Landmarks Along the Application of Laser Energy for Cardiovascular Therapy

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Historical Background of Lasers

Laser is an acronym for “light amplification by stimulated emission of radiation”. The development of lasers is based on Neil Bohr’s theory of quantum mechanics and Albert Einstein’s theory of stimulated emission [1]. Bohr theorized that energy is released in quanta of electromechanical energy from excited atoms known as photons while Einstein theorized that when an excited atom is struck by a photon of a certain wave length and direction it would release a photon of the same specific wavelength and direction. In 1958 Townes and Schawlow in the United States and Prokhorov in the Soviet Union further developed this concept leading to the first laser device to be built by Theodore Maiman in 1960 [2, 3].

Lasers are uniquely suited in the medical field because of certain features that include a monochromatic light that can be absorbed selectively by tissues with distinctive color as well as a coherent light that deposits high energy that can ablate tissue with precision cutting. Not long after the first ruby laser was developed, Dr. Leon Goldman, a dermatologist at the University of Cincinnati started to treat skin lesions with intense color (i.e., hemangiomas) in his laboratory [4]. Soon to follow was application of laser in ophthalmology for treatment of diabetic retinopathy and in general surgery for non-contact cutting that avoids the spread of tumor cells [5]. All these applications of the laser were initially delivered by hand-held rigid devices using mirrors to direct the laser beam. However, industrial advances in fiber optics led to the ability of transmitting lasers via flexible fibers. Fibers could then be threaded into body orafices via catheters that carry the laser light to treat target lesions deep into body cavities.

Continuous Laser Wavelengths for Angioplasty Procedures

Several early brief reports demonstrating the effect of laser on atherosclerosis were published using a ruby laser by McGuff (1963) and then with an argon laser by Macruz (1980) [6, 7]. Meanwhile, in the cardiovascular field, balloon angioplasty procedures were becoming widely used for the treatment of arterial blockages in the heart and peripheral circulation. Thus, the time was right to evaluate the use of laser technology in more depth. In 1982 Abela presented an initial report at the American College of Cardiology demonstrating the effect of three laser wavelengths (CO2; 10,600 nm, argon; 488;514 nm and Nd-Yag; 1060 nm) on atherosclerotic plaques [8]. The advantage of the argon and Nd-Yag lasers wavelengths was these could be easily transmitted via optical fibers whereas the CO_2 required articulated mechanical arms with mirrors [9]. However, all three wavelengths produced very similar tissue effects characterized by a central zone of plaque vaporization, surrounded by a zone of thermal injury and an adjacent outer layer of diffuse tissue disruption [10] (Fig. 27.1). Importantly, using fiber optic delivery systems it was possible to perform lasing in a blood filled medium with the fiber in direct contact with the tissue [11] (Fig. 27.2).

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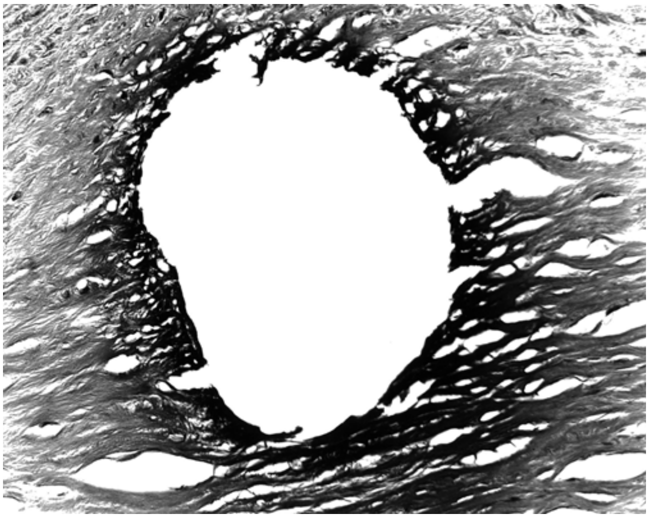

Fig. 27.1 Histology of laser effect on arterial plaque demonstrating a central zone of vaporization surrounded by a zone of thermal injury and a surrounding zone of diffuse tissue disruption (Abela et al. [10], with permission)

Fiber Optic Laser Delivery Systems

Reports on the effect of lasers in cardiovascular system began to emerge, including dissolving thrombus in cadaver hearts [12]. All these preliminary studies were conducted using continuous wavelength lasers. These lasers were adapted to optical fibers that had a small diameter (≤1 mm) but were flexible enough to pass through hollow catheters within the circulatory system to reach distant arterial targets under fluoroscopic guidance [13]. Meanwhile, modified fibers were also being produced. One such device had a metal ring at the tip to help with fluoroscopic visualization (Fig. 27.3). However, there were major limitations to these systems because they produced small arterial channels and caused frequent arterial perforations. Perforations were related to both the stiffness of the fiber optic tips as well as heat generated during laser delivery of continuous laser wavelengths. The focus then shifted to development of various approaches to improve optical fiber guidance and mechanical control.

Guiding Systems for Laser Angioplasty

In order to reduce arterial perforations, various guiding systems were developed and/or adapted.

Guide Wires

The initial system was to use a guide wire within the laser catheter in order to keep the fiber aligned with the vascular lumen. This was based on the work of John Simpson and that was then adapted by Anderson and Gruentzig to the laser catheter system [14, 15]. Consequently, irradiation from the tip would remain centered within the arterial lumen along the course of the guide wire [16].

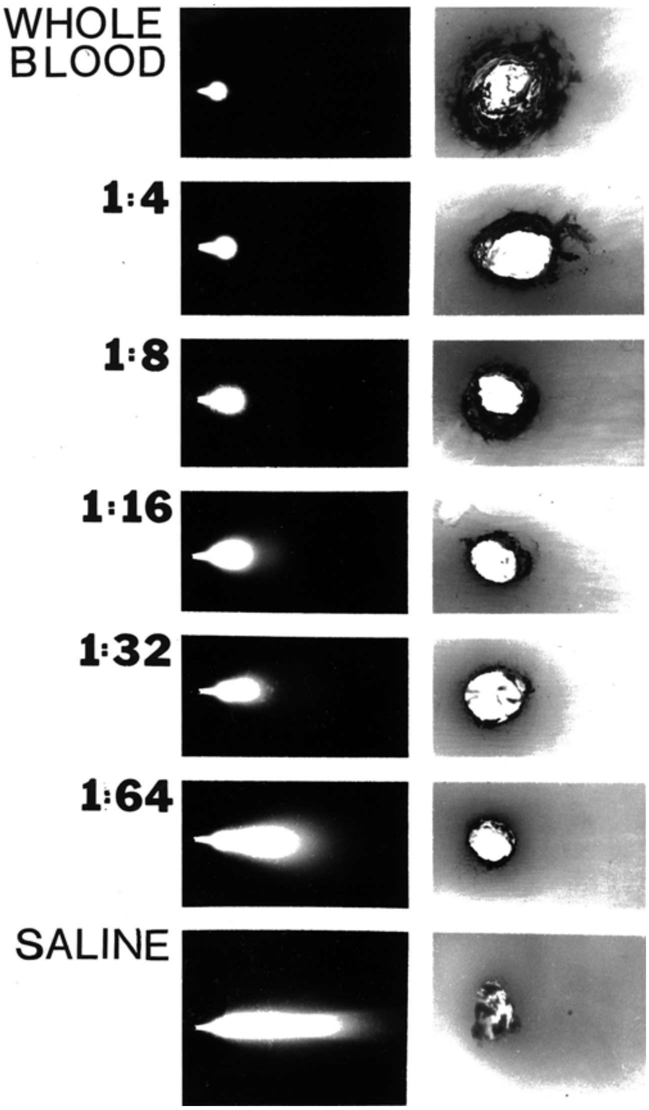

Fig. 27.2 *Left*, beam dispersion pattern in whole blood, saline solution and various blood-saline dilutions. The divergence angle increases from 15° in saline solution to 30° in 1:64. In whole blood the dispersion is spherical around the fiber tip. *Right*, larger craters are produced at increasing concentrations of blood, the largest being in whole blood. Charring at the lased site is also greater with increase concentrations of blood (Fenech et al. [11], with permission)

Angioscopy

Fiber bundles with lens tips were used to make angioscopic catheters that could be used to visualize the plaque and guide the fiber tips during irradiation of the plaque. However, these devices were often large, bulky and did not achieve the desired outcome of reduced perforation because they lacked catheter tip control. However, angioscopes advanced over

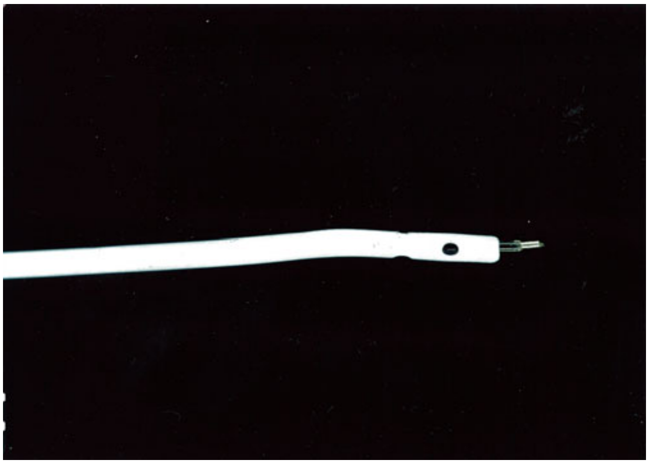

Fig. 27.3 Catheter with protruding optical fiber. The fiber has a metal ring placed at the tip to allow visualization with fluoroscopy (Courtesy of Abela GS)

guidewires evolved independently of lasers to be used for examining atherosclerotic plaques in vivo and identify unstable atherosclerotic plaques that may lead to acute cardiovascular events [17].

Fluorescence

Other systems were developed using tissue fluorescence as a feedback mechanism to help guide the laser procedure to localize plaque components while avoiding the native artery [18–21]. Those systems could also define the composition of the plaque by spectral signals to identify calcification, fibrous tissue and lipid content. Although this approach was able to distinguish plaques from the artery, it did not have an associated guidance system to address the limitations of the small channel size and arterial perforation with laser.

Ultrasound

Intravascular ultrasound (IVUS) was being developed at the same time when lasers were being evaluated for angioplasty. Although IVUS provided useful data on plaque morphology and composition, it did not resolve the perforation problem [22]. IVUS then evolved independently as a diagnostic tool for vascular procedures especially to identify arterial wall dissection and the severity of arterial stenosis.

Modified Fiberoptic Catheter Systems

‘Hot Tip’ Probe (Trimedyne, Inc, Lake Forest, CA)

In order to reduce the arterial perforation rate and also enlarge the arterial channel diameter in occluded arteries, the optical fiber tip was modified by adapting an olive-shaped metallic steel cap [23, 24]. The metal cap would then absorb laser energy to thermally vaporize the tissue [25, 26] (Fig. 27.4). However, this system required direct contact with the tissue. Moreover, it would also get very hot reaching temperatures above 100 °C which could then cause arterial perforations by thermal conduction to adjacent tissue. Those perforations were larger than the size of the optical fiber. To reduce perforations, a guide wire was adapted by inserting into the body of the metallic probe tip to help keep the fiber probe aligned with the arterial lumen (Figs. 27.5 and 27.6).

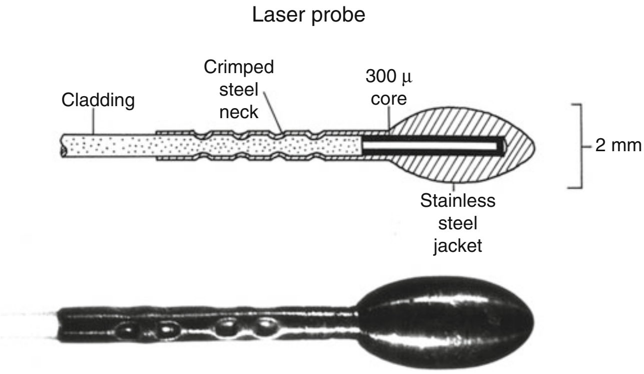

Fig. 27.4 Laser Thermal Probe with steel metal jacket enclosing the optical fiber tip. All the laser energy is absorbed by the fiber converting it into a ‘hot tip’ system that vaporized the atherosclerotic plaque tissue (Courtesy of Abela GS)

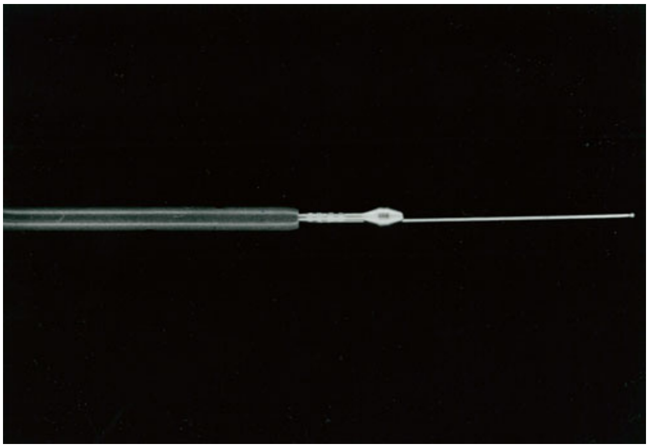

Fig. 27.5 Thermal probe with a 0.18” guide wire passing through an eccentric channel in the probe tip. The whole system is back loaded in a 7-F catheter to allow saline and contrast agent infusion (Courtesy of Abela GS)

Hybrid Probe (Trimedyne, Inc, Lake Forest, CA)

Given the above limitations, a hybrid probe was then developed by Abela et al. and this used the same type of metallic probe tip but had an open end with an optical fiber with

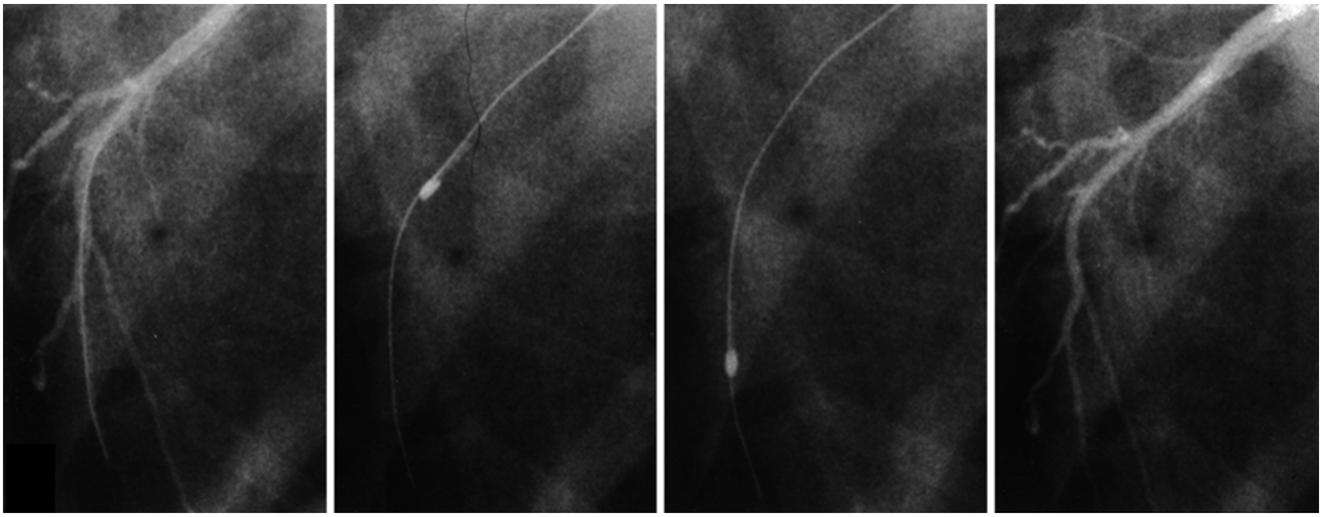

Fig. 27.6 Thermal probe passing into the coronary circulation of a dog demonstrating the flexibility of the probe to follow the guide wire (Courtesy of Abela GS)

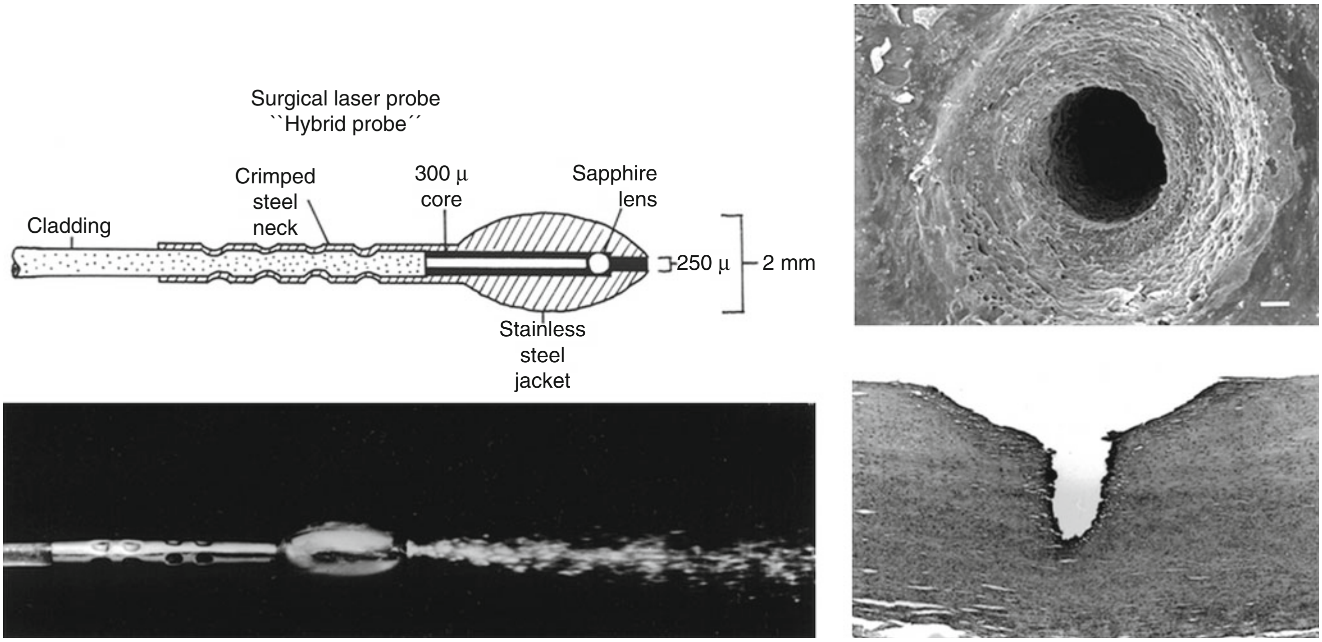

Fig. 27.7 *Left*, the Spectraprobe-PLR^{TM} or hybrid probe has a lens tipped fiber and a metal cap. The fiber discharges a laser beam from the tip and simultaneously heats up the metal probe (Abela et al. [27] J Am Coll Cardiol, with permission). *Right*, this creates a central channel that is further enlarged by the thermal effect of the probe (Courtesy of Abela et al. [26], with permission)

lensed tip to focus the laser beam [27]. This system created a pilot channel into which the metal probe would then follow to help orient the direction of the fiber [26] (Fig. 27.7). Although this was also a useful modification, perforations still occurred. Some of this was related to overheating of the probe. To address this problem the procedure was conducted by flushing normal saline at 22 °C during the lasing procedure to prevent thermal dispersion. Another modification was the addition of a thermocouple to the tip of the probe so that it would cut off the laser when the probe temperature exceeded 100 °C [28]. Despite these innovations arterial perforations were still a potential problem, especially in small diameter arteries. The challenge for laser angioplasty was to be able to revascularize the artery and obtain a channel equal to the native vessel without perforation. All the thermal probe systems required tissue contact and were activated by a continuous wavelength laser systems (i.e., argon, Nd-Yag).

Lensed Fibers

Other modifications included of lensed fibers that were made with the intent of focusing the laser beam when ablating the arterial plaque [29]. However, those were quickly transformed into thermal probe system once the lens became soiled by either blood or tissue debris at the treatment site. Thus, these systems also had similar outcomes as the thermal probes.

Laser Balloon Catheter (USCI-Bard, Billerica, MA)

A unique concept was developed by Spears that dispersed laser irradiation by scattering the light through an angioplasty balloon catheter [30]. Since the balloon is transparent to the light and simultaneously displace the blood when inflated allowing a scattered laser beam to irradiate the tissue. The concept behind this system was to cause 'biological stenting' of the tissue. This could seal dissections by balloon angioplasty and stabilize the plaque. Another endpoint was to prevent the high restenosis rate that was frequent following standalone balloon angioplasty. Moreover, to further enhance this system, a photosensitizer, hematoporphyrin derivative (HPD), with high affinity to atherosclerotic plaque would result in selective absorption of the laser light at 316 nm laser wavelength [31]. Although highly innovative, in practice, the expected outcomes of reduced restenosis and biological stenting were not realized.

Pulsed Laser Systems (Excimer, Ho:Yag) for Angioplasty Procedures

Given the hurdles with the continuous wave laser systems attention turned to pulsed lasers as a method to recanalize arterial obstruction. The rationale was that pulsed laser had the ability to vaporize calcific tissues and cut more precisely with less thermal injury to surrounding tissue [32]. Two major wavelengths were used for pulsed laser, Ho:Yag (2100 nm) and Excimer (308 nm Pulse width: 125–200 ns; fluence 30–60 mJ/mm^2). These effects were demonstrated by Cross and Bowker in the United Kingdom, by Clarke and Isner and Grundfest and Litvack in the United States [33–35]. Both are highly absorbed by the tissues making them precision cutting devices. A major breakthrough by Goldenberg was the ability to couple the excimer laser (XeCl 308 nm) to fiber optic bundles [36]. These were then used to deliver the laser beam in a forward direction from the catheter tip. Subsequent tip modifications were also made to disperse the beam at outward angles to achieve a wider cut of tissue than the size of the catheter tip.

High energy pulses had their own limitations including production of vapor bubbles that would expand and then implode generating photoaccoustic shock waves in the immediate environment [37–40]. These shock waves produced tissue dissection especially if the lasing was done rapidly and in the presence of blood. This could lead to intramural hemorrhage with separation of the arterial wall layers forming the appearance of a multilayered French pastry known as 'Mille Fueille' [41]. Thus, clearing the local milieu of blood during lasing was required to obtain the clean cuts that were seen in the in vitro experiments [42]. This procedure required that the lasing be performed slowly without forcing the catheter into the tissue to avoid mechanical dissection but rather have the catheter lead the way by precision cutting of plaque. Pulsed HoYag was also used but had more shock wave and thermal tissue effects than the excimer [41]. Various catheter systems were built with a central channel and surrounding fibers that could then cut a precise rounded channel around a guide wire. Although successful, this approach continued to require the need for follow up balloon angioplasty to obtain the size of channel comparable to the size of native artery. Furthermore, the anticipated effect of reduced restenosis using laser was not achieved.

Laser Thrombectomy

Thrombus plays a key role in the acute coronary syndrome (ACS) and it poses a challenge for revascularization. Moreover, thrombosis is associated with increased intra and post procedural complications. Distal embolization of the thrombus during percutaneous coronary intervention (PCI) can reduce microvascular perfusion which has been shown to be associated with poor prognosis.

Mechanical thrombolysis can be achieved with laser as thrombi have a high water content which helps in the absorption of the light. Also, the laser interacts with platelets and fibrin which are key components of the thrombus. Topaz et al. demonstrated that the mid pulsed ultraviolet and infrared lasers (i.e., excimer and holmium:YAG) can create acoustic shock waves with dynamic pressure on the fibrin mesh to break up the fibrin to cause thrombolysis [43]. Lasers can also alter platelet aggregation and can cause stunning in a dose dependent manner.

During ACS laser thrombectomy can be achieved both in native coronary arteries and venous grafts. Thus, the laser may be used as an alternative to treat a high thrombus burden especially in patients who failed thrombolysis or have contraindications for thrombolytics or IIb/IIIa receptor antagonists. In a study of 50 AMI patients excimer laser was effective in thrombus reduction by 83 % and an improved Thrombolysis In Myocardial Infarction (TIMI) flow [44].

In the CARMEL (Cohort of Acute Revascularization of Myocardial Infarction with Excimer Laser) multicenter, non-randomized, observational study Topaz et al. demonstrated that excimer laser was effective in AMI by significantly increasing TIMI flow and reducing target lesion stenosis [45]. Both native coronaries stenoses (79 %) and venous grafts (21 %) were included. A 91 % overall procedural success rate was achieved with minimal complications (0.6 % balloon related perforations, 0.6 % acute closure, 3 % laser induced major dissections). No laser related perforations were noted. Other key findings were that the maximal laser effect was noted in the lesions with large thrombus burden. Also, no distal embolization was noted among the 21 % of patients who had degenerated vein grafts.

Clinical Trials with Lasers

Lasing with Continuous Wave Lasers

Abela et al. were the first to receive FDA approval in the US to perform laser angioplasty in the peripheral circulation in humans using the thermal hybrid probe system. An initial study was performed in 11 patients evaluating the immediate effects of laser angioplasty in peripheral arteries using angioscopic guidance. This was initially performed in the operating room setting during peripheral artery surgery. A new vascular channel was created in 10 of the 11 patients who had totally occluded superficial femoral arteries [27]. Meanwhile, Cumberland et al. worked on peripheral arteries in humans with a laser activated thermal probe or ‘hot tip’ and had a 89 % primary success in creating a channel followed by balloon dilatation [46]. Sanborn et al. also reported on the use of peripheral laser thermal angioplasty as an adjunct to conventional balloon angioplasty [47]. They demonstrated a high success rate for femoropopliteal stenosis (77 %) and total occlusions (95 %). The 1-year cumulative clinical patency was also 77 % but longer lesions had lower patency rates in 1-year. Shorter lesions had better patency with laser angioplasty compared to balloon angioplasty alone. Other studies reported similar results [48].

Using a hybrid laser/thermal probe, Barbeau et al. demonstrated the feasibility of treating complex peripheral artery lesions using a combined laser angioplasty and percutaneous balloon approach. In this study overall technical success rate was 75 % (Figs. 27.8 and 27.9) [27, 49].

Excimer Laser Angioplasty in the Peripheral Circulation

PELA (Peripheral Excimer Laser Angioplasty) was a prospective, randomized trial in 251 patients (13 US and 6 German sites) with symptoms of claudication for greater than 6 months and >10 cm total superficial femoral artery (SFA) occlusion compared balloon angioplasty with laser assisted baloon angioplasty. No differences in outcomes (clinical events or patency rates) were demonstrated at 1 year follow up between the two approaches [50].

The Laser Angioplasty in Critical Ischemia (LACI) trial included 145 critical limb ischemia patients who were deemed to be unfit candidates for vascular surgery [51]. Patients were enrolled to test the effectiveness of laser-assisted balloon angioplasty. Procedural success rate was reported as high as 86 % and stenting was performed in only 45 % of limbs. Follow up at 6 months demonstrated a high limb salvage rate of 92.5 %, with 10 % mortality and 6 % major amputation rates.

Coronary Artery Studies

Initial results using the excimer laser catheter system (Spectranetics, Colorado Springs, CO) in the coronary circulation were very promising (Fig. 27.10). Early trials by Litvack et al. demonstrated that it was safe to ablate the atheroma and reduce coronary stenosis with the excimer laser. In a multicenter trial on 55 patients the mean minimal stenotic diameter increased from a baseline of 0.5 ± 0.4 to 1.6 ± 0.5 mm with laser treatment and to 2.1 ± 0.5 mm with balloon angioplasty [52]. Similarly Karsch. et al. in a small study (60 patients) also showed lasers were safe in treating both stable and unstable angina patients [53].

Similarly, Sanborn et al. in a multicenter trial on 141 patients demonstrated that laser assisted angioplasty was safe and feasible [54]. However, several trials have not shown benefit over conventional balloon angioplasty. LAVA (Laser Angioplasty Versus Angioplasty) trial was a randomized multicenter study in 215 patients that compared laser facilitated PTCA to balloon angioplasty alone [55]. There were more procedural complications and patient adverse events with laser without any difference in immediate and long term benefits. Similarly the AMRO (Amsterdam-Rotterdam) study in 308 stable angina patients compared excimer laser coronary angioplasty with balloon angioplasty and did not demonstrate improved angiographic success rate, myocardial infarction, coronary bypass surgery, repeat angioplasty or net mean gain in minimal lumen diameter [56]. The ERBAC (Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison) study showed that the success rate of procedure was higher with rotational atherectomy compared to laser angioplasty and balloon angioplasty [57].

However, the ELLEMENT study confirmed the feasibility of ELCA during contrast injection to improve stent under expansion in undilatable stented lesions [58]. Overall, given that balloon angioplasty was required to dilate the artery following laser procedure and the lack of prevention from restenosis with the laser despite the debulking of the plaque burden

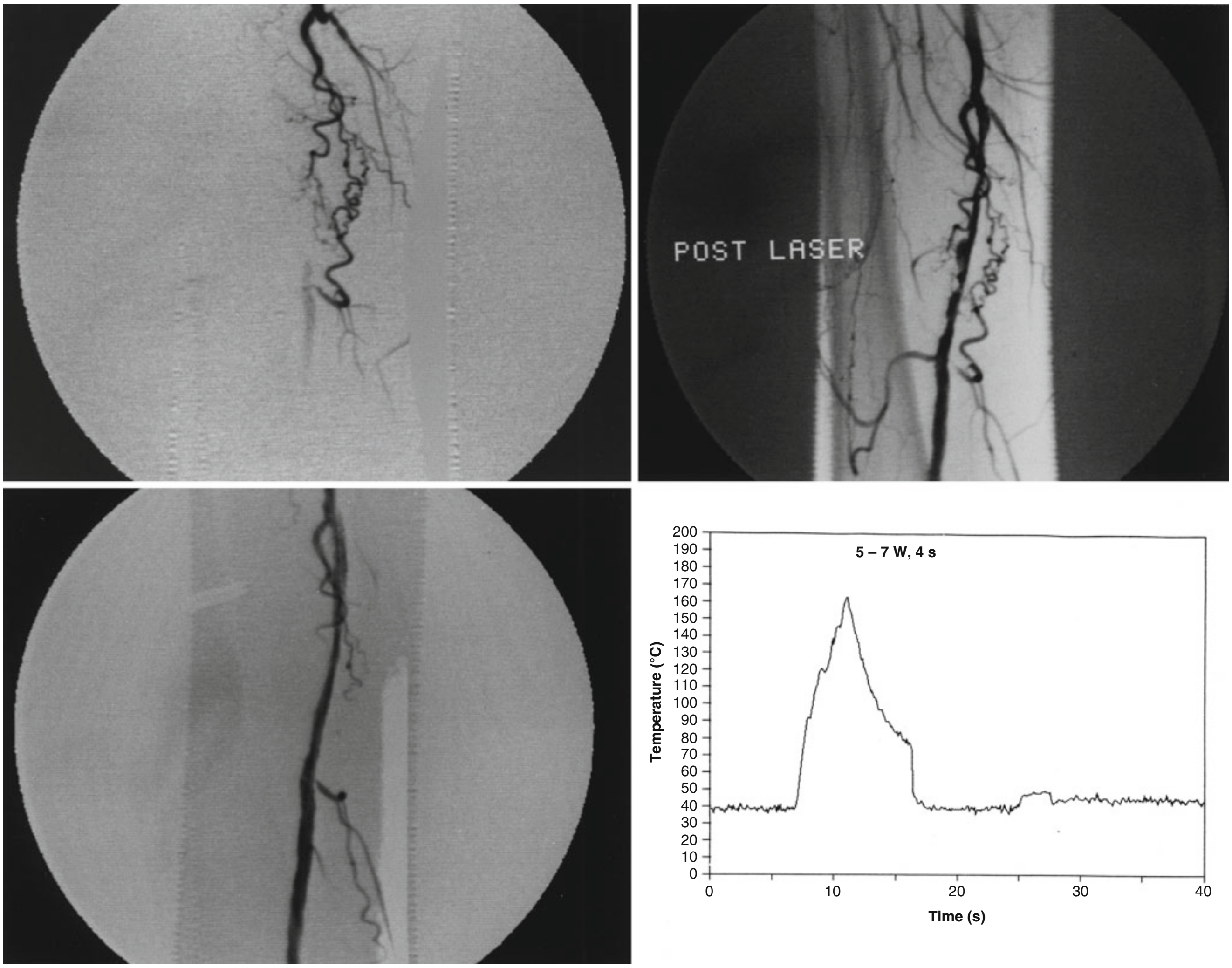

Fig. 27.8 Sequential digital angiograms of the right superficial femoral artery (*top left*) before laser recanalization with hybrid probe, (*bottom left*) after laser recanalization, and (*top right*) after balloon angioplasty. (*bottom right*) Probe temperature is plotted against time during laser recanalization of the occluded segment shown in (*top left*). Peak probe temperature of 168 °C which resulted in recanalization was reached at a power of 6 W and 4 S exposure (Barbeau et al. [28], with permission)

at the site, laser angioplasty gradually became less frequently used. Currently few clinical uses are considered for excimer laser angioplasty. These include the re-canalization of in-stent restenosis and left main coronary artery disease. Another area that still has occasional use of laser technology is in heavily calcific peripheral vascular lesions [59].

Laser Application for Trans myocardial Revascularization (TMR)

TMR was proposed as an option to treat patients with refractory angina to medical therapy. This was used as standalone therapy but more often as an adjunct to coronary bypass graft surgery. The concept was based on the ventricular sinusoidal system that supplies blood to reptilian hearts as well as the Vineberg technique of direct myocardial revascularization [60]. The physiological basis is that microchannels created by utilizing lasers can provide an alternative pathway for blood supply of the myocardium by direct perfusion from the left ventricle. However, autopsy studies demonstrated that the channels had become fibrosed and were occluded. Several explanations have been proposed for presumed benefits included such as stimulation of angiogenesis to improve perfusion, anesthetic effect due to destruction of the sympathetic fibers or a placebo effect. There have been multiple methods to create channels in the myocardium. Initially, P.K. Sen used acupuncture needles to create myocardial channels which inspired the use of lasers to create micro channels [61]. Mirhoseini and his colleagues used the CO_2 laser in a canine model and then in humans as an adjunct to CABG [62, 63]. Currently, the CO_2 laser (PLC Systems) and the holmium:YAG laser (Cardiogenesis, Sunnyvale, CA) are the only approved lasers for TMR in United States.

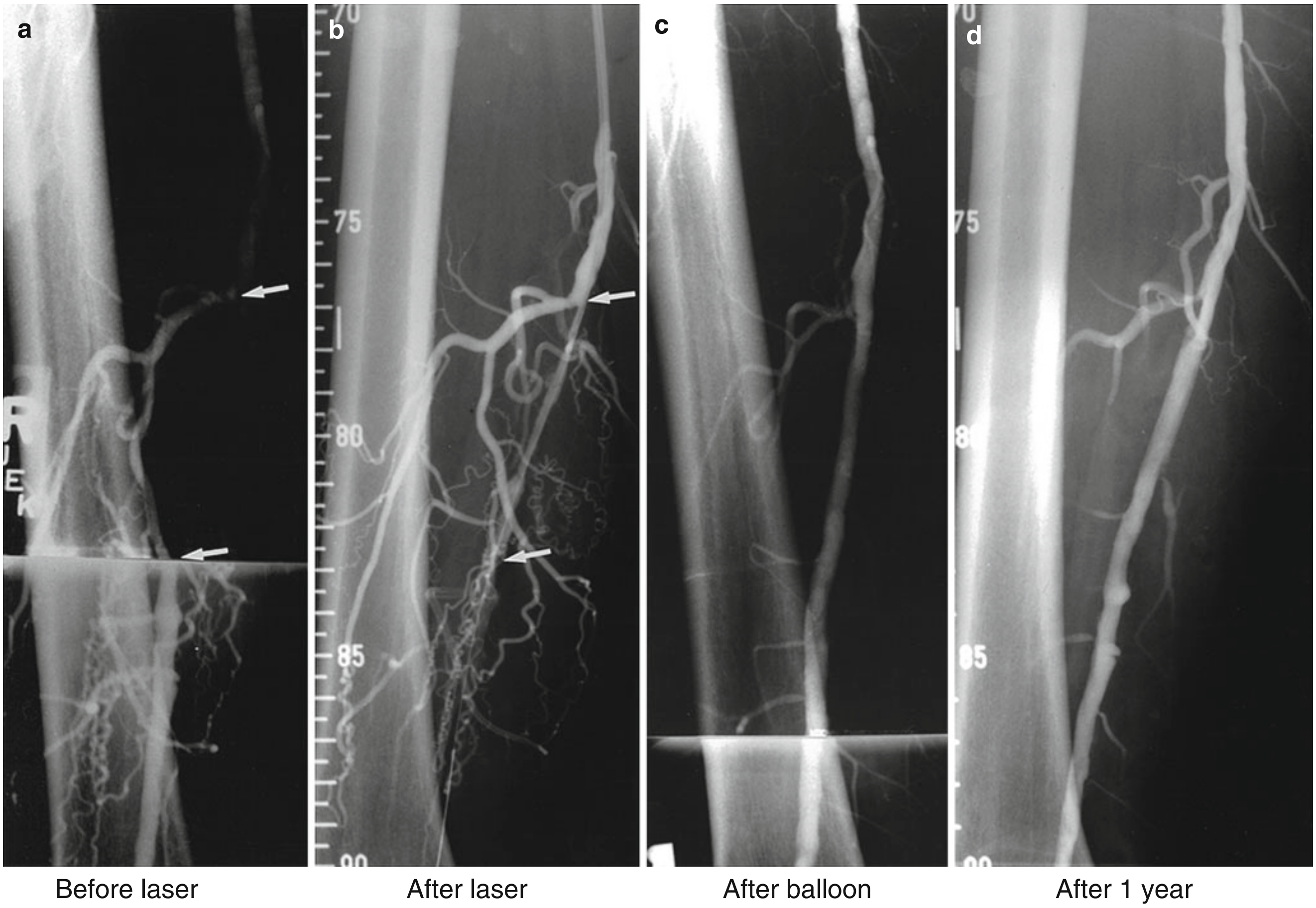

Fig. 27.9 Angiograms of a 61-year-old Caucasian man with <2 block right calf claudication of 7 months' duration (ABI = 0.66). (**a**) Control angiogram. (**b**) angiogram after laser recanalization with hybrid probe and guide wire still in the artery. (**c**) Further dilatation achieved following balloon angioplasty. (**d**) Angiogram at 1 year with widely patent artery (ABI >1) (Barbeau et al. [49], with permission)

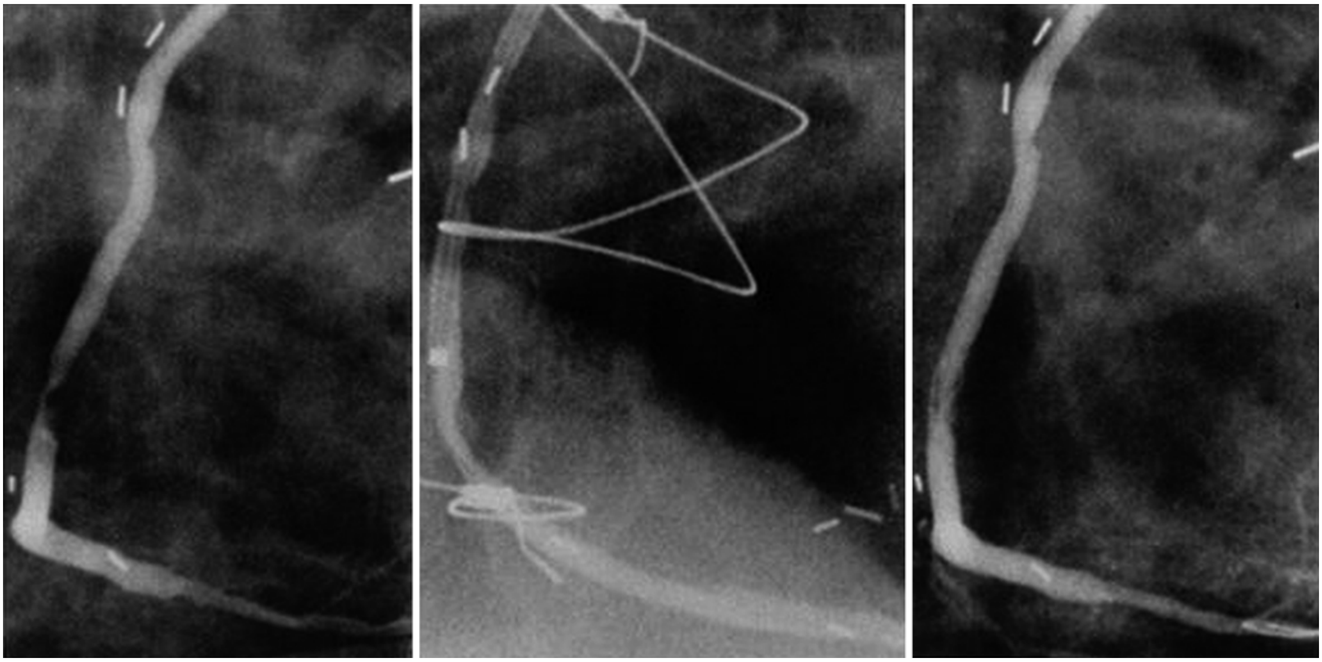

Fig. 27.10 Angiograms of saphenous bypass graft to the right coronary artery in a 51-year-old man who developed recurrent angina 5 years following coronary bypass surgery. *Left panel* shows a 90 % midgraft stenosis. The *middle panel* shows the stenosis after the first laser treatment using a 2.0-mm-diameter laser catheter as described. The catheter tip is seen above the lesion site. The *right panel* shows the final result following completion of laser angioplasty. Minimal residual stenosis (<20 %), and this was left as a laser stand-alone result (Abela et al. [77], with permission)

A sham controlled randomized trial by Leon et al. did not demonstrate a significant difference between a laser treated group and a sham group with respect to exercise duration, improved angina class or visual summed stress single-photon-emission computed tomography scores [64]. Currently, TMR is rarely used as a direct or adjunct treatment for non-bypassable regions of the myocardium.

Other Laser Applications

The excimer laser has been used effectively as a pacemaker lead wire extraction device and this continues to be an important and frequently used application [65–67]. Lasers have been very effective in treatment of varicose veins and this has become a very popular application [68]. Lasers have been used for arterial welding especially for small arteries [69, 70]. Lasers have also been used in electrophysiology as a method to ablate arrhythmia source in the heart including AV node ablation as well as for ventricular tachycardia foci and atrial fibrillation (Fig. 27.11) [71–74]. Photodynamic therapy of atherosclerotic plaque has also been tested with some potential for plaque stabilization [75, 76]. However, clinical applications have not been performed.

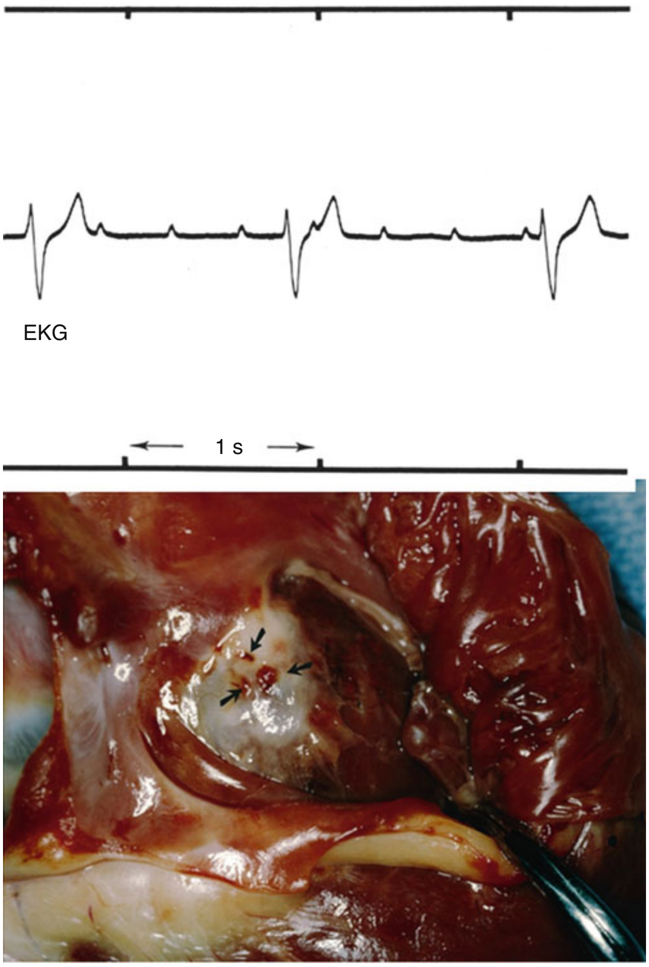

Fig. 27.11 *Top*, surface electrocardiogram (lead II) recorded following laser-induced complete heart block. There is a ventricular escape rhythm of 47 beats/min. *Bottom*, Superior portion of the septal leaflet of the tricuspid valve showing three thermal burns at lased sites. Curtis et al. [72], with permission

Summary

Laser applications in the cardiovascular field have generated much interest in both the cardiovascular community as well as the general public. Over the course of the last two decades clinical applications and basic research of the cardiovascular laser has transitioned to larger volume medical centers with cardiovascular subspecialties. The pulsed-wave, ultraviolet excimer laser that operates at the 308 nm wavelength of the light spectrum has become the primary system being utilized. Absorption of excimer laser energy within targeted biologic tissues creates unique effects on the non-aqueous components of the atherosclerotic plaque and on the accompanying thrombus resulting in vaporization and debulking of intravascular obstructions. Currently, the primary patient candidates for laser angioplasty are those with symptomatic coronary and peripheral arterial disease. These patients often present with complex atherosclerotic and thrombotic lesions which are considered non-amenable for standard technologies of percutaneous intervention or for surgical revascularization. The cardiovascular excimer laser system is approved in the US, Europe and Japan for treatment of symptomatic patients who require revascularization of diseased native coronary arteries, old saphenous vein grafts, chronic total occlusions and diseased peripheral arteries. This laser system is also used for extraction and removal of old and dysfunctional or abandoned pacemaker leads. As the technology continues to evolve the laser could be applied to the more challenging and complex arterial lesions. The most recent developments with laser applications have focused on percutaneous treatment of venous vasculature conditions including removal of permanent embolic protection filters from the inferior vena cava as well as venous thrombolysis. Treatment of varicose veins has been very successful and future developments are anticipated for arrhythmia ablation.

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