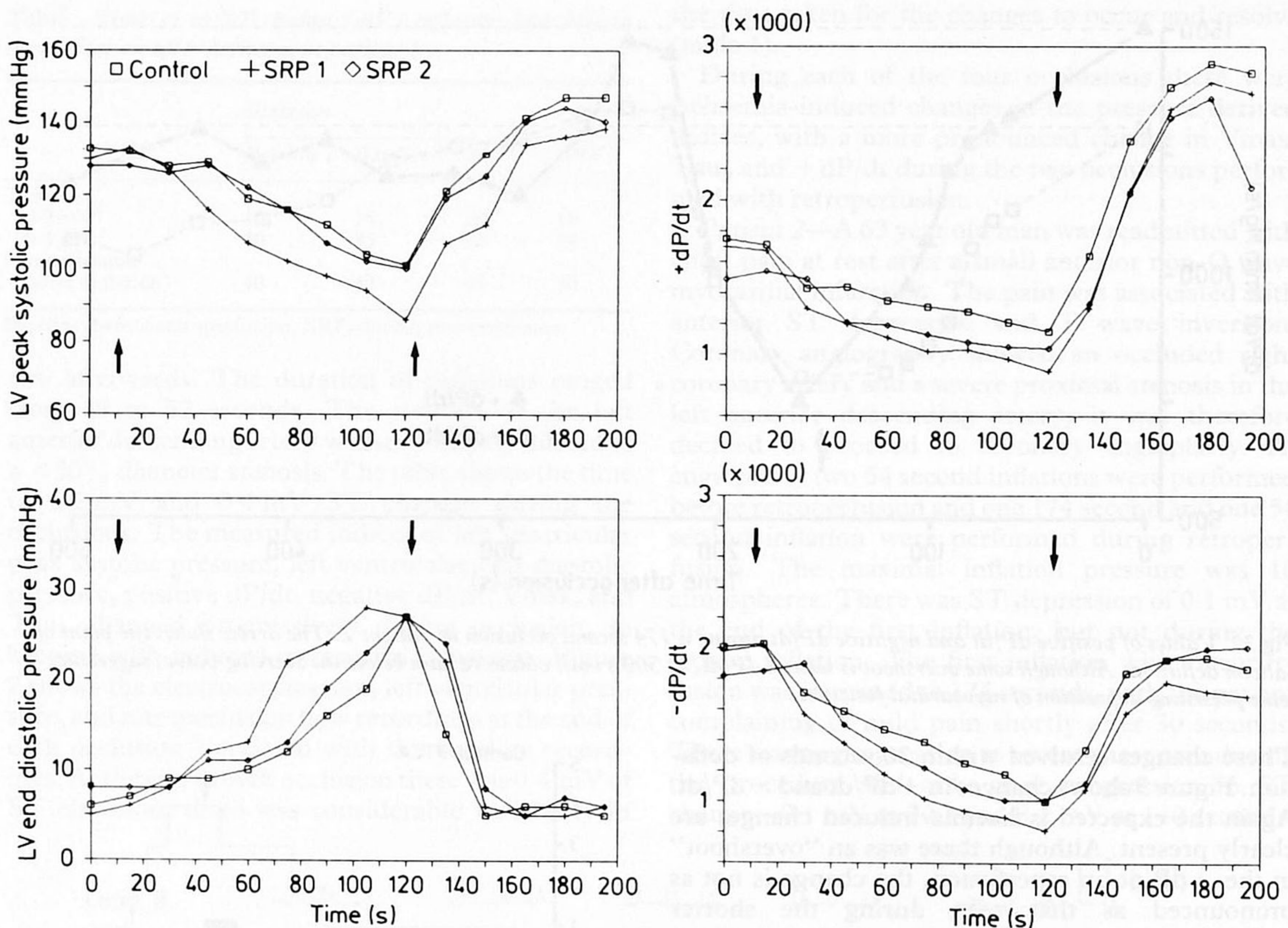


Fig 5 (a) Left ventricular peak systolic pressure and end diastolic pressure during one controlled occlusion and two with synchronised retroperfusion (SRP) in patient 3. The arrows show the onset of balloon inflation and deflation. There is essentially no difference between the occlusions with retroperfusion and the one without. (b) Changes in $+dP/dt$ and $-dP/dt$ for the same three occlusions, showing a similar pattern to that for left ventricular peak systolic pressure and end diastolic pressure.

the individual inflations (fig 5a). Similarly there was a reduction in V_{max} and dP/dt and increase in Tau_1 . There was a pronounced "overshoot" in positive dP/dt on deflation, before baseline values were restored. The changes in these variables all followed the same course during all the balloon inflations; retroperfusion did not produce any significant changes.

Discussion

FEASIBILITY AND SAFETY

Animal studies demonstrated that coronary sinus retroperfusion does not significantly damage the coronary sinus, the myocardium, or red blood cells.²⁻⁴ This was confirmed in a limited number of patients in whom the procedure was performed.⁹⁻¹¹ Although, with prolonged retroperfusion there does seem to be loss of the coronary sinus epithelium, which may lead to the formation of a fine layer of thrombus and even

small areas of haemorrhage adjacent to the sinus, this is not of any apparent clinical importance. In our study we had no information on the state of the coronary sinus epithelium, but no thrombus formation was identified by contrast injection of the sinus or by direct inspection of the catheter after removal. Furthermore, the lack of change of the haemodynamic variables during the control period of retroperfusion suggests that there was no adverse effect on myocardial function during normal anterograde flow, which accords with other reports.¹⁰

In all three patients the positioning of the catheter in the coronary sinus was a relatively simple procedure. In two patients a 0.018 inch high torque floppy guide wire was used to avoid entering the origin of the obtuse marginal vein. We found that once venous access was obtained the catheter could be positioned quickly so that when imaging is available it should be possible to set up the system and start retroperfusion within 15 minutes.

METHOD OF ASSESSMENT

There is no consensus about the most appropriate method of assessing improvement in myocardial perfusion and function during retroperfusion. Methods which have been used to demonstrate an improvement with retroperfusion in animals include the measurement of cardiac output, electrocardiographic change, regional and global left ventricular function by echocardiography, and postmortem assessment of myocardial ischaemia by intravascular indicators.

We chose to assess the effect of synchronised retroperfusion on myocardial ischaemia during angioplasty in three ways: (a) by evaluating the severity of chest pain and the length of artery occlusion before pain; (b) by monitoring the surface and in one case the intracoronary electrocardiogram; (c) by monitoring the left ventricular pressure and the pressure derived indices.

The assessment by the assessor and patient of chest pain in a stressed patient during an interventional procedure in which an experimental device is used is to some extent subjective. The use of an analogue scale may help to reduce this, but we believe that such an assessment will remain crude and will only be relevant when there are large changes.

ST change is widely used as an index of ischaemia although the variability of this measurement in the context of repeated coronary occlusion with intracoronary injections has not been well validated. Intracoronary electrocardiographic recordings taken from the balloon guide wire which overlies the area of ischaemic myocardium provides a more reliable measurement,¹⁵ although there may still be some variability when there are sequential artery occlusions, where alterations in the resting membrane potential may give a false impression of ST change.¹⁶ Perhaps the most reliable forms of measurement, particularly in assessing myocardial function, are left ventricular pressure and pressure derived indices. Serruys *et al* showed that measured changes correlate well with changes in regional and global left ventricular function and provide a reliable index for comparison during repeated episodes of ischaemia.¹⁴

EFFECTIVENESS OF PROCEDURE

An analysis of the individual's angina threshold and the documented ST change during coronary artery occlusion failed to show any consistent change during retroperfusion. Similarly, the change in left ventricular pressure and pressure-derived indices showed the predicted ischaemia-induced changes with no reversal during retroperfusion. Although there was a certain amount of variability in the time to chest pain and any given ST change the pressure-

derived indices were more consistent, suggesting that this is a more reliable method of assessment (figs 4 and 5). Several animal studies showed that retroperfusion can be effective in improving myocardial ischaemia and reducing infarct size. In our study we failed to show any convincing benefit of retroperfusion during acute myocardial ischaemia. There are several reasons why there might be a discrepancy between animal and human studies, and among these must be the suitability of the given animal model. The results from canine studies have generally been more favourable, than those in pigs.^{8,9} The capacitance and compliance of the human coronary sinus system is not known and it may be that this quantity of injected blood is insufficient to create the venocapillary gradient necessary to provide effective retroperfusion. The resting flow in the great cardiac vein varies from 40 to 99 ml/min at rest.¹⁴ Animal studies have shown that myocardial function is reduced if the resting flow falls by 20%, although some benefit in terms of myocardial salvage may be retained even when flow rates are reduced by as much as 70%.^{17,18} Even if only a proportion of a retrograde flow rate of 160 ml/min reaches the myocardium we might expect some improvement in function. Because the flow is limited to diastole, however, a large amount of the delivered blood is "washed out" before it reaches the capillary bed.

In our animal studies (unpublished data) we achieved effective retroperfusion in some cases with high flow rates and high coronary venous pressures by selective positioning of the catheter. In the present study we confirmed the position of the retroperfusion catheter in the great cardiac vein throughout the procedure in all three patients and demonstrated retrograde flow. Figure 2 shows a hand injection of 10 ml of contrast (not synchronised) producing clear visualisation of the anterior cardiac vein, with blushing of the myocardium, particularly in the septal area. The addition of contrast to the retroperfused blood during the procedure, however, suggested that synchronised delivery was much less effective at producing a myocardial blush, and it may be that higher flow rates will be necessary to achieve this. One of the very important considerations of using higher flow rates is the ability of the venous system to drain the increased volume of blood. In this report the comparatively slow deflation of the autoinflatable balloon is a serious limitation, and is one of the areas that need further development.

We feel that we performed appropriate monitoring to detect any improvement in the ischaemic state of the myocardium. The ischaemic response to repeated occlusion of the coronary artery may be variable; in particular the response may become blunted with repeated occlusions. By performing the occlusions

with retroperfusion after the control occlusions, any improvement in the ischaemic response due to an improvement in anterograde flow may have been falsely attributed to the retroperfusion. Left ventricular function as assessed by our haemodynamic measurements, however, showed no improvement during occlusions with retroperfusion in any of our patients. Improvement in ischaemia may not be the only potential benefit of retroperfusion. Mohl *et al* have developed the concept of pressure-controlled intermittent coronary sinus occlusion,^{19,20} in which the coronary sinus is occluded cyclically until a predetermined pressure is reached. Using the technique they have shown that toxic metabolites are washed out and this may be important in reducing the extent of infarction, particularly if subsequent reperfusion takes place. It is possible that this feature may also be a benefit of retroperfusion during transient ischaemia,²¹ but the limitations of our model prevented us from assessing this.

FUTURE APPLICATIONS

The use of coronary sinus retroperfusion has been proposed in several clinical settings including myocardial infarction and unstable angina, retroperfusion of thrombolytic and antiarrhythmic drugs, and for cardioplegia. It is doubtful whether the procedure will become widely used in myocardial infarction and unstable angina because more effective forms of treatment with greater potential are becoming available. Of the other medical proposals, the delivery of thrombolytic and antiarrhythmic agents are unlikely to be substantially more effective than intravenous administration and the additional time and expense of retroperfusion may not be justified.

If retroperfusion can be shown to be effective, however, it could become a valuable aid to percutaneous transluminal coronary angioplasty. It would permit longer occlusions in general and would mean that more critical lesions such as those of the left main stem could be dilated with reduced risk of myocardial damage. It could also be useful in salvaging myocardium in those procedures in which a total occlusion occurs, by providing effective perfusion of the ischaemic area while the patient is prepared for bypass surgery.

We feel the weight of our current data precluded the use of this technique in additional patients. We have, however, been able to identify potential modifications which should substantially improve the current delivery system. It remains to be seen whether improved techniques of anterograde perfusion will make retroperfusion obsolete, but any future clinical trial must be conducted in a controlled manner and its conclusions must be based on reliable and reproducible indices of myocardial ischaemia.

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