LASER CORONARY REVASCULARIZATION: AN EVALUATION OF METAL-CAPPED OPTICAL FIBRES

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ABSTRACT

Disappointment with the long term results of conventional revascularization techniques (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) has stimulated alternative approaches to the treatment of coronary artery disease. Conventional techniques restore distal blood flow, but do not remove obstructive tissue mass. Direct laser energy offers the potential for plaque vaporization and longer patency of the recanalized vessel but results in an unacceptably high perforation rate due to forward projection of the laser beam. Laser activated metal-capped optical fibres which convert laser energy into thermal energy effectively recanalize severely diseased peripheral vessels, but their efficacy and safety in the coronary circulation required definition.The studies reported in this thesis have demonstrated:

- the feasibility of using metal-capped optical fibres percutaneously to induce thermoablation without perforation in dog coronary arteries

but their use in human atherosclerotic coronary arteries is limited by:

- a poor primary success rate when used percutaneously in Man
- the formation of thromboembolic particles >1mm in size when used in blood
- the release of atherosclerotic debris greater than 50μm and up to 1mm in diameter
- an inability to vaporise calcific atheroma
- a tendency towards perforation through the contralateral "normal" arterial wall in the presence of eccentric stenoses
- the tendency of the metal cap to adhere to the arterial wall with resultant intraluminal flap formation on withdrawal of the metal cap .
- a stenotic effect on side branch origins

These studies have identified the role of perfusate, plaque geometry and composition in successful recanalization which are important considerations for all types of laser coronary angioplasty.

An Evaluation of Metal-capped Optical Fibres for Laser Coronary Revascularization

Chapter 6:
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CHAPTER 1

Introduction

"Surgery of the heart has probably reached the limits set by nature to all surgery. No new method and no new discovery can overcome the natural difficulties that attend a wound of the heart"

James Paget,1896.

At about the same time that Paget made this pessimistic prognostication Rehn (1897) successfully sutured a stab injury to the heart and Jaboulay (1896) described a technique for intima-to-intima anastamosis of blood vessels. Jaboulay's technique was further developed by his student Carrel who refined vessel anastamosis by the trifurcation technique. In time this technique was to provide the basis for many types of anastamotic vascular surgery, especially coronary surgery and organ transplantation.

Carrel, who was later awarded the Nobel Prize for medicine, presented a paper to the American Surgical Association in which he described the first recorded attempt at coronary surgery. This consisted of grafting a section of homologous carotid artery between the proximal end of the left coronary artery near the pulmonary artery and the descending thoracic aorta of a dog. He stated, " Unfortunately the operation was too slow. Three minutes after the interruption of the circulation, fibrillary contraction appeared, but the anastamosis took five minutes. By massage of the heart the dog was kept alive but he died two hours later" (Carrel,1910).

Indirect Myocardial Revascularization

The next phase of myocardial revascularization was pioneered by Claude Beck in the mid 1930's. He had noticed that cutting a band of adhesions compressing the heart resulted in

brisk bleeding from each end of the transected adhesion. This observation culminated in the development of the technique of scarification of the epicardium to bring new vessels to the heart, combined with a pectoral muscle flap to further increase the chances of neo-vascularization. Many subsequent modifications of the Beck procedure were developed both by Beck and others (Beck, 1936). Irritant pastes, chalk, magnesium silicate, sand, asbestos, phenol and Ivalon sponge were used to irritate the pericardium and omentum, lungs, spleen and segments of small bowel were employed as sources of new blood supply for the heart. The operative mortality was high (38%), but 90% of the surviving patients were said to be improved (McGoon, 1982).

Finally, Thompson (1939), encouraged by animal experiments reported by Beck introduced pericardial sac poudrage employing talcum powder, theorising that the resultant inflammation alone would bring new vessels from the pericardium to the epicardium of the heart. Because poudrage was a simple operation and carried a low mortality, and for lack of another approach, this procedure remained in vogue until as late as 1960.

In 1937 Gross reported experiments showing that occlusion of the coronary sinus in the dog increased the blood supply and reduced the incidence of myocardial infarction following ligation of a coronary artery. Thereafter, Beck incorporated subtotal ligation of the coronary sinus into his original operation and believed the results were improved. This became known as the Beck II operation.

In most of these operations the criteria for success were subjective, as highlighted by Beck:" in the majority of patients the degree of improvement is such that only by direct contact with the patient can this be appreciated".

From subtotal ligation of the coronary sinus it seemed a logical step to arterialisation of the coronary sinus, which was first reported in 1943 and adopted by Beck experimentally in 1945 and clinically in 1948 - on a man who died on the first postoperative day (Beck,

1948a/b). This operation was never widely employed, although it enjoyed some popularity for a short period.

The next major development occurred in 1950 when Vineberg and Miller described the implantation of the internal mammary artery into the myocardium in order to create new coronary collaterals (Vineberg, 1950). This procedure remained controversial until Sones and Shirley in Cleveland showed by angiography that small but definite collaterals could be seen in some cases (Sones, 1962). Vineberg later showed patency of such grafts studied up to 17 years later and also described the use of the right gastroepiploic artery if the internal mammary artery was not satisfactory (Vineberg, 1975). Subsequently Smith (1957) described a modification of the Vineberg procedure in dogs where he used free grafts of saphenous vein or nylon tubes anastamosed to the descending thoracic aorta of dogs and implanted into a myocardial tunnel after multiple holes had been made in the graft. In the same year Sabiston, Fauteux and Blalock employed canine carotid artery in a modification of the Vineberg procedure and showed that small but real anastamoses developed between the carotid artery and the coronaries (Sabiston, 1957).

Subsequently the Vineberg procedure was abandoned because of doubts as to the volume of blood supplied by the internal mammary artery, even in patients with good coronary connections.

However, Glover's bilateral internal mammary ligation operation for angina (Glover, 1960) remained popular until the mid 1960's. The basis for this operation revolved around the observation that minute anastamotic channels had been identified between the internal mammary arteries and the coronary circulation, and it was argued that distal ligation of the internal mammary arteries would divert blood through these channels into the myocardium. This procedure was subsequently discredited when sham operations without internal mammary ligation gave similar relief of angina.

Direct Myocardial Revascularization: Endarterectomy

Following the introduction of endarterectomy for occlusive disease of the abdominal aorta and its branches, similar techniques were proposed for atherosclerotic disease of the coronary arteries and Bailey, May and Lemon performed the first coronary endarterectomy in 1956 . In a classic paper (Bailey, 1957), they presented two successful endarterectomies of the left anterior descending coronary artery performed at normothermia without cardiopulmonary bypass. Both patients remained free of angina at three months post-surgery. Their technique was was different to that currently employed in that the artery was opened longitudinally distal to the obstruction, and a hollow silver curette was introduced which on withdrawal produced tubular casts of the intima of the occluded artery.

A year later Longmire, Cannon and Kattus reported a successful outcome in five of nine patients subjected to endarterectomies of the right and left anterior descending coronary arteries by means of a direct approach without cardiopulmonary bypass (Longmire, 1958). In distinction to Bailey and May they incised the artery directly over the diseased segment rather than using the distal, retrograde, blind technique.

Direct Myocardial Revascularization: Early bypass procedures

During the development of these early procedures the first attempts at direct surgical intervention on the coronary arteries were made. In 1950 Murray experimentally resected portions of canine coronary arteries and filled the gaps with vein grafts anastamosed to the cut ends of the coronary artery. He was discouraged by his initial results but he persisted. Then, in 1954 he reported success in five dogs, with grafts of either axillary or free carotid artery inserted between the ascending aorta and the coronary vessels by direct anastamosis. Following anastamosis he ligated the grafted coronary artery proximally and showed that

the grafts effectively protected the myocardium from infarction (Murray, 1954). These successes were facilitated by the use of heparin which Murray had introduced in 1940 for blood vessel surgery, and by the use of a polythene intraluminal shunt to maintain distal coronary perfusion during surgery. He was clearly a man of great talent and foresight. Witness the following statement put forward as early as 1940:

> ".... in cases of coronary stenosis with an adequate diagnosis, the development of coronary occlusion might be prevented and symptoms of stenosis completely eliminated by such an operation. To obtain this information, angiography might be necessary either in the x-ray department or on the operating table. When such information is available, there is a possibility that in suitable cases great improvement in the function of the coronary arteries might be obtained by the procedures described."

Murray's prediction was all the more impressive bearing in mind that it was to be another 18 years before the advent of selective coronary catheterisation (Sones, 1962).

In an important experiment in 1956 Thal reported a technique for the direct anastamosis of the internal mammary artery to the circumflex artery in dogs. He showed patency for up to six months (Thal, 1956).

In 1960 Goetz described a no suture technique of vessel anastamosis which they had developed in a canine model using tantalum rings to fashion a cuffed end-to-end internal mammary-coronary artery anastamosis and which had provided good patency rates.

On May 2nd, 1960 they successfully performed the first internal mammary-coronary artery graft, to the right coronary artery of a 38 year old patient. Although the patient survived the operation no further follow up data was given (Goetz, 1961).

In the same year Dubost reported the first case of direct coronary artery surgery in which cardiopulmonary bypass was used, although it had been in use for other forms of open heart surgery since 1953. Through a transaortic approach with the aid of full cardiopulmonary bypass and profound hypothermia with circulatory arrest they

successfully relieved a syphilitic obstruction of the right coronary ostium (Dubost, 1960).

In none of the aforementioned cases was coronary arteriography used preoperatively to locate the obstructions, nor was it used postoperatively to substantiate results. But in 1961 Senning reported the first successful coronary endarterectomy combined with patch grafting in a patient whose lesions had been defined by angiography preoperatively. A postoperative arteriogram demonstrated patency of both the left anterior descending (LAD) and circumflex coronary arteries which had been endarterectomised and patched (Senning, 1961).

Six years after Goetz had performed the first successful end-to-end internal mammary-coronary artery graft, Kolessov in Leningrad performed the first end to side anastamosis without ligation of the proximal coronary artery. He reported six cases with five survivors in the absence of cardiopulmonary bypass. All had a symptomatic improvement (Kolessov, 1967).

The Advent of Coronary Angiography

In 1958 Mason Sones (Sones, 1962), a paediatric cardiologist at the Cleveland Clinic, while attempting to perform a bolus, retrograde injection of dye across the aortic valve into the left ventricle noticed that the dye had inadvertently passed directly down the right coronary artery. The catheter had been in either the right coronary sinus or the right coronary ostium. Since the visualisation was far superior to root injection and the patient tolerated the procedure well, he proceeded to develop the technique of selective coronary angiography that subsequently led to the explosive development and application of direct coronary surgery.

In 1962 Sabiston, at Johns Hopkins Hospital, operated on a man who had previously undergone a right coronary endarterectomy but whose symptoms had recurred after a year when angiography had shown occlusion of the endarterectomised segment. At reoperation

reversed long saphenous vein was anastamosed to the ascending aorta with the aid of a partially occluding clamp. The distal end of the vein was then anastamosed to the transected end of the distal right coronary artery. Unfortunately the patient died three days later of an embolic stroke. Autopsy examination revealed thrombus at the aortic end of the graft and it was assumed that an embolus from this site had been swept into the cerebral circulation. This was the first case of saphenous vein-coronary artery bypass performed on a human, but Sabiston had been discouraged by the result and did not attempt another case for a further six years (Sabiston, 1974).

Garrett, Dennis and DeBakey performed the first coronary artery bypass graft as practised today. In 1973 they reported the seven year follow-up of a patient who had received aortocoronary bypass in 1964 using reversed long saphenous vein with an end-to-side distal anastamosis (Garrett, 1973).

Towards the end of the 1960's direct coronary surgery as we know it today enjoyed an explosion in popularity largely due to the enthusiasm of Favaloro and Effler at the Cleveland Clinic and Johnson and Lepley in Milwaukee who advocated an aggressive surgical approach to coronary artery surgery (Favaloro, 1969; Johnson, 1970). The use of hypothermic, cardiopulmonary bypass became more routine, and the belief that turbulence created by oblique end to side anastamoses would destroy the vein graft fell from favour.

Contemporary Coronary Artery Bypass Surgery

The rapid increase in the practice of coronary artery bypass grafting using reversed long saphenous vein between the aorta and a coronary artery with an oblique end to side anastamosis has been most marked in the United States of America. Over 100,000 operations had been performed by 1974 with an annual rate 770/million of population in 1980 resulting in approximately 130,000 during that year. Returns from the 40 units in the UK reporting to the Cardiac Surgical Register indicated that in 4057 isolated coronary grafts were performed in 1980 rising to 8332 in 1983 representing 170/million of population. The overall mortality was 3.4%.

Together with Sweeden, France and Germany Britain shares a rate of bypass operations that is about one sixth of the United States, a quarter of that in Australia and a third of that in Holland. Within the UK during the period 1977-1982 the rates varied considerably among regions. In 1982 the operation rates per million population were: UK 107, Scotland 165, Metropolitan regions 169, the rest of the UK 47.

Applying American figures to the incidence of new angina patients, the backlog of chronic stable angina patients, and patients who survive myocardial infarction and progress to angina, the estimated requirement of coronary artery bypass operations is 300-550/million population.

Vein Graft Patency

Despite initial enthusiasm and early success, the longer term results of coronary artery bypass using saphenous vein as a conduit suggest a problem with long term graft patency.

Coronary artery bypass surgery usually provides excellent symptomatic results. Prospective randomised studies (CASS, 1983; Takaro, 1983; Varnauskas, 1982; Mathur, 1979) have shown that surgery produces a symptomatic improvement in 75-90% of patients with up to 55% becoming asymptomatic and only 5-6% experiencing worsening of symptoms. In contrast, only about 10-15% of medically treated patients become asymptomatic, with 50% or more remaining severely limited by their angina.

Early and late graft patency has increased with improving surgical technique since the advent of coronary artery bypass grafting and cumulative rates of patency should be interpreted accordingly. Campeau (1975) reported two consecutive series of patients operated on between 1969-1970 and 1971-1972 respectively. In the second group graft patency at 1 year had improved from 67% to 85.5%, and the incidence of anastamotic strictures had decreased from 15.5% to 5.5%. In particular patency of grafts with initial resting flow rates of <50 ml/min had improved from 28% to 73%. All of these improvements were attributed to improved surgical technique.

Graft patency and mortality rates vary from centre to centre as shown by the CASS study, but reported patency rates probably represent minimum patency since in most studies >60% of recatheterizations are performed because of symptoms suggestive of ischaemia, rather than for reasons of pure scientific follow-up.

Nevertheless, patency among 8000 restudied patients between 1967-1979 at the Cleveland Clinic (Lytle, 1982) showed a gross patency rate of 82.9% with a patency rate of 79.7% in

the 759 grafts studied at a postoperative interval >48 months.

Other institutions have reported similar overall patency rates (Lawrie, 1977; Kouchoukos, 1978).

A synopsis of published reports on vein graft patency allows the general conclusion that the vein graft attrition rate is about 10% within the first month of surgery. These failures are generally held to be due to technical factors resulting in vein graft thrombosis. There is an additional failure rate of 10% between the first month and the end of the first year probably related to low graft flow due to poor distal runoff. Thereafter the attrition rate is 1-2% per year initially rising to 4% after six years (Manley, 1986). Late failure is initially due to a progression of intimal fibromuscular hyperplasia followed later by a form of atheroma. The end result is that approximately 50% of vein grafts are occluded by 10 years. This limitation has largely been overcome by the adoption of the internal mammary artery as a bypass conduit which shows a vastly superior long term patency, a longer reoperation free interval and an improved long term survival when applied to the LAD, as compared with vein grafts (Loop 1986; Cosgrove, 1986).

Factors affecting vein graft patency

Simple, direct evidence of diminished graft patency in the face of poor run-off is not available. However, the inference exists through an accumulation of studies which address the relationship of graft patency with:

1. recipient vessel size,
2. graft flow,
3. the state of the recipient myocardium
4. proximal coronary stenoses.

1. The diameter of the recipient artery appears to be the single best predictor of patency. Grafts to vessels with a diameter of 1.5 mm or greater have a significantly higher patency rate than grafts to smaller vessels, although an increase in diameter above 1.5mm does not appear to improve patency (Grondin 1972, Lésperance 1972, Walker 1972, Roth 1973, Cheesboro 1982a/b, Fuster 1985, Kaiser 1972). Although coronary artery calibre appears to influence patency within the first year, itmay not be a major factor thereafter.

2. Graft flow measured at operation has been shown to correlate with graft patency up to one year following surgery (Campeau, 1975).

Resting flows of less than 30-40 ml/min are associated with low early patency rates. Furthermore, failure to improve the resting flow with an injection of papavarine into the graft is a poor prognostic sign, presumably because this implies an inability of the respective vascular bed to dilate to demand. Grondin (1971a) reported papavarine response in 103 coronary vein grafts immediately following anastamosis with results almost identical to Moran (1971) who studied 31 grafts, although Grondin injected twice as much papavarine (20mg) as Moran. In the right coronary grafts Grondin reported a mean resting graft flow of 52ml/min rising to 110ml/min, and on the left a mean resting flow of 72ml/min rising to 150ml/min. No graft in Grondin's series remained patent with a resting flow of 30ml/min or less, or without a response to papavarine. Grafts with a flow of 50ml/min or greater remained patent in the early postoperative period. Cooper (1971) reported flow measurements in a series of 1092 grafts and concluded that graft patency was unlikely with an intraoperative flow measurement of less than 40ml/min. Thus, these studies indicate that a low resting graft flow together with failure to respond to a vasodilator is a grave sign.

In a further study Grondin (1971b) measured intraoperative blood flow in 157 grafts and correlated these measurements with early postoperative coronary and graft angiography.

correlated these measurements with early postoperative coronary and graft angiography. The overall patency rate was 88.5%. Mean flow had been 28 ml/minute in the occluded grafts and 66 ml/min in patent grafts. The mean flow doubled in both groups following injection of papavarine into the graft although 5 of the 18 occluded grafts failed to respond to papavarine. This phenomenon was not observed in patent grafts. In all but one occluded graft flow was less than 50 ml/min. Only 3 of 12 grafts with a flow of 25 ml/min or less remained open. They found no relationship between age, sex, weight or cardiomegaly on graft flow.

A similar operative test to assess the capacity of the distal vascular bed to accept blood flow involves clamping the functioning graft for 15 seconds to induce a subsequent reactive hyperaemia. It has been argued that induction of increased flow due to a reactive hyperaemia is a good prognostic sign, but this is disputed by those who argue that clamping the graft merely restores the vascular anatomy to its preoperative status and that the absence of a reactive hyperaemia is not significant.

*(3) **The state of the recipient myocardium*** may affect distal run-off and therefore graft flow rates.

To answer the question of whether scarred myocardium was detrimental to graft runoff Frey (1984) studied 99 grafts in 55 randomly selected patients at mean intervals of 1 and 9 years. At 1 year they found 90% patency of grafts supplying angiographically normal segments of myocardium as opposed to 53% of those supplying dyskinetic or akinetic areas. The same relationship was found at late follow-up with 53% of grafts to normal muscle showing wide patency, and only 32% of those to scarred myocardium remaining fully patent.

(4) The effect of a proximal coronary artery stenosis is unclear.

Does a proximal artery stenosis prime the potentially ischaemic myocardium to accept a greater flow or does it induce a competitive collateral circulation which diminishes graft runoff?

Rees (1976) noted higher patency in cases where the proximal artery was completely occluded. This led to the concept that ligation of the proximal coronary artery to eliminate competitive flow might improve graft patency. This was further endorsed by the finding by Blumbein (1976) who noted that graft patency was related to the degree of proximal arterial stenosis. Roth (1979) correlated intraoperative measurements with angiographic findings one year postoperatively and noted a small but significant increase in patency of grafts to vessels with a proximal stenosis >70%. In addition there was a highly significant positive correlation between increasing proximal stenosis and reactive hyperaemia, and a significant positive correlation between the mean resting graft flow and reactive hyperaemia. He argued that increasing proximal coronary artery stenosis resulted in a vascular bed capable of receiving increased flow from the graft. This may be due to greater ischaemia in the distal vascular bed, which then dilates and is able to provide good distal run off to a subsequent graft.

It has been shown experimentally in dogs that proximal coronary artery flow is directly related to bypass graft flow and that this interdependence results in a reduction in proximal coronary artery flow (Kakos, 1972). In addition if this segment contains a severe stenosis, institution of this competitive bypass flow may produce either a functionally total occlusion, or predispose the stenotic area to early thrombosis by severely limiting its flow. Conversely, the absence of a proximal coronary stenosis results in a reduction in graft flow. However, the distal coronary artery flow and pressure remain independent of these relationships and are restored in a physiological manner by direct revascularization.

This experimental finding is endorsed by angiographic follow-up of patients who have undergone bypass grafting. McLaughlin (1974) found progression of proximal disease in 55% of 125 grafted vessels, 46% progressing to total occlusion,the progression being most marked in the more severely stenosed segments. Of the lesions progressing to total occlusion 79% were grade 3/4 preoperatively. There was progression in only 7% of grafted distal segments. In the same period only 14% of non grafted vessels showed progression. Patent grafts were associated with disappearance of collaterals to the grafted vessels, while occluded grafts were associated with preservation of collaterals or appearance of new collaterals. These findings were in accordance with other observers (Maurer et al, 1974; Cibulski, 1973; Bourassa, 1974)

Stinson (1973) studied 30 vein grafts and found greater reactive hyperaemia in ischaemic areas and speculated that collateral flow to areas of abnormal myocardium might be inferior to that supporting functional muscle in the area of a stenosed coronary artery and that transient occlusion of a graft would be expected to produce a greater hyperaemic response. The generally lesser hyperaemic response in stenotic as compared to occluded arteries, was shown to be due to persistent flow through the stenotic segment during graft occlusion. Complete proximal obstruction of the coronary artery with rubber tubing intensified the reactive hyperaemia to the range observed in proximal occluded arteries. The number of grafts studied did not allow any firm correlations between intraoperative dynamics and graft patency.

Given these facts it is reasonable to postulate that graft patency is related to distal run off which in turn is related to the size of the recipient vessel and the state of the recipient myocardium. Thus it seems logical to assume that techniques which will improve distal run off are likely to improve graft patency in selected patients.

However, the elimination of proximal artery stenoses which "protect" the incumbent graft

from competitive native flow is likely to compromise graft flow. This point is important in the interpretation of the human percutaneous laser coronary angioplasty study (Chapter 3).

New Conduits and New Approaches

The disappointing long term results of coronary artery vein grafting and the desire to avoid extensive surgery has stimulated the search for new conduits and new approaches to the treatment of coronary artery stenoses.

The major advance in the search for an improved conduit has been the recognition of improved graft patency and patient survival when the internal mammary (IMA) (syn. internal thoracic) artery is used, particularly to revamp the left anterior descending coronary artery. Loop (1986) compared patients who received an internal mammary artery graft to the left anterior descending coronary artery alone or combined with one or more saphenous vein grafts (n=2306) with patients who had only vein grafts (n=3625). The 10 year survival rate (exclusive of hospital deaths) among those receiving an IMA graft as compared with vein grafts was 93.4% vs 88% (p=0.05) for single grafts, 90.0% vs 79.5% ($p< 0.0001$) for those with two vessel disease and 82.6% vs 71% ($p< 0.0001$) for those with triple vessel disease. Those who had only vein grafts had a 1.6 times greater risk of death during the 10 years and 1.4 times greater risk of myocardial infarction, a 2.0 times risk of reoperation as compared with those patients who received internal mammary grafts.

Subsequently the same group (Cosgrove, 1986) examined the first 1000 patients undergoing myocardial revascularization each year from 1971-78 to elucidate the determinants of reoperation. Twenty five predictors were examined. Young age was found to be the most important predictor, but the next two factors were the absence of an internal mammary artery graft and incomplete revascularization, both factors under surgical control. Thus in the surgical arena the IMA graft provides an improved conduit and complete revascularization represents a new approach.

The most impressive non-surgical advance has been the advent of percutaneous transluminal coronary angioplasty which is described overleaf.

Coronary Artery Balloon Angioplasty

History of Percutaneous Transluminal Balloon Angioplasty (PTCA)

An increasing appreciation of the limitations of saphenous vein bypass grafting, in particular the disappointing long term patency of vein grafts, has stimulated a search not only for alternative surgical conduits but also for alternative or complimentary approaches to myocardial revascularization. The search for an alternative surgical conduit has been partially realised with the development of internal mammary artery bypass grafting. The search for an alternative approach has centered around percutaneous transluminal coronary angioplasty (PTCA).

Direct surgical remodelling of arteries has been practised for many years, but remodelling of stenosed arteries by intraluminal distension was first shown to be effective by Dotter and Judkins in 1964. They used graduated probes inserted through an open arteriotomy to dilate discrete stenoses of the femoral artery (Dotter, 1964). The simple idea that an inflatable balloon on the end of an arterial catheter could be used to similar effect was explored by Andreas Grüntzig in the early 1970's. However the percutaneous application of such a principle had to await not only improvements in arterial and coronary catheterisation techniques but also the development of non-elastic balloons capable of withstanding the inflation pressures required to distort and split atheromatous plaque, and at the same time retaining a preformed size and shape.

Grüntzig and Hopff first described such a balloon catheter in 1974, and in 1976 Grüntzig used this catheter in femoral and iliac lesions (Grüntzig 1974 and 1976)

The first Percutaneous Transluminal Coronary Angioplasty (PTCA) was performed by Grüntzig in Zurich in September,1977. Since then the number of PTCA procedures performed annually has risen from 6 in 1977 to 100,000 in 1985 with an anticipated level

of 216,000 in 1988. Despite the impressive numbers the lack of long term results implies that the technique is still in its infancy and has yet to define its place in the treatment of coronary disease. Although initially confined to single vessel coronary disease in relatively healthy patients, PTCA is now being applied in patients with multivessel disease, vein grafts and patients who present a high surgical risk. Despite these changes the in hospital outcome is improving. Angiographic success rates have improved to nearly 90% and the overall success rate (measured as at least a 20% reduction of all lesions attempted, without death, myocardial infarction or coronary bypass surgery) is approaching 80%, with a mortality around 1%. (Kent, 1984; Detre, 1988: National Heart Lung and Blood Institute Registry data)

PTCA Procedure

PTCA is conducted under angiographic control. A short introducing sheath is placed in the femoral artery. Through this a long guiding catheter is passed into the aorta until it rests in the ostium of the appropriate coronary artery. Next a guidewire is advanced through the guiding catheter into the coronary artery and coaxed across the stenosis. The deflated dilation catheter is then advanced over the guidewire until the balloon straddles the stenosis. The position of the balloon is confirmed angiographically and the pressure gradient across the stenosis is measured. The balloon is then inflated to its predetermined size for about 30 seconds. Following deflation repeat angiography and pressure measurements across the stenosis are performed to assess the degree of stenosis reduction. A successful dilatation may require several balloon inflations.

The Mechanism of Dilatation

The mechanism by which angioplasty relieves arterial constriction remains unknown. Dotter put forward the theory that the lumen was enlarged by compression or displacement

of the atherosclerotic material. This may help to explain why no distinctive plaque morphology is seen after PTCA. Overstretching of the media and adventitia is probably an important component and may also explain why balloon dilatation is successful in arteries narrowed by other diseases such as fibromuscular dysplasia. Direct observation of arteries during angioplasty in experimental animals shows that the outer layers of the vessel distend to conform to the size of the inflated balloon and this distension appears to remain after the balloon has been removed.

Cadaver studies have shown that in many cases balloon angioplasty splits the atherosclerotic plaque and frees the media from the splinting effect of the atheroma (Block, 1984). Fogarty has shown that disruption of the plaque accounts for 87-93% of the overall increase in lumen area, plaque compaction for only about 1-1.5% (Fogarty, 1984). However, during PTCA the pressure gradient across the lesion is often only gradually abolished with successive inflations of the balloon. Embolization of atheromatous material has not been documented experimentally and clinical reports of embolism are rare, suggesting local containment of compressed material. Thus, gradual stretching and progressive loss of recoil of the media and adventitia seems to be an important mechanism, once the arterial wall has been freed from the splinting effect of the plaque by splitting.

Healing at the site of dilatation

The mechanism of arterial healing following high pressure balloon trauma is not well understood. Dissolution of the atheromatous material may account for the smoother appearance of the vessel lining at the site of PTCA on late angiograms. Fibrous retraction of the split plaque is also thought to occur during the healing process which may slowly increase luminal size. However, local intimal and medial damage may also account for the high early restenosis rate, which some observers have speculated is due to an accelerated local atherosclerosis.

It has been noted that the restenosis rate is higher in patients in whom coronary artery spasm can be induced during follow-up angiography at the site of the previous dilatation. This has led to the postulate that post dilatation spasm may have a role in early restenosis. Further studies are needed to delineate the factors that initiate early restenosis if this phenomenon is to be avoided.

Results and complications of PTCA

Initial success rates of PTCA have improved dramatically over the last few years with an associated reduction in complications, despite applying the treatment to increasingly complex patients. This is due to a combination of increased operator experience and improvements in catheter technology, particularly the development of the steerable catheter system.In most major centres the primary success rate for dilating a stenosis is now about 90%. The overall mortality is <1% but varies from 0.5% for straightforward cases to 3% for poor risk candidates.

Failure of PTCA may be early or late.

Early failure may be due to an inability to adequately dilate the stenosis, arterial dissection or other early local events such as spasm or thrombosis resulting in continuing angina or acute ischaemic changes on the electrocardiogram. Although coronary spasm and thrombosis can frequently be relieved by spasmolytic or thrombolytic drugs, urgent coronary surgery remains a possibility and rates range from <1% to almost 10% a variation which reflects patient selection and operator experience. The likely need for surgical intervention is higher in patients with unstable angina and those with a tight, long or eccentric stenosis. An analysis of the National Heart Lung and Blood Institute Registry (Cowley,1984) revealed that the most frequent indications for emergency operation were

coronary dissection (46%), coronary occlusion (20%), prolonged angina (14%) and coronary spasm (11%).

When urgent surgery is undertaken in PTCA patients the mortality is 3-4 times greater than that for routine CABG and the incidence of perioperative myocardial infarction up to 10 times higher (Page, 1986; Killen, 1985). Since PTCA patients usually represent patients with the lowest surgical risk, mortality and infarction comparisons are biased in favour of PTCA. In addition when urgent surgery is performed vein grafts are usually applied rather than the internal mammary artery in order to save the 15-20 minutes required for the dissection of the internal mammary artery prior to reperfusion resulting in a lower long term success rate both in terms of relief of angina and long term survival.

Although the increased morbidity and mortality can be avoided by establishing total cardiopulmonary bypass within 25 minutes (Reul, 1984) this is not generally feasible, but it emphasises the importance of recognising failure early and ensuring good and prompt surgical cover.

Late failure of PTCA is due to restenosis at the site of initial dilatation. This constitutes the most serious limiting factor of the technique. Within the first 3-4 months there is a consistent restenosis rate of 20-30%. However, after 4 months the incidence of restenosis is less than 1% per year. Re-dilatation of a recurrent stenosis carries a slightly better success and lower complication rate than initial dilatation.

Peroperative Transluminal Coronary Angioplasty

Diffuse or segmental distal coronary disease may reduce coronary bypass runoff and so jeopardise late graft patency. As in the case of peripheral vessels the first attempts to improve distal run-off in discretely diseased coronary vessels involved the use of graduated probes to dilate distally diseased segments, although the probes were primarily used as aids to accurate suture placement, luminal calibrators and luminal occluders to produce a dry operative field. Their use as dilators has not been systematically evaluated. Subsequently the technique of balloon dilatation has been employed with encouraging results in the short term. Long term results are not yet available. It has been shown that the diameter of a coronary stenosis can be increased by about 100% (range 30-300%) (Fogarty,1984; Ross, 1984). The short and medium term results vary due to inconsistent recatheterisation protocols and small patient populations. Nevertheless, early patency of the dilated sites can be shown to be between 70-85% (Mills,1984; Fogarty, 1984) although patency does not necessarily mean sustained improvement in diameter. Faro (1984) showed that at 10 days only 30% of dilated lesions showed continued improvement while 60% were unchanged and 8% were worse.Furthermore discrete lesions were 3 times more likely to be successfully dilated than diffuse lesions.

Although initial results are encouraging with an 80% patency rate within the hospital admission period, comments on the restenosis rate and long term patency are not yet possible given the small number of patients restudied.

The relationship between balloon angioplasty and surgical revascularization techniques

Although the number of PTCA procedures is increasing there has not been a significant impact on the number of surgical procedures performed. When optimally performed before or after elective coronary surgery, PTCA may in many instances add symptom free years to patients with progressive coronary artery disease, inoperable patients and those with a high surgical risk may be palliated by PTCA. When properly timed both PTCA and surgery contribute to improve the symptom free survival of patients with coronary artery disease.

The simultaneous combination of such innovative techniques as balloon or laser angioplasty with surgery could conceivably improve surgical results in a subset of patients in whom localized or diffuse disease compromises graft runoff and therefore threatens prolonged graft patency.

The Rationale for the use of Lasers in Vascular Recanalization

In the search for alternatives to coronary artery bypass grafting laser technology offers potential benefits over balloon angioplasty with its limited applicability and high restenosis rate.

It seems reasonable to assume that the intraluminal delivery of forms of energy capable of removing atherosclerotic mass may provide better long term results both for balloon angioplasty and for the treatment of diffuse or distal coronary disease at operation. The latter point is emphasised by the increasing numbers of patients with severe, diffuse triple vessel disease being referred for surgical revascularization (Naunheim, 1988; Davis, 1988)

Laser energy offers the following potential benefits:

1. It can vaporise limited amounts of tissue in a few seconds;
2. It has the potential for selective ablation of the atherosclerotic plaque;
3. It can be transmitted into arteries along thin optical fibres.

Laser Technology

Properties of laser light

The word **LASER** is an acronym derived from the words **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation.

Laser light has three specific properties which distinguish it from ordinary light:

1. It is **monochromatic**
2. The light waves are **parallel**
3. The waveforms of the photons are in phase or **coherent**

The generation of laser beams

The generation of laser light is dependent on three phenomena:

1. **Induced absorption** of photons by atoms
2. **Spontaneous emission** of photons by atoms
3. **Stimulated emission** of photons by atoms

A laser generator, in its simplest form, is composed of a tube (resonator cavity) with a mirror at each end. One of these mirrors is totally reflective while the other is only partially reflective. The resonator contains an "active" medium which may be either solid, liquid or gas. The atoms, molecules or ions which constitute the active medium may exist in either a high or low energy state. Normally, the number of atoms at a low energy level, in their ground state, exceeds the number in the excited state. However, those in their ground state can be raised to an excited state by incident energy which may be thermal or electromagnetic. This phenomenon is known as ***Induced Absorption.***

If the energy input to the medium is of sufficient intensity "population inversion" occurs. This means that the number of atoms, molecules or ions in the medium which are raised to the excited state exceeds the number which remain in the ground state. This is an essential

prerequisite to the amplification of the number of photons.

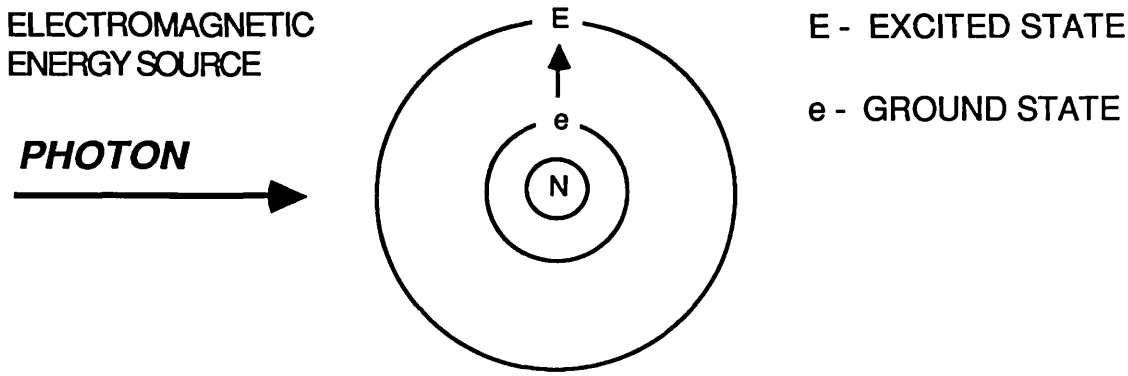

Fig. 1: Diagram of spontaneous absorption

The subsequent spontaneous return of the excited high energy electrons to the lower level results in the emission of each unit of absorbed energy as a photon. This process is referred to as ***spontaneous emission.***

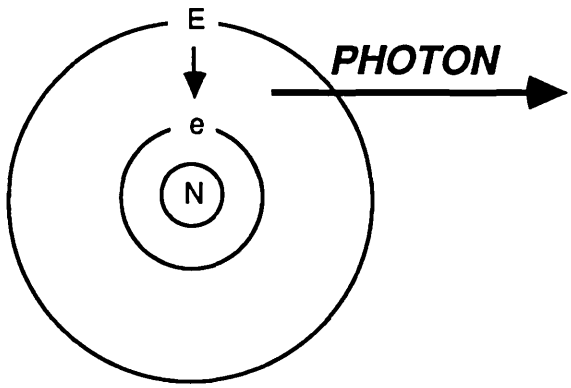

Fig. 2: Diagram of spontaneous emission

The wavelength of the emitted photon is specific for the medium.

If during the brief instant that the atom, molecule or ion is excited, it is further stimulated by a photon of the same wavelength the excited complex is stimulated to emit another photon in phase with, and in the same direction as the incident photon. The emission of this photon results in the atom returning to the ground state.

This is known as ***stimulated emission,*** and is illustrated in the following diagram.

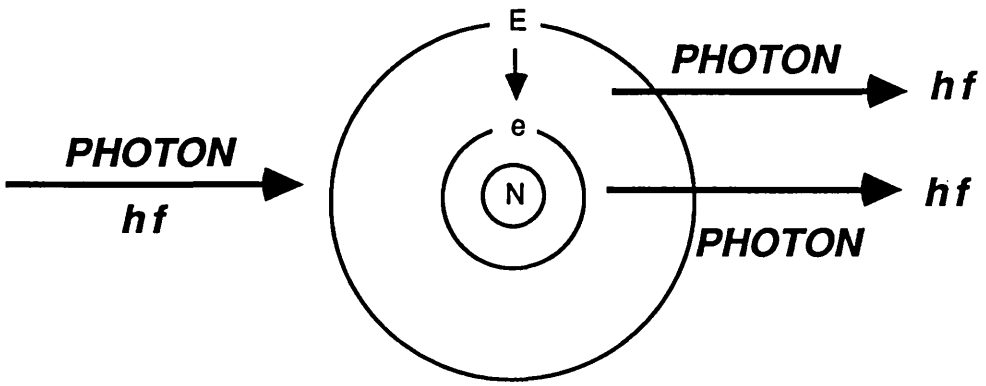

Fig 3: Diagram of stimulated emission

Most of the resultant photons impact on the sides of the tube and are lost as heat. However, if the two mirrors are perfectly parallel, the photons emitted along the axis of the tube are reflected between the mirrors. These photons will in turn collide with other excited atoms, molecules or ions so amplifying, by repeated stimulated emissions, the number of coherent photons travelling back and forth along the resonator axis.

The light so generated is initially confined to the resonator cavity; however, once a sufficient number of photons has been recruited some escape through the partially reflective mirror to form a laser beam.

Laser Technology

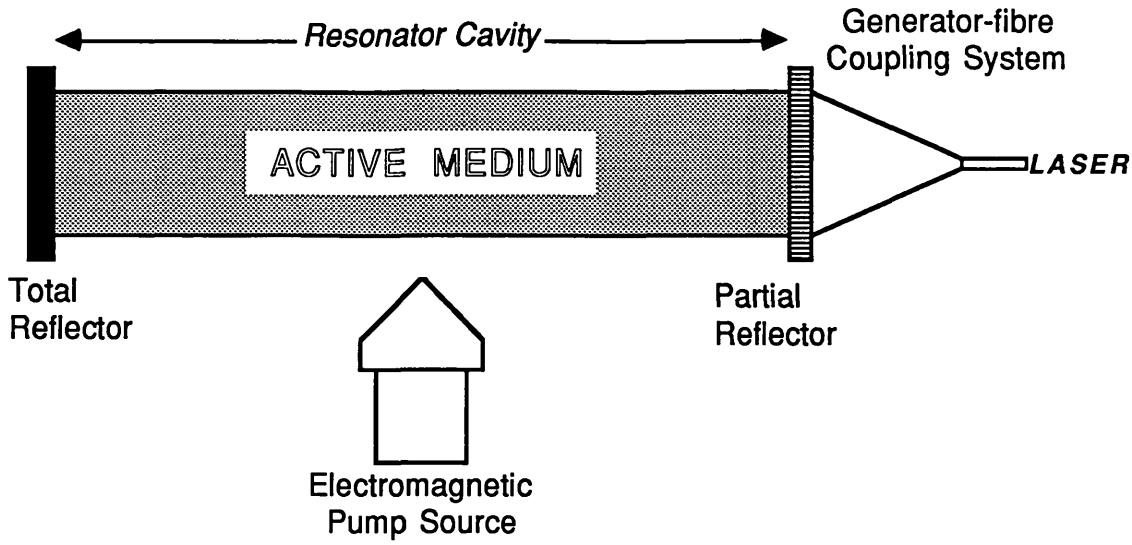

Fig. 4: Diagram of a laser generator

The laser beam has many physical properties in common with ordinary light; in particular the beam can be transmitted through thin optical fibres. However the laser beam has two distinctive properties:

1. All photons are in phase and travelling in the same direction; this allows the delivery of high density energy to localised targets.
2. Laser light is monochromatic since all photons have the same wavelength; this means that the absorption of laser energy can range from 0% to 100% depending on the optical characteristics of the target.

The energy of a laser pulse is expressed in Joules and is calculated by multiplying the power of the laser beam expressed in Watts by the duration of the laser pulse expressed in seconds.

Energy = Power x Time

Joules (J) = Watts (W) x Time (t)

Laser Technology

Continuous Wave Lasers have a constant power output with time. Argon and Nd:YAG lasers are the commonest continuous wave lasers used in cardiovascular medicine. The Nd:YAG wavelength (1,064nm) is absorbed by water but not haemoglobin, while the argon wavelengths (488nm and 514nm) are absorbed by haemoglobin and transmitted by water.

Pulsed Lasers deliver energy in brief, discrete pulses lasting millisesconds each of which is separated by an emission free interval. During this interval the energy is stored and amplified so that when suddenly released over an extremely short time interval a very high energy pulse is delivered. The pulsed laser which is the most widely used for vascular studies is the excimer laser which emits ultraviolet radiation.

A particularly rapid form of pulsing is known as Q-switching. In a laser with such a facility a shutter is placed between the resonator cavity and the partial reflector. If conditions are otherwise correct for laser activity and the closed shutter is suddenly opened the stored laser energy is released as a giant pulse lasting about 10^{-12} second with a peak power capacity as high as several hundred thousand kilowatts. The Q-switch is usually a liquid or solid optical shutter which is normally opaque but can be made transparent by the application of an electric pulse.

High energy pulsed beams should not be confused with short duration continuous wave beams in which the power is the same irrespective of delivery time. Although often referred to as pulsed beams these brief continuous wave pulses are better referred to as "chopped".

Laser Technology

Optical fibres

A laser beam is straight and parallel. Delivery of such a beam into intra-body cavities has been greatly facilitated by the development of optical fibre technology.

Optical fibres are made by extending long, thin glass rods into filaments. Their thinness and flexibility offers an attractive mode of transmitting laser light through the arterial tree to otherwise inaccessible areas.

Principles of Light Transmission along Optical Fibres

Snell's Law of Refraction states that when light is incident on the plane interface between two homogenous, isotropic media with different refractive indices, n_1 and n_2, the refraction of the light at the interface is governed by the expression:

$$n_1 \sin \alpha_1 = n_2 \sin \alpha_2$$

This means that a ray incident at an angle α_1 is refracted in the medium n_2 at the angle α_2 to the normal. Thus, if $n_1 > n_2$ then as the angle of incidence increases to a critical angle ($\alpha_c = \text{arc sin } n_2/n_1$), the refracted ray passes along the interface between the two media.

When $\alpha_1 > \alpha_c$ total internal reflection occurs. The intensity of energy in an internally reflected wave is equal to the incident wave.

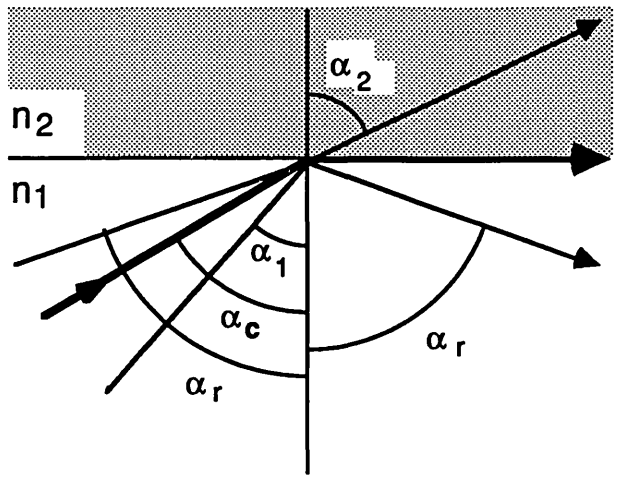

Fig 5: Principles of internal reflection

Step Index Fibres

An optical fibre consists of a long thin core of glass, quartz, plastic or liquid, surrounded by a cladding of similar compound of greater refractive index.The difference in refractive index between the core and cladding allows propagation of the light down the fibre by successive internal reflections. Air can act as a "cladding". However, such un-clad fibres are not commonly used because they deteriorate rapidly with use since conventional cladding also provides mechanical protection.

Consider a ray passing down the axis of the fibre. If the ray is incident at an angle θ on the polished end of the fibre it is refracted into the core at an angle $\theta_0 < \theta$ to the cylinder axis, since the air is less dense than the core. The ray then strikes the core cladding interface at an angle α_1. As long as the angle α_1 is greater than the critical angle (α_c) the ray will be totally reflected and will strike the other side of the cylinder at the same angle. Consequently, the angle that an arbitary ray makes with the axis is

preserved and the emergence angle of the ray is the same as the entrance angle.

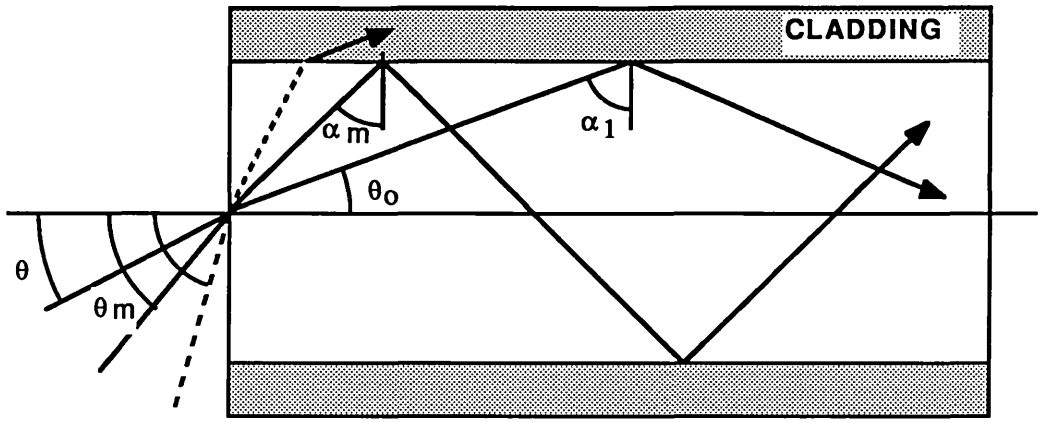

Fig 6: Internal reflection within a clad step index fibre

Factors of Practical Relevance for The Intra-arterial Transmission of Laser Energy

(1) Acceptance angle of the fibre

Referring to figure 6, the maximum acceptance angle of the fibre (θ_m) is the angle beyond which a ray will no longer be totally reflected and is given by the following equation:

$$n \sin \theta_m = \sqrt{n_1^2 - n_2^2}$$

Where n_1 and n_2 represent the refractive indices of the core and cladding respectively.

Thus, θ_m increases with the difference between the refractive indices of the core and

cladding. If the ray is incident at steeper angles than θ_m then the ray, after refraction at the entrance, strikes the core cladding interface at an angle less than the critical angle and thus refracts out of the core (dotted line in diagram above). Therefore, only the rays which enter the core of aperture θm will be guided. The quantity n sin θm has been defined as the ***Numerical Aperture*** (NA) of the fibre which is a descriptor of the overall acceptance angle of the fibre.

(2) Flexibility of the fibre

In the case of fibre bending, some of the rays which enter the fibre at angles less than θ_m come out along the curved fibre because they happen to strike the core wall at an angle less than α_c Generally, the entrapment of light in the fibre is acceptable up to a minimum radius of curvature equal to 4 fibre diameters (Kapany,1967). In practice this means a curvature radius of a few millimetres. Therefore, for most applications the bending radius does not present a problem..

(3) Light loss from the fibre

Light losses are generally due to the following reasons:

[a] *Absorption.* This is usually the main reason for losses and depends on the materials and their impurities.

[b] *Reflections at the fibre ends.* These losses cannot be overlooked in relation to the short fibres commonly used in medicine (1-3 metres).

[c] *Scattering.* Because the light is reflected many times, imperfections and

impurities at the core-cladding interface are of primary importance. Such imperfections may behave as microbendings and cause the rays to be deflected to angles smaller than the critical angle so that energy is lost from the core.

Graded Index Fibres

Step index fibres represent, in most cases, only a simple mathematical model. In reality, fibres often show a more or less smooth transition in refractive index. Recently, graded index fibres have been built where the refractive index transition is suitably graded with a continuous variation in refractive index along the radius of the fibre core. In practice, graded index fibres are also surrounded by a constant index cladding for mechanical protection and optical insulation.

Light propagation is characterized by a continuous refraction which follows the refractive index profile within the core. The maximum acceptance angle and the numerical aperture NA can be defined in the case of graded index fibres and depend on the maximum difference of refractive index between the core center and the cladding.

Though graded index fibres were developed for telecommunications, a special kind of self focussing graded index fibre, called "Selfoc" (Uchida, 1970), is of interest in medicine not only for image transmission but also because they seem to conserve the polarization plane of a laser beam better than usual fibres.

The attraction of such fibres lies in the potential ability of a single fibre to transmit focussed images. This would eliminate the requirement for extra optical systems such as lenses and allow a greatly reduced functional diameter not only because 1 rather than several fibres would be required to transmit an image, but also because that single fibre does not require cladding for its optical function. Such fibres may be smaller than 200μm.

The present restriction on using such a system is the rigidity of the fibre.

Structure of Optic Fibres

1. Quartz-plastic Optical Fibres

Quartz core and plastic cladding fibres are the most widely used to deliver high-power laser light (up to 100 W). These step index fibres can have a desired core diameter, quite large numerical apertures and very low attenuations. Further advantages are the low cost and the relative ease with which they can be maufactured. Silicone and Teflon are common cladding materials. Moreover, these fibres are usually jacketed with a material of high tensile strength and high modulus of elasticity. Typical specifications of commercially available quartz-plastic fibres are a core diameter in the range 100-600 μm, a silicone cladding of 300-750μm and a protective jacket of 400-1050μm. The corresponding bending radius is in the range 2-15 mm.

Another attractive characteristic of quartz fibres is their high transmission in the ultraviolet region. Special materials have been obtained, starting from synthetic fused silica, which show good transmission both in the UV (up to 0.15-0.2 μm) and in the near infrared (up to 3.5-4 μm).

Back burning of the plastic cladding at the distal fibre end due to laser radiation is an inconvenience of the quartz plastic fibres. To avoid this effect a glass cladding is preferable. Fibres made of two different glasses allow a good choice of refractive indices and consequently of the NA.

2. Plastic Fibres

Although glass is currently the most widely accepted material for the maufacture of optical fibres, plastic represents an interesting alternative for some medical appplications, in particular for illumination and imaging. The advantages of plastic fibres are that they possess good mechanical properties such as tensile strength and flexibility and can have a high NA, comparable with the best values of glass fibres. On the other hand, they are optically fragile and are damaged by high-power radiation. Moreover, they present a selective transmission of light and show losses much higher than their glass counterparts, particularly in the infrared region of the spectrum. A further advantage of plastic fibres is that they do not require protective shielding when bundled in medical instruments. Typical diameters of plastic fibres are in the range 10-100 μm. They are maufactured by extrusion from concentric containers of the raw materials in liquid form and are then enclosed in a polyethylene resin jacket if required.

3. Liquid Core Fibres

Another kind of step index fibre which seems attractive for illumination and laser transmission in medicine is the liquid core fibre. It consists of a glass or plastic capillary which is filled with a liquid of a higher refractive index. When a plastic capillary is employed, such a fibre can show a good flexibility for a relatively large core diameter; moreover, with an appropriate liquid core it is possible to achieve a good spectral response in the UV region. However a significant practical problem is that the inside wall of the capillary must have an extremely clean, polished and bubble free surface in order to reduce light energy losses to an acceptable value.

Laser Technology

Source-to-Fibre Coupling

The connection between the laser and the optic fibre is a potential site for high energy loss. In general, an estimate of the input coupling efficiency from the laser to the fibre can be obtained by considering the power transfer between the area of the radiating surface and the area of the receiving surface, taking into account the geometry of the two surfaces, the NA of the fibre and the radiation characteristics of the source. The efficiency is defined as the ratio between the power actually accepted by the fibre and the total power radiation by the source.

The quantity which describes the radiation characteristics of a source is its brightness (i.e.the distribution of emitted light intensity per unit angle). In the case of the common laser sources in medicine (He:Ne, Nd:YAG), the beam is highly collimated (divergence 1-15 mrad) with a gaussian intensity distribution. Therefore, it can be focused by a lens with a focal length of a few tenths of a micron and a very small cone aperture (for example, 2 degrees). Thus, efficiencies approaching 100 per cent are possible in theory. In practice, laser light is usually coupled to a single optical fibre. The lens that focusses the beam should be mounted to allow fine movements in all three planes (x,y,z). The focal length of the lens should be such that the focal spot size is no more than half the diameter of the fibre core. This should allow a coupling efficiency of $\geq 80\%$ to be achieved routinely (Sottini,1979).

Conventional sources are usually characterized by an emitting area much greater than the cross section of the fibre. Although this can be overcome to some extent by bundling fibres to present a larger effective receiving area, this approach is undesirable in the setting of laser angioplasty where a single, highly flexible fibre is desired. To overcome this problem a system of lenses and/or reflectors is used to present a reduced image of the emitting source to the proximal face of the optic fibre.

Laser Technology

Bare Optical Fibres

Bare fibres simply consist of a smooth, polished distal end from which the laser light emerges. The diameter of the emergent beam is therefore mainly determined by the diameter of the fibre core.

Modified Optical Fibres

The distal ends of optical fibres may be modified in such a way as to alter the distribution of the emergent beam.This is achieved either by etching the polished end of the bare fibre or by the application of a lens system onto the end of the fibre. The lenses are most commonly constructed from synthetic sapphire crystals.

Other modifications which will be discussed later include the application of a metal cap onto the end of the optic fibre to convert the laser energy into heat, and a hybrid system which transmits laser energy circumferentially through a transparent angioplasty balloon.

Laser Angioplasty

History

In the search for alternatives to coronary artery bypass grafting laser technology offers potential benefits over balloon angioplasty with its limited applicability, particularly in complete occlusions, and high restenosis rate.

It seems reasonable to assume that the intraluminal delivery of forms of energy capable of removing atherosclerotic mass may provide better long term results.

The attractive concept of vaporization of atherosclerotic plaque using transluminal laser energy has been stimulated by the development of, and dissatisfaction with, balloon angioplasty. The concept was first advanced by McGuff in 1963, but lay fallow for nearly twenty years until reinstated by Macruz in 1980 (McGuff, 1963; Macruz,1980). Numerous subsequent in vitro and in vivo studies using laser energy delivered through bare optical fibres have established the feasibility of laser recanalization through arteries affected by obliterative disease (Abela, 1983 &1985d; Ginsburg, 1985; Geshwind, 1984). Further studies showed that release of particulate debris downstream was unlikely to complicate the clinical application of laser revascularization (Case, 1985; Abela, 1985b; Vielilledent, 1984) and that in the short term restenosis was not a significant problem.

Despite these promising initial results, the clinical application of this technique has been delayed by the problem of arterial perforation (Ginsburg, 1985), which is particularly frequent in small, tortuous vessels like coronary arteries (Choy, 1984; Crea 1985a/b).

Strategies to reduce Arterial Perforation

It has been shown that most perforations during in vitro coronary laser angioplasty are thermal rather than mechanical and tend to occur either as a result of plaque displacing the optic-fibre and its emergent laser beam from the coaxial vector towards the wall of the vessel or simply as a result of forward projection of the laser beam impinging on the wall

of a tortuous vessel (Isner, 1985a).

Efforts to overcome the problem of vessel perforation have encompassed a variety of approaches. The alternatives may be considered according to the four individual components of a laser system for vascular recanalization:

1. the laser generator;
2. the guiding system;
3. the atherosclerotic plaque;
4. the optical fibre.

1. The Laser Generator

Lasers can be divided into two main types: continuous wave and pulsed

Continuous Wave (c.w.) lasers have a constant power output with time. Argon and Nd:YAG lasers are the commonest continuous wave lasers used in cardiovascular medicine. The Nd:YAG wavelength (1,064nm) is absorbed by water but not haemoglobin, while the argon wavelengths (488nm and 514nm) are absorbed by haemoglobin and transmitted by water. The choice of continuous wave lasers for laser angioplasty is largely historical. Argon and Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG) laser wavelengths could easily be transported by commercially available optic fibres that were sufficiently flexible and non-toxic.

The effect of c.w. laser energy on biological tissue is largely thermal with the channel of recanalization lined by a superficial zone of necrosis and charring with a wide subjacent zone of polymorphous lacunae caused by boiling of intracellular water. Clearly an extensive peripheral zone of injury is undesirable in thin walled coronary arteries, although

Laser Angioplasty

it may be tolerated in larger peripheral arteries.

The search for methods of eliminating this peripheral zone of damaged tissue has centered around two approaches. The first involves the delivery of very short, high energy pulses to vaporize materials so rapidly that transfer of heat to the non-irradiated subadjacent strata is negligible, hence the growing interest in pulsed laser sources. The second solution involves the utilization of ultraviolet photons which are well absorbed by biological tissues and disrupt molecular bonds resulting in photochemical rather than thermal tissue ablation.

Pulsed lasers deliver energy in brief, discrete pulses lasting millisesconds or less, each of which is separated by an emission free interval. During this interval the energy is stored and amplified so that when suddenly released over an extremely short time interval a very high energy pulse is delivered.

The two commonest pulsed lasers in use are the Excimer (Pulsed Ultraviolet laser) and the Nd:YAG although pulsed dye lasers of various wavelengths are now being examined. Pulsed lasers appear to offer three advantages over continuous wave lasers. Firstly, they significantly reduce or eliminate thermal injury to adjacent non-target tissue (Grundfest, 1985). This injury is avoided when the exposure time used for each pulse is so short that significant transmission of heat to adjacent structures does not occur, and the irradiated tissue has time to cool down during the pulse free interval. Second, control of the pulse duration and the repitition rate allows accurate control of tissue ablation (Murphy-Chutorian, 1986), whereas continuous wave lasers show wide variation in tissue response, despite rigidly controlled laboratory conditions (Shelton, 1986). Thirdly, the delivery of high energy pulses facilitates the ablation of calcific foci which on exposure to continuous wave laser become foci of intense heat which is then conducted to adjacent tissue and results in uncontrolled thermal damage and an increased risk of arterial

perforation particularly in the coronaries.

It remains unclear whether there is any real advantage of one wavelength over another when brief, discrete, high energy pulses are delivered to atherosclerotic tissue. Evidence is accumulating that unwanted adjacent thermal damage is largely a matter of pulse duration since thermal injury can be reduced by pulsing argon laser energy (Kramer, 1986) and analysis of photoproducts following excimer ablation implies a predominantly thermal process similar to c.w. lasers (Clarke,1987).

An obstacle to the clinical application of excimer lasers has been the problem of transportation of UV light down optical fibres, particularly at high peak power densities. Recently such fibres have been developed and are currently being employed, with apparent success, by Grundfest in the peripheral circulation although results await publication.

The intravascular medium in which lasing is performed is of crucial importance and relates to the type of laser generator employed. Of particular relevance is the high absorption of green-blue argon laser energy by red haemoglobin resulting not only in dissipation of energy through absorption but also by scatter. Furthermore, absorption and scattering inevitably results in damage to red blood cells (Abela, 1985b) with the potential risk of thromboembolism and local release of vasoactive ATP molecules. This has led to the concept of "contact" optical fibre tips where the tip of the optic fibre is abutted against the occlusive plaque to exclude the intravascular medium and increase the amount of laser energy reaching the plaque. The tip of the optic fibre is sheilded from damage either by a synthetic sapphire tip which may take the form of a lens (Geshwind, 1987; Verdaasdonk,1987), or simply by a glass bubble.

2. The Guiding System

Improper, nonaxial positioning of optic fibres within the vascular lumen may result in perforation. In addition manipulation of needle like optical fibres within an artery may be hazardous.

The use of steerable guide wires as a monorail over which the optic fibre can be advanced has been shown to allow safer intravascular manipulation of optic fibres together with improved coaxial alignment within the vessel lumen (Anderson, 1987)

Recently the development of specially designed balloon catheters containing a centrally positioned optic fibre has been found to provide effective intra-arterial coaxial alignment. Such a system also allows a choice of perfusate during lasing. Furthermore, a lens at the optic fibre tip causes the beam to diverge so reducing forward projection of the high energy beam and also increasing the potential diameter of recanalization. The system has been shown to be effective in the peripheral circulation using argon laser energy, and percutaneous coronary trials are just commencing (Nordstrom, 1986).

The use of angioscopes to identify and characterize arterial disease appears promising although this is currently limited to the peroperative approach since it requires displacement of blood by a transluscent fluid (Abela, 1986; Anonymous, 1987). Angioscopy allows good visualization of plaque even through a 1.8mm angioscope. Its main limitation is that it only allows examination of the ***surface*** of the plaque: it does not bestow the ability to estimate wall thickness or plaque composition, both of which are important features governing the energy profile required for safe recanalization. Furthermore, vision may be obscured during lasing by smoke or bubbles from the perfusate.

More recently the development of a prototype 2-D ultrasound transducer housed in the tip of a 4 French intravascular catheter offers the exciting possibility of visualization of arterial

wall structure beneath the surface with the ability to assess the composition of plaque with relation to calcification.

Another way to improve the guiding system is to use the optical fibre not only to deliver laser energy but also for simultaneous on-line identification and mapping of the atherosclerotic plaque by laser induced fluorescence detection (Deckelbaum, 1986; Leon, 1987; Sartori, 1987).The principle behind this technique is that the spectrum of laser light reflected off plaque and normal arterial wall is different and so spectral analysis may be used to "intelligently" identify the target atheroma in the absence of observer visualization. The most sophisticated solution along these lines has emerged from the Massachusetts Institute of Technology (Cothren, 1986). This group have developed a 2.5mm multifibre catheter containing 19 fibres of 100μm the distal end of which is covered with a transparent shield to protect the bare fibre tips. The tips are arrranged in such a way that the emergent beams overlap so that after firing one large 2.5mm crater is formed with an adjacent thermal injury zone equivalent to that that would be created by a single 2.5mm fibre. The catheter is coupled to the laser in such a way that each fibre can be fired individually. Each of the fibres is also employed for fast computerized spectral analysis by excitation fluorescence allowing discrimination between thrombus, atheroma and normal arterial wall. This system is still under development, but given the elevated costs of such technology it is unlikely that such a system will find wide application.

3. The Plaque

Following the initial demonstration that laser energy could vapourize arterial plaque and the appreciation that arterial perforation was a problem the search has continued for a laser source providing a wavelength selectively absorbed by atheromatous tissue but not by

normal arterial wall. This hope has not been realized to date, but recent work has shown preferential absorption by a factor of two, of blue light by yellow caretenoids in atheroma permitting selective ablation with radiation in the 420-530nm range (Prince, 1986). Furthermore, oral ingestion of beta-carotene has now been shown to result in a 50-fold increase in yellow plaque beta-carotene suggesting that pre-treating patients with oral beta-carotene could enhance selective plaque ablation (Prince, 1988). However, it remains to be seen whether such selectivity is adequate for clinical benefit.

It has also been shown in human cadaver aortas that the uptake of tetracycline is 4-fold greater by the atheroma than by the normal arterial wall resulting in more selective plaque ablation following ultraviolet laser irradiation than in untreated arteries (Murphy-Chutotian, 1985).

Alternatively plaque can be stained with haematoporphyrin derivatives (Spears, 1983). Exposure of stained plaques to a low energy laser beam of appropriate wavelength (630nm) might be expected to result in photochemical activation of the haematoporphyrin derivatives followed by the formation of free radicals which in turn produce gradual atherolysis. Since these derivatives are activated by very low laser energies the risk of vessel perforation would be negligible.

4. The Optical Fibre

Early experience with bare fibres showed that even when access problems were obviated by an intraoperative approach unpredictable perforation of adjacent coronary artery wall remained a restricting problem. Most perforations were seen in relation to calcific deposits, branch points and tortuous coronary segments (Isner, 1985a).

In addition the channel of recanalization is narrow since the diameter of the laser beam is determined by the diameter of the fibre optic core. The diameter of the core is limited by

Laser Angioplasty

flexibility of the fibre, and the combined diameter of the core and cladding in relation to vessel diameter. Generally fibres between 200-600μm are used.

Undoubtedly, from our own preliminary studies and those of others, the problem of perforation with bare optic fibres stems from uncontrolled forward projection of the laser beam.

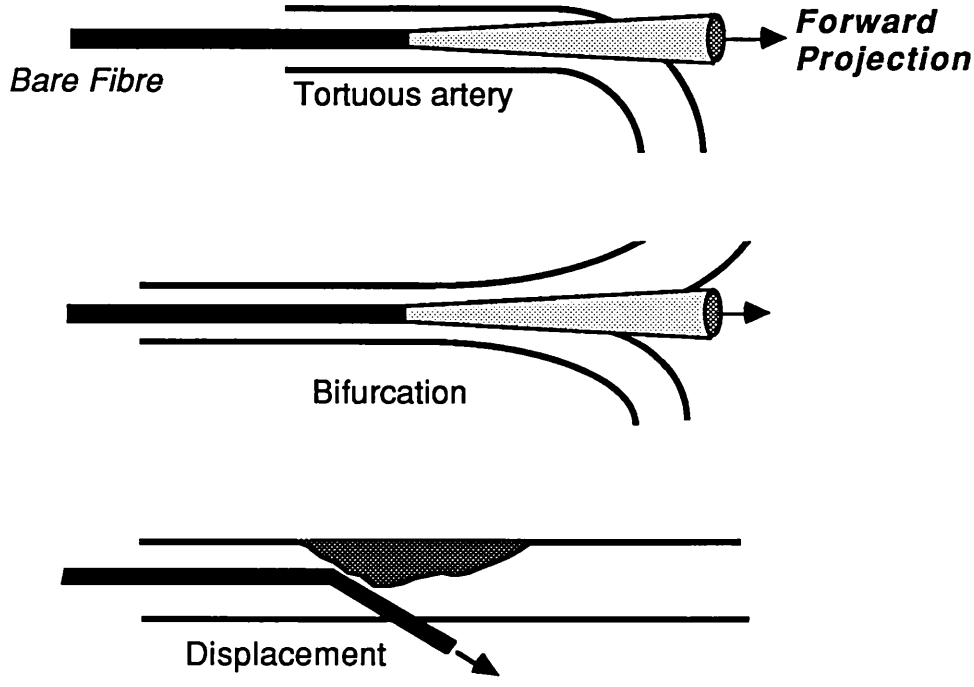

Figure 7: The main causes of arterial perforation with bare optical fibres

A further problem noticed with these fibres was "back-burning" with fibre tip melting and shortening (Ben-Sachar, 1986) which could conceivably distort and scatter the emergent beam adding to the problem of perforation.

The significance of forward projection is a particular problem within thin walled coronary arteries (Keogh, 1987b). In a series of preliminary studies to quantify this problem we

Laser Angioplasty

assessed the perforation thresholds of 6 fresh cadaver coronary arteries using an argon laser coupled to a 300μm core bare tip optical fibre. The time to perforation was noted when varying powers between 0.5 and 6 Watts were delivered with the fibre held:

1. at 90° to normal coronary wall - with tip contact, and
2. at 90° to normal coronary wall - with the tip 2.0mm from the arterial wall,
3. at 30° to normal coronary wall - with tip contact, and
4. at 30° to normal coronary wall - with the tip 2.0mm from the arterial wall.

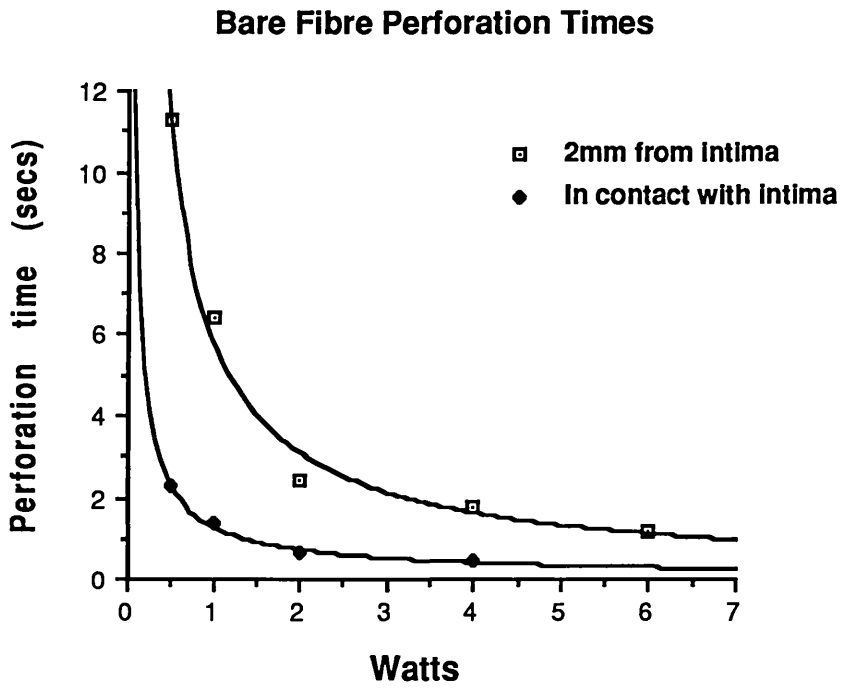

Figure 8: Coronary artery perforation times with a bare fibre held at 90° to the arterial wall.

When the fibre was at right angles to and in contact with the arterial wall with a confirmed distal output of 1Watt the perforation time in seconds was 1.36±0.2 (mean±SD, n=18).

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Changing the incident angle to 30° increased the perforation time to 1.93±0.4 (n=18). But if the fibre was held 2.0mm from the intima the perforation time increased to 6.47±0.87 at 90° (n=18) and 8.7±0.84 at 30° (n=18). These times were similar in the presence of soft atheroma.

The effect of solid, heavily calcified atheroma on the perforation time was examined at a further 20 selected sites. The fibre was held at 90° in contact with the plaque at 10 sites using 1 Watt and at another 10 sites using 8 Watts.

This type of atheroma consistently increased the perforation time to >20 seconds when 1 Watt was applied, although increasing the power to 8 Watts produced perforation in similar plaques in 2.3±0.94 seconds.

These results highlight the variability of tissue response in closely adjacent areas and the potential effect of plaque composition on safe coronary arterial recanalization.

Awareness of these problems has stimulated the development of a variety of ingenious fibres designed to eliminate or attenuate the forward projection of the beam while at the same time increasing the size of the recanalization channel.

Laser Angioplasty

Metal-capped Optical Fibres

By 1985 several facts were known:

1. The prime mode of action of continuous wave laser energy on biological tissue was thermal;
2. Raw laser light resulted in an unacceptably high perforation rate due to forward projection of the beam;
3. Laser light delivered through unmodified optical fibres resulted in a narrow channel of recanalization.

Thus it was clear that the intravascular delivery of laser light through unmodified fibres was unacceptable, but if the thermal effect could be localized then recanalization may be both safe and effective.

In an attempt to combine these considerations a novel fibre was developed which consisted of an optic fibre with a metal cap crimped onto the distal end. The metal cap would eliminate the forward projection of the laser beam and would be heated rapidly allowing a precise targeting of thermal energy. Furthermore, the dimensions of the channel of recanalization would depend not on the size of the fibre core, but rather on the size of the metal cap (Hussein, 1986).

More specifically the "laserprobe" consisted of two components: an optic fibre and a heat generating element.

The optic fibre was a multi-mode step index fibre consisting of core, cladding and jacket. The core diameter was 300μm and the outer diameter 650μm. The length was typically 4 metres.

The heat generating element consisted of a metal titanium alloy cap crimped onto the end of the optic fibre. An eccentric channel through the metal cap allowed the passage of a

guidewire to facilitate maintenance of a co-axial position within the artery.

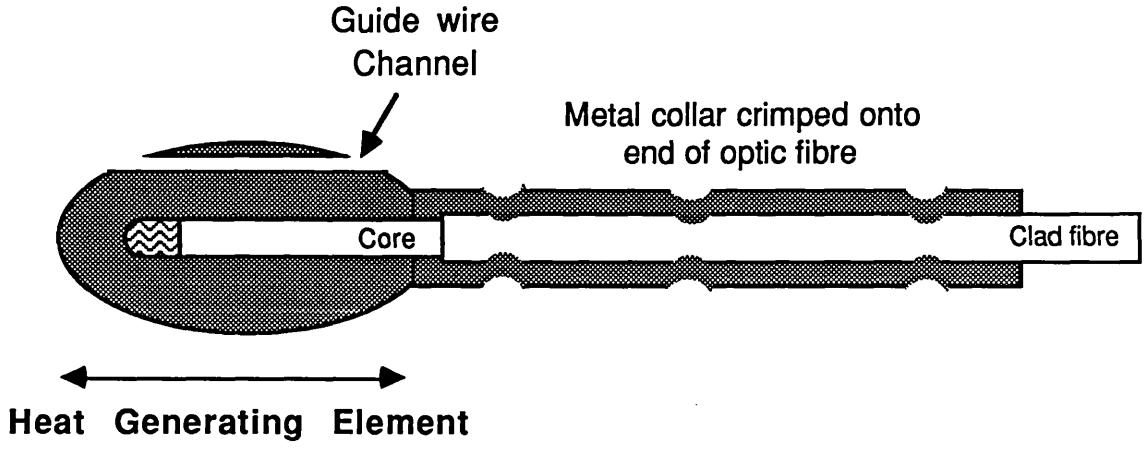

Figure 9: Diagramatic cross section through a metal-capped optical fibre

Initial studies by the probe designer (Hussein, 1986) demonstrated that the rate of rise of temperature and the final temperature reached in air were related to the power delivered. Using a 2.0mm diameter metal cap a temperature of 580°C could be generated on the surface of the metal cap with 2 Watts in 5.7 seconds; at 8 Watts a temperature of 1040°C was achieved in 2.8 seconds. Further in-vitro studies showed that the probe could create a channel through bovine muscle and that in this tissue the rate of rise of temperature was much slower reaching a plateau of about 400°C.

Early Studies on Efficacy and Safety

In a comparative study using a probe of this design Sanborn (1985) was able to widen iliac stenose in 8 of 12 atherosclerotic rabbits, but was able to widen only 2 of 12 using conventional bare fibres. Furthermore, there were 9 perforations with the bare fibre as opposed to only 1 with the metal-capped fibre.

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In another study Abela used atherosclerotic human coronary artery xenografts interposed into dog femoral arteries to compare efficacy of recanalization between bare and metal-capped optical fibres. He found a lower rate of perforation and a larger channel of recanalization using metal-capped optical fibres, with similar histological features in both groups (Abela, 1985a).

Addressing the issue of restenosis, which is the predominant limitation of balloon angioplasty, Sanborn showed a significantly reduced restenosis rate following metal cap recanalization as compared with balloon angioplasty in atherosclerotic rabbit iliac arteries supporting the hypothesis that removal of tissue mass may improve long term patency.

Clinical Studies

The application of these fibres in the peripheral circulation has been successful. Cumberland reported the use of a metal-capped optical fibre in 56 total peripheral artery occlusions. Successful recanalization was achieved in 50 (89%) providing an adequate channel for subsequent supplementary balloon dilatation. The perforation rate was 1 of 56 (Cumberland, 1986c) compared with 2 of 15 in an earlier group of patients when bare fibres were employed (Cumberland, 1986b). Of particular interest was the ability of the metal cap to recanalize 15 of 17 occlusions longer than 10cm, and 12 of 16 deemed impossible by existing angioplasty techniques.

In a separate series Myler (1987) was able to cross 57% of total peripheral artery occlusions which were not passable with a guidewire and hence not amenable to routine angioplasty. The lesion length varied from 1-39 cm and success varied inversely with occlusion length.

Sanborn has analysed the cumulative clinical patency (**not** angiographic patency) of 99 recanalized segments at one year following recanalization with a metal-capped optical fibre

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and balloon angioplasty. The overall patency rate was 82% including stenoses and occlusions. Once again an inverse relationship with length was observed: 93% patency for occlusions of 1-3cm and 67% for occlusions of >7cm.

CHAPTER 2

Thesis Design
&
Equipment

Aim and Structure of Thesis Studies

Experimental studies with metal-capped optical fibres suggest less vessel perforation and greater reduction in angiographically assessed stenoses than with bare fibres. Furthermore, clinical studies provide convincing evidence that these fibres can effectively and safely recanalize severely diseased peripheral arteries without a significant risk of perforation.

The aim of this thesis was to assess the feasibility of using metal-capped optical fibres for coronary recanalization. The thesis is based on a series of studies which are divided into three stages.

Stage 1 ***Laboratory feasibility study:***

In this stage the feasibility of percutaneous coronary lasing with metal-capped optical fibres was addressed.

Stage 2 ***Clinical feasibility study:***

Following successful percutaneous coronary lasing in dogs, percutaneous coronary lasing was attempted in Humans. However, difficulties encountered during this study, combined with a report of myocardial infarction in another study (Cumberland, 1986d), encouraged us to undertake a further series of laboratory studies in Stage 3.

Stage 3 ***Laboratory development study:***

a **The temperature profile** of the metal cap was determined in blood and saline

b. **Studies on potential causes of myocardial infarction:**

- Embolism due to: Thromboembolism
  Atherosclerotic embolism
- Side branch occlusion

c. **The histological effects** in human atherosclerotic coronary arteries to elucidate:

- Perforation thresholds in different media
- The effect of plaque geometry

The Laser

The laser employed in these studies was an 18 Watt argon laser system (Optilase™, Trimedyne Co., California) which produced an output of 12-14 Watts at the laser head.

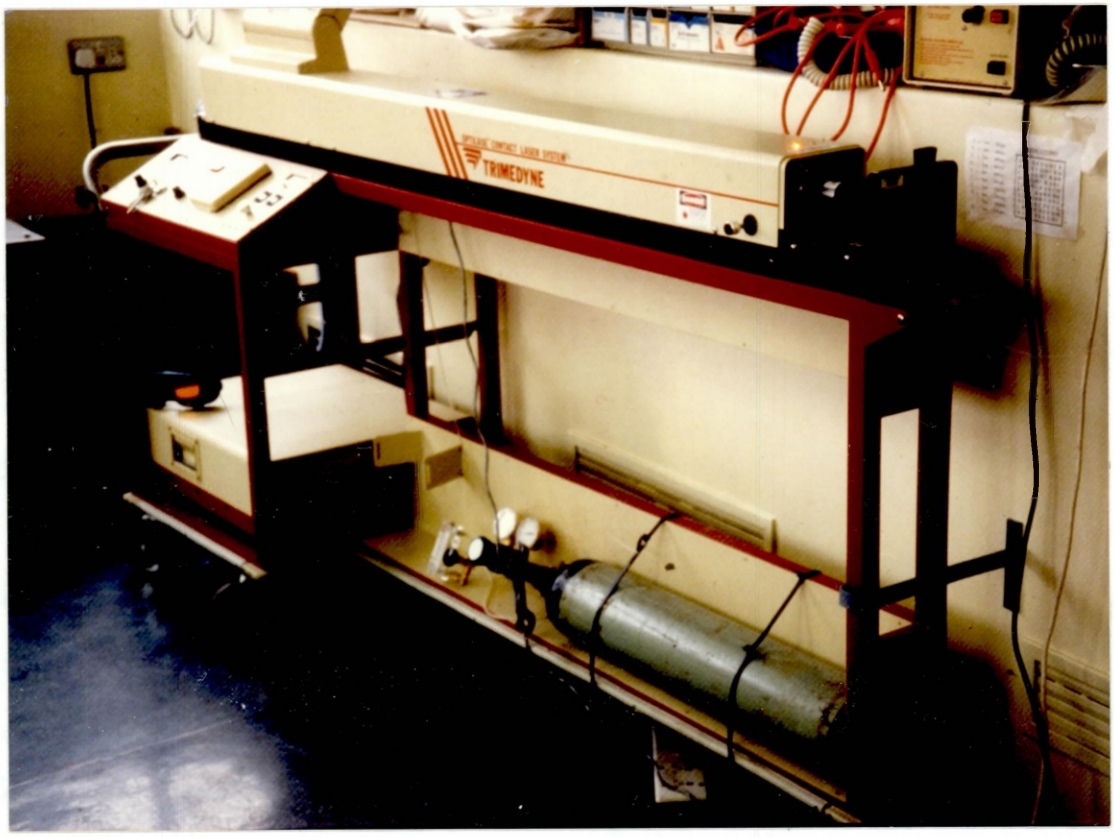


Figure 10: The Trimedyne Optilase™ Argon laser system used for these studies

Metal-Capped Optical Fibres

For the in-vitro studies a standard 2.0mm metal-capped optical fibre was employed (Laserprobe-PLR™ Plus Catheter 2.0mm). (See Fig.18). However, for the percutaneous studies in humans these were modified in our workshop to allow passage of the metal cap through a 9F percutaneous guiding catheter. This necessitated grinding the metal cap down to an external diameter of 1.5-1.7mm (See Fig.12)

CHAPTER 3

An Assessment of the Feasibility of Percutaneous Coronary IntimalThermoablation in Dogs

Introduction and Aims

Previous experimental studies have shown that transluminal laser irradiation of both normal and thrombosed coronary arteries, using bare optical fibres, results in perforation followed by cardiac tamponade. This complication was due to forward projection of the laser beam in tortuous arteries associated with cardiac movement resulting in misalignment of the laser beam. Since the metal cap converts the laser energy into local heat and eliminates forward projection of the laser beam the risk of perforation might be reduced. Earlier experimental and clinical studies have shown that metal capped optical fibres, compared to bare fibres, markedly decrease the incidence of perforation when lasing is attempted in peripheral arteries.

In the following study this hypothesis was assessed in live dogs.

Materials and Methods

A continuous wave argon laser, as previously described, was used. The radiation was delivered through a 200cm long, 300μm core silica optical fibre with a 1.5mm metal cap.

Animal Preparation

Twelve greyhound dogs, weighing between 25 and 35kg were anaesthetised using i.v. fentanyl (0.160mg/kg) and diazepam (1mg/kg). No heparin nor antiplatelet drugs were administered. Dogs were catheterised via the right carotid artery using a 8.3F Sones guiding catheter. The tip of the catheter was positioned in the left coronary ostium using a single plane image intensifier with a 6 inch field. The electrocardiogram was continuously monitored during the procedure.

The 12 dogs were randomly divided into 2 groups: those in which lasing was performed in the beating heart (n=6) and those in which lasing was performed in the fibrillating heart (n=6)

Lasing in the Beating Heart

In 6 dogs the metal-capped optical fibre was advanced through the guiding catheter into the circumflex artery for a distance of approximately 5cm. A control angiogram was obtained using sodium-meglumine diatrizoates (Renograffin - 76). Lasing was then performed at 6 Watts for 1 second. The optical fibre was then withdrawn by increments of 0.5 - 1.0 cm and lasing repeated after each repositioning using the same power but with increasing exposure times of 2, 3, 4, and 5 seconds. Repeat angiography was performed and the dogs sacrificed after 30-45 minutes.

Lasing in the Non-Beating Heart

In 6 other dogs the optical fibre was positioned in the circumflex coronary artery and the control angiogram performed. To assess the effects in reduced coronary blood flow, lasing was attempted in the fibrillating heart. Fibrillation was induced by intravenous potassium chloride. Lasing was then performed using the same protocol described above.

Post Mortem examination and Histology

The hearts were excised and examined for the presence of coronary perforation. The lased arteries were opened longitudinally and the sites with macroscopic evidence of thermoablation counted.Those segments with evidence of thermoablation were excised and fixed by immersion in 10% buffered formalin. Blocks were processed automatically with an Elliot tissue processor and 5μm sections were cut using a Cambridge rocking microtome. The sections were stained with haematoxylin and eosin and elastic Van Gieson.

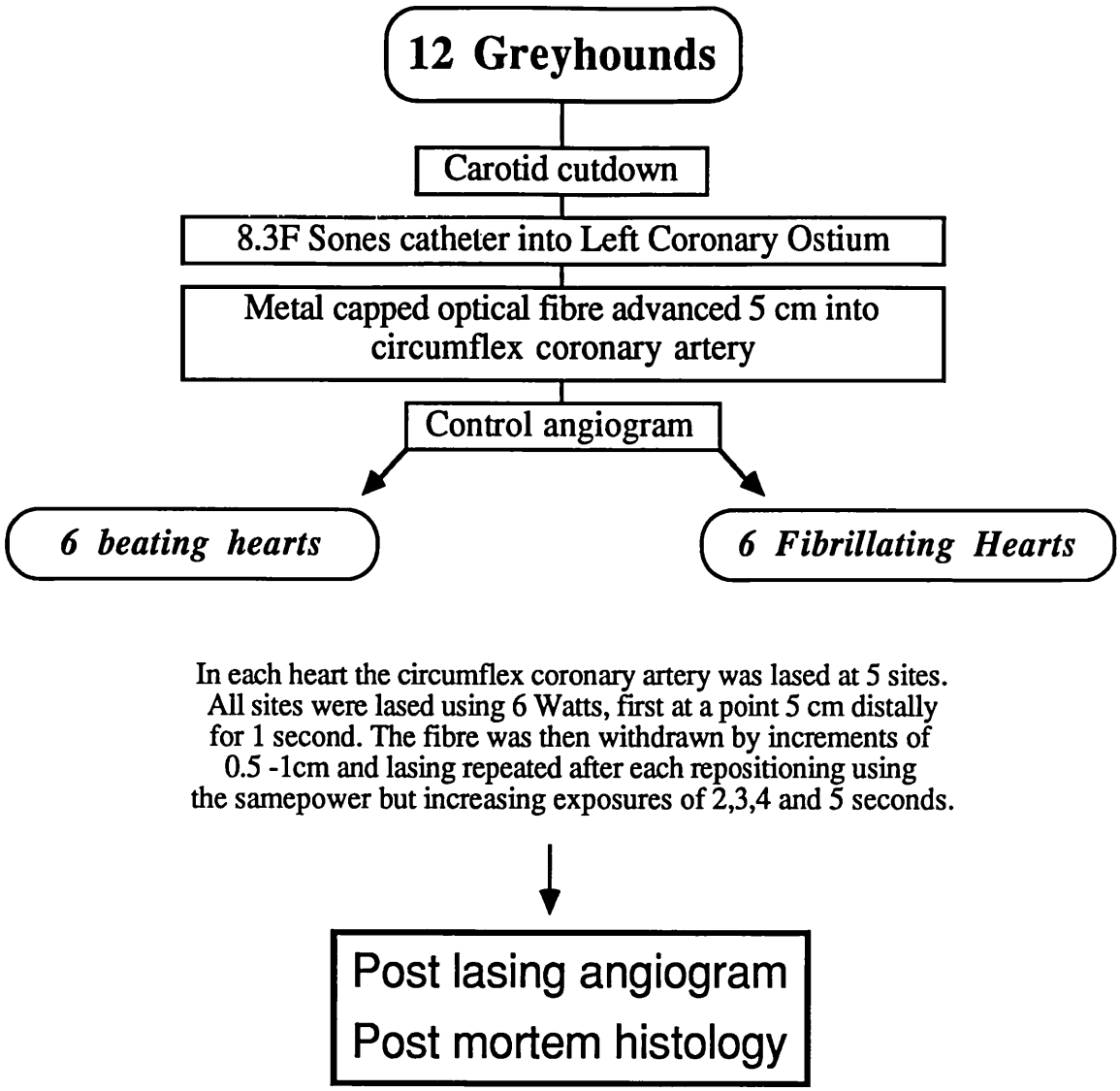


Figure 11: Flow diagram of the protocol followed to assess the efficacy of percutaneous intimal thermoablation in dogs using metal-capped optical fibres

RESULTS

A total of 60 different sites were lased in 12 coronary arteries: 30 sites in 6 coronary arteries in the beating heart and 30 sites in 6 coronary arteries in the fibrillating heart.

Table 1

Dogs	Angiographic Findings		Histological Findings	
	Pre-lasing	*Post-lasing*	*Intimal Thermoablation*	*Perforation*
6 Beating	Normal	Normal	6	Nil
6 Fibrillating	Normal	Not done	14	Nil

Angiographic Findings

Coronary angiography performed after positioning of the optical fibre and prior to lasing did not show evidence of coronary perforation in any of the 12 dogs. In the 6 dogs in which lasing was done in the beating heart, coronary angiography was repeated after the procedure and did not show signs of perforation or other major complications such as thrombosis, arterial dissection or aneurysm formation.

Angiography could not be performed in the 6 fibrillating dogs because there was inadequate forward coronary blood flow.

Post-mortem examination and Histology

Inspection of the 12 hearts did not show any perforations or peri-arterial haematomata. When the internal surface of the circumflex coronary artery was exposed in the 6 dogs in which lasing was performed in the beating heart, 6 of the 30 (20%) lased sites could be identified macroscopically. Thermal effects were seen at 5 of the 6 sites (83%) lased for 5 seconds but at only 1 of the 6 sites (16%) lased for 4 seconds; no thermal effects were seen with shorter exposures.

In the 6 dogs in which lasing was performed in the fibrillating heart 14 of the 30 (46%) lased sites could be identified. This percentage was significantly higher than that found in the other 6 dogs ($p<0.02$, chi square test).Macroscopic thermal effects were seen at all sites where exposures of 4 or 5 seconds were used but at only 2 of 6 sites (33%) where exposures of 3 seconds were used; no macroscopic thermal effects were seen with shorter exposures.

Histology

Microscopy of the excised arterial segments showed that in each case the intima and superficial myocytes had been ablated. The resultant surface was smooth with only trace amounts of cell debris and blood elements and minimal carbonisation. The remaining myocytes showed early evidence of coagulative necrosis, characterised by hypereosinophilia and polymorphous lacunae, consistent with early tissue vaporization (See Fig. 59, page 211). A common finding adjacent to the zone of maximal thermal damage was areas where the internal elastic lamina was preserved in spite of intimal ablation and coagulative necrosis of myocytes. A degree of detachment of the media from the adventitia and some devastation of the subjacent fat and myocardium was often noted. The magnitude of thermoablation and coagulative necrosis was greater for longer exposure

times; for similar exposure times it was greater in those arteries lased during ventricular fibrillation. Arterial perforation was not seen.

Discussion

In this study using laser energy delivered through metal-capped optical fibres, transluminal intimal thermoablation of coronary arteries in live dogs was achieved without perforation or other major sequelae by laser using metal-capped optical fibers. The thermal effects appeared reproducible and varied directly with laser delivery time. The occurrence of arterial perforation during transluminal delivery of laser energy through bare optical fibres in tortuous vessels is mainly due to the difficulty in controlling beam direction . Precise control is even more difficult to achieve in the beating heart. By contrast, the use of metal-capped optical fibres in this study was not associated with arterial perforation.

In stenosed coronary arteries, blood flow is likely to be very low or even absent, after the advancement of a metal-capped optical fibre. An estimation of the thermal effects in reduced coronary blood flow was obtained by lasing immediately after the induction of ventricular fibrillation in the dog model. In these non-beating hearts, using the same energies, the thermal effects were consistently more pronounced than those obtained in the beating heart. This is probably related to the fact that the absence of blood flow decreases heat dissipation.

Histology of the lased sites showed that thermoablation of the intimal layer resulted in the formation of a relatively smooth surface, with only limited areas of carbonisation. Although the de-endothelialized surface was occasionally lined by clumps of cell debris and blood elements, they never encroached upon the lumen. The histologic findings were similar to those observed after lasing with bare optical fibres (Crea, 1986; Abela, 1985; Gerrity,1983).

It is worth noting that the elastic lamina of lased vessels frequently appeared better preserved than the intima and the subjacent media. This was previously observed by Abela (1986) after argon lasing of human peripheral arteries with bare fibres; on this basis they suggested that the elastic lamina could be transparent to the laser beam acting as an "optical window". Since the elastic lamina was relatively better preserved in our study with metal-capped optical fibres, another explanation for this phenomenon might be that the elastic lamina is more resistant to thermal damage than the surrounding cellular tissue.

CHAPTER 4

An Assessment of The Feasibility of Percutaneous Human Coronary Recanalization using Metal-Capped Optical Fibres

Introduction and Aims

Given the encouraging results reported following the use of metal-capped optical fibres for recanalizing severely diseased peripheral arteries and the demonstration that effective intimal thermoablation could be achieved in the canine coronary circulation when these fibres were used percutaneously (Chapter 3), we undertook a study to assess the feasibility of percutaneous human coronary recanalization using these fibres.

Patients and Methods

Six male patients (aged 54-71, mean 59 years) who were referred for routine coronary artery bypass surgery were studied. All had multivessel coronary artery disease and stable angina refractory to medical therapy. In addition to other coronary lesions all had a significant stenosis (from 70% to 80% reduction in internal lumen diameter) of the left anterior descending (LAD) coronary artery. Laser recanalisation of the LAD lesion was attempted. Table 2 shows the clinical and angiographic details. The approval of the ethics committee and the written informed consent of patients were obtained.

Protocol

In order to ensure maximum patient safety it was decided to attempt the recanalizations at surgery. After sternotomy, paricardiotomy, cannulation of the ascending aorta, and administration of heparin (300 IU/Kg), a 9F arterial sheath was placed in the right femoral artery. The tip of the 9F guiding catheter was positioned, via the sheath, into the left coronary ostium and an angiogram was obtained. In the operating theatre angiography was recorded from fluoroscopy on to the videotape. A 0.012 inch diameter, 300 cm long Kaltenbach steerable guide wire was advanced across the left anterior descending artery using conventional angioplasty techniques and the stenosis was traversed. A 300μm core optical fibre fitted with a 1.5mm metal cap was coupled to an argon laser generator. Coupling and transmission efficiency, assessed before the procedure with a 300μm bare optical fibre,was found to be 90%. The metal-capped end of the fibre (fig 12) was then advanced over the guide wire (accommodated in a tunnel through the metal cap) to the site of the stenosis in the left anterior descending artery. When no further advancement could be achieved, a 6 W laser pulse was delivered for 4 seconds (energy = 24J). During the laser delivery gentle forward pressure was applied to advance the fibre through the

stenosis. If the stenosis was not crossed further laser pulses of 8W for exposure times of up to 8 seconds were delivered. After the stenosis had been crossed, the fibre was advanced during the cooling period for 1 - 2 seconds over a distance of approximately one centimetre to avoid adherence of the metal cap to the arterial wall. A laser pulse was also delivered during fibre withdrawal, with at least the same power as that used to cross the stenosis. Angiography was repeated after each laser pulse. At the end of the laser procedure cardiopulmonary bypass was started, an internal mammary artery graft was anastamosed to the left anterior descending coronary artery, and saphenous vein vein grafts were applied to the remaining diseased coronary arteries. Immediately after discontinuation of bypass and decannulation, heparinisation was reversed with protamine sulphate. In patients with successful laser recanalisation coronary angiography was repeated at 24 hours.

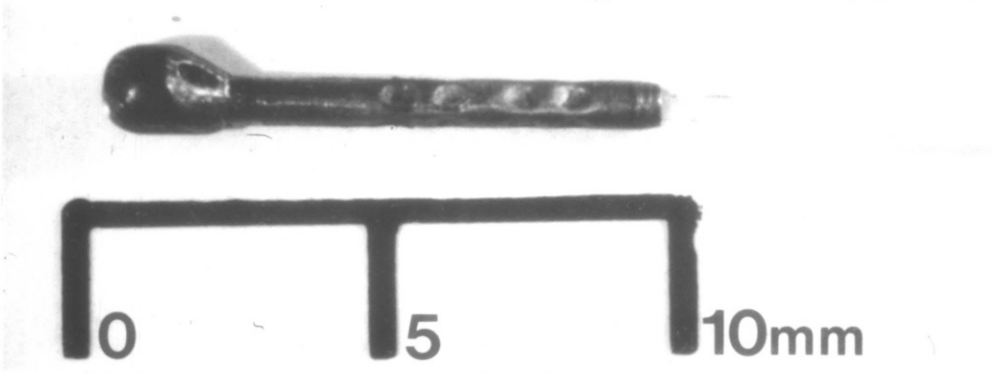


Figure 12

A photograph of the metal-capped optical fibre used in this study. It was modified in the workshop to facilitate passage through a 9F guiding catheter

RESULTS

The laser procedure reduced the severity of the left anterior descending artery stenosis in three of the six patients. In patient 2 the delivery of >112J at the same site caused coronary perforation. Therefore, in the subsequent four patients the delivery of laser energy in the absence of fibre progression was limited to <90J. In all cases, inspection of the metal cap after the procedure showed the presence of charred blood which could be scraped off with a scalpel blade. The results are presented in detail below and are summarised in Table 3.

Successful Laser Recanalisation

In patient 1 the first laser pulse (24J) did not permit fibre to be advancement through a 3 cm long 80% stenosis. The following three laser pulses (48J, 48J and 32J) resulted in the gradual progression of the fibre across the stenosis. A 100J laser pulse was delivered during withdrawal. Repeat angiography showed a reduction in the severity of the stenosis.

In patient 3 the initial two laser pulses (36J and 24J, respectively) did not allow advancement of the fibre through an 80% stenosis. This was achieved with the third 24J laser pulse. In addition, 48J were delivered during fibre withdrawal.

In patient 6 a 70% stenosis was traversed with the first 36J laser pulse; 32J were delivered during fibre withdrawal. In both cases repeat angiography showed that the severity of the stenosis had been reduced (figs 13 and 14).

Angiography at 24 hours demonstrated a patent internal mammary graft in all three patients; in two of these there was total proximal occlusion of the LAD.

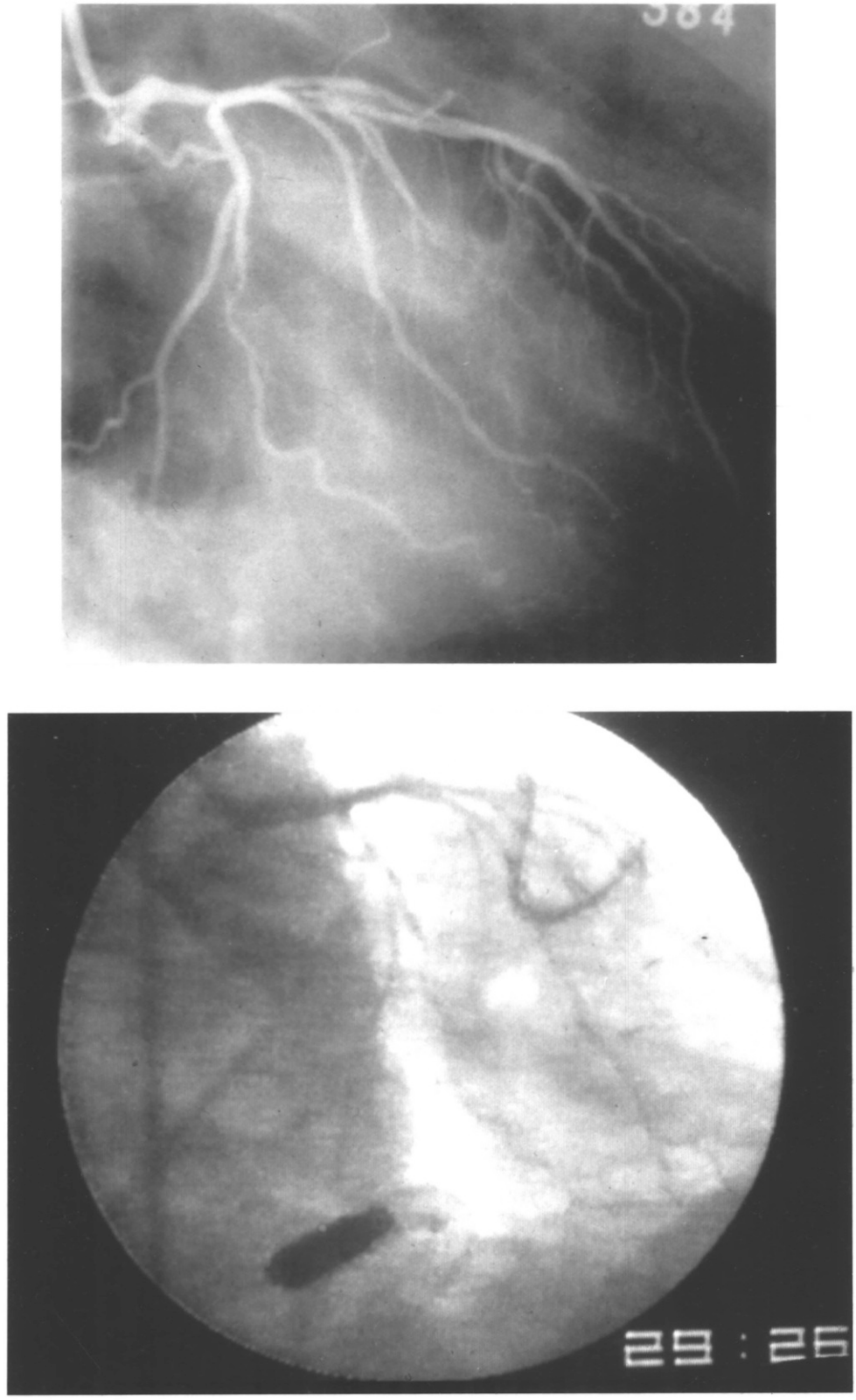


Figure 13: Angiograms of patient 3 before (upper panel) and immediately after (lower panel) the delivery of laser energy (132J), showing a reduction in the left anterior descending coronary artery stenosis

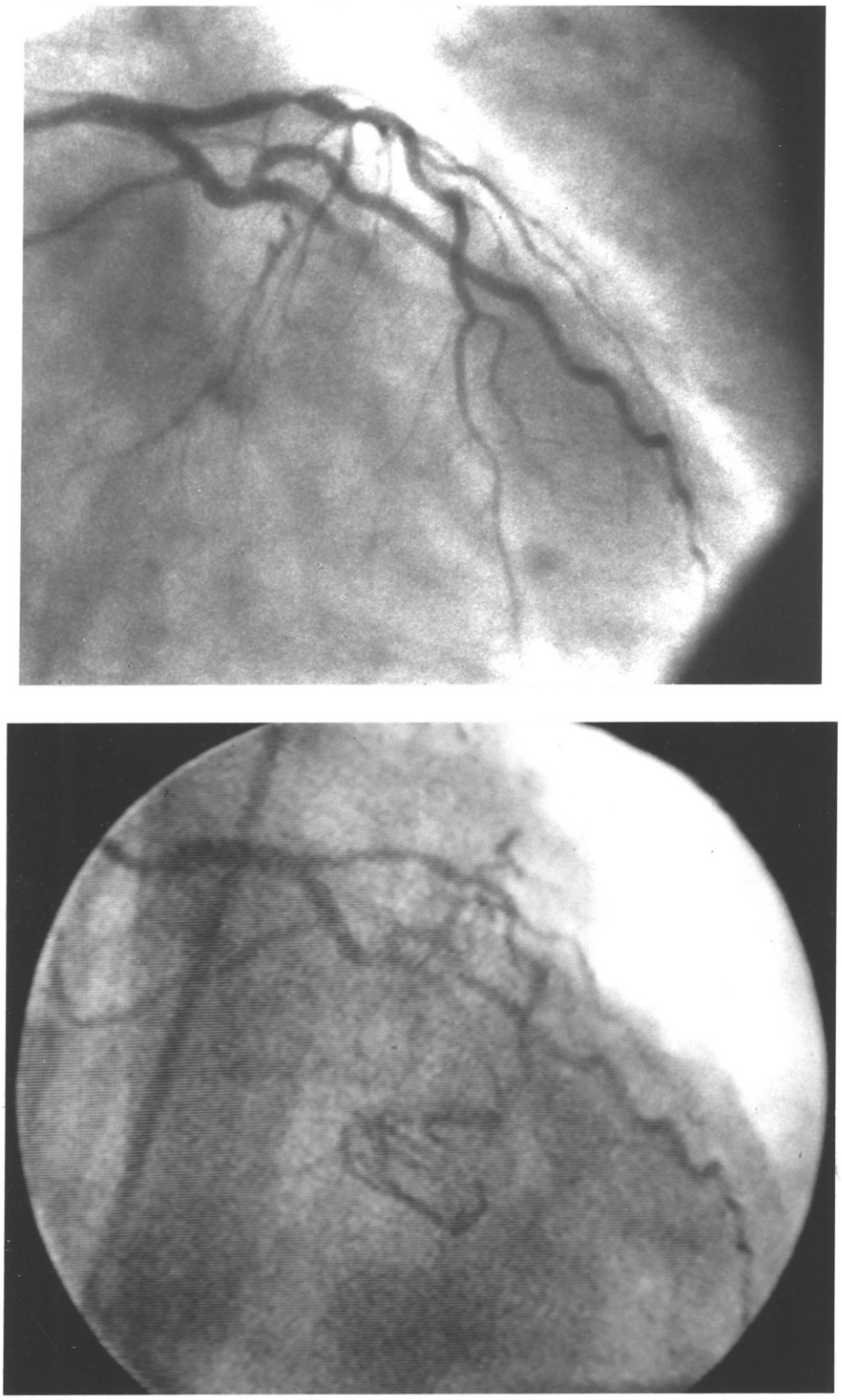


Figure 14: Angiograms of patient 6 before (upper panel) and immediately after (lower panel) the delivery of laser energy, showing a reduction in the left anterior descending coronary artery stenosis

Unsuccessful Laser Recanalization

In patient 2 the delivery of three laser pulses to a total of 112J failed to allow progression of the fibre through a 3cm long 80% calcific stenosis. Repeat angiography at this stage did not show any complications. After the delivery of an additional 80J laser pulse angiography demonstrated periarterial contrast extravasation, indicating coronary perforation. Inspection of the artery showed localized extravasation of blood with small petechial haemorrhages in the adjacent pericardial fat.Although the perforation was clearly visible there was no blood in the pericardial cavity. Cardiopulmonary bypass was promptly commenced and the perforation oversewn. Thereafter routine coronary artery bypass grafting was performed.

On the 7th postoperative day, following removal of the patient's epicardial pacing wire his condition rapidly deteriorated and he was transferred to the Intensive Care Unit. There was no clinical evidence of myocardial infarction or tamponade. He died 3 hours later. Post mortem examination revealed that part of the right ventricular wall had been disrupted at the site where the pacing wire had been attached. This had caused local tamponade resulting in death. Histological examination confirmed the presence of infarction in the LAD territory involving the right ventricular wall.

In patient 4 the fibre failed to cross an 80% stenosis despite the delivery of three laser pulses totalling 84J. During attempts to advance the fibre fluoroscopy showed bending of the fibre tip with loss of alignment of the metal cap from the co-axial position within the vessel lumen. Repeat angiography revealed that the stenosis was unchanged.

In patient 5 the fibre was advanced across a 70% stenosis without the requirement of laser energy. Two laser pulses totalling 96J were delivered during fibre withdrawal, but did not reduce the severity of the stenosis.

In patients 2 and 4 the metal cap adhered to the arterial wall after the delivery of laser energy. A 1 second laser pulse was necessary in these cases to detach the metal cap from the arterial wall.

TABLE 2: CHARACTERISTICS OF PATIENTS IN PERCUTANEOUS STUDY

Patient	Age	Sex	Duration of angina	Basal ECG	Baseline Angiography (%stenosis)		
					LAD	Cx	RCA
1	61	M	2 yrs	Q V1-V3	80% 3cm	90%	Normal
2	71	M	10yrs	Normal	80% 3cm	Normal	90%
3	60	M	2 yrs	Q II, III, aVF	80% 1cm	Normal	90%
4	54	M	11yrs	Normal	80% 1cm	90%	70%
5	56	M	3 yrs	Normal	70% 1cm	70%	90%
6	56	M	10yrs	Q II, III, aVF	70% 1cm	100%	80%

ECG = Electrocardiogram; Q = Q wave; LAD= Left anterior descending coronary artery;
Cx = Circumflex Coronary artery; RCA = Right coronary artery;

TABLE 3: RESULTS OF PERCUTANEOUS STUDY

Patient No.	Pulse Number	Power (Watts)	Duration	Energy (Joules)	Fibre Progression	Repeat Angiography: LAD stenosis	Repeat Angiography: Acute Complications
1	1	6	4	24	No	***Improved***	None
	2	8	6	48	Yes		
	3	8	6	48	Yes		
	4	8	4	32	Yes		
	*5	10	10	100	Yes		
2	1	6	4	24	No	**Unchanged**	Perforation
	2	8	6	48	No		
	3	8	5	40	No		
	*4	8	10	80	No		
3	1	6	6	36	No	***Improved***	None
	2	8	3	24	No		
	3	8	3	24	Yes		
	4	8	6	48	Yes		
4	1	6	6	36	No	**Unchanged**	None
	2	8	3	24	No		
	3	8	3	24	No		
5	*1	6	6	36	Yes	**Unchanged**	None
	*2	8	3	24	Yes		
6	1	6	6	36	Yes	***Improved***	None
	*2	8	4	32	Yes		

* Energy delivered on pull-back through stenosis

DISCUSSION

In this study percutaneous coronary laser recanalisation of a severe stenosis of the left anterior descending artery was attempted in six patients with metal-capped optical fibres at the time of coronary bypass surgery. In three patients the delivery of laser energy permitted the metal cap to cross the stenosis, and in all three a reduction in the severity of stenosis was confirmed at angiography. Multiple factors determined success or failure. The procedure was successful in patient 1 but not in patient 2, although in both the angiographic severity of the stenoses was similar. On direct observation and palpation during surgery, however, the stenosis in patient 2 was found to be more tortuous and heavily calcified than suggested by angiography. It is possible that the heat generated by the metal cap was insufficient to vaporise the calcified component of the atherosclerotic plaque. The reason for myocardial infarction in this patient is unclear. It was probably the result of 2 factors. Firstly, the metal-capped optical fibre remained within the coronary artery for a considerable period of time during the procedure (aprox. 30 minutes). This may have been partially occlusive. Secondly when the fibre was removed a coagulum was adherent to the metal cap. This will have had the effect of increasing the occlusive influence of the metal cap. It is likely that these factors were responsible for reduced myocardial perfusion resulting in peroperative infarction. In turn, this infarction probably prevented effective sealing at the site where the pacing wire was sutured onto the right ventricle, thus facilitating tamponade.

In patient 4, although the stenosis was less severe than in patients 1 and 2, malalignment of the fibre within the vessel lumen probably accounted for the lack of success. In patient 5 the metal cap was too small for the size of the artery and no apparent improvement in the severity of the stenosis was obtained despite the laser energy delivered during withdrawal of the fibre through the stenosis.

This study confirms the experimental observation that localized thermal energy from metal-capped fibres is associated with a lower risk of perforation than bare fibre delivery of laser energy. It also provides some information on the safety levels of laser energy which allow coronary recanalisation without perforation. It must be said, however, that the precise threshold for perforation is still uncertain because it is difficult to quantify the amount of pressure applied to the optical fibre which is itself an important variable (Welch,1987). Coronary perforation only occurred in one patient when 192 J was delivered at the same site. Perforation did not occur in five other patients in whom only 90 J was delivered when the delivery of laser energy was not accompanied by fibre advancement.

To minimise the risk of potentially serious complications in this early series of patients, the procedure was performed at the time of operation before cardiopulmonary bypass was started. The study design, therefore, does not assess medium and long term patency of treated vessels because occlusion of the left anterior descending artery (proximal to graft insertion) was favoured by the competitive flow from the graft, by the reversal of anticoagulation, and by the absence of antiplatelet treatment.

Other Studies using Lasers in the Coronary Circulation.

Choy (1984) attempted intraoperative coronary recanalization in 8 patients. In 5 retrograde recanalization was attempted using argon laser energy through a bare optical fibre via the arteriotomy prior to graft anastamosis. Recanalization was successful in 3 instances: only one recanalization remained adequately patent. The poor patency rate probably reflects a combination of a small channel of recanalization from an 85μm optical fibre and competitive graft flow. In a further 3 cases (Choy,1986) he attempted recanalization of totally occluded right coronary arteries supplying infarcted territory. In these cases the fibre was inserted through a distal arteriotomy, but bypass grafting to the recanalized vessels was not performed. Two recanalizations occluded at 15 days and the third patient refused angiography. Similarly in our series the 48 hour patency was only 1/3. Despite arguments which blame competitive graft flow for early reocclusion these results leave doubts regarding the thrombogenic potential of the residual surface.

However, Livesay at the Texas Heart Institute has used a hand held CO_2 laser with a metal barrel waveguide to successfully recanalize 47/51 stenoses and total occlusions. Early catheterisation in 20/31 patients has revealed a patency of 78% of laser treated arteries, including arteries with prior total occlusion and competitive flow (Personal communication). Nevertheless, doubts about thrombogenicity make the step to distal lasing more difficult from an ethical standpoint, even though the absence of competitive flow might significantly reduce the incidence of acute reocclusion. Livesay has recently commenced laser recanalization of selected, tight left main stem stenoses through an aortotomy and his results are awaited with interest. Frazier also at the Texas Heart Institute has recently been able to effectively recanalize a 3cm segment of heavily diseased and calcific left anterior descending coronary artery through an arteriotomy with an excimer laser in a patient about to undergo cardiac transplantation for ischaemic cardiomyopathy.

Other Studies with Metal-capped optical fibres in the Coronary Circulation

In two studies percutaneous coronary laser recanalisation with metal-capped optical fibres was attempted as an adjunct to balloon angioplasty in closed chest patients. Cumberland (1986d) used this technique in four patients with a severe coronary stenosis that could only be crossed with a guide wire but not with a balloon catheter. He used similar energies: 8 Watts for 5-10 seconds. Three of these four high risk patients developed myocardial infarction within 12 hours of the procedure although the mechanism of occlusion was not clear.

In a later study in patients with less severe coronary stenoses Sanborn (1987) reported successful laser recanalisation in four of seven patients, using powers of 8 Watts, apparently without acute complications. Failure in three patients was attributed to vessel tortuosity.

These modest results indicated that laser coronary angioplasty with metal-capped optical fibres although feasible failed to offer any significant advance over conventional balloon angioplasty

Stimulus for Further Laboratory Investigation

Percutaneous transluminal coronary balloon angioplasty (PTCA) offers a success rate in the region of 90% with a restenosis rate of approximately 20-40%. To succeed a new technique would need to offer either a higher success rate, a lower restenosis rate or be effective in those lesions not amenable to conventional PTCA.

The reported results of attempted percutaneous coronary laser thermal angioplasty using metal-capped optical fibres were not encouraging (Cumberland, 1986d; Crea, 1988; Sanborn, 1986). Successful recanalization was achieved alone or in combination with balloon angioplasty in only 10 (59%) of 17 patients. In order for the technique of laser thermal angioplasty to advance, the factors limiting its success must be defined and if possible overcome. The poor primary success rate may have been due to inappropriate plaque geometry or composition, or due to inadequate catheter delivery systems. Furthermore, 4 of the 17 patients suffered myocardial infarction for reasons which were unclear. A number of possibilities existed: thromboembolism, plaque embolism, thermal damage to side branches or intraluminal flap formation.

The following Chapters report a series of laboratory studies designed to define and undestand some of these influences.

CHAPTER 5

The Temperature Characteristics of Metal-Capped Optical Fibres in Blood and Saline

Introduction and Aims

Metal-capped optical fibres may be introduced into the coronary arteries either percutaneously or intraoperatively. These two approaches dictate the nature of arterial perfusate during lasing. The percutaneous approach necessitates activation of the fibre in blood, whereas the intraoperative approach allows a choice between crystalloid and blood. An understanding of the effect of different perfusates on the temperature of the metal cap under varying conditions of energy input is mandatory.

The temperature characteristics of the metal cap have been partially studied in saline and in bovine skeletal muscle (Hussein, 1986), but not in blood.

Therefore, we compared the temperature profile of the metal cap during lasing in a simulated artery in the presence of saline and blood.

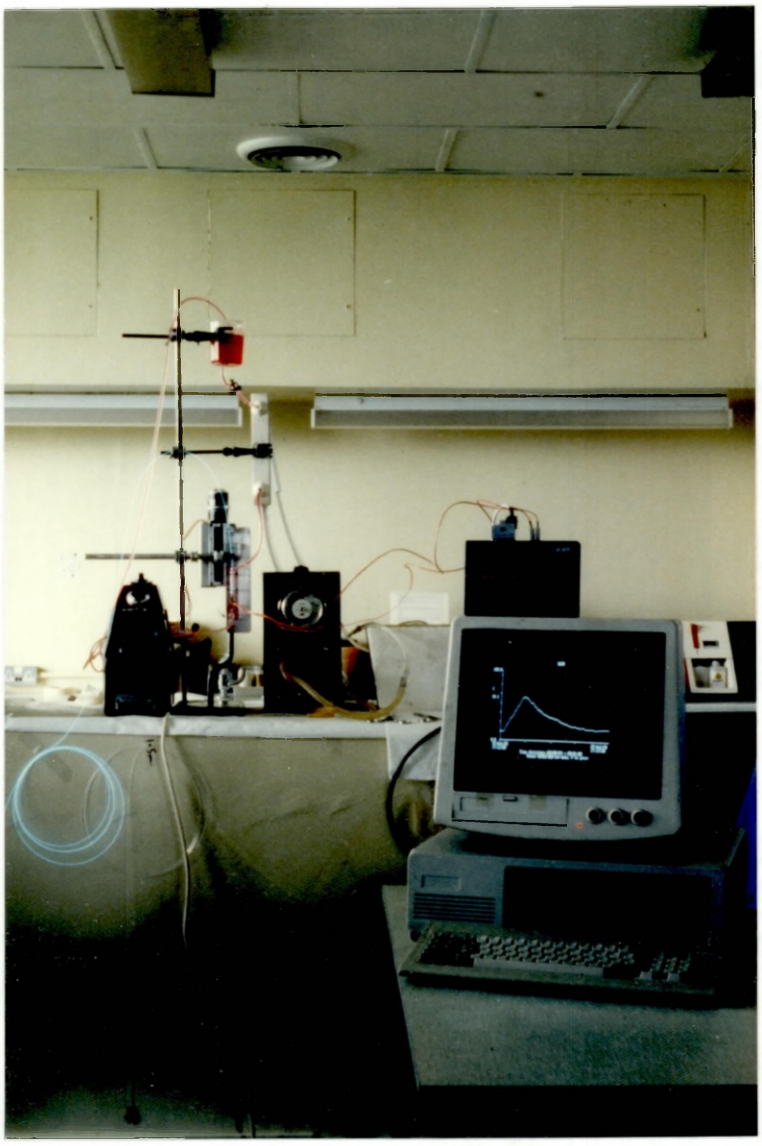


Figure 15

A photograph of the circuit used for studying the temperature characteristics of the metal cap under varying conditions.

Materials and Methods

In Vitro System

The test circuit shown in figure 11 consisted of five major components:

1. A simulated artery
2. A laser activated metal-capped optical fibre within the simulated artery
3. A recirculating perfusate
4. Two thermocouples: one welded to the metal cap and a second 10mm downstream.
5. A data logger and IBM Personal computer for data collection and analysis

The simulated artery was a 3.12mm transparent silicone tube. A silicone tube was chosen because of its ability to withstand high temperatures (>600^{o}C) without perforation. In order to reduce temperature artifacts produced by movement the silicone tube was held rigidly in a perspex scaffold.

The metal-capped optical fibre was a 2.0mm Laserprobe™ coupled to an argon laser. A type K (NiCr/NiCd) thermocouple was welded into the guidewire channel of the metal cap. The optical fibre was inserted through a side port in the circuit and the metal cap positioned in the simulated artery.

Perfusates

The silicone tube was incorporated into a circuit which allowed circulation of a perfusate at a predetermined flow using a calibrated Watson-Marlow peristaltic pump. The temperature of the circulating perfusate was kept constant by a heat exchanger (Churchill circuit incorporating a Travenol Pediatric Miniprime Heat Exchanger).

Two perfusates were used:

1. 0.9% saline
2. fresh human venous blood obtained from the author and colleagues. The mean haematocrit was 42 (Range 40-44). This was collected an a transfusion bag containing acid citrate dextrose anticoagulant. In addition 2000iu Heparin/500ml were added to ensure that no clot would form within the circuit

The thermocouples. Two Ni-Cr/Ni-Al (Type K) thermocouples were used to measure the temperature (a) within the metal cap by spot welding the thermocouple into the guidewire channel, and (b) 10mm downstream using a thermocouple mounted in a 21fg hypodermic needle held in position by the perspex scaffold. The millivolt output from the thermocouples was recorded at a sampling frequency of 5Hz (every 0.2 seconds) using a data recorder (Squirrel Data Logger, Type SQ2-4K SP, Grant Instruments, Cambridge). After each lasing the data points from the recorder were downloaded to an IBM PC computer for further analysis.

Pilot Study

During initial studies lasing was performed in blood, plasma and saline under varying conditions. Although a coagulum formed around the metal cap in blood and plasma no clot was found in the circuit. It soon became apparent that each optical fibre had a limited life span which was shortened by prolonged lasing at high temperatures. In addition the metal cap when activated with 12 Watts for 3-4 seconds reached a temperature greater than 600^{o}C in blood. Since temperatures greater than this could not be recorded by this system prolonged lasing seemed inappropriate. The final protocol was therefore based on a lasing period of 10 seconds.In addition, during theses studies, a third thermocouple also mounted in a 21fg hypodermic needle, was positioned just proximal to the apex of the metal cap but 0.5mm away from its surface. The aim of this was to measure the temperature of the coagulum. This was extremely difficult to position accurately and, furthermore, the position altered with the buildup of coagulum resulting in erratic and inconsistent temperature readings. It was therefore abandoned. Some of the pilot traces are included for illustrative purposes only (figure 19).

Final Protocol

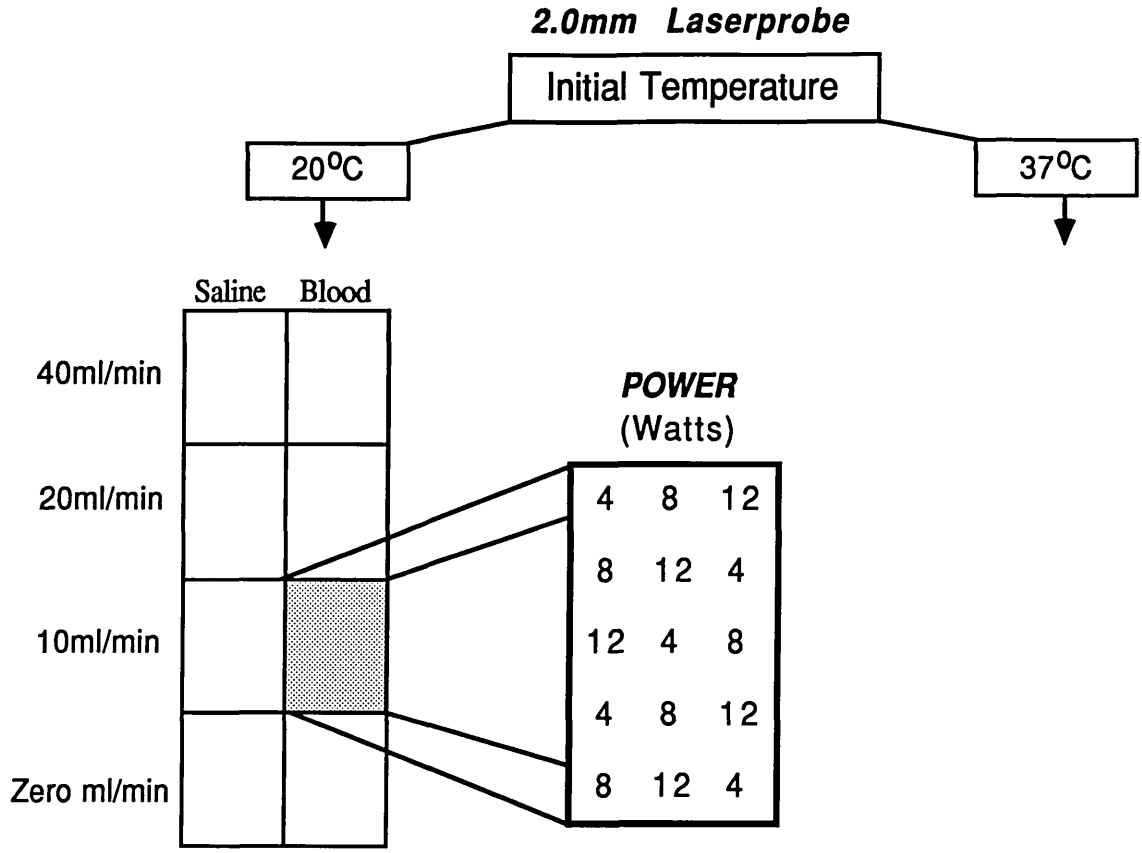


Figure 16: Diagrammatic representation of the final protocol showing the two starting temperatures and the four flow rates used for each perfusate. Five temperature profiles were recorded at each combination of three powers and four flow rates.

Duration of each lasing: 10 seconds: After each lasing the cooling profile of the metal cap was recorded until baseline temperature was reached.

Perfusate Flow rates: 0, 10, 20 and 40ml/min

Initial Temps prior to lasing: 20°C and 37°C

Powers: 5 lasings were performed at each of 4, 8 and 12 Watts for all combinations of initial temperature, flow and perfusate.

After each lasing in blood the metal cap was cleaned by scraping off the adherent coagulum with a blade.

The temperatures are reported in degrees centigrade as mean±SD.

Statistical comparisons were performed using one way analysis of variance and the Kruskal-Wallis test for comparison within a group and repeated measures analysis of variance for within and between group comparisons.

RESULTS

Saline

The temperatures reached by the metal cap from two different starting temperatures are shown in Table 4 and the profiles illustrated in figure 17.

Analysis of variance confirmed that both power and flow rate were important determinants of temperature ($p<0.001$ for both), and that the final temperature reached was significantly higher when the initial temperature was higher ($p<0.01$).

The mean temperature of the metal cap in static saline when when activated using 12 Watts reaches a temperature greater than boiling point due to bubble formation around the metal cap resulting in intermittent spikes of temperature reaching up to 140°C.

The temperature 10mm downstream never rose more than 5°C above the ambient circulating temperature prior to metal cap activation.

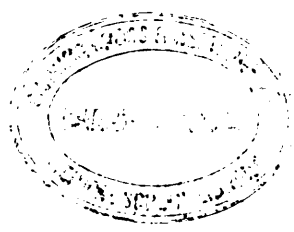


Table 4

TABLE X

THE RELATIONSHIP BETWEEN SALINE FLOW AND POWER INPUT ON THE TEMPERATURE OF THE METAL CAP

FLOW (ml/min)	POWER (Watts)	PLATEAU TEMPERATURE	
		Initial temp 21.4±0.9°C	Initial temp 38.2±0.7°C
Zero	4	38±4	61±6
	8	71±5	89±7
	12	107±11	109±14
10	4	57±9	68±8
	8	66±7	79±6
	12	74±9	88±8
20	4	34±5	46±4
	8	48±6	62±6
	12	57±6	71±9
40	4	28±3	48±5
	8	36±4	55±6
	12	41±5	68±8

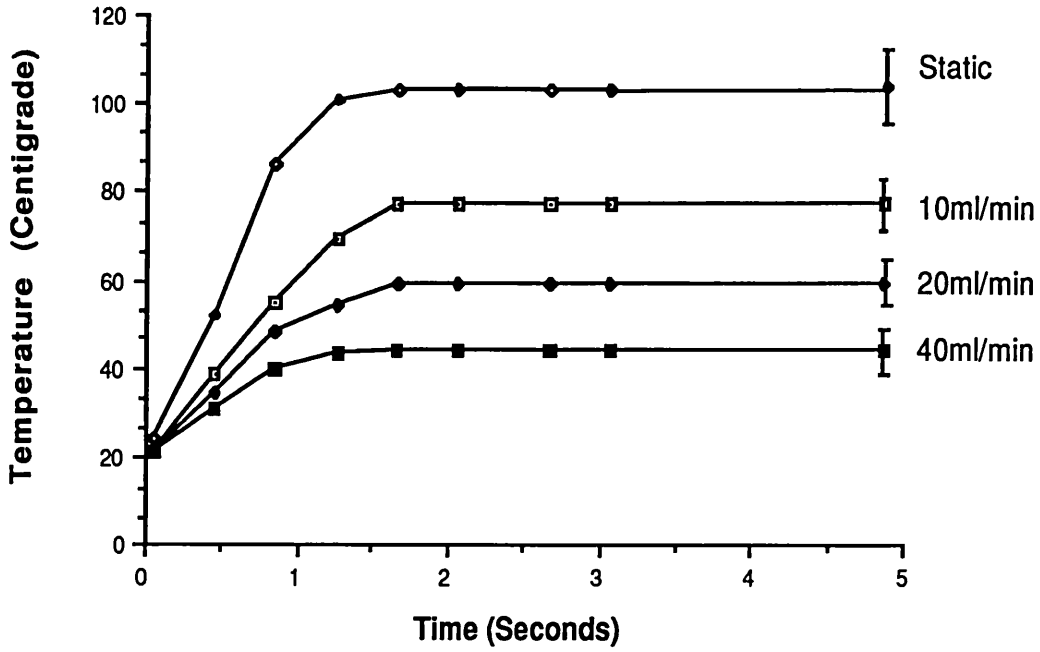


Figure 17(a): The effect of saline flow on metal cap temperature at 12 Watts

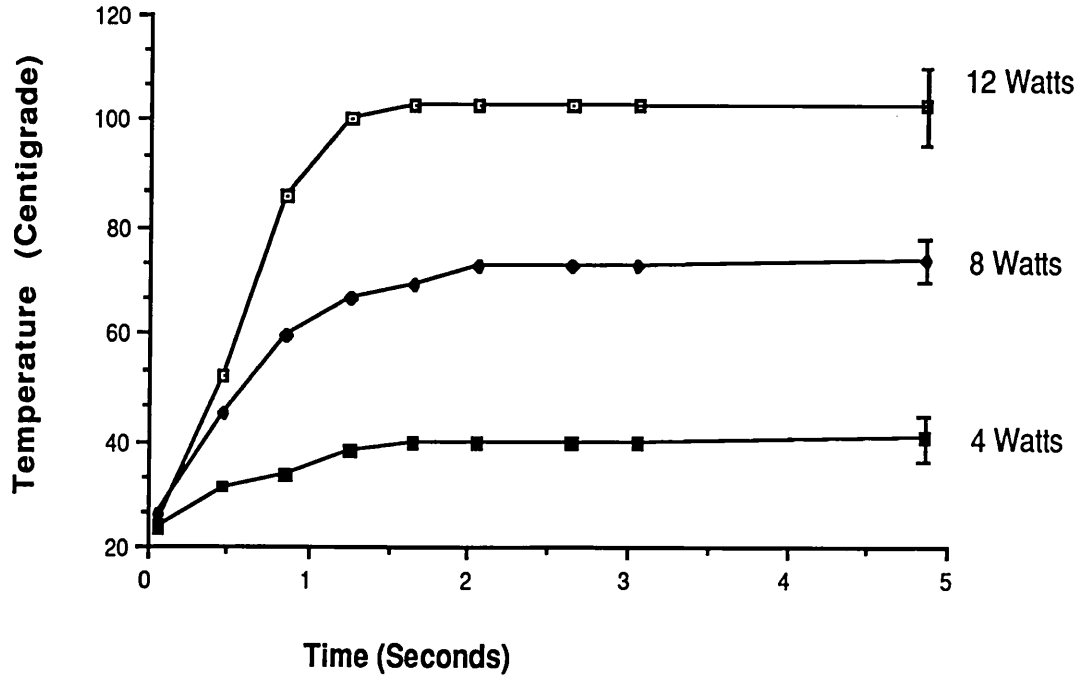


Figure 17(b): The effect of power on metal cap temperature in static saline

Blood

The Squirrel system used for recording temperature data points on floppy disks did not recognise temperatures >600°C. Since the temperature of the metal cap in blood may reach >600°C in 4 seconds the results are presented as the temperature reached at 3 seconds (Table 5).

The results indicate a significant increase in central cap temperature with increasing power ($p<0.001$).

Although, with increasing flow there appeared to be a lowering of temperature for equivalent powers this did not reach statistical significance for the flow rates examined at 8 or 12 Watts, but was significant for 4 Watts ($p<0.05$).

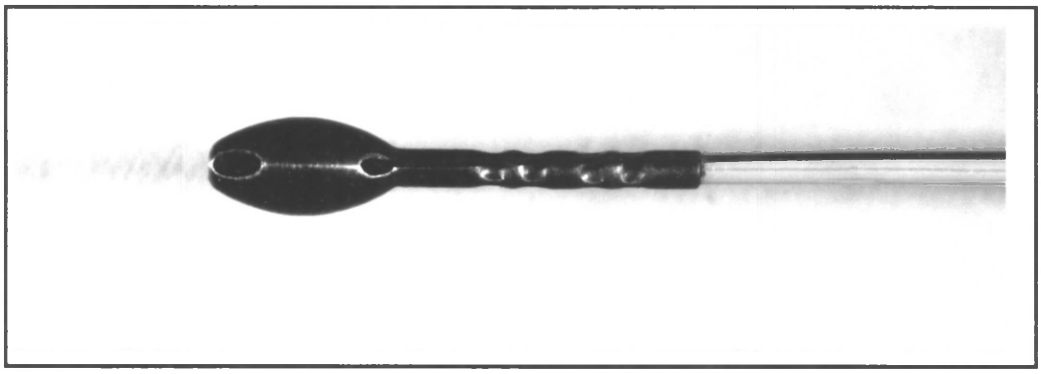
The initial temperature of the blood had no effect on the temperature developed at 3 seconds.

Table 5

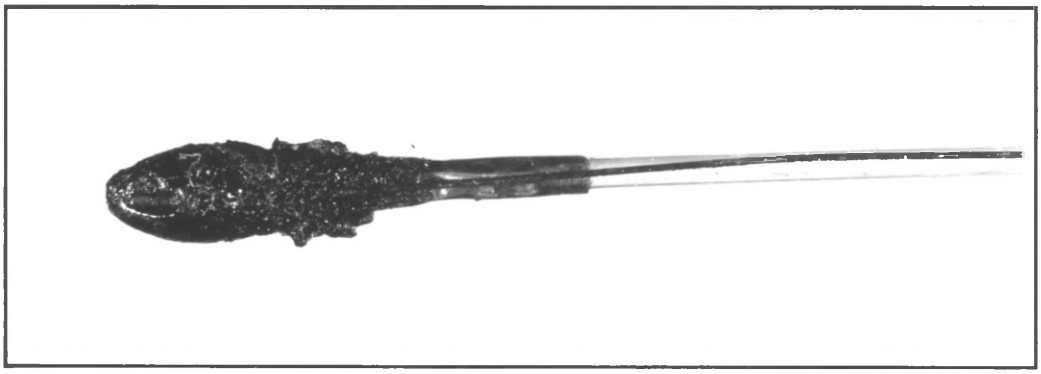
THE RELATIONSHIP BETWEEN BLOOD FLOW
AND POWER INPUT
ON THE TEMPERATURE OF THE METAL CAP

FLOW (ml/min)	POWER (Watts)	Temperature at 3 seconds (Degrees Centigrade mean ±SD)	
		Initial temp 22±1.1°C	Initial temp 39.7±1.5°C
Zero	4	113±18	132±21
	8	376±28	384±42
	12	488±63	494±52
10	4	150±28	141±31
	8	264±33	247±38
	12	504±56	519±47
20	4	139±32	151±24
	8	254±41	250±39
	12	496±78	489±55
40	4	96±21	113±23
	8	227±28	233±37
	12	509±59	470±65

New 2.0mm diameter metal-capped optical fibre



After 12 Watts x 9 seconds in blood



After 12 Watts x 9 seconds in blood, three times

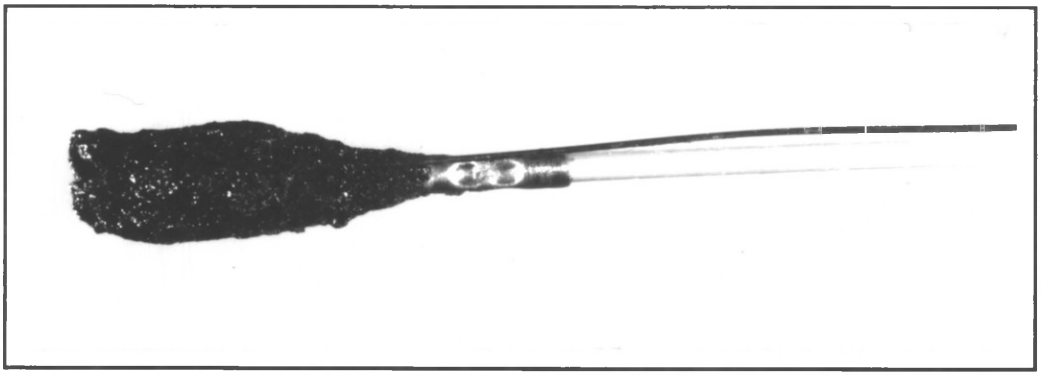


Figure 18

The three panels illustrate the formation of a coagulative coat following activation of the metal cap in a 3.12mm silicone tube during perfusion with blood flowing at 10ml/min .

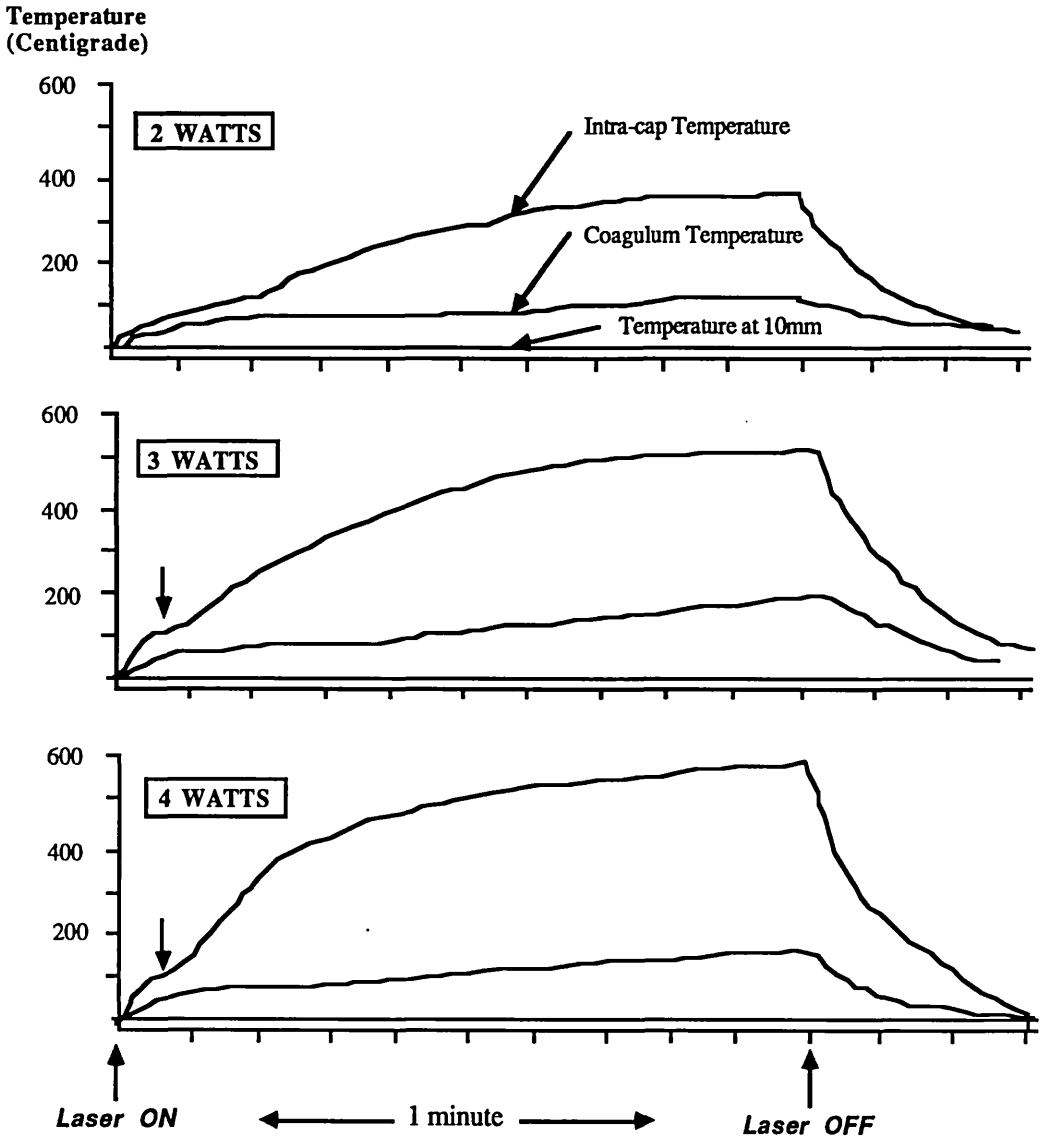


Figure 19

Three typical temperature traces obtained in blood during the pilot studies and reproduced for illustrative purposes to show the faster rate of rise and higher temperatures achieved with increasing power. Vertical arrows point to inflection points in the curves caused by vaporization of water at the surface of the metal cap.

Rate of cooling of the Metal cap in different perfusates

The rate of cooling in both saline and blood followed an exponential curve. A best fit curve for each study was computed and the temperature half-life calculated according to the following formula:

$$y = c + 10^{\lambda t}$$

$$\therefore t_{1/2} = {}^{\mathrm{Log}_{10} 2}/_{\lambda}$$

Where:

y = temperature

c = temperature at t = 0 secs

λ = temperature decay constant

t = time (seconds)

In the primary experiments the metal cap was heated in the circulating medium and then allowed to cool in that medium. In blood and plasma this resulted in the formation of an insulating coagulum around the metal cap resulting in a slower rate of cooling than in saline.

Three, problems arose from this design. Firstly, saline cooling curves could only be constructed within a narrow temperature range since in the presence of flow the temperature of the metal cap seldom exceeded 90°C. Secondly, if in the clinical setting recanalization were performed in saline then the hot metal cap emerging through a newly recanalized stenosis would be hotter than 100°C and would be followed by a gush of saline, possibly resulting in extremely rapid cooling. Thirdly, it is unlikely that the metal cap emerging from a recanalized stenosis would be covered with a thick, insulating coagulum. Furthermore, the cooling of the cap in blood may be sufficiently rapid to prevent the formation of such a coagulum.To overcome these reservations a further small study was conducted.

In this second study the clean metal cap enclosed in the same 3.12mm diameter silicone tube was heated in air using 12 Watts for 3 seconds to ensure a central cap temperature in the region of 600°C. Immediately after switching off the laser fluid (i.e. Blood or saline) at 10°C was pumped through the tube using a syringe pump. The runs were repeated 3 times at each combination of blood or saline at flow rates of 10, 20 and 40 ml/min. The central cap temperature was recorded as previously described every 0.2 seconds. Subsequent examination of the cooling curve allowed easy and accurate identification of the point at which the advancing face of fluid reached and engulfed the metal cap. A cooling curve was constructed from that point.

The small number of samples was unfortunately dictated by the attrition rate of the metal-capped optical fibres in a violently changing temperature environment.

The results are shown in Table 6.

In those studies which resulted in a coagulum around the metal cap the rate of cooling was flow dependent with a temperature half life of 3.95±0.4 secs at 10ml/min, 3.43±1.0 secs at 20ml/min and 2.59±0.6 secs at 40 ml/min. ($p < 0.05$). Although there was a tendency for more rapid cooling in the presence of blood at 20°C than at 38°C this was not statistically significant. However, in those studies where the cap was cooled with blood in the absence of an insulating coagulum cooling was significantly faster (Mean 3.23 vs 1.3 secs, $p<0.05$) with the half life ranging from 1.97 secs at 10ml/min, to 1.14 secs at 20ml/min and 0.89 secs at 40ml/min .

TABLE 6

Flow (ml/min)	Temperature Half-Life (Seconds) in Two Media		
	BLOOD		SALINE
	With Coagulum	*No Coagulum*	
10	3.95 ± 0.4	1.97 ± 0.6	0.185 ± 0.05
20	3.43 ± 0.8	1.14 ± 0.4	0.163 ± 0.03
40	2.59 ± 0.6	0.89 ± 0.3	0.139± 0.04
Mean Half-life	3.23	1.3	0.162

Cooling in saline was significantly faster than blood with or without an insulating coagulum. The temperature half life when cooling in saline was 0.185 secs at 10ml/min, 0.163 secs at 20ml/min and 0.139 at 40ml/min (Mean half-time: 0.162 secs). Given the small number of samples in the latter two groups the apparent effect of flow could not be confirmed statistically.

The results of these studies indicate that cooling of the metal cap is dependent on the perfusate and its flow rate, and in blood, the presence or absence of a coagulum coat.

Temperature characteristics in Plasma

The temperature profile of the metal cap in plasma was only examined in the absence of flow and is therefore not considered part of the original protocol.
Plasma was obtained by centrifuging fresh human citrated whole blood at 2400rpm for 10 minutes.The temperature profiles were measured under identical conditions to saline and blood as described previously.

At 4 Watts the temperature profiles observed were similar to those seen in blood, although the temperatures generated by 8 and 12 Watts were considerably and significantly lower than in blood. (See Table 7)

Table 7

THE EFFECT OF POWER INPUT ON THE CENTRAL CAP TEMPERATURE IN STATIC PLASMA

FLOW (ml/min)	POWER (Watts)	TEMPERATURE AT 3 SECONDS	
		Initial temp 23 ±1.3 °C	Initial temp 38.6±1.4 °C
Zero	4	103±21	115±23
	8	166±48	173±39
	12	374±95	359±74

Discussion

These results show that in laser systems employing metal-capped optical fibres the temperature of the metal cap is dependent on:

1. the power input,
2. the medium in which it is heated and,
3. the flow rate of the medium.

(1) Power is an important determinant of metal cap temperature, but the influence of power is significantly modified by the medium in which the metal cap is heated.

(2) The two most striking differences between the effects of saline and blood are:

(a) the inability of the metal cap to achieve temperatures in excess of 100°C in saline.

(b) the far higher temperatures generated in blood under equivalent conditions of power and flow

The fact that the metal cap does not generally reach temperatures greater than 100°C in saline is explained by heat dissipation due to the latent heat of vaporization of water. In contrast the results show that the probe temperature rises rapidly in blood reaching 500-600°C in about 3 seconds when 12 Watts are used. This is due to the formation of an insulating coagulum around the metal cap in the presence of blood (Fig. 18). The insulating coat is formed by the deposition of denatured plasma proteins on the surface of the probe which entrap blood elements and gases to produce a highly effective insulating coagulum (Fig. 20). Since this insulating envelope is formed by protein deposition which occurs from about 80°C, the initial temperature of the blood is of little consequence once deposition and insulation has begun.

(3) The effect of flow is different in saline and blood. Flow is an important determinant of temperature at all powers in saline. However this is not the case in blood. The temperatures generated in blood at powers of 8 Watts or greater are not related to blood flow. The reason for this is the formation of the insulating envelope around the probe at these powers. However, when only 4 Watts are used the envelope is less developed allowing greater transfer of heat into the surrounding fluid; the greater the flow the greater the heat transfer. It is interesting to note that the temperature achieved by the cap at 4 Watts in the presence of low blood flow (10ml/min) is higher than in static blood. This may be due to the fact that in the presence of limited flow the probe is in contact with more blood to provide a substrate for the formation of a coagulum. Furthermore, at low power (4 Watts) as flow increases so the temperature diminishes, possibly because at higher flows the cooling effect prevents the formation of such an effective insulating coagulum.

The coagulum

The insulating coagulum is an important issue if lasing is to be performed in blood. Some have argued that the layer could shield the vessel wall from excessive temperatures, but that as soon as the metal cap is forced against an obstruction the coat is disrupted or vaporised allowing direct contact with diseased tissue which in turn is vaporised.Thus the existence of such an envelope is potentially useful and consistent with the success of peripheral laser recanalization (Verdaasdonk, 1987). However, substantial protection of the arterial wall by the circumferential, insulating coagulum seems unlikely since during the pilot studies we found that the temperature of the coagulum itself may reach temperatures of >300^{o}C in the absence of flow, and it has been shown that aortic wall ablation occurs at 180^{o}C (Welch, 1987).

Furthermore, adherence of the probe to the vessel wall has been noted (Dr. D. Cumberland, Sheffield; Dr E. Deithrich, Arizona - personal communications). This

adherence can be overcome by a vigorous and sometimes aggressive to-and-fro motion within the vessel to free the metal cap. Although such a problem may not be detrimental within the relatively thick walled muscular arteries of the peripheral circulation it is potentially hazardous within thin walled coronary arteries, and thus the presence of a protein coagulum around the metal cap which may promote adherence is unlikely to be helpful in this setting. Indeed, the formation of such a coagulum might result in complete occlusion of the coronary artery which is not relieved when the metal cap is pulled back from the stenosis. Furthermore, the presence of an adherent coat gives concern over the possibility of distal embolization of potentially dangerous particulate material, or coagulative occlusion of neighbouring side branch origins.

These studies also shed some light on the nature of the insulating envelope. The similar temperature profiles in blood and plasma imply that deposition of denatured protein plays an important role in the genesis of the envelope. The temperatures generated by the metal cap are lower in plasma than blood. This implies that the insulation afforded by plasma proteins is not as effective as when blood cells are present. Recently, in an elegant study Verdaasdonk (1987) has demonstrated the presence of a gaseous layer between the envelope and the metal cap. This is further endorsed by scanning electron microscopy which reveals the spongelike nature of the coagulum (Fig. 20).

Given reservations about arterial adherence and thromboembolism in blood, the temperature characteristics of the metal cap in saline were also investigated. In a previous report from the inventor of the metal-capped optical fibre (Hussein, 1986), the temperature of a 1.5mm metal cap was measured in meat held in a saline bath. With a continuous power input of 9 Watts the temperature reached about 400^{o}C after 15 seconds. Continuous advancement allowed creation of a new channel through the meat confirming that temperatures sufficient to ablate tissue could be achieved and that the presence of saline did not prevent attainment of such temperatures once the tissue and metal cap were

Our studies revealed that the *mean* temperature of the cap never exceeded 100°C although intermittent sharp peaks of up to 120°C could be identified on the plateau and were associated with steam bubble formation. Such was the efficiency of saline at removing heat from the metal cap that at a flow rate of only 10ml/min the mean plateau temperature did not exceed 90°C at 12 Watts. Clearly, below 100°C the temperature attained was influenced by the ambient temperature of the circulating saline.

One major concern about the use of saline as a perfusate was whether there was a risk of hot or even boiling saline passing downstream causing diffuse damage to endothelium. The results of our studies indicate that this is not a problem. Even when the metal cap was heated to 470°C prior to being flushed with saline at only 10ml/min the temperature recorded 10mm downstream rose only 15°C .

Currently, metal-capped optical fibres are used percutaneously through blood in the peripheral circulation. In the coronary circulation the percutaneous application of these fibres will of necessity be through blood, while the peroperative approach allows a choice of perfusate. The two main contenders for the perfusate of choice are blood and saline. Consequently the data presented are of considerable relevance to the in vivo recanalization of stenosed or occluded coronary arteries.

The results of this study prompted further investigation into the potential for embolization from the coagulum (Chapter 6).

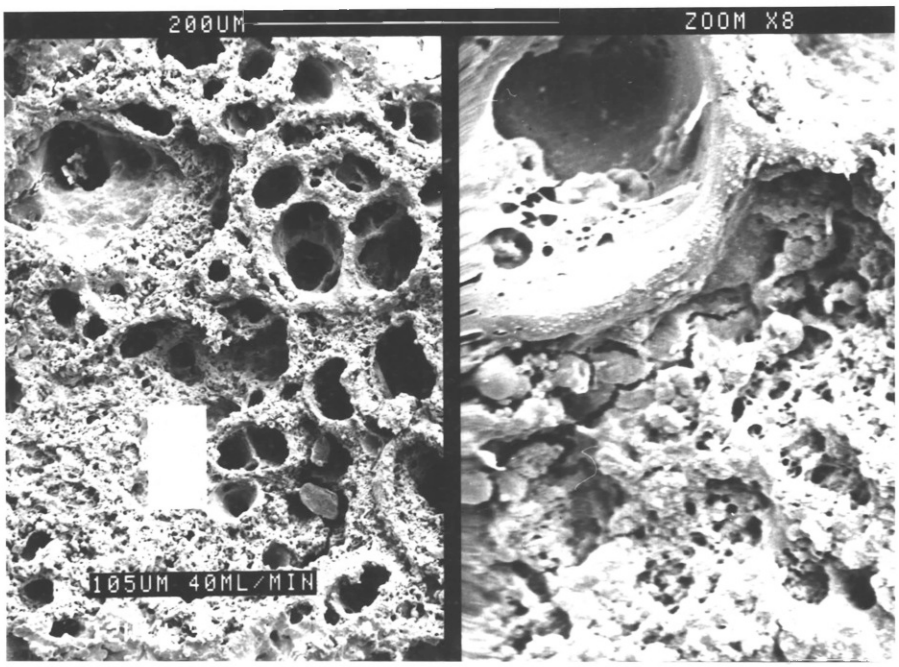


Figure 20

A scanning electron micrograph of the inner surface of the coagulum scraped off the metal cap. The 200μm scale refers to the left hand panel which illustrates the sponge-like nature of the coagulum. The area within the white rectangle is shown as a x8 zoom in the the right hand panel which shows a largely amorphous structure punctuated with gas bubbles and deformed cellular elements.

CHAPTER 6

An Assessment of the Potential for Thromboembolism

Introduction and Aims

Laser energy delivered in blood through bare optical fibers at energies sufficient to vaporize atherosclerotic tissue does not produce significant debris. However, the potential for metal-capped optical fibres to produce debris from the formed elements of the blood is undocumented.

The aim of this study was to assess the amount of debris formed by lasing fresh human arterial blood with a metal-capped optical fibre in an in vitro system simulating a human artery.

Materials and Methods

Blood

Fresh human heparinized blood obtained from the oxygenator of a cardiopulmonary bypass circuit during open heart surgery was used. The blood was centrifuged at 2400rpm for 10 minutes and the resultant packed red cells were rediluted with the same plasma to ensure a final haematocrit of 35%. Oxygen saturation ranged between 95% and 98%.

In vitro system

A 10cm long silicone tube with an internal diameter of 3.12mm was used to simulate a human artery. A 2mm metal capped optical fibre was advanced through a valved adaptor into the silicone tube. Blood was infused at constant flow through the side arm of the adaptor using a syringe pump (Sage Instruments Model 367, Cambridge, Massachussets). The blood flowed within the tubing around the metal cap and was then filtered by a series of 5 in-line stainless steel filters of decreasing size (225μm, 105μm, 70μm, 45μm and 25μm) contained in a filter housing connected to the distal end of the tube (Fig. 21)

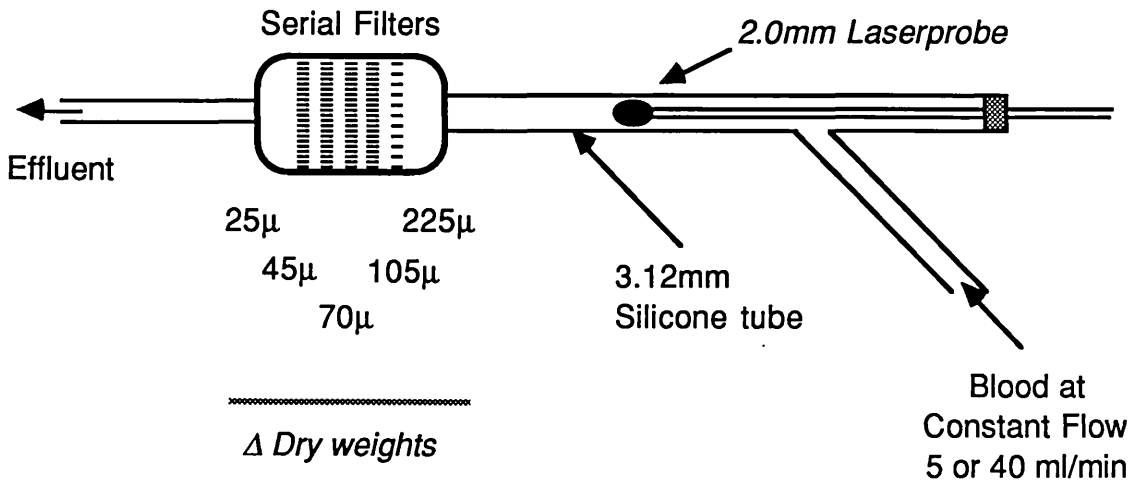


Figure 21: Diagram showing the in-vitro filtration system used to assess debris formation from blood following delivery of laser energy through metal-capped optical fibres.

Lasing Protocol

Argon laser pulses of increasing powers (4 Watts, 8 Watts and 12 Watts as measured at the laser head) and of increasing durations (3 secs, 6 secs and 9 secs) were used. Aliquots of 10ml of blood were infused through the silicone tube at a constant rate of either 40ml/min or 5 ml/min and the laser pulse delivered during the passage of blood. After each lasing the filters were removed and a new set of pre-weighed filters were installed in the filter housing.

For each flow rate blood was lased using the 9 possible combinations of power and pulse duration; a 10th (control) sample was obtained by passing the blood through the silicone tubing in the presence of the metal cap but without delivering laser energy. Following a run of 10 samples the debris adherent to the metal cap was scraped off with a scalpel, dried in air for 48 hours and then weighed. The tubing system and metal cap were rinsed with saline prior to the next run. A total of 10 runs were performed at each flow rate. The 9 combinations of power and pulse duration, together with the control were incorporated into a Latin square for subsequent statistical analysis (Fig 22).

A = 3sec . 4Watts
B = 6sec . 4Watts
C = 9sec . 4Watts
D = 3sec . 8Watts
E = 6sec . 8Watts
F = 9sec . 8Watts
G = 3sec . 12Watts
H = 6sec . 12Watts
I = 9sec . 12Watts
K = 0sec . 0 Watts

LATIN SQUARE

A	B	C	D	E	F	G	H	I	K
B	C	D	E	F	G	H	I	K	A
C	D	E	F	G	H	I	K	A	B
D	E	F	G	H	I	K	A	B	C
E	F	G	H	I	K	A	B	C	D
F	G	H	I	K	A	B	C	D	E
G	H	I	K	A	B	C	D	E	F
H	I	K	A	B	C	D	E	F	G
I	K	A	B	C	D	E	F	G	H
K	A	B	C	D	E	F	G	H	I

Figure 22: The Latin square designed for nine combinations of power and time plus a control.

Sample Analysis

Filters were washed in saline and in alcohol, allowed to dry for 24 hours, pre-weighed on a Mettler microbalance (E. Mettler, Zurich) and mounted in the filter housing. Following debris collection the filters, still contained in the filter housing were flushed with 10ml of saline followed by 10ml of pure ethanol at 40ml/ minute. The filters were then removed from the housing, dried for 24 hours and reweighed to assess the amount of debris entrapped.

For qualitative analysis 2 further lasings were performed at 12 Watts for 9 seconds at flow rates of 5 and 40 ml/min. Following lasing the filters were immediately flushed with Karnovsky solution to fix the debris to the filter and preserve morphology. These filters were critically point dried with CO_2 after dehydration to pure ethanol, then splutter coated with colloidal gold and examined with a Cambridge S200 scanning electron microscope.

Statistical analysis was performed using one and two-ways (including repeated measures) analysis of variance in order to assess the effect of power, time, flow and repetitive lasing on debris formation. Comparisons between the debris produced at specific laser energies and that produced by control samples were performed using the Wilcoxon signed rank test with 95% confidence limits. A 'p' value <0.05 was considered to be significant. All the results throughout the text and figures are expressed as mean $\pm$ 1 SEM.

Results

Quantitative analysis

The weight of coagulum scraped off the metal cap after each run ranged from 4.25 to 5.35mg (mean 4.8±0.21) (See Fig 23)

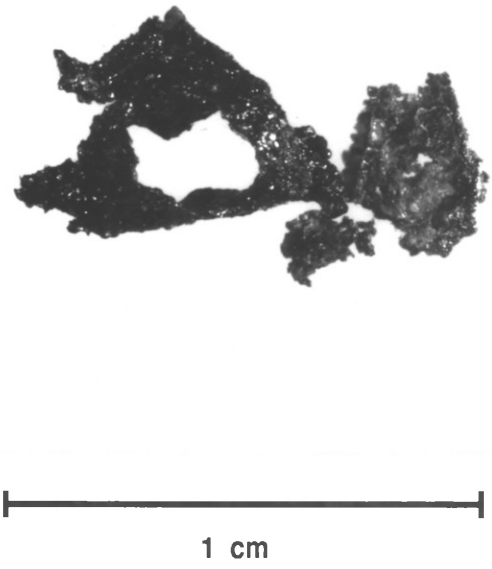


Fig 23: A typical coagulum cast scraped off the metal cap following exposure in blood. This specimen weighed 5.08mg

At high blood flow the delivery of laser energy resulted in significant debris formation compared to controls at all combinations of power and time. The difference in total debris weight between lased and control samples ranged from 36±16μg ($p<0.05$) at 4 Watts for 3 seconds up to 89±19μg ($p<0.001$) at 12 Watts for 9 seconds. At low blood flow the difference in debris weight between lased and control samples was not significant at 4

Watts (6±14μg) and at 8 Watts for 3 seconds (8±18μg). This difference was significant for the remaining combinations of power and time up to a maximum of 198±35μg ($p<0.001$) at 12 Watts for 9 seconds. The amount of debris captured by the 225μm and 105μm filters paralleled the pattern observed for total debris. The debris captured by the smaller filters was not significantly different from control in all cases but one (12 Watts for 9 seconds).

The experimental design, based on a Latin square, allowed further analysis to establish the relative influence of power, time, flow and repeated measurements with the same fibre on debris formation. At high blood flow power did not significantly influence the amount of total debris formation (337+169μg at 4 Watts, 358+130μg at 8 Watts, 371±151μg at 12 Watts), while it was largely time-dependent (306±138μg at 3 seconds, 355±153μg at 6 seconds, 406±159μg at 9 seconds, $p<0.02$). At low flow both power (230±41μg at 4 Watts, 323±48μg at 8 Watts and 461±63μg at 12 Watts, $p<0.001$) and time (266±48μg at 3 seconds, 345±52μg at 6 seconds and 402±53μg at 9 seconds, $p<0.001$) significantly influenced debris formation. The amount of debris formation at 4 Watts was significantly higher at high flow than at low flow (337±56μg and 230±41μg, respectively, $p < 0.05$). No significant difference, however, was found at 8 or 12 Watts.

Repetitive lasing

Two-ways analysis of variance showed that repetitive lasing did not significantly affect debris formation.

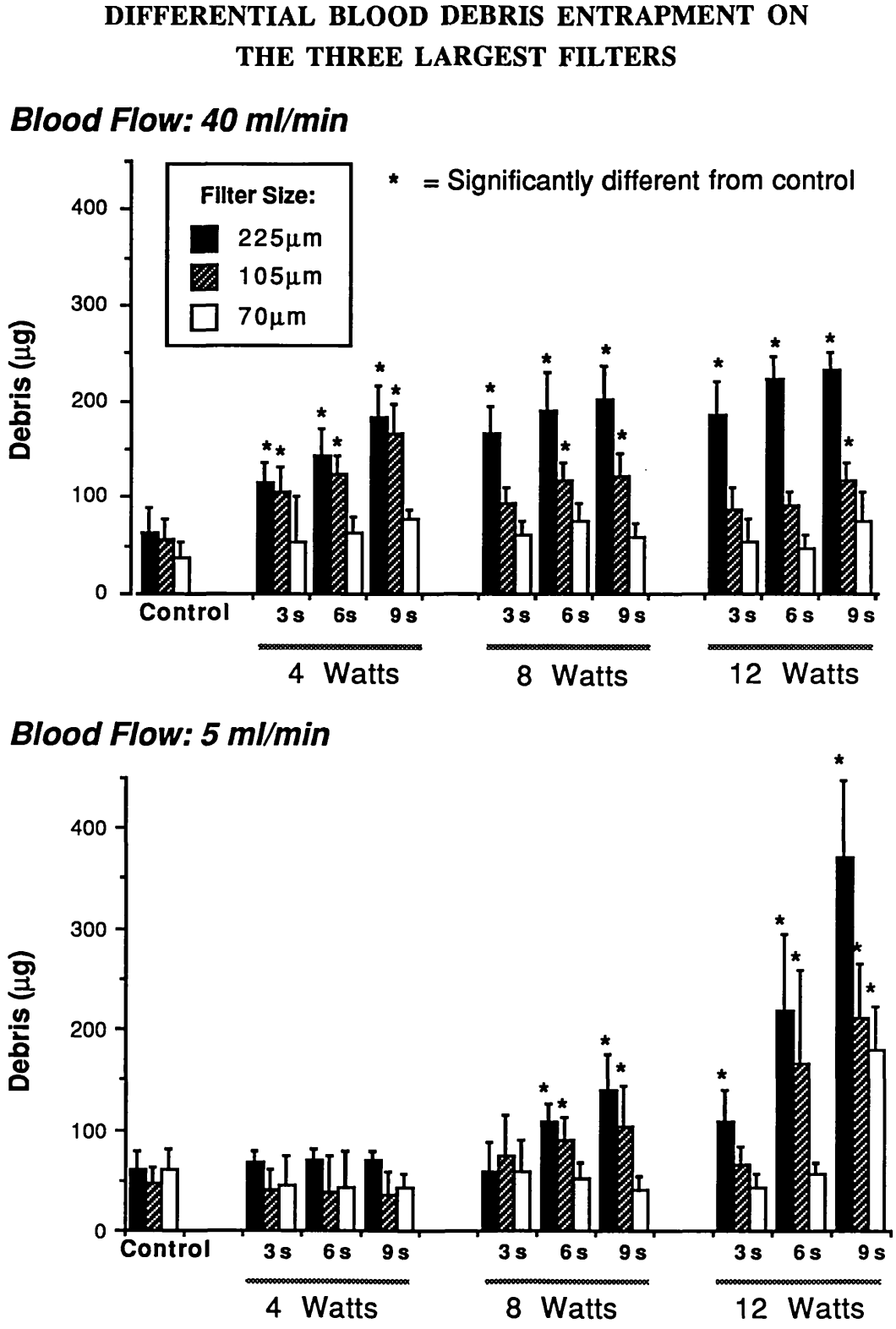


Figure 24: These graphs show the amount of debris collected on the filters following delivery of laser pulses of varying combinations of power and time at two flow rates.

TABLE 8: EFFECTS OF POWER AND TIME ON DEBRIS FORMATION AT TWO FLOW RATES
by Repeated Measures Analysis of Variance

FILTER	5ml/min			40ml/min		
	POWER	*TIME*	Power/Time Interaction	*POWER*	*TIME*	Power/Time Interaction
225μm	p<0.001	p<0.001	p<0.001	N.S.	p<0.005	N.S.
105μm	p<0.001	p<0.05	N.S.	N.S.	N.S.	N.S.
70μm	p<0.001	p<0.001	p<0.01	N.S.	N.S.	N.S.
45 & 25μm	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
TOTAL DEBRIS	**p<0.001**	**p<0.001**	**p<0.05**	**N.S.**	**p<0.02**	**N.S.**

This table illustrates that at 5ml/min total debris formation is significantly increased by both power and time.
The significant interaction between these two variables indicates a synergistic effect.
At 40ml/min only time significantly affects debris formation

(N.S. = Not Significant)

Table 9

THE EFFECT OF FLOW ON DEBRIS FORMATION AT DIFFERENT POWERS

by Repeated Measures Analysis of Variance

POWER	*DIFFERENCE BETWEEN FLOW RATES*	*POOLED TIME EFFECT*	*FLOW/TIME INTERACTION*
4 Watts	P<0.05	p<0.02	P<0.05
8 Watts	N.S.	p<0.005	N.S.
12 Watts	N.S.	p<0.001	p<0.002

This table shows that debris formation was significantly affected by flow at 4 Watts. In addition, time had a significantly different effect on debris generation between the two flow rates at 4 and 12 Watts.

(N.S. = Not Significant)

Qualitative Analysis

Scanning electron microscopy at low magnification of the debris entrapped by the 225μm filter following lasing with 12 Watts for 9 seconds showed the presence of large, friable conglomerates. Their size in some instances was in excess of 1mm (Fig. 25).

High magnification revealed that these conglomerates were composed mainly of erythrocytes at varying stages of denaturation embedded in a protein matrix. Thermal damage to the erythrocytes was characterised by swelling, by membrane fragmentation to form sub-cellular vesicles and by membrane fusion to form a complex three-dimensional meshwork (Figs.26-27).

The debris on the 105μm filters was smaller, showed less evidence of thermal damage and was composed mainly of clusters of spherocytes in the protein matrix (fig 25).

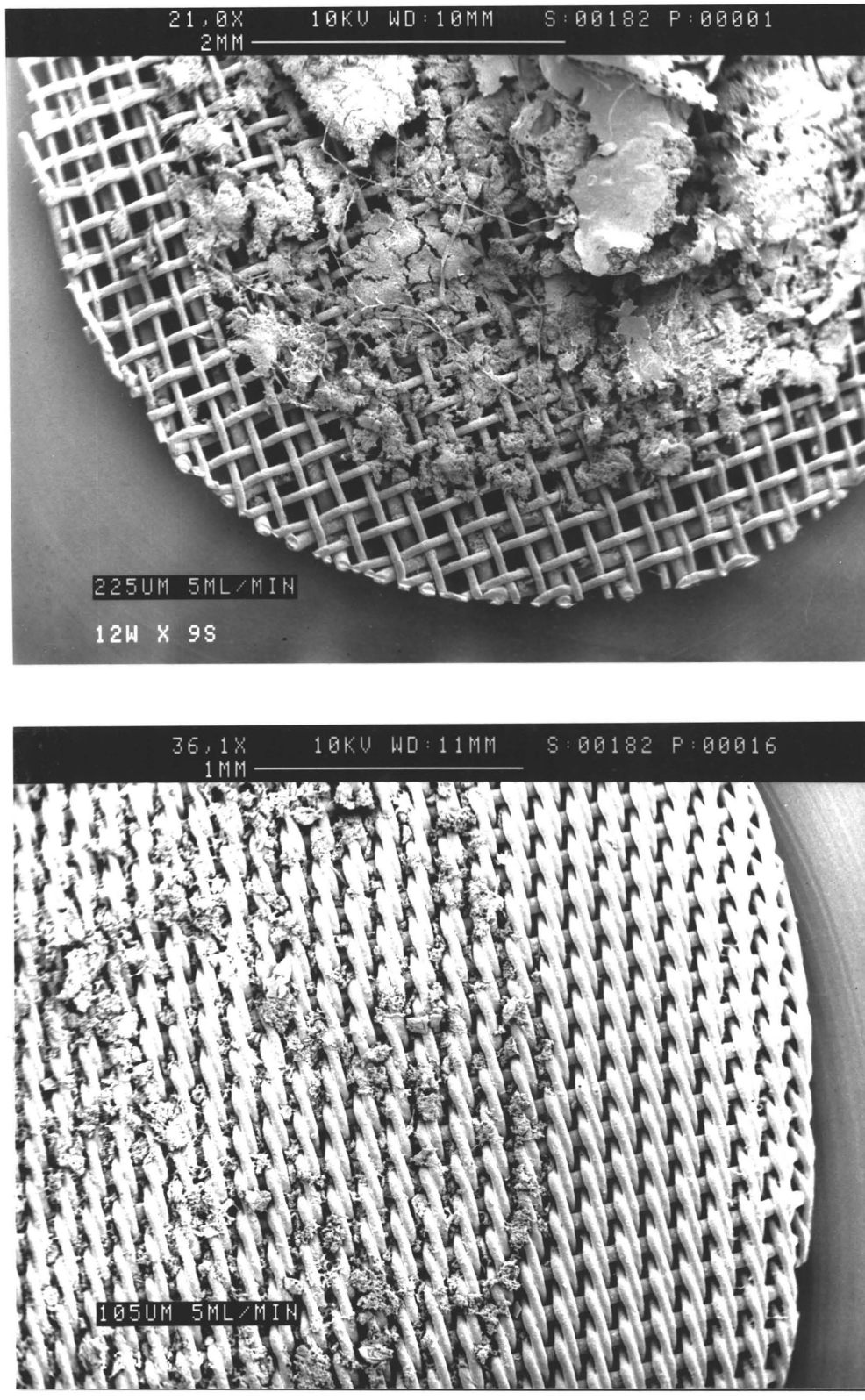


Figure 25: The upper scanning electron micrograph shows typical debris collected on a 225µm filter following lasing at 12 Watts for 9s. **The lower panel** shows a 105µm filter following the same exposure

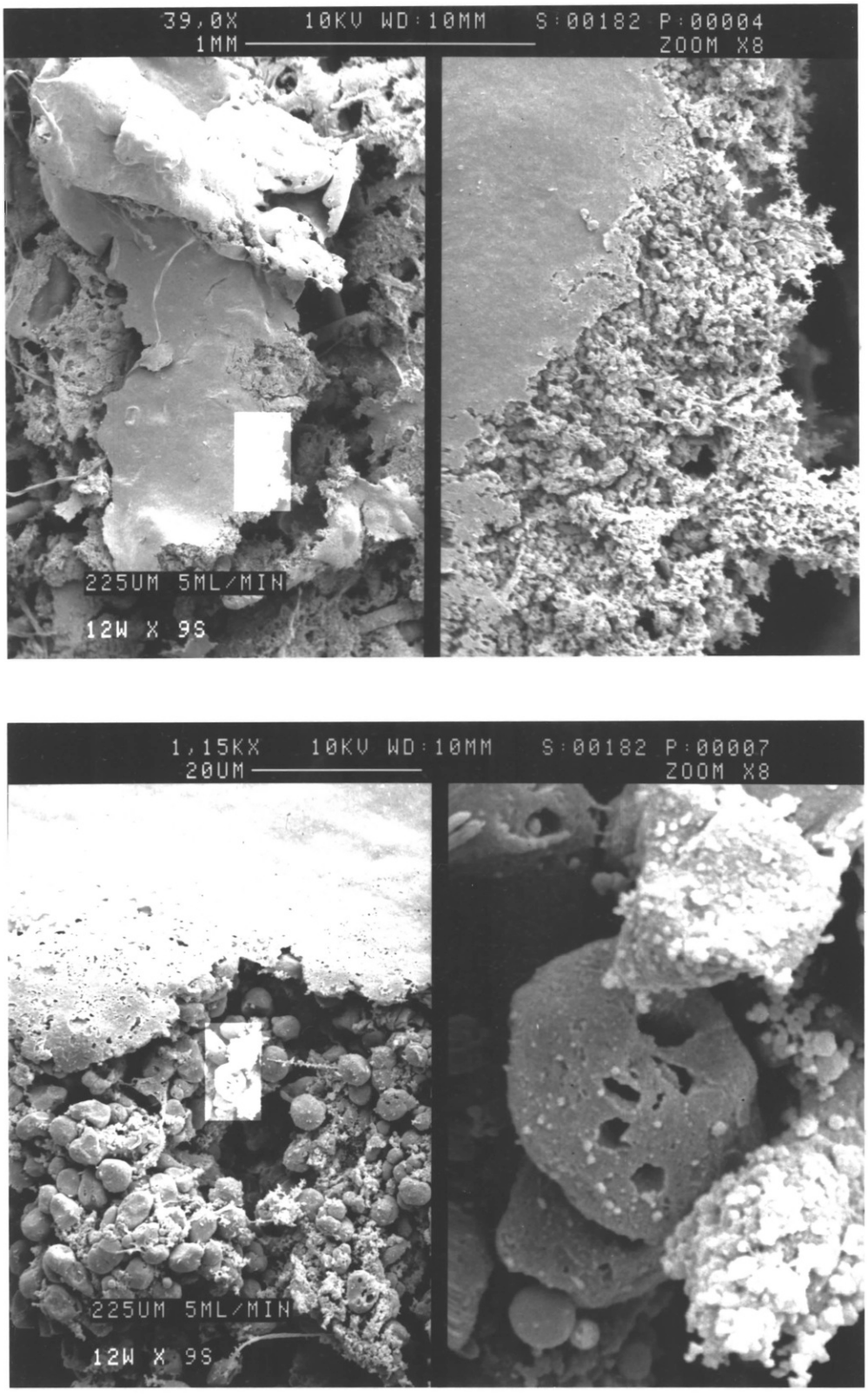


Figure 26: Electron micrographs illustrating the heterogeneous nature of the thromboembolic conglomerates. Red cells at varying stages of denaturation are incorporated into a complex, disorganised matrix. In each micrograph the scale line in the upper bar refers to the left panel and the right panel is a x8 zoom of the area within the white rectangle

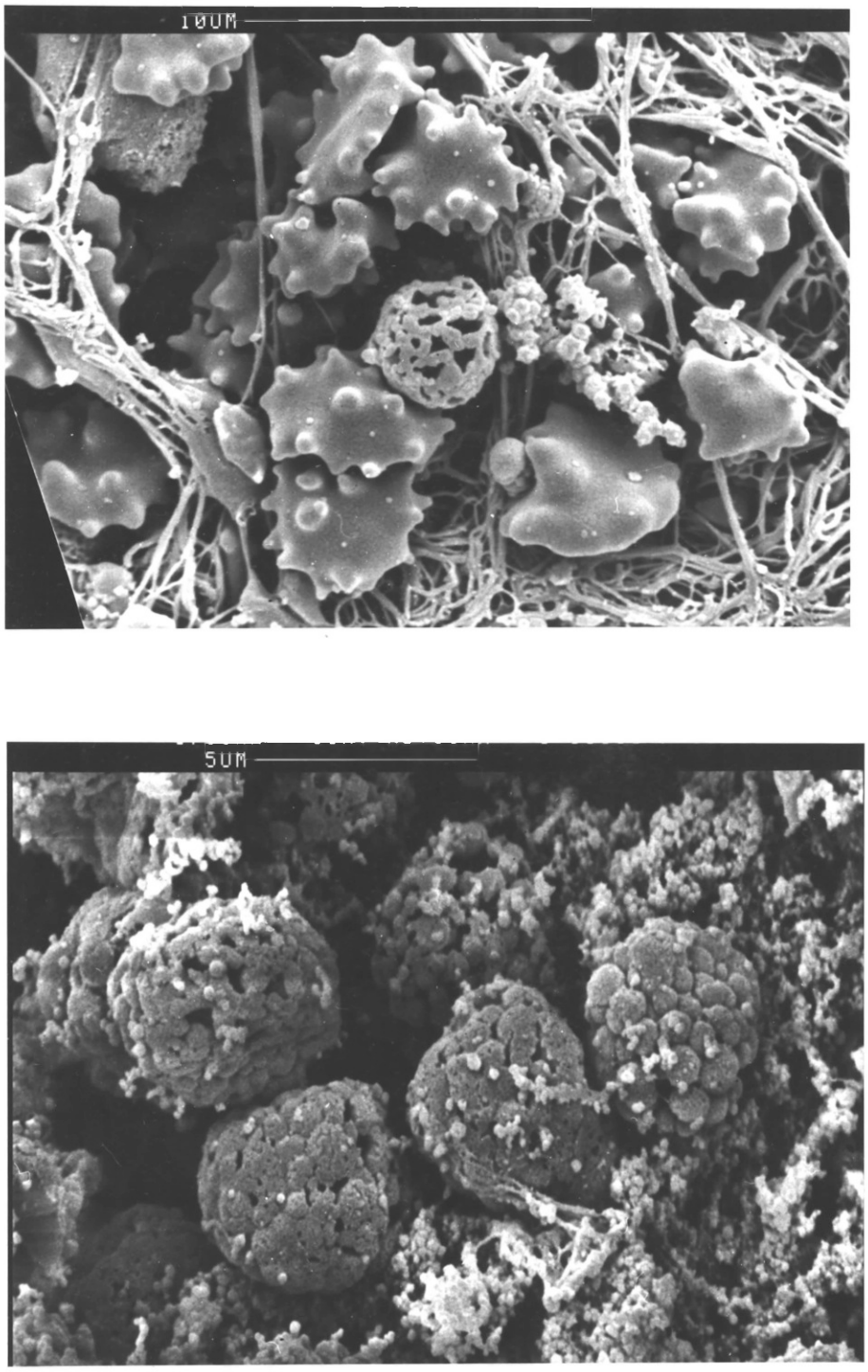
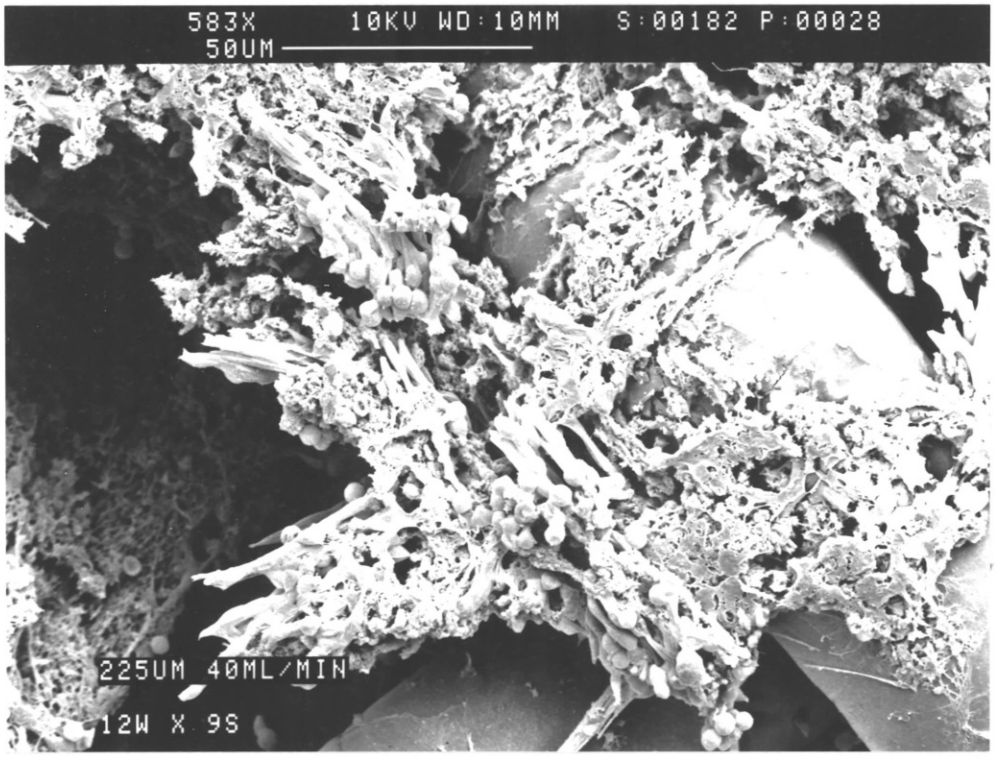


Figure 27: Both panels illustrate a spectrum thermally induced changes to erythrocyte morphology: vesicles are seen on the surfaces of spherocytes and anisocytes, these conglomerate into spherical forms of similar dimensions to the parent cells.



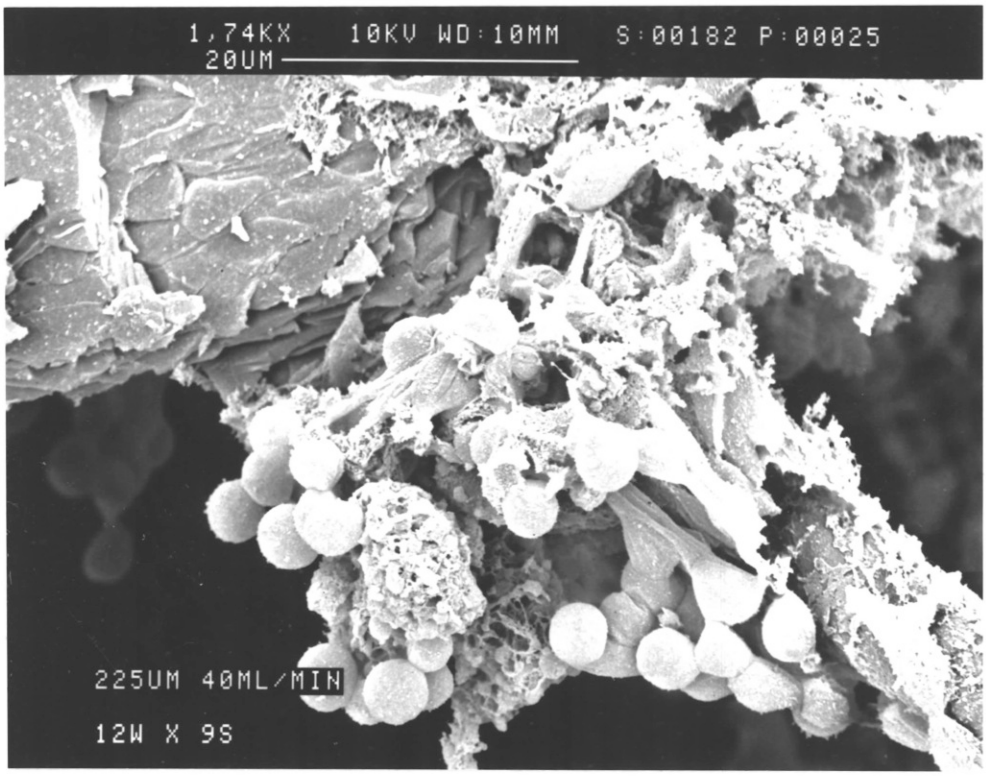


Figure 28: In some areas a membranous web is apparent which appears to be composed of fused cell membranes. In other areas the membranes take on a slate like appearance.

Discussion

This study demonstrates that laser energy delivered in blood through metal-capped optical fibers can generate significant amounts of cellular debris. At a low flow rate significant debris formation was observed only for powers of 8 Watts or higher, whereas at high flow rate this occurred at a power as low as 4 Watts. The fact that significantly more debris was generated at 4 Watts at higher blood flow is rather intriguing as more heat dissipation ought to occur under these circumstances. It is conceivable, however, that when low powers are used only at high flow rates does enough blood come into contact with the metal cap to generate debris detectable with our methodology. This reasoning is supported by the observation that, within the range of exposure times and powers selected for this study, at low flow the amount of debris was predominantly power dependent, whereas at high flow debris formation was predominantly time dependent.

Examination under the scanning electron microscope of the debris produced by lasing at 12 Watts for 9 seconds showed that large fragments (up to 2mm in diameter) can form when these high energies are used. The morphologic changes were similar to those observed following the delivery of laser energy through bare fibers (Crea, 1985). The heat produced by the metal cap caused coagulation of blood proteins to form sponge-like conglomerates. Membrane denaturation of red blood cells was also observed; this resulted in the formation of crenated cells and spherocyte formation probably due to an increase in membrane fluidity (Ahkong, 1973). Higher degrees of thermal damage were characterised by membrane fragmentation to form small vesicles and by membrane fusion which gave origin to a complex three-dimensional meshwork in which erythrocytes were no longer easily recognisable.

In the clinical situation the observed in-vitro effects may be modified. On the one hand, in the presence of a severe stenosis or total arterial arterial occlusion the metal cap is only

partially exposed to blood reducing the potential to form debris. On the other hand, contact of the metal cap with the stenosis may provoke dislodgement of debris adherent to the cap. Despite these limitations our results provide reference values for the maximum energy which can safely be used in the clinical setting without causing significant formation of cellular debris larger than 25μm. Although the physiological relevance of the debris found in this study is difficult to assess it is likely that, at least in the coronary circulation, it may be detrimental. The importance of using energies which do not provoke debris formation is highlighted by the inference that this is also likely to reduce haemolysis and the consequent release of ATP which could trigger platelet aggregation and thrombus formation.

In conclusion, using 2mm metal-capped fibers, argon laser pulses of not more than 8 Watts for 6 seconds should be employed in patients in order to minimise the risk of thromboembolism.

A possible alternative approach to avoid this problem is the delivery of laser energy during arterial flush with saline.

CHAPTER 7

An Assessment of the Efficacy of Atheromatous Plaque Ablation with Special Reference to Embolization

Introduction and Aims

Laser angioplasty offers the potential for removing atheromatous plaque, rather than simply remodelling it, as with balloon angioplasty. However, the possibility exists that plaque subjected to laser thermal angioplasty may fragment and produce distal atheromatous emboli within the coronary circulation. Such plaque embolisation is negligible following balloon angioplasty (Block,1982).

The aim of this study was to assess the ability of metal-capped optical fibres to vaporise the atherosclerotic plaque and to assess quantitatively and qualitatively any debris released during this process.

Material and Methods

In vitro System

Twenty fresh endarterectomy specimens removed from the right coronary artery of twenty patients undergoing coronary bypass surgery were collected. These were frozen in liquid nitrogen and stored at -80°C. Two hours before the experimental use the specimens were thawed at room temperature and then divided into 4 segments of similar length (ranging between 1cm and 1.5cm) which were immersed in 0.9% saline. Immediately prior to lasing each segment was removed from saline and excess water eliminated using filter paper. The specimen was then weighed with a microbalance (E. Mettler, Zurich) and fitted into a 5cm long silicone tube with an internal diameter of 3.12mm.

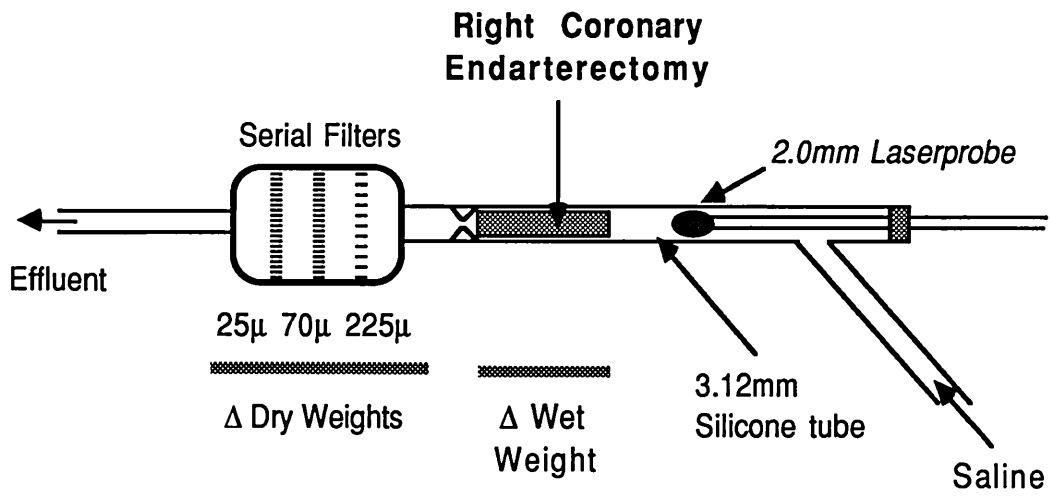


Figure 29: Diagram of the filtration system used to collect debris during lasing of human coronary endarterectomy specimens

Lasing protocol

An in-vitro system similar to that employed in the thromboembolism study was used. However, in this experiment a segment of human endarterectomy core was mounted in the silicone tube. Progression of the segment within the tube was prevented by a distal snare around the tube. The system was primed with 0.9% saline and the metal-capped fibre was advanced through a valved adaptor into the silicone tube. Three of the 4 segments from each of the endarterectomy specimens were exposed to laser pulses of powers of 4, 8 and 12 Watts for exposure times of 10 or 20 seconds. The remaining segment from each specimen was manipulated in the same way for the same period but without the delivery of laser energy and used as a control. During each lasing the metal cap was advanced to ensure maximal contact with the specimen. Following the delivery of each laser pulse the saline priming solution was filtered under gravity through a filter housing containing 3 in-line pre-weighed filters of decreasing pore sizes of 225μm, 70μm and 25μm. Each segment was then removed from the silicone tube; the tube was rinsed with 10ml of saline which was also filtered. The filters were removed from the filter housing, dried for 24 hours and reweighed to assess debris formation.

The weight and length of each endarterectomy segment were measured under identical conditions to those used prior to lasing; changes in weight and length were used as an index of the efficacy of laser ablation.

For morphological analysis 2 further specimens were lased at 12 Watts for 10 and 20 seconds. The effluent was filtered using a single 25μm filter which was immediately flushed with Karnovsky solution to fix the debris to the filter and preserve morphology. These filters were critically point dried with carbon dioxide after dehydration with pure ethanol and splutter coated with colloidal gold for examination under a scanning electron

microscope (Cambridge S2000).

Weight and length of specimens before and after treatment were compared using t-test for paired samples. The effects of different powers were compared using t-test for unpaired samples and analysis of variance, as appropriate. Values of $p<0.05$ were considered significant. All values are expressed as mean ± 1SD.

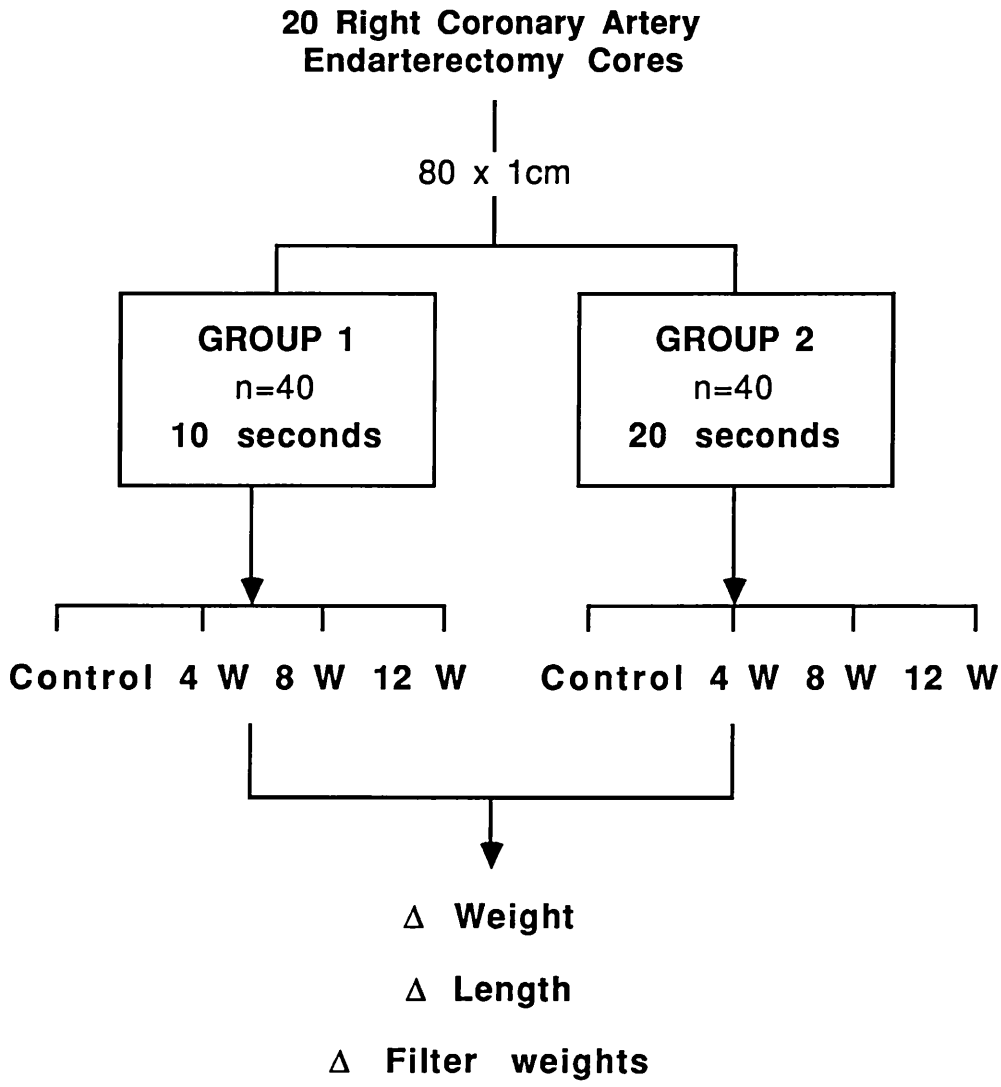


Figure 30: Diagrammatic representation of protocol

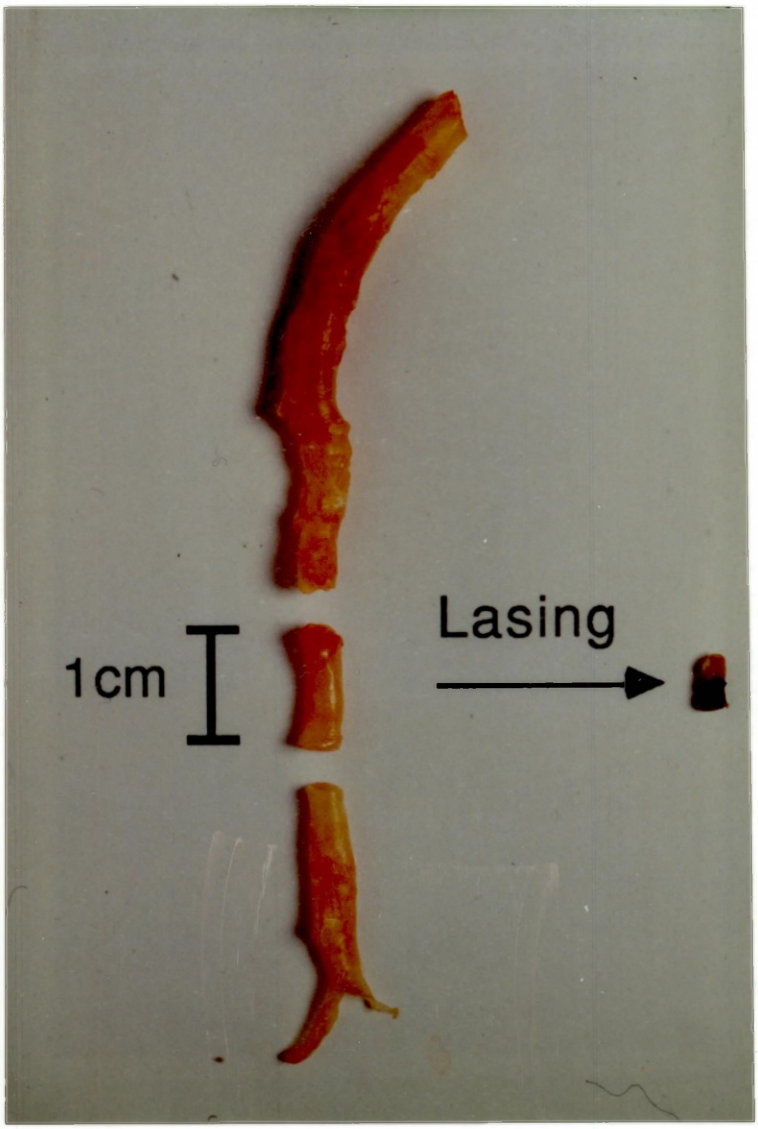


Figure 31

A photograph illustrating the effect of lasing a 1 cm endarterectomy segment using 12 Watts for 20 seconds.

Results

Effect of lasing on endarterectomy specimens

A total of 60 endarterectomy segments were lased (30 for 10 seconds and 30 for 20 seconds) and a further 20 segments were used as controls (10 for 10 seconds and 10 for 20 seconds). The weight of endarterectomy segments prior to lasing was 112 ± 74mg. Weight loss was more in lased segments than in controls (23 ± 14mg vs 5.4 ± 2.3mg, respectively, $p<0.001$) and was significantly more with laser pulses of longer duration (29 ± 16mg at 20 seconds vs 17 ± 6mg at 10 seconds, $p<0.001$). For each exposure time the effect was power-dependent; changes in weight at 4, 8,12 Watts for laser pulses of 10 and 20 seconds were 12 ± 2mg, 14 ± 4mg and 23 ± 6mg, respectively ($p<0.001$) and 16 ± 7mg, 28 ± 16mg, 42 ± 13mg, respectively, ($p<0.001$) (Fig. 33). Changes in length of endarterectomy segments paralleled changes in weight (Fig. 32).

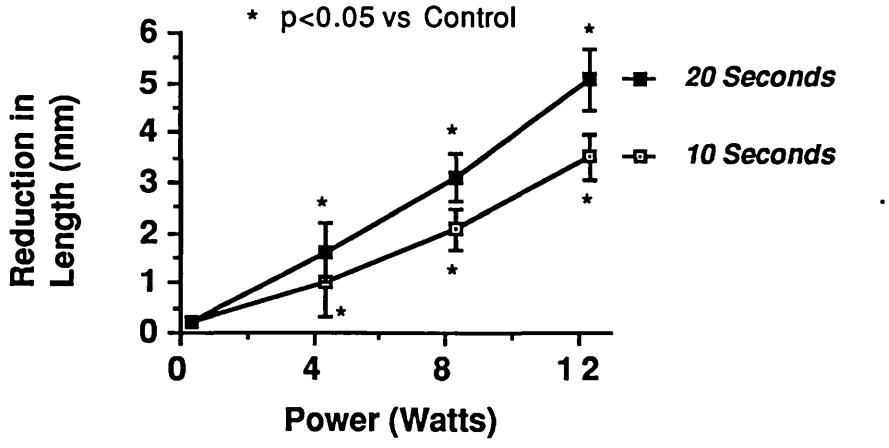


Figure 32: The graph shows increasing reduction in length of the specimens with increasing power. All combination of power and exposure time resulted in significant length reductions compared to controls.

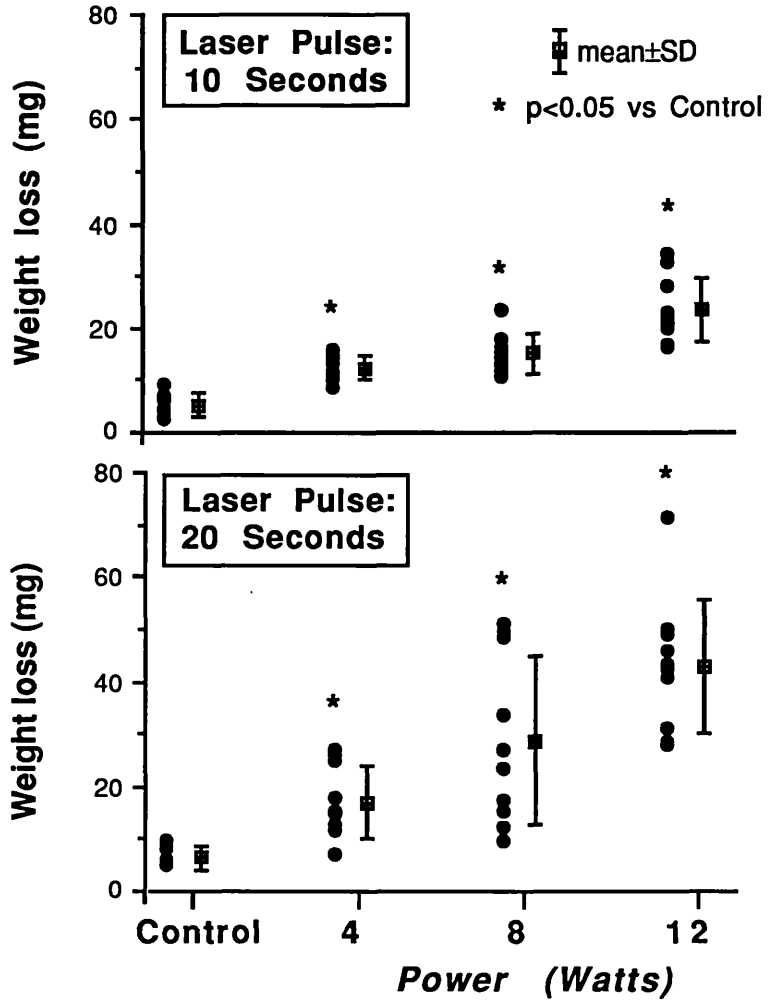


Figure 33:

The graphs show the effect of lasing with metal capped optical fibres on the weight of coronary endarterectomy specimens using powers of 4,8 & 12 Watts for exposures of 10 and 20 seconds. Each dot represents the weight loss of a single specimen following lasing. All combinations of power and exposure produced significant weight loss compared to similarly manipulated, non-lased control specimens.

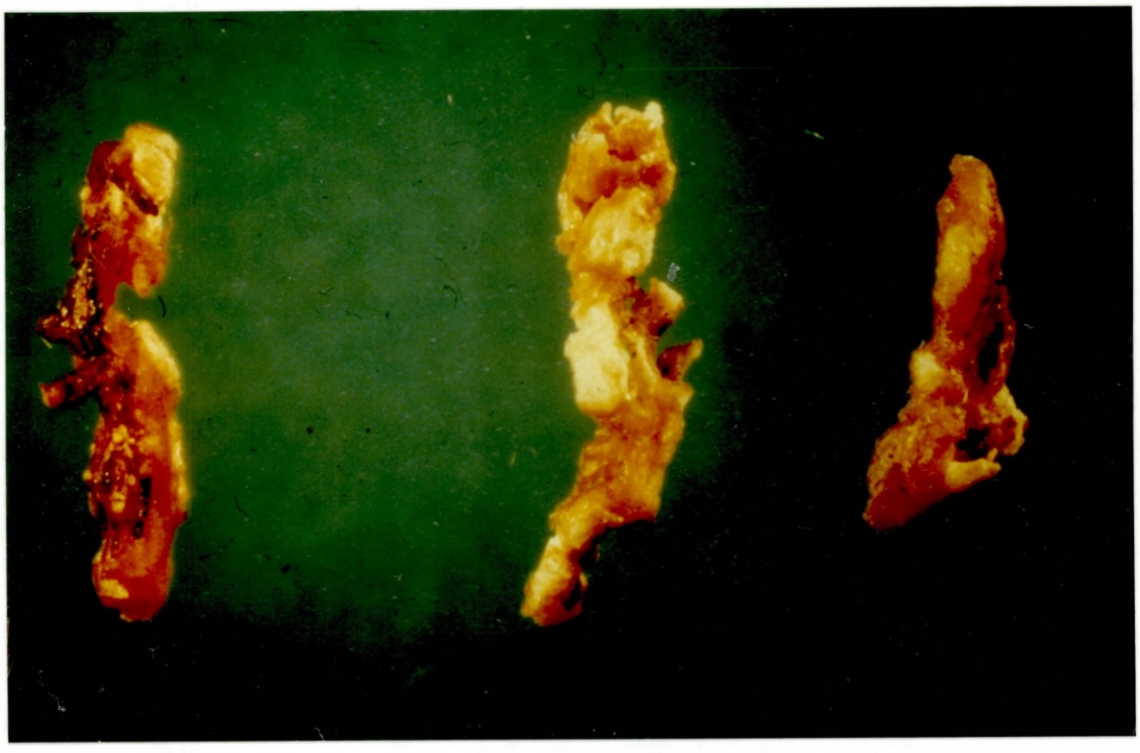


Figure 34

Three residual coronary artery endarterectomy segments after lasing with a metal-capped optical fibre using 12 Watts for 9 seconds. The segments have been reduced from 1.0cm to approximately 0.5 cm in length following lasing. The white areas are foci of discrete, thermally resistant calcification which have deflected the metal cap along the course indicated by the charring.

Debris formation during lasing

1. The total debris entrapped by filters following delivery of laser energy was significantly greater than that generated by control specimens : 275±116μg vs 155 ± 65μg, respectively ($p<0.005$). Laser pulses of longer duration produced significantly more debris (303 ± 144μg at 20 seconds vs 232 ± 53 μg at 10 seconds, $p<0.02$).

2. For each exposure time the debris generated was not power-dependent: total debris at 4,8,12 Watts for laser pulses of 10 seconds was 233 ± 71μg, 234 ± 56μg, 245 ± 35μg, respectively (p NS). Similarly total debris at 4,8,12 Watts for laser pulses of 20 seconds was 262 ± 98μg, 314 ± 203μg, 334 ± 116μg, respectively (p NS) (See fig. 35).

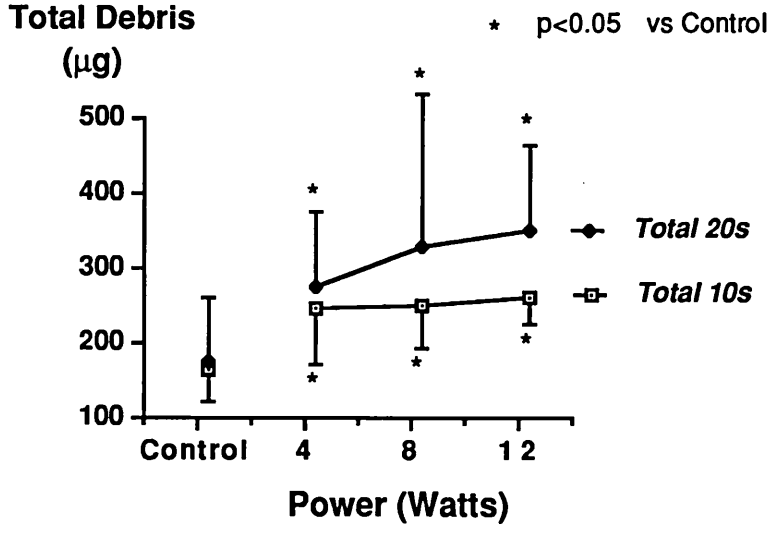


Figure 35.

This graph shows the total debris generated during lasing with metal-capped fibers of human coronary endarterectomy specimens. All combinations of power and exposure time resulted in significant debris formation compared to control specimens.

3. During lasing at 12 Watts significantly more debris was entrapped by smallest filters for both exposure times of 10 seconds (107 ± 20μg on 25μm filters, 63 ± 27μg on 70μm filters, 75 ± 26μg on 225μm filters, $p<0.02$) and 20 seconds (144 ± 68μg on 25μm filters, 81 ± 38μg on 70μm filters, 93 ± 36μg on 25 μm filters, $p<0.002$). These differences were not significant for powers of 4 and 8 Watts
(Tables 10 and 11).

4. Debris weight represented only a negligible fraction of the total weight loss of the endarterectomy specimens (1.4 ± 0.4%). This percentage was similar for laser pulses of 10 and 20 seconds. However, it was significantly less at higher powers for both exposure times of 10 seconds (1.8 ± 0.6% at 4 Watts, 1.7 ± 0.5% at 8 Watts, 1.1 ± 0.3% at 12 Watts, $p<0.01$) and 20 seconds (1.9 ± 0.9% at 4 Watts, 1.2 ± 0.8% at 8 Watts, 0.9 ± 0.3% at 12 Watts, $p<0.02$).

TABLE 10

DISTRIBUTION OF ATHEROMATOUS DEBRIS SIZE FOLLOWING LASING OF HUMAN ENDARTERECTOMY SPECIMENS WITH METAL-CAPPED OPTICAL FIBRES USING A 10 SECOND EXPOSURE WITH VARYING LASER POWERS

POWER	Debris (μg) on Different Size Filters				
	25μm	70μm	225μm	Total	
4 Watts	* 59±35	* 64±41	93±42	233±71	N.S.
8 Watts	* 66±40	* 81±41	87±31	234±56	N.S.
12 Watts	107±20	63±27	75±26	245±35	**p<0.002**
	p<0.01	N.S.	N.S.	N.S.	**ANOVA**
CONTROL	48±36	35±24	62±35	151±45	

ANOVA = One way analysis of variance * = not statistically different from control

This table illustrates that there is a tendency towards smaller debris formation when higher powers are used

TABLE 11

DISTRIBUTION OF ATHEROMATOUS DEBRIS SIZE FOLLOWING LASING OF HUMAN ENDARTERECTOMY SPECIMENS WITH METAL-CAPPED OPTICAL FIBRES USING A 20 SECOND EXPOSURE WITH VARYING LASER POWERS

POWER	Debris (μg) on Different Size Filters				
	25μm	70μm	225μm	Total	
4 Watts	* 69±34	87±26	109±47	262±98	N.S.
8 Watts	78±48	113±67	118±76	314±203	N.S.
12 Watts	144±68	81±38	93±36	334±116	p<0.02
	p<0.01	N.S.	N.S.	N.S.	ANOVA
CONTROL	56±24	44±32	59±44	159±86	

ANOVA = One way analysis of variance * = not statistically different from control

This table illustrates that there is a tendency towards smaller debris formation when higher powers are used

Scanning Electron Microscopy

Scanning electron microscopy at low magnification of debris showed the presence of numerous fragments smaller than 50μm, although some fragments of diameter up to 300μm were also observed (Fig. 36). Examination at high magnification revealed a sponge-like configuration suggestive of vaporization within the plaque (Fig. 37).

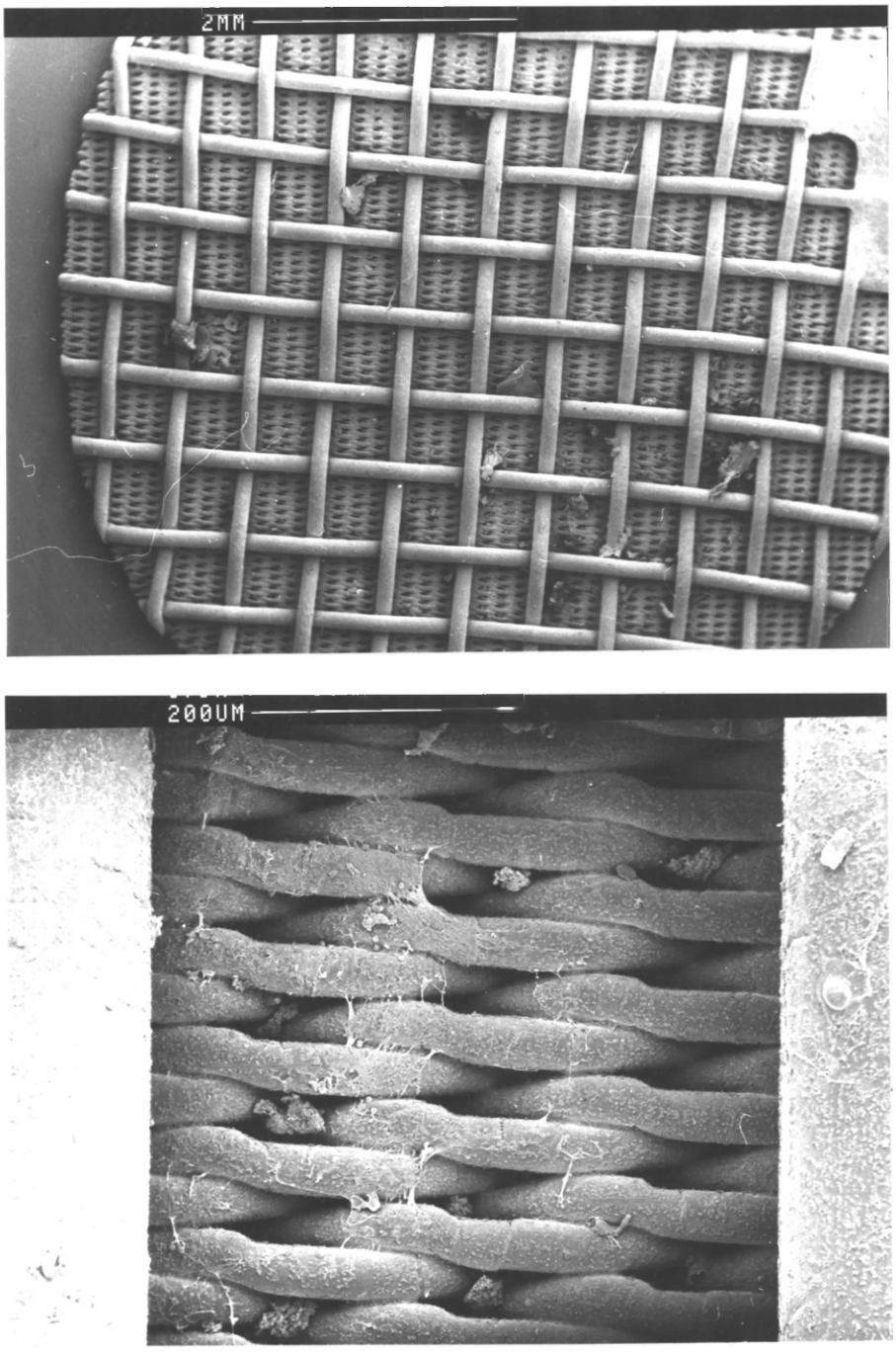


Figure 36:

Upper panel: Scanning electron microphotograph of debris collected on a 25μm filter during lasing of a human coronary endarterectomy segment at 12 Watts for 20 seconds. A few large fragments are seen. The vast majority of debris is formed by much smaller fragments (<50μm).

Lower panel: A higher power microphotograph of the same filter confirms the presence of numerous small fragments which are smaller than 50μm in diameter.

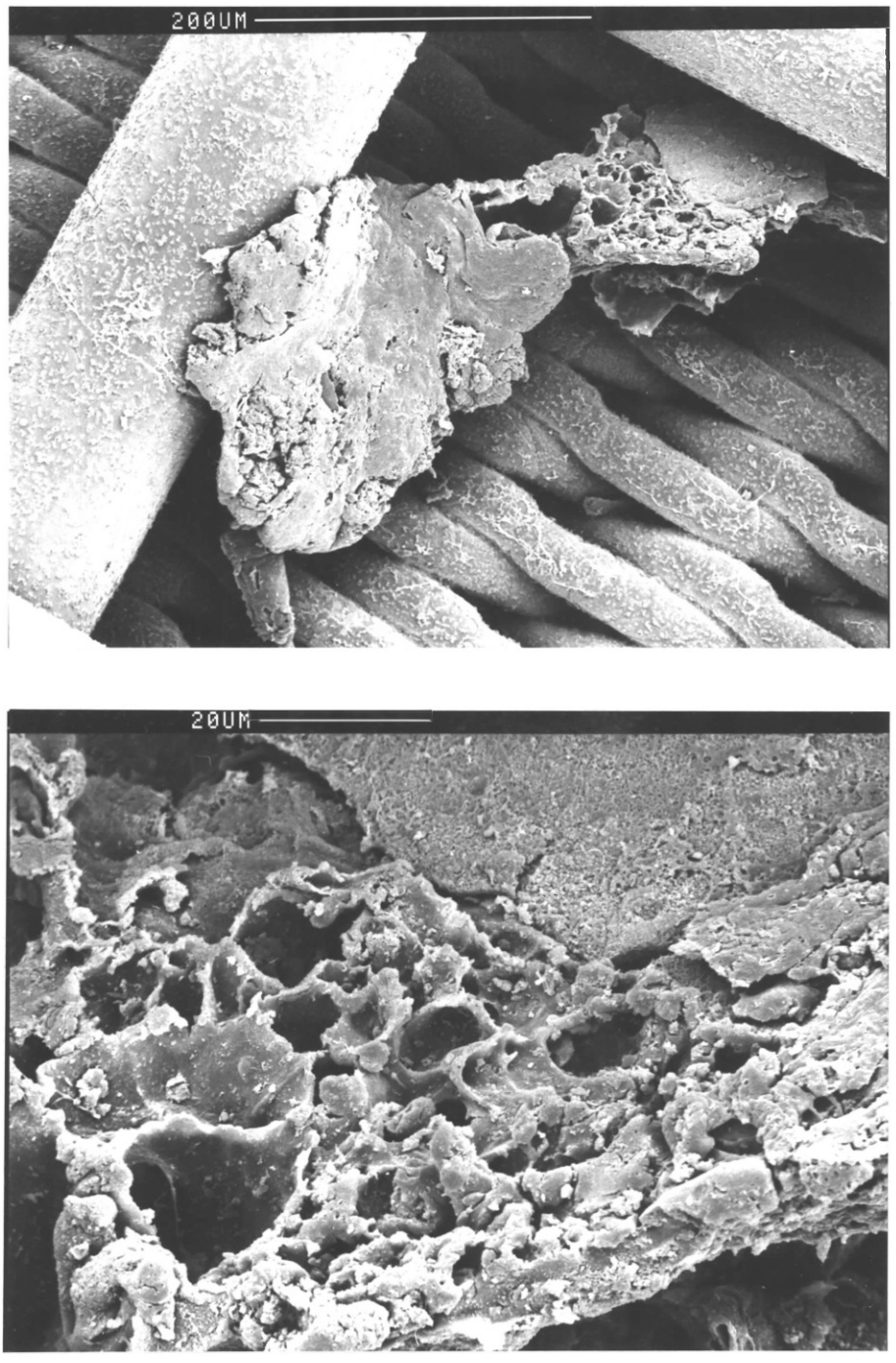


Figure 37

The scanning electron micrograph upper panel shows a large fragment of atheromatous debris. Closer examination (lower panel) shows evidence of boiling and bubble formation

Discussion

The results of this study demonstrate that the delivery of laser energy through metal-capped optical fibers results in a power dependent reduction of the weight and volume of human coronary endarterectomy specimens, although this is accompanied by an unacceptable release of particulate debris from the atherosclerotic plaque. We used human coronary endarterectomy specimens which reflect the heterogeneous nature of advanced human atherosclerosis. This in-vitro approach was preferred because it allowed a quantitative estimate of the amount of tissue which can be ablated. The variability of results produced by equivalent energies on different specimens illustrates that the composition of the plaque markedly influences the efficacy of laser thermal angioplasty. This is highlighted by the observed inability of the metal cap to remove calcific plaque even with an exposure of 12 Watts for 20 seconds. The resistance of calcific plaque to thermoablation reflects the experimental findings in cadaver hearts (Chapter 9) and our clinical experience in the coronary circulation (Chapter 4). This is not surprising given the fact that the temperatures generated by this technique (about 400^{o}C) are insufficient to vaporize the calcific component of the plaque (Welch, 1987). This study, however, does not provide information about the mechanism responsible for the decrease in volume of coronary endarterectomy specimens caused by laser treatment. This may be due to either tissue vaporization or dessication. Gross inspection of the specimens following each experiment led us to believe that dessication was an important, if not predominant, factor in mass reduction, presumably because water vaporization occurs at lower temperatures than organic vaporization.

The demonstration that part of the atherosclerotic plaque can be debulked in an energy-dependent fashion indicates that this technique offers a distinct advantage compared to conventional balloon angioplasty which only produces remodelling of the

stenosis. This debulking effect of laser angioplasty may be important in explaining the low restenosis rate at 1 year follow-up reported by Sanborn and Cumberland (1987) in patients in whom metal-capped optical fibers were used to perform laser-assisted balloon angioplasty of occluded femoral / popliteal arteries.

The results of this study also show that the decrease in volume of endarterectomy specimens during treatment with laser energy delivered through metal-capped fibers was accompanied by significant liberation of particulate material. At higher powers the debris was smaller (as indicated by the higher proportion of debris on smaller filters) and the ratio between debris weight and weight loss of the atherosclerotic plaque was lower. These findings indicate that the higher temperatures generated by higher powers result in greater and more complete vaporization of the target. However, scanning electron microscopy of filters showed that even at this higher energies debris up to 300μm can form. At these energies the size of embolic particles generated during the delivery of laser energy in blood may be >1mm in size.

The physiological significance of this debris is uncertain. It is worth noting that in a previous clinical study debris up to 218 grams in the weight was collected on a filter system during cardiopulmonary bypass (Gervin, 1974). This represents an amount of debris 10^6 times greater than that observed in the present study. Such debris was liberated into the human arterial circulation during cardiopulmonary bypass without any subsequent gross evidence of organ damage.

In our study the amount of debris produced during lasing with metal-capped fibres seems to be greater than that produced by balloon angioplasty. Block (1982) collected the effluent from iliac arteries of atherosclerotic rabbits following balloon angioplasty and found only a few single endothelial cells and cholesterol crystals. Experimental atherosclerosis, however, is markedly different from human disease and any direct comparison between the results of the two studies may be misleading. The comparison of our results using a

metal cap system with those obtained using bare fibres (Gessman, 1983; Kaminow, 1984; Case, 1985;) may also be inappropriate. Indeed, those studies with bare fibres were performed under various experimental conditions and, not surprisingly, produced markedly different results. Isner (1985) did not find significant particulate material following argon lasing of human calcified coronary arterial segments in saline at powers up to 4 Watts for 15-30 minutes. Conversely, Ben-Shachar (1986) found that following lasing of porcine vascular walls at 6.5 Watts for 10 minutes, fragments up to 3mm in diameter were generated.

In conclusion, the present study demonstrates that laser thermal angioplasty with metal-capped optical fibers results in a reduction in volume and weight of atherosclerotic plaque although this effect is variable. The delivery of higher energies appears to result in formation of smaller debris, although some fragments may be formed that are large enough to occlude small arteries and arterioles.

CHAPTER 8

The Effect of Intra-Coronary Thermal Energy on Side Branches

Introduction and Aims

The effect of the metal cap on adjacent tissue is thermal. If thermal ablation within the coronary circulation were to produce coagulative occlusion of side branches, such an effect would clearly be detrimental and might prejudice the clinical application of this technology within the coronary arteries. The effect of laser ablation with metal-capped optical fibres on side branch patency was therefore studied in the following experiment.

Materials and Methods

Experiment 1

The origin of the left anterior descending coronary artery (LAD) in 3 fresh canine hearts was cannulated and the artery perfused antegradely with saline at 150mmHg. Pre-lasing, biplanar cinéangiography of the LAD was performed during this perfusion by adding urograffin to the perfusate.

Following the pre-lasing angiography a distal arteriotomy was performed in the LAD and a 2.0mm metal-capped optical fibre advanced retrogradely into the proximal LAD. The LAD was then perfused with either blood or saline at 5ml/min. The metal cap was then activated using 10 Watts and withdrawn along the artery at a rate of 1cm/sec. Following lasing the LAD was ligated just proximal to the arteriotomy and repeat angiography performed under identical conditions to that prior to lasing.

Experiment 2

Pre-lasing, biplanar cinéangiography of the LAD was performed as described above on 10 freshly excised canine hearts, and two side branches identified and marked.

Following the pre lasing angiography a distal arteriotomy was performed in the LAD and a 2.0mm metal-capped optical fibre advanced retrogradely and positioned adjacent to the more proximal of the previously identified side branch origins. The LAD was then perfused with either saline or blood at 40ml/min and the metal cap activated, using 8Watts for 6 seconds, within the flowing perfusate. In this experiment the position of the metal cap remained static during lasing. Following lasing the LAD was insufflated with a mixture of barium and gelatine to facilitate subsequent histological sectioning. In each pair of hearts the perfusate at each site was alternated between blood and 0.9% saline.

A type K thermocouple was welded into the safety wire channel of the metal cap allowing temperature measurement at each site.

Angiographic Analysis

Care was taken to ensure constant rotational and skew angles, height and magnification factors during angiography of the hearts before and after lasing. Quantitative analysis of the side branch origins and adjacent LAD segments were performed using an automated computer based coronary angiography analysis system (Computerised Angiographic Analysis System [CAAS]; Pie Data Medical: See Fig. 38). The regions of interest were digitised and stored on a LSI 11/73 computer and the contour of the segment was plotted automatically by interpolation on the basis of signal density. This contour data was used to compute the % diameter stenosis from two standard views. The angiographic catheter was used as a scaling reference and this, together with pincushion distortion correction allowed the coronary artery diameters to be recorded as absolute values (millimetres).

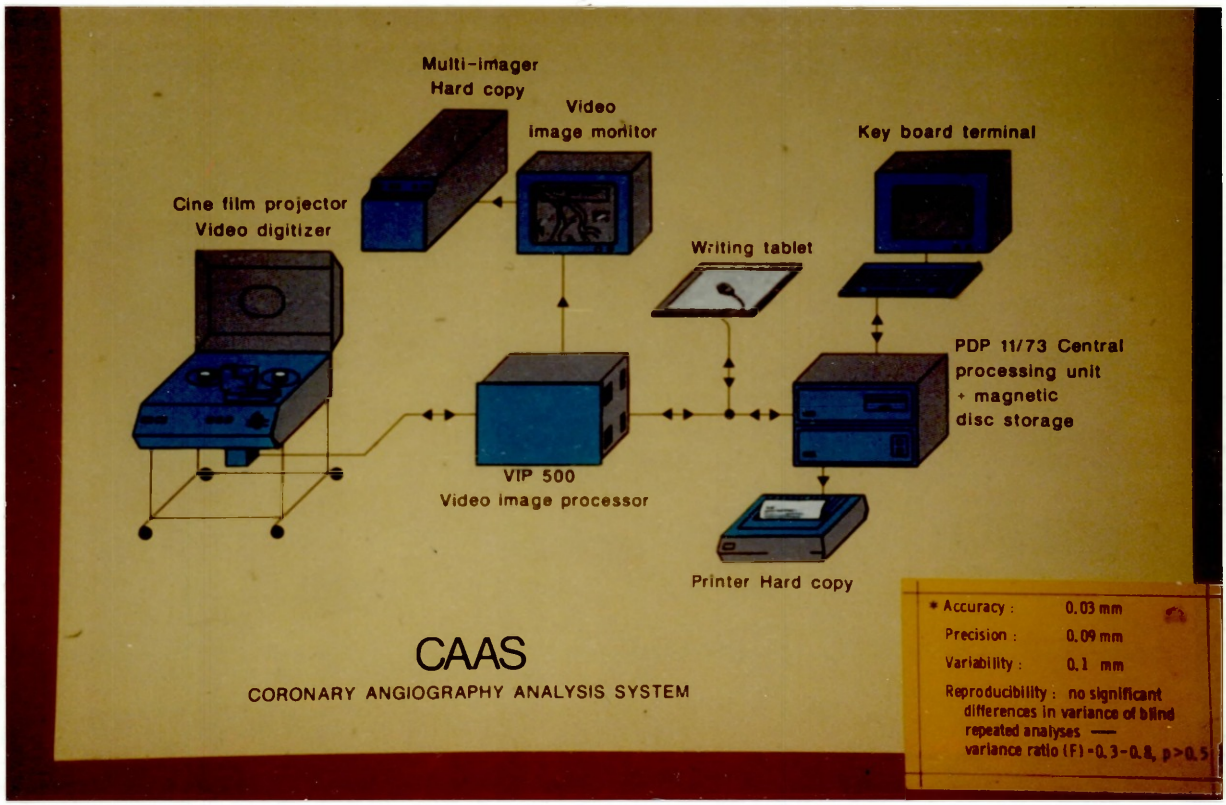


Figure 38

Computerised angiographic analysis system (CAAS) used for analysing the coronary angiograms before and after the application of intracoronary thermal energy.

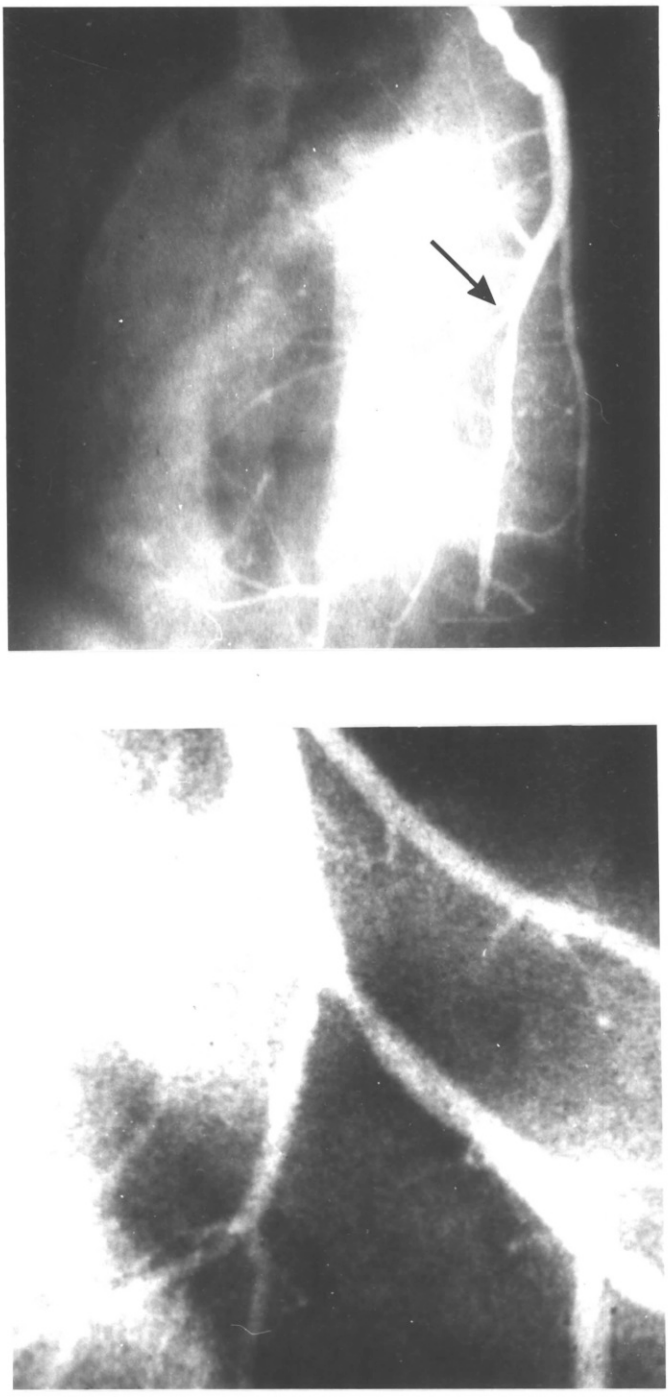
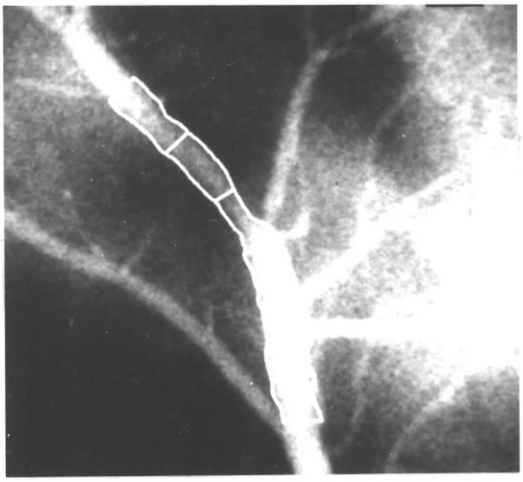
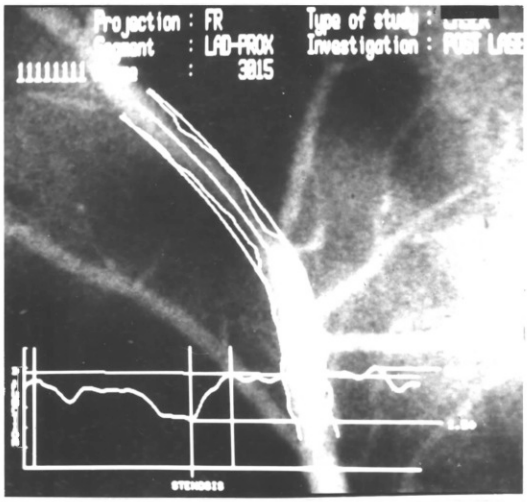


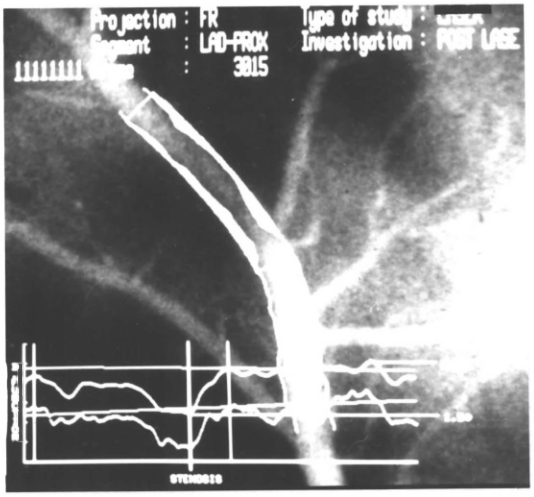
Figure 39: **Upper panel:** Angiogram of a canine left anterior descending coronary artery after the metal cap was activated using 8 Watts for 6 seconds adjacent to the origin of a proximal diagonal branch (Arrow). **Lower panel:** The same side branch origin. The image has been magnified and digitized prior to analysis with the Coronary Artery Analysis System (CAAS) (See fig 38, previous page)



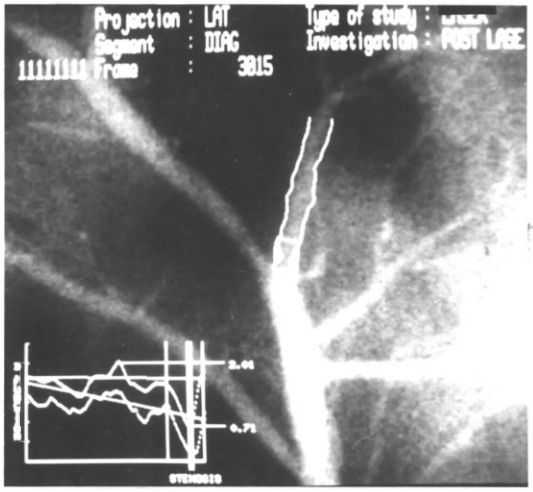
(a) Edge detection: the artery is scanned at right angles to its axis and points with the maximumum rate of change in dye density are plotted to form two lines representing the boundaries of the intra-arterial dye.. The proximal and distal extremities of the stenosis are then defined.



(b) Interpolation: The axis of the vessel is defined and the expected contour ofthe artery between the proximal and distal normal segments is plotted.
The diameter of the artery is plotted against length on the graph



(c) The stenosis is highlighted.



(d) A similar analysis along a side branch showing a stenosis at the origin.

Figure 40

Analysis sequence of angiogram shown in figure 40a. Panels (a) to (c) refer to analysis along the Left anterior descending coronary artery. Panel (d) shows a completed analysis along the side branch.

Results

Experiment 1

Twelve side branch origins were suitable for analysis. No perforations occurred and no side branches were completely occluded. The angiographic effects on both the left anterior descending coronary artery and side branches are tabulated (Table 12) and the stenotic effect on side branches is illustrated in Figure 41.

LEFT ANTERIOR DESCENDING CORONARY ARTERY				SIDE BRANCH			
MEAN % STENOSIS		MEAN DIAMETER		MEAN % STENOSIS		MEAN DIAMETER	
Pre	Post	Pre	Post	Pre	Post	Pre	Post
8.8±5.2	20.7±9.8	1.8±0.36	1.64±0.32	9.3±4.3	17±9	1.12±0.27	1.22±0.21
P<0.005		P<0.05		P<0.005		Not Significant	

Table 12

The % stenosis is expressed as mean±SD

Effect of Passing Metal Cap over Side Branch Origins

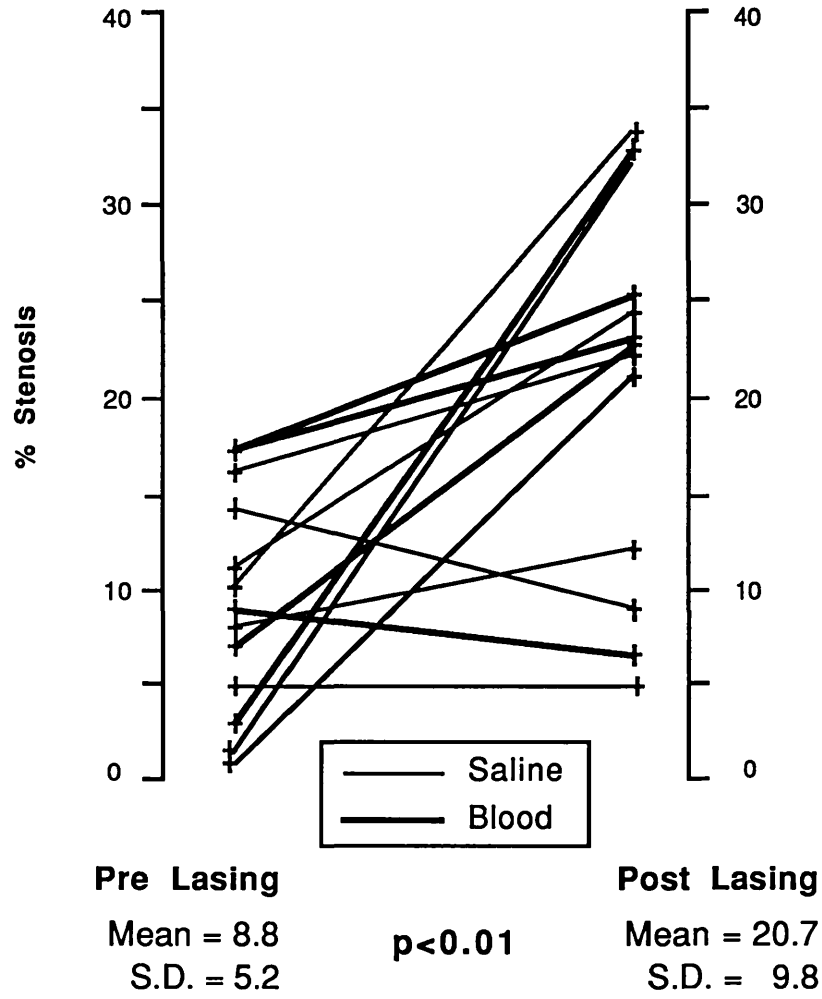


Figure 41

The stenotic effect of passing a hot metal cap at 1cm/min over normal canine side branch origins.

Experiment 2

Angiographic Results

Pre and Post lasing angiographic analyses were performed on 15/20 side branch origins. Twelve showed post lasing stenosis of the origin, while three showed "opening" of the orifice.Three perforations of the LAD occurred and 1 total occlusion of a side branch was seen in the absence of perforation. These latter 4 sites together with one side branch angiogram which was of poor quality, were not suitable for angiographic analysis. Perforation was always attended by strong adherence of the metal cap to the vessel wall, and in 2 cases resulted in intusussception of the LAD (See Fig. 44) which itself resulted in occlusion.

For the purposes of this study perforations and occlusions were accorded an equivalent rating of 100% stenosis since the effect of both on the blood supply to the distal vascular bed would be similar.

The results of the angiographic analyses are presented as mean±SD. Statistical comparisons were made using the Wilcoxon signed rank test for paired non-parametric data.

Angiographic Changes in Side Branch Origins

Lasing at side branch origins resulted in a mean increase in stenosis of the side branch origin from 14.7±12% to 45.2±31.6 (Δ 30.5±31.2, $p<0.001$). This tendency to stenosis was greater at the distal side branch where the stenosis increased from 16.1±11.9 to 66.2±33.7 (Δ 50.1±31.2; $p<0.005$) than at the proximal side branch where the increase was only from 13.4±13.8 to 26.3±12.5 (Δ 12.9±18.7%; $p<0.05$). The stenotic effect was independent of the perfusate used.

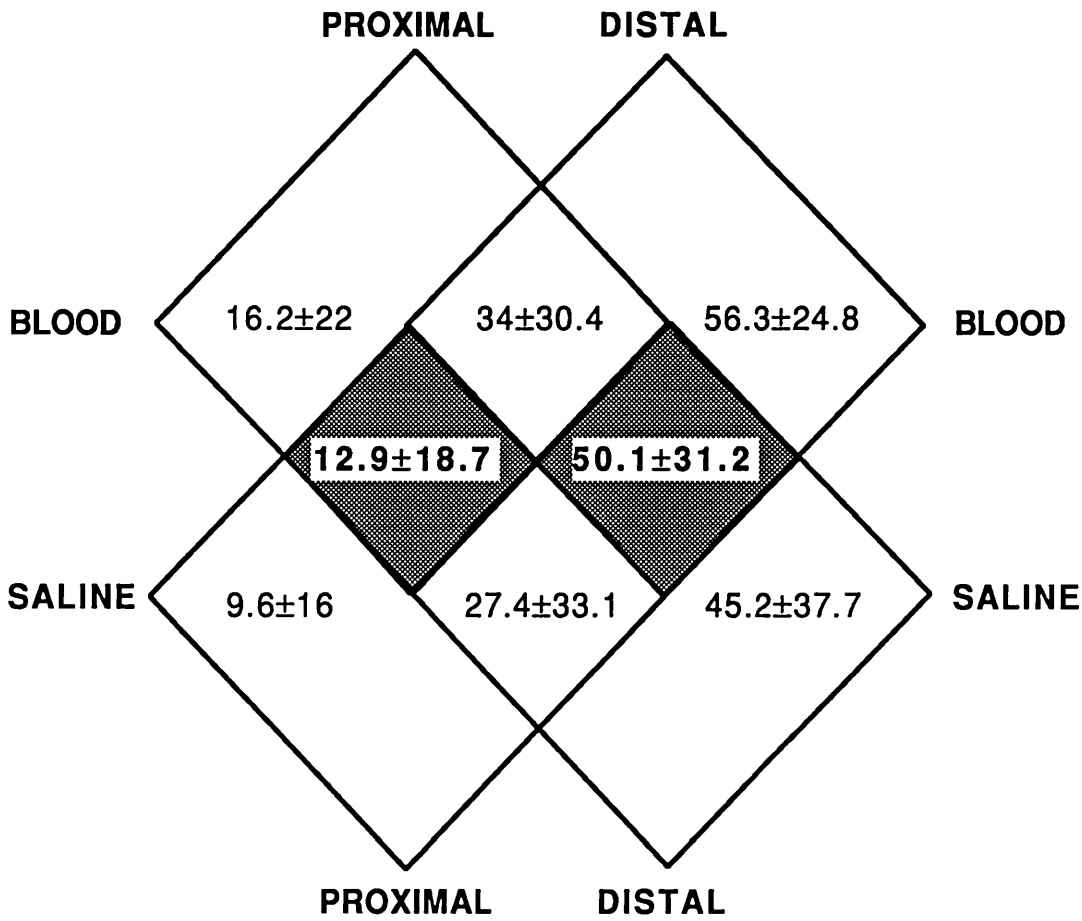


Figure 42

A Venn diagram illustrating the increase in percentage stenosis of side branch origins after lasing at different sites in blood or saline

TABLE 13

	Pre Lasing	Post Lasing	Significance
All Side Branches	14.7±12	45.2±31.6	p<0.05
All Proximal Side Branches	13.4±13.8	26.3±12.5	p<0.05
All Distal Side Branches	16.1±11.9	66.2±33.7	p<0.05
Proximal in Blood	12±10.9	28.2±13	p<0.05
Proximal in Saline	14.8±17.5	24.4±13.2	p>0.05
Distal in Blood	23±0.58	56.3±24.8	p<0.05
Distal in Saline	14±13.3	60±38.5	p<0.05
ALL in Blood	16.4±10.3	47.5±31.7	p<0.05
ALL in Saline	14.8±14.6	42.2±33	p<0.05

Table 11

Percentage stenoses of canine left anterior descending coronary artery *side branch origins* before and after the application of 8 Watts for 6 seconds to a 2.0mm metal-capped optical fibre placed adjacent to the orifice.

Angiographic Changes in the Left Anterior Descending Coronary Artery

A similar pattern was observed in the LAD where the mean increase in proximal stenosis following lasing was from 11.5±5.6 to 35.7±16 (Δ 24.2±16.4%, $p<0.005$) versus 13.2±8.4 to 77±32.1 (Δ 58.9±36.5%, $p=0.005$) at the distal site. Once again there was no difference between blood and saline.

The mean diameter of the LAD prior to lasing was 3.3±0.5mm in the proximal segment and 2.6±0.4mm in the distal segment ($p=0.006$). Although all perforations and occlusions occurred in the distal segment, there was no correlation between the size of the LAD at the site of lasing and the degree of stenosis induced in either the LAD or side branch.However there was a highly significant correlation (0.8) between the degree of LAD stenosis and side branch stenosis.

The degree of stenosis induced was independent of the perfusate used: Δ 32±29% in blood and Δ 27±33% in saline

It will be noted that the mean diameter of the LAD in the first series is considerably smaller than in the second series. This represents a sex difference in greyhounds: female greyhounds have smaller coronary arteries than male greyhounds.In the first experiment all three hearts were excised from female dogs, whereas in the second study all hearts were from male dogs.

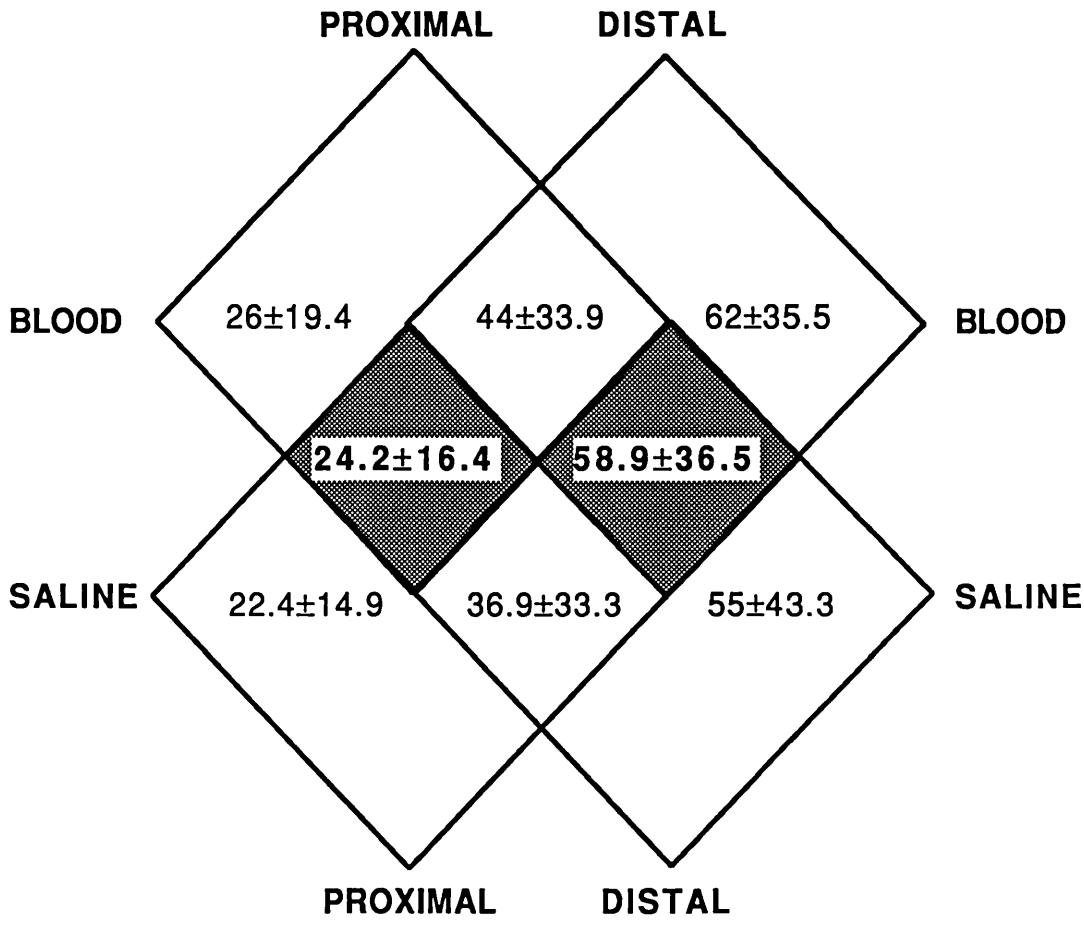


Figure 43

A Venn diagram illustrating the increase in percentage stenosis of the left anterior descending coronary artery at side branch origins after lasing at different sites in blood or saline

Temperature Measurements

The mean peak central cap temperature was 344°C in blood and 237°C in saline.

TABLE 14

Peak Central Cap Temperature (Mean±SD) Using 8 Watts for 6 Seconds In Canine Coronary Arteries at Sites of Side Branch Origins

	SALINE	BLOOD	
All Sites	237±107	344±82	p<0.05
Proximal	154±22	318±109	p<0.05
Distal	321±87	369±54	

The mean temperature at which perforation occurred was 381±42°C.

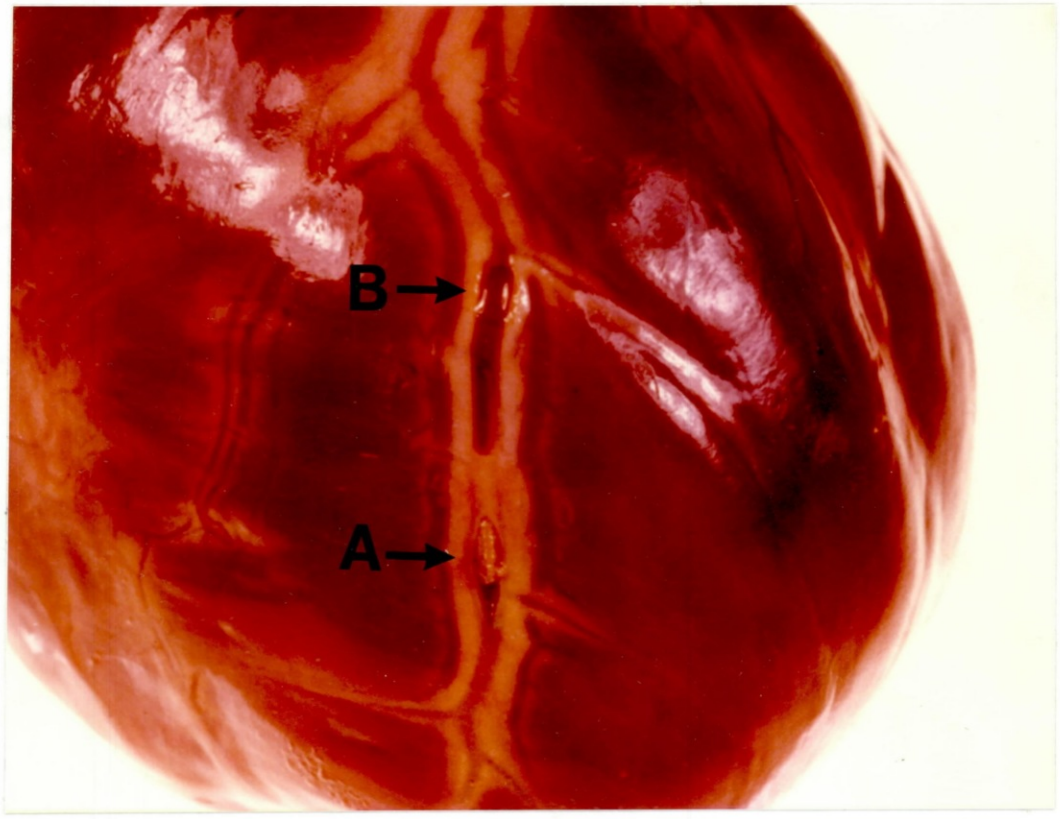


Figure 44

Photograph of a freshly excised canine heart showing the left anterior descending coronary artery. The metal-capped optical fibre was introduced through an arteriotomy at site A and activated at site B where a perforation is seen. On withdrawal of the optical fibre the metal cap was adherent to the arterial wall which underwent intususception and is seen protruding through the arteriotomy.

Discussion

The results of these studies indicate that the application of thermal energy in coronary arteries in the region of normal side branch orifices results in significant stenosis of that orifice and of the immediately adjacent parent vessel. Furthermore, using equivalent energies the tendency to stenosis and thermal damage was significantly worse in the distal vessel.

The relevance of these findings relates to the fact that in humans atherosclerotic stenoses in coronary arteries frequently occur near the origin of side branches. The stenotic effect of thermal angioplasty on normal side branches demonstrated in these studies potentially limits the clinical application of this technology. These findings are useful in defining the anatomy of segments which may be suitable for laser coronary angioplasty using metal-capped optical fibres. Clearly the results gleaned from this model are not appropriate for extrapolation to side branch origins splinted by atheroma.

In the first study where the hot metal cap was pulled back along the LAD intermittent adherence of the probe to the arterial wall was troublesome and prevented steady withdrawal. Furthermore, it was clear that the greatest stenoses occurred at the points of probe adherence within the LAD. Nevertheless, side branch stenosis occurred in the absence of adherence.

It may be speculated that protein denaturation and shrinkage may be responsible, since this occurs at lower temperatures (70-80^{o}C) than tissue ablation which appears to require temperatures in the region of 180^{o}C (Welch, 1987). Temperatures were not measured in the first experiment. However, temperatures of the metal cap were measured in the second experiment when the probe was stationary within the LAD. There was no correlation between temperature and degree of stenosis, possibly because protein denaturation occurred at temperatures well below those achieved by the metal cap. Interestingly, although there was no significant difference in the degree of stenosis induced when lasing

was performed in blood or saline, the metal cap in the proximal LAD reached significantly higher temperatures in blood than in saline (154±22 v 318±109°C) implying that a coagulum insulated the probe in the larger proximal segments. This appeared to be the case since a dense coagulum was seen on withdrawal the probe from the artery, although to a lesser extent than seen in the in-vitro studies described in Chapters 5 and 6. Furthermore, the temperatures in saline and blood (321±87 v 369±54°C) were similar in the smaller diameter distal segments endorsing the finding of Hussein (1986) that once in contact with tissue temperatures in the region of 300-400°C are achieved.

It will be noticed in Table 12 (Study 1) that the mean diameter of the origin of the side branches is increased following lasing. This 10% change in diameter, which does not reach statistical significance, is close to the resolution of the CAAS system and despite the precautions taken (See page 234) this probably reflects measurement error. This error would have been reduced in the second study when the mean diameter of the side branches was larger at 2.3±0.5mm (mean±SD) prior to lasing decreasing to 2.1±0.5 following lasing. In both studies, these measurements, were taken over a mean length of 11.9±2.7mm, equivalent lengths being used in the same hearts before and after lasing. The minimal influence of the stenosis on mean diameter in both studies is due to the fact that the mean length of stenosis was only 3.2±1.5mm representing only a small part of the whole measured segment over which the mean diameter was calculated.

Thus, in Study 1, where the metal cap was pulled along the LAD in contact with the entire measured segment, the mean diameter change is useful in quantifying the extent of thermal contraction in the LAD tissue along that measured segment. However, it is of little value in understanding the effect on adjacent side branches, unlike the percentage stenosis which is calculated from diameter measurements of the stenosed segments only.

In conclusion these studies demonstrate that the delivery of laser energy through metal-capped optical fibres may cause local stenosis of normal side branch origins due to a thermal effect.

CHAPTER 9

The Histological Effects of Metal-Capped Optical Fibres on Atherosclerotic Human Coronary Arteries

Introduction and Aims

Numerous in vitro studies have been performed to quantify the relationship between energy delivered and tissue damage using a variety of tissues, optical fibres and laser sources. Similarly, the relationship between energy, local temperature profile and tissue ablation using metal-capped optical fibres in human aorta have been documented (Welch, 1987), but no such information is available with respect to coronary arteries which have a significantly different structure from aorta.

The following chapter describes a feasibility study prior to the possible intraoperative application of this technology in the coronary circulation. An intraoperative model for lasing human coronary arteries was established with a view to determining (a) the histological effects of metal-capped optical fibres on human coronary arteries, (b) the optimal power range for inducing thermoablation without perforation, (c) which perfusate to use during in vivo lasing and (d) to examine the relationship between plaque geometry and thermoablation.

Fresh cadaver hearts were used as the intraoperative model since they closely resemble the cold, flaccid, asanguineous, non-beating intraoperative heart.

Materials and Methods

Cadaver Heart Preparation

12 fresh cadaver hearts were studied within 12 hours of excision. In order to simulate the intraoperative setting the aortic root was cross-clamped and perfused at 4^0C at a constant pressure of 150mmHg in a similar manner to the routine delivery of intraoperative cardioplegia. A distal coronary arteriotomy of similar dimensions to that required for saphenous vein bypass grafting was performed and the metal-capped optical fibre introduced retrogradely to lase different sites within the artery (Fig. 45). In each heart the same procedure was repeated in 2-5 main coronary branches. If there was no flow following the arteriotomy, despite adequate aortic pressure, an angiogram was performed to determine whether or not there was a complete occlusion of that coronary artery.

Lasing Protocol

Lasing was performed during perfusion with either saline or blood. In each artery a total of 1 to 5 laser pulses were delivered. Laser pulses at powers of 4, 6, 8 and 10 Watts for exposure times of 2,5,10,15 and 20 seconds were delivered to discrete sites. No attempt was made to select diseased sites since preliminary studies had revealed that perforation was most likely to occur through thin "normal" arterial wall rather than diseased arterial wall. Thus the perforation thresholds of normal artery were likely to represent the lowest perforation thresholds. The metal cap was not advanced during lasing. Each lased site was marked with a suture to facilitate subsequent histology.

Recanalization of 6 coronary occlusions was attempted anterogradely using 6 Watt pulses of 5-15 secs during perfusion with blood. Angiography with Urografin 360 was performed before and after lasing and recorded on videotape.

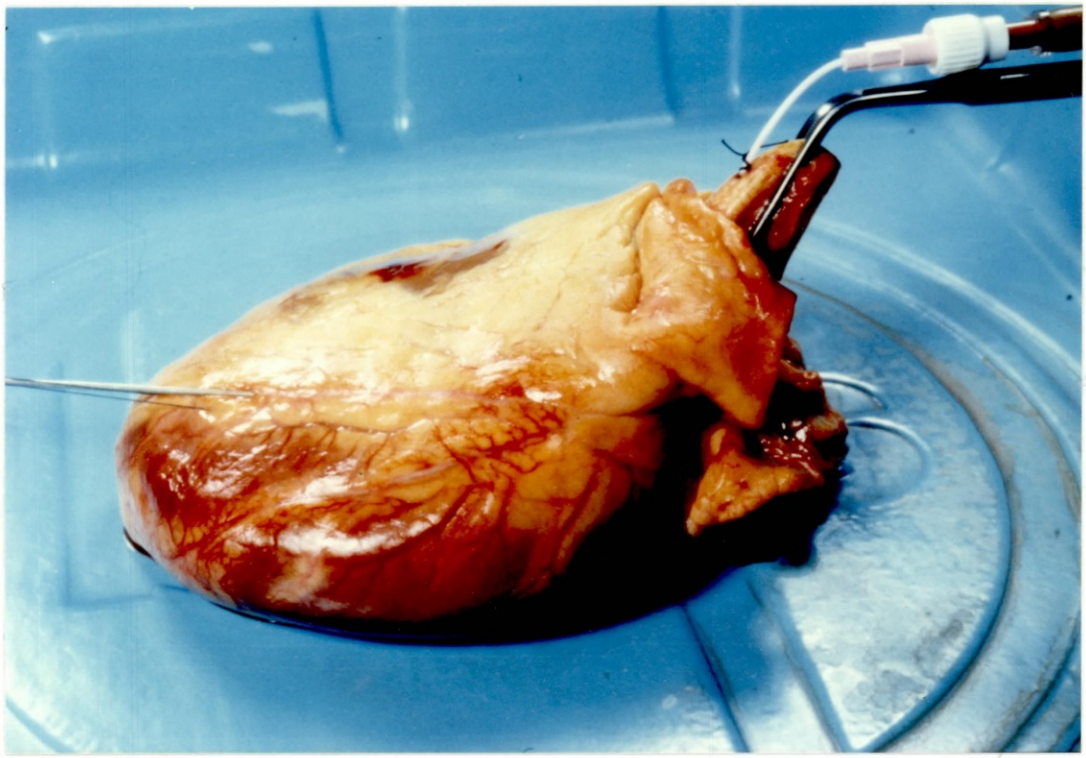


Figure 45

Photograph of the intraoperative cadaver heart model. A probe is seen entering a heavily diseased left anterior descending coronary artery. The aorta is cross clamped and a cannula has been inserted into the ascending aorta proximal to the cross clamp.

Histological Preparation

Following lasing each coronary ostium was cannulated and the coronary circulation insufflated with a solution of barium and gelatin sufficient to dilate the main coronary arteries. The heart was then fixed in a solution of 10% formaldehyde. Serial histological sections of the lased sites were stained by Elastic Haematoxylin and Eosin. Selected sections were also stained with Picro Mallory to assess the extent of protein denaturation.

RESULTS

A total of 115 sites were lased (50 in saline and 65 in blood).

Histological Effects

Normal or minimally diseased sites approximately 1.5 - 2.0 cm apart in the proximal two thirds of the right and left coronary vasculature were selected for lasing. Thermal effects were always associated with adherence of the metal cap to the arterial wall.

The following graduated histological effects were identified:

0. No obvious thermal injury. (Saline 25; Blood 27)
1. Circumferential eosinophilic staining or shrinkage of the media but without obvious tissue loss or flap formation. (Saline 6; Blood 3)
2. Loss of intima with intimal flap formation. (Saline 5; Blood 4)
3 Loss of intima and inner media with varying degrees of flap formation within the media. (Saline 7; Blood 9)
4. Extensive loss of intima and media with varying degrees of flap formation within the media and a disrupted adventitia, i.e.perforation. (Saline 7; Blood 22).

Microscopic thermal effects were characterised by charring of the superficial layers adjacent to the metal cap, a deeper broad zone of eosinophilia, vacuolation and protein denaturation suggestive of vaporization; often associated with flap formation .

The extent of thermal damage was clearly increased in smaller vessels where the probe was in closer contact with the arterial wall and when perfusate flow was reduced due to a proximal stenosis.

The characteristics of thermal injury described above are illustrated in figures 46-51.

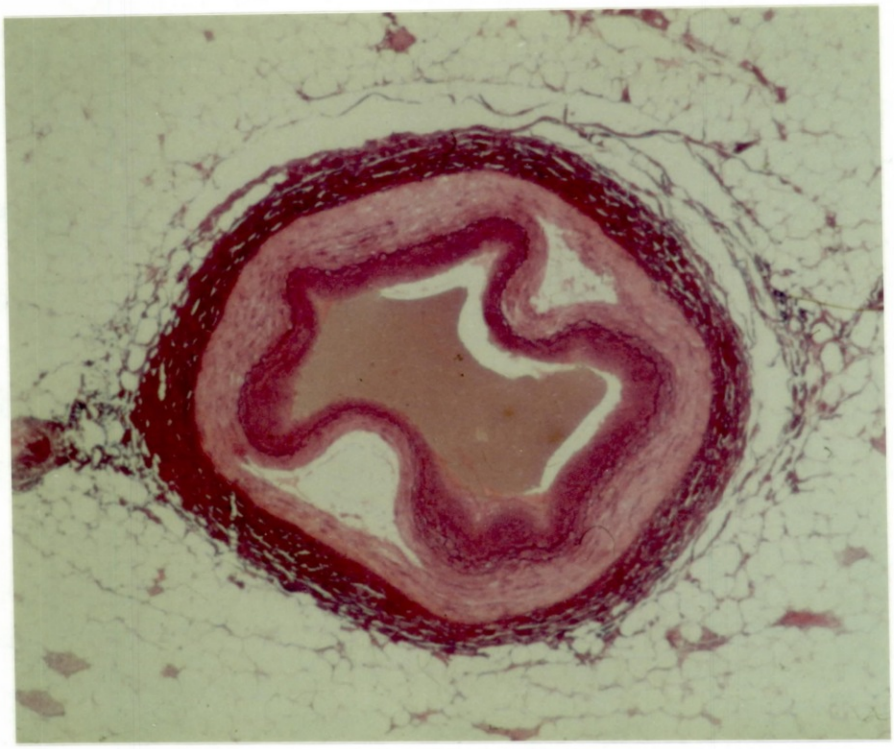


Figure 46

A photomicrograph of a human coronary artery following the application of thermal energy. There was metal cap adherence at this point. The photograph illustrates the effect of shrinkage and splitting of the media with invagination of the inner media and intima. The fact that the intraluminal barium and gelatin holds the same shape implies that this is not an artifact.

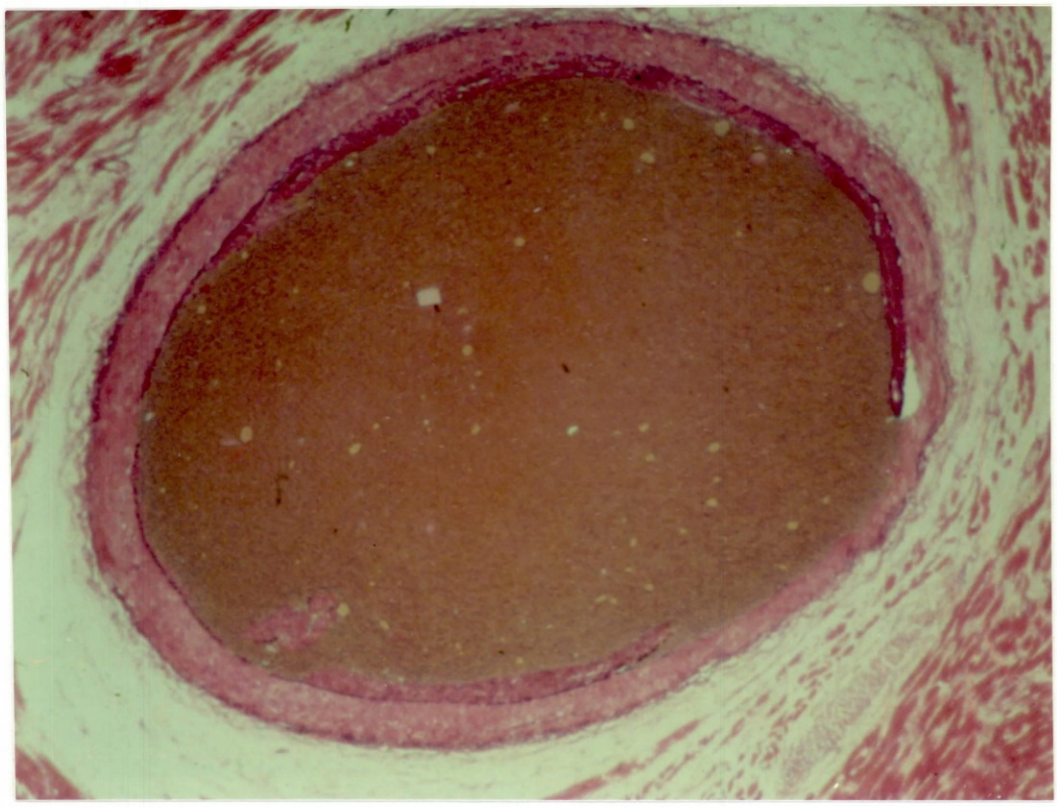


Figure 47:

Minor flap formation following some loss of intima between 3 and 5 o'clock. This was associated with adherence of the metal-cap to the arterial wall .

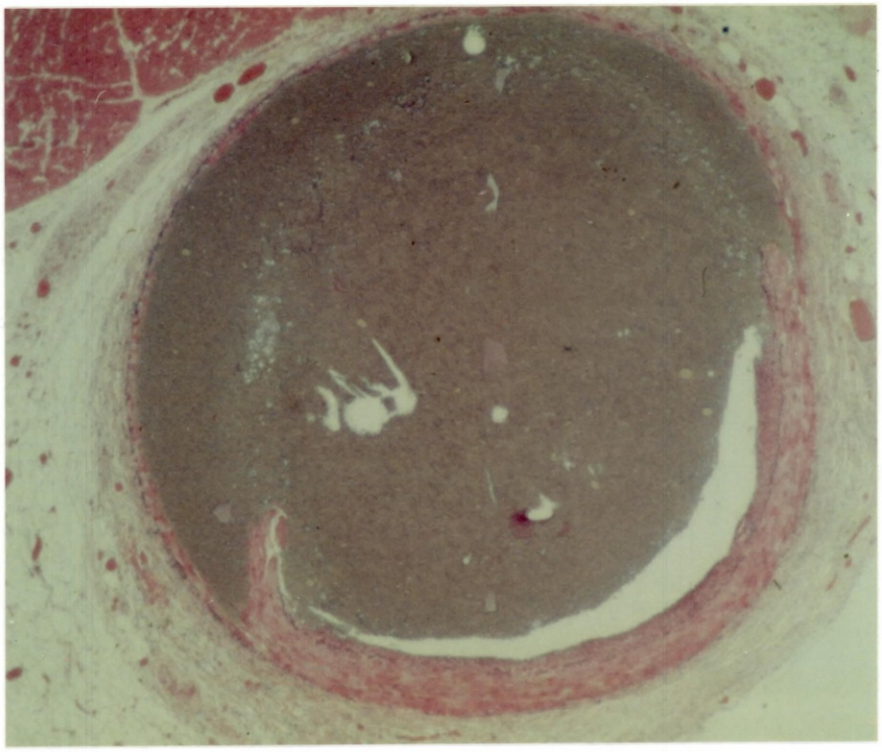


Figure 48:

Extensive loss of intima and inner layers of media with associated intraluminal flap formation following adherence of the metal cap to the arterial wall.

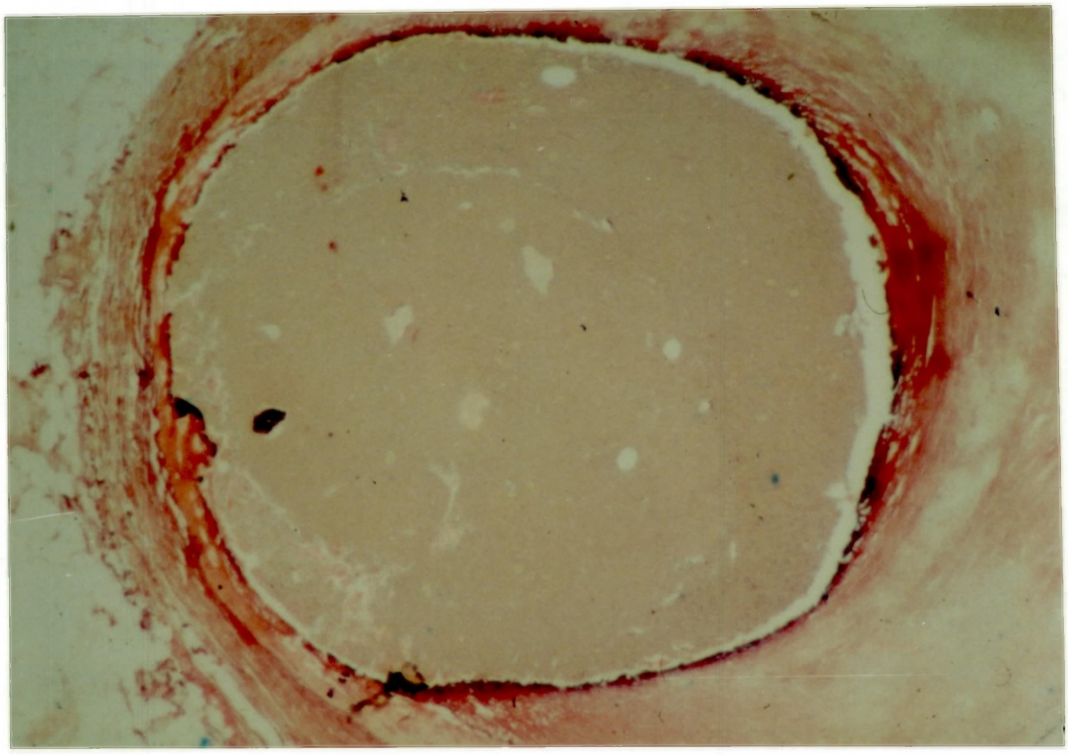


Figure 49a

The following two photomicrographs confirm the circumferential distribution of thermal energy. In the first photograph (49a) the rim of eosinophilic staining around the lumen reflects thermal damage.

This is confirmed by the picro-Mallory stain in the second photograph overleaf (49b) where normal protein stains blue but the denatured protein around the luminal circumference has failed to stain blue and remains red

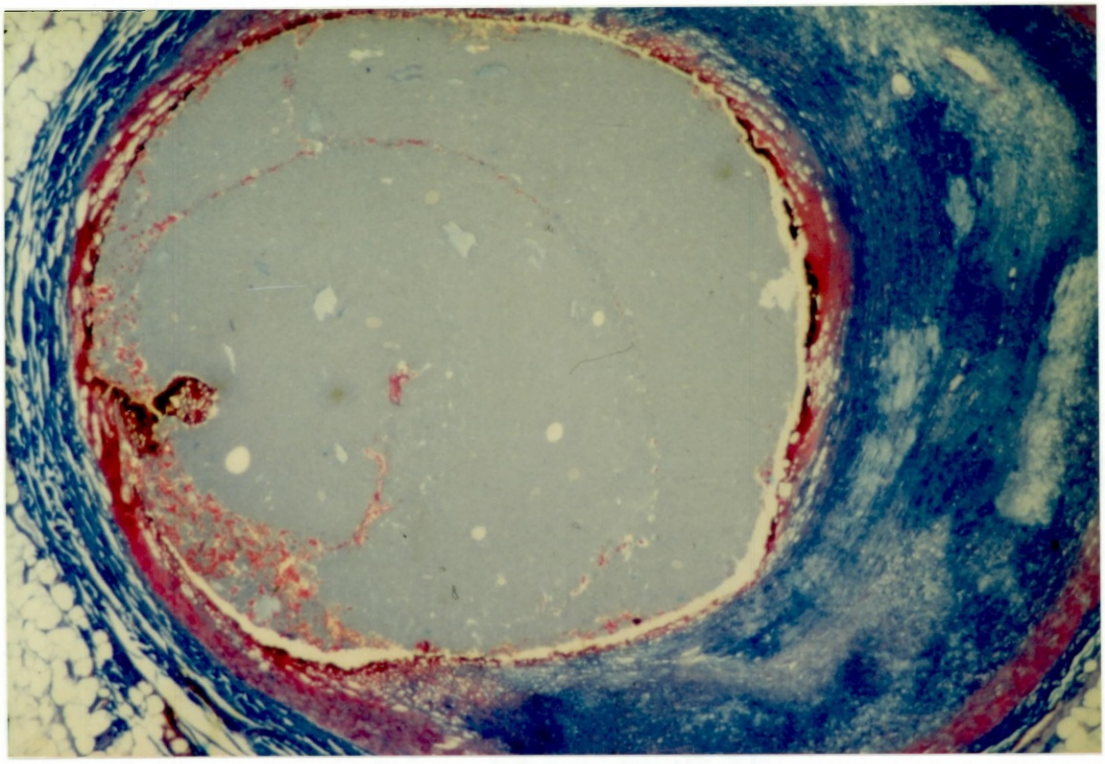


Figure 49b

In this serial section (adjacent to that in Fig 49a) stained with picro-Mallory normal protein stains blue. The thermally denatured protein fails to stain blue and remains eosinophilic (red). Notice the circumferential distribution of the eosinophilic denatured protein. The depth of thermal injury does not appear to be deeper on the atherosclerotic side of the artery implying that preferential ablation of atherosclerotic tissue, rather than normal arterial wall, does not occur.

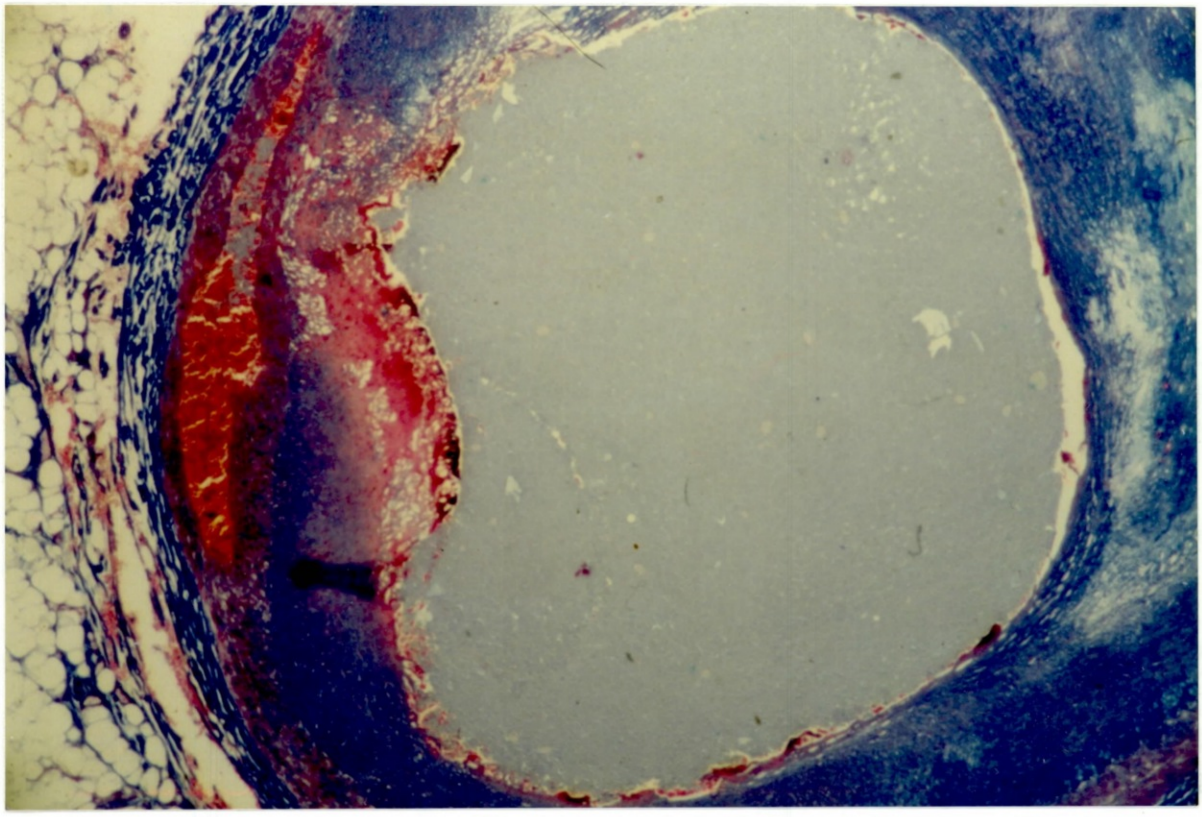


Figure 50

The circumferential distribution of energy may be modified by the shape of the lumen. Here a protuberance is ablated preferentially.

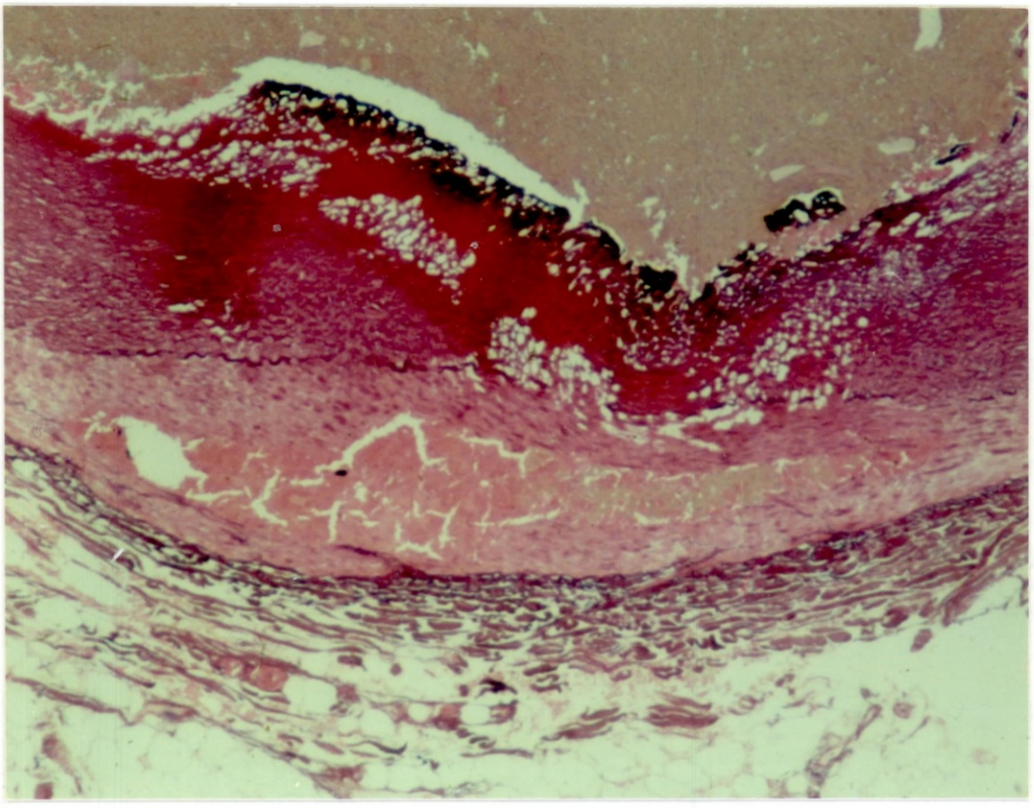


Figure 51:

A site of thermal damage ("thermoablation") reveals superficial charring with a subjacent zone of tissue showing eosinophilic staining and vacuolation suggestive of thermal damage. Notice the depth of tissue involved in the thermal injury.

The Effect of Energy Input

The results are shown in table 15a which consists of a matrix. Each square in the matrix represents a specific combination of laser power and delivery time. Within each square are three figures. The top left hand figure indicates the total number of sites lased using that particular combination of power and delivery time. The bottom left hand number represents the number of those sites where histological damage was seen, excluding perforation. The number in the upper right hand corner of the square represents the total number of perforations induced by that combination of power and time.

Flap Formation and Metal Cap Adherence

Thirty four sites showed some degree of thermal injury (18 in saline; 16 in blood) without perforation. Of these, metal cap adherence to the arterial wall occurred at 23 sites, and of these sites 17 exhibited some degree of flap formation.

Of the 29 perforations, 22 exhibited varying degrees of intraluminal flap formation.

Flap formation was not seen in the absence of adherence of the metal cap to the arterial wall.

Adherence of the metal cap varied from very light adherence which was easily overcome to severe adherence resulting in arterial intussusception which occurred at 5 sites.

TABLE 15a

The Effect of Perfusate on the Histological Effects of a 2.0mm Metal-capped Optical Fibre in Human Coronary Arteries

SALINE	2s	5s	10s	15s	20s
4 Watts					
6 Watts	3	3	5	5 *2*	5 1 *2*
8 Watts	3	5	5 *2*	5 *4*	5 2 *1*
10 Watts	3	5 *3*	5 *3*	5 3 *0*	3 1 *1*

BLOOD	2s	5s	10s	15s	20s
4 Watts	5	5 *2*	5 2 *2*	5 4 *1*	
6 Watts	5	5 2 *2*	5 3 *2*		
8 Watts	5 *1*	5 2 *3*	5 3 *2*		
10 Watts	5 *2*	5 2 *3*	5 4 *1*		

Total number of lased sites → **a** *c* ← *Number of perforations*

b ← *Number with histological damage*

Line separating energies causing histological damage from energies that do not

Line separating energies causing histological damage from energies that cause perforation

The Effect of Perfusate:

Statistical Analysis

The odds of an artery being perforated were modelled as a function of power of lasing, time of lasing and perfusate by logistic regression. The odds of the artery being either damaged or perforated were modelled in the same way. These regressions were carried out using the statistical software package GLIM (Generalised Linear Interactive Modelling).

Perforation only

After adjusting for the effects of time and power of lasing, the effect of perfusate was highly significant, with the odds of perforation being an estimated 168 times greater with blood than with saline [95% confidence interval 20 to 1430, $P<0.0001$ N.B. this confidence interval is not symmetric about 168 because the regression is done on the log-odds rather than the odds themselves; the confidence interval on the log scale *is* symmetric; log(168) lies half way between log(20) and log(1430)]. There was no evidence that this difference varied with the time or power of lasing.

Damage or perforation

The effect of perfusate was found to vary significantly with the time, though not with the power, of lasing. The estimated factor by which the odds of damage or perforation were greater with blood than with saline are shown below for various times.

Time of lasing (seconds)	5	10	15
Estimated odds ratio of damage or perforation in blood with respect to saline	34	1,160	40,100

Table 15b

Total Occlusions

Recanalization of 6 total occlusions was attempted using 8 Watts in the presence of blood. Five occlusions were successfully recanalized in right coronary arteries; a sixth occlusion in a left anterior descending coronary artery could not be recanalized due to heavy calcification.

Success was confirmed angiographically (Fig. 52). No perforations were identified either on angiography or histology. Adherence of the probe to the arterial wall after longer pulses was commonplace and histology revealed varying degrees of intraluminal flap formation in all five recanalized vessels (Figs. 53 & 54).

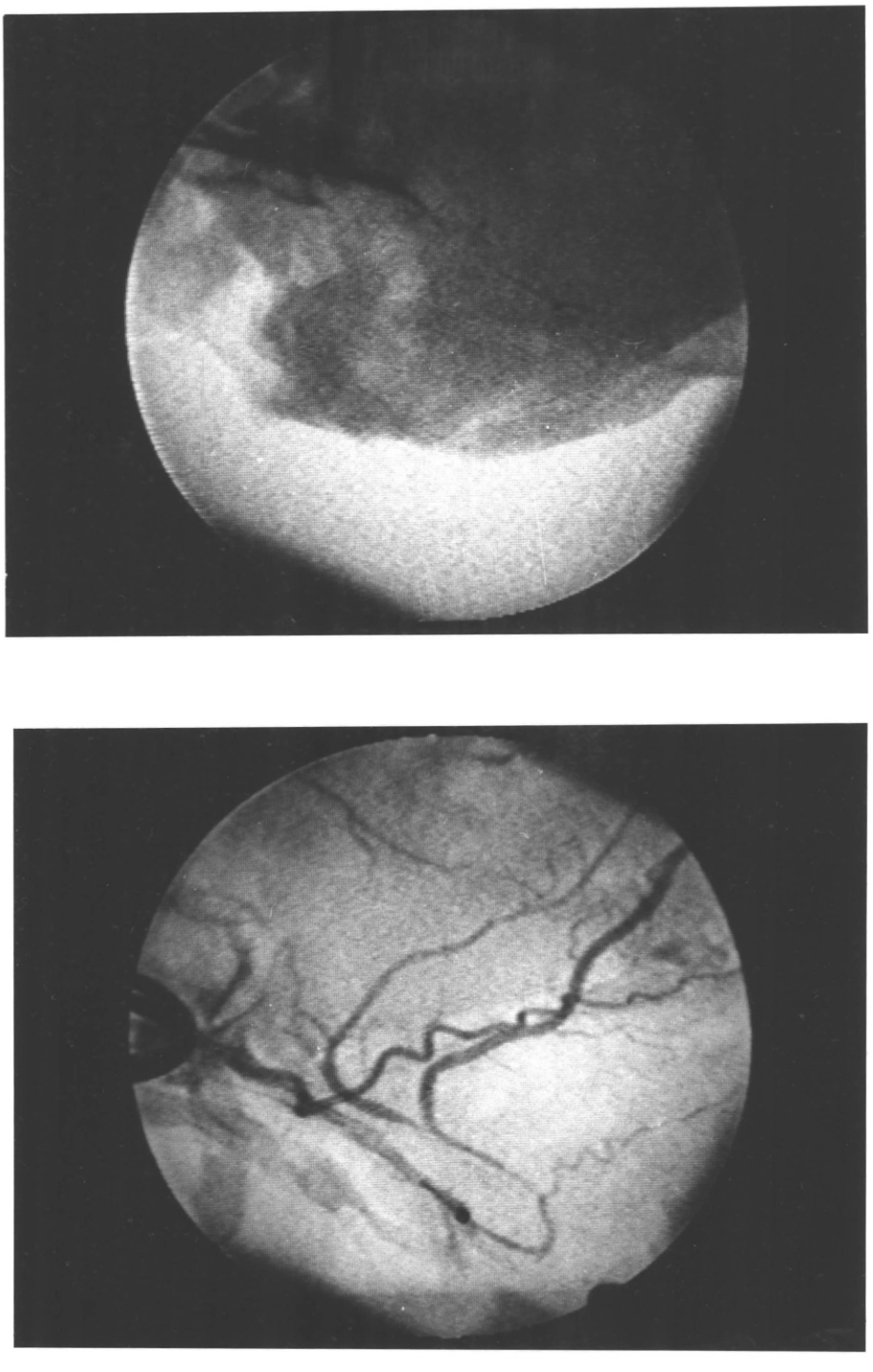


Figure 52

In-vitro right coronary angiograms taken pre (upper) and post recanalization (lower) showing that recanalization of total occlusions is possible. The tip of the metal-capped optical fibre can be seen in the recanalized artery.

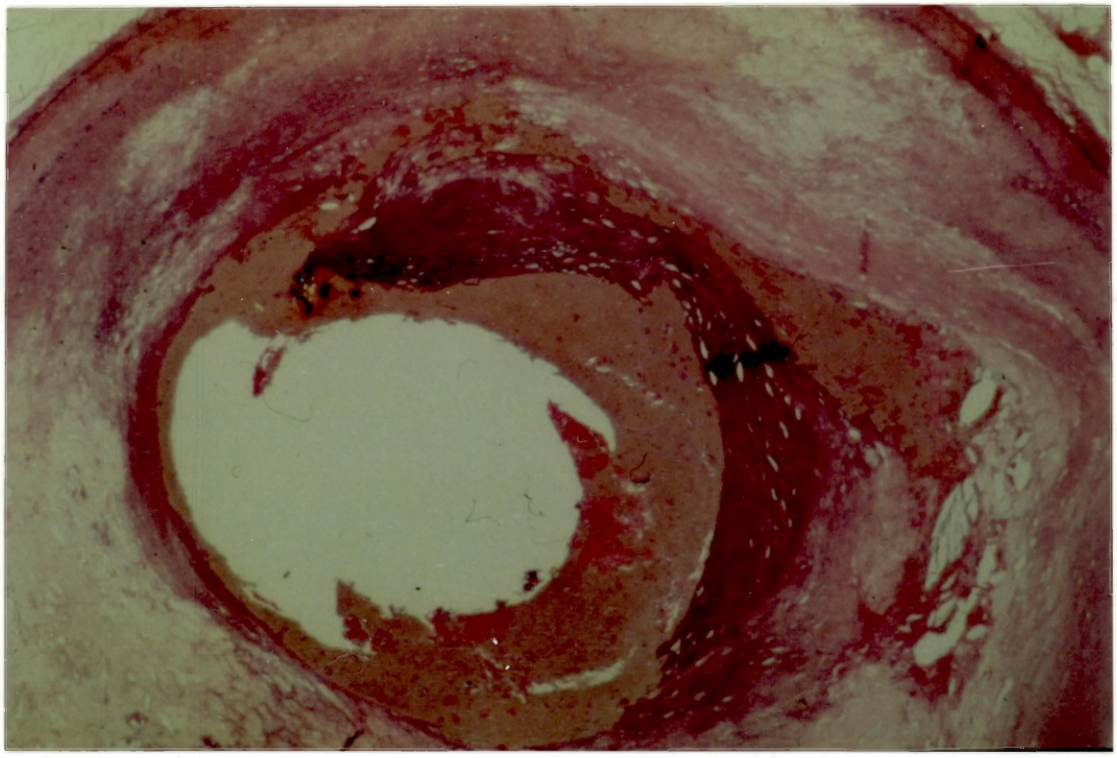


Figure 53: Photomicrograph through the recanalized artery shown in Fig. 52. Notice the eosinophilic intraluminal flap outlined by the homogeneous pink barium and gelatin.

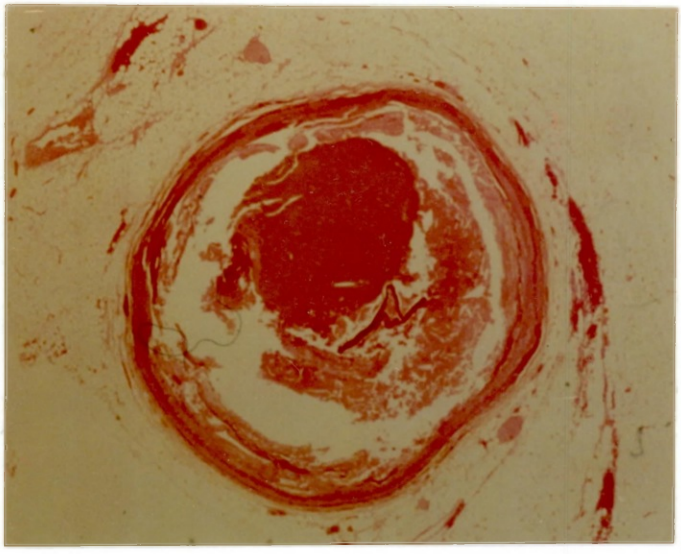


Figure 54: Photomicrograph following recanalization through thrombus. The neo-lumen is filled with barium and gelatin and is seen as the homogeneous circular zone within the thrombus. Note intimal fragment due to probe adherence.

Eccentric Lesions

The circumferential distribution of thermal energy from the metal cap is appropriate for concentric lesions and total occlusions. However, the effect of intense thermal energy in the presence of eccentric lesions was unknown. Therefore, the histological appearances following lasing of 25 eccentric lesions were studied. In all instances in which thermal injury was seen the injury appeared concentric with a varying degree of thermal injury to the contralateral normal arterial wall. In all cases of perforation (n=7) associated with eccentric lesions the perforation was through the contralateral "normal" arterial wall (Figs 56).

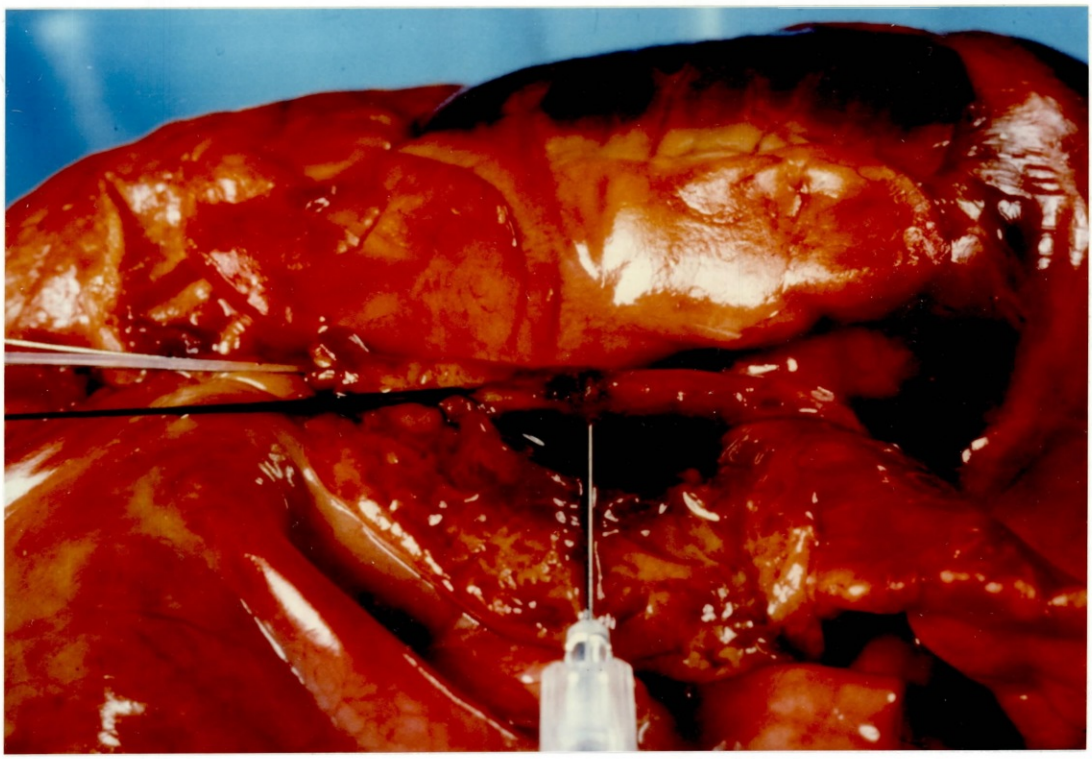


Figure 55: Photograph of a metal-capped optical fibre within a human circumflex coronary artery. The metal cap has not been activated: the dark area in the artery (needle pointer) is the metal cap seen through the *extremely thin* normal arterial wall opposite an eccentric lesion.

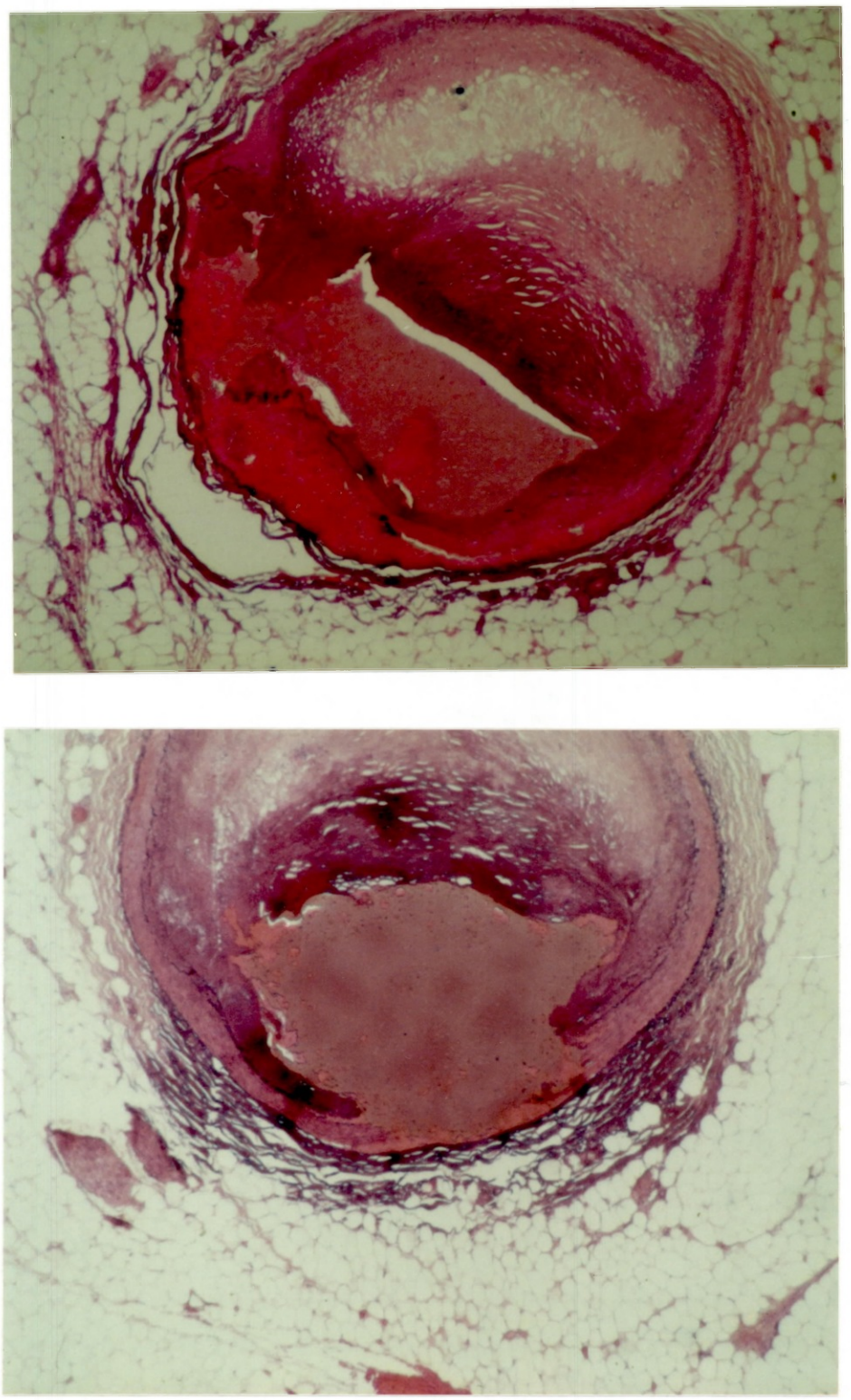


Figure 56: These two photomicrographs illustrate that there is no preferential thermal damage to atheroma at eccentric lesions, and highlight the risk of excessive thermal injury to the contralateral normal arterial wall.

Discussion

This study has shown that laser energy delivered through metal-capped optical fibres into human coronary arteries results in a spectrum of macroscopic and microscopic effects which are related to (a) the laser power, (b) the duration of laser delivery and (c) the arterial perfusate.

Examination of the frequency of perforation in the matrices in Table 15 reveals that for equivalent energies (Energy = Power x Time) laser power appears to be a more important determinant of thermal injury / perforation than the duration of exposure.

Furthermore, the results show that in saline there is a much wider and more predictable energy "window" which allows thermoablation without perforation.

This may be due to a combination of reasons. Firstly, the temperature studies have confirmed that tip temperatures are lower in the presence of saline than blood. Secondly, the presence of a coagulum around the heated probe may contribute to probe adherence and flap formation. Thirdly, the partial insulation afforded by the coagulum allows the temperature of the metal cap/coronary interface to soar to dangerous levels very quickly.

Adherence of the metal cap to the arterial wall was a significant problem, particularly in the presence of blood. Furthermore, adherence of the metal cap to the arterial wall resulted in varying degrees of intraluminal flap formation. At best light sticking occurred, but the metal cap could be easily released by the application of further heat; at worst the application of further heat in the thin walled artery resulted in perforation without release, so that withdrawal of the metal cap resulted in intussusception of the intima/media of the artery along the previously described plane in the media (Fig46). Although in the presence

of concentric atheroma this may result in an "endarterectomy" such an effect is generally undesirable. Sticking and flap formation were less pronounced with lower powers and in the presence of continuous forward movement. It was also less in saline than blood, but since temperature was not measured during this study the relative contributions of the blood coagulum and temperature towards this increased tendency to adhere remain unknown. Nevertheless, in both media it poses a significant risk in the absence of fibre advancement which may occur if fibre progression is inhibited by recalcitrant plaque.

Flap formation of varying degrees was a frequent occurrence. Such flap formation has also been noted consistently on angioscopic inspection of freshly recanalized femoral arteries following laser thermal angioplasty (M.Rees, Consultant Radiologist, Leeds: Personal communication). However, the pathophysiological and haemodynamic effects of these flaps is unclear. Kohchi (1987) performed autopsy examinations of 20 coronary artery sites from nine patients who had undergone percutaneous coronary balloon angioplasty. There was evidence of arterial wall splitting at all 20 sites (10 involved the intima and 10 involved the media). Twelve successfully dilated sites all showed evidence of a tear in the luminal surface even at 140 days after angioplasty. The tear was intra-intimal in 3 sites, transintimal in 5 and transmedial in 4 sites. It appeared that the splits/flaps healed by thrombus followed by smooth muscle cell ingrowth.

In vitro balloon dilatation of superficial femoral arteries revealed similar flap formation with separation of the plaque from underlying arterial wall (Lyon, 1987).

Similarly Rees in Leeds has reported angioscopic evidence of intraluminal flap formation in femoral arteries following recanalization using a rotational device (Kinsey catheter). Thus it would seem that some degree of flap formation attends most techniques of arterial recanalization and probably relates to a differential response between normal or less diseased arterial wall and heavily diseased arterial wall to thermal, radial (balloon) or

rotational energy. Furthermore, it appears that the presence of such flaps is not necessarily a harbinger of failure.

Failure to advance is likely to expose relatively "normal" arterial wall to the thermal insult where it becomes contiguous with the plaque. This was the main justification for interest in thermal damage and perforation thresholds of normal or minimally diseased arterial wall and provided the reason for studying perforation thresholds with a stationary metal cap.

Attempted recanalization of the six completely occluded coronary arteries confirmed that presence of calcium in a lesion significantly reduces the chance of successful recanalization. Minimal degrees of calcification were manifest as a "gritty" feeling with noticeable deflection of the metal cap away from the calcified plaque along the course of least resistance. Heavy and concentric calcification made advancement impossible.The inability of this particular type of laser delivery system to recanalise severely calcific disease is a major limitation.

Most isolated lesions in the coronary circulation are eccentric. However the distribution of thermal energy from the metal cap is circumferential. Although fibro-fatty plaque in aorta appears to be more susceptible to thermoablation than normal aortic tissue (Welch, 1987), this does not appear to be the case in coronary arteries. Not only are the walls of coronary arteries far thinner than aorta, but unlike aorta their connective tissue content is largely confined to the internal elastic lamina. These differences may explain the susceptibility of the of the "normal" contralateral arterial wall to perforation when this geometry exists. Furthermore, fibre displacement due to eccentric calcification may aggravate this problem.

In conclusion, this study has shown that recanalization of total occlusions with

circumferential thermal energy distribution is feasible. However, in the presence of eccentric lesions such a distribution of energy is inappropriate at energy levels sufficient to cause plaque ablation due to the risk of perforation. Furthermore, effective recanalization requires the application of forward force with some control of direction neither of which can easily be delivered percutaneously. The features outlined above probably contributed significantly to the low primary success rate in the human percutaneous study (Chapter 4).

CHAPTER 10

Discussion
&
Conclusions

Discussion

Disappointment with the long term results of conventional revascularization techniques (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) has spawned interest in alternative methods of coronary revascularization which offer the potential for improved long term success rates. Conventional techniques restore distal blood flow, but do not remove obstructive tissue mass. Laser energy offers the attractive theoretical potential for plaque vaporization and hence the potential for longer patency of the recanalized vessel. Initial attempts to transmit laser energy directly into blood vessels using bare optical fibres met with an unacceptably high perforation rate due to forward projection of the laser beam. Attempts to minimise this projection have included defocussing the laser beam on emergence from the fibre or placing a metal cap over the end of the fibre. The metal cap is heated by the laser energy allowing precise targeting of thermal energy. In addition the application of different sized caps allows some additional control over the diameter of the recanalized channel. Cumberland (1986) has clearly demonstrated that such a system can effectively recanalize severely diseased peripheral arteries. Furthermore, evidence is accumulating that the restenosis rate following thermal remodelling in peripheral vessels may be significantly lower than after conventional balloon angioplasty (Sanborn, 1986b, 1987).

Based on these encouraging early clinical results in the peripheral circulation several groups attempted percutaneous coronary recanalization using these fibres: Cumberland in Sheffield (1986d); our group at the Hammersmith Hospital (Chapter 3; Crea, 1988); and Sanborn in Boston (Sanborn,1986). The results of 17 patients have been published in detail. Successful recanalization with metal-capped optical fibres or metal-capped optical fibres in combination with balloon angioplasty was achieved in only 10 (59%) of the 17 patients.

The studies reported in this thesis have allowed us to conclude that although metal-capped optical fibres have a lower perforation rate than bare fibres their use in human atherosclerotic coronary arteries is limited by:

a. a poor primary success rate when used percutaneously **[Chapter 3]**

b. a tendency towards thromboembolism in the presence of blood with the release of embolic particles of up to 2mm in size **[Chapter 6]**

c. the release of significant atherosclerotic debris greater than 50μm and up to 1mm in diameter **[Chapter 7]**

d. an inability to vaporise calcific atheroma **[Chapters 7 & 9]**

e. a tendency towards perforation through the contralateral "normal" arterial wall in the presence of eccentric stenoses **[Chapter 9].**

f. the tendency of the metal cap to adhere to the arterial wall with resultant intraluminal flap formation on withdrawal of the metal cap **[Chapter 9].**

g. a stenotic effect on side branch origins which is worse in the presence of blood and in small vessels **[Chapter 8].**

Strategies for overcoming the limitations of metal-capped optical fibres and optimising their use in the coronary circulation depend on the identification and definition of the following conditions for their use:

1. The choice of perfusate during lasing
2. The choice of laser parameters
3. Atherosclerotic plaque geometry and composition
4. Methods of reducing adherence to the arterial wall

(1) *The Choice of Perfusate during Lasing*

A perfusate is required during lasing to keep the vessel distended. The choice of perfusate

is determined by two main factors:

(a) the temperature characteristics of the metal cap within that perfusate,

(b) the risk of embolization from the perfusate itself.

(a) The Temperature Characteristics of Blood vs Saline

The studies in Chapter 3 have shown that the temperature of the metal cap during lasing is related both to energy input and rate of heat (energy) dissipation. The temperature profiles are different when lasing is carried out in saline and blood.

In the presence of saline the latent heat of vaporization results in a maximum temperature of 100°C in the absence of flow , although once surrounded by steam the temperature occasionally rises to 150°C. When the saline is flowing effective heat dissipation by conduction prevents the temperature of the metal cap reaching 100°C. This may provide a protective effect when lasing is performed in saline since even in the presence of a severe coronary stenosis there is likely to be some flow around the metal cap before it completely occludes the stenosis. As the lesion is approached in the presence of flowing saline the temperature of the cap is unlikely to rise much above 70-80°C. At these temperatures significant damage to the normal wall proximal to the stenosis is unlikely. Once the cap occludes the lesion the temperature will reach 100°C in the absence of saline flow, at which point intracellular water within immediately adjacent cells will boil resulting in cellular disruption. The cell disruption allows the metal cap to advance. Once the cap enters the lesion the plaque insulates the metal cap allowing the the temperature to rise to 360-400°C (Deithrich, unpublished results from in vivo measurements during femoral recanalization) (Hussein, 1986).

Rapid cooling of hot metal cap as it emerges through the lesion followed by flowing saline will protect the distal "normal" arterial wall.

In contrast, lasing in blood results in a rapid rise to very high temperatures, in the region of 500°C after 3secs when 8-12 watts are used. Such high temperatures may be generated before entry of the metal cap into the stenosis and may induce thermal injury to the normal arterial wall on the pre-stenotic segment.

The histological studies have shown that lasing in blood narrows the range between those energies which cause the desired thermoablation and unwanted perforation. The use of a saline flush during lasing clearly allows amplification of this differential so increasing the safety margin of the procedure.

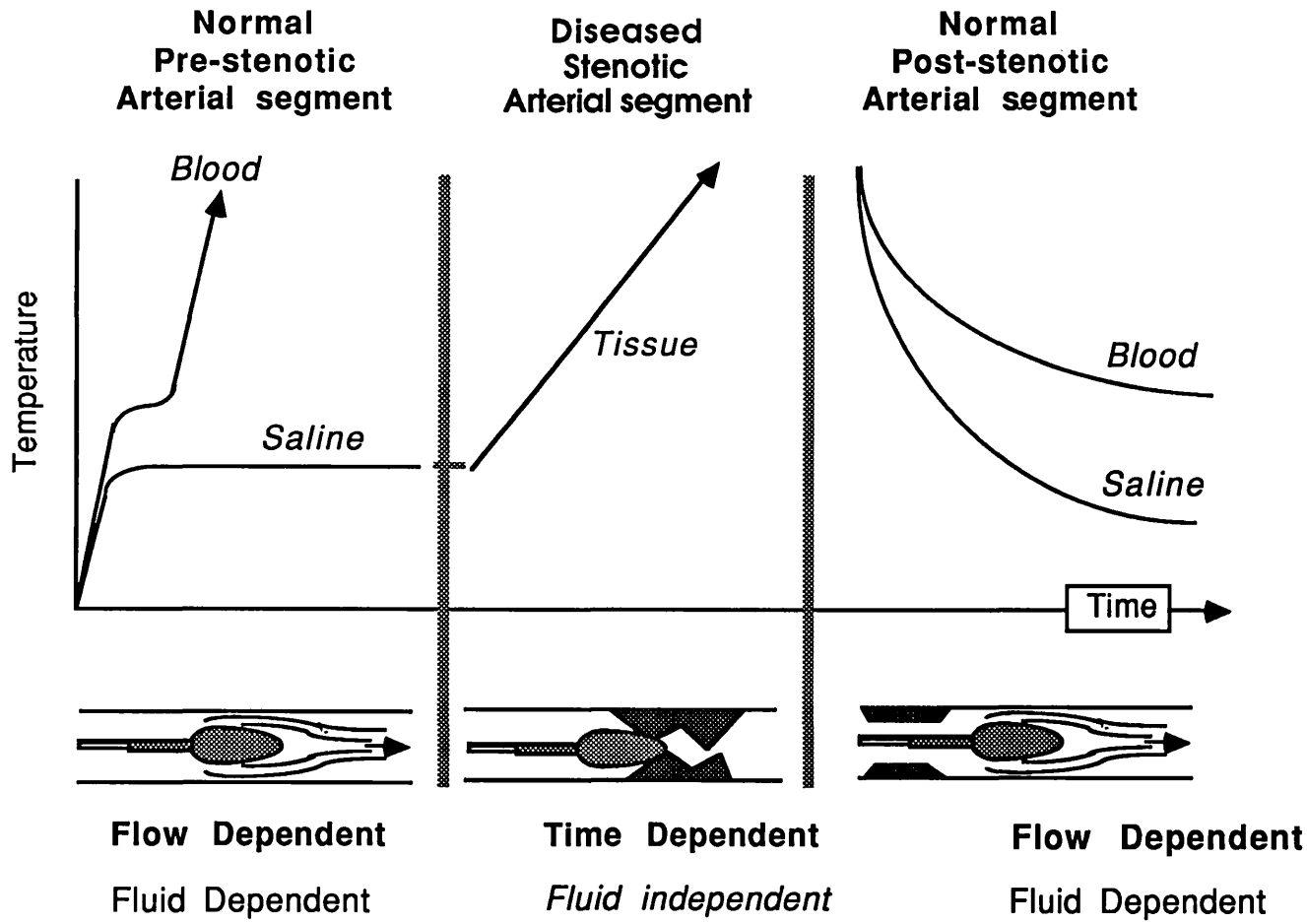


Figure 57: A diagrammatic representation of the temperature profile of the metal cap during the three phases of arterial recanalization: the approach to the lesion, the recanalization, and the cooling phase

(b) The Risk of Embolism from The Perfusate

Emboli from the perfusate may be either particulate or gaseous. This study has specifically addressed the issue of particulate thromboembolism and has demonstrated the generation of particulate debris in excess of 1mm when lasing with metal-capped optical fibres is performed in blood. Thromboembolic particles of this size would be capable of occluding small arteries (Arteriole: circa 30μm diameter). Although clinically significant thromboembolic problems have not been reported following laser thermal recanalization of peripheral arteries, the introduction of similar sized particles into the coronary circulation might be expected to result in significant distal ischaemia or even infarction. This concern is emphasised by evidence of myocardial infarction in 3 of 4 cases of percutaneous coronary laser angioplasty performed by Cumberland (1986d).

Two solutions to this potential problem exist. Firstly, energy parameters which allow recanalization without the generation of significant particulate debris have been identified in the thromboembolism study. This study revealed that at a low blood flow (5ml/min) significant thromboembolism did not occur when energies less than 8 Watts for 9 seconds were used. Secondly, the use of saline as the intra-arterial perfusate during lasing eliminates this problem. Avoidance of blood contact during *peroperative* laser thermal recanalization is easily achieved by perfusing the aortic root with crystalloid solution. Crystalloid flushing may also be achieved during percutaneous delivery using newly developed fibres which incorporate a flushing channel.

These studies have demonstrated, therefore, that during laser thermal recanalization saline is a safer perfusate than blood.

The Choice of Laser Energy

The choice of laser parameters (Power and Time) is determined on the one hand by (a) efficacy of ablation without perforation and on the other hand by (b) the generation of embolic debris either from the perfusate or from the atheroma.

(a) Efficacy of ablation without perforation

The cadaver heart study has demonstrated that if lasing is performed in saline there is a window between those energies which may result in therapeutic thermoablation and those which may cause perforation. In blood, however, this window is much narrower (Fig 15a). Furthermore, for equivalent energies there is a significantly greater risk of perforation in blood and this relative risk increases with increasing exposure time. Thus the energy requirements will be different in the two perfusates.

In saline, in the absence of movement of the metal cap, energies of 10 Watts for 10 seconds (100J) result in thermoablation without perforation when delivered to the same site. However, in blood similar energies carry a significant risk of perforation.

(b) Generation of embolic debris

The study on thromboembolism has clearly demonstrated that this is a potential problem which is both energy and blood flow dependent. In the presence of low blood flow (5ml/min) energies of 8 Watts for <9 seconds seconds do not result in significant thromboembolism although adherent coating of the metal cap occurs.

Debris from the atheroma was only investigated in saline. Although most debris was smaller than 50μm a few large fragments were released. However, there was a significant tendency towards smaller debris with higher powers.

Debris formation from the use of metal-capped optical fibres has not been previously assessed. However, atheromatous debris release has been studied using argon laser light (Grewe, 1986). Particle size when this method of vaporization is used is largely (54%) in the 10-20μm range with only 11% particles >50μm.

Thus for safe and effective recanalization the highest powers possible should be used since these will most effectively ablate plaque, allow forward advancement of the fibre will reduce the size of atherosclerotic debris. In blood 8 Watts for <6 seconds provides energies that are capable of ablating plaque and allowing forward

movement of the metal cap without causing significant thromboembolism.
However, in saline 10-12 Watts may be used for 10 seconds with effective atherosclerotic ablation, no serious risk of perforation and reduced atherosclerotic embolism. Once again there is a strong argument in favour of lasing in saline since this would eliminate or attenuate the thromboembolism risk.

The Type of Stenosis:

(a) concentric v eccentric

(b) calcified v non-calcified

(c) relation to side branches

The histological studies clearly identify concentric lesions and total occlusions as being the safest and most susceptible coronary artery geometry for recanalization. The delivery of circumferential energy to such plaque is appropriate. However, a similar distribution of thermal energy to eccentric lesions in vessels where the mural thickness of the thinnest adjacent wall may be less than 1mm results in an unacceptably high risk of perforation. It has been noted that the internal elastic lamina is more resistant to thermal damage than other arterial wall structures and it has been argued that the presence of this elastic tissue within the arterial wall opposite an eccentric lesion may facilitate preferential atheromatous ablation and act as a barrier against perforation (Abela, 1986). Although we have observed an intact elastic lamina despite thermal injury to adjacent tissue, including the adventitia, it is unlikely that a thermally compromised internal elastic lamina would provide enough mechanical strength to contain a perforation when adjacent structures have been destroyed. The cadaver heart study reported in this thesis has shown that preferential ablation of plaque does **not** occur when circumferential thermal energy is applied in coronary arteries with eccentric lesions and that all perforations associated with this geometry occur through the "normal" arterial wall.

The issue is further complicated by the unpredictable presence within the atheromatous plaque of calcium which is resistant to the temperatures which may reasonably be employed within the coronary circulation. These findings are at odds with some published results. Lee (1984) claimed that metal-capped optical fibres were capable of vaporising both fibro-fatty and calcified hyaline atheromatous plaques in human aorta. Similarly, Welch (1987) argued that the thermal conductivity of normal arterial wall is higher than atheroma and that this differential leads to the preferential dissolution of plaque, rather than arterial wall, in the presence of eccentric lesions. His study was conducted on human cadaver aorta with the probe held at right angles to the arterial wall at the junction between a fibro-fatty plaque and normal arterial wall. The plaque was not calcific. Given the high concentration of elastic tissue in normal aorta such a differential would be expected. Extrapolation of such findings into the coronary vasculature are not justified in view of the totally different structure between aorta and coronary arteries and the frequent presence of calcium in coronary lesions.

Despite these few favourable reports, concerns that this technique cannot recanalize calcific plaque are growing. Abela (1986) reported deflection of a 2.0mm metal-capped optical fibre by calcific atheromatous plaques in diseased segments of leg vessels. Furthermore, angioscopic inspection following recanalization revealed white flecks embedded in the wall of the neo-lumen suggesting residual calcium.

The findings reported in Chapter 7 following in-vitro lasing of heterogeneous human endarterectomy specimens clearly demonstrate that calcific foci are **not** vaporised by the metal cap (See fig. 34). Furthermore, in the cadaver heart study (Chapter 9) heavily calcific disease prevented recanalization of an occluded left anterior descending coronary artery.

Furthermore, it has been shown that heterogeneity between plaques results in an enormous

variation of response to equivalent doses of pure laser energy under highly standardised conditions (Shelton, 1986). Our findings are similar although the variation in the degree of histological damage for equivalent combinations of power and time may largely have been related to variations in arterial flow and artery size between hearts and different sites of lasing within the same vessel. We believe that such variability is a true reflection of the inherent variability in clinical coronary artery disease.

A further consideration is the proximity of the stenosis to a side branch. The study reported in Chapter 8 shows that thermal stenosis of normal side branch origins occurs when metal-capped optical fibres are activated within the adjacent parent artery . This effect has not previously been reported. Since coronary stenoses may lie close to side branches this effect may be an important consideration when analysing coronary arteries prior to laser thermal angioplasty. However, the study did not address the issue of side branches included in the atherosclerotic process.

Thus the coronary lesion most amenable to laser thermal angioplasty would be a concentric, non-calcified stenosis, not adjacent to a side branch orifice. The stenosis would be lased in saline using powers ≥ 8 Watts.

(4) Adherence of the metal cap to the arterial wall

Adherence of the metal cap to the arterial wall is a major limitation of this technique. Although adherence occurs when these fibres are used in the peripheral circulation it does not pose such a significant problem for 2 reasons. Firstly, the muscular skeleton of the large peripheral arteries is much stronger than thin walled coronary arteries and sticking of the metal cap can be overcome by force. Secondly, adherence can usually be overcome in the peripheral circulation by increasing the laser power until tissue vaporization occurs and the metal cap is freed. These two options are limited in the thin walled fragile coronary arteries and both approaches are attended by a high risk of perforation. Although not

initially recognised as a serious problem other workers are concerned with this problem (Dr D. Cumberland, Sheffield & Dr E. Dietrich , Arizona - personal communications; Abela 1986a). On the other hand Moosdorf (1988) who has extensive peroperative experience with this technique does not accept that adherence poses a problem. However, Moosdorf uses only 7 Watts to activate the metal cap during perfusion with cold cardioplegia solution. Thermographic imaging performed during activation of the metal cap shows that the temperature of the coronary artery reaches a maximum of 38°C. This supports the view that lasing in saline protects the normal arterial wall but also raises doubts as to whether the metal cap is vaporising stenoses or simply acting as a warm / hot dilator. Nevertheless, Moosdorf has shown that effective recanalization of proximal coronary stenoses can be achieved peroperatively during continuous infusion with cold crystalloid cardioplegic solution. Although he reported a successful reduction in stenosis in 17 of 20 stenoses, the passage of the probe was prevented by calcific stenoses in 2 patients and a perforation occurred at the site of a eccentric lesion in a third. Medium term angiographic follow-up is not available. These observations support the author's studies which indicate that even such controlled conditions do not overcome the problems of lesion geometry (eccentricity) and composition (calcification) in the clinical setting.

In summary uncalcified total occlusions or concentric lesions may be effectively recanalized using metal-capped optical fibres. However as efficacy increases so safety decreases. The safety of the recanalization is further decreased by the presence of thermally resistant calcific plaque and eccentric lesions.

Finally, widespread clinical applicability of this technique is likely to be limited by the inability to identify plaque geometry and composition prior to lasing and the problem of metal cap adherence to the arterial wall.

Table 16

	4 Watts	8 Watts	12 Watts
Efficacy of Ablation	Softens atheroma	Significant ablation	Significant ablation
Adherence/ Perforation	*Progressive* →		
Atheromatous debris	*Reduction in particle size* →		
Thrombo-embolism	Nil	Nil if < 9 s	Potentially severe

Table 16 summarises some of the findings from the studies reported in this thesis and illustrates that increasing efficacy of ablation is associated with increasing complications.

Alternative Techniques of Laser Coronary Angioplasty

The limitations of metal-capped optical fibres have rekindled interest in optical laser systems for coronary laser angioplasty. The following part of this discussion represents the author's personal view of the medium term future for laser coronary revascularization.

1. The laser

The choice of continuous wave lasers for laser angioplasty is largely historical. Argon and Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG) laser wavelengths could easily be transported by commercially available optic fibres that were sufficiently flexible and non-toxic.

However, the effect of continuous wave laser energy on biological tissue was found to be thermal, not only by gross inspection which reveals charring, but also by analysis of the photoproducts following vaporization of vascular tissues (Isner, 1985). The appearances are similar to those illustrated in figures 51 & 58 which show a superficial zone of necrosis with a subjacent zone of polymorphous lacunae. Such an extensive peripheral zone of injury is clearly undesirable in thin walled coronary arteries.

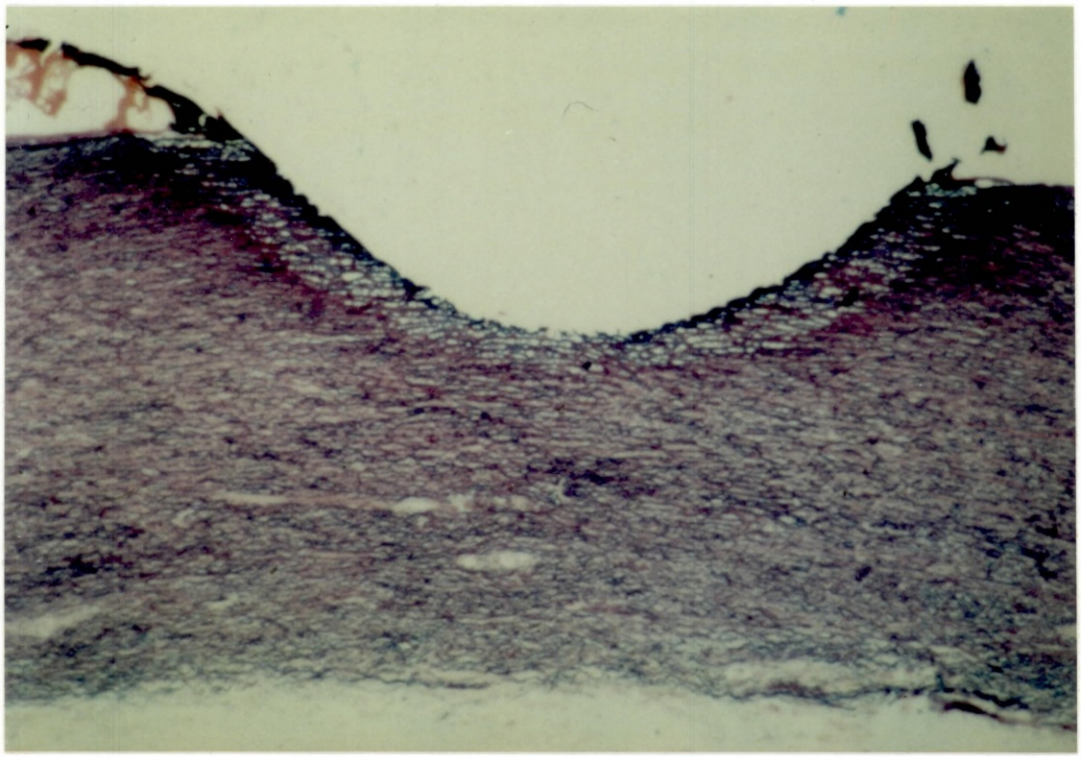


Figure 58 A photomicrograph (Trichrome Mallory) of a crater in human aorta formed by activating a metal cap on the intimal surface using 12 Watts for 9 seconds. Note the superficial charring with a broad subjacent zone of thermal injury characterised by polymorphous lacunae.

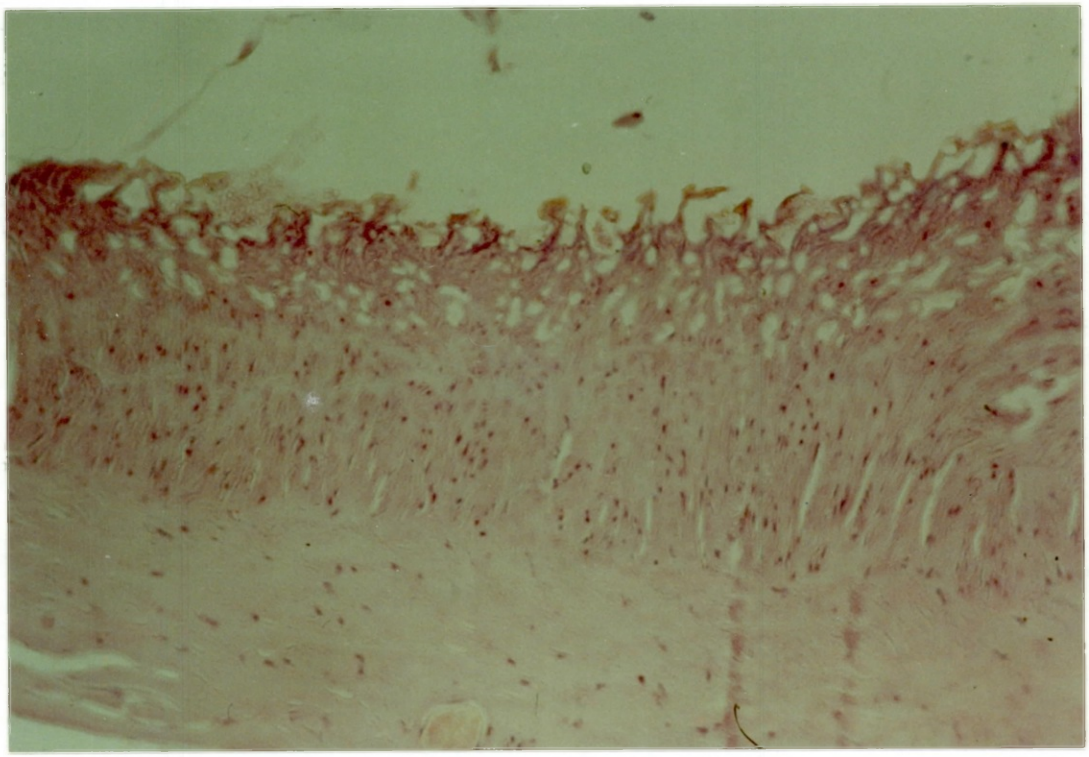


Figure 59: A photomicrograph (Haematoxylin & eosin) of a proximal canine circumflex coronary artery showing the effect of the metal cap following 6 Watts for 5 secs, delivered percutaneously into the beating heart (See Chapter 3, page 75). The photomicrograph shows a broad zone of thermal injury characterised by hypereosinophilic staining and polymorphous lacunae.

The search for methods of eliminating this peripheral zone of damaged tissue has centered around two approaches. The first involves the delivery of very short, high energy pulses to vaporise materials so rapidly that transfer of heat to the non-irradiated subjacent strata is negligible. The second solution involves the utilisation of pulsed ultraviolet photons (Excimer laser) which are well absorbed by biological tissues and appear to disrupt molecular bonds resulting in photochemical rather than thermal tissue ablation.

It would seem reasonable that the delivery of ultraviolet energy in nanosecond pulses might achieve tissue ablation by both of these processes so allowing a more controlled vaporization in the absence of peripheral thermal tissue damage. Such a hypothesis has been confirmed (Grundfest, 1985; Isner, 1985). Furthermore, the extent and rate of tissue damage can be accurately predicted and controlled (Shehab, 1988). Finally, the application of high energy nanosecond pulses of ultraviolet energy (308nm) is capable of vaporising calcified atheromatous plaque (Personal observation on calcified human aortic plaque, Spectranetics 308nm UV Pulsed laser).

However, recent work by Clark and Isner (1987) who analysed the vapour phase products of excimer ablation of cardiovascular tissue has shown that, despite previous beliefs, the process is largely thermal. The implication from this finding is that the important feature is probably pulsing rather than laser wavelength. This view is supported by the observation by Kramer (1987) that pulsed argon laser produces a smooth crater in atherosclerotic tissue without the subjacent coagulation necrosis seen with continuous wave argon laser or the metal cap.

The Guiding System

Previous studies on Ultraviolet laser delivery were limited by the inability to transport this energy via flexible optic fibres. More recently such fibres have been developed although they are not widely available.

The Fibre Tip

New metal-capped fibres

The definition of the criteria outlined above stimulated the development of a new design of metal-capped optical fibre. This fibre (See Fig. 60) is designed for intraoperative use. It is a three channel catheter. One channel carries an optic fibre for heating the metal cap, another allows the passage of a central guidewire and a third allows a continuous saline flush. The fibre also incorporates 2 safety wires within the catheter to prevent embolization of the metal cap should this become dislodged. This, however, is less likely than in the original design of fibre since the metal cap is not crimped onto the end of optic fibre; instead the end of the optic fibre floats loosely in the metal cap which is held in position by the safety wires.

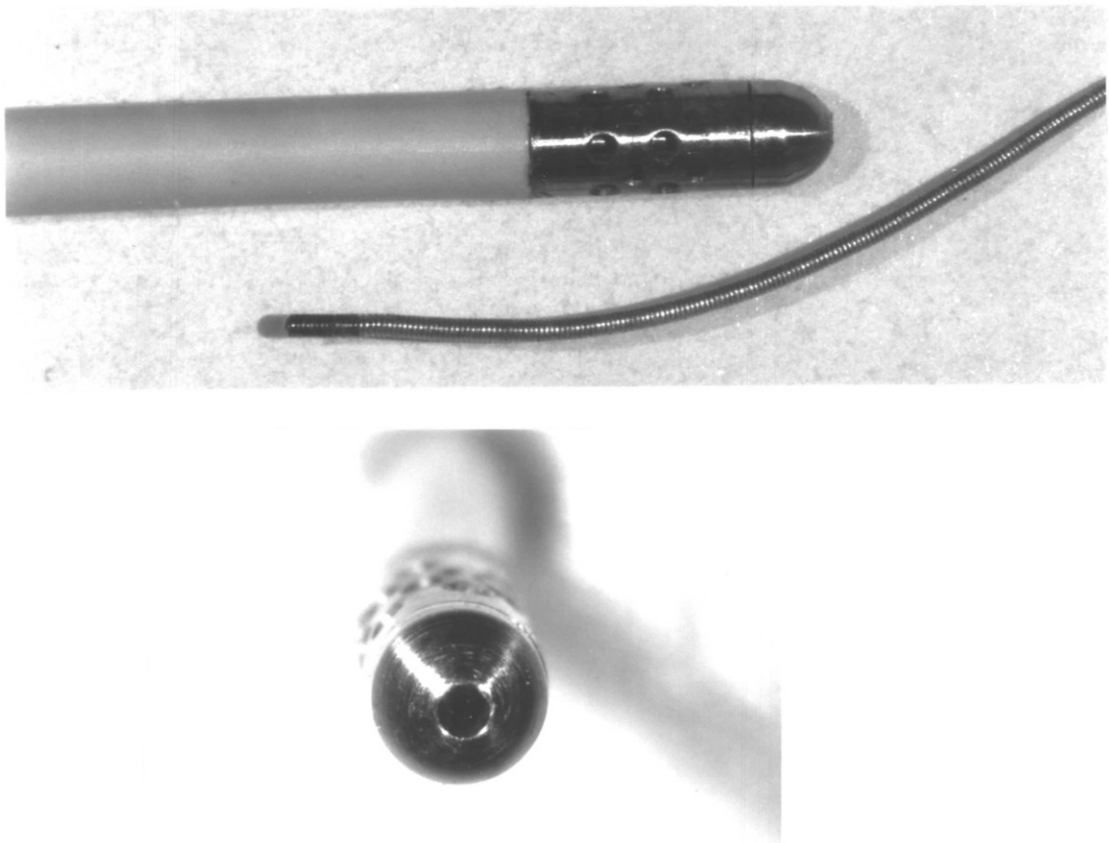


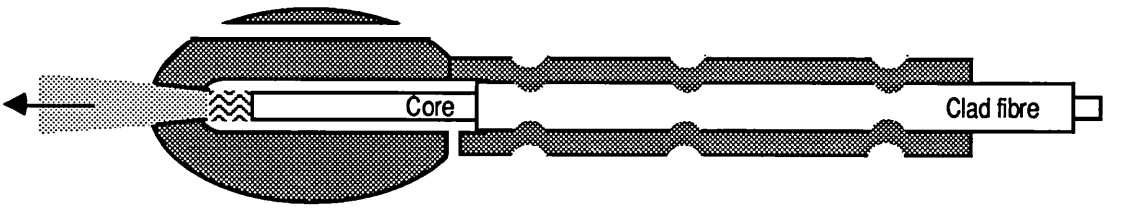
Figure 60: A three channel metal capped optical catheter designed for intraoperative use.

This type of fibre allows centralisation of the metal cap within the stenosis using a guidewire and a saline flush to prevent overheating of the proximal metal cap which might damage relatively normal proximal arterial wall. However, the stiffness of the catheter confines its use to the intraoperative approach.

Although such a fibre overcomes many of the problems outlined above, the inability to ablate calcified plaque remains, despite claims to the contrary (Lee, 1984). To this end a further fibre has been developed: The "hybrid hot tip" (See Fig. 61). This fibre allows 10-20% of the laser energy arriving within the metal cap to escape. This light is said to soften the atheroma, including calcified atheroma, in front of the probe so facilitating smooth advancement (Abela, 1986).

Figure 61

Hybrid Metal-Capped Fibre



Limited10-20% forward projection
of laser beam through central hole

Despite these two innovative modifications, three further problems remain: (1) eccentricity of coronary lesions, (2) conduction of heat through the full thickness of the coronary artery wall due to continuous heat from the metal cap, (3) adherence of the metal cap to the arterial wall.

These limitations effectively eliminate the metal cap as a safe, cost effective device for

coronary recanalization. The safety is limited by probe adherence contributing to intraluminal flap formation and perforation; cost effectiveness is compromised due to the low incidence of suitable lesions which cannot already be treated safely and effectively by conventional balloon angioplasty. Strong evidence regarding safety and improved restenosis rates would be required to justify the capital outlay required to purchase an 18 Watt Argon laser solely for use in the coronary circulation.

Sapphire Tipped Fibres

Sapphire tipped fibres consist of a synthetic sapphire crystal, screwed onto the end of a double lumen delivery catheter. Sapphire is transparent to argon and Nd:YAG radiation. One lumen in the catheter transmits the fibre optic, the other allows a continuous flush with saline. The saline flush not only keeps the proximal end of the tip cool in the face of scattered/reflected radiation but also reduces interference from blood at the plaque-tip interface. Such sapphire tips may have different focussing characteristics and have a varying size (Geshwind, 1987a; Verdaasdonk, 1987). In addition, the sapphire tip probably heats allowing a combination of laser light-tissue interaction and "hot tip" angioplasty. These features combined with an atraumatic shape make this fibre an attractive concept for laser angioplasty. It has been shown that such fibres can generate larger channels of recanalization with less risk of perforation than bare fibres (Geshwind, 1987b; Bowker, 1987). Furthermore, the atraumatic shape and optical characteristics of ball shaped sapphire tips allows them to recanalize curved vessels through a radius of curvature of as little as 2.5cm (Michaels, 1988). Sapphire tipped optical fibres have now been used successfully in peripheral vascular occlusions using both continuous wave (Fourrier, 1987) and pulsed Nd:YAG beams (Cross, 1987). Lammer has reported successful recanalization in 52 of 64 (81%) peripheral obstructions, with 6 (9%) perforations using continuous wave Nd:YAG and sapphire tips (Lammer, 1988). These preliminary reports in the peripheral circulation are encouraging although larger numbers

of patients and longer follow-up are required.

New Quartz Fibre Tip

We have developed a new 200μm core optical fibre designed to produce a corolla-like distribution of laser energy. This was initially developed by tapering the end of a bare fibre which provided divergence of the beam but did not totally prevent its forward projection. However, the tapered end was fragile and backburning occurred when it came into contact with tissue. To overcome both limitations a quartz cap (1.2 mm external diameter) was fitted on to the tapered fibre tip. This provided an angle of divergence of the laser beam from the fibre axis ranging between 25^{o} and 35^{o} without any forward projection of energy (Fig. 62).

Initial studies on human aorta and canine coronaries using this new optical fibre are encouraging. The fibre is able to create channels larger than those obtained with conventional bare fibres and can ablate a volume of tissue six times greater for equivalent amounts of laser energy. The lack of the forward projection of the laser beam may make the use of these fibres in tortuous coronary arteries safer than bare fibres.

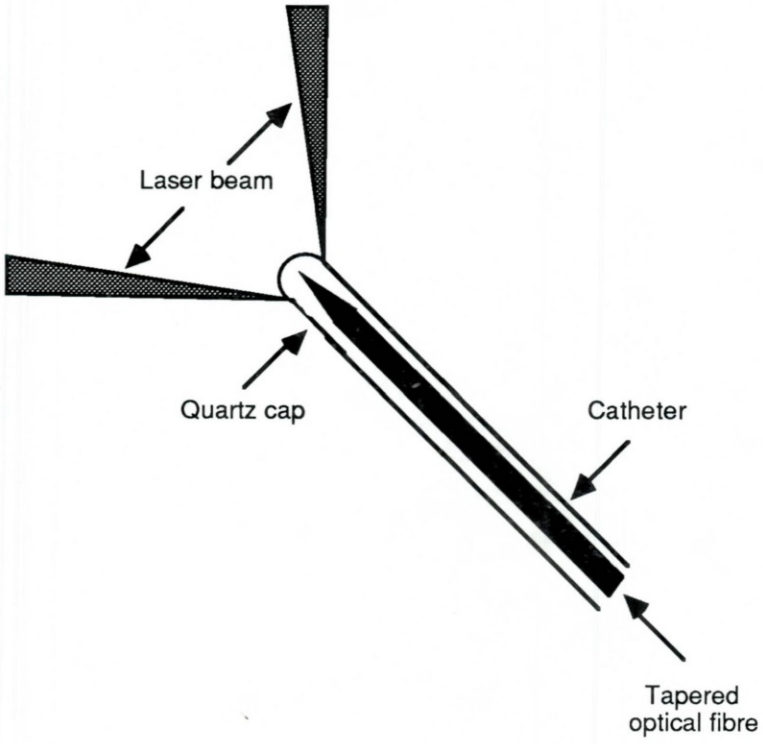


Figure 62: The upper diagram shows the structure of the new optic fibre. The lower photograph shows the distribution of argon laser light emanating from the tip.

The ability to ablate by irradiation may overcome some of the problems which limit the utilisation of metal-capped fibres and should also allow full exploitation of the properties peculiar to laser energy. Finally, the presence of the glass capsule appears to minimise the potential risk of mechanical trauma.

The application of circumferential energy to concentric lesions is logical as demonstrated by experimental results with the metal cap (Sanborn, 1985) and the success of balloon angioplasty when such geometry exists. However, both balloon angioplasty and laser angioplasty are compromised by eccentric lesions.
Therefore, it is likely that no single fibre tip will suffice for all plaques. The author believes that two types of fibre tip will be required: one to tackle concentric lesions and another to distribute energy in an eccentric arc.

The Hot Balloon

In an attempt to combine the proven effects of balloon angioplasty with those of laser energy Spears group have designed a new balloon catheter which allows mechanical stenosis dilatation during the delivery of Nd:YAG laser energy through the balloon wall. It has been hypothesised that continuous delivery of laser irradiation during balloon inflation might reduce the incidence of flap formation by local "welding" and that this "hot" balloon angioplasty could result in a lower restenosis rate than that encountered after conventional balloon angioplasty (Spears, 1987; Sinclair, 1987). Preliminary results in canine coronary arteries are exciting. It appears that intramural proteins in the irradiated coronary artery are denatured and that a dilated arterial "cast" of the balloon remains. Furthermore the diameter of the irradiated segment remains constant even during intracoronary ergonovine, while the artery on either side of the irradiated segment constricts vigorously: thus the

denatured arterial wall acts as its own stent.

Plaque Identification

The ideal system will be capable of identifying and distinguishing normal arterial wall from atherosclerotic plaque. Techniques vary from selective staining of atherosclerotic plaque (Abela 1982; Murphy-Chutorian, 1985) to spectral analysis of laser induced tissue fluorescence of arterial wall (Prince, 1986; Laufer 1988). The former has not proved practicable and the latter requires expensive complex equipment and remains at an experimental stage. Angioscopic guidance has been shown to be helpful in intraoperative peripheral laser angioplasty (Abela, 1986) although it remains an investigative tool. Angioscopy certainly allows good visualisation of plaque even through a 1.8mm angioscope. However, it only allows an evaluation of the surface of the plaque, and vision may be obscured during lasing by smoke or bubbles from a perfusate. More recently the development of a prototype 2-D ultrasound transducer housed in the tip of a 4 French intravascular catheter offers the exciting possibility of visualisation of arterial wall structure beneath the surface with the ability to easily assess the composition of plaque with relation to calcification.

The Future

The ideal combination of laser and delivery system does not exist. Because of their ability to ablate calcific plaque pulsed laser systems offer distinct advantages over continuous wave lasers, especially if coupled to an optic fibre with removable tips. The application of circumferential energy to concentric lesions is logical. However, both balloon angioplasty and laser angioplasty are compromised by eccentric lesions. Thus it is likely that, in the medium term future, no single fibre tip will suffice for all plaques. Two basic types of fibre tip will probably be required: one to tackle concentric lesions and another to distribute energy in an eccentric arc. Such a system might be operated in conjunction with intraluminal 2 dimensional echographic imaging allowing continuous visual feedback to assess rate of advancement, fibre orientation in relation to plaque geometry, wall thickness and degree of calcification of the plaque about to be vaporised.

CONCLUSION

Although metal-capped optical fibres appear to be effective in the treatment of peripheral vascular disease, the limitations outlined in this thesis will prevent such fibres becoming an established therapeutic modality in the coronary circulation.

APPENDIX

Discussion

on

Methodology

PERCUTANEOUS STUDIES

(1) Dog Study

This study was designed to assess the acute effects of in vivo delivery of intra coronary thermal energy. It demonstrated that intimal thermoablation could be achieved without perforation in normal canine coronary arteries. The circumflex coronary artery was used rather than the left anterior descending coronary artery simply because in greyhounds it is easier to access from the carotid.

The angiography in this study was performed using a portable C-arm and was recorded onto video tape. Although such a study would seem to provide an excellent opportunity to assess the vasomotor response to thermal damage, at least in the "beating heart" group, the nature of the equipment and recording made angiographic analysis of the sites of lasing with the CAAS system impossible and therefore attempts to measure epicardial diameter were abandoned. Angiography was used solely as an aid to detecting coronary arterial perforation.

Histology was performed not only to assess the extent of thermoablation but also to ensure that perforation had not occurred since angiography is a poor detector of perforation (Crea, 1986; Anderson, 1987; Gal, 1987).

Endothelial damage and the arterial response to surface injury are recognised as important factors predisposing to thrombus formation and the development of atherosclerotic lesions (Ross R, 1976; Ross R, 1986). Thus, with the advent of clinical trials it would be prudent to understand the type and amount of injury associated with specific laser sources, as well as the response of the arterial wall to that injury. Given that such a response may have a profound effect on arterial patency both acutely and in the long term, the main shortcoming of this study is that it did not address the issue of either the early response, i.e. 24-48 hours, or the chronic effects of thermal damage and healing within the coronary arteries.

In vitro histological studies have demonstrated that different lasers have vastly different effects on tissue. Continuous wave lasers (argon, carbon dioxide and Nd:YAG) all cause considerable thermal damage, in many ways similar to that caused by the metal cap. There have been several reports of the acute and chronic in vivo arterial responses to continuous wave laser irradiation. These may provide some insight into the arterial response to the metal cap since both insults have a large thermal element. Acute, severe thermal injury to the vessel wall may be observed in normal and atherosclerotic animal models, with either carbon dioxide (Gerrity, 1983; Treat, 1983) or argon (Abela, 1983b; Abela 1985d; Lee 1984c) lasers. Early gross morphological and histological responses include *enlarging* zones of tissue injury (Treat, 1983), platelet-fibrin thrombi (Gerrity, 1983; Treat, 1983) and medial necrosis (Lee, 1984c; Litvack, 1987b). Despite complete re-endothelialization between 2 and 8 weeks after injury, disadvantageous chronic effects occur, such as fibrous caps over residual necrotic tissue, perivascular inflammation causing adhesions to surrounding structures, and localised aneurysm formation (Gerrity, 1983; Litvack, 1987b). However, there is no evidence of accelerated atherosclerosis at the laser sites in normal (Treat, 1983; Abela 1985d; Litvack, 1987) or cholesterol fed (Gerrity, 1983; Abela, 1983b; Lee, 1984c) animals. Pathological specimens of human peripheral artery 2 weeks and 1 month after Nd:YAG laser recanalization have shown persistent thermal injury as well as areas of new fibrous intimal tissue and incomplete re-endothelialization (Geshwind, 1986b).

It is likely that that the arterial response to thermoablation with the metal cap would be similar given that the initial insult is similar. However, many factors influence the arterial response to injury including the size of the injury, the depth of the injury and the animal model used (Prevosti, 1988).

A possible limitation of extending this acute study done in fit, euthyroid dogs on a normal diet, to evaluate a chronic response is that it seems unlikely that the less favourable results

of plaque formation and intimal hyperplasia would occur at the sites of thermal injury, whereas such results might occur in an atherosclerotic animal model or even Man.

(2) Human Study

The human percutaneous study was hampered by the same limitations imposed on the animal study. Firstly the use of an image intensifier system in the operating theatre produced images which were not clear enough to be analysed by the CAAS system. Secondly the application of internal mammary artery grafts to the recanalized vessel produced a watershed phenomenon which predisposed to thrombosis precluding any meaningful comment on patency.

Both of these of these limitations are the direct result of considered ethical opinion and the resultant decision to perform laser thermal recanalization in the operating theatre on patients about to undergo coronary artery bypass grafting. This decision has proved to be correct since both minor complications (Cumberland, 1986) and major complications (Chapter 4; Rosenthal, 1989) may attend this procedure.

This study aimed to assess the ability of the metal cap to recanalize coronary arteries without supplementary balloon angioplasty, unlike those studies performed by Cumberland and Sanborn (Cumberland, 1986; Sanborn, 1987) where the "lased" lesions underwent immediate balloon dilatation so diluting their value for assessing the potential for this technique. Further reports of studies using the metal cap alone or in combination are anticipated.

TEMPERATURE STUDY

This study was conducted under highly controlled conditions in order to compare the thermal characteristics of the metal cap in different perfusates. Digital rather than analogue temperature recording techniques were chosen in order to facilitate statistical analysis. The temperature profiles recorded using this system are similar to those achieved by other investigators (Verdaasdonk, 1987) (Rosenthal, 1989, personal communication). The temperature characteristics of the metal cap appear to be different when it is in contact with tissue, when the temperature appears to reach a plateau at about 300-400°C (Barbieri, 1987; Hussein, 1986; Silverman, 1988; see also Chapter 9). This difference probably relates to the size and nature of the conduit in which the metal cap is activated, and the relative size of the metal cap within the conduit. The temperatures recorded in Chapter 8 (p167) are compatible with the rigid temperature studies performed in Chapter 5. The temperatures recorded in blood in canine coronary arteries are maximum temperatures after the application of 8 Watts for 6 seconds, whereas those recorded in Chapter 5 are maximum temperatures after only 3 seconds, so higher temperatures would be expected. Furthermore, higher temperatures would be expected in the distal vessels where flow is less and the vessel size is smaller. However, the temperatures recorded in the coronary arteries in saline are substantially different to those recorded in the silicone tube. The reason for this is that in the coronary arteries the metal cap may abut onto the arterial wall which then partly insulates the metal cap. In the proximal coronary arteries (diameter 3.3±0.5mm [mean±SD]) insulation from the artery is likely to be minimal, but bubbles may increase the effective insulation. The distal canine LAD mean diameter only 2.6±0.4mm [mean±SD], and saline flow would have been less, together allowing for greater arterial insulation and a higher temperature.

THROMBOEMBOLISM STUDY

Most *in vitro* studies to assess debris or microaggregate formation in blood focus on four different principles. Assessment by the determination of differential dry weights, as employed in this study, and screen filtration pressure measurements may be characterised as bulk measurement techniques; whereas measurement by electrical resistance (Coulter principle), or single file optical methods (laser flow cytometry) may be be described as single particle measurements with the ability of determining size distribution.

Differential Dry Weight Assessment of Microaggregates

During such an experiment all other factors influencing the formation of microaggregates need to be kept constant during a test series. This requirement is not easily fulfilled.
Important factors as described by Eisart (Eisart, 1979) are:

At Blood Collection:

1. *Individual differences between donors.*

In this study residual blood from the cardiotomy reservoir of a cardiopulmonary bypass circuit was used. This blood was dilute and required haemoconcentration to a packed cell volume of 35%. This resulted in a inevitable loss of volume so that the blood from each cardiac surgical patient was only used for two runs of ten samples as defined by the latin square. The blood was randomly allocated to these two runs by predetermined shuffled cards.

2. *Type of anticoagulant and extent of anticoagulation.*

The blood collected from the cardiotomy reservoir was fully heparinised.
After centrifugation and redilution to ensure a fixed haematocrit the blood was stored in blood transfusion bags containing acid citrate dextrose. Further anticoagulation parameters

were not measured. However no clot was seen within the tubing or filter housing. Furthermore, the small amount of debris measured on the filters during control samples implied that anticoagulation was adequate.

3. *Haematocrit.*

Constant haematocrit of 35% was ensured

4. *Storage temperature and length of storage.*

Blood was collected in the late afternoon, stored overnight at 4°C and centrifuged and rediluted the following morning prior to use. All collections were treated in a similar fashion.

During the filtration experiment:

5. *Priming.*

Prior to each sample the new filters in the filter housing were rinsed with 10ml 0.9% saline.

6. *Constant flow rate.*

A constant and repeatable flow rate was ensured by the use of a syringe pump to run each 10 ml blood sample through the system. When the syringe was empty the remaining blood within the tube was filtered under gravity prior to flushing the system with 10ml of 0.9% saline at 40ml/min, followed by 10 ml of ethanol.

During Sampling:

9. *Sampling after constant volume.*

This was built into the experimental design.

10. *Delay between sampling and measurement.*

All samples were subject to the same delay between sampling and weighing.

Thus most of the established criteria were fulfilled during the design and conduct of this experiment. However, two particular points remain. Firstly, the use of blood from a cardiopulmonary bypass circuit is not ideal. It is known that blood from a bypass circuit is

deficient in platelets, and to some extent protein and that the blood may contain increased numbers of spherocytes and crenated red cells. However, this does provide a useful source of human blood. Indeed, it may be argued that in the perioperative setting metal-capped optical fibres may be used in blood of this nature.

Secondly, size classification from stacked filters is is of less value than that achieved by single particle measurement systems. It is known that foreign material in blood is more or less immediately coated with a layer of protein, fibrin and various cells (Baier, 1969; Bischoff, 1972). For given material and blood parameters the total weight of this layer is proportional to the surface area exposed to the blood. In stacked mesh filter systems, which are a well established model for assessing microembolism, the individual filters within the stack are not equivalent either in surface area or in "open" area, both of which are largely determined by pore size. Therefore, for meshes of different pore size within a stacked filter system different differential weights due to different amounts of coating material should be anticipated without any debris or microaggregates being collected on the filters. Furthermore, the development of thrombus downstream on the rear side of mesh filters has been described (Eisert, 1979), although such a phenomenon was not observed in these experiments.

In this study although a thin layer of proteinaceos material was seen to coat the filters following the passage of blood there was no significant difference between the differential dry weights of the control filters of different sizes, implying that such a phenomenon may not have distorted the results. However, this does not mean that such a difference may not exist when blood which has been subjected to thermal insult is filtered. It is known that human red cell membranes fragment at 50°C due to increased membrane fluidity (Ahkong,1973). Such a change in fluidity might explain the membranous webs and cell fusion seen in the debris on the larger filters (Fig. 28).

The filters used in this study were made of stainless steel mesh. The mesh was purchased in sheets and the filters punched out by the author in our workshops using a specially made

7mm diameter circular punch. Following a pilot study analysis of the results revealed that some of the filters had lost weight despite the presence of obvious debris. Microscopic examination of the filters showed that fine fragments of the meshwork were being broken off the filters from the punched edge during mounting within and retrieval from the filter housing. Modification of the punch together with more careful selection of the filters for use and ultrasonic cleaning overcame this problem. There is a further inherent disadvantage in the use of stainless steel filters in that the weight of debris on each filter was only a small percentage of the weight of the stainless steel filter, a feature tending to reduce the sensitivity of the differential dry weight calculation.

PLAQUE EMBOLISM STUDY

The methodology in this study was derived from the previous study on the risk of thromboembolism.

However, the experimental design was extended to assess not only embolism, but also to provide a relative measure of the loss of mass following the application of thermal energy to human atheroma. Although several studies designed to assess the extent of tissue loss following the application of pure laser light have been published (Shelton, 1986; Geshwind, 1987a/b), there is no published study quantifying tissue loss using laser activated metal-capped optical fibres.

A few experimental studies have shown that metal-capped optical fibres are capable of either removing soft atheromatous aortic plaques (Welch, 1987; Lee 1984c) or recanalizing cadaver arteries (Abela, 1985a). However, none of these studies attempts to quantify the extent of tissue loss nor the associated debris release.

The prime aim of the study reported in this thesis was to determine whether embolism was a potential risk, the efficacy of ablation was a secondary consideration.

The first issue was which source of atheroma to study. Given the nature of animal atherosclerotic models the author had serious reservations about the applicability or validity of employing animal models for assessing debris release from, or efficacy of ablation of, this type of procedure. The homogeneous, cellular and lipid laden composition of artificially induced animal atheroma lends itself to effective ablation by a thermal mechanism as illustrated by studies on atherosclerotic rabbit iliac recanalization (Sanborn, 1986b). We therefore chose fresh human coronary endarterectomy specimens.

The potential advantages of such a model are obvious in that it is genuine human atheroma and it is heterogeneous; the disadvantages are less clear. Firstly, an endarterectomy core is

not surrounded by supportive tissue (outer media and adventitia), thus mounting in a tube becomes necessary but of necessity the tube has different thermal characteristics. Secondly, although heterogeneous it tends to consist largely of white, fibrous atheroma speckled to a varying degree with calcified foci. Due to its high fibrous composition this type of atheroma is less amenable to thermoablation than soft yellow atheroma. This may introduce a bias against efficacy of ablation which may not fairly represent the response of discrete, early, proximal coronary stenoses. Furthermore, the presence of calcific foci might be expected to increase the tendency to embolization.

The second issue, which posed some difficulty, was how to assess the extent of tissue loss during activation of the laser. In order to define each segment of atheroma two measurements were taken: length and weight. Length was measured with callipers after trimming of the 1 cm segment with a scalpel. Weight was more difficult to assess. The most accurate weights are dry weights, but dry weights were clearly inappropriate. We, therefore, opted for wet weight measurements.

The specimens were mounted in the silicone tube in a coaxial position with a distal snare around the tube to prevent advancement of the specimen. The metal cap was then introduced into the tube coaxially and advanced up to the end of the endarterectomy segment prior to activation. During pilot studies the aim of the experiment was to try to "recanalize" the specimen by applying constant forward force to the specimen through the optical fibre using a system of weights. However, such a system resulted in deflection of the metal cap along the path of least resistance between the silicone tube and the specimen. We therefore decided to manipulate the fibre by means of to and fro movements to ensure maximum contact with the specimen in an attempt to reproduce what happens in the clinical setting and to maximise tissue loss.

Gross inspection of the shrunken, charred and crisp specimens after lasing led us to believe

that dessication was an important if not predominant factor in mass reduction. This study was not designed to distinguish between dessication and vaporisation, although to have performed differential weight measurements on the residual specimens before and after dessication in a dessication chamber may have given some insight into this. We dessicated 10 x 1cm long fresh endarterectomy segments and found that weight was reduced from 106.7±24.3mg to 27.8±14.9mg representing a water content of 75±7.7% (mean±SD). Thus, if the weight loss of the residual specimens following lasing were to be less than 75% following further dessication, this would provide a simple measure of the degree of dessication.

The use of gravity filtration to filter the debris was a compromise. Given that many endarterectomy specimens are completely occluded arterial casts it was not generally possible to induce flow through the tube prior to or during lasing. Similarly following low power lasing, flow through the tube was not possible except slowly under gravity since any forced flow simply impinged the remaining specimen against the distal snare thereby inducing an occlusion. However, when high powers were used shrinkage of the specimen allowed flow with ease around, but not through the specimen. Nevertheless, filtration was always performed in an identical fashion to prevent any flow induced bias. This probably resulted in an underestimate of the amount of potential debris since vigorous flow through the specimen during or after attempted recanalization might be expected to dislodge more debris.

SIDE BRANCH STUDY

The aim of this study was to examine whether the metal cap compromised side branch origins and if so by how much. Any technique would have to allow a comparison of the side branches before and after lasing and should ideally allow a quantitative assessment of any change.

This consideration ruled out resin casting which would not allow a pre lasing comparison cast. In addition we considered angioscopy, but at that time high resolution angioscopes were not available and our early prototype did not offer sufficient resolution for effective examination; furthermore such an examination would only have allowed a qualitative assessment. We therefore opted for angiography since it fulfilled the two criteria of pre and post lasing comparison together with a quantitative assessment.

The limitations of visual interpretation of coronary angiograms are well documented. There are large intra and inter observer variabilities (Detre, 1975; DeRouen, 1977). This study employed a computer based system designed to obtain objective and reproducible parameters from cinéangiograms. However, the quality of both the angiographic investigation and the computer analysis are hampered by various sources of variation (Reiber P, unpublished communication).

In order to overcome variations due to subjective influences the following precautions were taken to standardise pre and post lasing angiography to minimise potential sources of variation:

(1) *The X-ray gantry was fixed* so as to eliminate any differences in height and angle between the X-ray tube and heart.

(2) *The heart was perfused at a constant pressure* of 150mmHg during both the pre and post lasing examinations.

(3) *Variations in the quality of mixing of the contrast agent* were eliminated by premixing

the urograffin with the saline perfusate prior to infusion.

(4) *Calibration* was performed using a 7F metallic Tibbs catheter, constructed in our workshops for this purpose. The same Tibbs catheter was used in each heart.

(5) Optical sources of error include *pin cushion distortion and magnification errors.* The former was corrected by taking an angiogram of a grid during each experiment. The distortion was analysed and corrected by the CAAS system. Magnification errors were eliminated by the fixed gantry height.

Following the post lasing examination the coronary arteries were insufflated with a mixture of barium and gelatin to facilitate subsequent histological examination. The aim of the histology was to see whether any of the narrowings were due to tissue debris or blood coagulum.

Unfortunately due to a processing error less than a quarter of the side branches were available for examination making any comment on the histological effects invalid.

This study was conducted in excised canine hearts since the laser and X-ray facilities were in different locations. However, it would have been interesting to have performed such a study in vivo to see whether the post lasing stenoses produced any demonstrable ischaemia and, perhaps more interestingly, to see whether there was a vasospastic component superimposed on the fixed stenoses demonstrated in this study.

CADAVER HEART STUDY

This is a descriptive histological study initially undertaken to examine the gross histological effects of the metal cap on the coronary arteries. The study was conducted by necessity over a long period in two institutions with differing facilities. Ideally, lasing at pre determined equivalent energies would have been performed at adjacent sites in blood or saline. This would have allowed comparison of histological damage at paired sites within the same artery when lasing was performed in saline or blood, so making statistical analysis easier. Ultimately the study was conducted on twelve different hearts each of which was perfused with either blood or saline, depending on the availability of human blood through the local blood bank. This, combined with the limited number of hearts and the outstanding difference in perforation thresholds between the two perfusates, resulted in unequal numbers in each group. Furthermore, the lack of paired sites forced upon the statistical analysis the assumption that the influence of each heart was either negligible, equivalent or random. The latter assumption was employed, since the influence of different sized and diseased arteries could not be considered equivalent across all hearts.

The odds of an artery being perforated were modelled as a function of power of lasing, time of lasing and nature of perfusate by logistic regression using the statistical software package GLIM (Generalised Linear Interactive Modelling) (Baker, 1978).

Since the temperature of the metal cap is influenced by perfusate, power, time and flow rate it would be interesting to compare temperatures in the two perfusates and relate these to the degree of histological damage. Work is already underway at Trimedyne to invoke a feedback loop to control maintain constant metal cap temperature. Such control would make an understanding of the relationship between histological damage and temperature

extremely useful.

Finally, it would be interesting to know the intra arterial temperature relative to adventitial temperature as measured by thermograpic imaging. Recent studies have shown that despite high central cap temperatures little change in temperature is felt by the adventitia, implying that the arterial tissue is itself an effective insulator (Silverman,1988) . The adventitial temperature immediately prior to perforation in peripheral arteries is only 76±2.2°C. However, to date no study has correlated intra luminal temperature with adventitial temperature. Such a correlation could provide a useful monitor if such devices were to be used intraoperatively.

STATISTICAL ANALYSIS

All descriptive statistics and simple comparisons (t-tests, Mann Whitney U test, Wilcoxon signed rank test, 1 and 2 way ANOVA) were performed using the statistical software package Statworks for the Macintosh.

The more complex analyses were conducted on the University of London mainframe computer. Repeated measures ANOVA was performed using the Minitab statistical package and logistic regression analysis using the statistical software package GLIM (Generalised Linear Interactive Modelling)

The suitability of all statistical analyses has been checked by the resident statisticians at the Royal Postgraduate Medical School (Mr V Aber and Mr N. Alexander).

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Communications Arising from This Thesis

PUBLICATIONS DERIVING FROM THE ABOVE STUDIES

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