"STUDIES OF THE LASER THERMAL PROBE IN CARDIOVASCULAR DISEASE"

Eric Rosenthal MB ChB MRCP
Guy's Hospital, London

Thesis submitted to the University of Cape Town
for the Degree of Doctor of Medicine, August 1989

To Rochelle, Abigail and Adam

In the beginning God created the heaven and earth. Now the earth was unformed and void and darkness was upon the face of the deep; and the spirit of God hovered over the face of the waters and God said "let there be light". And there was light. And God saw the light, that it was good ....

Genesis 1.1

ABSTRACT

The initial use of optical fibres to transmit laser energy intravascularly was accompanied by a high rate of perforations and the production of inadequate vascular channels when used for recanalisation. The laser thermal probe - in which all laser energy is converted into heat by a metal cap at the tip of the fibre, prior to tissue application - was one of the earliest modifications designed to overcome these problems.

The studies in this thesis were concerned with the application of the laser thermal probe to percutaneous peripheral and coronary artery angioplasty and His bundle ablation. In vitro studies were commenced in March 1987 when the first (argon) laser generator was installed in the cardiac catheterisation laboratory at Guy's Hospital and these were followed by clinical studies in three groups of patients: nine with peripheral artery occlusions, three with coronary artery stenoses and four with supraventricular arrhythmias using either argon or Nd-YAG energies.

Suggestions that enhanced safety might be possible with on-line monitoring and/or control of the probe temperature were studied by recording the temperature responses in simulated circulations at flow rates observed clinically. The highly variable temperatures recorded in blood indicate that these measures are unlikely to contribute to improvements in either efficacy or clinical safety.

An earlier report of successful peripheral artery recanalisation using

the laser thermal probe was confirmed in the patients studied here, though a learning curve was evident. Coronary laser angioplasty had also been performed in a few patients with a similar device but without as much success. A more flexible "over the wire" laser probe was assessed here, first in cadaver coronary arteries and then in three patients undergoing coronary angioplasty. The lack of success seen with this laser thermal probe relates to the considerable differences found between peripheral and coronary arteries: percutaneous accessibility, vessel size and the susceptibility to thermal injury being the most important. These aspects and subsequent developments in coronary laser angioplasty are discussed further.

The final chapter considers a hitherto new area for laser thermal probe application - the interruption of arrhythmia circuits. Cadaver and electrophysiological studies indicated that ablation of the bundle of His might be possible with this device - without the need for a general anaesthetic. The course of the first patient ever to undergo this procedure is described, as well as the implications for percutaneous His bundle ablation using other energy sources.

ACKNOWLEDGEMENTS

Dr Paul VL Curry was instrumental in acquiring the laser generators used in these studies and was my supervisor for this thesis. Through his guidance I have learned the technique of percutaneous transluminal coronary angioplasty and also obtained "hands on" experience with him during the performance of coronary laser angioplasty. For all of these I am grateful.

I would like to thank Dr John Reidy for joining with us in these studies. From him I have learned a great deal about interventional vascular radiology and together with him I have gained practical experience of laser thermal probe angioplasty.

Dr Joe Montarello provided constant support during both the in vitro and in vivo studies and shared in the "highs" and "lows".

Thanks are also due to Drs Nuala Fagg and Tim Palmer for the histological analyses, Eddie Boyd for manufacturing the thermocouples, Clifford Bucknall and Stefano Foussas for assistance with temperature measurements and Ms Liz Joyce for radiographic support both "in" and "out" of hours.

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1) Journal of Interventional Radiology - Figs. 3.7 and 3.8.
2) American Journal of Cardiology - Figs. 4.5 - 4.7.
3) Lasers in Surgery and Medicine - Figs. 4.2, 4.9 - 14.
4) Pacing and Clinical Electrophysiology - Figs. 5.2 - 5.5.

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PREFACE

Patients with coronary artery disease who do not have incapacitating symptoms nor adverse prognostic factors are usually satisfactorily managed with medical treatment alone. The remainder however, usually require invasive therapy including coronary artery bypass grafting or percutaneous transluminal balloon coronary angioplasty and both procedures carry high initial success rates. Coronary artery bypass grafting is limited by graft failure (both early and late) and difficulty in adequately revascularising distal lesions and smaller vessels. Percutaneous balloon angioplasty is primarily limited by the inability to cross and dilate certain lesions (occlusions and very tight stenoses) and has a recurrence rate approaching 30%. In addition there is a small incidence of periprocedural acute vessel closure due to severe endovascular trauma. In peripheral artery disease percutaneous transluminal angioplasty has come to play an increasingly important role - to the extent of replacing bypass surgery in a large number of patients. Its ability to successfully treat long occlusions is however limited and these lesions also carry a high recurrence rate.

Management of intractable or life threatening arrhythmias often requires open chest cardiac surgery or percutaneous intracardiac catheter direct current ablation. During both of these procedures depression of conduction may occur (anaesthesia and manipulation of surgery and "stunning" during the electrical shock) so that the efficacy may only be determined some hours to days after the procedure with occasional suboptimal results. Direct current ablation avoids the invasiveness of the open chest procedures, but uses large amounts of energy which is not deposited discretely. Cardiac chamber rupture, late ventricular dysfunction, arrhythmias and sudden death may result, probably due to the high intracavity pressure effects. His bundle ablation may be less susceptible to the serious side effects of intracavity shocks but also has a failure rate of up to 30%.

The attraction for using laser energy in these situations is the potential for delivering concentrated energy very accurately to specific targets in order to create a precise effect. Of major importance is the ability to use a percutaneous non-surgical approach. Vaporisation of atheromatous obstructions rather than leaving them in situ (bypass grafting) or merely stretching and splitting them (balloon angioplasty) would be a major advance. Arterial obstructions that are currently impassable to the balloon may be able to be dilated once the laser has created a new intravascular channel. Distal lesions could be vaporised and help to complete revascularisation. Perhaps the most promising role for the laser in this setting would be to initially "debulk" larger lesions allowing more controlled balloon dilatation with fewer acute occlusions and late recurrences. Against these advantages the dangers of perforation, spasm and thrombosis, need to be evaluated. Interruption of pathological arrhythmia circuits might also be accomplished by creating highly specific lesions though at a risk of cardiac perforations and arrhythmias.

A high incidence of complications and poor overall results attended the early clinical studies with conventional fibre optic delivery of laser energy leading to a number of modified approaches. The laser thermal probe, consisting of an optical fibre for transmitting laser energy to rapidly heat a metal cap at it's tip, offers a number of theoretical advantages. The probe is capable of being introduced from the peripheral vasculature in standard percutaneous fashion and manipulated to the required intravascular sites. All the laser energy is converted into heat prior to tissue application and thus remains highly localised. Previous investigators have shown this approach to be practical and effective in some peripheral artery occlusions but its clinical role remains to be defined. The studies in this thesis were directed at assessing the efficacy and limitations of the laser thermal probe during percutaneous peripheral and coronary artery angioplasty and His bundle ablation and at measures that might enhance its safety.

Chapter 1 serves as both an introduction to the use of lasers in cardiovascular diseases as well as a review of current progress, some of which occurred at the time that the studies in the succeeding chapters were performed. Chapter 2 assesses the thermal responses of laser probes in artificial circulations and the relevance of monitoring probe tip temperature clinically. Chapters 3, 4 and 5 describe the clinical studies in patients with peripheral and coronary artery disease and supraventricular arrhythmias respectively as well as the relevant in vitro work.

1. AN OVERVIEW OF LASERS IN CARDIOVASCULAR DISEASE

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1.1 HISTORICAL PERSPECTIVE

(a) From light to laser

While light and its major source the sun were long held in awe by many primitive peoples - indeed the sun was often deified and offered human sacrifice - it has only been in recent times that the exact nature of light has been elucidated. Recognised as a source of power and healing by the ancients - Archimedes attempted to ignite the sails of the approaching Roman fleet by reflecting the sun's rays with parabolic mirrors and the ancient Egyptians used sunlight to treat vitiligo - full exploitation of these effects has only been realised with the recent development of the laser (1-3).

Seventeenth century investigators were able to confirm that light was an emission but could not decide whether it was of a particulate or waveform nature. The prevailing view changed as each set of experiments emphasised one or other of these mechanisms. In 1905 Einstein expanded on the quantum theory of Plank and recognised the dual nature of light which could behave either as waves or particles (photons) depending on the type of experiment. Spontaneous and random emission of light photons from excited (or high energy) atoms or molecules is normally balanced by absorption of those photons by atoms in the (predominant) low energy state. In 1917 Einstein theorised that stimulated emission might occur when a photon or quantum of light of the correct energy collided with an excited atom to release its energy as a photon of light (4). The stimulated photon would be of the same frequency and wavelength and most importantly be in phase with the incident photon.

The first practical application of this theory was by Townes and his co-workers in 1953 who were able to amplify microwaves by stimulated emission after increasing the proportion of excited molecules ("population inversion") in ammonia gas. They coined the phrase "maser" an acronym for (m)icrowave (a)mplification by (s)timulated (e)mission of (r)adiation (1). Shortly after Schawlow and Townes proposed the extension of this technology to include wavelengths in the visible spectrum (2): the l for (l)ight replacing the m in (m)aser. In 1960 the first stimulated emission of visible wavelengths was reported by Maiman using a solid block of ruby (the ruby laser) (3).

(b) Medical applications of the laser

Medical exploitation of the ruby laser was rapid. Ophthalmologists were the first to use the brief but intense ruby light pulses to create highly controlled retinal burns for repairing retinal detachments. Thermal damage to surrounding non-target tissues during the prolonged applications necessary with the conventional xenon photocoagulator and the need for anaesthesia were thereby avoided (5-8). The red ruby light was however not absorbed by red cells and its role was soon supplanted by the continuous wave argon laser (9) whose wavelength was more effective for vessel coagulation (10). Almost equally rapid was its application to dermatology where argon light was found to be selectively absorbed by pigmented skin lesions (11-13). Research into its use for malignancies was also initially promising (14-17). It was recognised that the laser effects were primarily thermally mediated (as was clear in ophthalmological use) though the intense delivery was thought to be beneficial (18). It became apparent however that the high intensity pulses resulted in debris being explosively ejected during the irradiation of tumours with dispersion of viable cells and it fell into disrepute as a treatment for cancer (19-20). In 1965 the CO_2 laser which emitted infrared light in a continuous mode was developed (21). The high power was delivered at a wavelength which was almost completely absorbed by water (and therefore also tissue water) so that it could be used to create precise surgical incisions. Initially used for middle ear surgery (22) the precision and blood coagulating effects were more usefully employed for laryngeal surgery (23) and then more widely in general surgery (24), for excision of burns (25), in gynaecology (26) and in neurosurgery (27). In the early 1970's the Nd-YAG laser (28) which had greater penetrating power but was also subject to considerable scattering in tissue was found to be transmissible via optical fibres (29). Shortly after both Nd-YAG and argon laser energies were used by gastroenterologists to induce haemostasis in bleeding ulcers at endoscopy (30-32) opening the way to further remote medical applications. Development of the dye laser (32) allowed a choice of specific laser wavelengths and this found use in dermatology (33) and ophthalmology (34). The most recently discovered class of lasers was the excimer (= excited dimer - the active medium formed by a mixture of a halogen and rare gas) laser (35) emitting wavelengths in the ultraviolet range of the spectrum with very high energy photons. These have been used for precise corneal sculpting that does not leave any detectable thermal damage along the incision margins (36).

(c) Early cardiovascular applications

During the early medical developments, laser technology was only cursorily directed to the cardiovascular system. In 1963 McGuff et al (in addition to their systematic studies of laser energy as an anti-tumour therapy) used the pulsed ruby laser to destroy cadaver artery plaque (14) but the extension of this idea was delayed for nearly two decades. Yahr and colleagues performed microvascular anastomoses with a neodymium-glass laser in 1964 (37) but little further work was done until interest was renewed in 1979 (38) - though the technique is still not applied clinically to any important degree (39). Arapov and co-workers described the first cardiac application using a CO_2 laser to assist intra-operative pulmonary valvotomy in 1974 with purportedly good results (40) though this work does not appear to have been extended. Finally in 1977 Mirhoseini used the CO_2 laser to replicate Sen's technique (41) for direct myocardial revascularisation by creating channels between the myocardial sinusoids and the left ventricular cavity. Experiments in dogs were successful at preserving left ventricular function after coronary artery occlusion and the laser channels were found to remain patent for longer than Sen's needle acupuncture tracts (42). Performed as an adjunct to conventional coronary artery bypass grafting (43) obvious clinical benefit has not been apparent. Human myocardium does not have the extensive sinusoidal network seen in the canine myocardium and later studies have shown that even the laser channels do not remain patent for longer than two weeks (44).

In 1980 Macruz and co-workers followed up on the initial atheroma studies of McGuff but also used the laser for large and small vessel anastomosis, pulmonary valvotomy and mitral chordal shortening studies in animal models. Using both CO_2 and argon energy they were able to remove atheromatous plaque (fibro-fatty and calcific) from cadaver aorta and showed that thermal damage was limited - theorising that the "smooth" charred surface would not be thrombogenic. Laser lesions were created in dog femoral and carotid arteries which at later study were devoid of thrombus and showed re-endothelialisation. More importantly the group transmitted argon light via an optical fibre introduced into a cardiac catheter and were able to "repair" artificial "pulmonary stenoses" via a percutaneous approach. Using the same system they recanalised carotid artery stenosis preparations in dogs though also caused some perforations (45). At the same time Choy independently developed a similar approach (46) and using argon light transmitted via an optical fibre / catheter system was able to vaporise atheroma in cadaver coronary arteries (47). Choy and his co-workers then extended this work to disobliteration of human thrombi in dog and rabbit models (48). Subsequent in vitro (49-55) and in vivo animal studies (56-63) - with a leading role played by Lee et al and Abela et al - confirmed the ability of laser energies to vaporise atheromatous and thrombotic vascular obstructions.

These encouraging reports led to the first percutaneous human revascularisation procedure by Ginsburg in 1983 in a patient with a subtotally occluded femoral artery and threatened leg amputation (64). Shortly thereafter Choy attempted intra-operative coronary revascularisation with the production of very small channels and one out of five perforations (65). At follow up all of the vessels were occluded although competing flow from the concomitant saphenous venous grafts was thought to be partially responsible. Subsequent series of peripheral artery angioplasty were disappointing - small channels and perforations being the predominant problem (66,67) - and modifications to the basic "bare fibre" laser approach began to be explored. While this early work was in progress laser energy also began to be investigated for use in ablation of ventricular arrhythmogenic foci (68-70) and the bundle of His (71,72), atrial septostomy (73), relief of congenital pulmonary and aortic stenoses (74) and coarctation of the aorta (74,75), myoplasty in hypertrophic cardiomyopathy (76) and even decalcification of adult stenotic aortic valves (77,78).

1.2 BIOPHYSICS OF LASER ENERGY

(a) Laser physics

Lasers may be described by the nature of the active medium, the precise wavelength of light emitted, by their mode of action and their power but certain basic features are common (79-81). All lasers consist of an active medium, an excitation mechanism, and a pair of mirrors surrounding the active medium. The active (or gain) medium in which the laser action occurs may be in a solid, a gas or less commonly a liquid state. The excitation mechanism (or power source) which raises the energy state of the active medium varies and may be an electrical currents (solid state or gas lasers), a flash lamp (solid or liquid state lasers) or indeed another laser (solid or liquid state lasers). The light emitted from molecules in the active medium propagates itself through the medium and photons in the long axis are repeatedly reflected between the two mirrors at either ends recruiting further photons. The one mirror is totally reflective but the second is partially reflective allowing a controllable amount of laser light to exit the cavity through it. Laser light is monochromatic (of a single wavelength) and coherent (the light waves are in a single phase and in the same direction) and it is these two properties which contribute to the intensity of the output.

The power output of the laser is dependent on the specific active medium itself, the amount of power input by the excitation mechanism and the length of the active medium chamber. In general solid state lasers are far more compact than gas lasers which require a long chamber to amplify the power to similar levels. The spectrum of light emitted from a laser is a function of the active medium molecules (representing the change in energy states) and is usually restricted to a few discrete wavelengths (e.g. CO_2 = 10.59 um; Nd-YAG = 1.06 um; Argon = 488 and 514.5 nm; Xe-Cl = 351 nm). Electronic and optical mechanisms may be used to select or reject a particular wavelength/s. It is also possible to double or triple the frequency of the original light by passing the output through a non-linear crystal and recombining the laser beam with itself though this entails a loss in the power output. The liquid state, dye lasers emit a broad band of wavelengths which can be "tuned" with an optical selection mechanism so that a range or specific wavelengths within the band can be obtained.

The mode of action of lasers is determined by the manner in which the excitation energy is delivered or "pumped" to the gain medium. Continuous wave lasers are driven by a constant source of energy (such as an electric current) passing through the medium and replenishing energy lost as laser discharge through the mirror. In some lasers the active medium is only able to be excited by a sudden rise in energy producing a brief laser emission and then returning to the non-energized state. These pulsed lasers may be driven by flash lamps or high voltage electric discharges and the resultant energy output is far greater than continuous wave lasers (mega - kilowatt range vs <100 watts). The greater peak instantaneous powers however are only short-lived (nano - microseconds) although may be efficiently repeated at rates that are dependent on the pumping mechanism. In contrast the continuous wave lasers whilst able to produce a continuous output are rather inefficient in the utilisation of the power source.

(b) Biological effects of laser energy

Absorption by tissue molecules of the incident photons is the basis for any laser effects. Not all light is absorbed and depending on the optical properties i.e. wavelength, some may be reflected or transmitted to deeper tissue planes. Scattering of transmitted light within tissue leads to an increase in the irradiated volume and the extinction of the incident light is thus a function of both absorption and scattering (82,83). Absorbed photons will raise the energy levels of the molecules with either conversion to chemical energy (photochemical effects), emission of a lower energy photon (fluorescence) and/or conversion to heat. More complex effects include shock waves generated by thermal expansion, molecular bond disruption by very high energies and laser beam induced optical changes increasing the focusing of the beam in the tissue (18,84)

The rise in temperature and any damage depends on 1) the optical properties of the light (principally wavelength and colour-related absorption), 2) the irradiance parameters (laser power, beam diameter and irradiation or exposure time) and 3) thermal properties of the actual tissue (specific heat, conduction and thermal relaxation time and the rate of blood flow) (85).

Temperatures up to 55-60 ^{o}C cause reversible coagulation of protein but are tolerated for only brief periods. At greater temperatures irreversible denaturation occurs with shrinkage of collagen. The degree of collagen shrinkage is proportionate to the tension applied to the tissue; veins perfused with heated blood shrink at 70 ^{o}C while arteries do so at temperatures of 75 °C (86). At these temperatures thrombus forms as the heat coagulated red cells initiate platelet aggregation (87,88). The combination of shrinkage and thrombosis is sufficient to obliterate vessels up to 1.0 mm in diameter but larger vessels require, in addition, pressure to appose the thermally coagulated walls allowing "welding" (89). At 100 °C tissue water begins to boil with great expansion in volume and explosive disruption of cell walls liberating steam ("vapour trails"). Residual cell matter experiences a rise in temperature only once all cellular water has evaporated and tissue vaporisation (i.e. conversion to gaseous products) occurs at temperatures in excess of 160 °C (90-92). At temperatures in excess of 300-400 °C carbonisation of solid material occurs. During this process heat is also conducted to surrounding tissue which will undergo changes according to the temperature attained. The rate of temperature rise is dependant on the thermal conductivity of the neighbouring tissue but is also critically dependent on the rate of energy delivery (93). In general where the rate of energy delivery is high there is less time for thermal conduction to occur and the surrounding area is less affected (94,95). Where absorption is high (and scattering low) localised effects are also more apparent.

(c) Cardiovascular effects of laser energy.

(1) Continuous wave lasers

It soon became apparent that the commonly used continuous wave lasers (CO_2, argon and Nd-YAG) ablated atheroma by a similar thermal process (51). Both normal vessel and atheroma subjected to continuous wave energies demonstrated a crater of variable depth from which tissue had been removed and this was lined with a layer of charred material. Immediately adjacent to this was a second zone of polymorphous lacunae or vacuoles (49,51,57,59,96-99). Initially thought to represent "acoustic" injury from "shock" waves produced during vaporisation (51) they are now considered to represent expansion of gasses from boiling cells or nuclei (96). Beyond these vacuoles was a third zone of oedema, collagen shrinkage and coagulative necrosis of cells (manifested by hypereosinophilic staining) gradually merging with the undamaged tissue. The extent and depth of damage increased with increments in the power or duration of application and seemed to correlate best with the total energy delivered (51). This was at variance with previous non-cardiac studies (94,95) and later studies revealed that delivery of energy over very short intervals reduced the thermal injury zone adjacent to the crater compared to identical energies delivered over a longer interval (96,100). Arterial wall appeared to be more resistant to thermal injury than (non-calcific) atheromatous plaque (101,102). The effects on cardiac tissue were similar but the extent of damage differed. For the same amount of energy more extensive damage occurred in myocardium than elastic or muscular arteries (97) while calcified valves demonstrated the greatest amount of charring (78). Shortening of chordae tendiniae and valve cusps occurred with even subperforative injury (45,97). Analysis of gaseous products from all tissues revealed typical thermal combustion degradation products (103). During the vaporisation process cellular water was converted to steam, and the remaining matter thermally combusted producing water vapour, carbon monoxide and light hydrocarbon gasses, dissolved protein fragments and heterocyclic nitrogenous compounds, and solid carbon particles and cellular debris (103,104). Analysis of the non-filterable debris after ablation of atheroma and thrombus rarely reveal particles greater than 9.37 um (104,105) and recognised or important embolism appears to be infrequently recorded clinically and experimentally (106).

Much of the early work was performed with an air-tissue interface so that energy parameters were not readily applicable in vivo unless a dry bloodless field could be created. As was apparent from non-cardiac use, CO_2 energies produced the least penetrating craters while Nd-YAG produced the most extensive damage with considerable subdjacent thermal coagulation (79-81). Rate of flow and the specific optical and thermal properties of saline or blood dramatically influenced the tissue effects. CO_2 energy effects were markedly attenuated in saline or blood (being highly absorbed by the water content) at depths of 2.9 and 30 um respectively (82,107). Despite the considerable attenuation by water - in small volumes and depths of saline, heating of the saline may lead to typical thermal lesions. Difficulty in transmitting CO_2 energy without heat loss over non-toxic optical fibres has limited its cardiovascular applications: a single report of successful intravascular transmission has not been developed any further (108). Clearly defined planes can be developed in "dry" fields and in one centre it has been found to be effective for intra-operative coronary endarterectomy using a hand held wave guide (109). Argon light is strongly absorbed by haemoglobin so that there is limited transmission through blood. In stationary blood the divergence angle increases to 30^{o} (15^{o} in saline) with less forward projection yet the tissue effects are greater with wider and deeper craters than in saline. During energy delivery gas is liberated and it is assumed that the blood itself is heated (and vaporized) indirectly heating the tissue (110). In contrast with flowing blood little damage occurs presumably due to lower absorption by each volume of blood and therefore less transmission of heat to the tissue. Nd-YAG energies are easily transmitted through blood but again the lesions are increased in its presence (stationary or flowing) when compared to saline. While a gas bubble also forms at the tissue interface and may contribute to thermal effects (100), it has been postulated that charred blood attached to the crater is better at absorbing the light further increasing the local heating (51,111). Superfusion with cold saline or blood attenuated the thermal effects of all lasers (51,100) by acting as a heat sink.

Vascular healing after thermal damage has not been intensively studied but was on the whole favourable. Various animal studies including atherosclerotic models or those with human thrombus or vessel implantations have been studied and reveal the formation of a fibrin platelet plug followed by re-endothelialisation over the ensuing days. A depressed area often remains with a degree of intimal thickening and chronic inflammatory cellular infiltrate. Re-endothelialisation is usually complete by two to four weeks after CO_2, argon or Nd-YAG energies (57,59,60,112-114) although in a single canine femoral artery, healing was said to be complete five days after vaporisation of a thrombus (48). While acute perforations were not uncommon in these studies aneurysm formation was only reported in a small proportion of animals in two studies (atherosclerotic rabbit model and porcine carotid artery implanted into the aorta) (59,60). A comparison between balloon angioplasty and laser thermal effects in the atherosclerotic rabbit model revealed larger mean luminal diameters and less fibrocellular proliferation four weeks after the laser procedure (115). Human atheroma is different to animal models and less encouraging was a report of persistent thermal damage without re-endothelialisation in two femoral arteries two to four weeks after initially successful laser/balloon angioplasty - although thrombus formation was absent at this time (116).

(2) Pulsed lasers

Pulsed lasers such as the ultraviolet wavelength xenon chloride excimer lasers produce much greater peak powers though over very brief time intervals. Histology of vessel subjected to pulsed excimer energy is remarkable for the "clean" edges without charring or any of the other typical features of thermal injury (117-119). The high peak powers of excimer lasers have been postulated to have a non-thermal photochemical effect on the tissue causing disruption of chemical bonds but this is controversial (120). The energies used are theoretically enough to break chemical bonds, ejected fragments have a velocity greater than expected for thermal vaporisation and tissue temperatures are lower than those measured during thermal ablation (121). In addition if low peak pulse powers are used or pulsed energy is unfocused (and therefore effectively at a lower energy density) thermal damage may occur - the implication being that insufficient energy to break chemical bonds is delivered. The contrary view is that the effects are predominantly thermally mediated but that heat is able to disperse between pulses so that tissue temperature does not rise, craters show less charring and vacuolation and thermal coagulation is absent. Evidence to support this is the fact that lower energy visible and infrared wavelengths if delivered in a pulsed form e.g. Q-switched (an optical mechanism designed to briefly store and thus increase the gain medium energy) Nd-YAG or very high peak power CO_2 lasers can produce identical histological results despite lacking the energy per pulse necessary for "photochemical disruption" (122). In addition if pulsed excimer energies are delivered for extended periods thermal damage is apparent implying that the thermal diffusion capacity has been overwhelmed (123). Finally gas chromatography of degradation products is similar for both continuous and excimer lasers (124). Until recently the ability to transmit these energies without damage to the optical fibre has precluded the use of this energy intravascularly (125-127). Of interest was the paradoxical ability of pulsed CO_2 and excimer energy to be transmitted effectively through blood even though absorption spectra of water (CO_2) and haemoglobin (excimer) predict this is unlikely. This is thought to be due to a "Moses effect" (128) whereby pulsed energy creates an optical cavity ("channel") caused by a true acoustic transient (shock wave) - due to rapid thermal expansion of (129) the highly energised molecules.

The theoretical advantages of using pulsed lasers to avoid thermal damage adjacent to the vaporised area has not been demonstrated to have clinical benefit to date. The repair process of the continuous wave energies is on the whole benign in animals (except for two reports of aneurysm formation) and in humans. The few studies performed using pulsed energies reveal a similar repair process with initial thrombus formation and re-endothelialisation but much less subjacent reaction (128,130-132). Of more importance is the demonstration that, in vitro, laser application produces vasoconstriction with continuous wave energies but vasorelaxation with pulsed energy (or continuous wave energies too low to ablate the wall and raise the temperature) (133). In canine coronary arteries delivery of similar amounts of energy via continuous wave lasers has caused spasm that does not occur with pulsed energy (134). One study has however also recorded spasm with pulsed excimer energy in a rabbit model (135).

1.3 CURRENT STATUS OF CARDIOVASCULAR LASERS

(a) Intravascular delivery of laser energy

The ability to transmit large amounts of energy over distance (without significant loss) and concentrate it onto a small target area for a specific effect is the major attraction for using the laser in cardiovascular disease. Many different lasers have been explored in the cardiovascular system but none have been found to be ideal for any particular application. While the wavelength, power output and mode vary considerably with different lasers, these differences can only be exploited clinically if an adequate mechanism exists to conduct the light to the target tissue. For intravascular application five separate components need to be integrated:

1. The laser source itself (wavelength, power, mode);
2. An accurate coupling mechanism from the laser to
3. Optical fibre/s which can transmit the light via
4. A catheter delivery system to
5. A terminal energy delivery interface at the target tissue.

The optical fibres used for intravascular laser energy delivery have major limitations when used in their simplest form for vascular recanalisation - i.e. as a fibre protruding from a catheter. The highly collimated beam of light emitted from the fibre is only able to create a neolumen fractionally larger than the fibre diameter itself due to the small degree of beam divergence. The largest fibres capable of intravascular delivery have a diameter of 600 um and are difficult to manipulate except in straight segments of relatively large arteries. The smaller fibres (<100 - 300 um) are more flexible and manoeuvrable but create correspondingly smaller channels.

The optical fibres are radiolucent and thus difficult to position coaxially resulting in perforations - both mechanical from the sharp tips and thermal during energy delivery (60,62,63,66,67,112,113, 136-138). This is particularly evident in the tortuous coronary arteries, at branch points or when the plaque is eccentric (139), and underlines the insensitivity of fluoroscopy as the sole monitor of progress. The transition from atheroma to normal vessel is rarely sharply demarcated heightening the difficulties in measures designed to improved atheroma recognition and/or selective ablation. Atheromatous deposits are heterogeneous in their composition which further detracts from easy recognition. Fatty and fibrous plaques are also more easily vaporised than calcified plaque which is only efficiently ablated by pulsed lasers (140). Attempts to displace blood to avoid absorption of the laser energy (balloon occlusion and/or saline flush) may be nullified by the presence of subintimal haemorrhage in a plaque which may still heat up excessively and perforate (141). In addition thinning of the media is well recognised with atherosclerotic disease (142) and indeed plaques may replace much of the vessel wall leaving only a thin layer of normal media/adventitia (143) narrowing the margin for total plaque ablation without perforation.

The "ideal" laser system for treating obstructive vascular disease might thus include the following features:

1. A laser wavelength selectively absorbed by atheroma - and reflected or scattered by normal vessel.
2. Localised atheroma vaporisation without adjacent tissue thermal damage during the ablation process.
3. Efficient coupling and transmission via optical fibres that are non-toxic and flexible.
4. A catheter delivery system that is both atraumatic and easily guided and manipulated.
5. A tip design that allows delivery of sufficient energy for ablation to the necessary vessel diameter.
6. An identification system for reliably distinguishing atheroma from the normal vessel wall - either laser based or external to the laser.

Current strategies for maximising the effectiveness and safety of laser angioplasty will be discussed with reference to:

1) Improvements in atheroma detection and selection
2) Modifications to the distal tip of the laser

(b) Targeting the plaque

Despite the imprecise transition between plaque and normal arterial wall attempts have been made at improving plaque uptake of specific wavelengths and plaque identification either before or during laser energy delivery.

(i) Enhancement of atheroma ablation

A number of studies have shown that the optical absorption, transmission and reflection characteristics of normal wall and atheroma are different (as are their thermal properties). Absorption spectra of normal and atheromatous wall show only very small differences with argon (144,145), pulsed Nd-YAG (111) and near ultraviolet wavelengths (146). While atheroma will absorb more energy at these wavelengths the ablation thresholds are not sufficiently different to utilise clinically (146). More recently a differential selectivity of 10-100 fold has been found with pulsed wavelengths of 480-490 nm in saline (147). Enhancement of this process has been attempted by administration of exogenous substances that are taken up by plaque to a greater extent than the normal vessel. Preferential absorption has been shown at 631 +/- 5 nm with haematoporphyrin derivative (148), at 355 nm with tetracyclines (149) and at 465 nm with carotenoids (150). In the atherosclerotic rabbit model administered haematoporphyrin derivative the selectivity for atheroma was not enough to prevent both medial and endothelial damage after delivery of light dose rates far lower than were necessary to cause thermal ablation (151) or produced inconsistent effects (152). Orally administered carotenoids are selectively taken up by atheroma (50 fold increase above normal levels) but in vivo effects of delivering 461 nm light are yet to be performed (153).

(ii) Enhancement of atheroma recognition

Fluorescent Spectroscopy: While selective plaque destruction appears difficult to attain due to the small absorption difference between atheroma and normal wall (even in the presence of chromophores) recognition of optical differences may be useful. Discrimination of atheroma from normal wall by induced fluorescent spectroscopy has been recognised to be possible for some time (154-155) but the optimum wavelengths to be used clinically are not clear as yet. Leon et al using wide-band blue light demonstrated a fluorescent absorption intensity ratio of 2:1 between normal and diseased vessel at 540 nm in vitro (156). Using a different approach, Deckelbaum et al found that fluorescent intensities were also able to discriminate between different morphologies of atheroma: maximum intensities at 514 nm for normal; 448 for fibrous atheroma; 538 nm for fatty plaque. Using this system in which the "normal" spectra falls "between" that of different types of atheroma would require analysis of the ratios of the three spectral intensities (157). Further enhancing this approach is the preserved ability to perform fluorescent spectroscopy during laser ablation without distorting the spectral display so that the change to "normal" wall can be recognised (156,158). These differences and hence the diagnostic ability are likely to be further enhanced by the use of chromophores and this has been demonstrated by Prevosti et al using haematoporphyrin derivative (159). Surface fluorescent spectra at 631 nm could not discriminate between normal and atheroma until sensitised with haematoporphyrin derivative.

Non-laser: Simultaneous angioscopy has been used usually on an intra-operative basis to target the lesions prior to and to monitor progress during delivery of energy (56,58,160). Even this approach has only met with limited success at avoiding perforations (101). Finally intravascular ultrasonic delineation of the vessel diameter, wall thickness and constituents is being investigated but its impact on guiding laser systems is yet to be evaluated (161).

(c) Optical fibre modifications

From the earliest studies of intravascular energy delivery it was apparent that coaxial alignment was critical to avoid perforating the wall. Measures to enhance positioning included sheathing the fibres within radiopaque catheters, placing markers on the fibre tip and using steerable guide wires placed within the catheter alongside the fibre (162-163). An alternative approach to enable coaxial alignment was to support the fibre within an inflated balloon in the vessel (106,164). While these manoeuvres contributed somewhat to improvement of coaxial alignment they did not enhance the ability to create a larger lumen. Geschwind et al used an asymmetric balloon to align the fibre parallel to the wall but not in the centre of the vessel. By rotating the balloon it was possible to create a larger lumen than if the fibre had been kept in a single plane (165).

It was only after considerable fibre tip modifications, however, that it became possible to create a lumen substantially larger than the fibre diameter. Paradoxically it was by deliberately "sacrificing" some of the intrinsic features of laser energy (i.e. the finely focused beam and the direct laser tissue interaction) that finally allowed reliable clinical applications.

(1) Metal capped optical fibres

The recognition that thermal mechanisms were the basis of recanalisation by all continuous wave lasers led to an approach designed to maximise thermal transfer to the treated surface. The bare fibre tip was encased in a metal cap (Fig. 1.1) which absorbed all the incident laser energy and then became rapidly heated ("hot tip") - achieving temperatures in excess of 1000 $^{\circ}C$ for a 2.0 mm tip in air (166). Lower temperatures were recorded in fluid or solid media with their greater heat dissipation capabilities (i.e. lower insulation) but these were sufficient to allow recanalisation of occluded arteries in vitro (167).

The smooth oval tip avoided mechanical perforations while the localisation of the energy at the tip prevented laser beam perforations. In dog and atherosclerotic monkey models thermal lesions in coronary arteries were created without acute complications and there was no evidence of thrombosis on later follow up (168,169,170). The incidence of perforations was markedly reduced by comparison with bare fibre angioplasty using similar energy parameters in the atherosclerotic rabbit model (171). In addition the channels produced were much larger than those produced with bare fibres alone and this finding was confirmed during recanalisation of human coronary artery segments implanted into canine femoral arteries (168). Finally what was most encouraging was that the larger channels made in a rabbit model showed less restenosis than the channels found after balloon dilatation - confirmation for the first time that laser recanalisation might indeed be superior to balloon dilatation (115).

An alternative version allowed 10-20% of the light to exit via a central channel into which was set a small sapphire lens for an additional laser tissue interaction (101). In practise, however, this device functions similarly to the "basic" metal capped "hot tip" fibres (172).

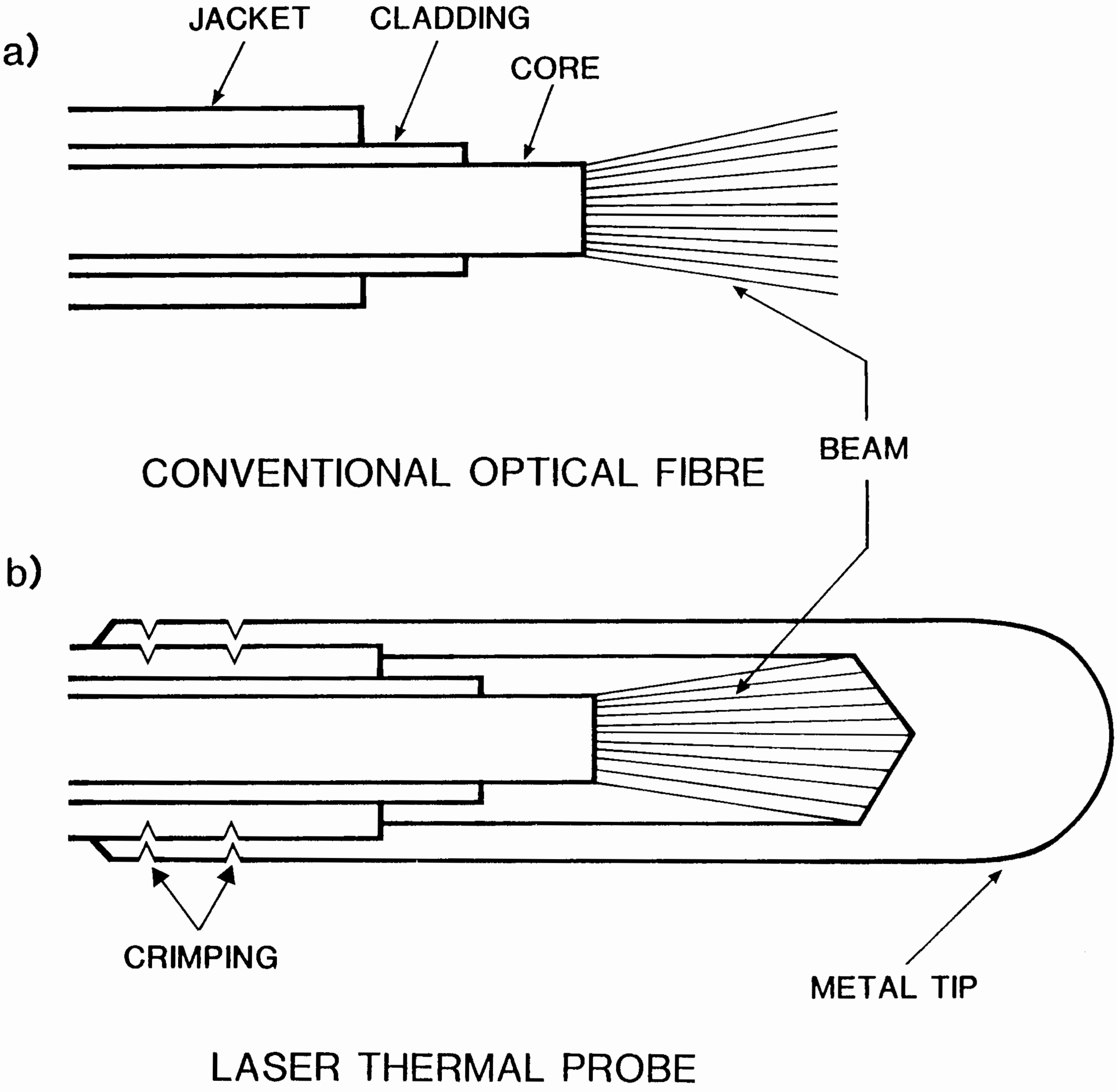


Figure 1.1 Diagram illustrating the principle of the "hot tip" laser thermal probe.

These experimental results were confirmed in patients with long femoro-popliteal artery obstructions in many of whom conventional balloon angioplasty had failed (173). The technique was then extended to patients with coronary artery disease though with a lesser measure of success (174,175). Further experience with this type of system is described in the following chapters.

(ii) Sapphire Tipped Optical Fibres

When placed at the tip of an optical fibre the sapphire acts as both a lens to diverge the laser emission (usually Nd-YAG) while absorbing some of the light (+/- 50%) and heating up itself (176). The larger diameter tip - up to 2.2 mm - avoids the perforation problems of the bare fibre and recanalises by a combination of mechanisms i.e. direct laser tissue interaction and an indirect thermal mechanism as with the metal capped thermal probe. The larger channel produced by the divergent beam is further enlarged by thermal compression during passage of the tip and possibly by additional thermal ablation. The high temperature attained by the sapphire requires a cooling system to prevent damage and the complexity of tip perfusion reduces the flexibility of the "probe" so that delivery to smaller tortuous vessels is difficult. Early in vitro and in vivo animal studies demonstrated a favourable recanalisation rate with a low failure/perforation rate (114,177,178) and clinical success in peripheral artery recanalisation has followed (179).

(iii) Optical Shields and Lenses

The simplest modification to the optical fibre was to fuse the tip into a sphere of up to 1.2 mm ("glass ball tipped fibre") which increased the light divergence and whose smooth surface was less traumatic to the vessel wall (180). A preliminary report suggests that these are both safe and effective in vivo (181).

Another approach was to place an optical assembly containing a small lens at the end of the fibre. Divergence of argon light by the lens into a 40^{o} cone, both limited the penetration to 2-3 mm while enlarging the beam size from the 200 um fibre, producing +/-2.0 mm diameter craters in vitro. The lensed fibre is passed through a vascular catheter which is flushed continuously to prevent blood entering the space between the lens and the fibre during in vivo use (182).

Perhaps the most sophisticated assembly is the multifibre catheter of Cothren et al (183). A clear optical shield protects the 19 fibres (100 um diameter) from blood or tissue contact. Fibre combustion during tissue or blood vaporisation is thereby avoided, preventing distortion of the optical transmission characteristics of the individual fibres (180). The beams of the fibres overlap so that the catheter can ablate its own diameter (2.5 mm) but the depth of thermal damage on the outer margin is only as wide as that seen with a single 100 um fibre. Successful in vivo animal studies using argon energies have been performed recently (184,185). It is further envisaged that each fibre will be used to obtain spectroscopic information allowing only fibres directly opposite plaque to be activated. The major drawback with this system is the complexity of use and the expense which may limit its clinical application.

(iv) Laser Balloon

While the rationale of most laser refinements, at least as initially conceived, was to avoid balloon dilatation a different approach is that of delivering laser energy <u>through</u> a balloon. With this system the advantages of balloon angioplasty are consolidated and improved. During the last inflation a diffusing fibre tip terminating in the balloon delivers Nd-YAG energy circumferentially to the artery wall. This seals balloon dissection planes, plaque fissures and intimal flaps and compresses any thermally produced vacuoles so leaving a smoother surface. In addition the coagulated vessel wall (peak temperatures of 100 - 140 ^{o}C) loses its (passive) elastic recoil or (active) spasm potential becoming a "biological stent" (186). After heating for 15-30 seconds the balloon is left inflated for a further 15-30 seconds during cooling so that collagen contraction does not "recoil" and narrow the lumen. Current studies are evaluating the most effective energy delivery parameters for achieving satisfactory vessel wall welding (187-189).

1.4 SUMMARY

Shortly after the laser was developed its properties were applied to the treatment of ophthalmic and dermatological conditions with considerable success. Cardiovascular application was relatively late compared to other medical fields but was spurred on by the development of flexible optical fibres that could transmit laser energies intravascularly. In particular its ability to vaporise atheroma was confirmed in cadaver and animal studies with a favourable healing response. The initial clinical studies, however, were disappointing due to both a high perforation rate and the ability to produce only small vascular channels with laser energy alone.

A great diversity of approaches is now being employed to enhance the effectiveness and safety of laser angioplasty. Optimisation of energy dosimetry and wavelength, use of pulsed energy, enhanced plaque detection methods and modifications of the delivery systems are all undergoing intense evaluation. The "ideal" laser angioplasty system has yet to be developed.

At the time the studies in this thesis were performed the metal capped fibres had begun to show promise after the initial wave of enthusiasm for bare fibre angioplasty had abated. During the course of these studies alternative approaches became more attractive, and some may yet supersede the "hot tip" technique which in comparison may appear crude. Nevertheless this has been the first device to clearly establish a clinical role for laser angioplasty.

2.0 THERMAL PROPERTIES OF METAL TIPPED LASER PROBES

2.1 INTRODUCTION

The use of metal-capped optical fibres for percutaneous laser thermal angioplasty has achieved considerable success in peripheral artery occlusions (173). Lesions that are impassable to the conventional guide wire and balloon technique are easily recanalised using the "hot tip" probe and importantly the incidence of perforations is very low, particularly when compared to bare fibre laser angioplasty (171,Section 3.4). The success of this technique has led to its extension to the treatment of coronary artery disease, although a higher incidence of side effects with spasm, perforation and myocardial infarction have been seen (174,175,190,Section 4.3). While the application of this technique to coronary artery disease also requires considerable laser probe design modifications, it is possible that the small coronary vessels are more susceptible to thermal injury.

The degree of vessel wall damage is proportional to the amount of energy delivered to the vessel wall and the mechanical pressure applied during energy delivery (102). The temperature attained by the probe depends upon the rate of energy delivery and period of application, the mass of the probe tip, the specific heat of the probe tip materials, and the rate of heat dissipation into the surroundings. All these factors are either constant or controllable except the last one. Thus the rate of heat dissipation is the only important unknown factor in determining the probe tip temperature. Very little, however, is known about the temperature developed in the laser probe tip in vivo; previous studies have looked at the temperature developed in vitro (102,191) and that of the surrounding tissue (192). The development of a thermal feedback control system may be useful to limit excessive injury but requires detailed information on heat dissipation in different environments the and minimal effective temperatures for atheroma vaporisation. The aim of this study was to measure the effects of flow on the temperature attained by the probe both in saline and in blood during flow rates observed clinically.

2.2 METHODS

(a) Laser Probes

Peripheral artery laser probes manufactured by Trimedyne Inc (Santa Ana, Calif, USA) were used in this study. The "standard" 2.0 mm peripheral probe (PLR Plus) consisted of a 300 um optical fibre capped with a 2.0 mm oval metal tip. Attached to the tip was a safety wire used for retrieval in the event of dislodgement in vivo and a stiffening/torque wire for enhancing the advancement through resistant atheroma. For this study, the torque wire was removed and a thermocouple inserted into the torque wire channel. The thermocouple consisted of 0.006" Chromel and Alumel thermocouple wires (type "K") which were spot-welded to form a junction of 0.014-0.016" in diameter. The thermocouple wires were threaded through the torque wire channel and the junction was firmly wedged in place. A fine, polytetrafluoroethylene insulating sleeve covered one of the wires over its entire length to prevent any loss of the thermocouple voltage (Fig. 2.1). The temperature of the thermocouple was measured using a digital thermometer (Model 611-234; RS Components Ltd., UK), interfaced to a strip chart recorder (Servoscribe M; Servogor, Berks, UK). The 2.5 mm tip probes (Laserprobe-SLR) had a more rounded leading edge and was mounted on a 600 um fibre. A type "K" thermocouple was embedded in the tip during manufacture to allow in vivo measurement of probe tip temperatures (Fig. 2.2). Insulation was not present on the 3 mm of thermocouple wire adjacent to the junction which together with the optical fibre was enclosed in a polyurethane sleeve.

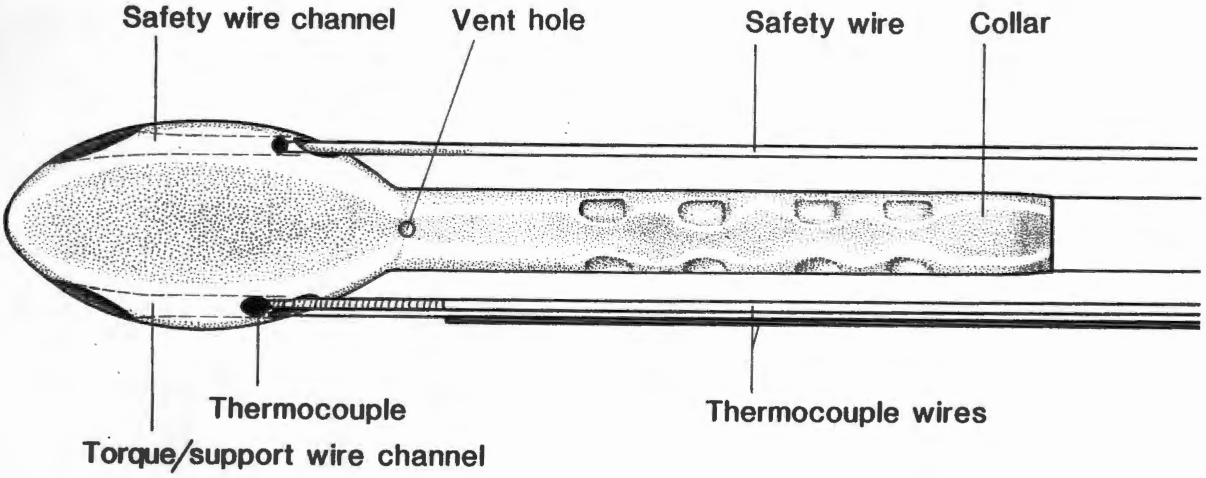


Figure 2.1: Diagram of 2.0 mm tip peripheral artery laser probe modified to enable tip temperature recording.

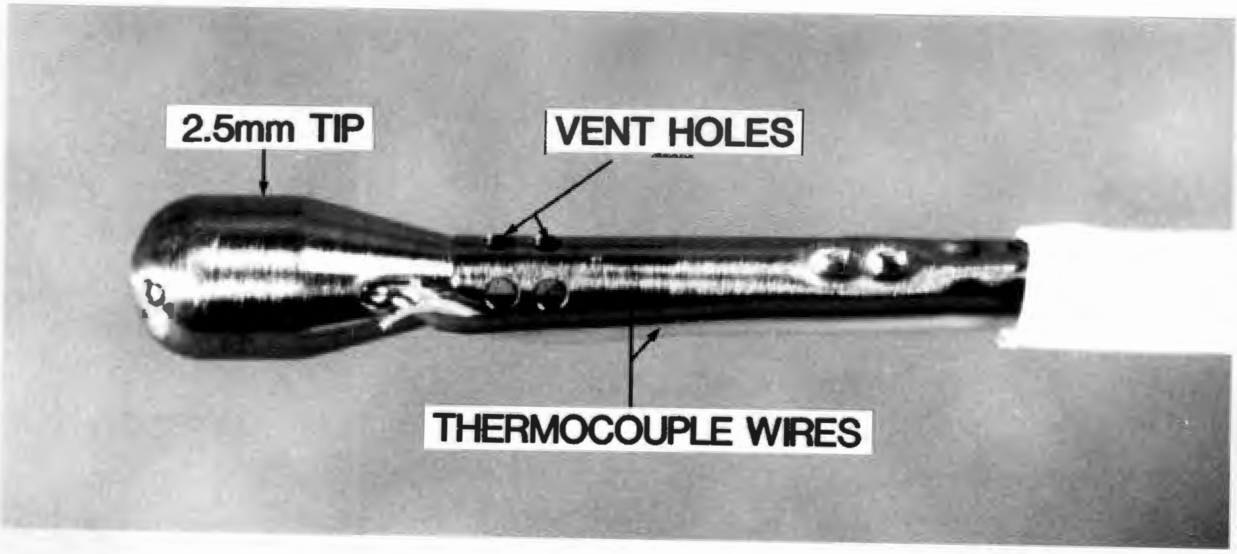


Figure 2.2: 2.5 mm tip peripheral artery laser probe with a thermocouple incorporated in the tip.

(b) Laser Generator

During this and all the subsequent studies (Sections 3,4,5) one of two laser generators were used: the Optilase Argon generator with power outputs up to 13.5 Watts and the Cardiolase 4000 Nd-YAG laser with outputs up to 40 Watts (both Trimedyne Inc, Santa Ana, Calif.). Prior to each use of either generator, the power output was calibrated using an appropriate sized bare fibre and a power meter.

(c) Flow Model

The recirculating flow rig (Fig. 2.3) consisted of a compliant reservoir connected via a roller pump (H.R. flow inducer; Watson-Marlow Ltd, Fulmouth, England) capable of delivering up to 240 ml/minute, to a heat exchanger coil, leading to a straight polyethylene tube (the test segment) and returning to the reservoir. The reservoir, heat-exchanger coil and test section were all submerged in a water-bath maintained at a constant 37 ^{O}C with a heater mixer (TE-7 Tempette; Jencons Scientific, Beds, UK). The laser probe was inserted through a haemostatic valve into the test segment and temperature was measured during energy delivery with varying flow rates. The test section (6.0 mm diameter) could be renewed if damaged or replaced with fresh postmortem human femoral or carotid arteries. The reservoir was able to be filled with saline or fresh heparinised human blood after priming the system with the appropriate medium.

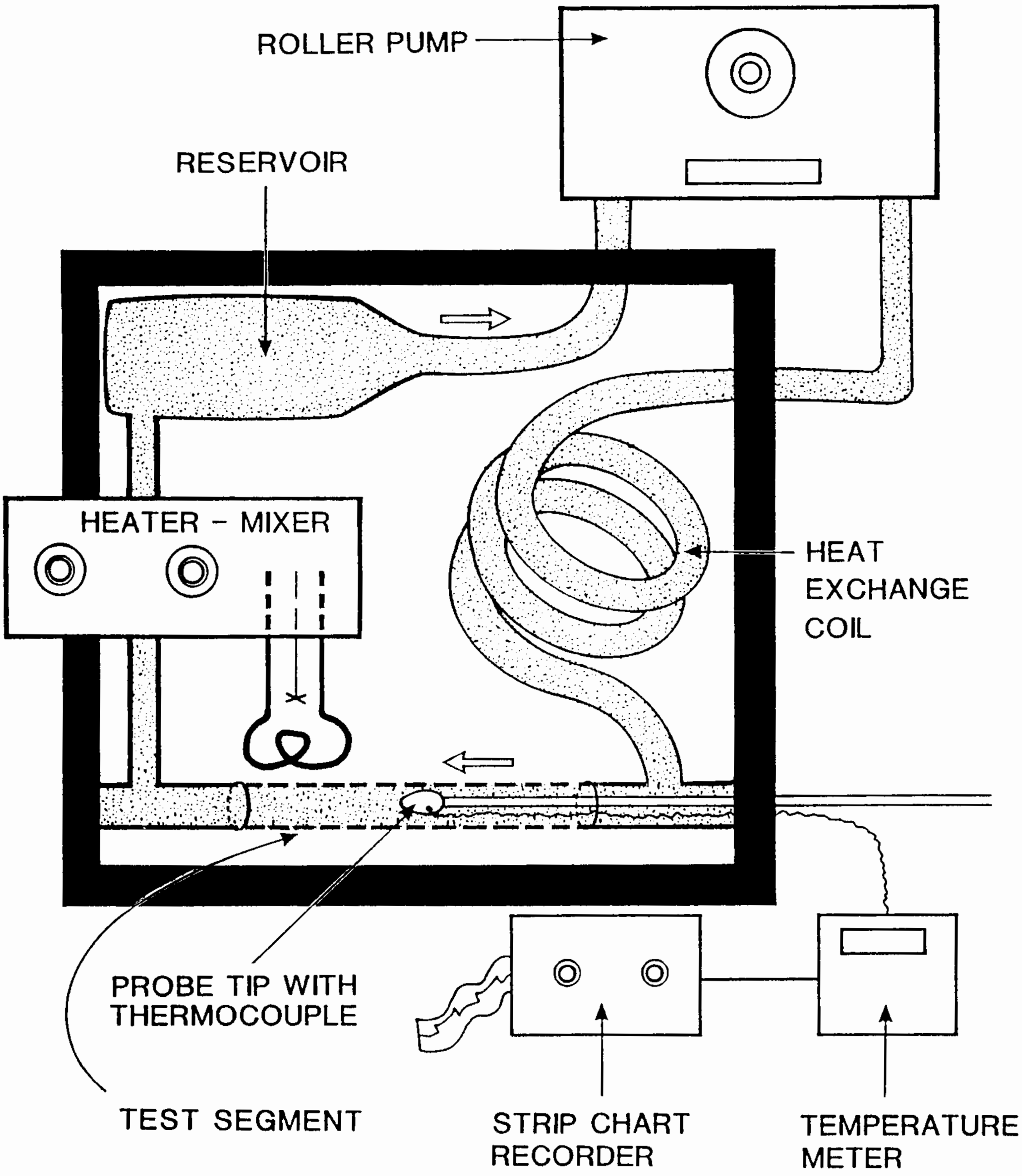


Figure 2.3: Diagram of flow apparatus with test segment submerged in water bath maintained at a constant 37 °C. The arrows indicate the direction of flow.

(d) Measurements

Temperature-time curves at different flow rates were recorded at paper speeds of 1 cm/second and unless stated all composites are those of consecutive temperature-time curves from the same probe at a single session. The peak temperatures at the various laser powers and application periods were obtained by recording the temperature-time curves at slower paper speeds and calculating the means of 3-5 consecutive peak measurements. All graphs derived from these calculations are composed of information obtained from a single probe during a single study session. During the course of this study 5 modified 2.0 mm peripheral artery probes and 3 purpose built 2.5 mm peripheral artery thermocouple probes were used.

2.3 RESULTS

(a) Saline Circulation

In stationary saline both the 2.0 and the 2.5 mm probes rapidly attained temperatures around 100 ^{o}C at outputs above 7 and 9 Watts respectively. The peak rate of rise was greater with the 2.0 mm probe, reflecting its smaller mass, with both probes reaching stable temperatures within 1 and 1.5 seconds respectively. At greater power outputs, the temperature was maintained at around 100 ^{o}C with more vigorous bubble formation (boiling), but in some probes after 3-5 seconds there was a gradual rise in temperature above the plateau (Fig. 2.4a). The maximum temperature in these probes reached 103-109 ^{o}C.

During maximum flow the rate of temperature rise was similar but with a lower more rapidly attained plateau (Fig. 2.4b). During sequential testing at increasing flow rates the peak (plateau) temperature fell with each increment in flow (Fig. 2.5). A 2.5 mm probe tested at outputs of 1-13 Watts over a wide range of flow rates showed a linear rise in temperature with increasing output up to around 85 ^{o}C at which point the rate of rise decreased and eventually plateaued at 100 ^{o}C (Fig. 2.6). At temperatures of 85 ^{o}C or greater a fine cloud of bubbles appeared to be dislodged from the probe tip with "true" boiling at 100 ^{o}C. At high flow rates the period of energy delivery had only a small effect on the peak temperature whereas at low flow rates it assumed a greater significance (Fig. 2.7). The peak temperature was clearly power output dependant with a slower rate of rise at lower outputs (Fig. 2.8).

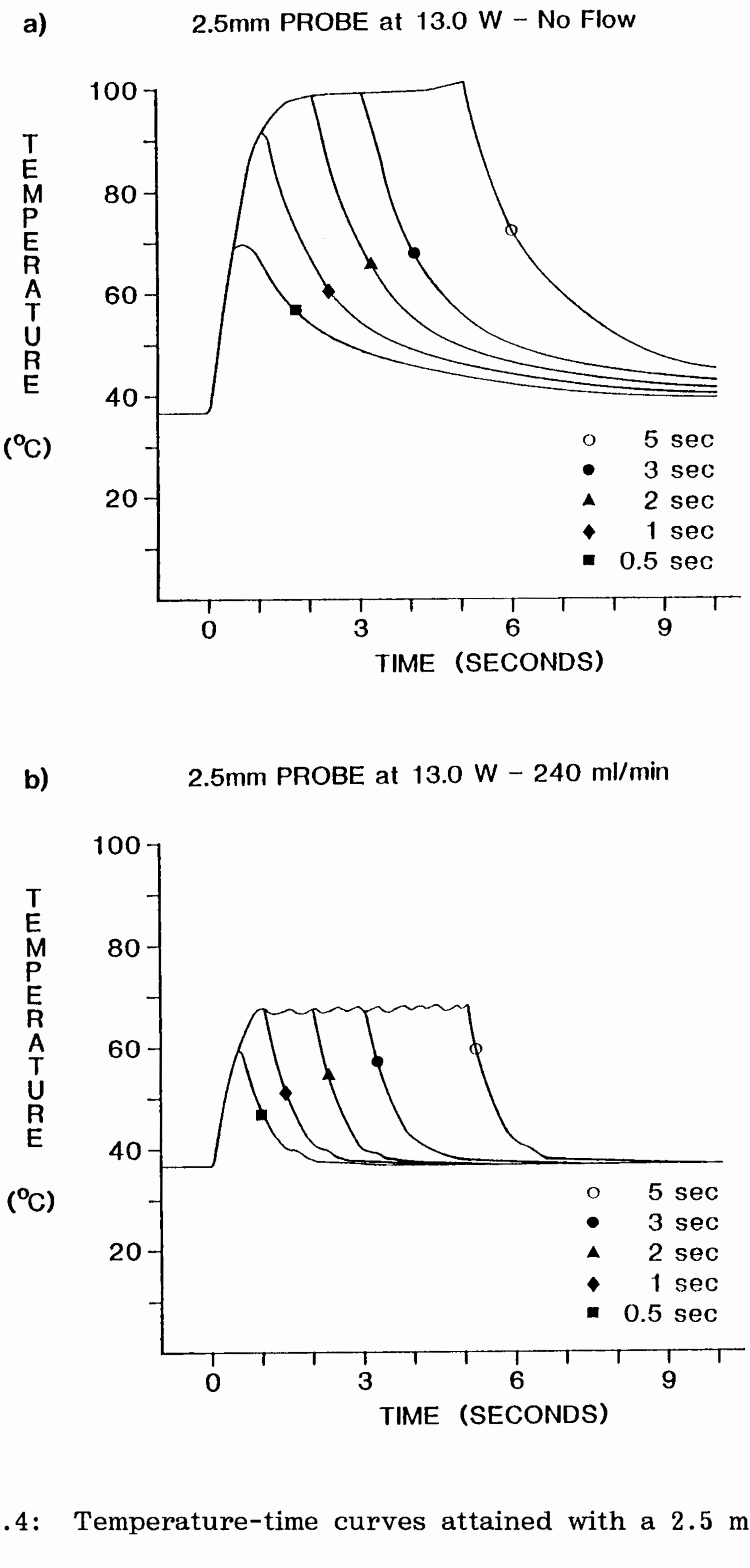


Figure 2.4: Temperature-time curves attained with a 2.5 mm probe at a power output of 13.0 Watts for 0.5-5.0 second applications in a) stationary saline and b) saline circulating at 240 ml/minute.

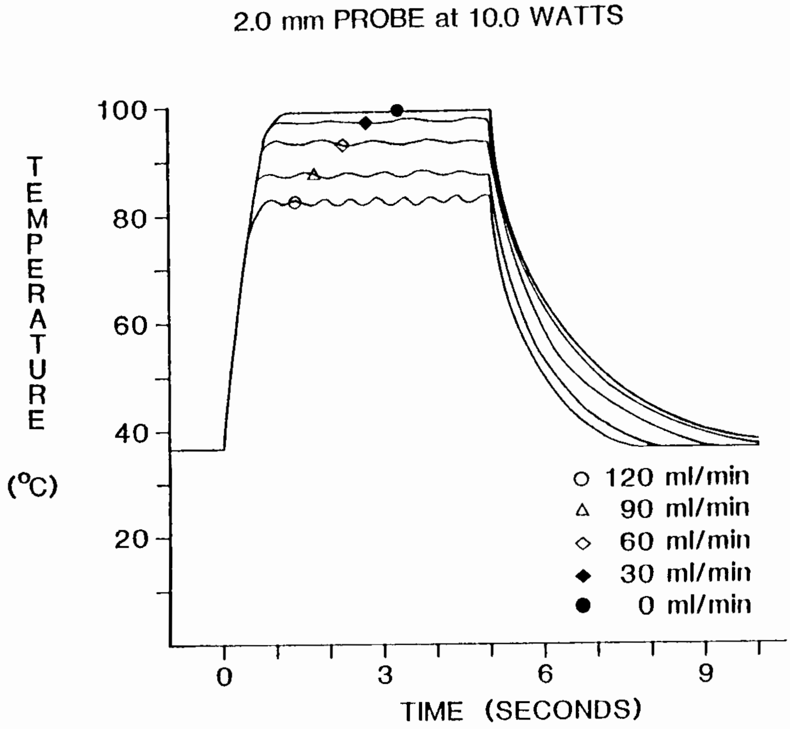


Figure 2.5: Temperature-time curves during application of 10.0 Watts for 5 seconds with a 2.0 mm probe at flow rates of 0-120 ml/minute in saline.

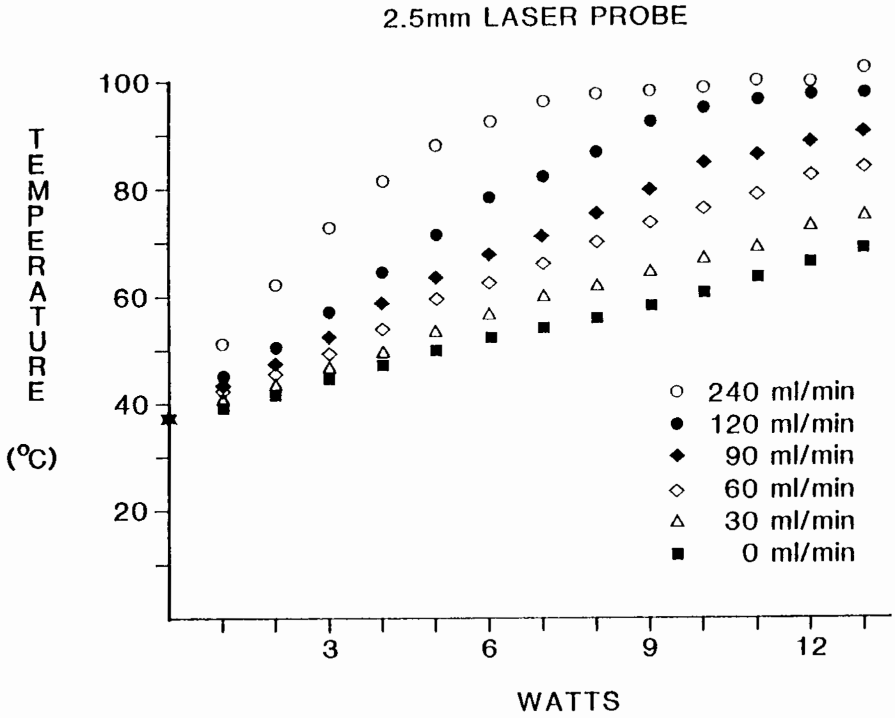
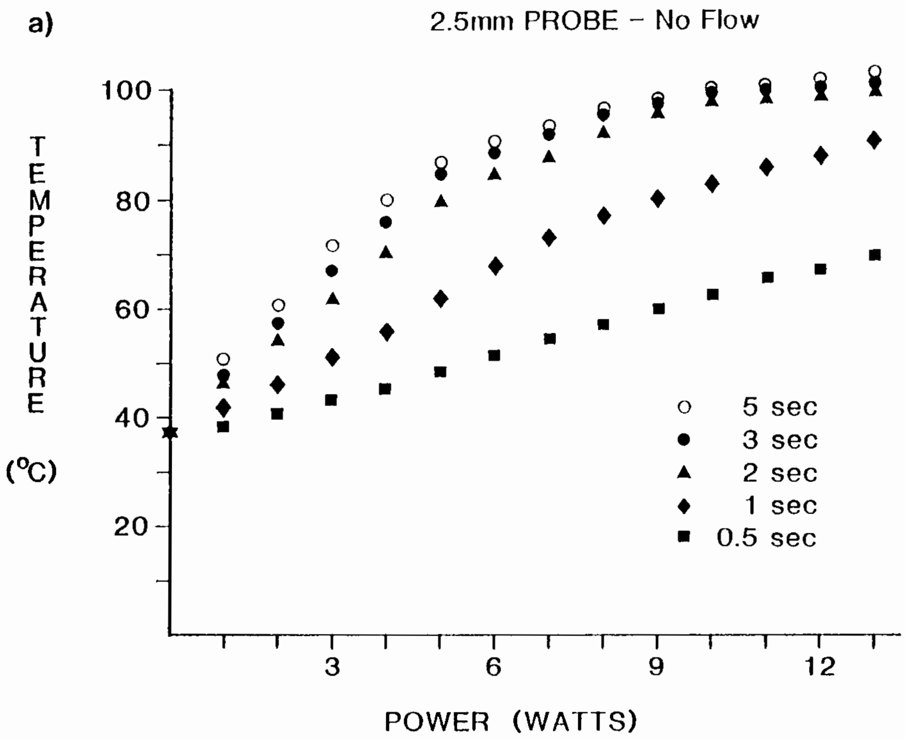


Figure 2.6: Peak temperatures recorded in a 2.5 mm probe, after 5 seconds, at flow rates of 0-240 ml/minute (saline) demonstrate a linear rise in temperature to 85-90 °C with increasing outputs, plateauing out at 100 °C.



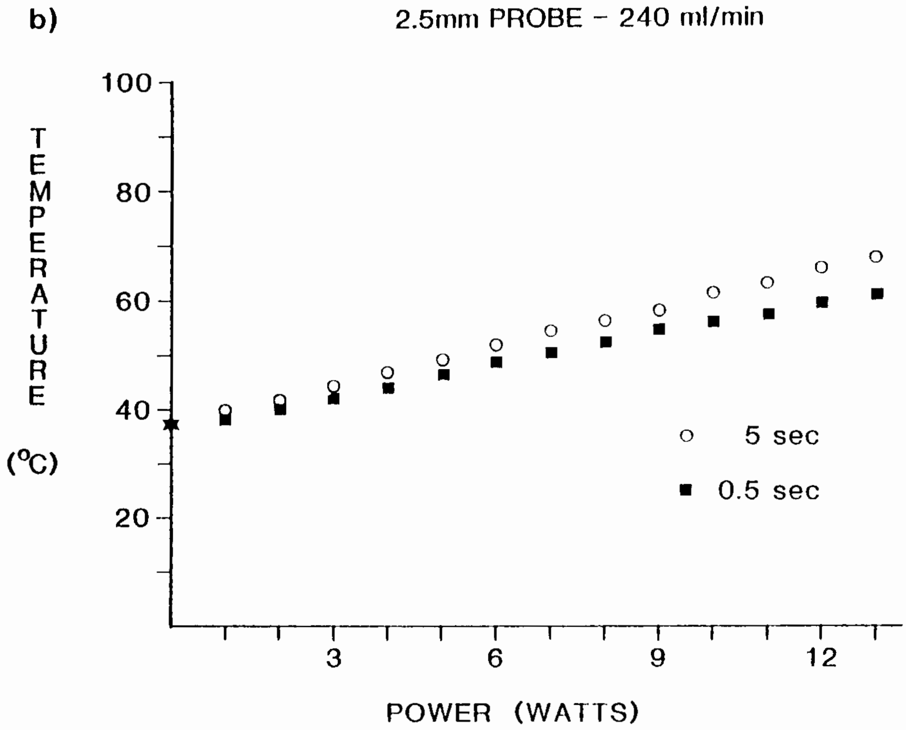


Figure 2.7: Peak temperatures attained by 2.5 mm probe after applications of 0.5-5.0 seconds in a) stationary saline and b) saline at 240 ml/minute showing that peak temperature is less dependant on the duration of energy delivery at high flow rates.

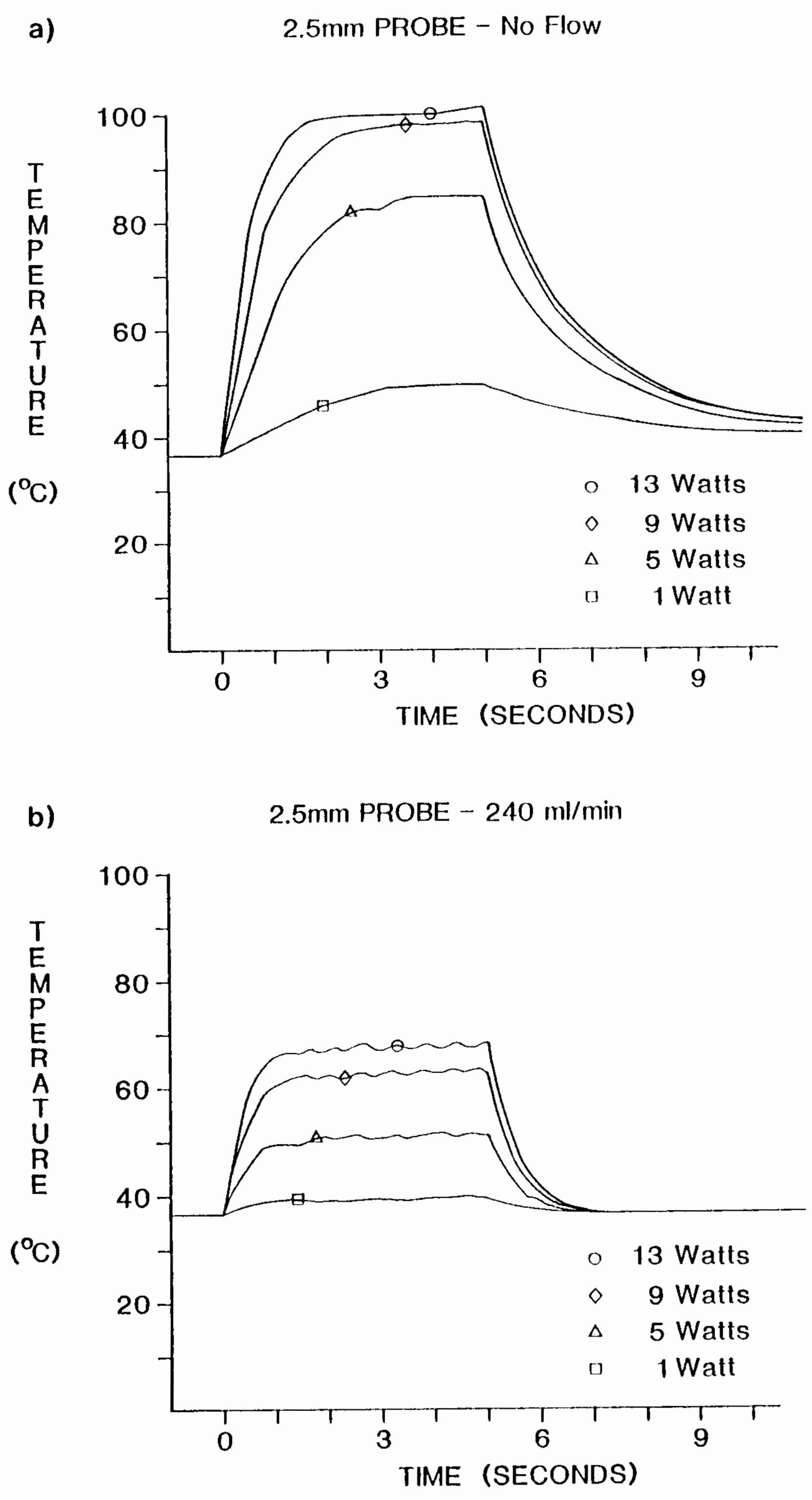


Figure 2.8: Temperature-time curves for a 2.5 mm probe after 5 second applications at power outputs of 1-13 Watts in a) stationary saline and b) saline at 240 ml/minute. Intermediate output curves have been omitted for clarity

No two similar sized probes (either 2.0 or 2.5 mm diameter tips) displayed identical temperature responses with greater discrepancies seen during high flow rates (Fig. 2.9). There were also minor variations in temperature responses for a particular probe between studies. While the results obtained during a single study session were relatively constant for a particular probe (standard deviations +/-1 °C for plateau measurements), on some occasions repetitive testing produced "inconsistent" readings (both Argon and Nd-YAG energies) requiring a whole sequence to be repeated. The thermocouple was sensitive to the flow currents and when its channel was positioned closer to more turbulent flow displayed greater oscillations in the stable plateau temperature: simply removing and replacing the probe in the test segment could thus alter the temperature response. In one study the temperature clearly changed suddenly while the power output and flow remained constant even though the plateau phase had been attained (Fig. 2.10). After energy applications sufficient to raised the temperature to bubble formation, vigorous agitation was needed to remove adherent bubbles, else slightly higher temperatures than would be expected were noted on subsequent testing. Boiling at the tip could occur at similar power outputs with recorded temperatures varying as widely as 95-107 °C on different occasions in the same probe.

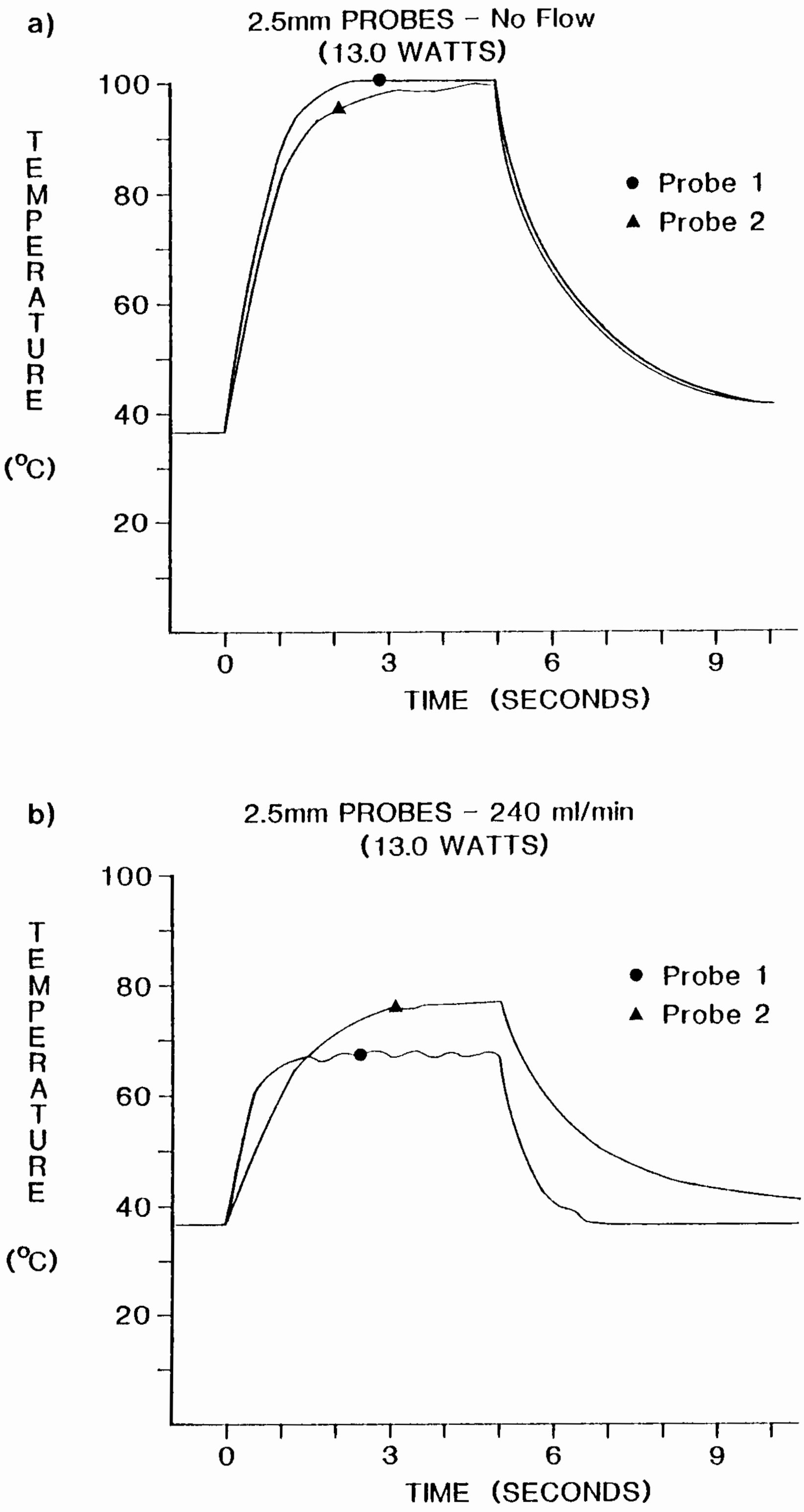


Figure 2.9: Temperature-time curves for two 2.5 mm probes during 13.0 Watt applications for 5 seconds in a) stationary saline and b) saline at 240 ml/minute.

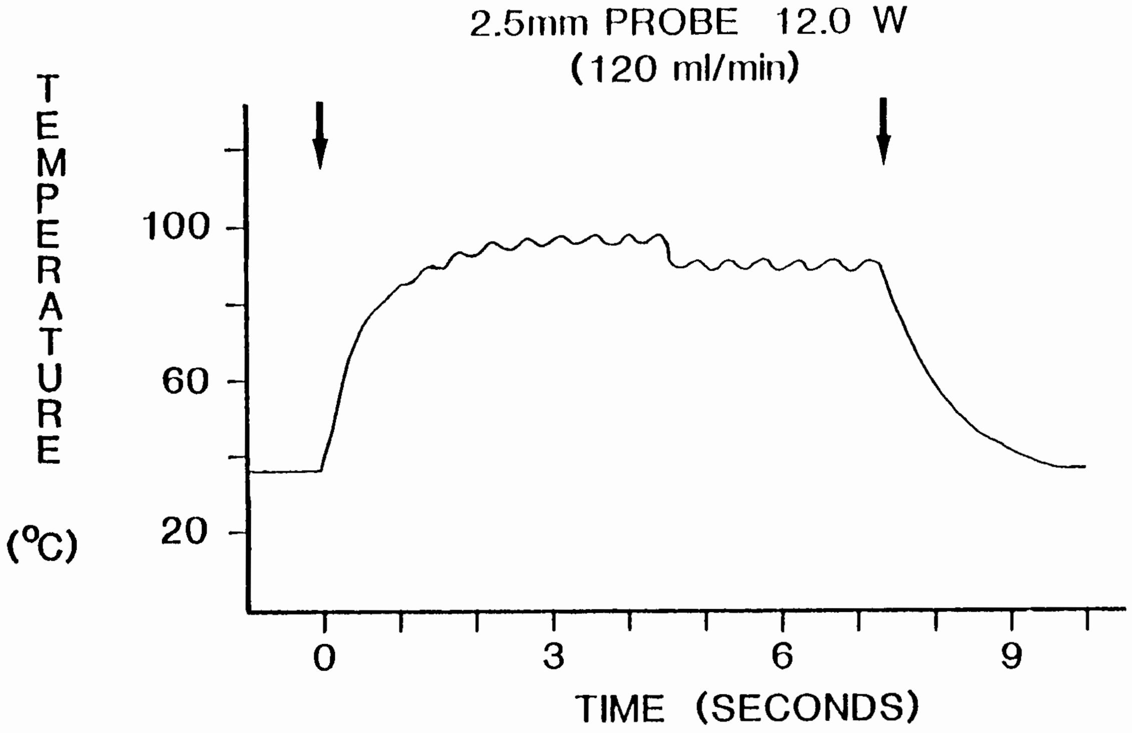


Figure 2.10: Temperature-time curve of a 2.5 mm probe with constant flow and power output showing a sudden change in the "stable" plateau temperature.

(b) Blood Circulation

The temperature responses in blood were highly variable at low to medium flow rates. It was only at high flow rates with short duration, low energy applications that they became reproducible. When the 2.5 mm probe was used at the highest flow rate the peak temperatures were linear over the 1-13 Watts up to a temperature of 100 ^{O}C (Fig. 2.11a). Once the temperature of the probe had exceeded 85-90 ^{O}C in blood, a variable amount of clot and char was found to be adherent to the tip and this increased during subsequent testing. Clot/char on the tip produced initially successive increments in temperature (Fig. 2.11b) despite maintained constant laser and flow parameters. After repeated energy applications the temperature became more reproducible (for each probe) reaching 250-550 ^{O}C (10-13 Watt applications for 5 seconds), despite subsequent variations in the blood flow, usually plateauing at around 700 ^{O}C over a further 5-10 seconds. Initial testing in more slowly flowing blood rapidly heated the tip to as high as 700 ^{O}C over a 5 second period with the 2.0 mm probe at 10 Watts (Fig. 2.12).

After char was present on the tip, returning it into a saline circulation produced completely different temperature response curves with a slower rise and fall though higher peak temperatures. In the example shown (Fig. 2.13) the temperature rise was linear up to 100 ^{O}C, plateauing at 120 ^{O}C, yet did not boil the saline. Removal of clot/char resulted in temperature-time responses closer to that obtained prior to use in blood but this was not easy to do without damaging the tip/fibre junction or the thermocouple insulation.

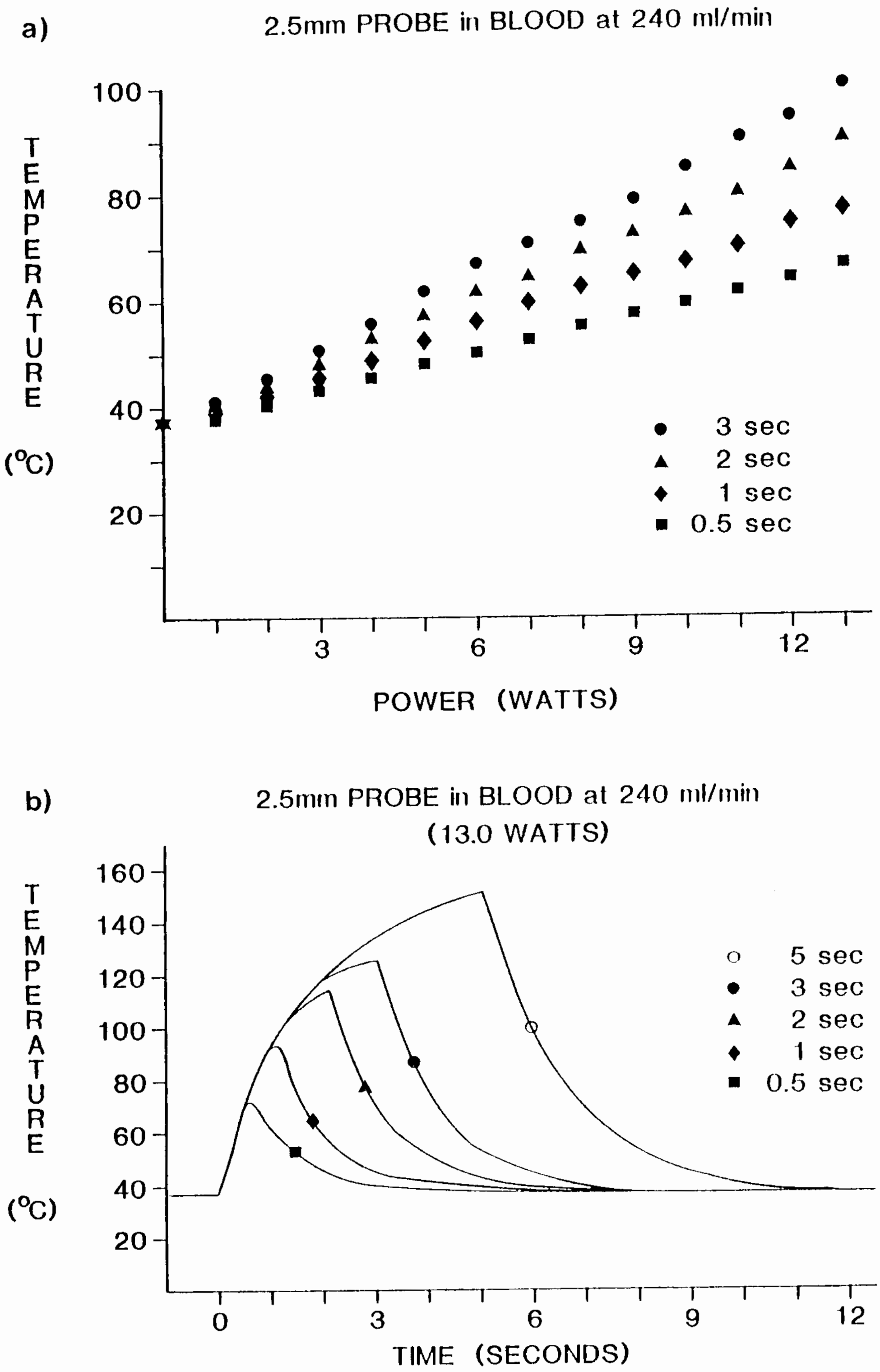


Figure 2.11: a) Peak temperatures attained by a 2.5 mm probe in blood at 240 ml/minute for applications up to 3.0 seconds. b) After performing the series in (a) where the tip temperature in blood reached 102 ^{0}C, successive temperature-time curves do not describe a similar curve with increasingly rapid rises. Note that the peak temperatures for applications of 0.5-3.0 seconds are now higher than in (a).

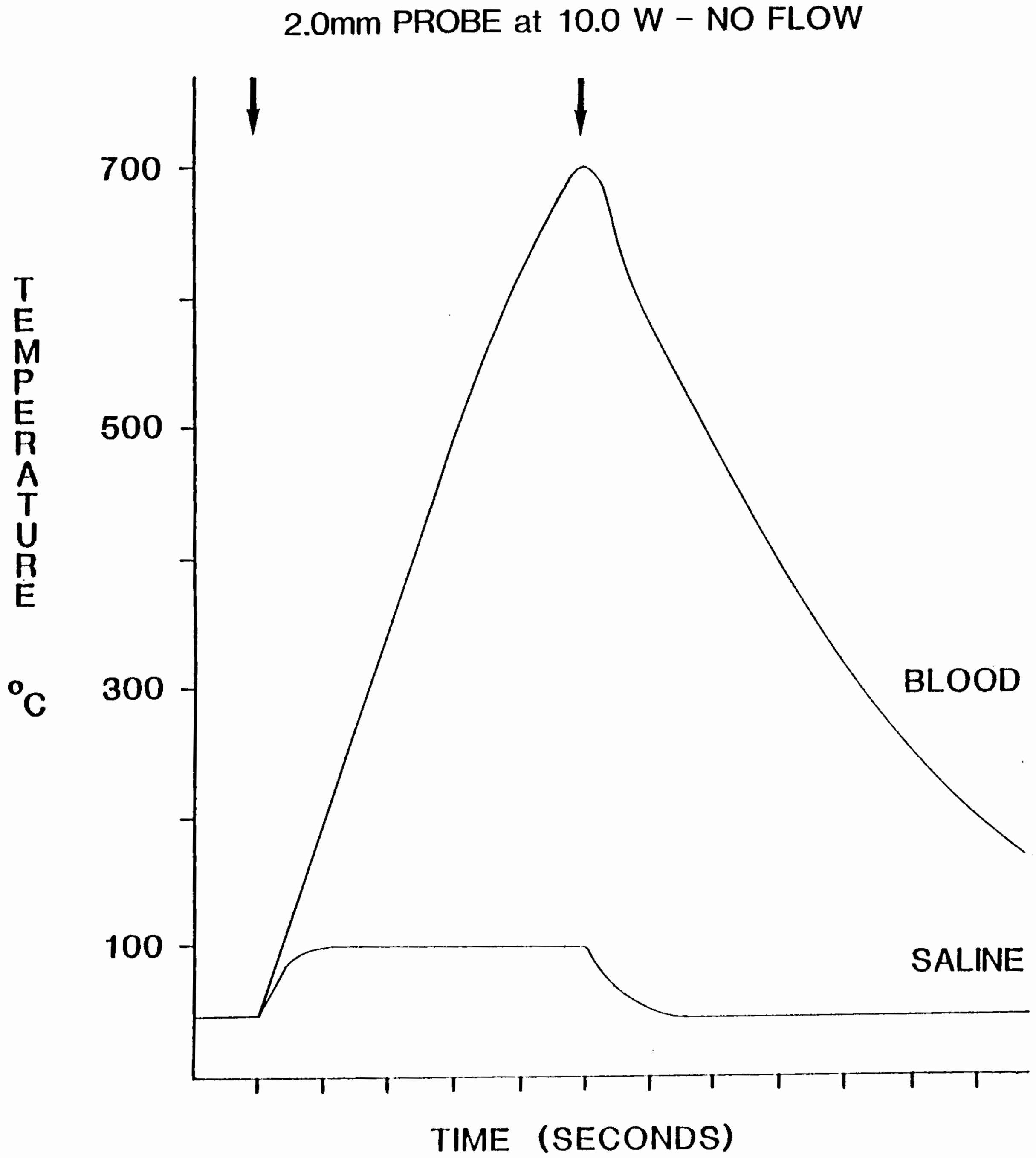
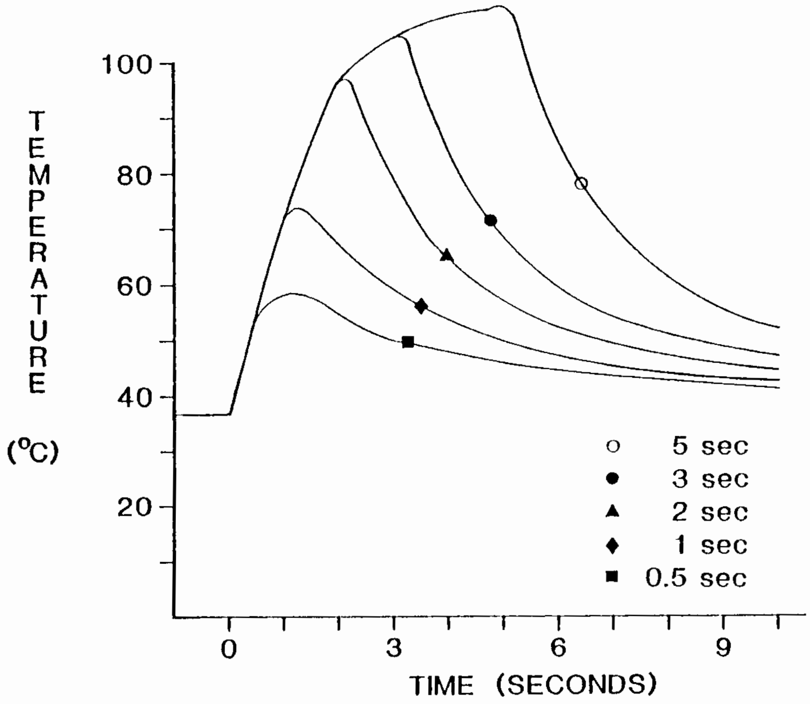


Figure 2.12: Temperature-time curve of a 2.0 mm tip probe after 10 Watts for 5 seconds - first in saline and then in blood.

a) 2.5mm PROBE at 13.0 WATTS - No Flow
(SALINE after exposure to BLOOD)



b) 2.5mm PROBE at 13.0 WATTS - 240 ml/min
(SALINE after exposure to BLOOD)

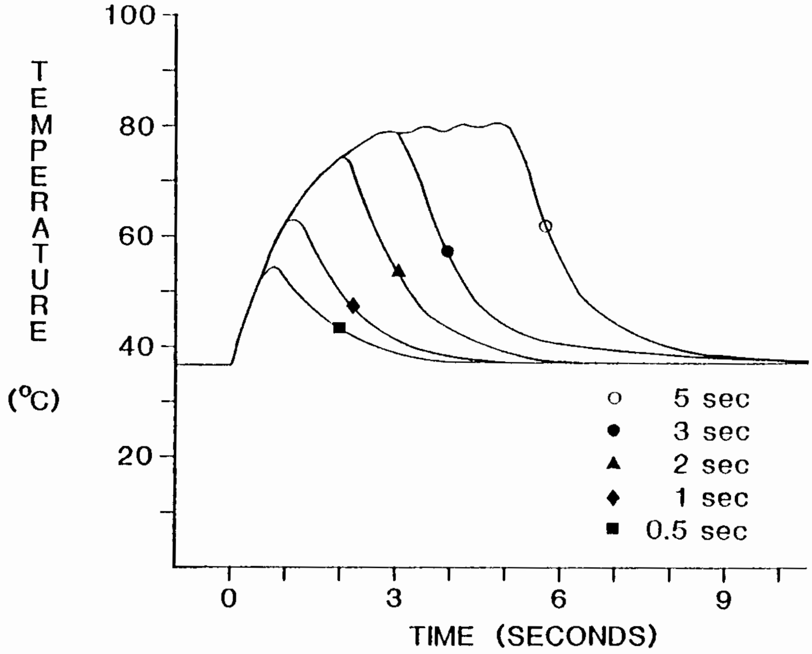


Figure 2.13: Same probe as in Figure 2.11 re-studied in a) stationary and b) saline at 240 ml/minute. Despite a temperature of 120 °C after 5 seconds in stationary saline boiling at the tip is absent indicating an insulating effect of the surrounding char material.

(c) Human Artery Circulation

Temperature-time and temperature-output responses in femoral and carotid artery segments were similar to those obtained in the plastic tube segments either in blood or in saline. Variability and inconsistencies were greater, however, due to inadvertent tip - vessel wall contact (either by noting adherence between power delivery sequences or on incising the vessel after the study). Vessel wall contact in stationary saline never elevated tip temperatures above 110 ^{o}C. An attempt was made to quantify the vessel penetration time in blood circulations by simultaneously kinking the vessel segment and advancing the probe onto the vessel wall. Greater amounts of clot/char build-up retarded advancement of the probe and the more rounded 2.5 mm probe tip penetrated the wall less easily than the 2.0 mm tip. The time varied from 30-90 seconds in blood depending upon the state of the probe but probe attrition during the preceding studies did not allow a comprehensive analysis.

2.4 DISCUSSION

Laser assisted angioplasty as a means of overcoming some of the limitations of the conventional balloon procedure has become a viable manoeuvre using the "hot tip" thermal probe in peripheral arteries (173). Its extension to coronary disease has been less successful (174,175) due to the considerable differences found between peripheral and coronary arteries. The thicker walled wider diameter peripheral vessels appear to be less prone to spasm and more resistant to the deleterious effects of heat. In order to develop a successful thermal control approach it is essential to appreciate both the probe temperature achieved in different environments (i.e. flowing blood, clot, atheroma, wall) as well as the probe temperatures required to penetrate differing compositions of atheroma (fatty, fibrous, calcified) while in those environments.

In vitro studies of the "hot tip" probe applied to human aorta in air show that tip temperatures in excess of 180 ^{o}C are required for ablation. Tissues temperatures at the same time are usually less than half the probe tip temperature (102). In a study of probe tip temperature during recanalisation of occluded peripheral arteries in vitro the temperature attained ranged from 130 +/- 20 ^{o}C for fatty plaque obstruction to 280 +/- 72 ^{o}C for calcified obstructions. In some calcified obstructions temperatures greater than 400 ^{o}C were unable to recanalise the vessel (193). In another study where the probe tip temperature was held constant, by continuously varying the output with thermocouple feedback control, the depth of ablation (in vivo canine femoral arteries) was reported to be directly proportional to the tip temperature over a range of 50-400 ^{o}C (194).

This study is the first to look at the probe tip temperature developed over a wide range of laser powers, application periods and flow rates. In saline the results were relatively reproducible and the probe tip usually reached a steady temperature at around 100 ^{O}C in stationary saline and up to 110 ^{O}C where there was vessel contact. At high flow rates the peak temperatures attained were considerably lower and less dependant on either the laser power or the time over which it was applied. Thus in vivo perfusion with saline would considerably reduce the probe temperature and any "lateral" heating effects of vessel not in direct contact with the tip (Section 4.4).

In attempting to analyse temperature changes that might be useful for a feedback algorithm several inconsistencies were apparent. The rate of temperature development and peak temperatures varied between probes, particularly at high flow rates. Variable optical fibre to metal cap coupling during manufacture or positioning of the thermocouple within the tip may account for this. Thus even if algorithms can be developed for maximising the ablation : perforation margin it would be important to adjust this by testing each probe in saline at known flow rates.

Variability in the same probe is difficult to explain but may be due to intermittent vent hole obstruction, inaccuracies in temperature measurement, probe tip insulation effects or generator output instability. The vent hole normally functions to allow the escape of any gases or fluid between the end of the fibre and the surrounding metal cap as excessive expansion could force the metal cap off the fibre. This also allows some loss of heat: hence intermittent obstruction to the vent hole channel by microdebris (in the circulating medium) between energy delivery sequences could affect the recorded temperatures. This phenomenon is likely to be accentuated in the 2.0 mm probe with its single small vent hole (and in blood). The temperature measured will depend on the exact position of the thermocouple within the probe tip as there is a small delay in temperature spread across the probe (102), effective thermal contact, and the success of insulating the thermocouple wires from the junction inside the tip to the temperature meter. Micro-displacement of the junction or its insulation during use (as in negotiating the haemostatic valve) might be important. In addition the temperature in the thermocouple channel is highly sensitive to oscillations in flow: exposure to the mainstream flow or eddy currents and partial or intermittent obstruction of its channel by debris or bubbles could also affect the recorded temperatures. Tip insulation by small vapour bubbles (air coming out of solution at +/- 85 ^{o}C or boiling near 100 ^{o}C) resulted in slightly higher tip temperatures if these bubbles were not meticulously removed from the probe tip surface. This probably accounts for the late rise in "plateau" temperatures seen in some studies. Small variations in the generator output become important at low flow rates. In the single instance where a stable plateau temperature suddenly changed this may have been due to a change in the generator output or dislodgement of a bubble from the thermocouple channel.

In blood the probe tip temperatures attained were variable reaching up to 700 ^{o}C in stationary blood within 5 seconds. When heated in a blood medium the laser probe coagulated blood surrounding it with the formation of a thin layer of char and thrombus which became more extensive over time (191). This tended to slow the rate of rise (and fall) in temperature and while the peak temperatures were higher the clot/char prevented dissipation of heat to the surroundings. Using aluminium capped fibres (temperatures in air are only 50% of the Trimedyne probes used here) Silverman et al found that adventitial temperatures in vitro were similar when lasing in blood or saline despite the higher probe temperature in blood (195). In vivo the blood medium might initially raise tip temperatures and enhance ablation until the development of a coagulum insulates it and then retards further ablation. After a number of energy delivery sequences the temperature profile is likely to become reproducible with the development of a larger clot. In clinical practice the probe is constantly agitated to try prevent char build up: the degree of tissue contact and any "abrading" effect on the char while negotiating an obstruction are additional complicating factors in interpreting the temperature response.

Conclusions: It is unlikely that probe tip temperature monitoring or stabilisation via a thermal feedback control circuit will be able to limit thermal damage in blood. Probe tip temperature is critically dependant upon the rate and amount of char and clot build-up and the rate of blood flow at any given time. Char build up will depend on the blood flow at the time of energy delivery while blood flow in relationship to the probe will vary during the recanalisation process itself. A controlled saline flush at the time of laser thermal angioplasty may allow a constant temperature to be developed due to the heat sink effect of saline and the absence of char/coagulum build-up. This may only be effective however in stenotic disease and not while the probe is traversing a long occlusion. Finally, elimination of the variability in temperature responses of the probes themselves would be necessary for such an approach.

3.0 PERIPHERAL ARTERY LASER THERMAL PROBE ASSISTED ANGIOPLASTY

3.1 INTRODUCTION

Percutaneous transluminal angioplasty in peripheral artery disease is a well established procedure with high technical success rates in stenotic disease (196). The success rate in occlusions is not as high mainly due to difficulties in negotiating the lesion with a guide wire, and this is more common with older and longer lesions. The guide wire tip may dissect the wall of the artery and even perforate it with successive attempts often re-entering the false channel. The long term success rate of dilatation is highly dependant on an adequate distal "run off" but in addition the length of the occlusion is also inversely proportional to the long term outcome (197-201).

Early attempts at laser recanalisation using conventional optical fibres were often technically successful but balloon dilatation was always necessary. In some of these patients laser energy was only delivered during retrograde withdrawal after the fibre had successfully negotiated the lesion or was used for subtotal occlusions. Thus the clinical benefit from the procedure appeared to be marginal (66,67,138). The initial study of the laser thermal probe by Cumberland et al was encouraging, with a high recanalisation rate (albeit still requiring balloon dilation) and low perforation rate, and included many patients with prior unsuccessful balloon angioplasty procedures (173).

This study assessed the abilities of the laser thermal probe to cross peripheral artery occlusions. In addition the effectiveness of laser ablation in its own right and the mechanisms of success or failure were addressed.

3.2 METHODS

(a) Patients

Patients were referred from Guy's hospital and its peripheral catchment hospitals by physicians, surgeons and radiologists. In 8 of the 9 patients treated, previous angioplasty procedures had failed or were considered to be impossible or very difficult using conventional techniques. In one patient the laser was used in two relatively short occlusions with the aim of simultaneously "debulking" rather extensive adjacent non-occlusive disease. Informed consent was obtained from each patient who otherwise received standard pre and post angioplasty care. Heparin 20,000 units was infused over 24 hours in successful cases but antiplatelet therapy was not used routinely. Ankle-brachial indices were measured before and after the procedure with a sphygmomanometer and/or Doppler.

(b) Laser Probes

The "hot tip" laser probes (Fig. 3.1) consisted of an olive shaped metal cap 4 mm long and 2 mm in diameter which was firmly fixed onto a 300 um core optical fibre by a 6 mm metal collar. A 3.5 cm safety wire was attached to the metal cap and crimped onto the fibre proximally to enable retrieval in the event that the metal cap detached itself (by attaining sufficiently high temperatures to melt the optical fibre). In addition a 175 cm support wire was attached to the tip to enhance the coaxial force that could be applied to the lesion. The probe itself was rather inflexible due to the terminal 1 cm long metal components (tip plus collar) as well as the rather stiff 300 um fibre. The ability to steer the probe was thus rather limited: collar angulation (ex vivo) with rotation of the probe was the only manoeuvre available apart from advancement.

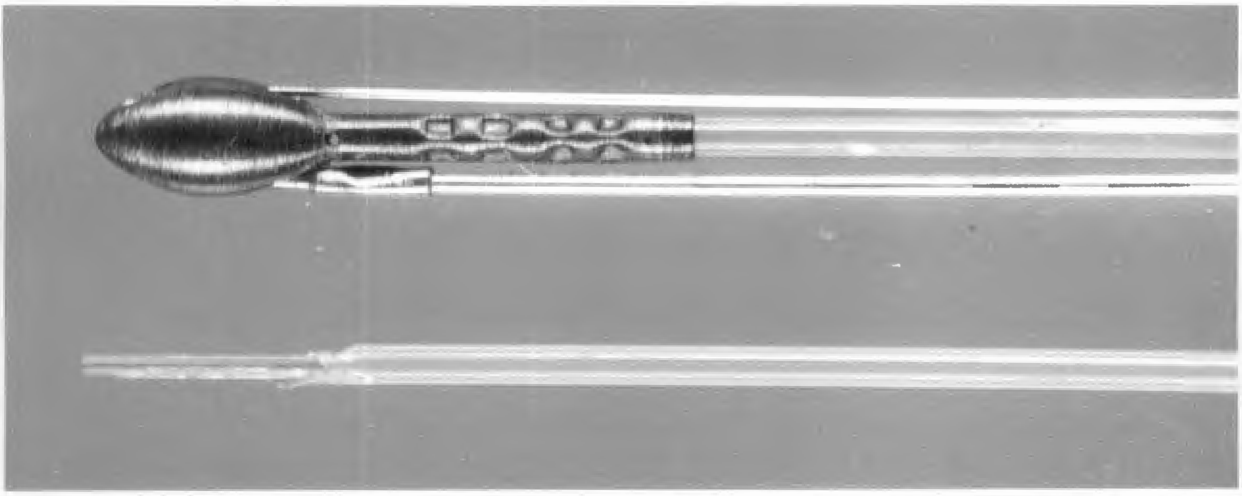


Figure 3.1: A 2.0 mm tip laser probe with its 300 um core fibre. A safety wire (upper) and support wire (lower) are attached to the tip. Alongside is the corresponding 300 um core bare optical fibre with its jacket partially removed at the tip (see also Figure 1.1).

(c) Procedure

The procedures were performed in the cardiac catheterisation laboratory where the laser generator was installed using fluoroscopy with video playback and cine-angiography. Prior to each treatment the argon laser generator was set at 10 Watts and output was checked using a bare fibre and a power meter. The laser probe was introduced through an 8F haemostatic sheath placed in the ipsilateral femoral artery in all but one patient (brachial approach). Advancement using fluoroscopy was guided by marking skeletal and other land marks (such as the limits of the occlusion and origins of collaterals) on the video screen. During energy delivery a continuous to and fro motion was used which was maintained for 3 - 5 seconds after power was switched off to avoid the probe adhering to the vessel wall. Contrast was used frequently to monitor progress through these lesions none of which had been crossed by a guide wire. On crossing the occlusion free movement of the probe in the distal vessel and contrast administration confirmed its intraluminal position. Balloon dilation then proceeded using guide wires and balloons of appropriate dimensions. After the procedure the cine-angiograms were projected onto a screen and vessel and lesion diameters measured before and after each intervention with callipers (referenced to the 2.0 mm diameter tip).

3.3 RESULTS

The probe successfully recanalised 8 of the 10 occlusions (length 1-12 cm) after 1 to 10 energy applications (total energies of 70-1100 Joules). During energy delivery three patients had some discomfort which was mild in two and moderate in one - similar in intensity to contrast administration. Advancement of the probe was relatively rapid and resistance to progression was infrequent. Even when the probe perforated the vessel wall in two cases the tactile sensation was no different to that of intravascular progression and the perforation was only apparent after deviation of the probe from the expected course or after contrast administration. In three patients after crossing the occlusion with the laser probe the guide wire was unable to follow leading to a further two unsuccessful cases with perforations in both. In the third patient the guide wire was replaced with the laserprobe which was then easily re-advanced across the lesion without further energy delivery. The fibre itself was cut proximally and used as a guide wire for balloon placement. Subintimal dissection with re-entrance into the lumen and subsequent successful balloon dilatation was evident in two patients. While the first instance was readily apparent during the procedure in the second it was only evident on review of the developed cine-angiograms.

In the six occlusions (five patients) successfully recanalised by the laser and subsequently dilated with the balloon the long term outcome was mixed. In a patient with Buergers disease and rest ischaemia no improvement occurred despite improved large vessel flow. In a second patient with rest pain and poor distal run off (double occlusion) only modest improvement occurred due to early occlusion of the distal lesion. In three patients very good short term results were present but one relapsed two weeks later with a presumed re-occlusion. In the two remaining patients complete symptomatic relief was maintained over a year later (Fig. 3.2).

Clinical characteristics of the patients and the procedural technicalities are summarised in Table I and described further in the following case reports.

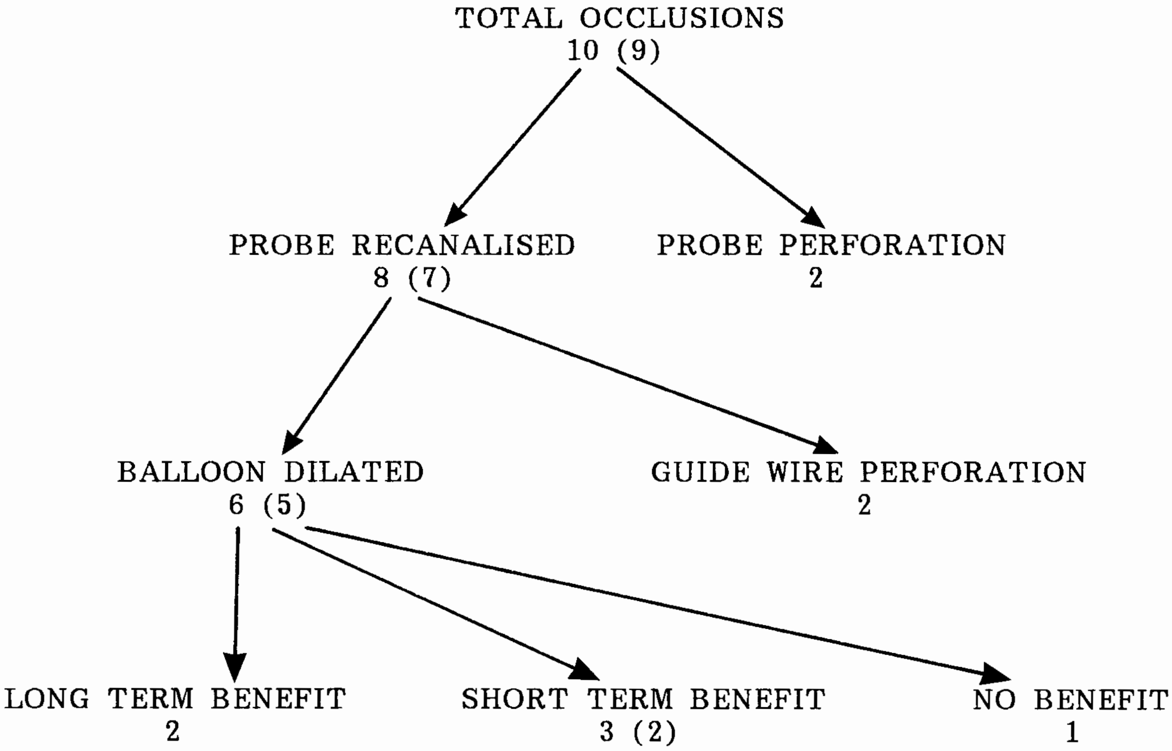


Figure 3.2: Out come of laser thermal probe assisted angioplasty in 10 peripheral artery occlusions (9 patients).

Table I - OUTCOME of LASER THERMAL PROBE ASSISTED ANGIOPLASTY in PERIPHERAL ARTERY OCCLUSIONS

PATIENT	1 (FM)	2 (AM)		3 (LC)	4 (SB)	5 (FB)	6 (LB)	7 (WR)	8 (DT)	9 (EW)
Age	77	60		75	37	64	76	62	52	74
Sex	M	M		M	M	M	F	M	M	M
Ischaemic Heart Disease	-	-		-	-	-	-	-	-	CABG
Hypertension	-	-		-	-	-	15 Years	-	-	-
Diabetes	-	-		-	-	-	-	12 Years	-	-
Cerebrovascular Disease	-	-		-	-	-	-	-	-	-
Other		COAD			BUERGERS				AVR/SBE	
Smoker	Ex	Ex		Ex	YES	YES	Ex	YES	NO	Ex
MEDICATION										
Aspirin (mg/day)	-	-		75	-	75	-	-	-	-
Dipyridamole (mg/day)	-	-		300	-	300	-	-	-	-
Praxiline (mg/day)	-	-		-	-	-	300	-	-	300
Other	-	Bronchodilators Prednisilone		-	-	-	Labetalol Spirinolactone	Insulin	Moduretic	Nifedipine Moduretic
CLAUDICATION SEVERITY										
Distance (meters)	200	0		25	0	200	200	150	1000+	200
Duration (years)	1.5	6/12		6/12	4/12	7.0	2.0	1.5	5.0	3.0
Rest Pain	-	YES		YES	YES	-	-	-	-	-
Threatened Infarction	-	YES		-	YES	-	-	-	-	-
OCCLUSION										
Site	FEMORAL	FEMORAL	POPLITEAL	FEMORAL	FEMORAL	ILIAC	FEMORAL	FEMORAL	POPLITEAL	FEMORAL
Length (cm)	7.8	1.0	2.5	7.5	5.0	2.0	6.1	12.3	5.4	8.1
Proximal Diameter (cm)	4.7	4.2	3.1	5.5	6.6	9.2	5.9	5.2	3.1	5.7
Distal Diameter	4.1	4.0	3.1	4.9	3.5	9.0	5.0	5.2	3.1	5.7
Ankle / Brachial Index	0.7	0.42		0.3	-	0.71	0.54	0.7	0.4	0.56
Previous Angioplasty	YES	-	-	YES	-	YES	YES	-	-	YES
LASER ANGIOPLASTY										
Power (Watts)	10	10	10	10	10	10	10	10	10	10
Energy Deliveries	5	1	6	4	4	1	2	3	4	11
Total Energy (Joules)	500	80	380	590	340	70	170	300	210	1100
Minimum Diameter	1.6	1.0	0.5	0.5	1.0	1.0	0.5	-	-	1.0
Maximum Diameter	3.5	2.0	2.0	1.6	3.8	1.5	1.8	-	-	2.0
Perforation	-	-	-	-	-	-	-	YES	YES	-
Pain	Minimal	-	-	-	-	-	-	-	Minimal	Moderate
Dissection	-	-	-	-	-	YES	YES	-	-	-
BALLOON ANGIOPLASTY										
Guide Wire Passage	NO	+	+	NO	+	+	+	-	-	NO***
Balloon Diameter	-	4	4	-	6	10	6	-	-	6
Minimum Diameter	-	3.5	3.0	-	4.5	9.1	4.7	-	-	3.7
Maximum Diameter	-	4.0	3.1	-	4.7	10.2	5.5	-	-	5.2
Ankle / Brachial Index	0.7	0.66		0.3	-	0.92	1.03	0.7	0.44	0.69
CLINICAL OUTCOME										
Benefit	-	+		-	-	+++	++++	-	-	+++
Surgery				Femoro-popliteal Bypass	Above Knee Amputation					
Relapse		3/12 (Iliac Stenosis)								2/52

CABG = coronary artery bypass grafting
COAD = chronic obstructive airways disease
AVR = aortic valve replacement

*** = Use of "cold" laser probe to negotiate the lesion prior to balloon dilatation.
SBE = subacute bacterial endocarditis

Patient 1 (FM)

A 77 year old man had claudication in the right calf after walking 200 yards on the flat forcing him to rest for five to ten minutes after a further 400 yards. His symptoms had been present for 18 months and 10 months previously angiography had revealed an 8 cm total occlusion of the right popliteal artery (Fig. 3.3 [1]). Conventional angioplasty was unsuccessful and he was subsequently referred for a laser procedure.

Angioplasty Procedure: The 2 mm laser probe was advanced via an 8F sheath in the right femoral artery to the proximal end of the occlusion. Energy at 10 Watts was delivered with applications of 13, 8, 9 and 4 seconds whilst the occlusion was crossed and a further 16 second application during withdrawal across the entire length of the lesion. Angiography revealed an irregular tract with a minimum diameter of 1.6 mm and a maximum of 3.5 mm (Fig. 3.3 [2]). During subsequent passage of the tract with a conventional J guide wire and balloon dilatation catheter the guide wire perforated close to the end of the occlusion (Fig. 3.3 [3]). Thereafter it proved impossible to recross the lesion and the procedure was abandoned.

Post Angioplasty Course: The patient developed a large haematoma in the popliteal fossa which did not impede mobility or perfusion via his original collaterals and he was discharged 48 hours later. The haematoma resolved over the succeeding 4 weeks and his physical limitations were unchanged. He declined any further interventional procedures or surgery.

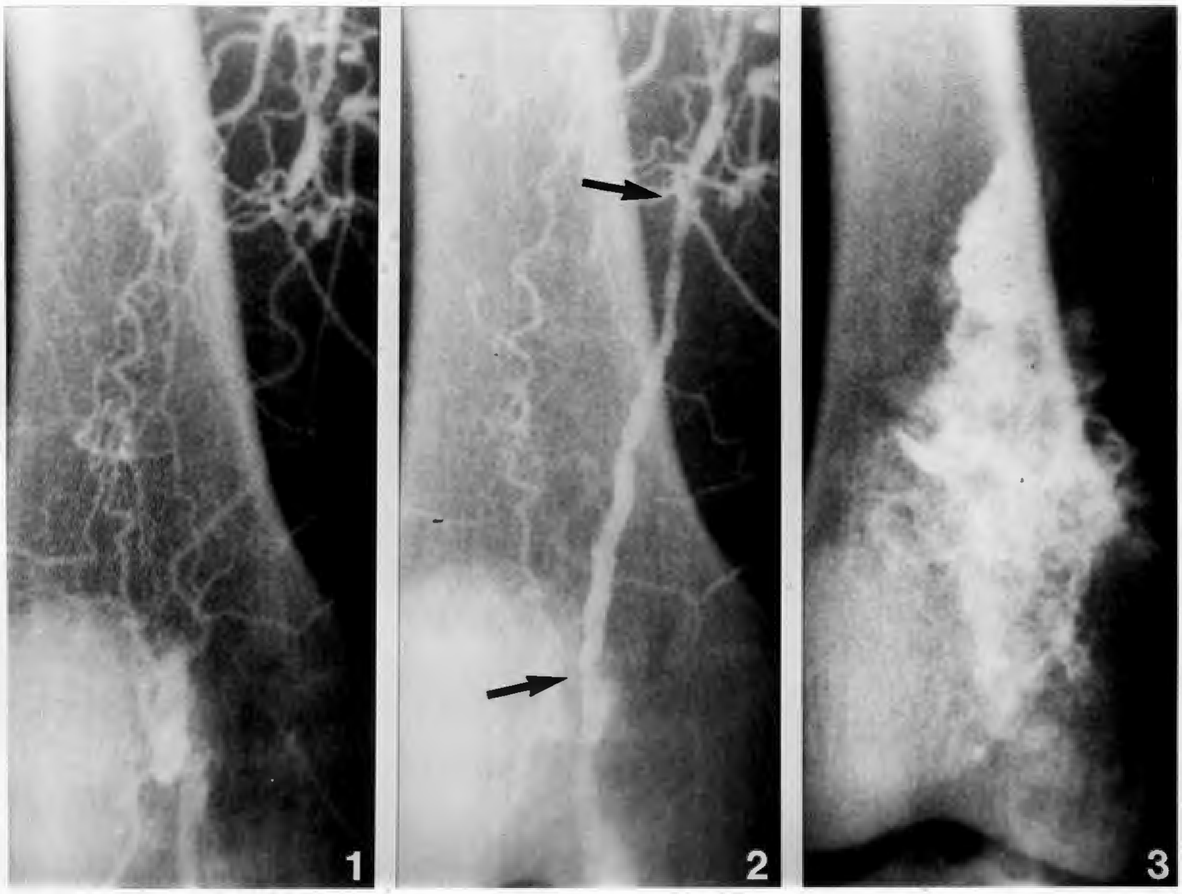


Figure 3.3: The 8 cm occlusion in the right popliteal artery [1] is easily crossed by the laser probe and produces a 1.6-3.5 mm channel [2]. During passage of the guide wire a perforation occurs and it is thereafter impossible to recross the lesion. There is extensive dye extravisation [3] with the development of a large popliteal haematoma.

Patient 2 (AM)

This 60 year old man had a traumatic right below knee amputation as a young man and suffered from severe chronic obstructive airways disease requiring domiciliary nebulizers and oral steroid therapy. He was admitted with rest pain due to ulceration over the 1st and 5th digits of his left foot of 6 weeks duration. Foot pulses were absent below the left femoral pulse and the ankle/ brachial index was 0.42. Arteriography revealed short occlusions of the distal superficial femoral artery (1 cm) and of the popliteal artery (2.5 cm) with extensive non-occlusive disease and poor distal run off.

Angioplasty Procedure: The 2 mm probe easily crossed both occlusions requiring 8 seconds at 10 watts for passage through the proximal lesion while six applications were delivered to the distal lesion - 3, 6, 8 and 6 seconds during forward passage and 6 and 9 seconds during withdrawal. At this time the luminal diameter appeared to be a maximum of 2 mm at both sites. A 4 mm balloon was then inflated in the proximal lesion resulting in a lumen of 3-4 mm throughout its length. At this point the second lesion had re-occluded, though it was easily crossed with a guide wire alone and dilated to a diameter of 3 mm with the 4 mm balloon.

Post Angioplasty Course: Three days later his foot felt warmer with less pain and the ankle/brachial index had improved to 0.66. The doppler wave forms however suggested that the popliteal lesion had re-occluded with maintained patency at the proximal femoral artery lesion. The improvement was only short lived and three months after the procedure he continued to experience rest pain and his ulcers had not healed. Nine months later balloon dilatation was performed for a right iliac stenosis together with a chemical sympathectomy and there was gradual healing of his foot ulcers.

Patient 3 (LC)

This 75 year old man had worsening claudication in his left calf over a six month period and was only able to walk for 25 yards on the flat. In the weeks prior to his admission he had begun to suffer with rest pain at night. There were no foot pulses below the left femoral pulse and angiography revealed a 7.5 cm occlusion of the distal superficial femoral and popliteal artery with run off to a patent posterior tibial vessel only (Fig. 3.4 [1]). Conventional angioplasty was attempted at a peripheral hospital without success.

Angioplasty Procedure: The 2.0 mm laser probe easily crossed the lesion with two applications of 10 and 7 seconds and the channel was further enlarged with additional 20 and 21 second withdrawal and re-advancements (Fig. 3.4 [2]). The resultant channel measured 0.5-1.6 mm in diameter (Fig 3.4 [3]) but the J guide wire was unable to negotiate the whole lesion and perforated the vessel wall at a distance of 4 cm (Fig. 3.4 [4]). Thereafter it was impossible to pass either a variety of floppy tipped guide wires or the laser probe itself without entering the false tract and the procedure was abandoned.

Post Angioplasty Course: There were no symptoms or signs of the perforation and four months later he underwent femoro-popliteal bypass grafting. Postoperatively he had a myocardial infarction and a further fatal myocardial infarction three weeks later. Postmortem examination was not performed.

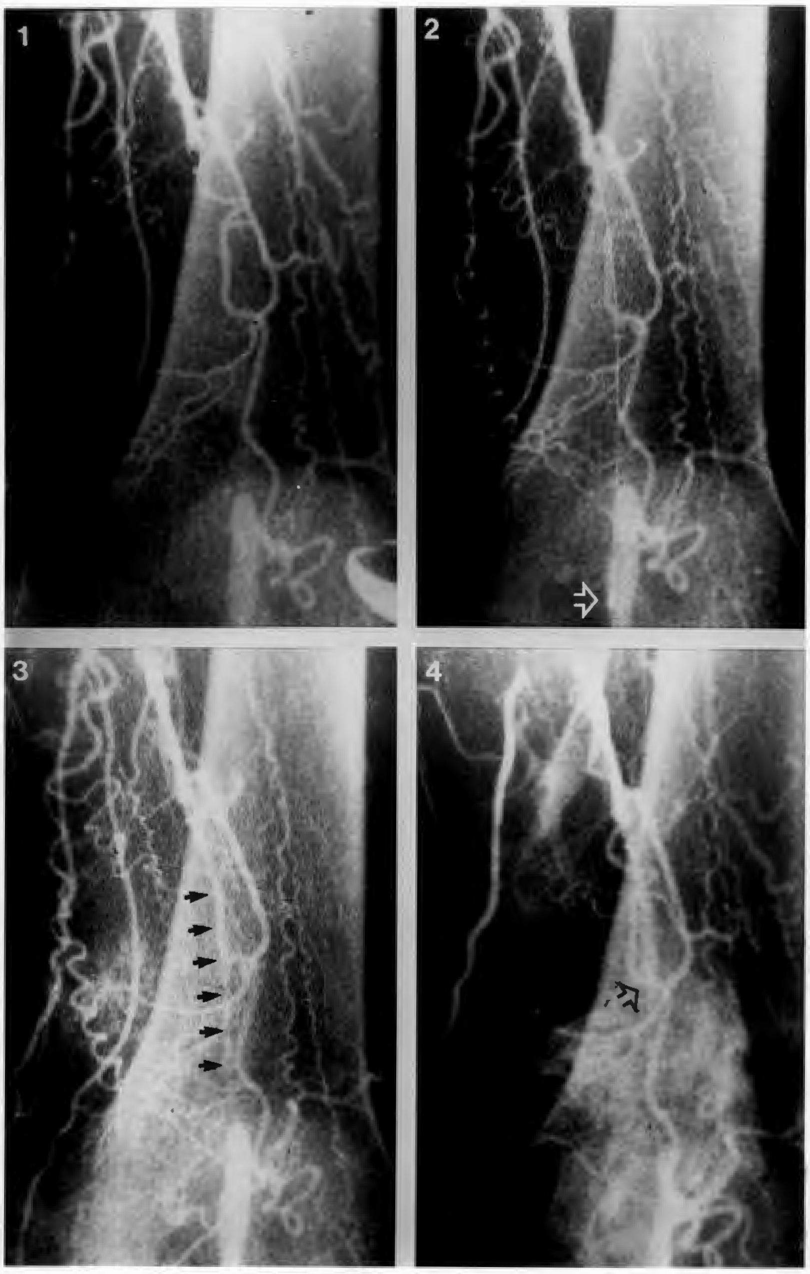


Figure 3.4: The distal superficial femoral occlusion [1] is easily crossed by the laser probe (white arrow) in [2]. A narrow tract (black arrows) is apparent [3] but the guide wire perforates (open black arrow) with dye extravisation [4].

Patient 4 (SB)

A 37 year old man with Buergers disease, who continued to smoke, underwent sequential amputations culminating in bilateral below knee amputations. He presented with rest pain and a swollen tender ischaemic stump on the right with a barely palpable femoral and absent popliteal pulse. Angiography revealed a 5 cm occlusion of the common femoral artery which did not allow direct percutaneous access for angioplasty (Fig. 3.5 [1]).

Angioplasty Procedure: The laser probe was introduced via a 9F long sheath (internal diameter of 2.3 mm; Angiomedics, France) inserted through a left brachial arteriotomy and advanced to the common femoral stump (Fig. 3.5 [2-3]). The lesion was crossed with two applications of energy at 7 and 8 seconds and was further dilated with two applications during withdrawal for 9 and 10 seconds (Fig. 3.5 [4]). During the last two energy deliveries it became noticeably more difficult to continuously agitate the probe. Contrast administration revealed that the original occlusion had consisted of a proximal and distal occlusion with a much larger lumen between these two points after laser energy delivery (Fig. 3.5 [5]). On attempting to withdraw the probe back into the sheath resistance was encountered although the probe was still able to be advanced quite freely through the lesion itself. An exchange guide wire was then passed down the sheath alongside the laser probe and across the lesion allowing the sheath and probe to be removed as a single unit. Difficulty was again encountered on final withdrawal through the brachial arteriotomy and this was found to be due to a build up of char on the probe tip (Fig. 3.6). Dilatation with a 6 mm

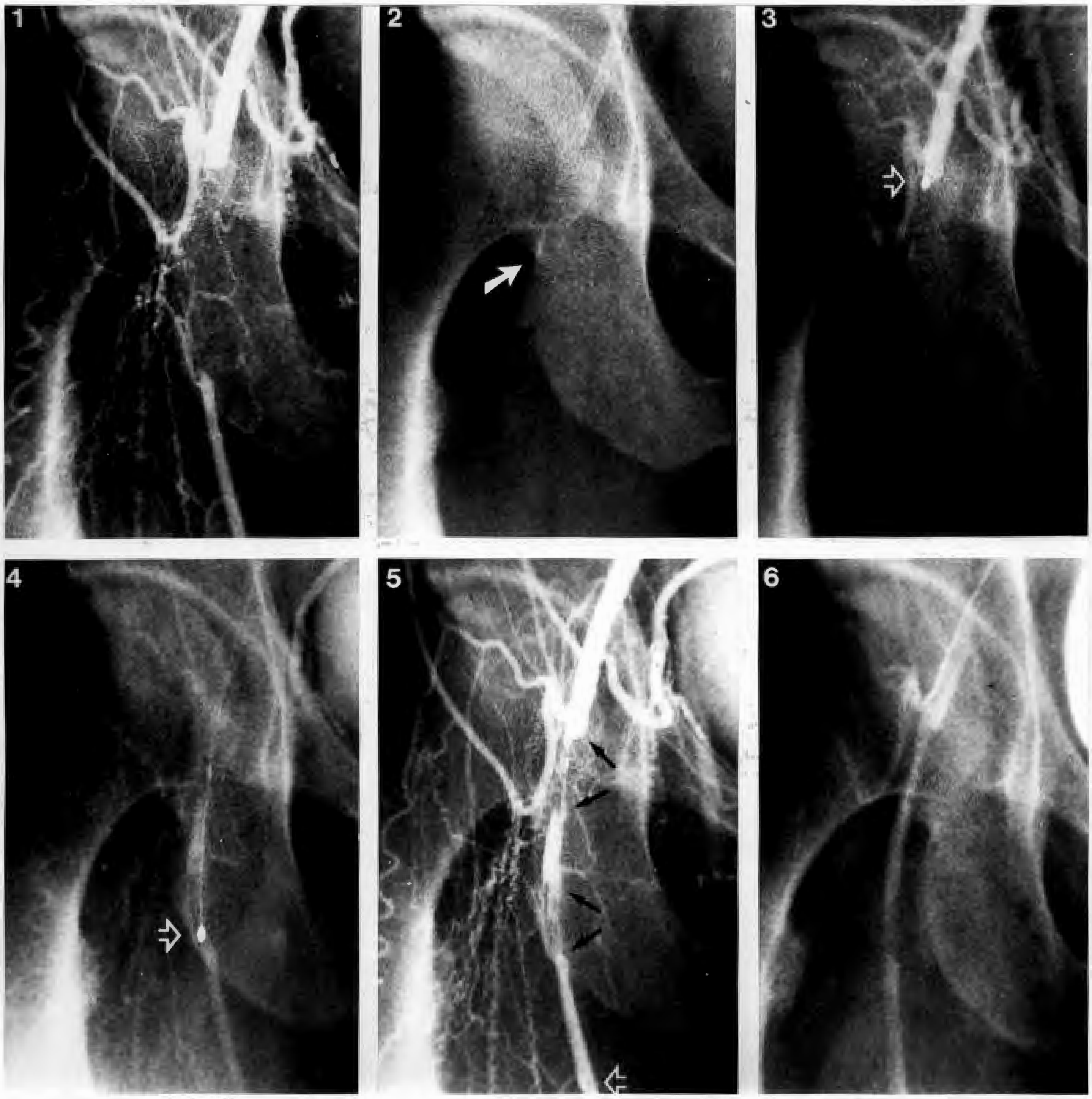


Figure 3.5: The common femoral artery has a 5 cm occlusion with some calcified lesions (white arrow) [1-2]. The guiding sheath is advanced to the stump [2] and the laser probe (open white arrow) is advanced through the lesion [3-4]. After initial passage of the probe it is apparent that the occlusion consisted of shorter proximal and distal occlusions (black arrows) with an intervening relatively normal segment [5]. After balloon dilatation the lumen is much improved (half strength contrast injection) [6].

balloon resulted in a 4.5-4.7 mm vessel (Fig. 3.5 [6]).

Post Angioplasty Course: Despite the technically successful angioplasty procedure his symptoms were not improved and an above knee amputation was performed 3 days later. This stump remained ischaemic and required a revision 2 months later. Eight months later he was admitted with mesenteric ischaemia and two months after that with digital ischaemia.

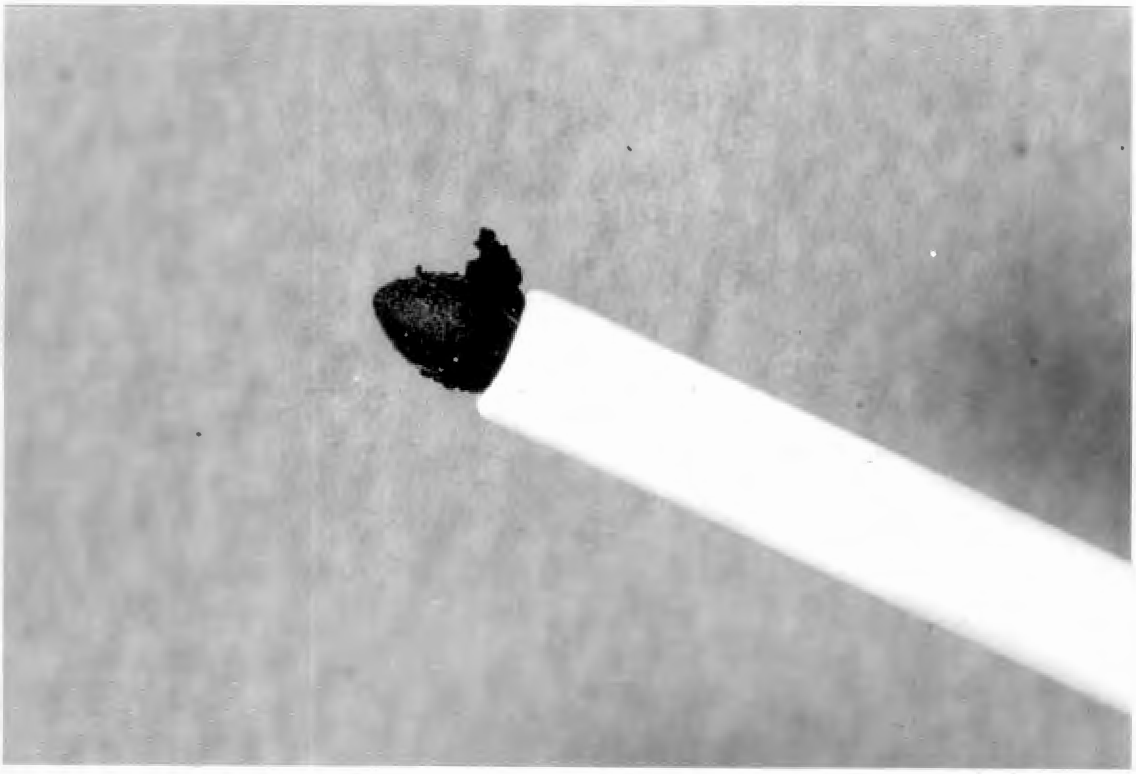


Figure 3.6: A large spur of char is adherent to the probe tip which prevents its withdrawal into the guide sheath.

Patient 5 (FB)

A 64 year old man had a seven year history of left calf claudication at a distance of 200 yards. Pulses were absent on the left and the ankle-brachial index was 0.71. Angiography revealed a 2 cm occlusion of the left common illiac artery but angioplasty was unsuccessful (Fig. 3.7 [1])

Angioplasty Procedure: The contralateral femoral artery was first cannulated and a pigtail catheter placed proximal to the lesion in the aorta. Contrast administration enhanced successful puncture of the ipsilateral impalpable femoral artery and the 2 mm laser probe was advanced to the lesion (Fig. 3.7 [2]). After a single application of laser energy for 7 seconds the probe had virtually crossed the length of the occlusion but was seen to be in a plane parallel to the anticipated lumen (Fig. 3.7 [3]). Further energy was not delivered but gentle pressure was able to advance the probe into the aorta (Fig. 3.7 [4]). Angiography confirmed a 1-1.5 mm channel medial to the anticipated lumen (Fig. 3.7 [5]). After passing a deflated 10 mm balloon through this tract it assumed a position closer to that of the anticipated lumen. A single inflation was then able to restore the vessel to its normal calibre (Fig. 3.7 [6]).

Post Angioplasty Course: The peripheral pulses were palpable immediately after the procedure and the ankle/brachial index rose to 0.97. The patient had a dramatic improvement in his exercise tolerance which persisted over a year later. Review of the films confirmed that the laser probe had passed through a tract adjacent to that of the expected lumen but there was no evidence of a dissection or extravasation on the final injection.

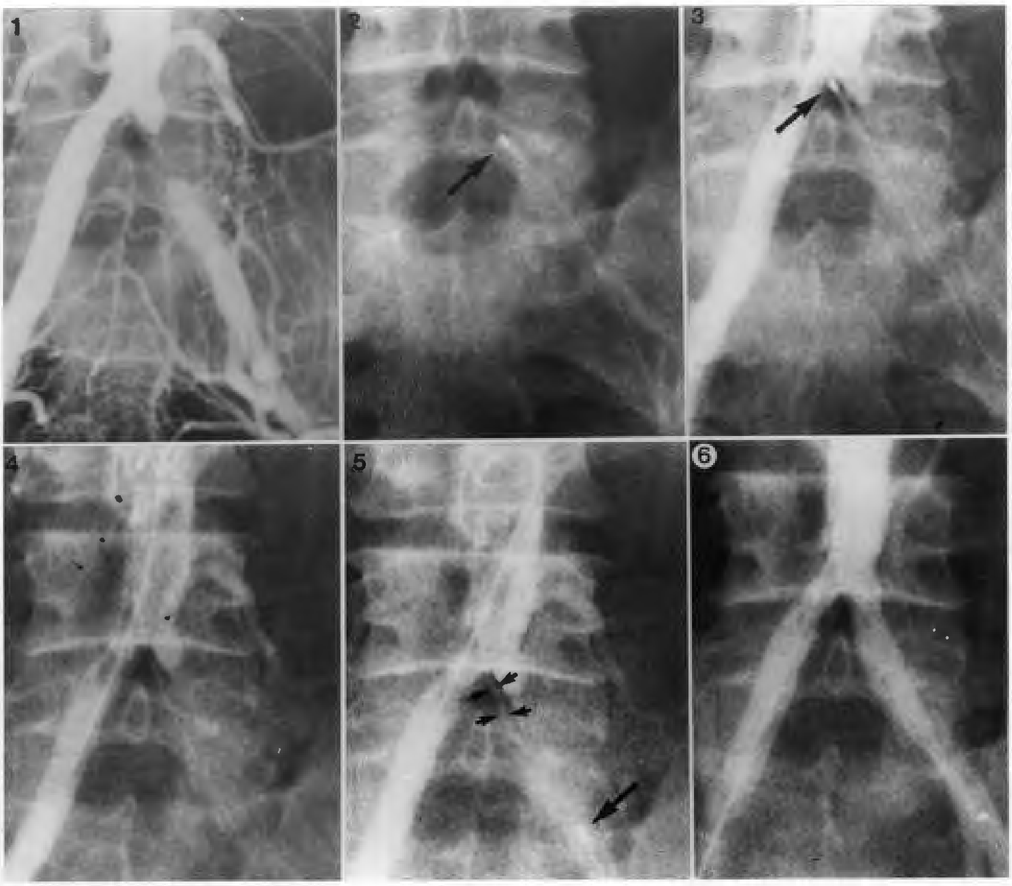


Figure 3.7: The 2 cm iliac occlusion [1] is approached retrogradely from the femoral artery and the laser probe (tip arrowed) is advanced with slight buckling [2]. The probe tip is seen to lie inferomedial to the proximal stump [3], as is the support wire after advancing the probe into the aorta [4]. After withdrawal of the probe to the distal vessel a tract (small arrows) is clearly seen [5] but after balloon dilatation recanalisation is complete [6].

Patient 6 (LB)

A 76 year old woman presented with a two year history of right calf claudication at a distance of 200 yards. The foot pulses were only weakly palpable with an ankle/brachial index of 0.54. A 6 cm occlusion of the distal superficial femoral artery was found with numerous collaterals draining into a large siphon at the distal end of the occlusion in the popliteal fossa (Fig. 3.8 [1]). A discrete posterior tibial stenosis was also present. After an attempt at conventional angioplasty had failed at a peripheral hospital she was referred for laser probe angioplasty.

Angioplasty Procedure: The 2 mm laser probe easily crossed the occlusion after 8 seconds (Fig. 3.8 [2]) and the channel was further enlarged with a 9 second application during probe withdrawal. The channel produced was less than 1 mm in diameter at its narrowest point (Fig. 3.8 [3]) but after dilatation with a 6 mm balloon a normal calibre channel was obtained (Fig. 3.8 [4]). This enabled dilatation of the posterior tibial vessel with a 4 mm balloon at the same session.

Post Angioplasty Course: Review of the developed cine-films revealed a double lumen involving the drainage popliteal siphon distal to the end of the occlusion which had occurred at the time of the laser probe advancement (Fig. 3.8 [2-4]). Doppler studies showed that the ankle/brachial index had increased to 1.03 and she remained symptom free over a year later.

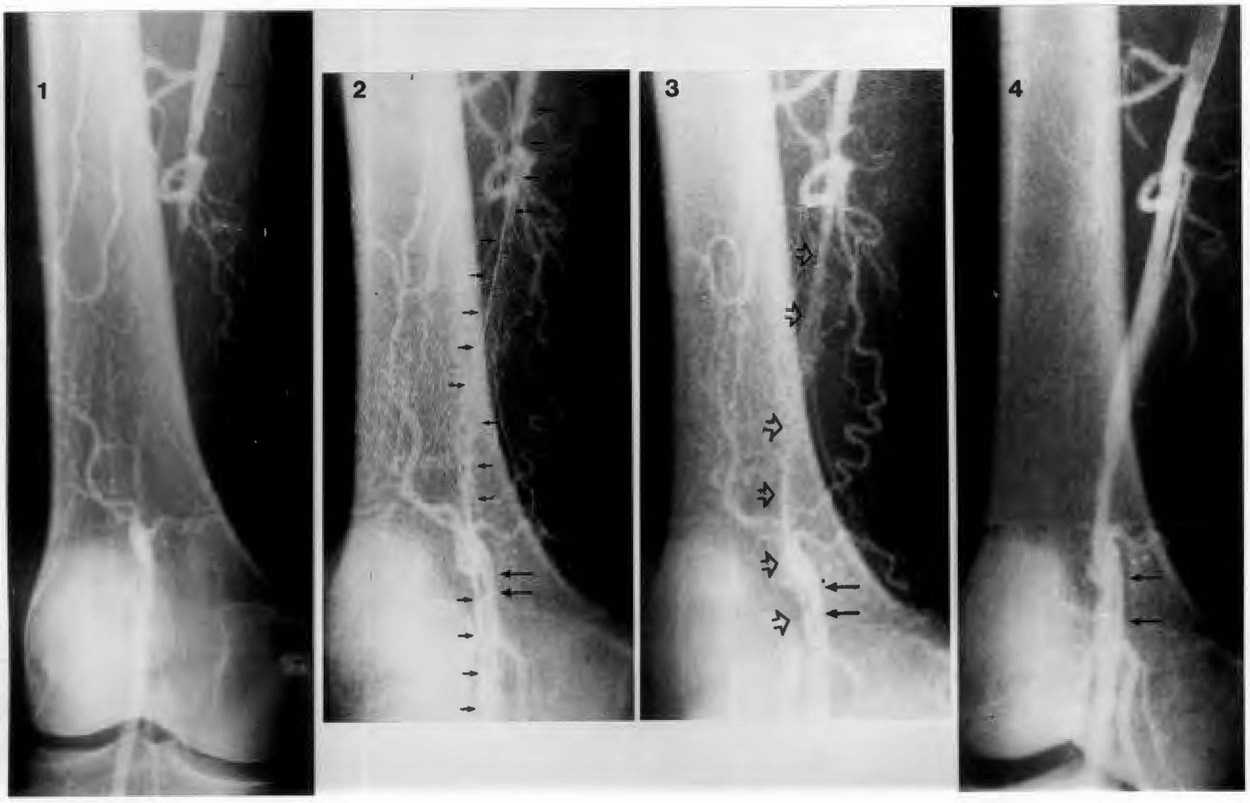


Figure 3.8: The 6 cm distal femoral occlusion [1] has been crossed by the laser probe [2] and its position is marked by the radio-opaque support wire (small arrows) with a double lumen present in the popliteal artery (large arrows). In panel 3 the probe has been withdrawn and the empty arrows show the residual tract. After balloon dilatation is completed a residual double lumen is still present [4].

Patient 7 (WR)

This 62 year old insulin dependant diabetic man had suffered with claudication in both calves for eighteen months. Pain was worse in the left calf and he continued to smoke 10 cigarettes a day. There was diffuse disease throughout the right superficial femoral artery and popliteal on the right and a 12 cm long occlusion of the left superficial femoral artery (Fig. 3.9 [1]).

Angioplasty Procedure: The 2.0 mm probe was advanced relatively easily through the occlusion using three energy applications at 11, 10 and 9 seconds (Fig. 3.9 [2]). At 2-3 cm proximal to the end of the occlusion, however it appeared to enter a side branch (Fig. 3.9 [3]) and then deviated away from the popliteal artery with a false tract formation (Fig. 3.9 [4]). Further attempts using the laser probe (without energy delivery) and guide wires resulted in persistent entrance into the false tract.

Post Angioplasty Course: Despite the perforation he did not develop a haematoma and his symptoms were unchanged after the procedure. He elected to discontinue smoking and to consider a repeat procedure some months later if his symptoms persisted.

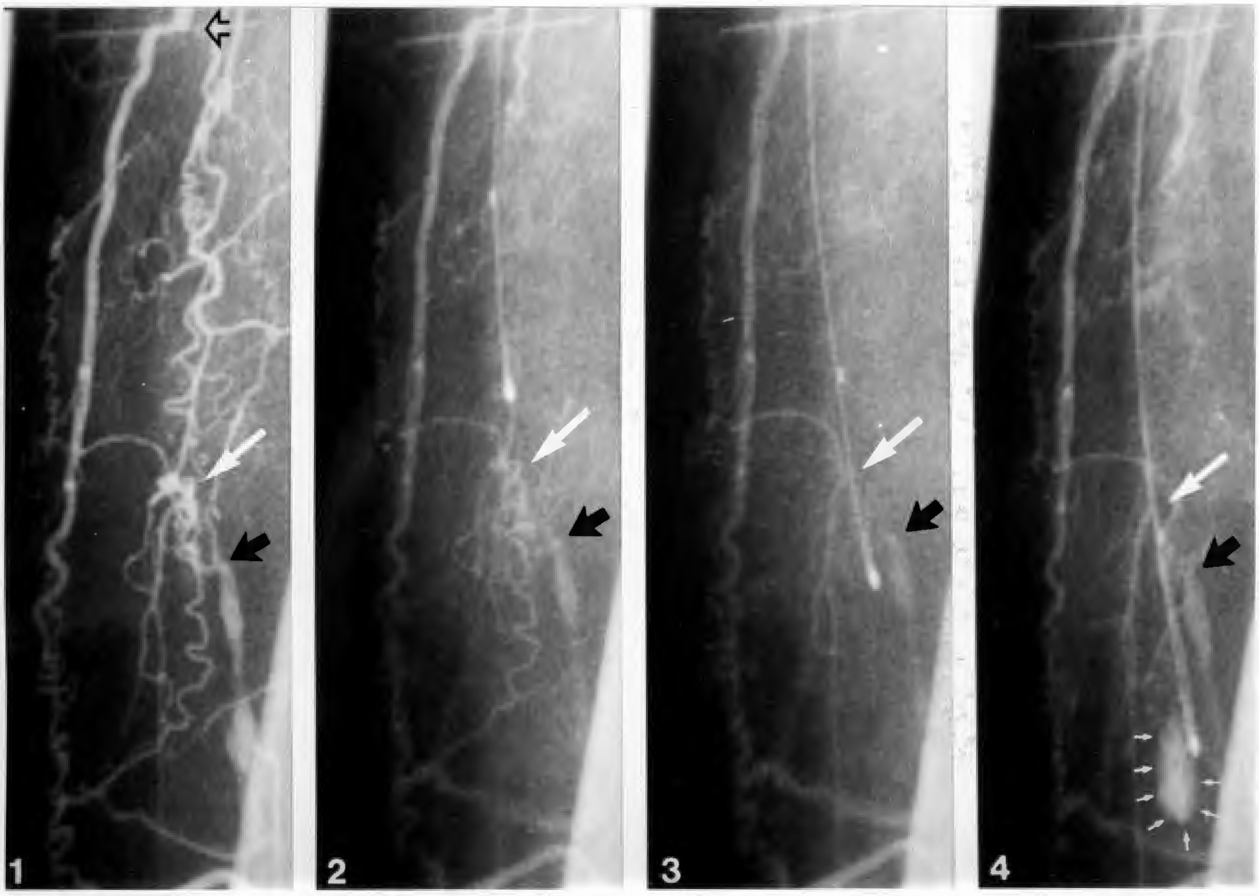


Figure 3.9: The proximal and distal ends of the distal superficial artery occlusion are marked by the open and closed black arrow respectively and the origin of a collateral network by the white arrow [1]. The laser probe advances within the lumen until the point where the collaterals originate [2-3] and then deviates with a resultant perforation and small amount of dye extravisation (small white arrows) [4].

Patient 8 (AT)

This 52 year old man had developed left calf claudication after an aortic valve replacement for infective endocarditis five years previously. Angiography previously had revealed occlusion of the distal popliteal artery with the trifurcation vessels filling via collaterals (Fig. 3.10 [1]). Conventional angioplasty was not attempted because it was thought to be unlikely to succeed and he was then referred for laser assisted angioplasty.

Angioplasty Procedure: When the 2 mm probe was advanced into the stump of the popliteal artery it appeared to be pointing towards the peroneal artery (Fig. 3.10 [2]) but on advancement during laser energy delivery it immediately diverted towards the anterior tibial artery (Fig. 3.10 [3]). Four applications of energy at 5, 7, 3, and 6 seconds were delivered and it appeared that the probe was on course for the anterior tibial artery. The probe then deviated medially and a false tract was created (Fig. 3.10 [4]).

Post Angioplasty Course: The patient did not develop a haematoma and circulation to his foot was unchanged. He was subsequently lost to follow-up.

Figure 3.10: There is an occlusion of the popliteal artery with collateralisation of the trifurcation vessels [1]. The laser probe (open white arrow) appears to be heading towards the peroneal artery [2] but deviates towards the anterior tibial artery [3]. Just proximal to the end of the occlusion it perforates the vessel (solid white arrow) causing a small amount of dye extravisation (small white arrows) [4].

Patient 9 (EW)

This 74 year old man presented six years after coronary artery bypass grafting with claudication in the left calf at a distance of 200 yards. His symptoms had been worsening over the preceding three years and at the time of admission he had begun to experience nocturnal cramp. There were no pulses present below the femorals and angiography revealed an 8 cm occlusion of the left superficial femoral artery with diffuse disease in the right superficial femoral artery (Fig. 3.11 [1]). An angioplasty procedure to the occluded left superficial femoral artery failed at a peripheral hospital and he was referred for laser angioplasty.

Angioplasty Procedure: The 2 mm probe was easily advanced across the total length of the occlusion using 11 applications of energy ranging between 9 to 11 seconds and advancing only 2-3 cm with each application (Fig. 3.11 [2-3]). Despite delivery of a total of 1100 Joules energy the channel produced was only 1-2 mm in diameter and it was impossible to cross with a J guide wire. The laser probe was then easily re-advanced through the lesion without energy delivery and the laser fibre cut and used as the "guide wire" for a 6 mm balloon. After 6 inflations the lumen was increased to a diameter of only 3.7-5.2 mm (Fig. 3.11 [4]). Review of the cine-angiograms revealed a mobile mural thrombus in the popliteal artery but this was no longer present after passage of the laser probe (Fig. 3.11 [1-4]). Its presumed dislodgement was clinically innocuous and in all probability its presence would not have been detected if cine-angiography had not been used.

Post Angioplasty Course: The ankle brachial index increased from 0.56 - 0.69 and the patient experienced marked symptomatic improvement. Two weeks later he noticed a recurrence of calf pain while walking with limitations similar to before the procedure but declined further investigations.

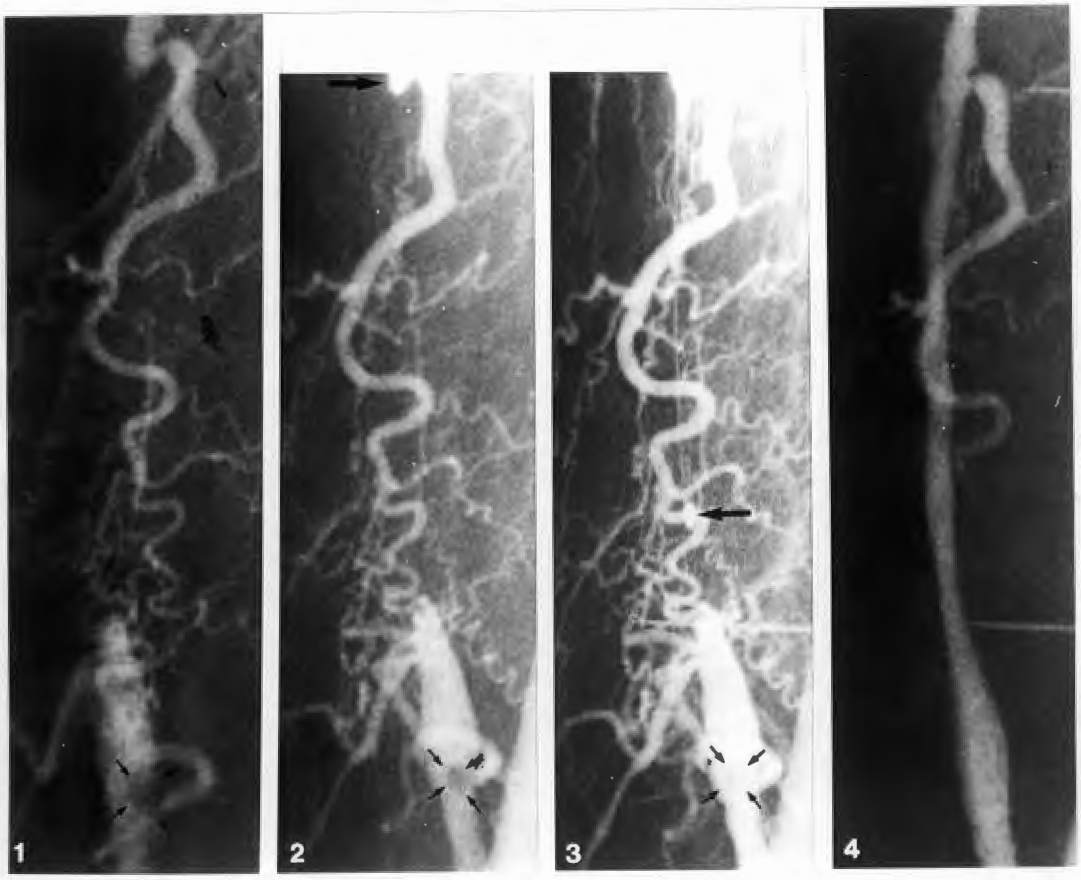


Figure 3.11 The 8 cm occlusion [1] is easily crossed by the laser probe (black arrow) and dilatation proceeds uneventfully [4]. A small mobile thrombus (small black arrows [2-3]) is present in the popliteal artery but this is no longer apparent after passage of the laser probe and balloon dilatation.

3.4 DISCUSSION:

Various manoeuvres are used to cross peripheral arterial occlusions but all run the risk of subintimal dissection or even perforation. The risk increases proportionately to the amount of force used and success decreases with increasing occlusion length (197-201). The onset of subintimal dissection often heralds failure as subsequent attempts to cross the lesion using different guide wire and catheter combinations invariably follow the false tract. Advancement down the subintimal channel is difficult with a guide wire alone while stiffer catheters are more prone to perforation.

Laser energy was first used clinically in order to overcome some of the limitations of the conventional guide wire and balloon procedure in long occlusions in the femoro-popliteal segment (66,67,138). Laser angioplasty using bare optical fibres however was accompanied by a high perforation rate due to mechanical penetration of the wall with the stiff bare fibre or due to energy delivery with the fibre in an eccentric position. While these perforations were innocuous even successful procedures only produced small increments in luminal diameter which were not thought to be clinically beneficial (66,67,138). In a number of these lesions laser energy was only delivered in a retrograde fashion once the occlusion had been crossed and as balloon dilatation was always a necessary accompaniment to the procedure its advantage was minimal (66,67). The laser thermal probe presents a smooth oval shaped tip to the occlusion allowing the use of relatively large amounts of force with a low risk of mechanical perforation (168,171). It has even been used as an "atraumatic" guide wire without energy delivery though with only limited success (202). During energy delivery the tip is rapidly heated and steadily ablates obstructive atheroma as it is advanced and produces larger channels than bare fibres (171). Nevertheless balloon dilatation is still necessary and is able to produce much greater improvements in luminal calibre than the laser probe alone. Patient 5 where the 1 mm channel was increased to 9 - 11 mm is a good example while in patient 2 the small channel produced had already closed off in the time taken to dilate the proximal lesion. Build-up of char on the probe may be substantial in long segment occlusions and may "insulate" the probe so preventing further efficient ablation of atheroma (Chapter 2.3). This was particularly evident in patient 4 where the spur of char hindered further manipulation and made the tip too large to withdraw into the sheath. In patient 9 where the greatest amount of energy was delivered the channel was no better than in the other patients indicating that tip insulation and/or composition of the occlusion are critical at determining the amount of atheroma ablation and thus the residual tract size.

There is evidence from in vitro application of thermal energy to aortic strips to suggest that the normal vessel wall is less vulnerable to heat than atheroma though these studies were performed in air with low powers (102). Clinical perforations are infrequent (173,203,204-209) and thought to occur when a particularly resistant (often heavily calcified) lesion deflects the advancing probe against and through the opposite normal vessel wall (210,211). During its blind negotiation of the occlusion, entrance into side branches or collaterals may also misdirect the probe tip resulting in failure. The latter appears to be the reason for the perforation in one of these patients; in the other the probe "deviated" off course for no obvious reason but presumably followed the line of least resistance. Peripheral artery perforation is usually uneventful as it usually occurs towards the end of a long occlusion segment so that in the absence of balloon dilatation flow is low. Resistance from the lesion itself however is indistinguishable from that of the vessel wall and was no different in either the perforations or subintimal dissections described here. It is interesting that after laser thermal energy delivery it was possible to perforate the vessel with the guide wire alone in two of these cases. It is unclear whether the channel left after the laser recanalisation is more prone to perforation because of the irregular surface or heat weakened segments or both. In the last patient of this series the guide wire would not traverse the channel, but the smooth oval metal probe did so easily and was used as a guide wire for the balloon thereafter, suggesting the former mechanism is at least in part responsible.

Subintimal dissection has been recorded previously using the laser probe (173,203) but it was unclear whether as in two of these patients dilatation was still possible through the subintimal tract. It is likely that the probe progressed through atherosclerotic plaque after deviation away from the central "soft" intimal atheroma but that in the absence of sufficiently large contralateral calcific deposits the media nevertheless prevented further lateral displacement. This is almost certainly the explanation in the iliac occlusion where the bulk of the deflated balloon alone was able to reconnect the "false" and "true" channels. In the other case two definitive channels remained so that substantial intimal thickening must have been present to prevent their "coalescence". It is still surprising that the non-dilated original lumen remained widely patent. Two other studies, one surgical (212) and one cadaveric (211) have found subintimal dissection for greater or lesser lengths to be very common and it seems as though this may be one of the mechanisms of successful dilatation. It is possible that unrecognised subintimal dissection and even perforation are commonplace with both balloon angioplasty and the newer interventional techniques as local tamponade has been shown to mask angiographic documentation of perforations later found to be present on histology (162,213).

The patients treated here had, by and large, more difficult lesions than the standard patient in whom angioplasty is attempted. The definition of "difficult" is necessarily subjective though recanalisation of lesions in which angioplasty has previously failed is probably a reasonable indicator. No comparative literature exists for the outcome of non-surgical treatment of unsuccessful angioplasty, but even by excluding the patient with the two short occlusions this leaves a 75% technical success rate with the laser probe (6 out of 8). Cumberland's initial study reported a success rate of 78% in occlusions that had failed or were considered "impossible" or "difficult" for conventional angioplasty. The overall success rate including their "easy occlusions" was 89% (173) which compared favourably to the 26-78% achieved by a number of groups in total occlusions using guide wires alone (197-201).

The long term results in this series were not impressive but needed to take into account the "learning curve" (with two "technical successes" converted into failure with the guide wire) and the selection of patients. Of the five patients with technically successful results (six lesions) two had poor run off (three lesions) and were not clinically improved by the procedure. In the remaining three patients two had a good long term result. A larger series of laser thermal probe angioplasty by Sanborn et al shows a one year patency rate of 77% (203) compared to that in conventional series ranging from 56-84% of successful procedures (197-201). Other smaller series of laser thermal angioplasty (7 - 46 patients) have been reported with success rates between 48 - 90% (204-209,211) and in none were perforations or dissections of any important consequences. The lowest success rate was in the largest series (209) which identified occlusions greater than 15 cm or below the knee as having the worst results. Conversely in the only series in which a failed conventional angioplasty procedure was a prerequisite for inclusion, was there a success rate of 78% in 14 patients (206). In one series high grade stenoses were also included (207). Of the patients successfully treated (all with a balloon procedure after the laser) 75 - 80% have remained clinically improved over follow up periods of 1 - 9 months. Thus, once the laser probe has allowed balloon dilatation to proceed the results are at least as good as in those lesions in which a guide wire is able to cross by itself. It is however by no means clear whether the thermal debulking or ablation of atheroma that accompanies the procedure is in itself important for long term patency. There was no correlation between the amount of energy delivered during recanalisation and the lumen diameter either before or after balloon dilatation in this or any of the other studies.

The laser probes used in this small series have undergone further developments aimed at improving the lumen and avoiding the need for balloon dilatation. The original "hybrid" probe studied by Abela intra-operatively (101) has been used for percutaneous angioplasty and larger luminal calibres have been claimed (214). It has been postulated that the "free" laser beam (now more commonly of the deeper penetrating Nd-YAG wavelength) component "softens" the atheroma allowing easier passage with less lateral deviation and more efficient ablation (214). The probes have all been 2.5 mm or greater with more rounded tips and this alone could account for the larger luminal diameters than were achieved previously by the 2.0 mm "hot tip" probes. Furthermore once the initial channel has been produced larger probes may then be passed over a guide wire to further enlarge the lumen. The hybrid and larger "hot tip" probes (up to 5.0 mm diameter) have also been used at the time of vascular surgery with or without concomitant endarterectomy, balloon dilatation and bypass grafting. Dietrich reported on over 1000 lesions so treated with over 80% success though many had short stenotic lesions only or had not undergone balloon angioplasty attempts (212,215). This large though heterogeneous series does therefore not add evidence to suggest the laser probe approach is superior to conventional percutaneous angioplasty or even bypass surgery. Indeed a study of peripheral angioplasty in a community hospital with access to a thermal probe found that 84% of 120 procedures in a 7 month period were successful with the guide wire and balloon alone. In 6 cases in which the conventional procedure failed the thermal probe was successful in 4. They felt that the laser had not significantly increased the number of patients amenable to angioplasty and that it was not cost effective for a small hospital (216) as has been noted by others (202).

Laser energy heating of the metal tip is also no longer the only available heat source. Radiofrequency heating of metal tips has been shown to be as effective at crossing total occlusions despite a lower working temperature (500 ^{o}C in air). Major advantages are the lower costs and mobility of the radiofrequency generator (217,218). Long term results are still awaited but it is likely that these will be similar to those seen after laser "hot tip" procedures. It is unclear whether these devices could produce the "larger" channels seen with the increased diameter and hybrid probes.

The contact sapphire tipped fibres have also established themselves in this setting. One series comparing the sapphire tipped fibres to the thermal probes found they produced larger channels with a slightly higher success rate (78% versus 82%) but this was not a randomised study (14 thermal probe; 74 sapphire tip) (206). Other studies with 8-33 patients have shown similar recanalisation rates with this system (178-180, 219-221). In a small proportion of patients balloon angioplasty has not followed when the lumen was felt to be adequate with the laser alone - at least 50% of the original lumen (219) though in another study vessels so treated occluded soon after the procedure (221).

Argon energies delivered via lensed fibres have also been successful at recanalising total occlusions (88% of 26 attempted) without any adverse effects. The lensed fibre is passed through a "centering balloon" which maintains coaxial alignment but the lumen obtained is inadequate unless followed by subsequent balloon dilatation (222).

The first successful clinical application of a "smart" laser with fluoroscopic monitoring has recently been reported (223). A low power helium-cadmium laser emitting 325 nm light is used to induce intravascular fluorescence with on-line spectroscopic analysis. Only if the analysis confirmed the signals are from atheroma was laser energy at 480 nm from a tunable dye laser delivered through the same optical fibre. In 19 patients recanalisation was possible in lesions that were impassable to a guide wire though in 1 the channel was too small to allow the balloon catheter to complete the recanalisation. The first pulsed excimer systems have also been used successfully, though need to have a guide wire across the lesion before energy delivery and also require balloon dilatation to complete the procedure (224,225).

A number of new interventional techniques have also been applied to the treatment of occlusive peripheral vascular disease. These include various atherectomy catheters and rotational devices aimed at either substantially removing the atheroma and/or finding a safe path through occlusions to allow subsequent balloon angioplasty (226-229) as well as balloon expandible stents to hold the vessel open (230). The Simpson atherectomy catheter and the transluminal extraction catheter can excise and remove atheroma from the body without the need for subsequent balloon dilatation but require the lesion to have been crossed by a guide wire first (227,228). The former is a time consuming process even in short segment disease and recurrences have been reported while the latter has only recently entered clinical use. The rotational devices are able to cross difficult occlusions although embolism and perforations have been recorded and they need to be followed with balloon dilatation (202). While the long term effects still require to be studied systematically it appears that all of these techniques exhibit an appreciable relapse rate (231).

Conclusions: Laser thermal probe assisted angioplasty is clearly capable of enabling successful balloon dilatation in lesions that were previously impassible to a guide wire and balloon system. While recognised subintimal dissection using a guide wire usually prevents successful dilatation, this is not necessarily true of the laser probe. The hot tip may "find" alternative routes through obstructive atheroma with subsequent re-entry into the distal lumen possibly being a feature of its mode of action. On its own, however, the laser probe does not produce adequate channels and the balloon remains a complimentary and essential part of the procedure. Larger, "hybrid", radiofrequency thermal probes; sapphire tipped, lensed and spectroscopically guided laser systems; "atherectomy" devices and stents are all being intensively investigated at present but all the series are too small (often with continual modifications to the equipment) to allow assessment of the relative superiority of any of these for long term patency. For the majority of lesions balloon dilatation alone is possible and seems to be adequate. For resistant occlusions the laser thermal probe has been the most successful of the "newer" interventional techniques at effecting recanalisation. Non-laser thermal probes, lensed, sapphire, pulsed and "smart" laser systems and rotational recanalisation devices have also been shown to be effective but convincing benefit from removal of atheroma in lesions amenable to balloon angioplasty remains to be shown for any of these techniques.

4. CORONARY ARTERY LASER THERMAL PROBE ASSISTED ANGIOPLASTY

- 4.1 INTRODUCTION
- 4.2 CORONARY ACCESSIBILITY OF LASER PROBES
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4.1 INTRODUCTION

The early negative experience with bare fibre peripheral artery laser angioplasty was followed by similar results after intracoronary application. Performed at the time of coronary surgery, to enhance safety, the small channels produced and the competing blood flow of the concomitantly placed grafts (65) or the poor distal run off in non-bypassed previously occluded vessels (232) resulted in early closure of all the vessels. Only after the demonstration of clear benefit in the peripheral arterial system using the metal tipped laser thermal ("hot tip") probe were percutaneous coronary artery studies first undertaken (174,175).

Successful percutaneous laser thermal probe assisted coronary angioplasty was reported by Cumberland et al (174) and Sanborn et al (175) in 1986. They used modified peripheral artery probes that were advanced over guide wires - and all lesions were first crossed with the guide wire - in lesions that had not previously undergone balloon angioplasty. While not all the procedures were successful - indeed in some failures subsequent balloon angioplasty was successful - these were the first demonstrations that percutaneous delivery of laser energy could be used to vaporise coronary atheroma.

The following studies describe the in vitro and in vivo handling characteristics of laser probes in the coronary vasculature as well as the effects of delivering laser thermal energy both clinically and in a cadaver preparation. Finally an assessment of the likely developments in coronary laser angioplasty is made.

4.2 CORONARY ACCESSIBILITY OF LASER PROBES

While the femoro-popliteal segment is a common testing ground for assessing coronary artery interventional techniques the conditions pertaining to peripheral artery angioplasty do not necessarily apply to percutaneous coronary angioplasty. Modifications in probe design that appear necessary to facilitate coronary application extrapolated from the peripheral arteries may detract from the efficacy of the method and invalidate much of what has been learned in the periphery. The aim of this study was to assess the differences in currently available laser probes which might highlight important design features for enhancing safe percutaneous laser thermal probe assisted coronary angioplasty.

(a) METHODS

Two different peripheral artery probes in clinical use and three investigational coronary artery laser probes manufactured by Trimedyne Inc (Santa Ana, Calif.) were studied using an arterial tree model and in cadaver hearts to assess their handling characteristics.

(1) Probes

1) The 2.0 mm tip peripheral artery laser probe (Fig. 4.1 [A]) with a 300 um core optical fibre, a safety wire attached to the tip and a supporting torque wire was the "conventional" probe used in the previous thermal and peripheral artery studies.

2) The 1.5 mm tip peripheral artery probe (Fig. 4.1 [B]) had a 300 um

optical fibre and a more rounded eccentrically positioned tip. This has been used for thermal angioplasty in smaller peripheral arteries in a similar way to the larger version (173). For intracoronary use the torque wire is removed to allow passage of a standard coronary angioplasty guide wire through the tip thus facilitating coaxial alignment and subsequent exchange for balloon dilatation catheters (174,175).

3) The 1.7 mm tip coil catheter probe (Fig. 4.1 [C]) consisted of a 116 um core optical fibre contained in a flexible polyurethane cardiac catheter. The distal 2 cm of fibre, between the catheter and the tip, was enclosed in a floppy spiral metal coil further enhancing its terminal flexibility. A guide wire channel passed up the length of the catheter and through the centre of the tip allowing it to be advanced over an 0.014 inch guide wire (Fig. 4.2).

4) The 1.3 mm tip coil catheter probe (Fig. 4.1 [D]) was of a similar design to the 1.7 mm coil probe but the tip has a platinum coating aimed at reducing welding to tissue at high temperatures.

5) The 1.7 mm side hole tip catheter probe (Fig. 4.1 [E]) has a 200 um fibre and central guide wire channel. The tip side holes allow tip perfusion during energy delivery aimed at reducing vessel side wall temperature.

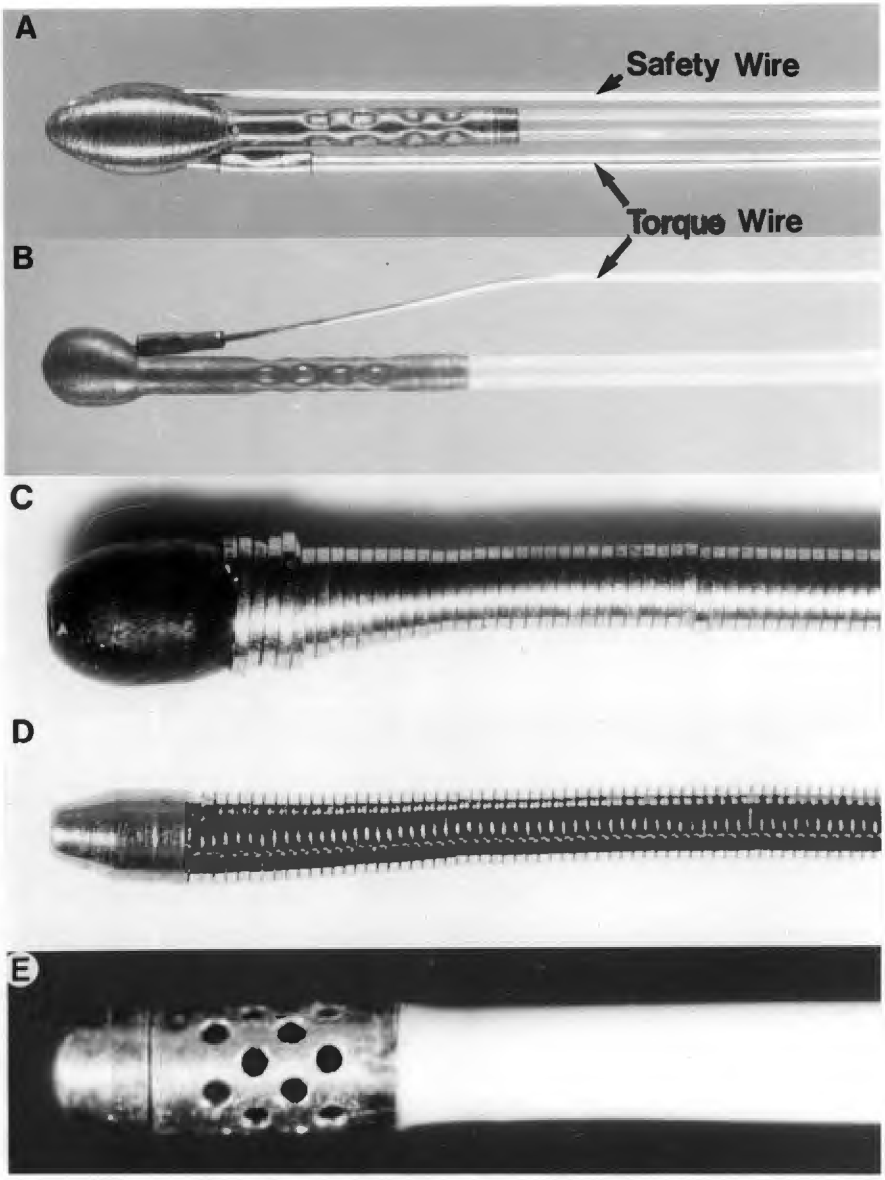


Figure 4.1: A) 2.0 mm tip peripheral artery probe. B) 1.5 mm tip peripheral artery probe with torque wire that can be removed and replaced with a coronary guide wire. C) 1.7 mm coil catheter probe. D) 1.3 mm platinum coated tip coil catheter probe. E) 1.7 mm multiple side-hole tip catheter probe (catheter portion identical to that of C and D but without the 2.0 cm coil interspersed between the catheter and tip).

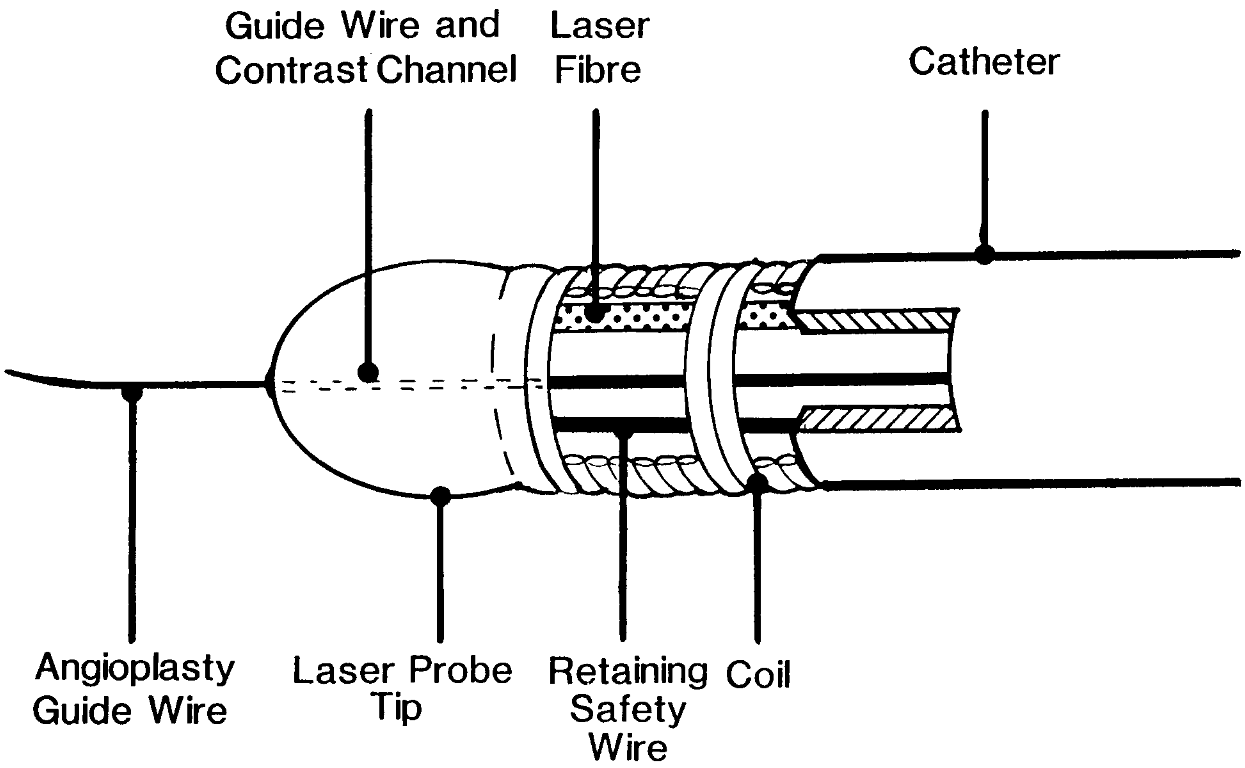


Figure 4.2: Cross-sectional diagram of the 1.7 mm tip flexible coil catheter laser probe.

(2) Arterial tree model

The greater vessels in the Anatomaid Model (Meditech; USA) are made from clear plastic and designed to allow realistic simulation of percutaneous coronary artery catheterisation and evaluation of catheter manipulation and control characteristics.

(3) Cadaver heart preparation

Four intact human cadaver hearts were obtained at postmortem and the coronary ostia were cannulated with coronary guiding catheters. The proximal 1 cm of the left main stem and right coronary arteries were dissected free from the epicardium to place a ligature which held the guiding catheter in place. The distal vessel was drained with small venous cannulae to allow contrast removal and prevent excessive tissue staining. Cine-radiography was then performed during laser probe manipulations.

(b) RESULTS

The 2.0 mm laser probe was unable to pass through any of the 9F coronary guiding catheters although was able to pass through a 9F large lumen unformed guiding catheter with an internal diameter of 2.3 mm (Chapter 3.3; patient 4). When used in the model of the greater vessels it was found that the tip of the catheter was repeatedly displaced from the coronary ostium whilst the probe was advanced around the aortic arch due to the inflexible nature of the probe. Even when "coaxed" around the arch with the guide catheter tip held in the ostium it was unable to negotiate the last curve into the coronary ostium. The remaining probes however were all able to be advanced into either coronary artery via 8F and 9F guiding catheters from either "brachial" or "femoral" approaches.

In the cadaver heart preparation the 2.0 mm probe was unable to be advanced more than 2 to 3 cm into the proximal coronary artery segments without exerting considerable pressure on the vessel wall (Fig. 4.3). Thus in access terms alone this probe was clearly unsuitable for coronary use.

The 1.5 mm probe was able to be passed to the distal coronary vessel quite easily via 8F or 9F preformed guiding catheters both over the eccentrically placed guide wire and alone. In tortuous vessels however it was prone to extreme displacement of the coronary vessels (Fig. 4.4).

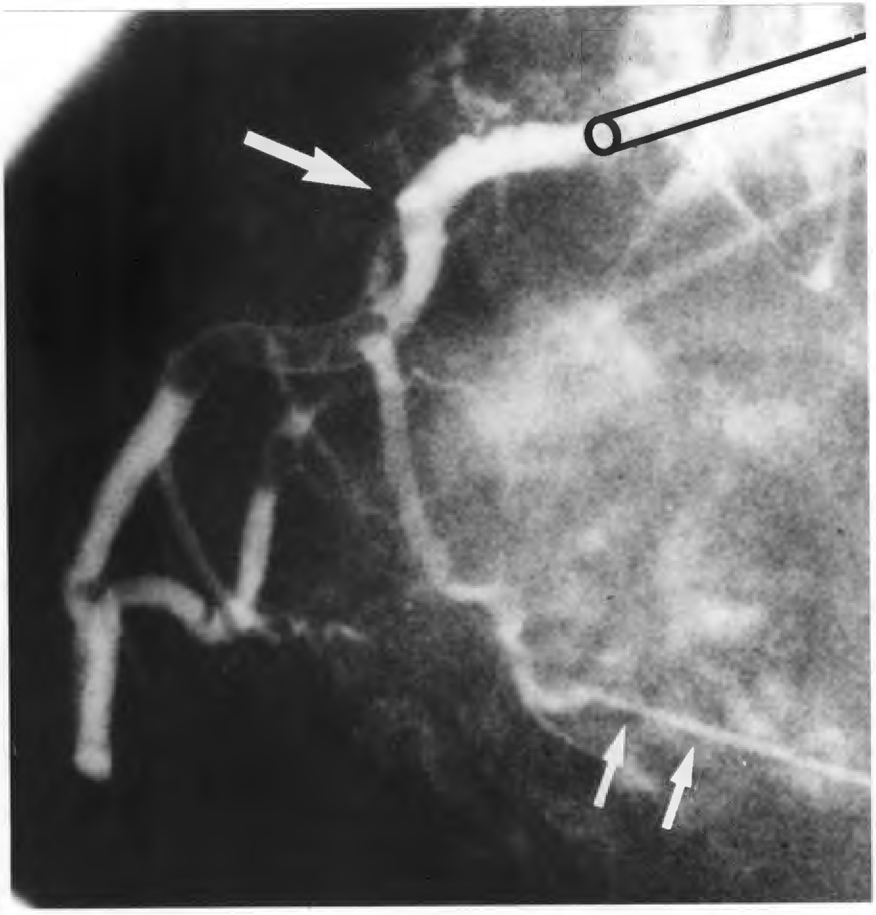


Figure 4.3: The 2.0 mm tip probe (single arrow) is unable to pass down the right coronary artery in a cadaver specimen and exerts pressure against the wall. Guiding catheter is outlined and drainage cannula indicated by smaller arrows.

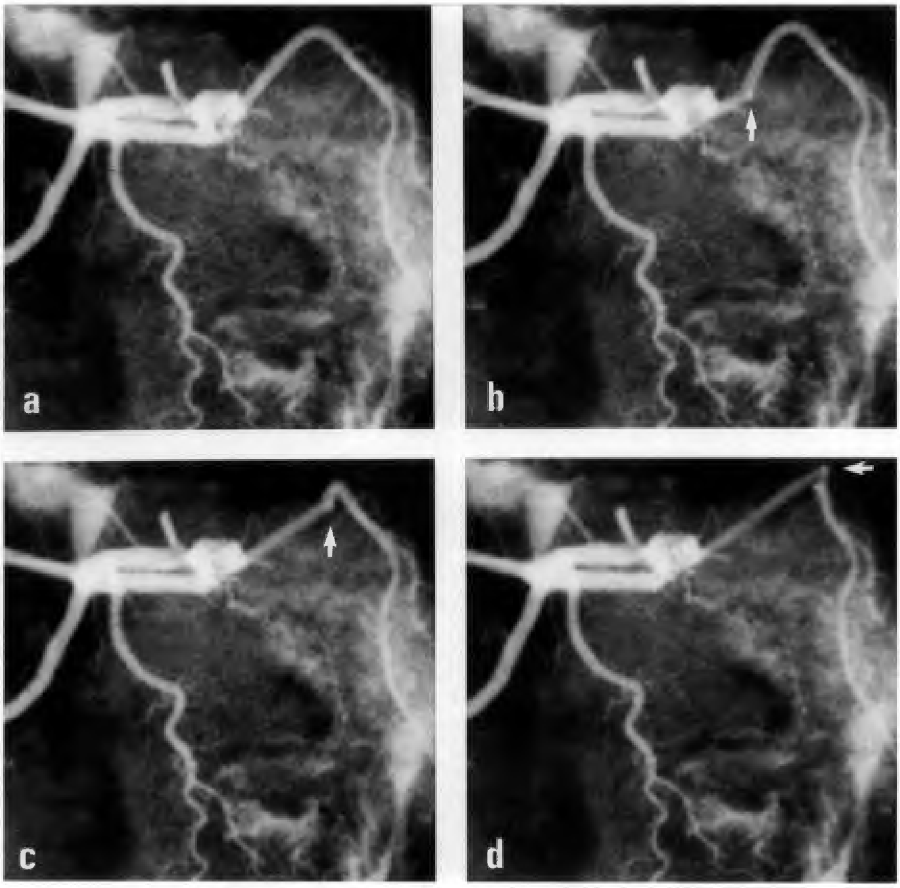


Figure 4.4: Control left coronary angiogram in (a). The 1.5 mm probe (tip shown by arrow) produces gross displacement of the circumflex coronary artery during advancement (b-d). The probe was eventually made to "turn the corner" with additional force.

Both of the coil catheter probes were very easily manoeuvred in the cadaver preparation and could easily access terminal branches through tortuous segments over the guide wire.

The 1.7 mm tip side hole probe catheter was not of a length suitable for percutaneous use (designed for intra-operative use) and was used with a short introducing catheter in the cadaver preparation only. It was easily manoeuvred in both coronary arteries but realistic simulation of percutaneous delivery was not possible.

(c) SUMMARY

The original 2.0 mm tip peripheral artery probe was too large and rigid to access the coronary tree even if sufficiently large preformed guide catheters were available. The smaller 1.5 mm version whilst able to do so caused marked displacement of vessels in tortuous segments limiting its suitability to lesions in proximal or straight segments only. The experimental "over the wire" catheter probes with smaller diameter optical fibres were easily able to access the distal vessels without excessive displacement. Additional properties of these probes (platinum coating and perfusion side holes) were not assessed in this study.

4.3 CORONARY ARTERY LASER THERMAL PROBE ASSISTED ANGIOPLASTY

(a) METHODS

Laser thermal probe balloon angioplasty was attempted in three patients using the 1.7 and 1.3 mm tip flexible coil catheter probes found to have good handling characteristics in vitro (Chapter 4.2). The study protocol was approved by the Guy's Hospital Ethics Committee and informed consent was obtained from each patient. Originally intended as the pilot study for a randomised trial of balloon versus laser thermal probe assisted angioplasty, patients in whom balloon angioplasty had been or was likely to be unsatisfactory were initially included. The patients were prepared as for a routine balloon angioplasty but for an additional antithrombotic effect aspirin 300 mg 3 times/day and dipyridamole 100 mg 3 times/day were commenced two days before the procedure. For the second and third patients intravenous dextran and isosorbide dinitrate infusions were also commenced 15 minutes before the procedure. Prior to the angioplasty heparin 10,000 U was administered via the arterial sheath and a temporary pacing electrode was placed in the right ventricular apex.

(b) RESULTS

Patient 1 (MW)

A 67 year old woman with a 4 year history of angina on minimal effort had successful balloon angioplasty for a proximal eccentric 95% left anterior descending coronary artery stenosis (Fig. 4.5 [1 - 3]).

Symptoms returned after 6 months and angiographic restenosis with a second less severe lesion more distally was found (Fig. 4.5 [4]). The remaining coronary arteries were angiographically normal with a left ventricular ejection fraction of 66%. A thallium perfusion scan confirmed reversible anteroseptal ischaemia adjacent to a fixed perfusion defect. She was admitted for laser assisted angioplasty whilst taking propranolol 10 mg 3 times/day, diltiazem 60 mg 3 times/day, and isosorbide mononitrate 20 mg twice daily.

Angioplasty Procedure: The laser probe was first advanced via a 9F introducing catheter over the guide wire through both lesions. Argon laser energy was then delivered during two separate withdrawals of the probe, using a continuous to and fro motion, for 7 and 8 seconds respectively (70 and 80 Joules). The lumen diameter improved significantly at the primary stenosis site after "hot" but not "cold" passage of the probe but a large diagonal vessel was occluded (Fig. 4.5 [6]). A 3.0 mm balloon catheter (Simpson Ultralow Profile 3.0 mm balloon; ACS, Calif, USA) was exchanged for the laser probe over the guide wire and further enlarged the lumen leaving only a minimal stenosis (Fig. 4.5 [7 - 8]). A few minutes after the last balloon inflation she experienced severe chest pain and angiography demonstrated total occlusion of the left anterior descending coronary artery (Fig. 4.5 [9]). Intracoronary nitrates were ineffective but balloon dilatation successfully reopened the vessel. Patency was only short lived and the sequence of occlusion and reopening was repeated several times during which she required resuscitation with fluid, inotropes, external cardiac massage and ventilation. She regained spontaneous output but the vessel remained occluded.

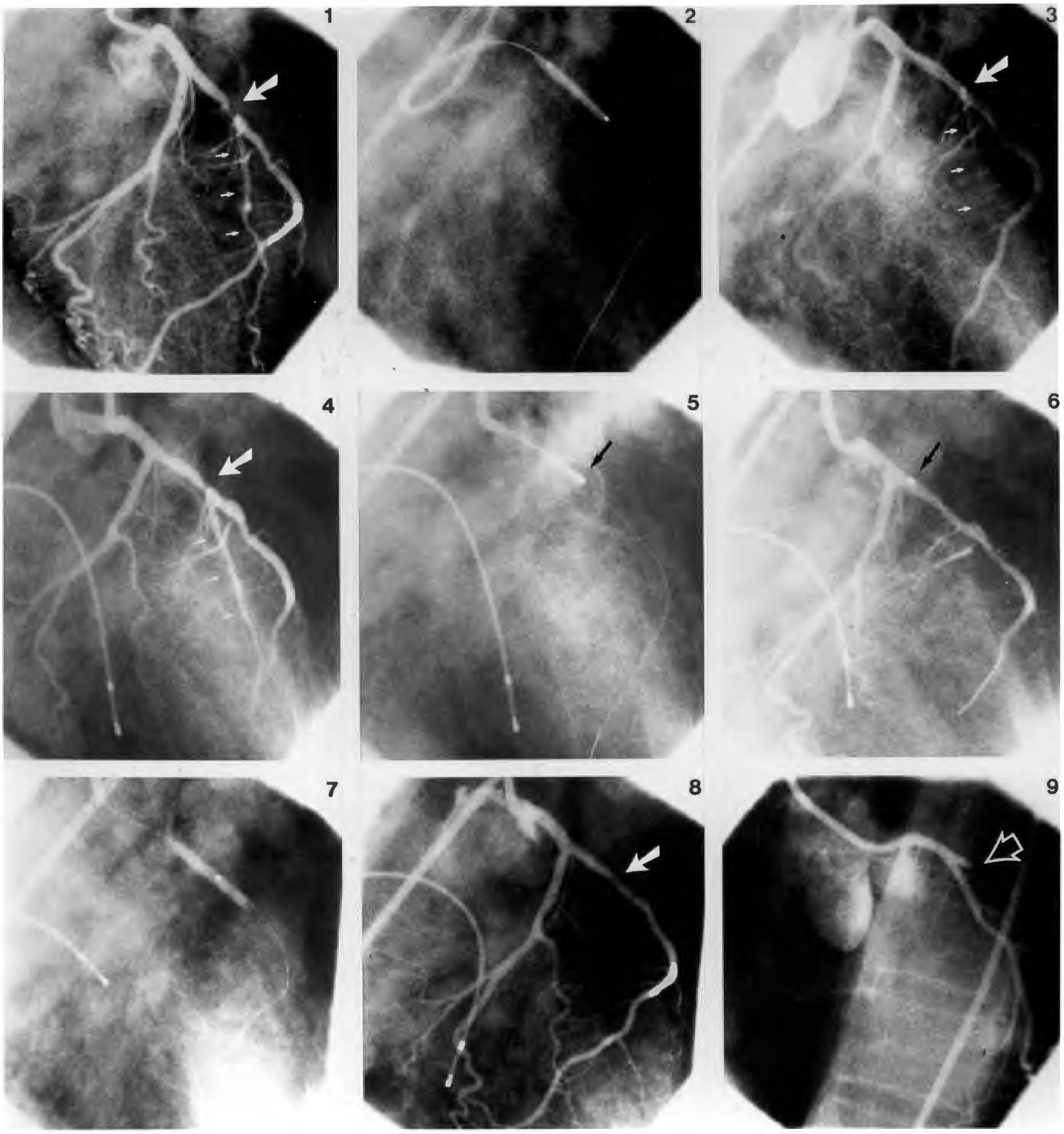


Figure 4.5: Left anterior descending coronary artery (right anterior oblique view) has a 95% stenosis (large white arrow) which is successfully dilated preserving the diagonal vessel (small white arrows) [1 - 3]. Recurrence of the lesion [4] is treated with the laser thermal probe (black arrow) [5] resulting in substantial improvement in lumen calibre but loss of the diagonal vessel [6]. Balloon inflation further improves the luminal calibre [7 - 8] but is followed by total occlusion (left anterior oblique view) [9].

Post Angioplasty Course: At emergency bypass grafting a single saphenous vein graft was placed to the left anterior descending coronary artery. Arteriotomy confirmed absent flow without evidence of internal thrombosis or macroscopic charring. Whilst on cardiopulmonary bypass a haemoperitoneum was noted and splenectomy and repair of liver lacerations resulting from external cardiac massage were required to arrest the bleeding. The postoperative ECG revealed some loss of voltage with T wave inversion across the anteroseptal leads. The following day she had an episode of ventricular fibrillation and a second laparotomy was performed to remove packs left at the splenectomy site. She became septicaemic and died 2 weeks after the angioplasty.

Postmortem Findings: The coronary vessels were perfusion fixed with 10% formaldehyde at a pressure of 100 mmHg and injected with a barium sulphate and gelatin mixture. Radiography revealed patency of the graft and at both the angioplasty sites but persistent occlusion of the diagonal branch. Intimal disruption and haemorrhage extending into the media was evident at both balloon dilatation sites on histology (Fig. 4.6 [A]). Intimal charring with vacuolation was observed at a number of sites and char material blocked the origin of the diagonal branch (Fig. 4.6 [A and B]). The left ventricle showed patchy areas of fibrosis and of recent infarction in the anteroseptal region but no evidence of embolism.

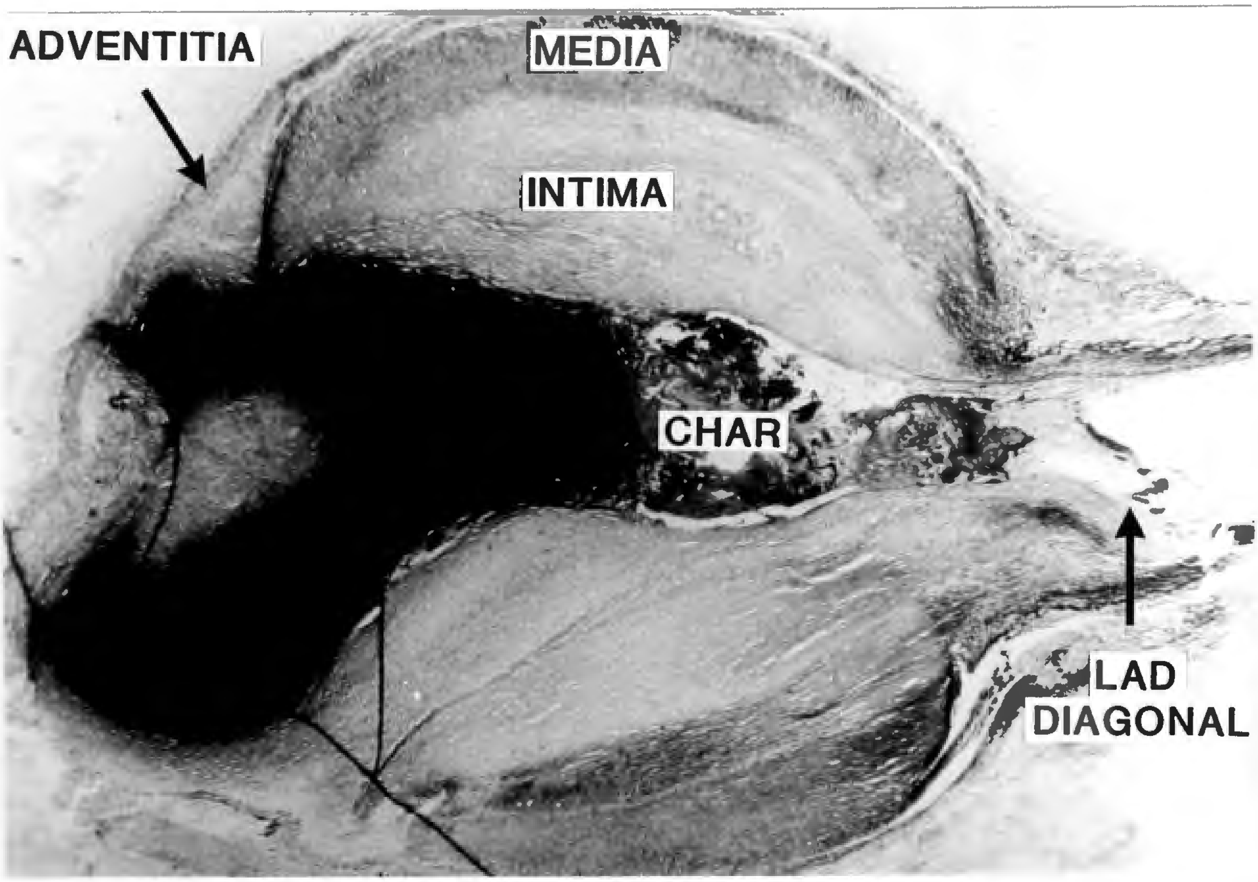


Figure 4.6: A) Section through left anterior descending coronary artery at origin of diagonal vessel. There is considerable fibro-fatty atheromatous deposition and hyperplasia of the intima with residual intimal vacuolation. Splitting through to the media has occurred to the left of the figure. The lumen is filled with barium and some postmortem thrombus and char material is seen in the origin of the diagonal. Elastin-MSB - magnification X 30.

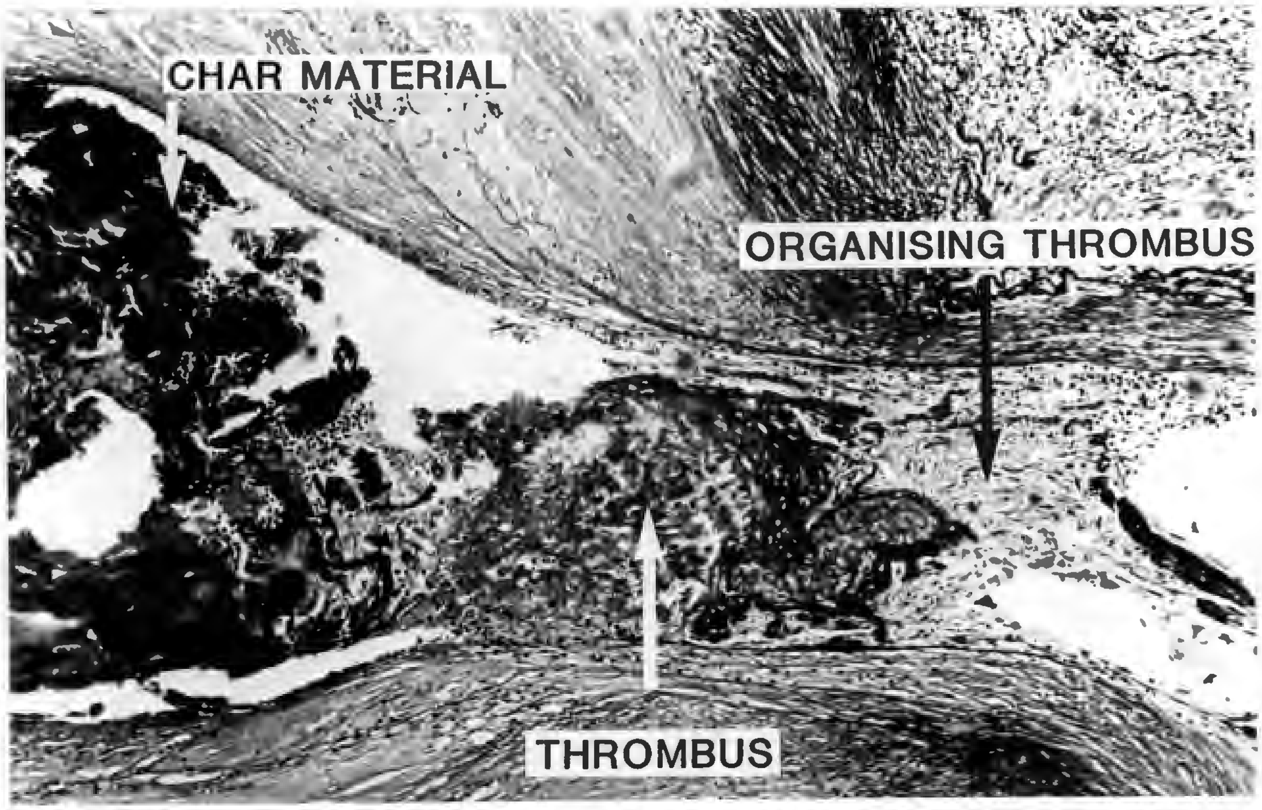


Figure 4.6: B) Higher power view of diagonal origin with char obstruction. Organisation of the associated thrombus is taking place. Elastin-MSB - magnification X 100.

Patient 2 (TH)

A 54 year old man developed angina a year after saphenous vein coronary artery bypass grafting. Angiography revealed a single patent graft to the occluded left anterior descending coronary artery and a small right coronary artery. The circumflex artery had a 90% stenosis proximal to a large marginal branch and a 70% stenosis in the distal lateral circumflex branch (Fig 4.7 [1]). He completed 8 minutes of the Bruce protocol with chest discomfort and lateral ST. depression whilst taking propranolol 10 mg 3 times/day and nifedipine 5 mg 3 times/day. Reversible ischaemia in the circumflex territory was confirmed by thallium scintigraphy and the resting left ventricular ejection fraction was only 33%.

Angioplasty Procedure: Balloon angioplasty was attempted in the first instance and the proximal more significant lesion was successfully dilated (Simpson Ultralow Profile 3.0 mm balloon; ACS, Calif, USA) but the balloon was unable to cross the distal lesion. The laser probe was then advanced over the exchange guide wire but was also unable to progress without energy delivery. An initial tendency for the laser probe to displace the guide catheter was corrected by further advancement of the guide catheter into the circumflex artery (Fig 4.7 [2 - 3]). Laser energy (argon) was then delivered on 3 occasions for 4, 5 and 6 seconds (40, 50 and 60 Joules) while simultaneously attempting to advance the probe through the lesion. In view of the lack of progress despite adequate guide catheter support it was decided to abandon the procedure. The probe could not be withdrawn over the guide wire and further difficulty was encountered in withdrawing them both as a single unit due to adherence of the probe tip to the vessel wall. After withdrawal it was noted that char on the probe tip extended onto the distal 1 cm of guide wire. Angiography showed the distal AV circumflex artery to be occluded with extravasation of dye (Fig 4.7 [4]).

Post Angioplasty Course: The patient experienced chest discomfort which responded to opiates and echocardiography excluded a pericardial leak. The creatinine phosphokinase rise and ECG changes confirmed a non-Q wave lateral wall myocardial infarction and at one week angiography showed occlusion at the laser site but maintained patency at the balloon dilatation site (Fig 4.7 [5]). He experienced intermittent stabbing chest pain for a further two weeks which settled without specific treatment and the erythrocyte sedimentation rate did not rise. Three months later the patient was able to exercise on the Bruce Protocol to 9 minutes without chest discomfort or ST changes and exercise was discontinued due to fatigue.

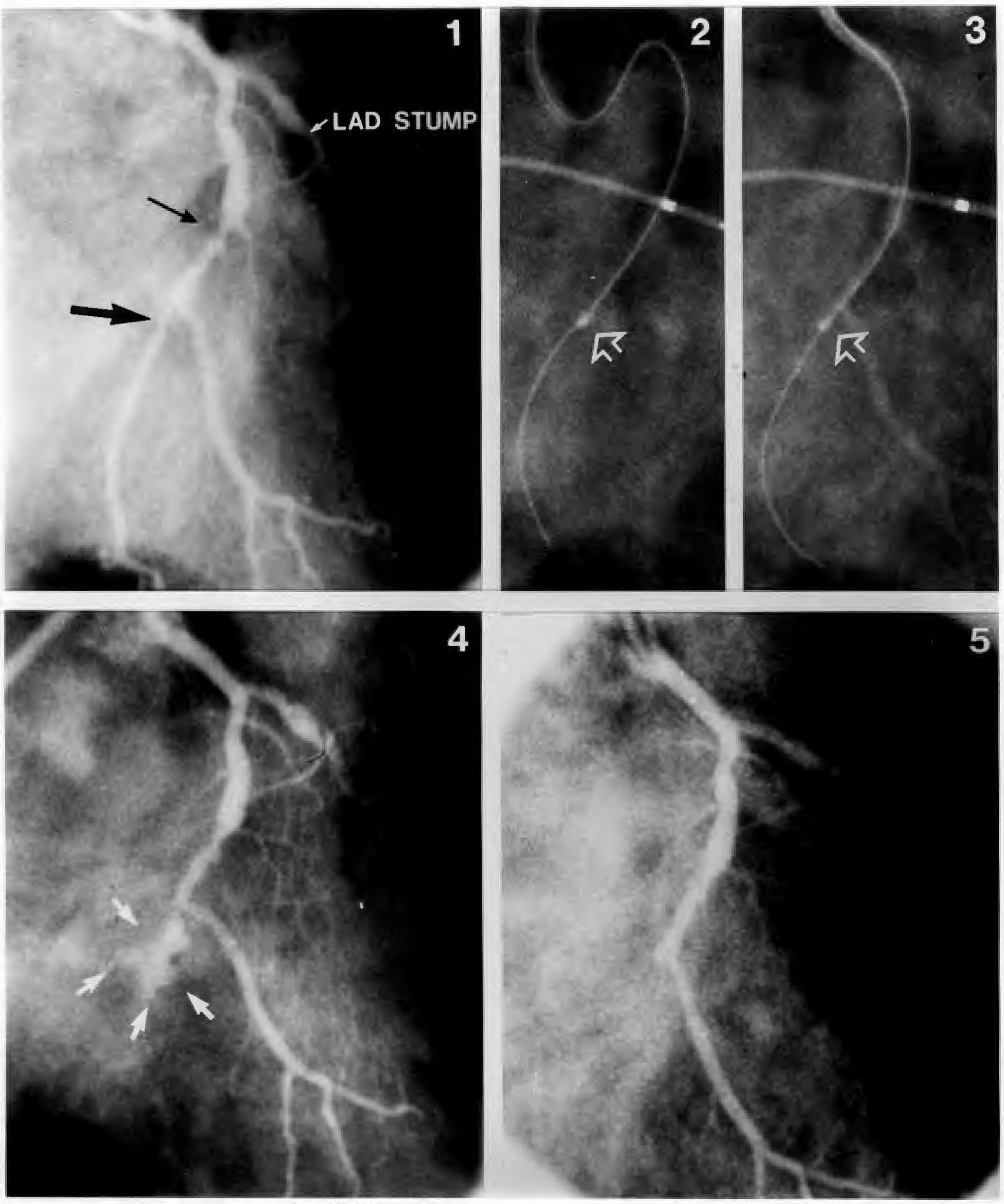


Figure 4.7: Right anterior oblique view showing circumflex artery with two stenoses [1]. The proximal (small black arrow) undergoes balloon dilatation only. During initial manipulation of the laser probe (open white arrow) there is displacement of the guiding catheter which is overcome by advancement of the guiding catheter into the circumflex artery [2 - 3]. Withdrawal of the adherent probe after energy delivery reveals the distal AV circumflex to be occluded with dye extravasation (white arrows) [4]. One week later the proximal (balloon) site is patent but the distal branch remains occluded [5].

Patient 3 (MC)

A 48 year old male smoker with a three year history of angina developed a non-transmural lateral wall myocardial infarction. His cholesterol was elevated at 7.3 mmol/l with triglycerides of 2.3 mmol/l and bezafibrate 400 mg daily had been commenced. He could only complete 7 minutes of the Bruce Protocol, whilst taking acebutalol 100 mg 2 times/day, nifedipine 20 mg 2 times/day, isosorbide dinitrate 10 mg 3 times/day, with chest pain and 1 mm ST depression inferolaterally. The thallium exercise scan revealed a perfusion defect in the circumflex territory with partial reperfusion on delayed imaging. The resting ejection fraction fell from 57% to 47% with stress (hand grip) and this was associated with hypokinesia in the posterolateral free wall. Angiography revealed a mildly (globally) dilated hypocontractile left ventricle with minor plaque disease in the left anterior descending coronary artery and a subtotal occlusion of a dominant left circumflex coronary artery (Fig. 4.8 [1]).

Angioplasty Procedure: The coronary guide wire was easily able to cross the subtotal occlusion in the circumflex artery and it was elected to precede to laser angioplasty over this guide wire. A 1.3 mm coil catheter probe was advanced over the guide wire to the lesion and argon energy at 8 Watts was delivered for 5 seconds whilst trying to cross the lesion (Fig. 4.8 [2]). Despite easy tracking of laser probe over the guide wire there was no progress and it was decided to abandon the procedure and not persevere as in the previous patient. A 3.0 mm Simpson Ultra Load Profile Balloon replaced the laser probe on the guide wire and after a little manipulation (including optimal positioning of the guide catheter) the balloon was able to cross the lesion. The transtenotic gradient of 115 mmHg was reduced to +/- 10 mmHg after 8 inflations at 6-9 atmospheres for 30-60 seconds. There was an excellent appearance post dilatation (Fig. 4.8 [3]).

Post Angioplasty Course: Heparin and isosorbide dinitrate were infused intravenously for 24 hours as per routine and he was discharged 48 hours after the procedure. He continued to take aspirin and dipyridamole and two months later completed 13 minutes of the Bruce Protocol without any ST changes. At elective catheterisation 6 months later there was a 30-40% irregular narrowing at the site of the angioplasty.

(c) SUMMARY

Laser thermal probe energy was used during percutaneous coronary angioplasty in three patients. In the first patient energy delivery improved the lumen but this was associated with closure of an important side branch. After balloon angioplasty the vessel went into intractable spasm and emergency bypass surgery was required. The patient died of septicaemia two weeks later and at necropsy evidence of thermal and balloon dilatation damage was present. In two patients the probe was unable to transmit sufficient axial strength to allow recanalisation of the lesion during energy delivery. In one a perforation (and occlusion) was caused when the adherent probe was withdrawn while in the other balloon angioplasty was able to proceed uneventfully after the laser probe failure.

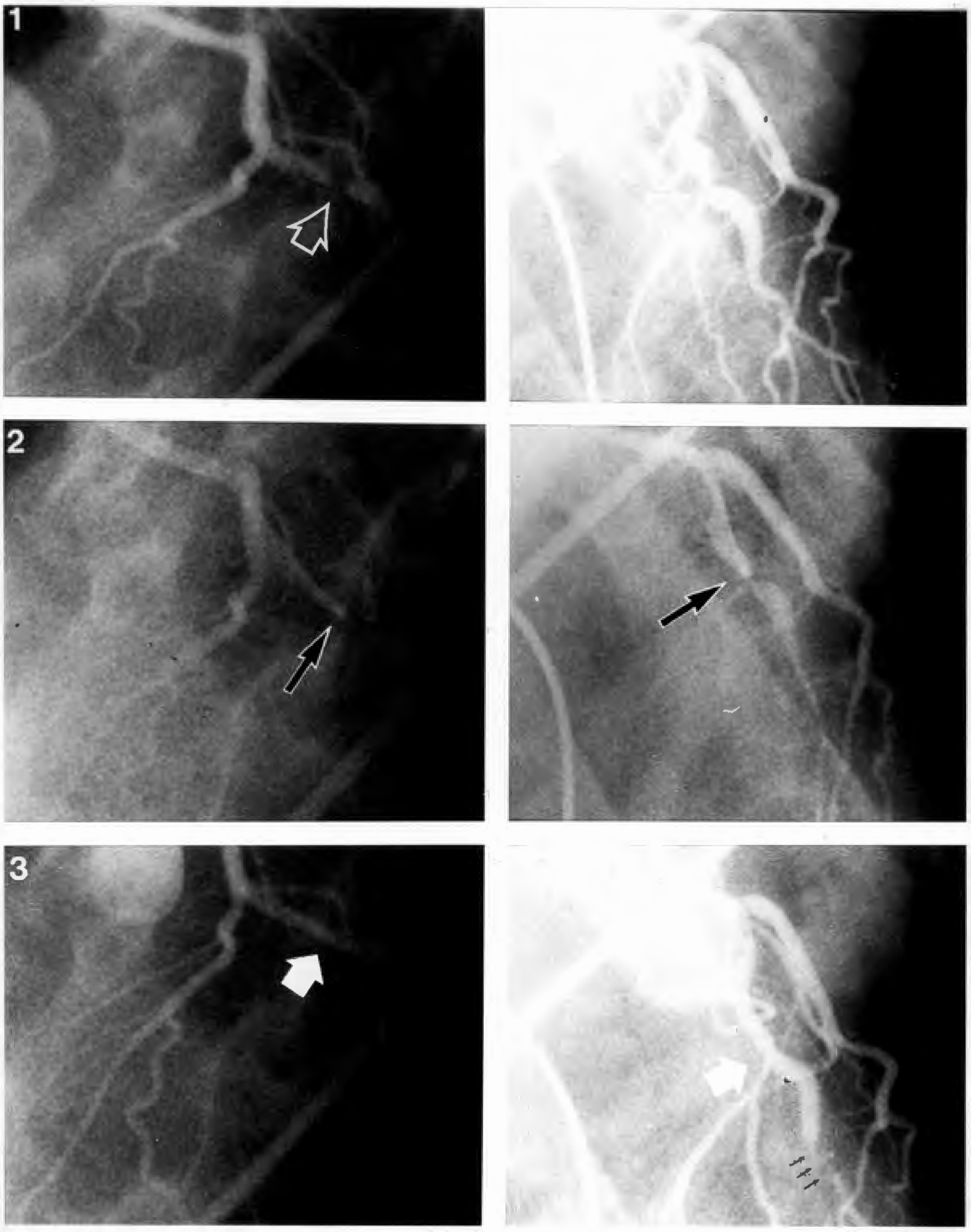


Figure 4.8: Subtotal occlusion of the circumflex coronary artery [1] seen in left anterior oblique view on the left and right anterior oblique view on the right (open white arrow). The 1.3 mm laser probe (black arrow) is easily advanced to the lesion [2] but is unable to recanalise it during energy delivery. After balloon dilatation there is an excellent angiographic appearance (white arrow). Distal guide wire induced spasm (small black arrows) resolves shortly there after [3].

4.4 IN VITRO EFFECTS OF LASER THERMAL ENERGY IN CORONARY ARTERIES

After the rather disappointing clinical results despite the seemingly favourable handling characteristics of the coil probes further in vitro studies were undertaken. It appeared essential to assess the damage caused to smaller vessels such as the coronary arteries before any further clinical applications. While the handling defects of the coil probes were apparent from the in vivo use little quantitative information was available about thermal effects in smaller vessels. In order to further assess the phenomenon of lateral wall damage during slow or non-progression of probes impeded by lesions, laser thermal energy was delivered to perfused cadaver coronary arteries with a stationary probe.

(a) METHODS

(1) Coronary artery preparation

Cadaver hearts from patients without occlusive coronary artery disease obtained at routine postmortem within 36 hours of death were suspended in a water bath, kept at a constant 37 °C. A standard Judkins 9F coronary guiding catheter was positioned in the ostium of the left and/or right coronary artery and the distal vessel was cannulated to allow continuous perfusion of the vessel being studied. Major branches not cannulated distally were ligated when possible to prevent excessive extravasation of contrast into the myocardium. The coronary segments were then continuously flushed with 0.9% saline at 37 °C and a mean pressure of 100 mmHg (Fig 4.9).

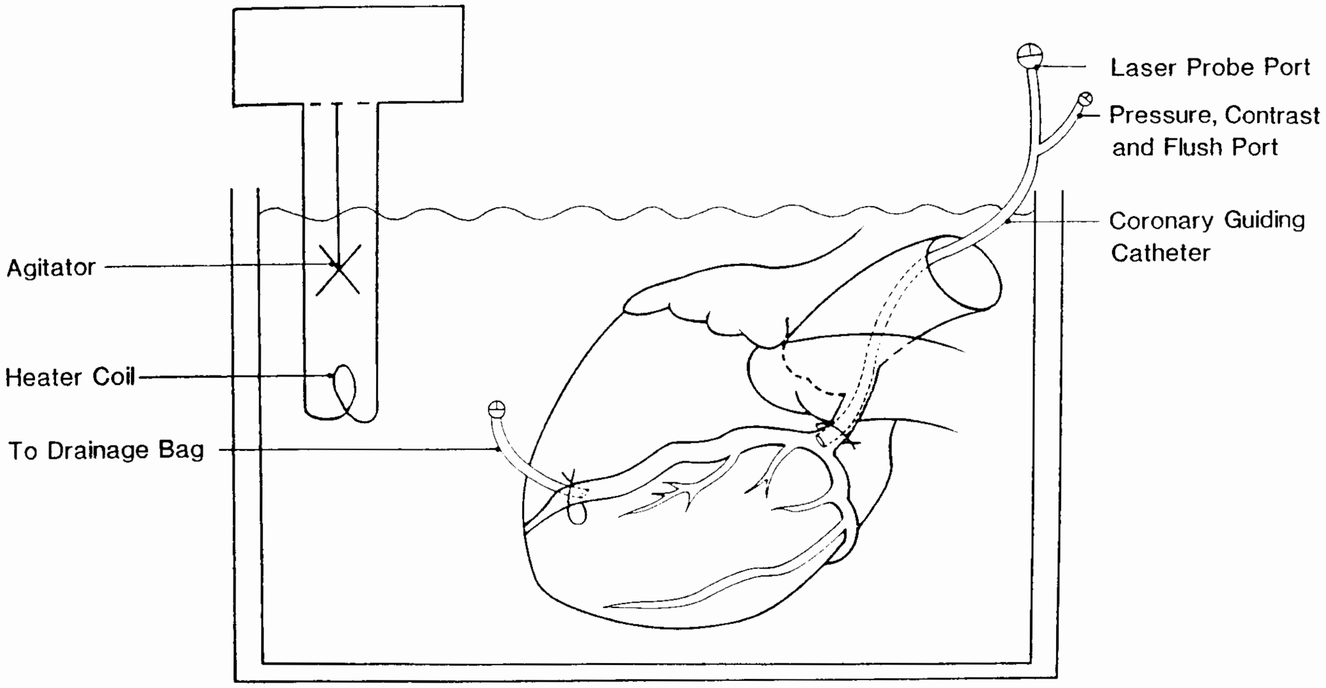


Figure 4.9: Cadaver heart preparation allowing for introduction of the laser probe, contrast and perfusate and distal coronary artery drainage.

(2) Procedure

An initial angiogram using Urograffin 370 was performed to delineate the coronary anatomy and select disease free, non-tortuous areas for subsequent laser energy delivery. A 1.7 mm tip coil laser probe of the type used in patients 1 and 2 was then advanced via the guiding catheter over a guide wire to the selected segment. Prior to argon energy delivery the vessel was irrigated with saline to remove all contrast. One, two or three exposures of 10 Watts for 5 seconds were delivered to successive segments. After delivery of laser energy, the probe was moved to see if any adherence had occurred. A further angiogram was then performed to exclude any perforations and in the absence of contrast extravasation the probe was advanced to the next segment and the procedure repeated. During energy delivery the saline perfusion was either stopped by occluding the distal drainage port (i.e. fluid distension but no flow - to mimic stasis in the proximal stump of an occlusion or tight stenosis) or controlled at a rate of 60 ml per minute.

On completion the vessel was incised longitudinally for macroscopic assessment and photography. After formalin fixation the vessels were examined under a dissecting microscope and representative blocks were taken of visible lesions. Where a lesion was not seen the appropriate area was divided into several blocks and processed. Paraffin sections were cut and stained with haemotoxylin and eosin and a combined elastin-MSB stain. The angiograms were projected onto a screen and the vessel and probe tip diameters measured with callipers. A vessel to probe tip diameter ratio was then established for each segment using the angiogram performed immediately prior to laser energy delivery.

(b) RESULTS

Laser thermal energy was delivered to 25 segments of coronary artery (mean diameter 2.8 mm, range 1.9-4.0 mm) in five cadaver hearts using four laser probes (Table II). Access to all segments was facilitated by the flexibility of the probe assembly.

Adherence of the probe to the vessel wall occurred in 19 of the 25 segments in all of which the vessel to probe ratio was less than or equal to 2.1 : 1. Gentle traction was successful in dislodging the probe from 14 of these segments. Further traction alone resulted in perforations in two segments. The additional use of 1-2 seconds of laser energy at 10 Watts during traction was able to free the probe in the remaining three albeit with a perforation in one. In all three instances where vessel perforation occurred, the vessel to probe diameter ratio was less than 1.6 : 1 and flow through the vessel was absent. In two instances the adherent probe was dislodged by traction alone while in the third a perforation occurred despite additional laser energy delivery (Fig. 4.10). After withdrawing the probe a fracture of the distal coil was found (Fig. 4.11) and it is possible that this contributed to the vessel perforation. Use of this probe in eight previous segments - contrary to the manufacturers recommendations of a single procedure use - is likely to have weakened the coil which then dehisced either during placement in the coronary segment or during the initial attempted withdrawal.

TABLE II RESULTS OF LASER THERMAL ENERGY DELIVERY TO CORONARY ARTERY SEGMENTS

VESSEL-PROBE RATIO	CUMULATIVE ENERGY (J)	SEGMENT FLOW	PROBE ADHERENCE	VISIBLE CHAR	VESSEL PERFORATION
2.4	50	-	-	-	-
2.3	50	+	-	-	-
2.2	50	+	-	-	-
2.2	100	+	-	-	-
2.1	50	-	-	-	-
2.1	100	-	+	+	-
2.1	150	+	+	-	-
2.0	50	+	+	-	-
1.9	100	-	+ *	+	-
1.9	100	+	+	-	-
1.8	100	-	+	-	-
1.7	150	-	+	+	-
1.7	150	+	+	-	-
1.7	100	+	+	-	-
1.6	100	-	-	-	-
1.5	50	-	+ *	+	+ $
1.5	50	-	+ *	+	-
1.4	150	+	+	-	-
1.4	150	-	+	+	+
1.4	50	+	+	-	-
1.4	50	-	+	-	-
1.3	150	+	+	-	-
1.3	100	+	+	-	-
1.2	150	-	+	+	-
1.1	50	-	+	+	+

Results of laser thermal energy delivery to 25 cadaver coronary artery segments using stationary 1.7 mm flexible laser probes. Flow during energy delivery was maintained at a rate of 60 ml/minute (+) or stopped i.e. 0 ml/minute (-).

* = Use of additional laser energy during probe dislodgement (1-2 seconds @ 10 Watts).

$ = Coil dehiscence.

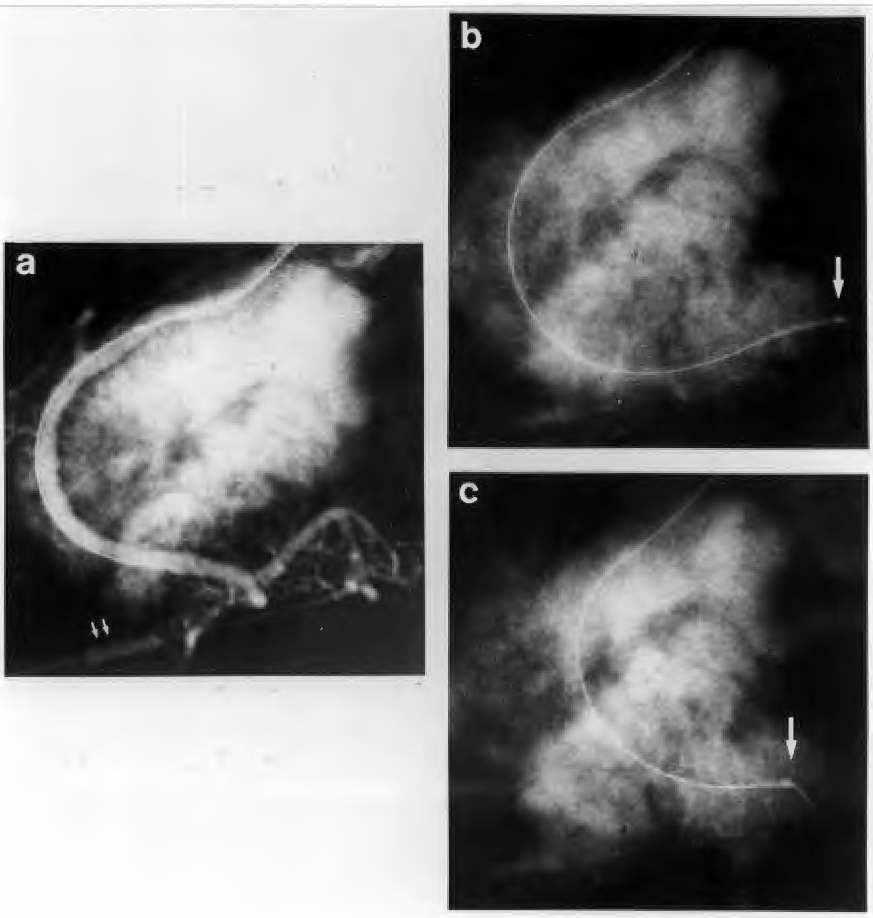


Figure 4.10: Degree of traction necessary to free probe from right coronary artery. a) Preliminary angiogram. b) Laser probe advanced over guide wire to posterior descending branch before delivery of 50 Joules. c) Marked displacement of vessel during traction to free probe. Large arrow indicates probe tip. Small arrows show the drainage cannula.

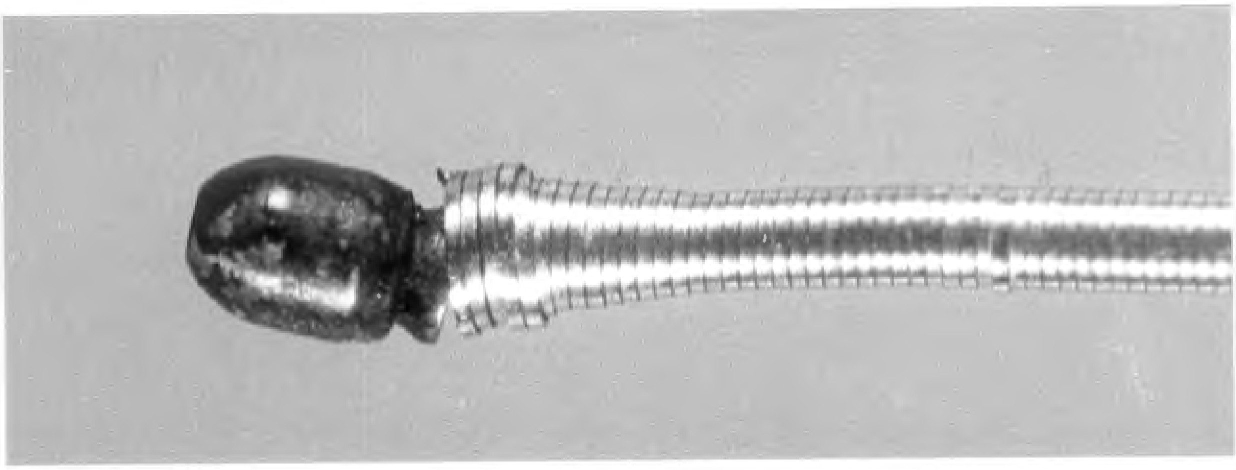


Figure 4.11: Fracture of coil found after freeing probe with traction.

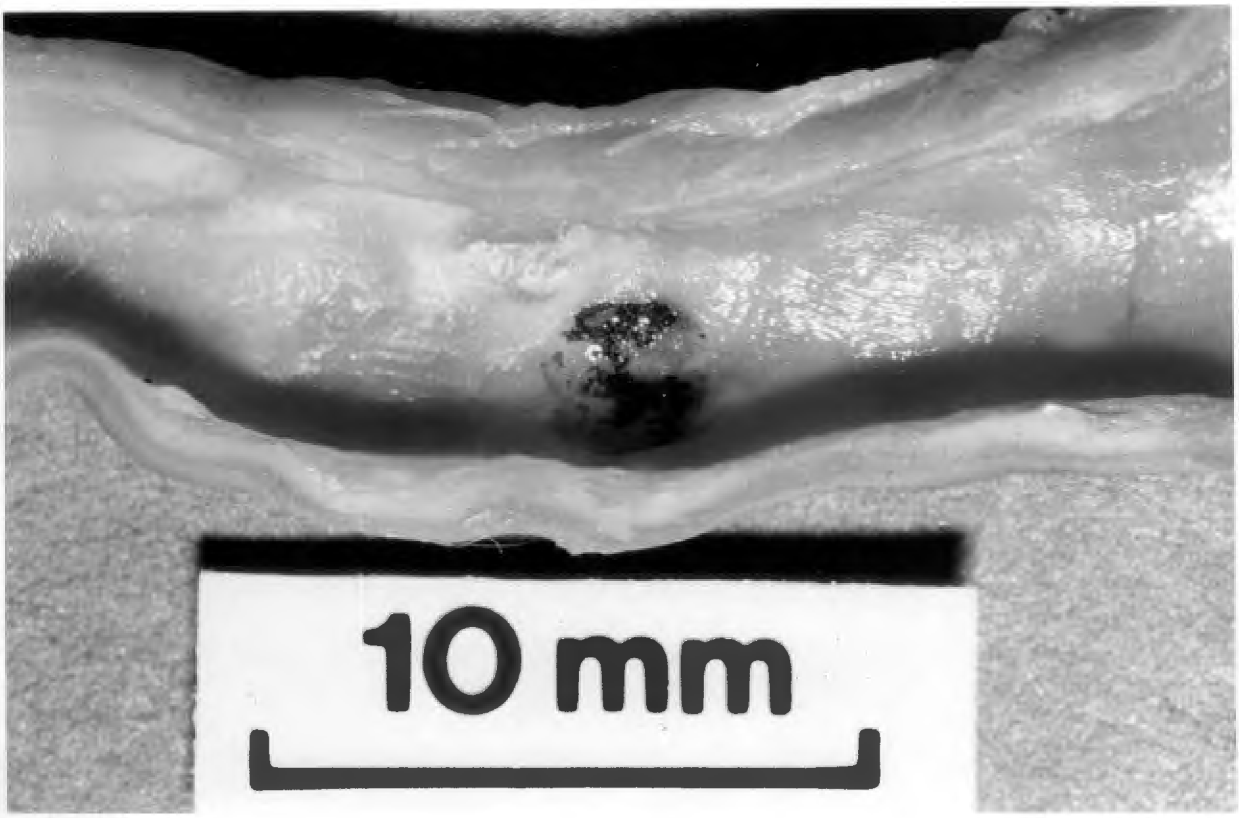


Figure 4.12: Charring of Right Coronary Artery after a cumulative total of 100 Joules laser thermal energy (Vessel to probe ratio of 2.1:1).

Macroscopic examination revealed charring of the endothelial surface in 8 of the 19 adherent segments (Fig. 4.12) and in 7 of these the vessel to probe diameter ratio was less than 2.0 : 1. In the remainder evidence of laser delivery was difficult to see even under the dissecting microscope. Light microscopy identified areas in two macroscopically undamaged segments showing evidence of thermal damage with carbonisation of the luminal surface and subintimal vacuolation extending less than 0.1 mm deep (Fig 4.13).

Charring was notably absent in all of the segments perfused simultaneously with energy delivery (0/12) and none required additional laser energy to dislodge the probe. In contrast charring was present in 8 of 13 segments not perfused ($p < 0.01$). Histology of charred segments revealed accentuation of the changes seen in areas where macroscopic damage was not apparent. Extensive carbonisation overlay the vacuolated tissue which extended into the media and adventitia with a deeper zone of tissue eosinophilia and coagulation (Fig. 4.14). The depth of thermal damage after 50 Joules ranged from 0.2 mm in a segment with a vessel to probe ratio of 1.9 : 1 to 0.7 mm in a segment with a ratio of 1.1 : 1. Only the angiographically perforated segments revealed evidence of histological perforation.

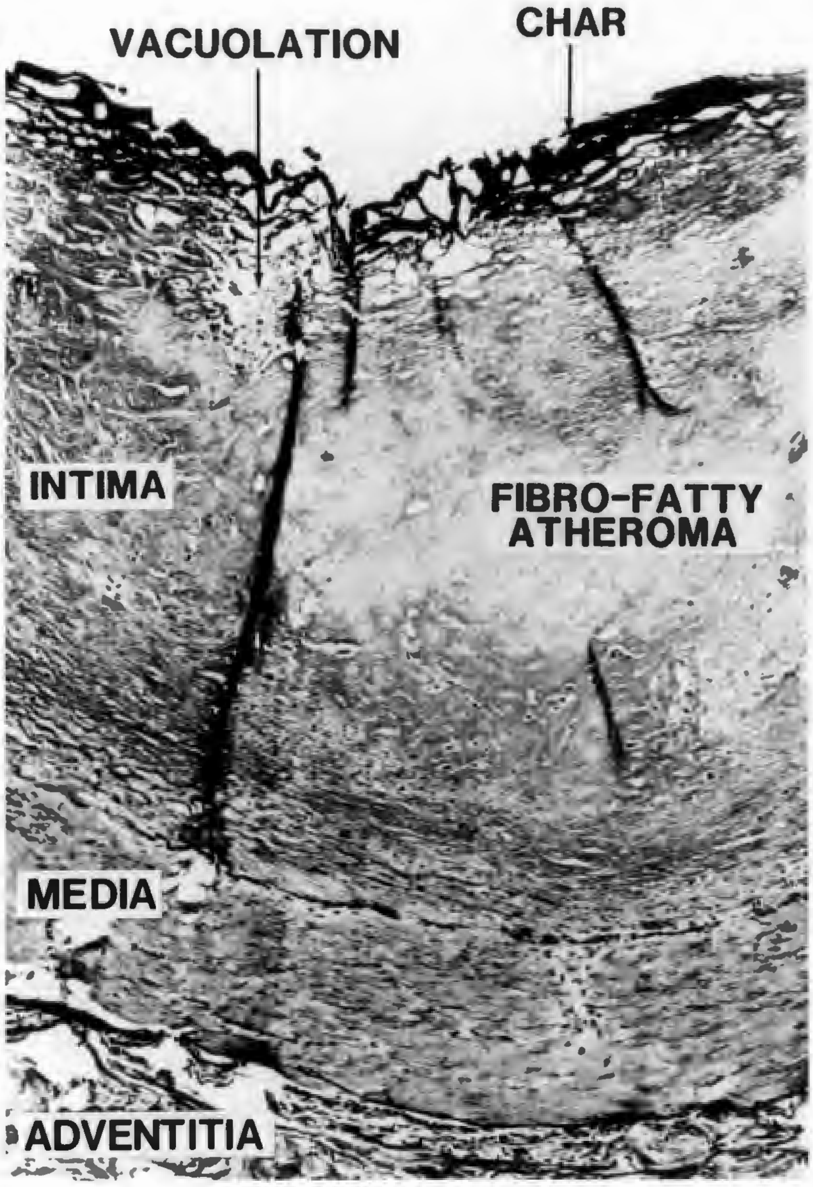


Figure 4.13: Histology of area without macroscopic change showing (1) carbonization of luminal surface and (2) subintimal vacuolation. Elastin-MSB, magnification X 100.

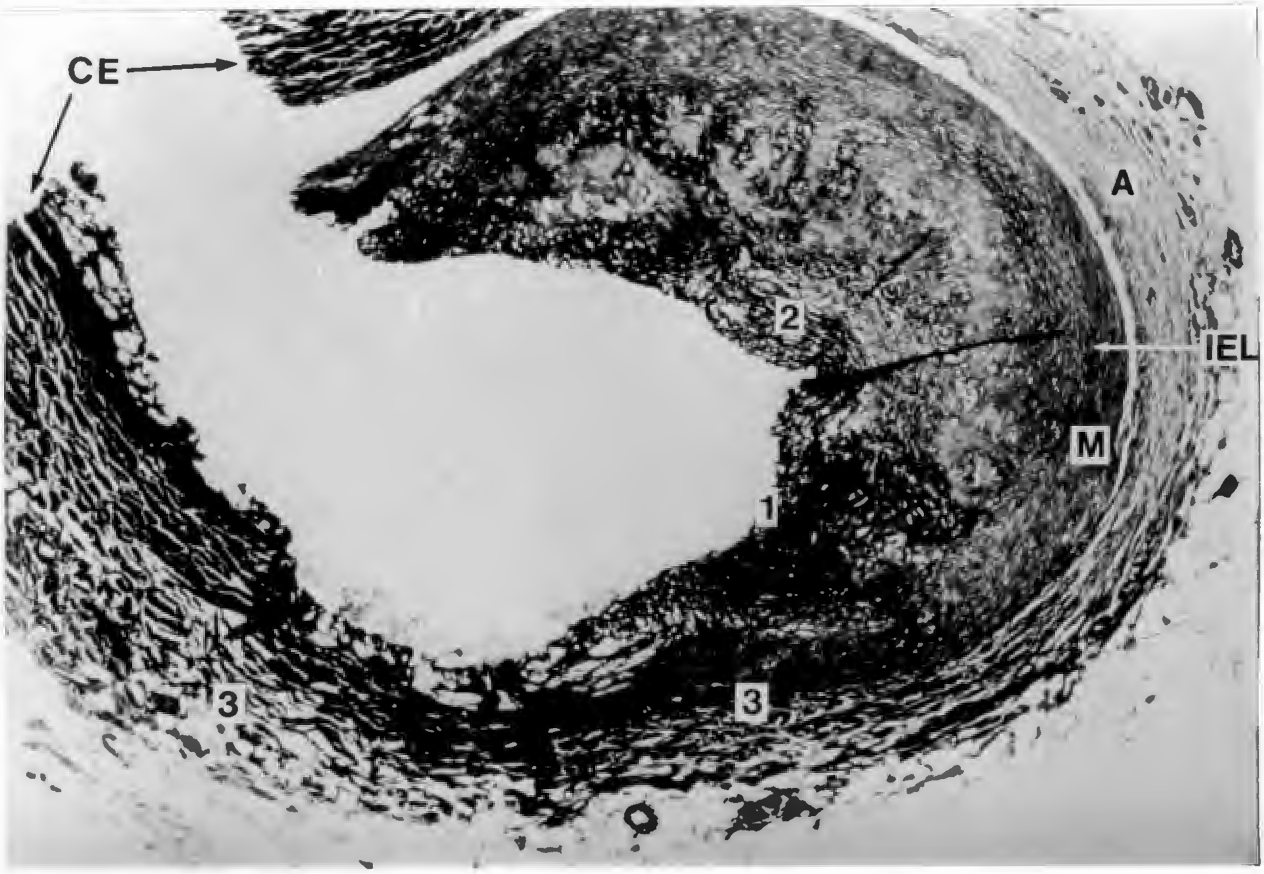


Figure 4.14: Histology from a charred segment reveals (1) intimal carbonisation with extensive (2) vacuolation and (3) eosinophilic coagulation extending to the media and adventitia. The artifactual tissue processing split between media and adventitia is not present in the extensively damaged sector. M = media, A = adventitia, IEL = internal elastic lamina, CE = cut edges. Elastin-MSB, magnification X 40.

(c) ADDENDUM

During this study a cadaver preparation was found to have a subtotal occlusion of the left anterior descending coronary artery (Fig. 4.15). Argon energy at 10 Watts was delivered continuously whilst attempting to recanalise the lesion over the guide wire. After 10 seconds the force applied to the probe was further increased and the fibre snapped between the guide catheter haemostatic port and the operator's hand producing a sheet of flame (Fig. 4.16). The probe tip was adherent to the vessel but was withdrawn without a perforation though with unravelling of the coil. On sectioning the vessel, charring was present but the probe had made little progress through the lesion (Fig. 4.17).

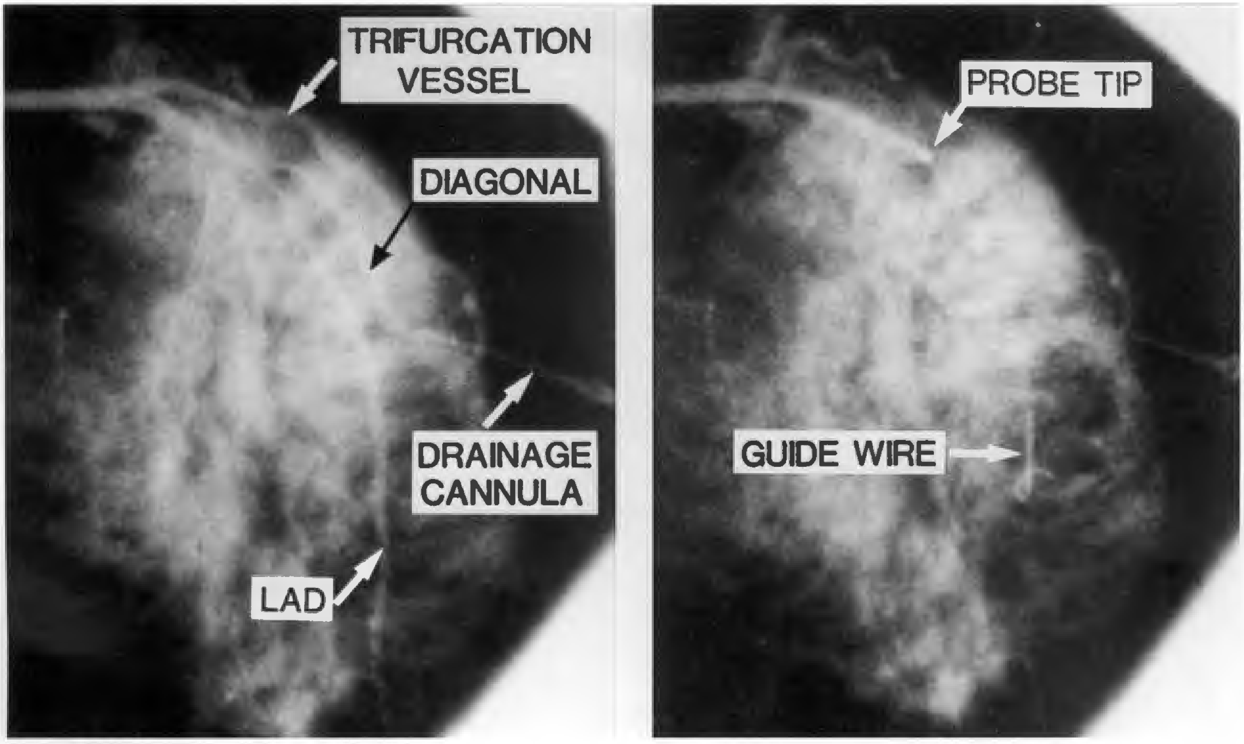


Figure 4.15: a) Tight stenosis of the left anterior descending coronary artery (LAD) proximal to the origin of a large diagonal (LADD) branch with attempted advancement in b).

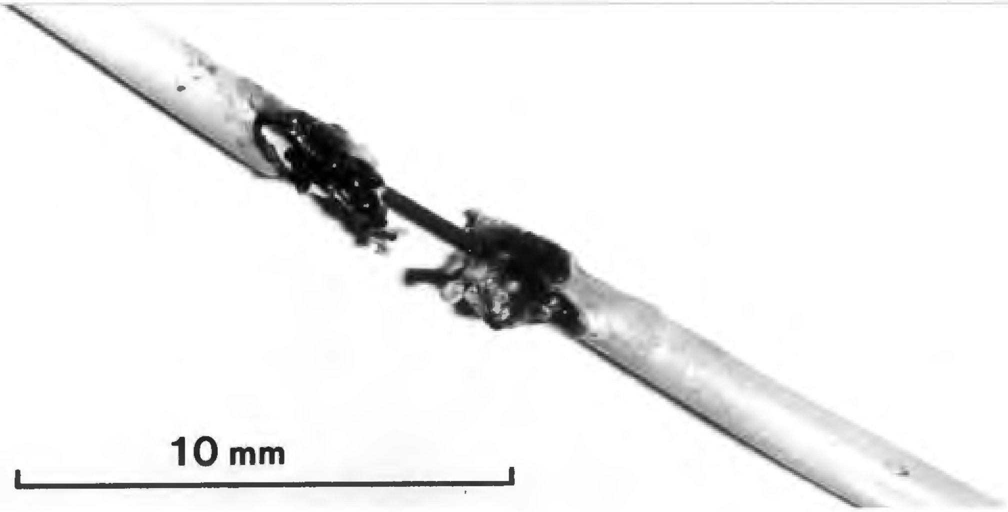


Figure 4.16: Disrupted catheter edges at site of fibre fracture with guide wire traversing the gap.

Figure 4.17: Charring at the site of the stenosis after energy delivery (circled area from angiogram Fig. 4.15).

(d) LIMITATIONS OF THE MODEL

The laser probes were heated in a saline medium and as blood is a better insulator (191,Chapter 2) the probe temperature would have been higher and damage more marked at the flow rates used. In vivo the greater tip temperature might thus diminish the degree of protection seen with flow in this study. If blood had been used as a perfusate this would have allowed only a single use for each probe as char and thrombus formation would have altered the thermal transfer with successive applications (Chapter 2). The specific heating and insulation properties of myocardium and pericardial fat are likely to be different in vivo but by leaving the vessel in situ this model is more realistic than if the vessels had been dissected and suspended free from the heart. Flow in coronary vessels with severe stenoses will be low and will fall further when the advancing probe occludes the effective lumen. Thus the controlled flow rate of 60 ml/minute is unlikely to be attained in vivo. Nevertheless the difference in effects that can be expected during conditions of stasis and normal flow suggest that rapid passage of the probe across a lesion to re-establish flow will help to limit damage. Clearly total occlusions impeding probe passage will present the greatest challenge (but so too did the high grade stenoses in patients 2 and 3) and it was for this reason that the effects during complete stasis were studied. While the leading edge of the probe tip was not in vessel wall contact it was not possible to be certain how firmly the lateral aspect of the probe tip was applied to the vessel wall. Anatomical factors including vessel tortuosity and distance down the vessel would have determined the degree of lateral contact and consequent vessel damage (102). This may explain why the amount of delivered energy was not absolutely correlated with the observed effects. Electron microscopy might well have revealed evidence of thermal damage in some segments with adherence and no apparent light microscopy changes though it is unlikely that significant intimal damage would have been missed. While the probe tip temperature was not measured during this study it is unlikely that vessel wall contact would have been identifiable by higher temperatures (Chapter 2).

(e) SUMMARY

Laser thermal energy delivered to stationary probes in cadaver coronary arteries was found to cause thermal damage at energies as low as 50 Joules. Adherence to the lateral wall was common but did not always imply macroscopic damage. Macroscopic damage however was only present when vessels were not perfused during energy delivery. Where gentle traction failed to free the probe significant lateral wall adherence was present. All three segments which perforated had vessel to probe tip diameter ratios less than 1.6 : 1. In two traction alone was used to dislodge the probe tip and was clearly excessive. The use of supplemental laser energy during further sustained traction is likely to have prevented perforation in two segments where the tip was firmly adherent. In the third perforation however even this step was unsuccessful and the perforation may have been caused by dehiscence of the coil which then embedded itself into the vessel wall. Further evidence of the unsuitability of this probe design was found in a single stenotic lesion where the flexible probe could not be advanced through the lesion during energy delivery and the fibre proximal to the guide catheter snapped during attempted forceful advancement.

4.5 DISCUSSION

Laser thermal probe assisted angioplasty as a means of overcoming some of the limitations of the conventional balloon procedure is clearly a viable manoeuvre in peripheral arteries (Chapter 3.4). The extension of this procedure to coronary arteries has not met with the same degree of success (174,175, Chapter 4.3) and needs to be reappraised in the light of coronary anatomy and the currently available delivery systems. Furthermore its role in coronary artery disease is yet to be defined in the current setting of modern balloon angioplasty techniques. While inability to primarily dilate lesions which have been crossed with a guide wire or repeated recurrence after initial successful balloon dilatation are now uncommon, acute occlusions and a recurrence rate of 20-40% are unresolved problems (233-235). Reliable percutaneous treatment of total occlusions (as is now possible in peripheral arteries with contact laser techniques) is only possible in recent occlusions and distal endarterectomy, either percutaneously or as part of bypass grafting, remains a speculative goal. It is in these areas that laser assisted angioplasty has to demonstrate superior results for it to be accepted clinically.

The effectiveness of percutaneous laser thermal probes (as well as sapphire, lensed and spectroscopically guided systems) in peripheral vessels cannot automatically be extrapolated to the coronary circulation. In peripheral artery angioplasty the distance from the percutaneous access point to the lesion is usually short and the vessels are straight, of large calibre and motionless. Substantial axial force may be used during advancement and while not quantifiable clinically this force has been shown to increase the degree of ablation with contact laser systems (102). This might simply reflect improved heat transfer due to better thermal coupling but thermal compression of the heated area could also be responsible. In addition delay in advancement and adherence to the lateral wall is uncommon as the proximity to the lesion allows a more rapid to and fro motion during advancement.

Intracoronary "hot tip" laser assisted angioplasty is however, technically more demanding. Smaller probes incorporating a greater degree of flexibility are required for percutaneous access through preformed guiding catheters. Access, however, is not the only criterion for successful coronary artery laser recanalisation. Sufficient axial strength to enable progression through the lesion but without excessive trauma to the vessel - either mechanical or thermal is also essential. Thus a probe that is able to access the coronary tree but is nevertheless too rigid, may still damage the vessel. The earliest probes designed for the peripheral circulation were too large and inflexible for use in the coronary tree. The smaller peripheral artery probes (1.5 - 1.7 mm tips) were modified by creating an eccentric guide wire channel through the tip itself to facilitate coaxial advancement and subsequent balloon exchange. Suitability was limited to proximal portions and straight coronary segments. Three studies of percutaneous coronary laser thermal angioplasty using this type of probe have been performed with mixed results (174,175,190).

During a per-operative coronary artery study using cumulative energies of 68-272 Joules, occlusions were seen at 24 hours in 2 out of 3 initially successful cases. Competing flow from the concomitantly placed bypass grafts is likely to have contributed to these early occlusions (190). This is not inevitable as in a single case report of intra-operative laser probe use (with a more flexible device), both the graft and treated vessel were patent at a week (236). Two percutaneous "over the wire" laser thermal probe coronary artery studies using the adapted peripheral artery probes (energies of 40-80 Joules) have been reported. In neither series were acute complications encountered although in the larger one inability to recanalise the lesion occurred in 3 out of 7 patients (175). In the smaller series 1 patient of the 4 had a transmural myocardial infarction and 2 patients had enzyme rises all occurring within 24 hours of the procedure (174). Clearly spasm, thrombosis or embolism from the laser sites could be implicated although it would be impossible to exclude balloon angioplasty related complications. It was for this reason that aspirin and dipyridamole were added to the angioplasty regimen for the patients studied here.

In the first patient a large diagonal vessel close to the left anterior descending coronary artery stenosis was occluded during energy delivery before balloon dilatation. The finding of char in the origin of the diagonal vessel at postmortem confirms that the thermal effect in the smaller coronary vessels is not as innocuous as it seems to be in the peripheral circulation. The subsequent occlusion is likely to have been caused by spasm at the site of the lesion although clearly both thermal or balloon dilatation damage could be implicated. Repeated coronary spasm has been seen in canine coronary arteries during laser thermal energy delivery though not with similar amounts of pulsed energy (134). The avoidance of excessive thermal damage is thus critical and demands the minimum of energy necessary to recanalise the lesion. The probe tip size is important: in the saline perfused cadaver coronary arteries, vessel to probe diameter ratios of > 2.0:1 were needed to reliably avoid thermal damage. While "flowing" saline was protective in this model the greater temperatures attained in blood (at least initially - Chapter 2.4) may demand an even smaller tip size. Hence to be applicable at most common balloon angioplasty sites, probes with tip diameters less than 1.3 mm are required. If the primary aim of the procedure however is only to make the first channel to enable subsequent balloon angioplasty then even smaller probe tips will be acceptable and should reduce the extent of thermal damage.

While excessively rigid probe may prevent or limit percutaneous use to proximal and straight segments, at the other end of the spectrum, excessively flexible probes, will lack axial strength to facilitate advancement (patients 2 and 3 and cadaver stenosis) despite the ease of access. Non-advancing probes are prone to welding to the vessel wall either proximal to or at the lesion site (190). Perforation, particularly on dislodgement may occur and thermal damage might possibly increase the risk of spasm and thrombosis. While perforations using the laser probe are uncommon both experimentally (168,171) and clinically (173,203,204-209) they have tended to occur either with non-coaxial advancement or when excessive force is used with calcified and eccentric plaques (210,211). The flexible probes used here are unable to transmit excessive force and perforations due to a different mechanism were observed i.e. forceful dislodgement of adherent probes. Until the development of a probe tip surface that does not adhere to tissue at high temperatures it would seem that delivery of a small amount of laser energy together with further gentle traction is the best action in this setting. Attempting to advance adherent probes, already held up at the site of a lesion, during additional laser energy delivery, is likely to cause further lateral wall damage. The perforation encountered in the second patient (and the accompanying occlusion) is evidence of such unwanted thermal effects. Tamponade may have been prevented by pericardial adhesions from the previous bypass grafting procedure or by thrombogenicity of the severely damaged segment (i.e. a cauterising effect). In the intra-operative study of percutaneous "hot tip" laser angioplasty using adapted peripheral artery probes a perforation occurred during advancement but was contained in the epicardial fat (190). Whilst the primary problem in this patient was clearly that of imperfect catheter probe design it highlights the danger in delivering excessive thermal energy in the coronary system. Finally percutaneous endarterectomy of distal vessels, an additional postulated role for lasers in coronary artery disease, is unlikely to be successful with "hot tip" probes. Nevertheless such a procedure performed intra-operatively without the constraints of the delivery systems and where spontaneous termination of spasm could be awaited with safety might yet succeed.

The results of the in vivo applications here with the highly flexible probes, together with the subsequent cadaver studies suggested that thermal probes might only be suitable for "pilot hole" recanalisation prior to balloon dilatation. Extensive "debulking" procedures or distal endarterectomies appeared likely to be deleterious if performed percutaneously. Cumberland has since been able to cross three out of four total coronary occlusions that could not be crossed with a guide wire, using an 0.18 inch thermal probe capped guide wire (237). The vessel to probe diameters with this system approach those seen in peripheral artery laser thermal angioplasty thus increasing the safety margin.

The in vivo and in vitro experience here together with that of others has led to further coronary thermal probe design modifications (238). The optical fibre in coil catheter probes has been increased to a diameter of 200 um while similar catheters without a coil have been made, both measures reducing the unwanted excessive flexibility. In addition the side hole tip probe catheter has been produced in a length for percutaneous use. Preliminary reports of a multicenter study in 47 patients including both native vessel and vein graft stenoses (11 recurrent after balloon angioplasty) have been more successful (239,240). Detachment of the probe in one patient (model without safety wire) was fatal after emergency bypass surgery; in four the probe could not cross the lesion but balloon dilatation was successful in three - a similar setting to patients two and three here; there was one acute closure and 17 re-stenoses within six months for only a 49% success rate over six months (57% of successful procedures). While careful attention to selection criteria, pre and post angioplasty anticoagulation and antispasm regimes, and improved catheter probes have clearly improved the technical success rate, obvious benefit over balloon angioplasty is not apparent.

A move to enhance thermal "debulking" by using larger probe tips (1.9 mm) heated more rapidly (15 Watts) has been made very recently. It is postulated that the delivery of heat in this fashion will cause more vaporisation without time for much thermal diffusion and therefore excessive injury or spasm as seen with the smaller metal tipped probes. In two patients (one native coronary artery and one vein graft) the procedure was reported to be successful producing channels that did not need subsequent balloon dilatation (241). It is of course possible that rather than lessening thermal injury the more intense heat is able to coagulate the muscle completely so that the spasm potential is reduced. Interestingly the radiofrequency "hot tip" probe catheters have also been shown to be successful in a small clinical report (242).

Laser balloon angioplasty (using a diffusing tip to deliver Nd-YAG energy through a balloon to seal balloon dilatation trauma - Chapter 1.7) intentionally thermally coagulates the whole vessel wall. Applied at the end of a standard coronary balloon angioplasty procedure, insufficient studies have been done to allow an assessment of the impact on acute closure and restenosis (243). The preliminary results, however, do indicate that restenosis is not abolished with this technique (244). Further competition for the laser based technologies may come from the development of radiofrequency heated balloons which have yet to be applied clinically (245).

Since the use of pulsed excimer energies in peripheral arteries for total occlusions, an "over the wire" system has also been used in a patient with coronary artery disease though balloon angioplasty was still required (246). Perhaps the most impressive work is that of Foschi et al who have used a lensed argon fibre (Chapter 1.7) to cross total occlusions without the benefit of a guide wire (247). In 25 of 27 patients, lesions through which a guide wire could not be passed, have been initially recanalised with this system and then enlarged with balloon angioplasty. While it is too early to tell what the restenosis rate with this technique will be (and already 5 recurrences have occurred) it is highly encouraging that lesions that would not have been amenable to conventional balloon angioplasty have been successfully treated.

Finally the "atherectomy" and "extractor" catheters, and rotational devices are also beginning to be applied in coronary arteries (228,248). The former two require guide wires but the latter may also be used in total occlusions. Coronary artery stents have come to play a role in lesions with acute closure immediately after angioplasty or where recurrent stenoses have occurred but seem to be accompanied by a restenosis rate similar to that of conventional angioplasty (249). Still on the horizon is the use of ultrasonic energy to accomplish atheroma ablation (250).

Conclusions: The "hot tip" laser thermal probe has not been as successful as its peripheral artery counterpart though both smaller diameter probes (causing less vessel damage) and larger diameter probes (perhaps completely coagulating the vessel wall) have shown some promise. The laser balloon which uses a non-ablative thermal mechanism to maintain the dilatation effected by balloon angioplasty has also been shown to be useful. More sophisticated systems including the pulsed excimer and in particular the lensed argon systems have been shown to be safe and practical. None of these laser systems (nor indeed any of the newer interventional techniques) have yet been shown to reduce the recurrence rate. Further development of the existing technologies and the clinical application of multifibre, spectroscopically guided pulsed lasers are awaited.

5. HIS BUNDLE ABLATION WITH THE LASER THERMAL PROBE

5.1 INTRODUCTION

Percutaneous direct current catheter ablation of the Bundle of His has revolutionised the management of patients with otherwise uncontrollable supraventricular arrhythmias (251,252). Successful ablation is now achieved in over 60% of cases with single or multiple high energy shocks (253). In addition "modification" of AV nodal conduction occurs in a further 15% so that medical control of the arrhythmia becomes possible. High energy shocks have since been used to ablate accessory pathways (254,255), as well as atrial (256) and ventricular arrhythmogenic foci (257,258), although with lower success rates and a higher tendency for complications including coronary sinus rupture acutely and late ventricular arrhythmias or sudden death (255,258).

These complications have prompted the search for more controllable energy delivery systems or sources. A number of avenues using "low energy" direct current shocks have been tried but without consistent success (259-261). Radio frequency energy can be applied without the need for general anaesthesia and successful ablation has been reported recently (262,263). The development of flexible optical fibres capable of being passed down vascular catheters has led to the application of argon and Nd-YAG laser energy for ablation of the bundle of His with the ability to produce localised lesions in dogs (71,72,264,265). A separate electrode placed at the bundle of His, however, is necessary to guide the laser fibre prior to energy delivery. This is an unsatisfactory approach as alignment can only be approximate and poor control of the emergent energy resulted in cardiac perforations and tamponade (71). The laser thermal probe has not previously been used for His Bundle ablation but has the advantage that electrograms can be recorded from the metal cap itself obviating the need for an additional guiding electrode.

The following studies were designed to:

1) Assess the degree of damage caused by the laser thermal probe when applied to the bundle of His area and adjacent intracardiac structures in cadaver hearts.
2) To confirm that the metal cap could be manoeuvred adjacent to the bundle of His and record electrograms of sufficiently good quality.
3) To perform laser thermal probe ablation of the bundle of His in patients with refractory supraventricular arrhythmias.

5.2 METHODS

(a) Laser probes

The standard peripheral artery laser probe with a 300 um optical fibre capped by a 2.0 mm diameter metal tip was used for these studies. For clinical use the probe was adapted by sheathing the torque wire with 5F Cournand, "head hunter" or multipurpose catheters (Fig. 5.1). This provided insulation so that extraneous electrograms were not recorded and also enhanced the control of the laser probe assembly during intracardiac manipulation.

(b) Cadaver hearts

Fresh cadaver hearts were obtained at routine postmortem and suspended in a water bath controlled at 37 ^{o}C. The laser probe tip was applied sequentially to the tricuspid annulus at the base of the triangle of Koch, the AV membranous septum, the Foramen Ovale, the right atrial appendage, the septal leaflet of the tricuspid valve, the interventricular septum, and the right ventricular free wall. Argon energy at 10 Watts for 5, 10 and 15 seconds (50, 100 and 150 Joules) was delivered to all these sites using gentle pressure. Where tissue adherence did not allow easy dislodgement of the probe an additional 1-2 seconds of energy was delivered during sustained traction to free the probe. The lesions were photographed and histological analysis performed on sections taken through the centre of each lesion.

(c) Patients

The adapted laser probe was evaluated during diagnostic electrophysiological studies. The probe was advanced through a 9F haemostatic sheath via the right femoral vein to the right atrium, right ventricle and into the His bundle position. Unipolar electrograms (indifferent needle electrode placed subcutaneously at femoral vein puncture site) were recorded and compared to those obtained with standard electrophysiological catheters.

In a patient with refractory paroxysmal atrial fibrillation, His bundle ablation was attempted using the modified laser probe. The protocol was approved by the Guy's Hospital ethical committee and written informed consent was obtained.

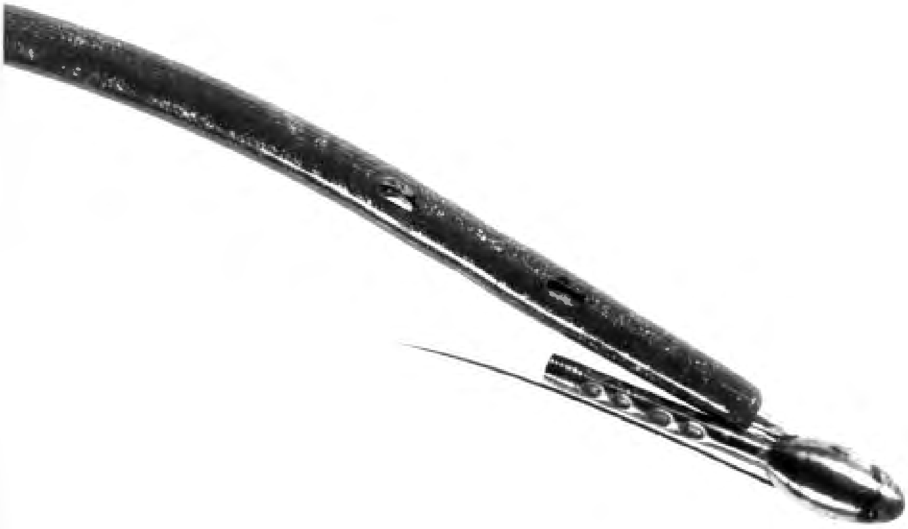


Figure 5.1: 2.0 mm diameter tip probe with support wire sheathed in a 5F multipurpose catheter for in vivo use.

5.3 RESULTS

(a) Cadaver hearts

Charred craters were created at all sites with all three energy levels in 9 cadaver hearts (Table III). The crater diameter varied from 1.5 mm to 2.2 mm on the surface with smaller craters in muscular structures than in fibrous structures. Even when the probe passed completely through the right ventricular free wall and interventricular septum the tract diameter was always less than 2.0 mm. The more fibrous atrial free wall, interatrial septum, tricuspid valve leaflet and AV membraneous septum frequently exhibited transmural charring (Figs. 5.2 A - D). During some of the longer applications the leading edge of the tip perforated these structures but the opposite surface lesion was always less than 1.0 mm in diameter. Close inspection of transmurally charred lesions did not reveal obvious perforations. Histology of these lesions confirmed transmural thermal damage and in some minor perforations were apparent though preparation artefact could not be excluded. The tricuspid annulus was never perforated with the energies used. Histology confirmed the typical changes of thermal damage: a thin layer of char lined the crater and covered an area of vacuolation below which was a variable zone of tissue coagulation. Five second bursts were inadequate to significantly damage the Bundle of His (Fig. 5.3 A) whilst 10 - 15 seconds bursts produced craters to a sufficient depth (Figs. 5.3 B and C). It was noteworthy that the zone of thermal coagulation was still able to damage the Bundle of His even when the crater was slightly off target.

Table III

SITE	TIME	n	TRANSMURAL CHAR	PERFORATION
Foramen Ovale	5 sec	9	2	-
	10 sec	9	7	-
	15 sec	9	6	3
Right Atrial Appendage	5 sec	9	-	-
	10 sec	9	5	-
	15 sec	9	7	2
Tricuspid Valve Leaflet	5 sec	9	7	-
	10 sec	9	7	-
	15 sec	9	4	5
Interventricular Septum	5 sec	9	-	1
	10 sec	9	2	2
	15 sec	9	1	8
Right Ventricular Free Wall	5 sec	9	-	-
	10 sec	9	-	2
	15 sec	9	5	4
A V Membranous Septum	5 sec	3	3	-
	10 sec	3	3	-
	15 sec	3	2	1
Tricuspid Annulus	5 sec	9	-	-
	10 sec	14	-	-
	15 sec	19	-	-

Effects of laser thermal energy of 50 - 150 Joules (5 - 15 seconds at 10 Watts) delivered to right heart sites.

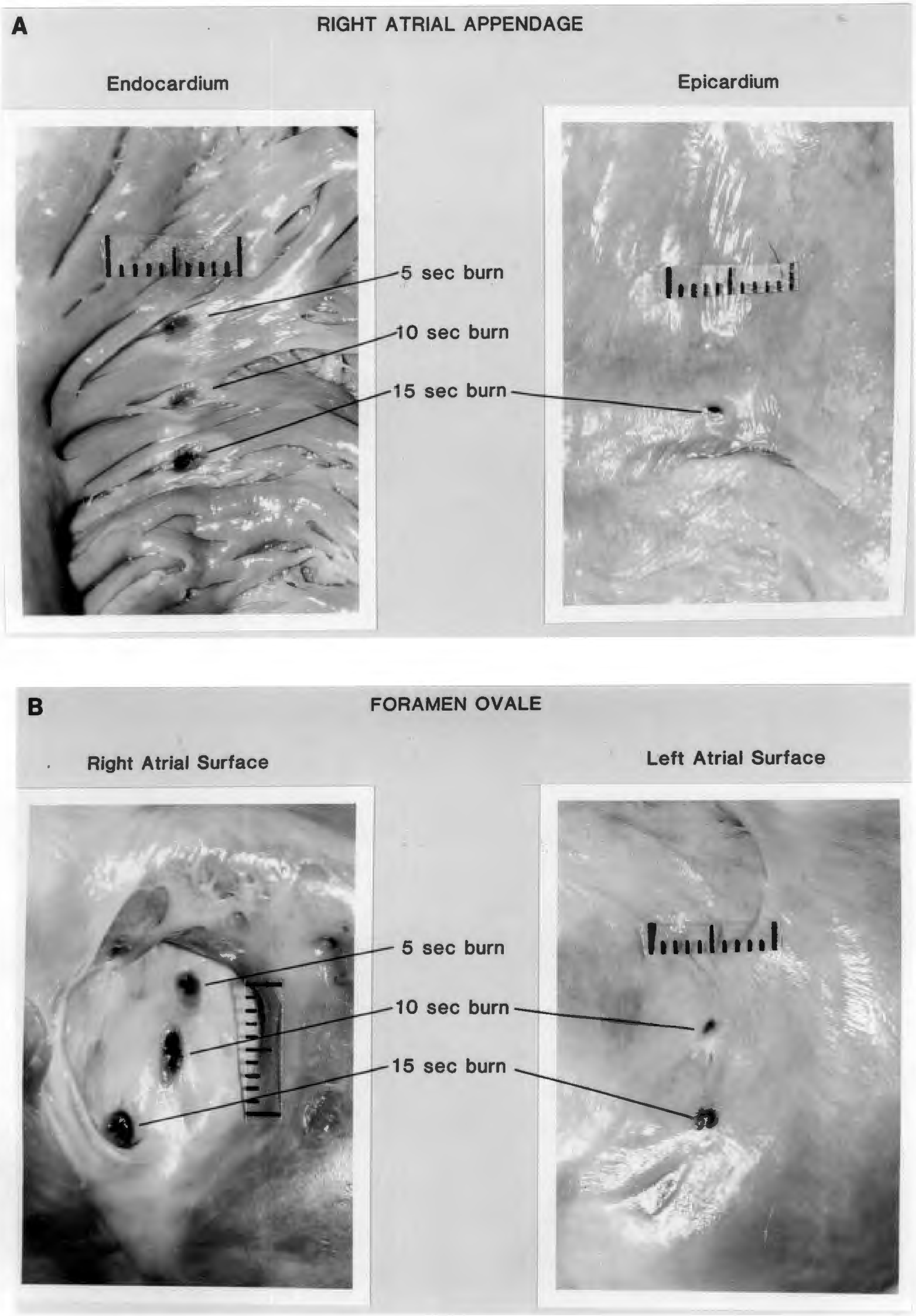
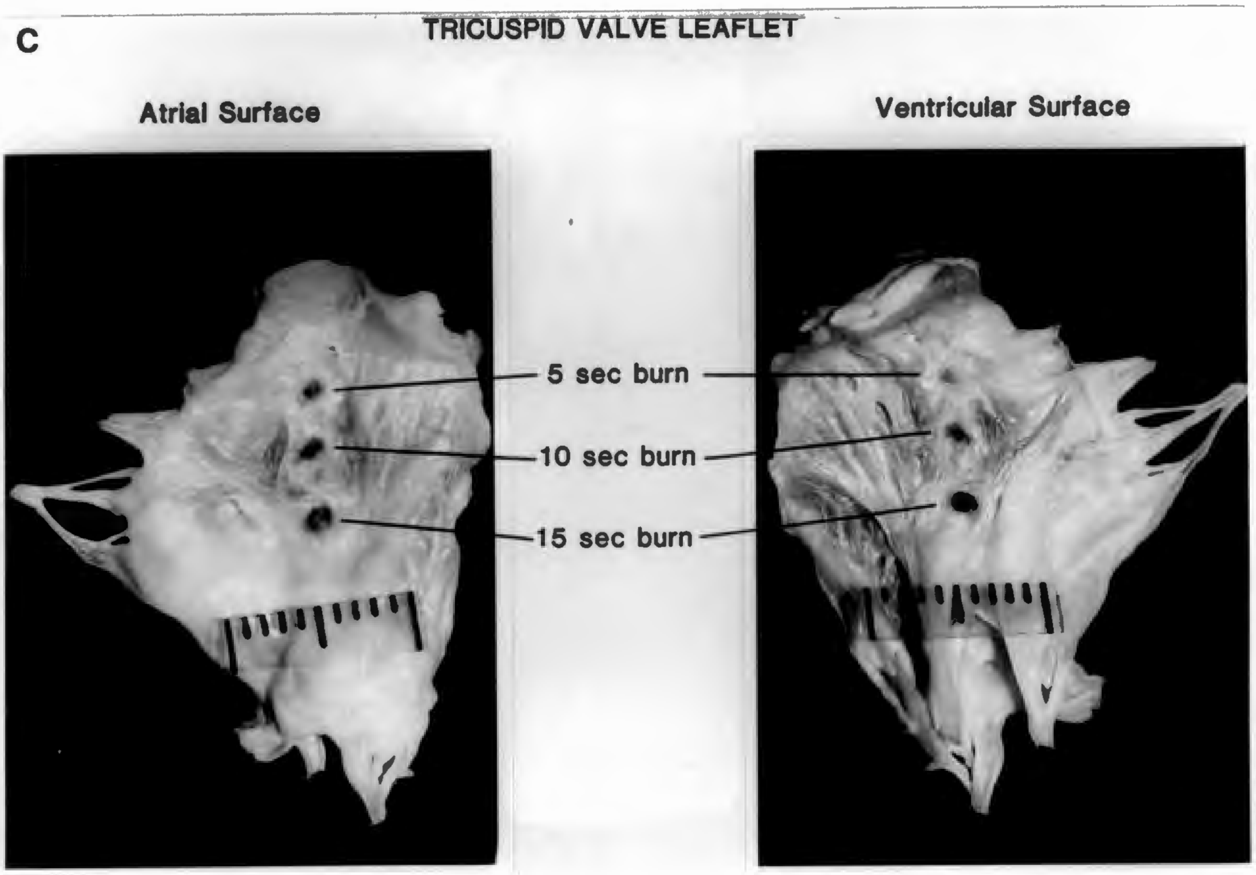


Figure 5.2: Examples of the craters produced during laser thermal energy delivery at 10 Watts



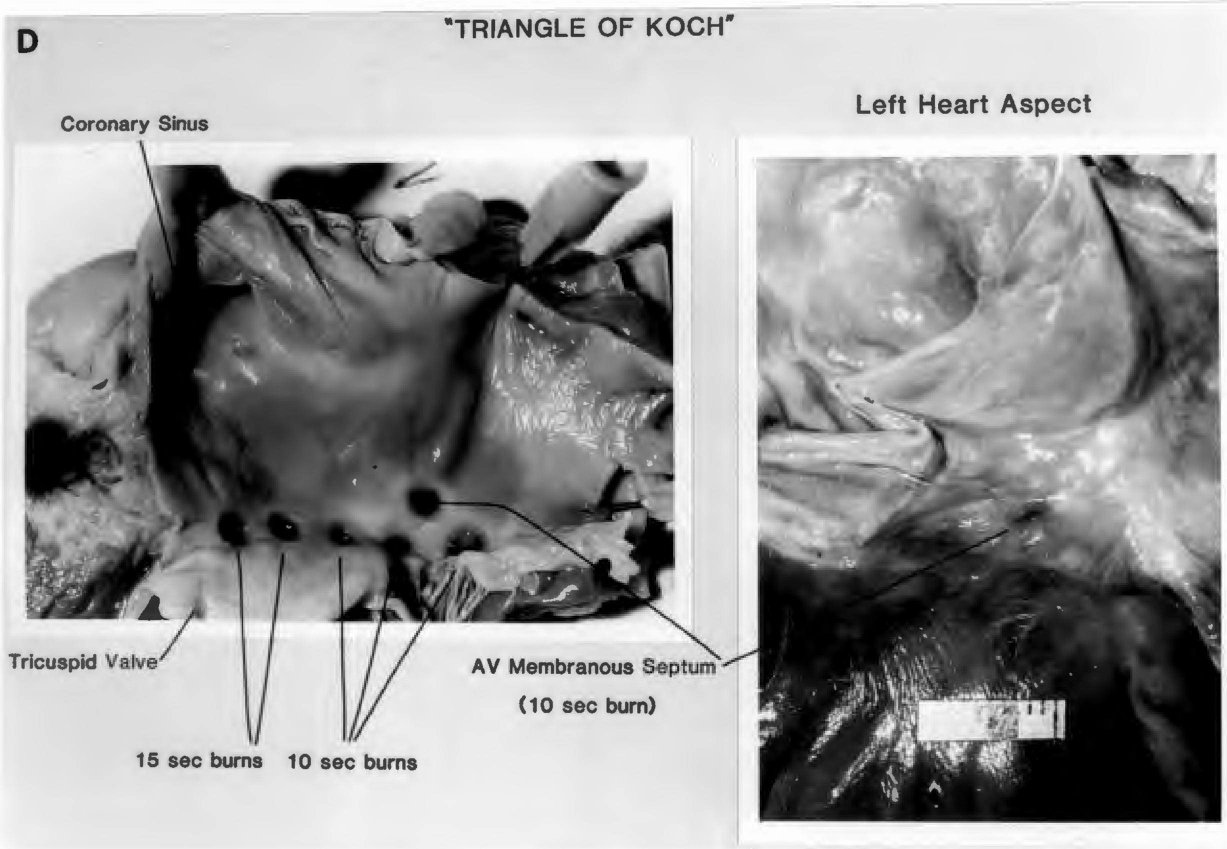
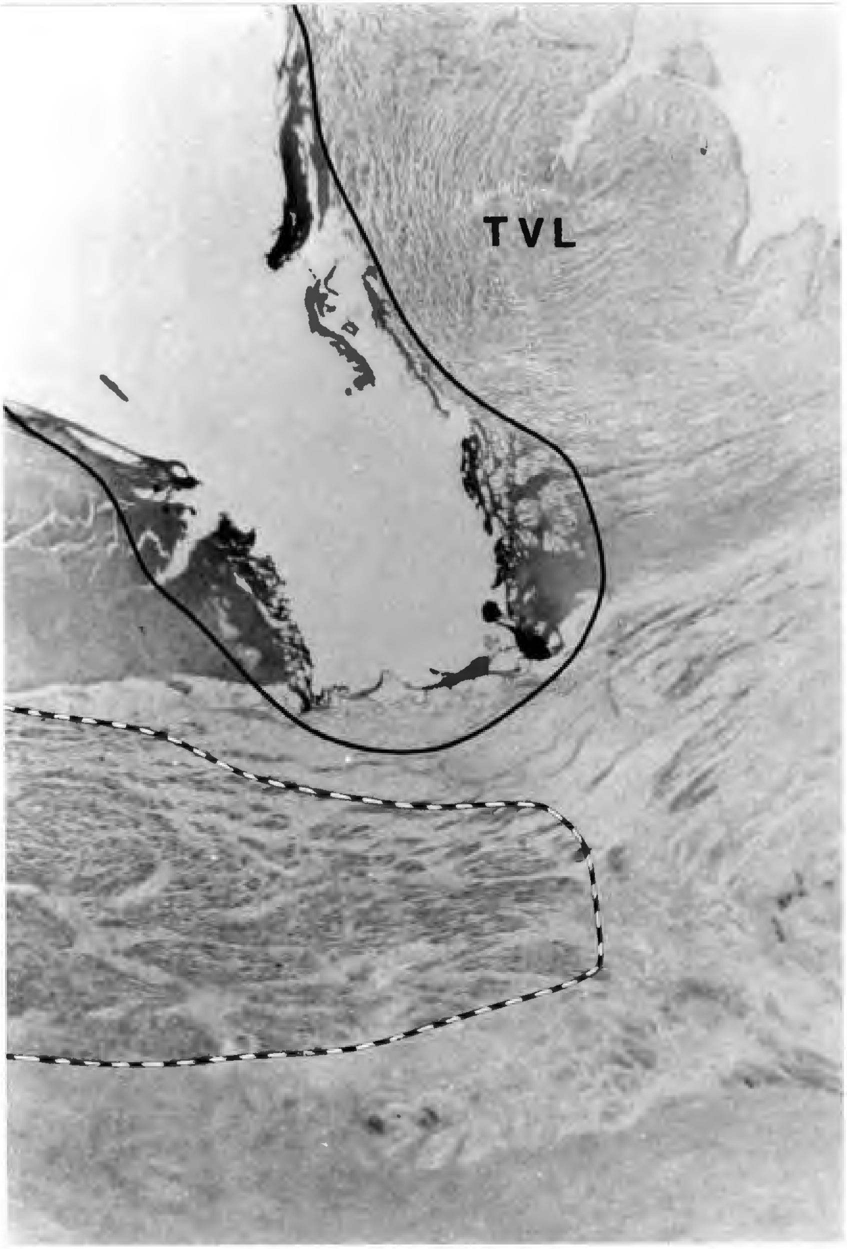


Figure 5.2: Examples of the craters produced during laser thermal energy delivery at 10 Watts



Figures 5.3: In this and the next 2 panels the bundle of His is enclosed in dotted lines while the extent of thermal damage is delineated with a solid line (i.e. crater, surface char, tissue vacuolation and thermal coagulation zone). TVL = Tricuspid Valve Leaflet, IVS = Interventricular Septum. Haematoxylin and Eosin; magnification x 40.

(a) 5 second crater (10 Watts) is not deep enough to damage the bundle of His.

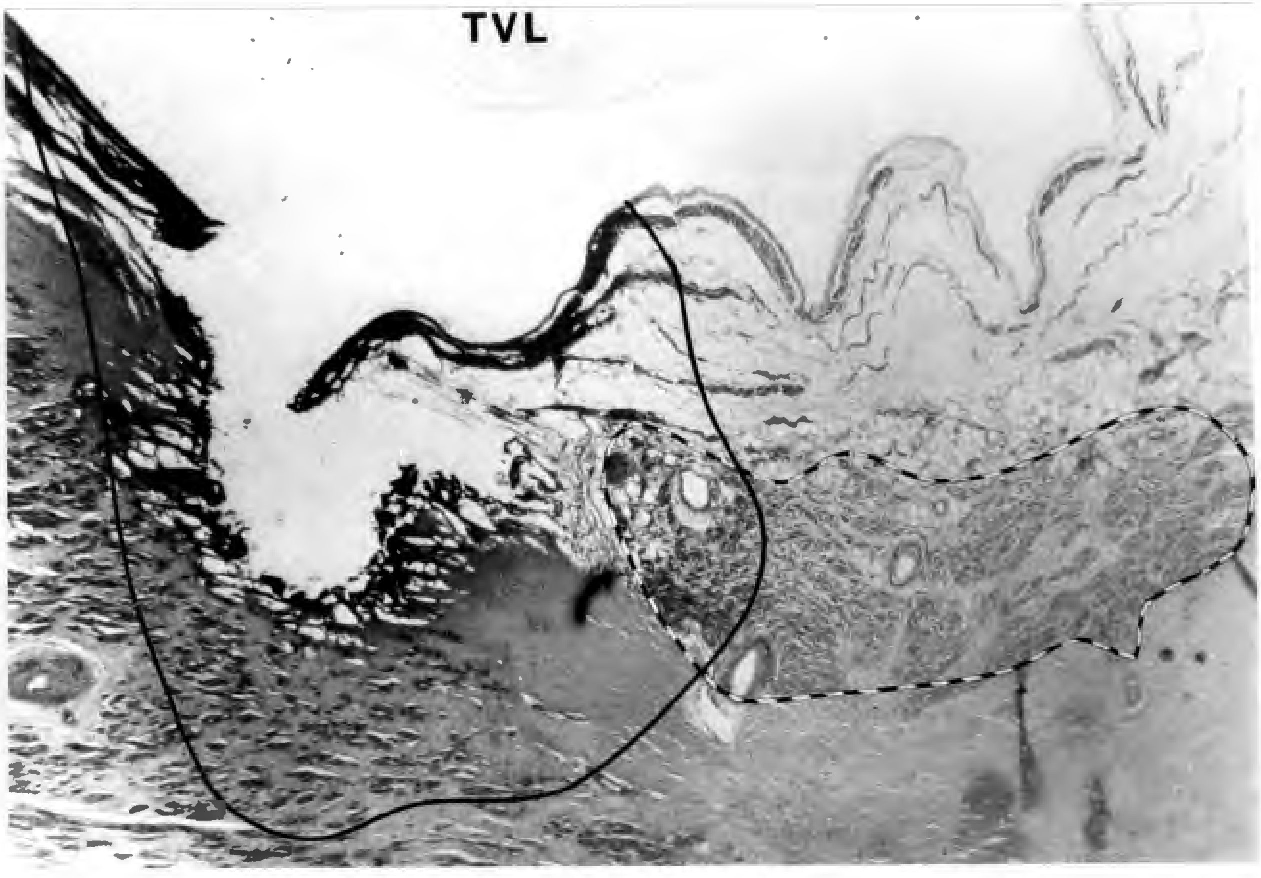
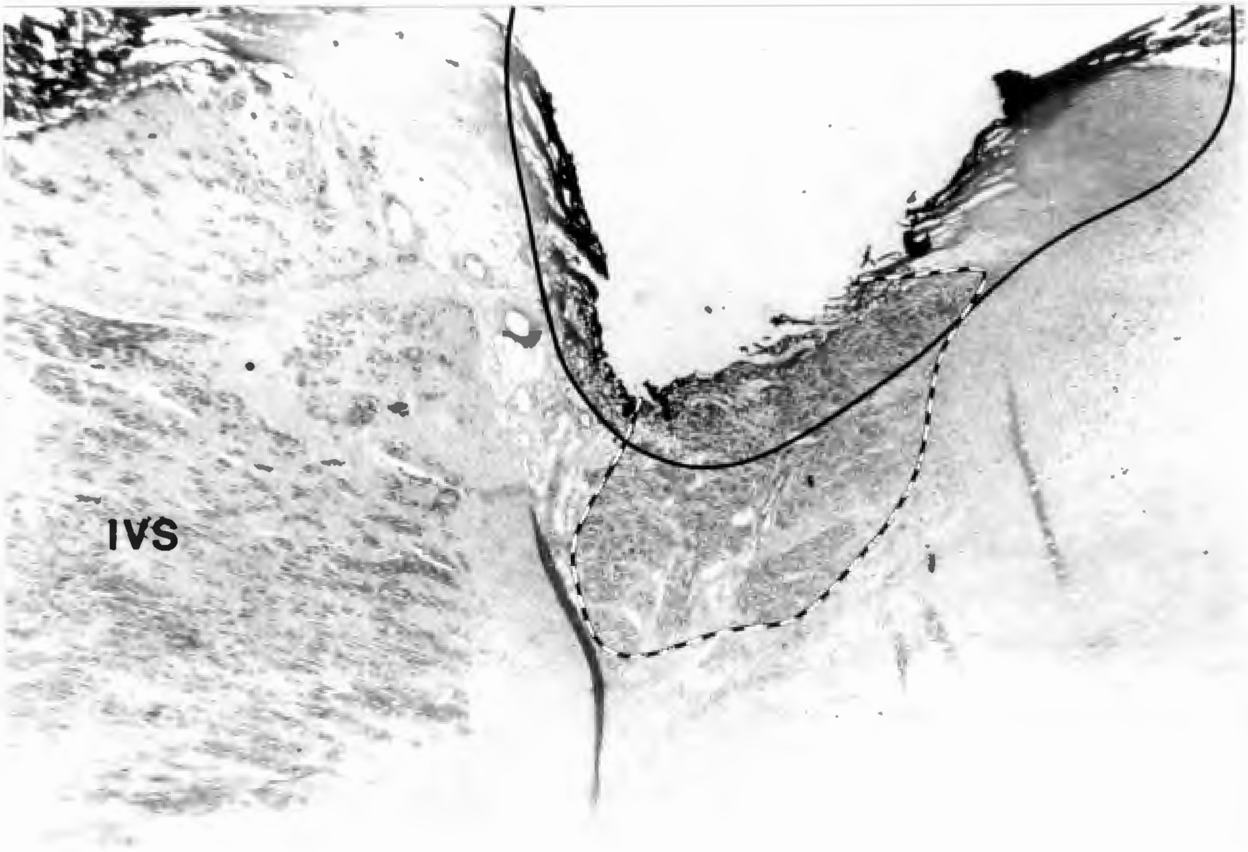


Figure 5.3 (b) 10 second crater (10 Watts) to the correct depth is not directly above the bundle of His. The thermal coagulation zone how ever extends to encompass a portion of the bundle.



Figures 5.3 (c) 10 second application (10 Watts) partially vaporises bundle of His with additional thermal coagulation beyond the crater limits.

(b) Electrophysiological studies

In three patients undergoing electrophysiological studies (a woman aged 26 with supraventricular tachycardias, and a woman of 56 and a man of 63 undergoing standard direct current His bundle ablation) the modified probe assembly was easily manoeuvred into standard electrophysiological positions despite being slightly less flexible than 5F and 6F USCI bipolar electrodes (Fig. 5.4). The unipolar electrograms closely matched those of the conventional electrodes although the laser probe was more susceptible to alternating current interference (Figs. 5.5 a and b).

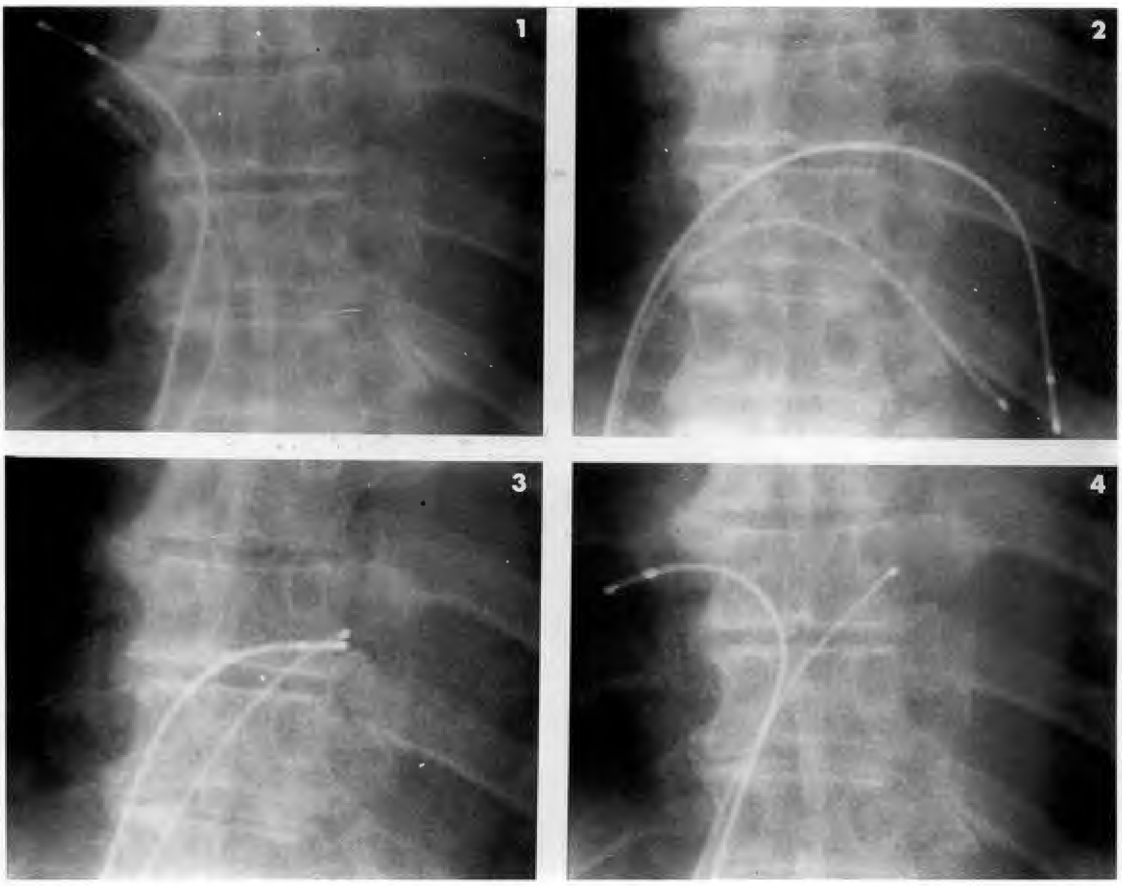
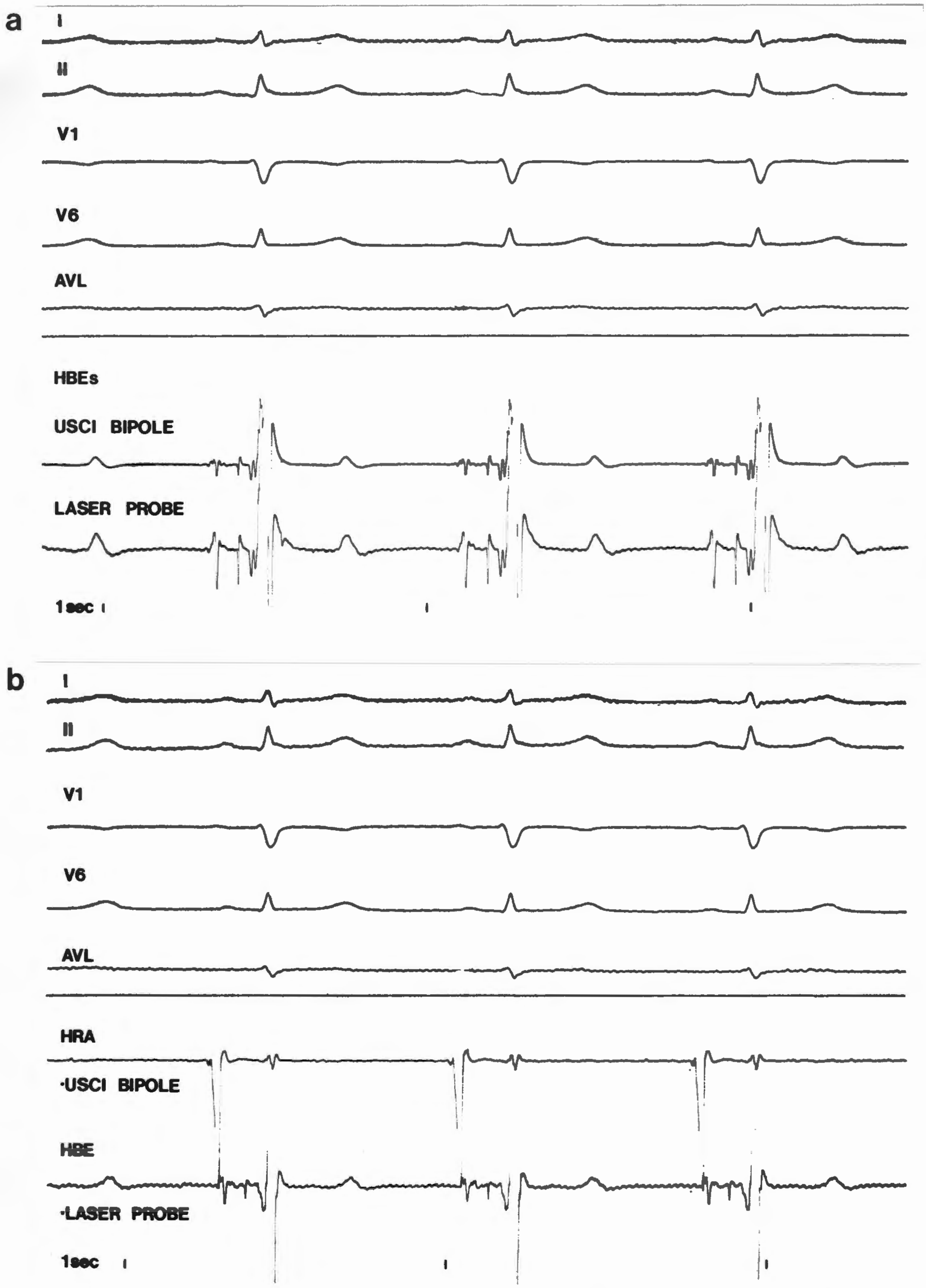


Figure 5.4: Modified laser probe and 6F bipolar electrode catheter in 1) right atrium, 2) right ventricle, 3) His bundle position, 4) Laser probe in His position and bipolar catheter in high right atrium.



Figures 5.5 Surface and intracardiac electrograms accompanying: a) Fig 5.4 panel 3 and b) Fig. 5.4 panel 4.

(c) Percutaneous His bundle ablation

A 60 year old woman (JS) with the sick sinus syndrome experienced numerous disabling attacks of paroxysmal atrial fibrillation. Treatment with digoxin, propranolol, disopyramide, quinidine and amiodarone singly or in combination had been ineffective or caused side effects (photosensitivity on an adequate amiodarone dosage). The frequency of palpitations had been increasing over 9 years to the point where she began to experience two to three attacks per day lasting from a few minutes to hours and disturbing her by the rapid erratic palpitations. During tachyarrhythmias she had occasional dizziness but no true syncope. Repeated 24 hour Holter monitoring had revealed numerous episodes of atrial flutter and fibrillation with rates of up to 150-170 beats per minute as well as bradycardic episodes with rates as low as 35 beats per minute in sinus rhythm. Despite the bradycardic episodes symptoms were always clearly attributable to her rapid palpitations. She was admitted for His bundle ablation and agreed to participate in a study of the efficacy of the laser thermal probe for this purpose.

<u>Laser His Bundle Ablation</u>: Using local anaesthesia a 5F bipolar temporary pacing lead was passed from the right femoral vein to the right ventricular apex. A 2.0 mm peripheral artery laser probe with its torque wire sheathed in a 5F Cournand catheter was then advanced via a 9F haemostatic sheath in the right femoral vein to the His bundle position. Adequate unipolar His bundle electrograms were recorded via the thermal probe but it was immediately apparent that the probe tip was only "resting" against the AV septum. Laser thermal energy from the Nd-YAG generator at 12 Watts for 10 seconds was delivered without any

apparent effect. During energy delivery however the intracardiac signal displayed marked interference (Fig. 5.6). The laser probe was then withdrawn, char cleaned off the tip and the Cournand insulation sheath replaced with a 5F "head hunter" catheter. At the same time the collar of the laser probe was angulated - both the latter manoeuvres aimed at enhancing tissue contact. The probe was re-advanced and after obtaining a good signal albeit again without firm tissue contact 12 Watts for 15 seconds was delivered without affecting conduction. After decharring the probe the final energy delivery sequence at 12 Watts for 30 seconds was delivered but once again without any effect. At no time did the patient experience discomfort during the delivery of energy.

Withdrawal of the probe through the introducer sheath on this occasion proved to be complicated. It became apparent that more torque wire than optical fibre had been withdrawn but it was difficult to advance the torque wire at this point and withdrawing the optical fibre resulted in it fracturing at the point of attachment of the safety wire. It was then only possible to remove the torque wire, tip and residual optical fibre still attached to the tip, by simultaneously removing the introducer sheath and dissecting down from the puncture site to the vein entrance point. Review of the cine-frames revealed that wide separation (and hence disparate advancement) of the radiolucent optical fibre and the torque wire had occurred during manipulation (Fig 5.7).

A 6F bipolar electrode catheter was then advanced through the right femoral vein into the His bundle position and after the induction of general anaesthesia a single 300 Joule shock produced complete heart block. Just prior to pacemaker implantation the following day she suddenly resumed sinus rhythm and a further conventional His bundle ablation shock produced complete heart block albeit only for 24 hour again. She remained in first degree AV block and subsequently a ventricular demand pacemaker set at a back-up rate of 50 beats per minute and low dose amiodarone (100 mg daily) were able to maintain her free from symptomatic tachycardias without precipitating undue bradycardias or drug side effects.

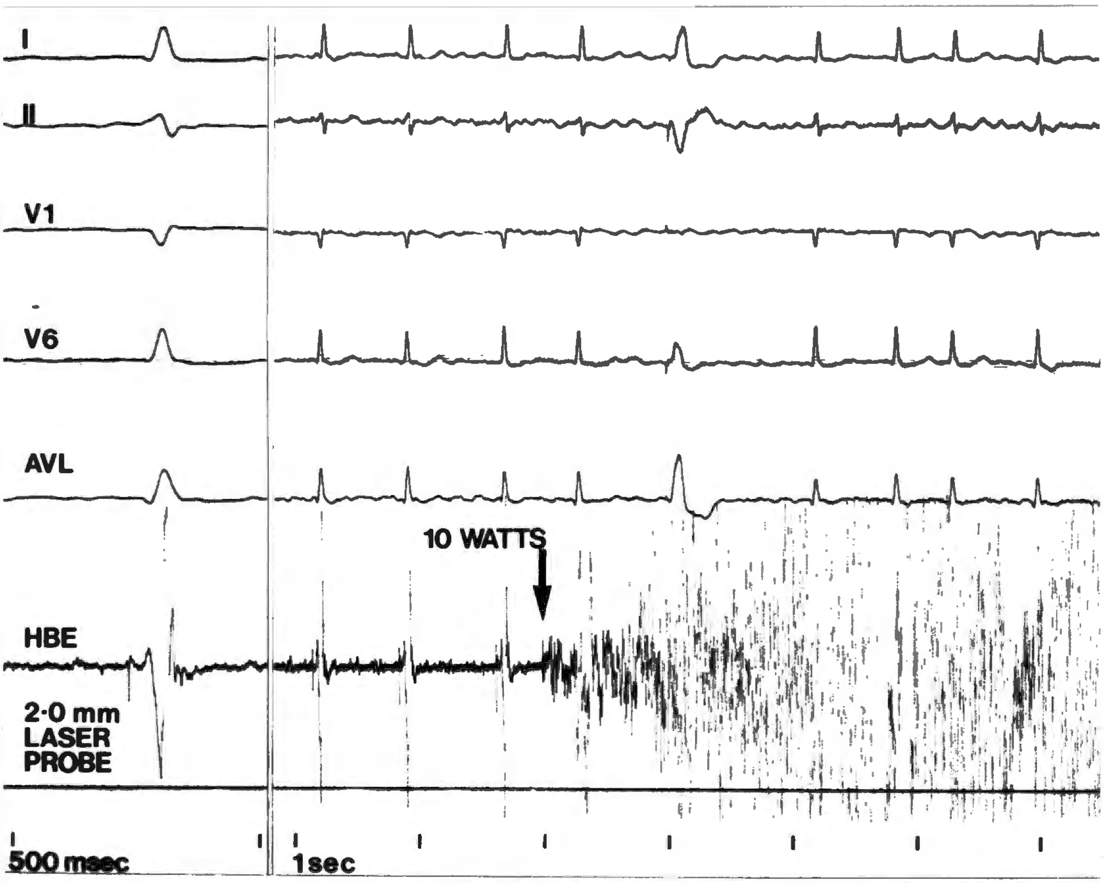


Figure 5.6: Surface and intracardiac signals (laser probe) during attempted laser thermal ablation of the bundle of His.

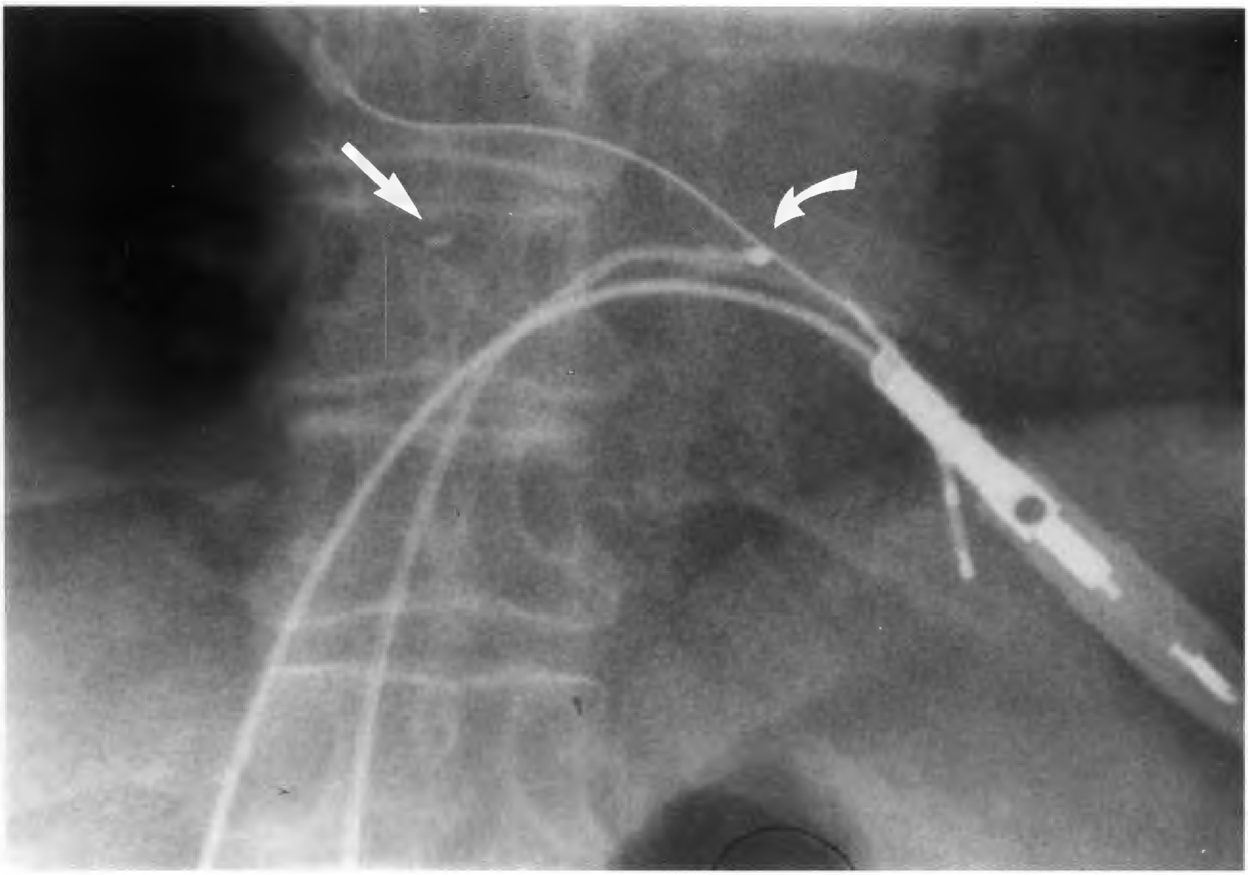


Figure 5.7: Cine-frame during intracardiac manipulation reveals wide separation of the catheter containing the support wire and the optical fibre. The curved white arrow indicates the point of attachment of the safety wire to the optical fibre. The straight arrow points to the probe tip in the His bundle position. (A surface electrode partially obscures the temporary pacing lead)

5.4 DISCUSSION

Narula and colleagues first used argon laser energy to ablate portions of the AV node in dogs and were able to produce discrete areas of tissue damage which led to modification of AV nodal conduction. They used a bare 200 um fibre housed in a 7F angiographic catheter which was positioned in close proximity to a bipolar 5F electrode catheter placed in the His bundle position. Argon energy of 2.5 Watts for 90 seconds (225 Joules) produced complete heart block in one out of three dogs whilst in the remaining two perforation with tamponade occurred (71). Macroscopic analysis revealed a 3 x 4 mm area of damage in the His bundle area with a zone of haemorrhage on the left heart surface. In a subsequent series using lower energies (0.7-1.4 Watts for 10 - 90 seconds) 1st to 3rd degree AV block was obtained and persisted in 6 dogs to follow-up at four weeks (72). Subsequent studies by Weber using Nd-YAG energy (264) and Curtis et al using argon energy (265) have also been successful at causing heart block in canine preparations.

Accurate location of the bundle of His before the delivery of ablative energy is essential and must apply to direct current and all other energy sources. It is only by so doing that the minimum effective energy can be decreased thereby preventing the deleterious effects of excessive or poorly directed energy. In clinical practise the size of the His bundle spike and the relative sizes of the atrial and ventricular signals are used to indicate the proximity of the recording electrode to the His Bundle. Positioning radiolucent bare optical fibres near to a reference electrode would be imprecise even with biplane radiographic imaging. Even if the fibre was close to the electrode the angle of incidence of the fibre tip with the target could not be predicted with any degree of certainty and this might account for the tamponade seen in the earlier study (71).

Weber used a bare fibre housed in a catheter with a distal ring electrode to enhance localisation and no perforations occurred as long as the fibre tip was kept in the catheter (264). If, however, the recorded electrogram is not from the very tip of the electrode, but from its side, then the fibre will still not be aligned with the target. The current technique for recording the His bundle electrogram in humans is by withdrawal of an electrode from the right ventricle so that the leading edge is unlikely to be adjacent to the His bundle. To overcome this problem Curtis inserted the ring electrode catheter with its fibre via an atriotomy (265). This enabled the fibre to be aligned perpendicularly to the bundle of His and only microscopic (haemodynamically insignificant) perforations were seen in the AV septum. In 5 of 6 dogs complete heart block was achieved with 3-15 applications of energies of 30 - 90 Joules. In using this technique these energy parameters do not necessarily apply to percutaneous delivery of energy. Weber has further modified his approach by including retractible prongs on the distal ring electrode to grip the endocardium at the electrophysiologically directed target (266). As yet this has only been used for ablation of ventricular myocardium in a canine model. A number of centres are currently using lasers (argon, Nd-YAG and even excimer) for ablation of myocardial arrhythmogenic foci (267-270). These are performed under direct vision intra-operatively and rely on non-vaporative thermal injury to irreversibly destroy these foci. The precise application and absence of a blood medium do not allow these energy parameters to be extrapolated to percutaneous energy delivery.

In using the radio-opaque metal tipped laser probe both energy delivery and localisation are obtained with the same device so that accurate delivery of energy does not rely on positioning the energy delivery system adjacent to a separate bundle of His locating system. Furthermore the laser energy is confined to the probe tip so that remote cardiac perforations should be avoided while at the energies used damage in the His bundle area would be limited. The cadaver study served as a preliminary feasibility approach to the in vivo application of laser thermal probe His bundle ablation. While the study was performed in saline which limits probe tip temperatures to around 100 ^{o}C (Chapter 2), in flowing blood at rates of 1 litre/minute similar temperatures are observed (191), so that thermal damage effects should be comparable. Perforation tract diameters were not measured in an intact pressurised heart and might therefore be greater in vivo while lesions showing transmural charring only might have been converted to perforations under pressure. Even so septal and tricuspid perforations are unlikely to be of clinical importance if the probe was marginally misdirected in vivo, though this cannot be said for the free wall lesions. The depth of damage is also related to the force applied (102): this was not quantified this but pressure "similar" to that used in positioning intravascular electrodes was used. Precise application of the probe tip was possible in vitro but without modification to the delivery system application of the side of the tip rather than the leading edge might occur resulting in a wider but more shallow area of damage and only "modification" of AV nodal conduction.

The in vitro studies had seemed to suggest a promising technique for accurate delivery of discreet amounts of energy at the His bundle but the extension to the in vivo situation proved to be disappointing. While there was no difficulty in recording a good His bundle signal this clearly did not equate with precise enough application of the tip. It was also clear that the energy parameters might be underestimates for in vivo application and thus a higher power was used for longer periods. This adaptation of the peripheral artery laser probe is therefore clearly not suitable and a dedicated probe with a shape designed to maximise pressure at the His bundle is required. In addition to obviate any potential "bow stringing" of the separate optical fibre and torque wire it would be necessary for them both to be incorporated in a single catheter.

Narula et al have recently developed a similar system using a metal tipped catheter which is "preshaped" to locate the Bundle of His. The same metal tip is then heated using electrothermal energy but has only been used to partially modify AV nodal conduction according to a preliminary communication (271). Although marginally more effective than the laser thermal probe in the patient studied here, it would appear to suffer from the same limitations. Thus accurate "location" of the bundle of His does not necessarily imply sufficient contact and it is this factor which is the greatest hurdle to safe and effective low energy His bundle ablation whatever the energy source.

Conclusions: His bundle ablation using the metal tipped laser thermal probe was possible in cadaver hearts and energy delivery produced localised lesions. The probe itself was capable of being used to locate the bundle of His by obtaining good quality unipolar electrograms. Obtaining an adequate His bundle electrogram however, does not imply adequate contact of the electrode with the endocardium overlying the bundle of His. Quite clearly this is the limiting factor in all forms of percutaneous His bundle ablation and argues for innovative measures to enhance delivery of energy much more closely to the His bundle.

CONCLUSIONS

The work in this thesis confirms the "hot tip" laser thermal probe to be clinically useful in peripheral angioplasty where it enables balloon dilatation of lesions previously impassable to a guide wire and balloon system. The channel produced by the laser thermal probe (and indeed by other devices such as the sapphire tip, lensed argon and pulsed lasers) are in themselves inadequate at present. Extension of these techniques to patients with lesions amenable to primary balloon dilatation is currently not justifiable, in the absence of evidence that their use can reduce the recurrence rate compared to balloon angioplasty alone. Prospective randomised treatment trials are now urgently required in this area to evaluate the importance of "debulking" atheroma. Radiofrequency heated probes may also prove to be as effective as the laser heated probes with the advantages of lower cost, easier portability and (user) safety. Other more sophisticated laser systems and non-laser interventional devices are still being investigated but have not achieved the clinical status of the laser probe in peripheral vascular disease.

In the small number of patients with coronary artery disease treated here the laser thermal probe was not found to be very effective. While others have since had better results using slightly different equipment even these are only as much as would be expected with current coronary balloon angioplasty techniques. For total occlusions the use of very narrow diameter probe tips may allow safe "pilot hole" recanalisation to facilitate subsequent balloon dilatation. This would in many ways resemble the (successful) approach in peripheral arteries and in this form the technique may yet retain a limited role, though its future is otherwise in doubt. Even the use of a thermal feedback control system would appear to be unlikely to be able to limit excessive vessel damage. Alternative laser technologies (including the pulsed excimer and lensed argon systems) are likely to surpass it though they have still to confirm their early promise. Progress in the non-laser based technologies has come to rival the current laser systems though the likely ultimate interventional technique is unknown. A multifibre (for adequate lumen diameter), pulsed (to avoid excess thermal damage), spectroscopically and/or ultrasonically guided laser system would appear to be the most taxing technically. If shown to be practical this device might still be able to achieve the goal of total laser revascularisation that appeared so promising at the beginning of the 1980s.

For His bundle ablation the major limitation was inability to deliver laser thermal energy precisely to the His bundle despite recording an adequate unipolar His bundle electrogram from the tip. This is relevant to all percutaneous techniques whatever the energy source: an adequate His electrogram does not guarantee proximity of the electrode to the endocardial surface. Refinements in the percutaneous approach to enhance the delivery of the energy source to the endocardium over the His bundle are needed to allow the use of the minimum effective energy. Only by so doing will higher success rates with lower side effects be possible.

REFERENCES

1. Gordon JP, Zeiger HJ, Townes CH.
The Maser; New Type of amplifer, frequency standard and spectrometer.
Phys Rev 1955; 99: 1264-1274.

2. Schawlow AL, Townes CH.
Infrared and optical masers.
Phys Rev 1958; 112: 1940-1949.

3. Maiman TH.
Stimulated optical radiation in ruby.
Nature 1960; 187: 493-494.

4. Einstein A.
Zur Quantentheorie der Strahlung.
Physiol Z 1917; 18: 121.

5. Zaret MM, Breinin GM, Schmidt H, Ripps H, Siegel IM, Solon LR.
Optical lesions produced by an optical maser (laser).
Science 1961; 134: 1525-1526.

6. Zaret MM, Ripps H, Siegel IM, Breinin GM.
Laser photocoagulation of the eye.
Arch Ophthalmol 1963; 69: 97-104.

7. Kapany NS, Peppers NA, Zweng HC, Flocks M.
Retinal photocoagulation by laser.
Nature 1963; 199: 146-149.

8. Flocks M, Zweng HC.
Laser coagulation of ocular tissues.
Arch Opthalmol 1964; 72; 604-611.

9. Bridges WB.
Laser oscillation in singly ionised argon in the visible spectrum.
Appl Phys Lett 1964; 4: 128-130.

10. Zweng HC, Little HL, Peabody RR.
Argon laser photocoagulation of diabetic retinopathy.
Arch Opthalmol 1971; 86: 345-400.

11. Goldman L, Wilson R.
Treatment of basal cell epithelioma by laser radiation.
JAMA 1964; 189: 773-775.

12. Goldman L, Blaney DJ, Kindel DJ, Richfield DF, Franke EK.
Pathology of the effect of laser beam on the skin.
Nature 1963; 197: 912-914.

13. Goldman L, Ingelman JM, Richfield DF.
Impact of the laser on nevi and Melanomas.
Arch Derm 1964; 90: 71-75.

14. McGuff PE, Bushnell D, Deterling RA Jr.
Studies of the surgical applications of laser (Light Amplification by Stimulated Emission of Radiation).
Surg Forum 1963; 14: 143-145.

15. McGuff PE, Deterling RA Jr, Gottlieb LS, Fahimi HD, Bushnell D.
Surgical applications of laser.
Ann Surg 1964; 160: 765-777.

16. Goldman L, Wilson R, Hornby P, Mayer R.
Laser radiation of malignancy in man.
Cancer 1965; 18: 533-545.

17. McGuff PE, Deterling RA Jr, Gottlieb LS, Fahimi HD, Bushnell D, Roeber F.
Laser surgery of malignant tumours.
Dis Chest 1965; 48: 130-139.

18. Goldman L, Rockwell RJ.
Laser action at the cellular level.
JAMA 1966; 198: 641-643.

19. Minton JP, Moody CD, Dearman JR, McKnight WB, Ketcham AS.
An evaluation of the physical response of malignant tumour implants to pulsed laser radiation.
Surg Gynaecol Obstet 1965; 121: 538-544.

20. Ketcham AS, Hoye RC, Riggle GC.
A Surgeon's appraisal of the laser.
Surg Clin North Am 1967; 47: 1249-1263.

21. Patel CKN.
CW high-power N2-CO2 laser.
Appl Phys Lett 1965; 7: 15-17.

22. Stahle J, & Hogberg L.
Laser and labyrinth: Some preliminary experiments on pigeons.
Acta Otolaryng 1965; 60: 367.

23. Strong MS, Jako GJ.
Laser surgery in the larynx. Early clinical experience with continuous CO2 laser.
Ann Otol Rhinol Laryngol 1972; 81: 791-798.

24. Mullins F, Jennings B, McClusky L.
Liver resection with the continuous wave carbon dioxide laser: Some experimental observations.
Amer Surgeon 1968; 34: 717-722.

25. Levine N, Ger G, Stellar S, Levenson SM.
Use of a carbon dioxide laser for the debridement of third degree burns.
Ann Surg 1974; 179: 246-252.

26. Kaplan I, Goldman J, Ger G.
The treatment of erosions of the uterine cervix by means of the CO2 laser.
Am J Obstet and Gynec 1973; 41: 795-796.

27. Asher PW: The use of the CO2 laser in neurosurgery. In:
Kaplan I ed. Laser Surgery II
Jerusalem: Jerusalem Academic Press, 1978: 76-78.

28. Geusic JE, Marcos HM and Van Uitert LG.
Laser oscillations in Nd-doped yttrium aluminium, yttrium gallium and yttrium gadolinium garnets.
Appl Phys Lett 1964; 4: 182-184.

29. Nath G, Gorisch W, Kiefhaber P.
First laser endoscopy via a fibreoptic transmission system .
Endoscopy 1973; 5: 208-213.

30. Dwyer RM, Yellin AE, Craig J, Cherlow J, Bass M.
Gastric hemostasis by laser phototherapy in man.
JAMA 1976; 236: 1383-1384.

31. Kiefhaber P, Nath G, Moritz K.
Endoscopical control of massive gastrointestinal hemorrhage by irradiation with a high-power Neodymium-YAG laser.
Prog Surg 1977; 15: 140-155.

32. Soffer BH and McFarland BB.
Continuously tuneable, narrow band organic dye lasers.
Appl Phys Lett 1967; 10: 266-267.

33. Greenwald J, Rosen S, Anderson RR, Harrist T, MacFarland F, Noe J, Parrish JA.
Comparative histological studies of the tuneable dye (at 577mm) laser and argon laser: the specific vascular effects of the dye laser.
J Invest Dermatol 1981; 77: 305-310.

34. Bass MS, Cleary CV, Perkins ES, Wheeler CB.
Single treatment laser iridotomy.
Br J Opthalmol 1979; 63: 29-30.

35. Searles SK and Hart GA.
Stimulated emission at 281.8 nm from XeBr.
Appl Phys Lett 1975; 27: 243-245.

36. Trokel SL, Srinivasan R and Braren B.
Excimer laser surgery of the cornea.
Am J Ophthalmol 1983; 96: 710-715.

37. Yahr WZ, Strully KJ, Hurwitt EJ.
Non-occlusive small arterial anastomosis with Neodymium laser.
Surgical Forum 1964; 15: 224-226.

38. Jain KK, Gorisch W.
Repair of small blood vessels with Neodymium YAG laser:
A preliminary report.
Surgery 1979; 85: 684-685.

39. Jain KK.
Sutureless extra-intracranial anastomosis by laser (letter).
Lancet 1984; 2: 816.

40. Arapov AD, Vishnerskii AA Jr, Abdullaev FZ, Korchagin VA,
Mirtskhulava KA, Sorgin ME.
A preliminary report on laser application in cardiosurgery.
Eksp Khir Anesteziol 1974; 4: 10-12.

41. Sen PK, Udwadia TE, Kinare SG, Parulkar GB.
Transmyocardial Acupuncture.
J Thorac Cardiovasc Surg 1965; 50: 181-189.

42. Mirhoseini M.
Surgical techniques and modalities for myocardial
revascularisation.
In: Second Henry Ford Hospital International Symposium on
Cardiac Surgery. ed Julio C Davila.
New York: Appleton-Century-Crofts, 1977 595-597.

43. Mirhoseini M, Fisher JC, Cayton M.
Myocardial revascularization by laser: A clinical report.
Lasers Surg Med 1983; 3: 241-245.

44. Hardy RI, Bove KE, James FW, Daplan S, Goldman L.
A histologic study of laser-induced transmyocardial channels.
Lasers Surg Med 1987; 6: 563-573.

45. Macruz R, Martins JRM, Tupinnamba HS, Lopes EA, Varbas H,
Penna AF, Carvalho VB, Armelin E, Decourt LV.
Possibilidades terapeuticas do raio laser em ateromas.
Arq Bras Cardiol 1980; 34: 9-12.

46. Choy DSJ.
Fibreoptic laser tunnelling device; the laser catheter, in:
Beijing/Shanghai Proceedings of an Internal Conference on
Lasers. New York : Wiley - Interscience, 1980: 685-690.

47. Choy DS, Stertzer SH, Rotterdam HZ, Bruno MS.
Laser coronary angioplasty: experience with 9 cadaver hearts.
Am J Cardiol 1982; 50: 1209-1211.

48. Choy DS, Stertzer S, Rotterdam HZ, Sharrock N, Kaminow IP.
Transluminal laser catheter angioplasty.
Am J Cardiol 1982; 50: 1206-1208.

49. Lee G, Ikeda RM, Kozina J, Mason DT.
Laser dissolution of coronary atherosclerotic obstruction.
AM Heart J 1981; 102: 1074-1075.

50. Lee G, Ikeda R, Stobbe D, Ogata C, Theis J, Lui H, Mendizabal RC, Reis RL, Mason DT.
Vaporization of human thrombus by laser treatment.
Am Heart J 1983; 106: 403-404.

51. Abela GS, Normann S, Cohen D, Feldman RL, Geiser, EA, Conti CR.
Effects of carbon dioxide, Nd-YAG, and argon laser radiation on coronary atheromatous plaques.
Am J Cardiol 1982; 50: 1199-1205.

52. Lee G, Ikeda R, Herman I, Dwyer RM, Bass M, Hussein H, Kozina J, Mason DT.
The qualitative effects of laser irradiation on human arterio sclerotic disease.
Am Heart J 1983; 105: 885-889.

53. Lee G, Ikeda RM, Stobbe D, Ogata C, Chan MC, Seckinger DL, Vazquez A, Theis J, Reis RL, Mason DT.
Effects of laser irradiation on human thrombus: demonstration of a linear dissolution-dose relation between clot length and energy density.
Am J Cardiol 1983; 52: 876-877.

54. Theis JH, Lee G, Ikeda RM, Stobbe D, Ogata C, Lui H, Mason DT.
Effects of laser irradiation on human erythrocytes: considerations concerning clinical laser angioplasty.
Clin Cardiol 1983; 6: 396-398.

55. Geschwind HJ, Boussignac G, Teisseire B, Laurent D, Benhaiem N, Gaston A, Becquemin JP.
Laser angioplasty: Effects on coronary artery stenosis (letter)
Lancet 1983; ii: 113-114.

56. Lee G, Ikeda RM, Dwyer RM, Hussein H, Dietrich P, Mason DT.
Feasibility of intravascular laser irradiation for in vivo visualization and therapy of cardiocirculatory diseases.
Am Heart J 1982; 103: 1076-1077.

57. Gerrity RG, Loop FD, Golding LAR, Erhart LA, Argenyl ZB.
Arterial response to laser operation for removal of atherosclerotic plaques.
J Thorac Cardiovasc Surg 1983; 85: 409-421.

58. Ward H.
Laser recannalization of atheromatous vessels using fiber optics.
Lasers Surg Med 1984; 4: 353-363.

59. Van Stiegmann G, Kahn D, Rose AG, Bornman PC, Terblanche J.
Endoscopic laser endarterectomy.
Surg Gynecol Obstet 1984; 158: 529-534.

60. Lee G, Ikeda RM, Theis JH, Chan MC, Stobbe D, Ogata C, Kumagai A, Mason DT.
Acute and chronic complications of laser angioplasty: vascular wall damage and formation of aneurysms in the atherosclerotic rabbit.
Am J Cardiol 1984; 53: 290-293.

61. Abela GS, Crea F, Seeger JM, Franzini D, Fenech A, Normann SJ, Feldman RL, Pepine CJ, Conti CR.
The healing process in normal canine arteries and in atherosclerotic monkey arteries after transluminal laser irradiation.
Am J Cardiol 1985; 56: 983-988.

62. Crea F, Fenech A, Smith W, Conti CR, Abela GS.
Laser recanalization of acutely thrombosed coronary arteries in live dogs: early results.
J Am Coll Cardiol 1985; 6: 1052-1056.

63. Abela GS, Normann SJ, Cohen DM, Franzini D, Feldman RL, Crea F, Fenech A, Pepine CJ, Conti CR.
Laser recanalization of occluded atherosclerotic arteries in vivo and in vitro.
Circulation 1985; 71: 403-411.

64. Ginsburg R, Kim DS, Guthaner D, Toth J, Mitchell RS.
Salvage of an ischemic limb by laser angioplasty: description of a new technique.
Clin Cardiol 1984; 7: 54-58.

65. Choy DS, Stertzer SH, Myler RK, Marco J, Fournial G.
Human coronary laser recanalization.
Clin Cardiol 1984; 7: 377-381.

66. Geschwind HJ, Boussignac G, Teisseire B, Benhaiem N, Bittoun R, Laurent D.
Conditions for effective Nd-YAG laser angioplasty.
Br Heart J 1984; 52: 484-489.

67. Ginsburg R, Wexler L, Mitchell RS, Proffit D.
Percutaneous transluminal laser angioplasty for treatment of peripheral vascular disease. Clinical experience with 16 patients.
Radiology 1985; 156: 619-624.

68. Lee G, Ikeda RM, Theis J, Stobbe D, Ogata C, Lui H, Reis RL, Mason DT.
Effects of laser irradiation delivered by flexible fiberoptic system on the left ventricular internal myocardium.
Am Heart J 1983; 106: 587-590.

69. Vincent GM, Knowlton K and Dixon JA.
Haemodynamic effects of neodymium: YAG laser injury of the myocardium.
Lasers Surg Med 1984; 3: 360-367.

70. Isner JM, Michlewitz H, Clarke RH, Estes NA 3d, Donaldson RF, Salem DN, Bahn I, Payne DD, Cleveland RJ.
Laser photoablation of pathological endocardium: in vitro findings suggesting a new approach to the surgical treatment of refractory arrhythmias and restrictive cardiomyopathy.
Ann Thorac Surg 1985; 39: 201-206.

71. Narula OS, Bharati S, Chan MC, Embi AA, Lev M.
Microtranssection of the His Bundle with laser radiation through a pervenous catheter: Correlation of histologic and electrophysiological data.
Am J Cardiol 1984; 54: 186-192.

72. Narula OS, Boveja BK, Cohen DM, Narula JT, Tatjan PP.
Laser catheter-induced atrioventricular nodal delays and atrioventricular block in dogs: Acute and chronic observations.
J Am Coll Cardiol 1985; 5: 259-267.

73. Bommer WJ, Lee G, Riemenschneider TA, Ikeda RM, Rebeck K, Stobbe D, Ogata C, Theis JH, Reis RL, Mason DT.
Laser atrial septostomy.
Am Heart J 1983; 106: 1152-1156.

74. Riemenschneider TA, Lee G, Ikeda RM, Bommer WJ, Stobbe D, Ogata C, Rebeck K, Reis RL, Mason DT.
Laser irradiation of congenital heart disease: potential for palliation and correction of intracardiac and intravascular defects.
Am Heart J 1983; 106: 1389-1393.

75. Zeevi B, Gal D, Abramovici A, Berant M, Blieden LC, Katzir A.
Carbon dioxide fiberoptic laser for treatment of coarctation of the aorta.
Am Heart J 1987; 113: 1518-1519.

76. Isner JM, Clarke RH, Pandian NG, Donaldson RF, Salem DN, Konstam MA, Payne DD, Cleveland RJ.
Laser myoplasty for hypertrophic cardiomyopathy. In vitro experience in human postmortem hearts and in vivo experience in a canine model (transarterial) and human patient (intraoperative).
Am J Cardiol 1984; 53: 1620-1625.

77. Lee G, Embi A, Stobbe D, Chan MC, Bommer W, Riemenschneider TA, Mendizabal R, Seckinger DL, Ikeda RM, Vazquez A, Reis RL, Mason DT.
Effects of laser irradiation on cardiac valves: transcatheter in vivo vaporization of aortic valve.
Am Heart J 1984; 107: 394-395.

78. Isner JM, Michlewitz H, Clarke RH, Donaldson RF, Konstam MA, Salem DN.
Laser-assisted debridement of aortic valve calcium.
Am Heart J 1985; 109: 448-452.

79. Fuller TA.
The physics of surgical lasers.
Lasers Surg Med 1980; 1: 5-14.

80. Polanyi TG.
The physics and basic instrumentation of surgery with lasers.
in: New Frontiers in Laser .Medicine and Surgery
Atsumi K (Ed) 1983: 49-58.

81. Bourgelaise DBC, Itzkan I.
The physics of lasers.
Cutaneous Laser Therapy, Arndt KA, Noe JM, Rosen S (eds), John Wiley, New York. 1983: 13-25.

82. Halldorsson TH, Langerholc J.
Thermodynamic analysis of laser irradiation of biological tissue.
Appl Optics 1978; 17: 3948-3958.

83. Halldorsson TL, Rother W, Langerholc J, Frank F.
Theoretical and experimental investigations prove Nd YAG laser treatment to be safe.
Lasers Surg Med 1981; 1: 253-262.

84. Garmire E, Chiao RY, Townes CH.
Dynamics and characteristics of the self-trapping of intense light beams.
Physical Rev Letters 1966; 16: 347-349.

85. Svaasand LO, Boerslid T, Oeveraasen M.
Thermal and optical properties of living tissue: application to laser-induced hyperthermia.
Lasers Surg Med 1985; 5: 589-602.

86. Gorisch W, Boergen KP.
Heat-induced contraction of blood vessels.
Lasers Surg Med 1982; 2: 1-13.

87. Grant L, Becker FF.
Mechanism of inflammation. Laser-induced thrombosis, histochemical considerations.
Arch Path 1966; 81: 36-41.

88. Wiedeman MP.
Vascular reactions to laser in vivo.
Microvasc Res 1974; 8: 132-138.

89. Sigel B, Dunn MR.
The mechanisms of blood vessel closure by high frequency electrocoagulation.
Surg Gyn and Obst 1965; 121: 823-831.

90. Welch AJ, Valvano JW, Pearce JA, Hayes LM, Motamedi M.
Effect of laser radiation on tissue during laser angioplasty.
Lasers Surg Med 1985; 5: 251-264.

91. Welch AJ.
The thermal response of laser-irradiated tissue.
IEEE J Quantum Electron 1984; QE 20: 1471-1481.

92. Priebe LA, Cain CP, Welch AJ.
Temperature rise required for production of minimal lesions in the Macaca Mulatta retina.
Am J Ophthalmol 1975; 79: 405-413.

93. Marchesini R, Andreola S, Emanuelli H, Melloni E, Schiroli A, Spinelli P, Fava G.
Temperature rise in biological tissue during Nd:YAG laser irradiation.
Lasers Surg Med 1985; 5: 75-82.

94. Mihashi S, Jako GJ, Incze J, Strong MS, Vaughan CW.
Laser surgery in otolaryngology: interaction of CO2 laser and soft tissue.
Ann New York Acad Sci 1976; 267: 263-295.

95. Stern LS, Abramson AL, Grimes GW.
Qualitative and morphometric evaluation of vocal cord lesions produced by the carbon dioxide laser.
Laryngoscope 1980; 90: 792-808.

96. Eldar M, Battler A, Gal D, Rath S, Rotstein Z, Neufeld HN, Akselrod S, Katzir A, Gaton E, Wolman M.
The effects of varying lengths and powers of CO2 laser pulses transmitted through an optical fiber on atherosclerotic plaques.
Clin Cardiol 1986; 9: 89-91.

97. Ben-Shachar G, Sivakoff MC, Bernard SL, Dahms BB, Riemenschneider TA.
Acute continuous argon-laser induced tissue effects in isolated canine heart.
Am Heart J 1985; 110: 65-70.

98. Wollenek G, Laufer G, Fasol R, Zilla P, Wolner E.
Laser-induced vascular lesions by cw-NdYAG or pulsed UV lasers during angioplastic procedures.
Thorac Cardiovasc Surgeon 1986; 34: 63-65.

99. Eugene J, McColgan SJ, Pollock ME, Hammer-Wilson M, Moore-Jeffries EW, Berns MW.
Experimental arteriosclerosis treated by argon ion and neodymium-YAG laser endarterectomy.
Circulation 1985; 72 (Pt 2): 200-206.

100. Lee BI, Rodriquez ER, Notargiocomo A, Ferrans VJ, Chen Y, Fletcher RD.
Thermal effects of laser and electrical discharge on cardiovascular tissues: implications for coronary artery recanalization and endocardial ablation.
J Am Coll Cardiol 1986; 8: 193-200.

101. Abela GS, Seeger JM, Barbieri E, Franzini D, Fenech A, Pepine CJ, Conti CR.
Laser angioplasty with angioscopic guidance in humans.
J Am Coll Cardiol 1986; 8: 184-192.

102. Welch AJ, Bradley AB, Torres JH, Motamedi M, Ghidoni JJ, Pearce JA, Hussein H, O'Rourke RA.
Laser probe ablation of normal and atherosclerotic human aorta in vitro: a first thermographic and histologic analysis.
Circulation 1987; 76: 1353-1363.

103. Isner JM, Clarke RH, Donaldson RF, Aharon A.
Identification of photoproducts liberated by in vitro argon laser irradiation of atherosclerotic plaque, calcified cardiac valves and myocardium.
Am J Cardiol 1985; 55: 1192-1196.

104. Case RB, Choy DS, Dwyer EM, Silvernail PJ.
Absence of distal emboli during in vivo laser recanalization.
Lasers Surg Med 1985; 5: 281-289.

105. Choy DS, Stertzer S, Loubeau JM, Kesseler H, Quilici P, Rotterdam H, Meltzer L.
Embolization and vessel wall perforation in argon laser recanalization.
Lasers Surg Med 1985; 5: 297-308.

106. Geschwind HJ, Teisseire B, Boussignac G, Vieilledent C.
Laser angioplasty of arterial stenoses.
Cardiovasc Intervent Radiol 1986; 9: 313-317.

107. Yoon G, Welch AJ, Motamedi M, van Gemert MJC.
Development and application of three-dimensional light distribution model for laser irradiated tissue.
IEEE J Quant Electron 1987; QE-23: 1721-1732.

108. Eldar M, Battler A, Neufeld HN, Gaton E, Arieli R, Akselrod S, Levite A, Katzir A.
Transluminal carbon dioxide-laser catheter angioplasty for dissolution of atherosclerotic plaques.
J Am Coll Cardiol 1984; 3: 135-137.

109. Livesay JJ.
Intraoperative laser coronary angioplasty.
Thorac Cardiovasc Surg 1988; 36 Suppl 2: 150-154.

110. Fenech A, Abela GS, Crea F, Smith W, Feldman R, Conti CR.
A comparative study of laser beam characteristics in blood and saline media.
Am J Cardiol 1985; 55: 1389-1392.

111. Cross FW, Mills TN, Bown SG.
Pulsed Nd-YAG laser effects on normal and atheromatous aorta in vitro.
Lasers Life Sci 1987; 1: 193-211.

112. Marco J, Silvernail PJ, Fournial G, Choy DS, Fajadet J, Case RB.
Complete patency in thrombus-occluded arteries two weeks after laser recanalization.
Lasers Surg Med 1985; 5: 291-296.

113. Abela GS, Staples ED, Conti CR, Pepine CJ, Faro RS, Knauf DG, Alexander JA, Hay DA, Roberts AJ.
Immediate and long-term effects of laser radiation on the arterial wall: light and electron microscopic observation.
Surg Forum 1983; 34: 454-456.

114. Douville EC, Kempczinski RF, Doerger PT, van der Bel Kahn J, Sankar MY, Joffe SN.
Effects of Nd:YAG laser energy on the arterial wall: evaluation of a new contact delivery system.
J Surg Res 1987; 42: 185-191.

115. Sanborn TA, Haudenschild CC, Garber GR, Ryan TJ, Faxon DP
Angiographic and histologic consequences of laser thermal angioplasty: comparison with balloon angioplasty.
Circulation 1987; 75: 1281-1286.

116. Geschwind H, Fabre M, Chaitman BR, Lefebvre-Villerdebo M, Ladouche A, Boussignac G, Blair JD, Kennedy HL.
Histopathology after Nd-YAG laser percutaneous transluminal angioplasty of peripheral arteries.
J Am Coll Cardiol 1986; 8: 1089-1095.

117. Deckelbaum LI, Isner JM, Donaldson RF, Clarke RH, Laliberte S, Aharon AS, Bernstein JS.
Reduction of laser-induced pathologic tissue injury using pulsed energy delivery.
Am J Cardiol 1985; 56: 662-667.

118. Isner JM, Donaldson RF, Deckelbaum LI, Clarke RH, Laliberte SM, Ucci AA, Salem DN, Konstam MA.
The excimer laser: gross, light microscopic and ultrastructural analysis of potential advantages for use in laser therapy of cardiovascular disease.
J Am Coll Cardiol 1985; 6: 1102-1109.

119. Grundfest WS, Litvack F, Forrester JS, Goldenberg T, Swan HJ, Morgenstern L, Fishbein M, McDermid IS, Rider DM, Pacala TJ, Laudenslager JB.
Laser ablation of human atherosclerotic plaque without adjacent tissue injury.
J Am Coll Cardiol 1985; 5: 929-933.

120. Linsker R, Srinivasan R, Wynne JJ, Alonso DR.
Far-ultraviolet laser ablation of atherosclerotic lesions.
Lasers Surg Med 1984; 4: 201-206.

121. Lane RJ, Wynn JJ, Geronemus RG.
Ultraviolet laser ablation of skin: healing studies and a thermal model.
Lasers Surg Med 1987; 6: 504-513.

122. Deckelbaum LI, Isner JM, Donaldson RF, Laliberte SM, Clarke RH, Salem DN.
Use of pulsed energy delivery to minimize tissue injury resulting from carbon dioxide laser irradiation of cardiovascular tissues.
J Am Coll Cardiol 1986; 7: 898-908.

123. Anderson RR, Parrish JA.
Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation.
Science 1983; 220: 524-527.

124. Clarke RH, Isner JM, Donaldson RF, Jones G-2d.
Gas chromatographic-light microscopic correlative analysis of excimer laser photoablation of cardiovascular tissues: evidence for a thermal mechanism.
Circ Res 1987; 60: 429-437.

125. Boulnois JL.
Photophysical processes in recent medical laser developments: a review.
Lasers Med Sci 1986; 1: 47-68.

126. Singleton DL, Paraskevopoulos G, Taylor RS, Higginson LAJ.
Excimer laser angioplasty: tissue ablation, arterial response, and fiber optic delivery.
IEEE J Quant Electron 1987; QE-23: 1772-1782.

127. Litvack F, Grundfest WS, Goldenberg T, Laudenslager J, Pacala T, Segalowitz J, Forrester JS.
Pulsed laser angioplasty: wavelength power and energy dependencies relevant to clinical application.
Lasers Surg Med 1988; 8(1): 60-65.

128. Isner JM, DeJesus SR, Clarke RH, Gal D, Rongione AJ, Donaldson RF.
Mechanism of laser ablation in an absorbing fluid field.
Lasers Surg Med 1988; 8: 543-554.

129. Bell CE, Landt JA.
Laser-induced high pressure shock waves in water.
Appl Phys Lett 1967; 10: 46-51.

130. Isner JM, Gal D, Steg PG, DeJesus ST, Rongione AJ, Halaburka KR, Slovenkai GA, Clarke RH.
Percutaneous, in vivo excimer laser angioplasty: results in two experimental animal models.
Lasers Surg Med 1988; 8: 223-232.

131. Cross FW, Bowker TJ, Bown SG.
Arterial healing in the dog after intraluminal delivery of pulsed Nd-YAG laser energy.
Br J Surg 1987; 74: 430-435.

132. Prevosti LG, Leon MB, Smith PD, Dodd JT, Bonner RF, Robinowitz M, Clark RE, Virmani R.
Early and late healing responses of normal canine artery to excimer laser irradiation.
J Thorac Cardiovasc Surg 1988; 96: 150-156.

133. Isner JM: Spasm. In:
Isner JM, Clarke RH, eds. Cardiovascular Laser Therapy.
New York: Raven Press, 1989: 121-148.

134. Mohr FW, Jakubowski A, Grundfest W, Litvak F, Papiaonnu T, Forrester J.
Thermal Damage to Coronary Arteries: Excimer vs "Hot Tip" Lasing (abstract).
Circulation 1987; 76 (IV): 524.

135. Wollenek G, Laufer G.
Comparative study of different laser systems with special regard to angioplasty.
Thorac Cardiovasc Surg 1988; 36(Suppl 2): 126-132.

136. Crea F, Abela GS, Fenech A, Smith W, Pepine CJ, Conti CR.
Transluminal laser irradiation of coronary arteries in live dogs: an angiographic and morphologic study of acute effects.
Am J Cardiol 1986; 57: 171-174.

137. Bowker TJ, Fox KM, Cross FW, Poole-Wilson PA, Bown SG, Rickards AF.
Perforation thresholds and safety factors in in vivo coronary laser angioplasty.
Br Heart J 1988; 59: 429-437.

138. Cumberland DC, Tayler DI, Procter AE.
Laser-assisted percutaneous angioplasty: Initial clinical experience in peripheral arteries.
Clinical Radiology 1986; 37: 423-428.

139. Isner JM, Donaldson RF, Funnai JT, Deckelbaum LI, Panadian NG, Clarke RH, Konstam MA, Salem DN, Bernstein JS.
Factors contributing to perforations resulting from laser coronary angioplasty: observations in an intact human postmortem preparation of intraoperative laser coronary angioplasty.
Circulation 1985; 72 (suppl II): II 191-199.

140. Prince MR, LaMuraglia GM, Teng P, Deutsch TF, Anderson RR.
Preferential ablation of calcified arterial plaque with laser-induced plasmas.
IEEE J Quant Electron 1987; QE-23: 1783-1786.

141. Lawrence PF, Dries DJ, Moatamed F, Dixon J.
Acute effects of argon laser on human atherosclerotic plaque.
J Vasc Surg 1984; 1: 852-859.

142. Yater WM, Traum AH, Brown WG, Fitzgerald RP, Geisler MA, Wilcox BB.
Coronary artery disease in men eighteen to thirty-nine years of age: report of eight hundred sixty-six cases, four hundred fifty with necropsy examinations.
Am Heart J 1948; 36: 683-722.

143. Isner JM, Donaldson RF, Fortin AH, Tischler A, Clarke RH.
Attenuation of the media of coronary arteries in advanced atherosclerosis.
Am J Cardiol 1986; 58: 937-939.

144. Van Gemert MJC, Verdaasdonk R, Stassen EG, Schets GACM, Gijsbers GHM, Bonnier JJ.
Optical properties of human blood vessel wall and plaque.
Lasers Surg Med 1985; 5: 235-237.

145. Kaminov IP, Wiesenfield JM, Choy DSJ.
Argon laser disintegration of thrombus and atherosclerotic plaque.
Appl Optics 1984; 23: 1301-1302.

146. Selzer PM, Murphy-Chutorian D, Ginsburg R, Wexler L.
Optimizing strategies for laser angioplasty.
Invest Radiol 1985; 20: 860-866.

147. LaMuraglia GM, Murray S, Anderson RR, Prince MR.
Effect of pulse duration on selective ablation of atherosclerotic plaque by 480- to 490- Nanometer laser radiation.
Lasers Surg Med 1988; 8: 18-21.

148. Spears JR, Serur J, Shropshire D, Paulin S.
Fluorescence of experimental atheromatous plaques with haematoporphyrin derivative.
J Clin Invest 1983; 71: 395-399.

149. Murphy-Chutorian D, Kosek J, Mok W, Quay S, Huestis W, Mehigan J, Profitt D, Ginsburg R.
Selective absorption of ultraviolet laser energy by human atherosclerotic plaque treated with tetracycline.
Am J Cardiol 1985; 55: 1293-1297.

150. Prince MR, Deutsch TF, Mathews-Roth MM, Margolis R, Parrish JA, Oseroff AR.
Preferential light absorption in atheromas in vitro.
Implications for laser angioplasty.
J Clin Invest 1986; 78: 295-302.

151. Spears JR.
Percutaneous laser treatment of atherosclerosis: an overview of emerging techniques.
Cardiovasc Intervent Radiol 1986; 9: 303-312.

152. Litvack F, Grundfest WS, Forrester JS, Fishbein MC, Swan HJ, Corday E, Rider DM, McDermid IS, Pacala TJ, Laudenslager JB.
Effects of hematoporphyrin derivative and photodynamic therapy on atherosclerotic rabbits.
Am J Cardiol 1985; 5: 667-671.

153. Prince MR, LaMuraglia GM, MacNichol EF Jr.
Increased preferential absorption in human atherosclerotic plaque with oral beta carotene. Implications for laser endarterectomy.
Circulation 1988; 78: 338-344.

154. Anderson PS, Gustavon A, Stenram U, Svanberg K, Svanberg S.
Diagnosis of arterial atherosclerosis using laser-induced fluorescence.
Lasers Med Sci 1981; 2: 261-266.

155. Kittrell C, Willett RL, de los Santos-Pancheo C, Ratliff NB, Kramer JR, Mault EG, Feld MS.
Diagnosis of fibrous arterial atherosclerosis using fluorescence.
Appl Optics 1985; 24: 2280-2281.

156. Leon MB, Lu DY, Prevosti LG, Macy WWJr; Smith PD, Granovsky M, Bonner RF, Balaban RS.
Human arterial surface fluorescence: atherosclerotic plaque identification and effects of laser atheroma ablation.
J Am Coll Cardiol 1988; 12: 94-102.

157. Deckelbaum LI, Lam JK, Cabin HS, Clubb KS, Long MB.
Discrimination of normal and atherosclerotic aorta by laser-induced fluorescence.
Lasers Surg Med 1987; 7: 330-335.

158. Cutruzzola FW, Stetz ML, O'Brien KM, Gindi GR, Laifer LI, Garrand TJ, Deckelbaum LI.
Change in laser-induced arterial fluorescence during ablation of atherosclerotic plaque.
Lasers Surg Med 1989; 9: 109-116.

159. Prevosti LG, Wynne JJ, Becker CG, Linsker R, Shires GT.
Laser-induced fluorescence detection of atherosclerotic plaque with hematoporphyrin derivative used as an exogenous probe.
J Vasc Surg 1988; 7: 500-506.

160. Lee G, Ikeda RM, Stobbe D, Ogata C, Embi A, Chan MC, Reis RL, Mason DT.
Intraoperative use of dual fiberoptic catheter for simultaneous in vivo visualization and laser vaporization of peripheral atherosclerotic obstructive disease.
Cathet Cardiovasc Diagn 1984; 10: 11-16.

161. Yock PG, Linker DT, Thapliyal HV, Arenson JW, Samstad S, Seather-Angelsen BAJ.
Real-time two dimenstional catheter ultrasound: a new technique for high-resolution intravascular imaging (abstract).
J Am Coll Cardiol 1988; 11: 130A.

162. Anderson HV, Zaatari GS, Roubin GS, Leimgruber PP, Gruentzig AR.
Steerable fiberoptic catheter delivery of laser energy in atherosclerotic rabbits.
Am Heart J 1986; 111: 1065-1072.

163. Anderson HV, Zaatari GS, Roubin GS, Leimgruber PP, Gruentzig AR.
Coaxial laser energy delivery using a steerable catheter in canine coronary arteries.
Am Heart J 1987; 113: 37-48.

164. Geschwind H, Boussignac G, Teissiere B, Vielledent C, Gaston A, Becquemin JP, Mayiolini P.
Percutaneous Transluminal Laser Angioplasty in Man (letter).
Lancet 1984; i: 844.

165. Geschwind HJ, Teisseire B, Boussignac G, Vieilledent C.
Transluminal laser angioplasty in man.
Semin Intervent Radiol 1986; 3: 31-36.

166. Hussein H.
A novel fibreoptic laser probe for treatment of occlusive vessel disease.
Optical Laser Technol Med 1986; 1: 457-459.

167. Lee G, Ikeda RM, Chan MC, Dukich J, Lee MH, Theis JH, Brommer WJ, Reis RL, Hanna E, Mason DT.
Desolution of human atherosclerotic disease by fiber optic laser-heated cautery cap.
Am Heart J 1984; 107: 777-778.

168. Abela GS, Fenech A, Crea F, Conti CR.
"Hot tip": another method of laser vascular recanalization
Lasers Surg Med 1985; 5: 327-335.

169. Theis JH, Lee G, Chan MC, Ikeda RM, Lee MH, Rink JL, Steffey EP, Thomas WP, Mason DT.
Effects of simultaneous viewing and vaporization of plaques using the steerable, laser-heated metal cap in the atherosclerotic monkey model.
Lasers Surg Med 1987; 7(5): P 414-420.

170. Crea F, Davies GJ, McKenna WJ, Pashazadeh M, Allwork SP, Kidner P, Maseri A.
Transluminal laser treatment of coronary arteries in live dogs with metal-capped optical fibres: effect of blood flow on the degree of intimal thermoablation.
Lasers Med Sci 1987; 2: 159-163.

171. Sanborn TA, Faxon DP, Haudenschild C, Ryan TJ.
Experimental angioplasty: circumferential distribution of laser thermal energy with a laser probe.
J Am Coll Cardiol 1985; 5: 934-938.

172. Borst C.
Percutaneous recanalization of arteries: status and prospects of laser angioplasty with modified fibre tips.
Lasers Med Sci 1987; 2: 137-151.

173. Cumberland DC, Sanborn TA, Tayler DI, Moore DJ, Welsh CL, Greenfield AJ, Guben JK, Ryan TJ.
Percutaneous laser thermal angioplasty: initial clinical results with a laser probe in total peripheral artery occlusions.
Lancet 1986; i: 1457-1459.

174. Cumberland DC, Starkey IR, Oakely GDG, Fleming JS, Smith GH, Gioti JJ, Tayler DI, Davis J.
Percutaneous laser-assisted coronary angioplasty (letter).
Lancet 1986; ii: 214.

175. Sanborn TA, Faxon DP, Kellet MA, Ryan TJ.
Percutaneous coronary laser thermal angioplasty.
J Am Coll Cardiol 1986; 8: 1437-1440.

176. Verdaasdonk RM, Cross FW, Borst C.
Physical properties of sapphire fibre tips for laser angioplasty.
Lasers Med Sci 1987; 2: 183-188.

177. Geschwind HJ, Blair JD, Mongkolsmai D, Kern MJ, Stern J, Deligonul U, Kennedy HL.
Development and experimental application of contact probe catheter for laser angioplasty.
J Am Coll Cardiol 1987; 9: 101-107.

178. Bowker TJ, Cross FW, Bown SG, Rickards AF.
Reduction of vessel wall perforation by the use of sapphire tipped optical fibres in laser angioplasty (abstract).
Br Heart J 1987; 57: 88.

179. Fourrier JL, Brunetaud JM, Prat A, Marache P, Lablanche JM, Bertrand ME.
Percutaneous laser angioplasty with sapphire tip (letter)
Lancet 1987; i: 105.

180. Geschwind HJ, Kern MJ, Vandormael MG, Blair JD, Deligonul U, Kennedy HL.
Efficiency and safety of optically modified fiber tips for laser angioplasty.
J Am Coll Cardiol 1987; 10: 655-661.

181. White CJ, Ramee SR, Card H, Abrahams LA, Renu V, Wade CE, Aita GS, Geschwind HJ, Sobol SM.
Laser angioplasty in atherosclerotic swine: recanalization of occluded iliac arteries using a glass 'ball tip' fiber (abstract).
J Am Coll Cardiol 1987; 9: 189A.

182. Nordstrom LA, Castaneda-Zuniga WR, Lindeke CC, Rasmussen TM, Burnside DK.
Laser angioplasty: controlled delivery of argon laser energy.
Radiology 1988; 167: 463-465.

183. Cothren RM, Hayes GB, Dramer JR, Sacks B, Kittrell C, Feld MS.
A multifiber catheter with an optical shield for laser angiosurgery.
Lasers Life Sci 1986; 1: 1-12.

184. Kramer JR, Bott-Silverman C, Ratliff NB, Strikwerda S, Loop FD, Shearin A, Cothren RM, Kittrell C, Feld MS.
Removal of atherosclerotic plaque using multiple short exposures of argon ion laser light.
Am Heart J 1987; 113: 1038-1040.

185. Kjellstrom BT, Bylock AL, Bott-Silverman C, Engelmann GL, Gerrity RG, Kittrell C, Cothren RM, Hayes GB, Feld MS, Kramer JR.
Removal of surgically induced fibrous arterial plaques by argon ion laser angiosurgery using a multifiber delivery system. An experimental study in the dog.
J Thorac Cardiovasc Surg 1988; 96: 925-929.

186. Spears JR.
Percutaneous transluminal coronary angioplasty restenosis: potential prevention with laser balloon angioplasty.
Am J Cardiol 1987; 60: 61B-64B.

187. Jenkins RD, Sinclair IN, Anand R, Kalil-AG Jr, Schoen FJ, Spears JR.
Laser balloon angioplasty: effect of tissue temperature on weld strength of human postmortem intima-media separations.
Lasers Surg Med 1988; 8: 30-39.

188. Anand RK, Sinclair IN, Jenkins RD, Hiehle-JF Jr, James L, Spears JR.
Laser balloon angioplasty: effect of constant temperature versus constant power on tissue weld strength.
Lasers Surg Med 1988; 8: 40-44.

189. Jenkins RD, Sinclair IN, Anand RK, James LM, Spears JR.
Laser balloon angioplasty: effect of exposure duration on shear strength of welded layers of postmortem human aorta.
Lasers Surg Med 1988; 8: 392-396.

190. Crea F, Davies G, McKenna WJ, Pashazadeh M, Keogh B, Kidner P, Taylor KM, Maseri A.
Laser recanalisation of coronary arteries by metal-capped optical fibres: early clinical experience in patients with stable angina pectoris.
Br Heart J 1988; 59: 168-174.

191. Verdaasdonk RM, Borst C, Boulanger LHMA, van Gemert MJC.
Laser Angioplasty with a Metal Laser Probe ("hot tip"): Probe Temperature in Blood.
Lasers in Medical Science 1987; 2:153-158.

192. Labs JD, White RI Jr., Anderson JH, Williams GM.
Thermodynamic Correlates of Hot Tip Laser Angioplasty.
Invest Radiol 1987; 22: 954-959.

193. The Effect of Plaque Composition on Laser Recanaliation using a Thermal Probe (abstract).
Silverman SH, Haley RA, Abela GS, Seeger JM.
Circulation 1988; 78(4-II): 504.

194. Vincent MG, Johnson M, Fox J, Gary S, Hammond E, Strickland R.
Thermal Laser Contact Probe Angioplasty. Influence of Constant Tip Temperature (abstract).
Circulation 1988; 78(4-II): 504.

195. Silverman SH, Khoury AI, Abela GS, Seeger JM.
Effects of blood flow on laser probe temperature in human arteries.
Lasers Surg Med 1988; 8: 555-561.

196. Zeitler E, Richter EI, Seyferth W.
Femoro-popliteal arteries. In: Dotter CT, Gruentzig A, Schoop W,Zeitler E, eds. Percutaneous transluminal angioplasty. Technique, early and late results.
Berlin: Springer-Verlag, 1983: 105-114.

197. Martin EC, Fankuchen EI, Karlson KB, Dolgin C, Collins RH, Voorhees AB Jr, Casarella WR.
Angioplasty for femoral artery occlusion: comparison with surgery.
AJR 1981; 137: 915-919.

198. Gallino A, Mahler F, Probst P, Nachbur B.
Percutaneous transluminal angioplasty of the arteries of the lower limbs: a 5-year follow-up.
Circulation 1984; 70: 619-623.

199. Krepel VM, van Andel GJ, van Erp WFM, Breslau PJ.
Percutaneous transluminal angioplasty of the femoropopliteal artery : Initial and long term results.
Radiology 1985; 156:325-328.

200. Hewes RC, White RI Jr, Murray RR, Kaufman SL, Chang R, Kadir S, Kinnison ML, Mitchell SE, Auster M.
Long term results of superficial femoral artery angioplasty.
AJR 1986; 146: 1025-1029.

201. Murray RR Jr, Hewes RC, White RI Jr, Mitchell SE, Auster M, Chang R, Kadir S, Kinnison ML, Kaufman SL.
Long segment femoropopliteal stenosis: is angioplasty a boon or a bust.
Radiology 1987; 162: 473-476.

202. Wexler L.
Percutaneous transluminal angioplasty of peripheral vascular occlusions: A clinical perspective.
J Am Coll Cardiol 1989; 13: 1555-1557.

203. Sanborn TA, Cumberland DC, Welsh CL, Greenfield AJ, Guben JK.
Percutaneous laser thermal angioplasty: initial results and 1 year follow-up in 129 femoropopliteal lesions.
Radiology 1988, 168: 121-125.

204. Sanborn TA, Greenfield AJ, Guben JK, Menzoian JO, LoGerfo FW.
Human percutaneous and intraoperative laser thermal angioplasty: initial clinical results as an adjunct to balloon angioplasty.
J Vasc Surg 1987; 5: 83-90.

205. Fleisher HL, Thompson BW, McCowan TC, Ferris EJ, Feifsteck JE, Barnes RW.
Human percutaneous laser angioplasty. Patient selection criteria and early results.
Am J Surg 1987; 154: 666-669.

206. Lammer J, Karnel F.
Percutaneous transluminal laser angioplasty with contact probes.
Radiology 1988; 168: 733-737.

207. McCowan TC, Ferris EJ, Barnes RW, Baker ML.
Laser thermal angioplasty for the treatment of obstruction of the distal superficial femoral or popliteal arteries.
AJR 1988; 150: 1169-1173.

208. Wautrecht JC, Vandenbosch G, Delcour C, Van-Bunnen Y, Motte S, Bellens B, Dereume JP, Struyven J.
[Transluminal percutaneous angioplasty by thermal lasers. 20 cases of peripheral artery occlusion.]
J Mal Vasc 1988; 13: 351-355.

209. Seeger JM, Abela GS, Silverman SH, Jablonski SK.
Initial results of laser recanalization in lower extremity arterial reconstruction.
J Vasc Surg 1989; 9: 10-17.

210. Keogh B, Crea F, Davies G, Taylor K, Pashazadeh M, Foale R, Kidner P.
Angioscopy and intra-operative coronary laser angioplasty (letter).
Lancet 1987; ii: 969.

211. Tobis J, Smolin M, Mallery J, Macleay L, Johnston WD, Connolly JE, Lewis G, Zuch B, Henry W, Berns M.
Laser-assisted thermal angioplasty in human peripheral artery occlusions: Mechanism of Recanalization.
J Am Coll Cardiol 1989; 13: 1547-1554.

212. Dietich EB - Arizona Heart Institute, Phoenix.
Personal Communication, September 1988.

213. Gal D, Steg PG, Dejesus ST, Rongione AJ, Clarke RH, Isner JM.
Failure of angiography to diagnose thermal perforation complicating laser angioplasty in a rabbit.
Am J Cardiol 1987; 60: 751-752.

214. Cumberland DC, Belli AM, Myler RK, Stertzer SH, Crew JC.
Combined laser/thermal recanalization of peripheral artery occlusions.
J Am Coll Cardiol 1989; 13: 13A.

215. Diethrich EB, Bahadir I.
Results of 664 peripheral laser-assisted angioplasties (abstract).
Heart and Vessels 1988; 4: 52.

216. Levy JM, Hessel SJ, Horsley WW, Cook GC, Dickey JE.
Value of laser-assisted angioplasty in the community hospital.
Radiology 1989; 170: 1017-1018.

217. Grundfest W, Litvack F, Hickey A, Adler L, Foran R, Levin P, Segalowitz J, Hestrin L, Forrester J.
Radiofrequency thermal angioplasty for the treatment of peripheral vascular occlusive disease: Preliminary results of a clinical trial (abstract).
J Am Coll Cardiol 1989; 13: 14A.

218. Lee G, Marsden RR, Scharf D, Weiss JA, Falk RL, Temes GD, Pool GE, Coons H, Argenal AJ, Wixson D, Mason DT.
Percutaneous laser angioplasty of peripheral atherosclerotic obstructions by the unicorn-cap (Tm) probe system:
A multicenter study (abstract).
J Am Coll Cardiol 1989; 13: 14A.

219. Pilger E, Lammer J, Kleinert R, Ascher W, Bertuch H.
Laser angioplasty with a contact probe for the treatment of peripheral vascular disease.
Cardiovasc Res 1988; 22: 149-153.

220. Cross FW, Bowker TJ.
Percutaneous laser angioplasty with sapphire tips (letter).
Lancet 1987; i: 330.

221. Fourrier JL, Marache P, Brunetaud JM, Mordon S, Lablanche JM, Prat A, Gommeaux A, Bertrand ME.
[A new method of laser angioplasty by contact sapphire: preliminary results. Apropos of 20 cases].
Arch Mal Coeur 1988; 81: 253-258.

222. Nordstrom LA, Castaneda-Zuniga WR, Young EG, Von Seggern KB.
Direct argon laser exposure for recanalization of peripheral arteries: early results.
Radiology 1988; 168: 359-364.

223. Geschwind HJ, Dubois-Rande JL, Shafton E, Boussignac G, Wexman M.
Percutaneous pulsed laser-assisted balloon angioplasty guided by spectroscopy.
Am Heart J 1989; 117: 1147-1152.

224. Katzen BT, Schwarten DM, Kaplan JO, Cutcliff W.
Initial experience with an excimer laser in peripheral lesions.
Circulation 1988; 78 (Supp II): II-417.

225. Litvack F, Grundfest W, Adler L, Hickey A, Segalowitz J, Hestrin L, Goldenberg T, Laudenslager J, Forrester J.
Percutaneous excimer laser angioplastyin humans.
Circulation 1988; 78 (Supp II): II-295.

226. Hansen DD, Auth DC, Vracko R, Ritchie JL.
Mechanical thrombectomy: a comparison of two rotational devices and balloon angioplasty in subacute canine femoral thrombosis.
Am Heart J 1987; 114: 1223-1231.

227. Simpson JB, Selmon MR, Robertson GC, Cipriano IR, Hayden WG, Johnson DE, Fogarty TJ.
Transluminal atherectomy for occlusive peripheral vascular disease.
Am J Cardiol 1988; 61: 965-1016.

228. Stack RS, Califf RM, Phillips HR, Pryor DB, Quigley PJ, Bauman RP, Tcheng JE, Greenfield JC.
Interventional cardiac catheterization at Duke Medical Center.
Am J Cardiol 1988; 62 (Supp F): 18F-24F.

229. Vallbracht C, Liermann D, Prignitz I, Beinborn W, Landgraf H, Paasch C, Roth FJ, Kollath J, Schoop W, Bamberg W, Kaltenbach M
Results of low speed rotational angioplasty for chronic peripheral occlusions.
Am J Cardiol 1988; 62: 935-940.

230. Palmaz JC, Schatz RA, Richter G, Gardiner G, Becker G, Garcia O
Intraluminal stenting of iliac artery stenosis: Preliminary report multicenter trial.
Circulation 1988; 78 (Supp II): II-415.

231. Selmon M, Robertson G, Hinohara T, White N, Rowe M, Simpson J.
Factors associated with restenosis following successful peripheral atherectomy.
J Am Coll Cardiol 1989; 13: 13A.

232. Choy DS, Marco J, Fournial G, Stertzer S.
Argon laser recanalization of three totally occluded human right coronary arteries.
Clin Cardiol 1986; 9: 296-298.

233. Holmes DR, Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Greuntzig AR, Kelsey SF, Detre KM, van Raden MJ, Mock MB.
Restenosis after percutaneous transluminal coronary angioplasty (PTCA): A report from the PTCA registry of the National Heart, Lung and Blood Institute.
Am J Cardiol 1984; 53: 77C-81C.

234. Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS, King SB-3, Greuntzig AR.
Restenosis after successful coronary angioplasty in patients with single-vessel disease.
Circulation 1986; 73: 710-717.

235. Blackshear JL, O'Callaghan WG, Galiff RM.
Medical approaches to prevention of restenosis after coronary angioplasty.
J Am Coll Cardiol 1987; 9: 834-848.

236. Lee G, Sommerhaug RG, Argenal A, Chan MC, Rink D, Mason DT.
Clinical laser revascularisation of coronary obstruction with the coaxial-guided laser-heated metal cap catheter.
Am Heart J 1987; 114: 1524-1526.

237. Bowes RJ, Cumberland DC, Belli AM, Oakley GDG, Myler RK, Stertzer SH, Crew JC, Linnemeier TJ.
"Laser wire" for percutaneous angioplasty of complete peripheral and coronary arterial occlusions - initial clinical results. (abstract).
J Am Coll Cardiol 1989; 13: 60A.

238. Hussein H - Trimedyne, Santa Ana, Calif.
Personal communication January 1988.

239. Sanborn TA, Bonan R, Cumberland DC, Faxon DP, Leachman DR, Linnemeier TJ, Myler RK.
Percutaneous coronary laser-assisted, ballon angioplasty with flexible, central lumen laser probe catheters (abstract).
Circulation 1988; 78(II): II-295.

240. Linnemeier TJ, Bonan R, Cumberland DC, Faxon DP, Leachman DR, Myler RK, Sanborn TA.
Human percutaneous laser-assisted coronary angioplasty of saphenous vein bypass grafts: Early mulicenter experience (abstract).
Circulation 1988; 78(II): II-295.

241. Linnemeier TJ, Cumberland DC.
Percutaneous Laser Coronary Angioplasty without Balloon Angioplasty (letter).
Lancet 1989; i: 154-155.

242. Hoher M, Hombach V, Hopp HW, Eggeling T, Kochs M.
Percutaneous coronary "hot-tip" angioplasty in man using a radiofrequency catheter (abstract).
Circulation 1988; 78 (Supp II): II-296.

243. Spears JR, Reyes VP, James LM, Sinofsky EL.
Laser balloon angioplasty: Initial clinical percutaneous coronary results (abstract).
Circulation 1988; 78 (Supp II): II-296.

244. Spears JR, Reyes V, Sinclair IN, Hopkins B, Schwartz L, Aldridge H, Plokker HWT.
Percutaneous coronary laser balloon angioplasty: Preliminary results of a multicenter trial.
J Am Coll Cardiol 1989; 13: 61A.

245. Lee BI, Becker GJ, Waller BF, Barry KJ, Connolly RJ, Kaplan J, Shapiro AR, Nardella PC.
Thermal compression and moulding of atherosclerotic vascular tissue with use of radiofrequency energy: Implications for radiofrequency balloon angioplasty.
J Am Coll Cardiol 1989; 13: 1167-1175.

246. Litvack F, Grundfest W, Hickey A, Jakubowski A, Mohr F, Segalowitz J, Hestrin L, Goldenberg T, Laudenslauger J, Narciso H, Forrester J.
Percutaneous coronary excimer laser angioplasty in animals and humans (abstract).
J Am Coll Cardiol 1989; 13: 61A.

247. Foschi A, Myers G, Crick WF, Friedberg HD, Snyder D, Nordstrom LA.
Laser angioplasty of totally occluded coronary arteries and vein grafts: preliminary report on a current trial.
Am J Cardiol 1989; 63 (Supp F): 9F-13F.

248. Pinkerton C, Simpson J, Selmon M, Robertson G, Hinohara T, Hollman J, Baim D.
Percutaneous coronary atherectomy: Early experiences of multicenter trial (abstract).
J Am Coll Cardiol 1989; 13: 108A.

249. Urban P, Sigwart U, Kaufmann U, Kappenberger L.
Restenosis within coronary stents: Possible effect of previous angioplasty (abstract).
J Am Coll Cardiol 1989; 13: 107A.

250. Siegel RJ, DonMichael TA, DeCastro E, Fishbein MC, Hashemi Z Adler L, Bookstein J, Forrester JS.
In vivo recanalization of total atherosclerotic arterial occlusions: Combined use of an Ultrasonic Probe and Balloon Angioplasty System (abstract).
J Am Coll Cardiol 1989; 13: 195A.

251. Scheinman MM, Morady F, Hess DS, Gonzales R.
Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias.
JAMA 1982; 248: 851-855.

252. Gallagher JJ, Svenson RH, Kasell SH, German LD, Bardy GH, Broughton A, Critelli G.
Catheter technique for closed-chest ablation of the atrioventricular conduction system. A therapeutic alternative for the treatment of refractory supraventricular tachycardia.
N Engl J Med 1982; 306: 194-200.

253. Morady F.
A Perspective on the Role of Catheter Ablation in the Management of Tachyarrhythmias.
PACE 1988; 11: 98-102.

254. Morady F, Scheinman MM.
Transvenous catheter ablation of a posteroseptal accessory pathway in a patient with the Wolff-Parkinson-White syndrome.
N Engl J Med 1984; 310: 705-707.

255. Fisher JD, Brodman R, Kim SG, Matos JA, Brodman E, Wallerson D, Waspe LE.
Attempted Nonsurgical Electrical ablation of Accessory Pathways via the Coronary Sinus in the Wolff-Parkinson-White syndrome.
J Am Coll Cardiol 1984; 4: 685-694.

256. Gillette PC, Wampler DG, Garson A Jr, Ziner A, Ott D, Codey D.
Treatment of Atrial Automatic Tachycardia by Ablation Procedures.
J Am Coll Cardiol 1985; 6: 405-409.

257. Morady F, Scheinman MM, diCarlo LA, Davis JC, Herre JM, Griffin JC, Winston SA, de Buitleir M, Hantler CB, Wahr JA, Kou WH, Nelson SD.
Catheter Ablation of Ventricular Tachycardia with Intracardiac Shocks: results in 33 patients.
Circulation 1987; 75: 1037-1049.

258. Davies DW, Nathan AW, Camm AJ.
Three Deaths After Attempted High Energy Catheter Ablation of Ventricular Tachycardia (abstract).
Br Heart Journal 1986; 55: 506-507.

259. Holt P, Boyd EGCA, Crick J, Sowton E
Low energies and Helifix electrodes in the successful ablation of atrioventricular conduction.
PACE 1985; 8: 639-645.

260. McComb J, McGovern B, Garan H, Ruskin JN.
Management of refractory supraventricular tachyarrhythmias using low energy transcatheter shocks.
Am J Cardiol 1986; 58: 959-963.

261. Saksena S, Tarjan PP, Bharati S, Boveja B, Cohen D, Joubert T, Lev M.
Low-energy transvenous ablation of the canine atrioventricular conduction system with a suction electrode catheter.
Circulation 1987; 2: 394-403.

262. Borggrefe M, Budde T, Podczeck A, Breithardt G.
High Frequency Alternating Current Ablation of an Accessory Pathway in Humans.
J Am Coll Cardiol 1987; 10: 576-582.

263. Bowman A, Fitzgerald D, Friday K, Luck KH, Naccarelli G, Lazzara R, Jackman W.
Catheter Ablation of Selected Segments of the AV Conduction System using Radiofrequency Current (abstract).
PACE 1988; 11: 489.

264. Weber H, Hessel S, Ruprecht L, Unsold E.
A new electrode quartz fibre catheter for electrically guided percutaneous Nd-YAG laser photocoagulation of the subendocardium (abstract).
PACE 1987; 10: 411.

265. Curtis AB, Abela GS, Griffin JC, Hill JA, Normann SJ
Transvascular argon laser ablation of atrioventricular conduction in dogs: Feasibility and morphological results.
PACE 1989; 12: 347-356.

266. Weber H, Enders S, Keiditisch E.
Percutaneous Nd: YAG laser coagulation of ventricular myocardium in dogs using a special electrode laser catheter.
PACE 1989; 12: 899-910.

267. Saksena S, Hussain SM, Gielchinsky I, Gadhoke A, Pantopoulos D
Intraoperative mapping-guided argon laser ablation of malignant ventricular tachycardia.
Am J Cardiol 1987; 59: 78-83.

268. Downar E, Butany J, Jares A, Stoicheff BP.
Endocardial photoablation by excimer laser.
J Am Coll Cardiol 1986; 7: 546-550.

269. Svenson RH, Gallagher JJ, Selle JG, Zimmern SH, Feldor JM Robicsek F.
Neodymium-YAG laser photocoagulation: a successful new map-guided technique for the intraoperative ablation of ventricular tachycardia.
Circulation 1987; 76: 1319-1328.

270. Isner JM, Estes NA, Payne DD, Rastegar H, Clarke RH, Cleveland RJ
Laser-assisted endocardiectomy for refractory ventricular tachyarrhythmias: preliminary intraoperative experience.
Clin Cardiol 1987; 10: 201-204

271. Narula OS, Salerno JA, Chimenti M, Finzi A, Pagnoni F.
Abolition of Supraventricular Tachycardia by an Electrothermal Catheter: Follow-up Observations (abstract).
PACE 1988; 11: 907.

PAPERS IN SUPPORT OF THESIS

Preliminary communications have been presented at the following society meetings or symposia:

Laser probe design - Features of the optimum probe for coronary angioplasty.
Rosenthal E, Montarello JK, Curry PVL.
British Cardiac Society, Belfast, March 1988.
British Heart Journal 1988; 59: 623-624.

Laser thermal probe ablation of the bundle of His.
Rosenthal E, Montarello JK, Fagg N, Curry PVL.
North American Society of Pacing and Electrophysiology,
Los Angeles, May 1988.
PACE 1988; 11: 522.

Lateral thermal effects of coronary laser probe angioplasty.
Rosenthal E, Montarello JK, Palmer T, Curry PVL.
Cardiostim 88 - 6th International Congress, Monaco, June 1988.
PACE 1988; 11(Supp II): 926.

Peak laser thermal probe temperature is flow dependent.
Rosenthal E, Montarello JK, Curry PVL.
6th British Medical Laser Association Meeting, London, July 1988.
Lasers in Medical Science 1988; 3(abstracts): 313.

From peripheral to coronary arteries: Experience with percutaneous laser thermal angioplasty.
Rosenthal E, Montarello JK, Reidy J, Curry PVL.
2nd International Symposium on Lasers in Cardiovascular Diseases,
Vienna, October 1888.
Heart and Vessels 1988; 4: 59.

His bundle ablation : Accurate localization and ablation using the laser thermal probe.
Rosenthal E, Montarello JK, Bucknall CA, Fagg N, Curry PVL.
2nd International Symposium on Lasers in Cardiovascular Diseases,
Vienna, October 1888.
Heart and Vessels 1988; 4: 59.

Percutaneous laser thermal angioplasty : Early experience in peripheral and coronary arteries.
Rosenthal E, Montarello JK, Reidy J, Yates AK, Curry PVL.
British Cardiac Society, Wembley, November 1988.
British Heart Journal 1989; 61: 99.

Publications:

Subintimal dissection and false tract formation during successful laser thermal probe ("Hot Tip") angioplasty.
Rosenthal E, Curry PVL, Reidy J.
J of Interventional Radiology 1989; 4: 1-4.

His bundle ablation with the laser thermal probe ("Hot Tip"):
A feasibility study.
Rosenthal E, Montarello JK, Bucknall CA, Fagg N, Curry PVL.
PACE 1989; 12: 812-822.

Thermal effects of stationary "Hot Tip" laser coronary probes -
An in vitro assessment.
Rosenthal E, Montarello JK, Palmer T, Curry PVL.
Lasers Med Surg 1989; 9: 229-236.

Coronary artery thermal damage during percutaneous "Hot Tip"
laser assisted angioplasty.
Rosenthal E, Montarello JK, Palmer T, Curry PVL.
Am J Cardiol 1989; 64: 116-120.