Laser Physics and Laser-Tissue Interaction

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Within the last few years, lasers have gained increasing use in the management of cardiovascular disease, and laser angioplasty has become a widely performed procedure. For this reason, a basic knowledge of lasers and their applications is essential to vascular surgeons, cardiologists, and interventional radiologists. To elucidate some fundamental concepts regarding laser physics, we describe how laser light is generated and review the properties that make lasers useful in medicine. We also discuss beam profile and spotsize, as well as dosimetric specifications for laser angioplasty. After considering laser-tissue interaction and light propagation in tissue, we explain how the aforementioned concepts apply to direct laser angioplasty and laser-balloon angioplasty. An understanding of these issues should prove useful not only in performing laser angioplasty but in comparing the reported results of various laser applications. ***(Texas Heart Institute Journal 1989;16: 141-9)***

Key words: *Lasers; angioplasty; angioplasty, laser-assisted*

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This work was supported in part by the Free Electron Laser Biomedical/Materials Program: ONR contract N14-86-0875.

Presented at the laser symposium of the Texas Heart Institute titled "Lasers: Current and Future Cardiovascular Applications," held 22-24 January 1989 at the Westin Galleria Hotel, Houston, Texas

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This article describes some basic concepts regarding physics and laser-tissue interactions that are important to laser angioplasty. Removal of tissue by means of ablation and the diagnostic applications of fluorescence for identification of normal and diseased tissue are described elsewhere in this issue.

Laser Properties

Imagine that an atom has been raised to an excited state (e_2) as shown in Figure 1. If a photon with energy (e_2-e_1) causes the atom's energy level to drop from e_2 to e_1, this change will generate a 2nd photon that will be in phase with—and propagate in the same direction as—the excitation photon. This phenomenon, which is called stimulated emission, is the basis of laser light generation. If the 2 original photons come in contact with 2 additional excited atoms, this interaction will result in another pair of photons, traveling in the same direction and having the same phase. If more atoms become excited, additional in-phase photons will be generated, and the process could continue indefinitely. If one had a medium of infinite length, filled with excited atoms, it would be possible to generate a significant light output. For a practical system, however, one requires a laser medium of finite length, with the addition of optics, so that the light can bounce back and forth through the medium, stimulating additional photons on each pass. Therefore, a typical laser consists of an optical cavity, a laser medium, and 2 mirrors: 1 at each end of the cavity. One mirror, which is "partially transmitting," is the source of the laser output; about 2% to 3% of the light inside the cavity is transmitted. Lasing is possible when more than one-half of the atoms in the laser medium are in the excited state, that is, when population inversion is achieved.

Consider the continuous-wave Nd:YAG laser schematically illustrated in Figure 2. A continuous-wave laser requires continuous population inversion, which, in this case, is achieved by continually pumping light from a xenon source into the laser medium. As in this example, the mirrors may merely be reflective coatings on the ends of the crystal. In contrast, if the xenon light source is pulsed, pulsed laser light can be provided.

Lasers have 3 primary properties that have been utilized by the medical community. The 1st of these is monochromatic emission. Upon entering a prism, white light spreads into a spectrum; the resulting colors illustrate the band of wavelengths of which the color "white" is composed. A laser beam generally consists of a single wavelength. Quite often, lasers with visible wavelengths are described in terms of their color: the argon laser beam is blue or blue-green, the He-Ne laser beam is red,

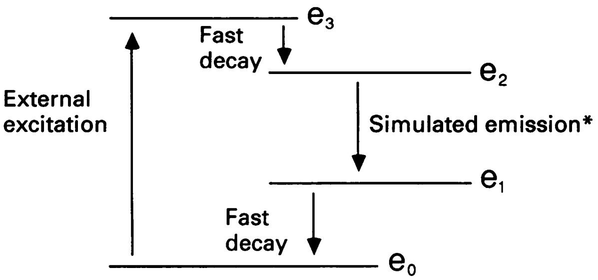

Fig. 1 *Four-level energy diagram. Population inversion is achieved between levels 1 and 2.*

**A population inversion must exist between e_2 and e_1.*

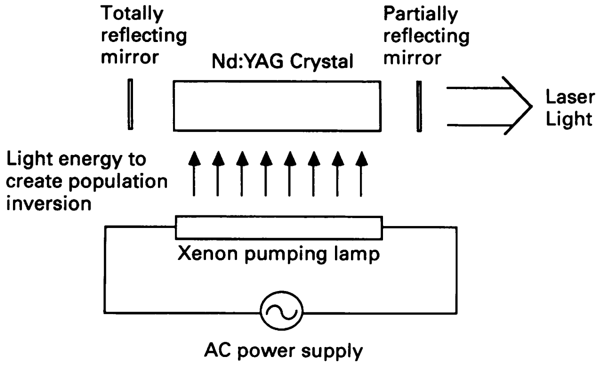

Fig. 2 *Block diagram of the components of a continuous-wave Nd:YAG laser.*

and so on. A laser's characteristic color is associated with the energy gap shown in Figure 1; the transition from the excited state to the lower state represented by the laser medium is denoted by $\Delta e = h/\lambda$, where h is Planck's constant and λ is the wavelength.

The 2nd primary property that makes lasers useful in medicine is collimation, or low divergence, of the laser beam. Lasers differ from most conventional light sources, which emit light in all directions. If a light from a 60-watt bulb enters the eye directly, it may cause a mild form of flash blindness; the resultant bleaching affects the entire eye. A collimated beam, however, acts as a point source—like a magnifying glass, which can light a fire by focusing the sun's rays. When a laser beam is directed toward the eye, the cornea-lens system focuses the beam onto the retina, to a point image of about 20 µm. A continuous-wave beam as weak as 20 milliwatts can burn the eye faster than the eyelid can react. Therefore, in working with 20-watt, 30-watt, and 40-watt lasers, the surgeon's potential risk is considerable.

The 3rd medically useful property of lasers, coherence, is a new consideration for diagnostic applications in medicine. "Coherence" refers to the fact that all of the laser light is in phase. When a laser beam's different "rays"—traveling slightly different distances—are imaged together, bright and dark spots are formed because of the interference patterns.

Beam Profile and Spotsize. Quite often, the laser beam is described as though it had a uniform irradiance (W/m^2): a spotsize 1 mm (0.1 cm) in diameter (area = $\pi d^2/4$) and a laser output of 1.0 watts would produce an irradiance of 127.3 W/cm^2 (the power of the laser divided by the spotsize). Most often, the laser beam assumes a Gaussian shape (that of a normal distribution), as shown in Figure 3A; this makes it harder to determine the exact irradiance (W/cm^2) at any point across the beam. There is a peak irradiance, and the irradiance decreases with distance from the center of the beam. This may be important in situations in which there are large variations in power: the ablation hole or coagulation area may depend upon some threshold irradiance (W/cm^2). As power is increased, the irradiance in the tail of the Gaussian profile increases, and the distance of the critical threshold from the center of the beam becomes larger. For this type of profile, the spotsize is often referred to as the $1/e^2$ radius, or diameter, of the beam; at this radial distance from the center of the beam, irradiation is lower by a factor of 0.135 ($1/e^2$) relative to the peak irradiance. About 85% of the power of the laser beam is present within the $1/e^2$ diameter. Lasers frequently become misaligned, so that the irradiance assumes a donut-like configuration (Fig. 3B): the irradiance profile has a dip in its center that may also cause difficulties in determining the correct dosimetry.

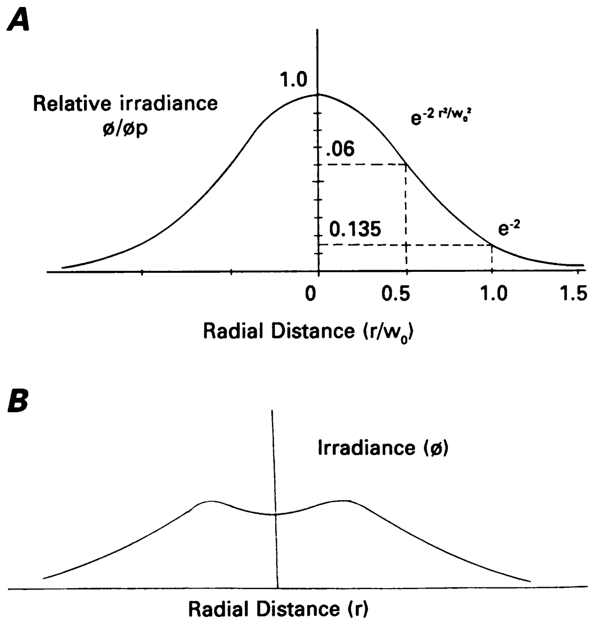

Fig. 3 *Irradiance profiles of **A)** Gaussian and **B)** donut-shaped beams.*

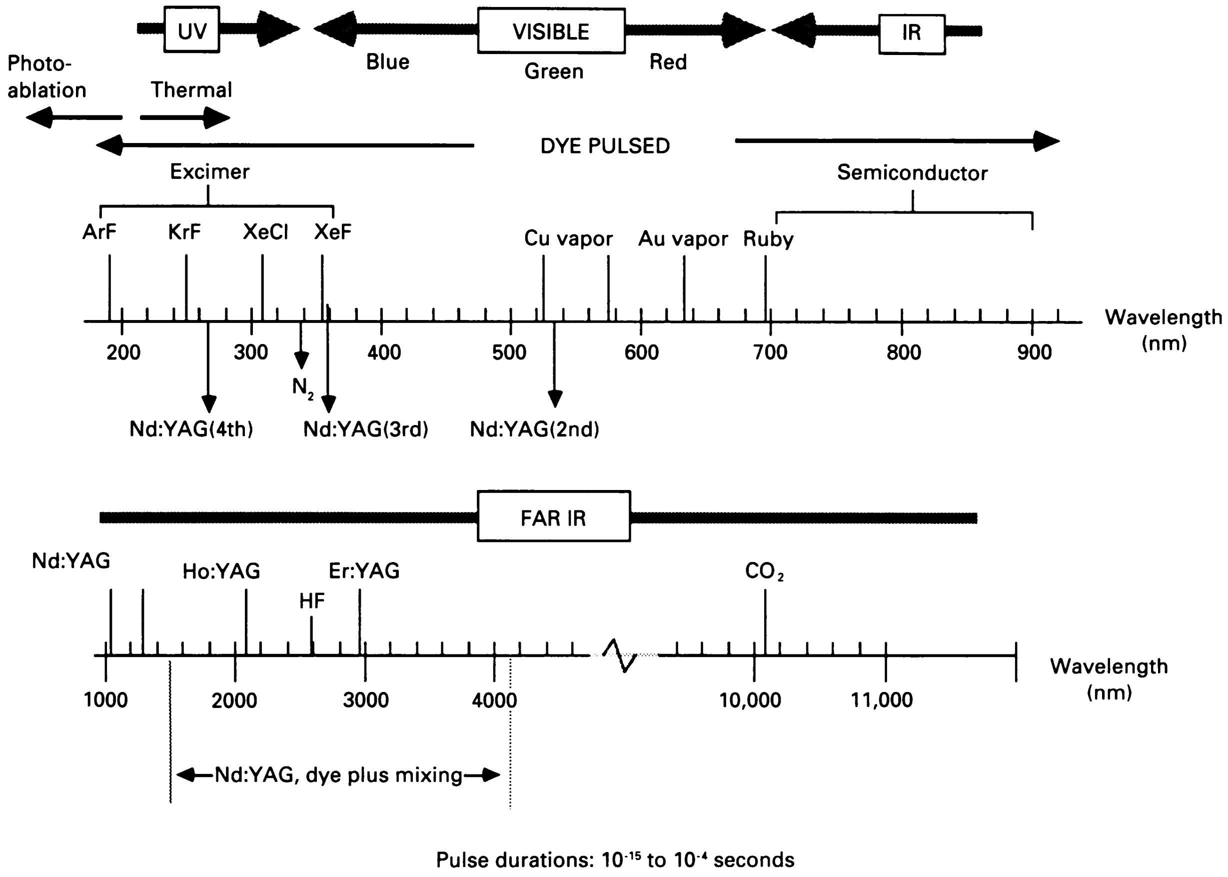

Fig. 4 *Pulsed lasers available for clinical and research applications.*

Typically, the amplitude profile of the laser beam assumes a Gaussian shape rather than a uniform configuration, so the beam cannot be focused into a point. Nevertheless, a minimum spotsize can always be achieved. It is important to remember that the minimum focus is a function of wavelength; a much better focus can be achieved with ultraviolet and visible wavelengths than with infrared wavelengths. Whereas it is difficult to focus a CO_2 laser beam to spotsizes smaller than a few hundred microns, ultraviolet or visible laser sources can be focused to 10 microns or less.

Beam Wavelength. Laser light is electromagnetic energy; its spectrum ranges from gamma rays, X rays, ultraviolet light, and visible light through the infrared and radio wavebands. Currently, lasers are commercially available in the ultraviolet through the mid-infrared spectrum.

Pulsed and continuous-wave lasers available for medical applications have wavelengths that extend from 193 to 10,600 nm. A number of the pulsed-laser systems are depicted in Figure 4. Virtually all portions of the 193- to 10,600-nm spectrum are represented. For cardiovascular applications, the following devices are now undergoing—or being considered for—clinical trials: the excimer laser, in the ultraviolet range (308 nm); the argon laser (approximately 500 nm); the frequency-doubled Nd:YAG device (530 nm); the Nd:YAG laser (1060 and 1300 nm); the Ho:YAG (1940 nm); and the Er:YAG laser (2940 nm). Whatever the application may be, wavelength is extremely important.

Variables for Continuous-Wave versus Pulsed Dosimetry. Dosimetry for continuous-wave applications should specify 3 variables: power, irradiation time, and spotsize. How should dosage be described for a repetitive pulsed laser? Should the sequence of pulses be described in terms of peak power, average power, or energy per pulse? Laser power is not constant during a pulse: it is more triangular in shape (Fig. 5A). Therefore, the average power pulse, instead of being equal to the peak power divided by the pulse duration, is closer to one-half of that value. Usually, pulsed lasers are described in terms of the energy contained in each pulse—the integrated power of a pulse. Graphically, the pulse energy is represented by the area under the power curve, as illustrated in Figure 5B. The energy of each pulse is an important factor for describing dosimetry in laser angioplasty. The interval between pulses is another important

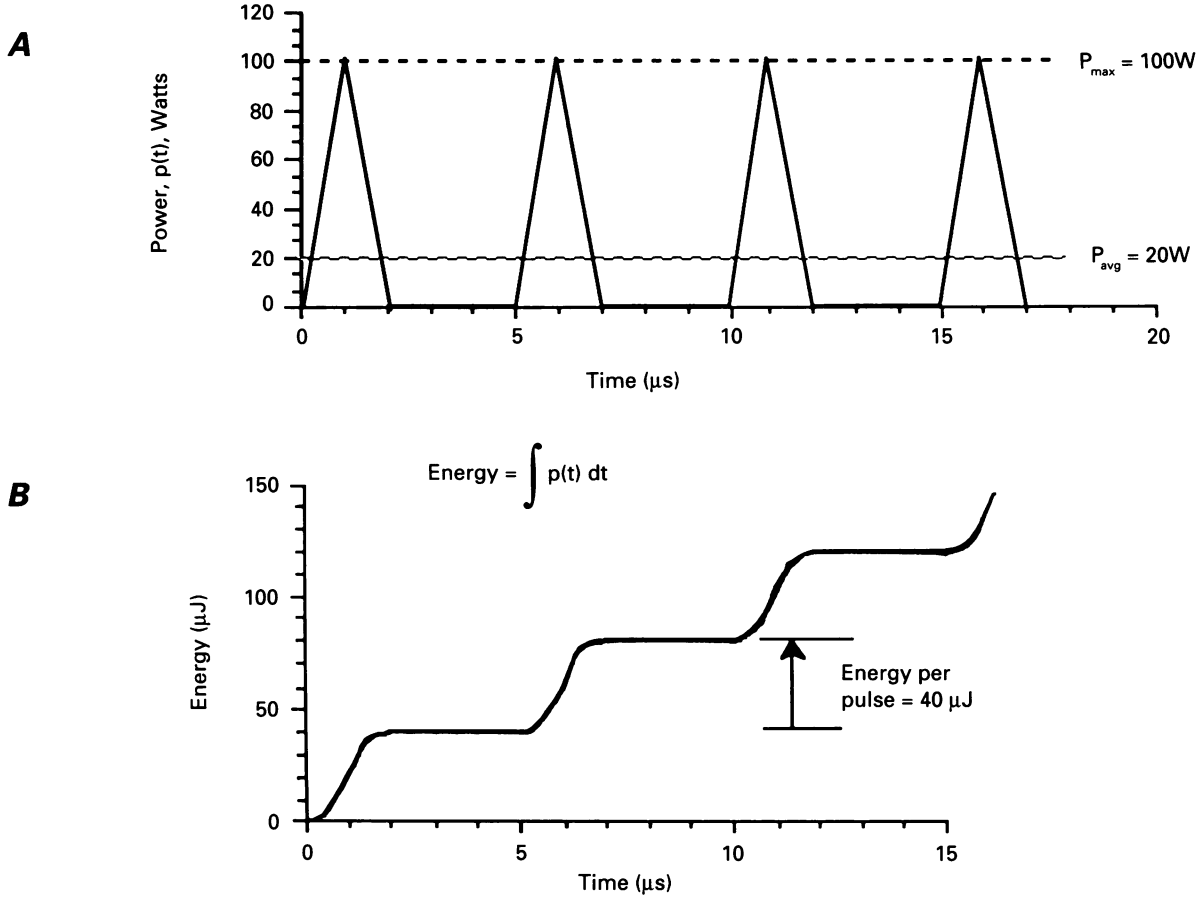

***Fig. 5** Relation between **A**) pulse power and **B**) pulse energy.*

variable; this interval should be long enough for debris to be removed before the next pulse is applied.

What is the time profile of a laser pulse? Is a laser pulse really a single pulse? For Q-switch lasers (which have a nanosecond pulse-length), mode-locked lasers (which have a picosecond pulse-length), and dye lasers (which have a microsecond pulse-length), the answer is yes. But for the long pulse-mode of the Nd:YAG, Ho:YAG, and Er:YAG lasers, which lasts for several hundred microseconds, the pulse consists of a microstructure of microsecond-long pulses. When used for angioplasty, each of these "micropulses" can ablate a bit of tissue. Therefore, an Er:YAG laser wavelength that would normally penetrate only a micron of tissue could remove a depth of tissue on the order of 100 microns with each long pulse.

The most important laser variables for laser angioplasty are 1) exposure duration, 2) wavelength, 3) spotsize, and 4) power (for continuous-wave lasers) or energy (for pulsed lasers); these 4 irradiation variables should be kept in mind when one is comparing the reported results of various laser applications. Unfortunately, only 2 or 3 of these variables are usually reported; rarely are all 4 cited. If the power and spotsize are given, however, it is possible to calculate the irradiance (W/cm^2). Given the exposure duration, one can differentiate the effects of nanosecond-, microsecond-, or even second-long exposures. Another important aspect is the spotsize. In a fiberoptic transmittal system, fibers measuring 100, 200, 300, or 600 microns in diameter are typically used for laser angioplasty. Usually, the exiting beam has a divergence of about 7°. If the user changes from a 100-μm to a 200-μm fiber, the ratio of the spotsizes increases by a factor of 4. The ratio of spotsizes between the 100-μm and the 600-μm fiber is 36. Therefore, if the same power were put into each fiber, the irradiance (W/cm^2) in the 600-μm fiber would be 1/36th of that in the 100-μm fiber. In angioplasty systems, the area irradiated is often determined by the size of the fiberoptic and the distance of the delivery tip from the irradiated surface.

What wavelengths can be transmitted with a low hydroxide silica fiber? Can the CO_2 laser wavelength pass through such fibers? What about the Er:YAG or Nd:YAG wavelengths? The best transmission efficiency is around 1.3 μm, which is 1 of the wavelengths of the Nd:YAG laser. Beyond 1.3 μm, infrared losses start to occur, and 2.5 µm is about the maximum infrared wavelength that can be transmitted through this fiber. In the ultraviolet range, there are also significant losses. The energy per pulse and the pulse duration are other limiting factors with use of a low-hydroxide silica fiber.

What kind of pulses can be passed through the fiber? Isner and colleagues[1] have demonstrated that, at 308 nm, a 10-ns pulse with sufficient energy to ablate plaque can be passed through a standard 400-µm fused silica fiber. If the pulse is stretched to 75 ns, however, a higher pulse energy can be passed through the same fiber. The ratio of the index of refraction between media at their interface is a key to the propagation of the laser beam into tissue. If there is a difference in the index of refraction between the surfaces (e.g., from air to tissue or from air to a fluid), the beam in the tissue or fluid will be directed toward the normal (perpendicular to the surface), since air is optically less dense than the tissue or the fluid; reflectance will then occur at the same angle as the angle of the incident beam (Snell's law). This factor is important not only in considering the impact of light upon tissue but in analyzing how light from a laser-delivery system is coupled to tissue. Consider the contrasting measurements of focus that can be achieved with a sapphire tip in air and water or tissue. In air, a sapphire tip can have a very tight focus; but, when the same tip (which has an refraction index of about 1.6) is placed in water or in tissue with an index of about 1.4, it loses the focusing ability that it displayed in air.

Another important physical concept to be considered is hemodynamics: what size lumen is necessary for laser angioplasty? For a 1-cm stenosis, one needs a lumen of at least one-half the diameter of the blood vessel. For longer stenoses, a lumen very close to the original size of the vessel is needed to prevent immediate restenosis.

Laser-Tissue Interaction

Three types of reactions occur when laser light interacts with tissue: photochemical, photothermal, and photoplasmal.

In photochemical reactions, very low-power irradiation inactivates cell function by means of induced toxic chemical processes: temperature increase is indiscernible.

In photothermal reactions, laser light is absorbed by tissue chromophores and is converted to heat; this process is accompanied by a local temperature increase, and the heat is conducted to cooler regions. Greater degrees of heat result in denaturization, necrosis, and even vaporization and spallation (that is, splintering of the tissue). This is the type reaction that occurs in laser angioplasty. At the 198-nm wavelength, there is sufficient energy to allow bond-breaking, which is a photoablation process. If the irradiance is on the order of 10^8 or 10^9 W/cm^2, plasma formation takes place in a photoplasmal reaction. If the electric field is sufficiently strong, the result is a small region of plasma that is associated with high electric fields, dielectric breakdown, shockwave formation, and tissue rupture. Once the plasma forms, the tissue's absorption properties become immaterial; the plasma itself becomes the absorber, taking up all the laser energy directed into it. Another plasma-related consideration can be illustrated with a nonlaser example: if a firecracker is placed on the ground and lit, most of the explosive pressure is directed into the air; if some soil is placed over the firecracker, however, the explosive shock can be directed into the ground. Similarly, in angioplasty, an overlying fluid can be used to confine the shockwaves to the direction of the plaque.

Light Propagation in Tissue. Normally, when a laser beam is directed toward tissue, the resulting direct reflection accounts for only about 3% of the incident light. The remaining light goes into the tissue, where absorption and scattering take place. The rate of heat generation depends on the rate of absorption of photons within the tissue. Scattered light that is absorbed may cause heating outside the laser beam. With wavelengths such as those produced by the Nd:YAG (1060 nm), which are deeply penetrating, 30% to 50% of the light actually reemerges from the tissue. If a hand delivery system is being used, the back-scattered light may heat the operator's hand.

When the tissue's absorptive capacity is very high relative to its scattering ability, the laser beam remains strongly collimated in the tissue, and the penetration depth is a function of the wavelength-dependent "absorption coefficient." With wavelengths characteristic of the argon laser (approximately 500 nm), the amount of absorption and scattering may be about equal within cardiovascular tissue; therefore, some diffuse light will be present outside the laser beam. With the red and near-infrared wavelengths that range as high as 1500 nm, scattering may be dominant; in these cases, a sizable ball of light surrounds the laser beam in the tissue.

Penetration depth is defined as the depth at which the collimated beam has been attenuated by factor e^{-1} (37%). Its functional dependence on wavelength for soft, noncolored tissue such as vessel wall is shown in Figure 6. Blue light (approximately 460 nm) yields poor penetration; that of the red and near-infrared wavelengths (650 to 1100 nm) is considerably deeper. Deeper penetration continues until water absorption becomes relatively great, causing the penetration depth to decrease rapidly. The penetration depth of the collimated laser beam is the reciprocal of the sum of the tissue absorption coefficient and the scattering coefficient. The absorption

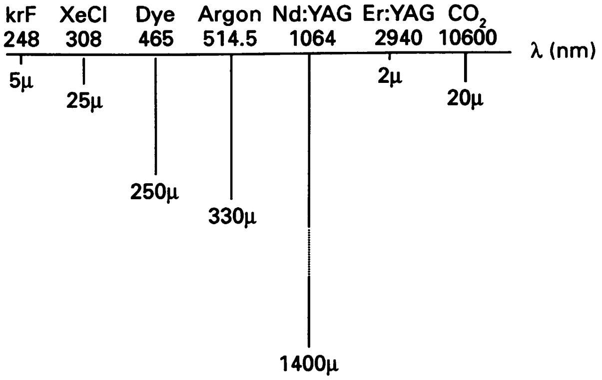

Fig. 6 *Penetration depth of a collimated beam.*

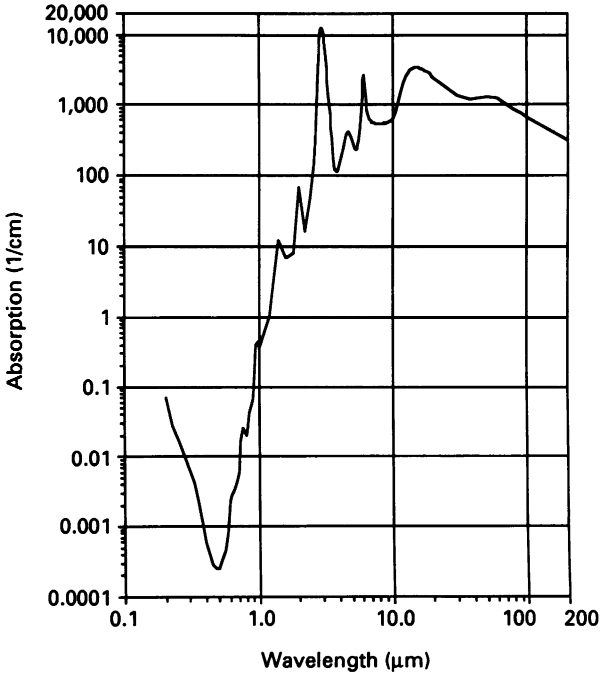

Fig. 7 *Absorption characteristics of water.*

and scattering properties at each wavelength are important, because of the rapid variations in absorption associated with different materials (chromophores) in tissue.

The water absorption curve in Figure 7 shows that the absorption coefficient of water is about 0.001 cm^{-1} in the visible band. At these wavelengths, light transmits quite well through water; this is not the case, however, at the YAG wavelength of 1060 nm, where the absorption coefficient is about 1.0 cm^{-1}. At this wavelength, light travels through water for about 1 cm before its magnitude is reduced by 67%. At longer wavelengths, absorption increases until it peaks at about 3.0 μm, where the penetration depth is less than 1.0 μm. Almost any penetration depth can be achieved by selecting the proper wavelength between 1.0 and 3.0 μm along the water-absorption band. Tissue is certainly not water, but it contains enough water that the water absorption curve can indicate how the absorption properties of a particular chromophore (water) affects laser-tissue interaction as a function of wavelength. With a penetration depth of less than 1.0 μm, one can expect to achieve very precise ablation—without thermal destruction of adjacent tissue—because of the confined absorption of laser light. Notice that the CO_2 laser, at 10.6 μm, has a smaller absorption coefficient than the Er:YAG device, at 2.94 μm, and that the CO_2 wavelength thus penetrates deeper.

Looking at Figure 6, one might marvel that an Nd:YAG laser could be used for ablation. Undoubtedly, the tissue is carbonized by intense Nd:YAG irradiation, creating a highly absorptive surface for continued Nd:YAG irradiation.

How is heat generated in tissue? Heat generation is determined by local absorption of laser light. Heat is transferred to cooler regions by means of conduction, which depends upon the tissue's thermal conductivity and diffusivity.

Diffusion time, or time constant of a thermal response, is typically defined as τ [seconds] = $\ell^2/4\alpha$, where α is diffusivity. In selecting the characteristic length, ℓ, for laser irradiated tissue, there are 2 considerations: the penetration depth and the beam diameter. If the penetration depth is very shallow, the characteristic length will equal the penetration depth. If the collimated laser beam penetrates deeply into the tissue relative to the laser spotsize, however, the characteristic length will equal the laser beam radius. Heat will then be conducted radially, rather than downwards, into the tissue. If the characteristic length is about 1 mm, the diffusion time will be on the order of 20 msec. Thus, during a 10-ns irradiation with a Q-switched laser, thermal events will take place much faster than the thermal diffusion time of 20 msec.

In direct laser angioplasty, the goal is vaporization of tissue. The absorbed light is converted to heat, which causes an increase in the local temperature; above a certain critical temperature, any additional heat will vaporize the tissue. Let us consider an extremely low-power irradiation, so that the various thermal events can be separated: temperature response is illustrated in Figure 8. When the tissue temperature reaches about 100 °C, water vaporizes, dehydrating the tissue. This water loss causes the thermal properties to change: both the conductivity and the diffusivity are reduced, and a rapid increase in temperature occurs before vaporization of the tissue. Hence, the typical thermal events associated with laser irradiation of vascular tissue include coagulation, basophilic changes (at around 66 °C), dehy-

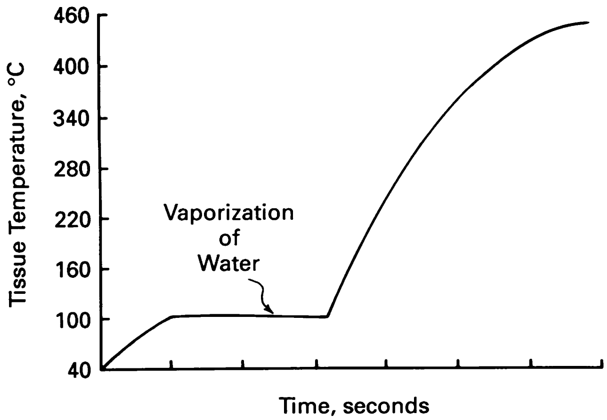

Fig. 8 Thermal events associated with ablation.

dration (at about 100 °C), vacuolization (at approximately 120 °C), and photocarbonization (above 217 °C). The removal of tissue occurs at temperatures above 100 °C.

Figure 9 presents the actual temperature measurements for argon laser irradiation of an 8-watt, 2-mm spotsize. A rapid increase in temperature is followed by a "pop," which is caused by the so-called "popcorn" effect. Before the removal of tissue occurs, temperatures below the surface of the tissue will exceed surface temperature. Afterwards, there is a sudden decrease in temperature due to the loss of the heated tissue. Continued irradiation causes the temperature to increase to about 360 °C. This is followed by a repetitive cycle, in which there is local carbonization and burning off of the carbonized portions. Interestingly, a change in laser power does not alter the process. The events depicted in Figure 9 occurred at almost the same temperatures but at different times.

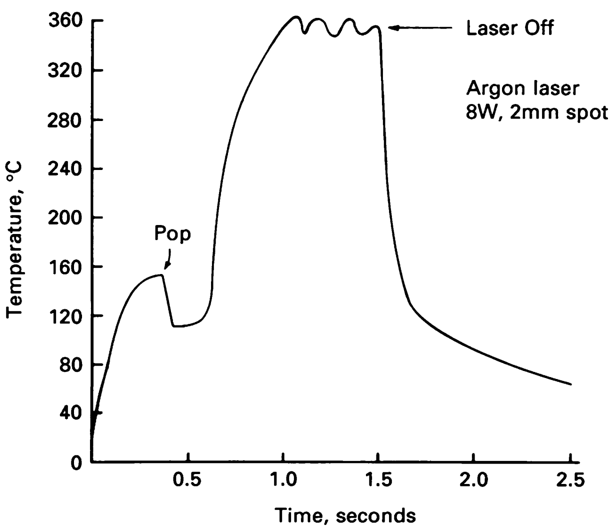

Fig. 9 Temperature response associated with argon ablation of a vessel wall.

In Figure 10, ablation depths measured at the Massachusetts Institute of Technology[2] are presented as a function of spotsize. A power of 5 watts was used. Vaporization depth as a function of irradiation time was measured for spotsizes of 1000, 500, and 250 µm. Because of the constant power and the variable spotsize, each curve represents a different irradiance (W/cm²). Between the 250- and 1000-µm spotsizes, there is a factor of 4 increase in diameter or a factor of 16 increase in irradiance (W/cm²). Therefore, it takes longer to achieve the same hole depth when the irradiance is decreased by increasing the spotsize. Interestingly, the 250- and 500-µm curves lie virtually on top of each other. This seems strange in light of the factor of 4 increase in irradiance that occurs between the 500- and 250-µm spotsizes. As the spotsize becomes smaller and smaller, some other very interesting interactions must be happening in the tissue.

Direct Laser Angioplasty. In direct laser angioplasty, selective ablation may be an ideal treatment. If this approach is not possible, the next best procedure may be to identify the type of tissue before irradiating it: will the laser beam hit atheroma or normal tissue? Selective ablation has been suggested by Prince and associates,[3] who found that, with yellow atheroma specimens, there was a selective difference in tissue absorption at certain wavelengths. These investigators suggest that, at 465 nm, this difference is large enough that the dosimetry for plaque ablation will not injure the normal tissue. Unfortunately, some of the intermediate plaques tested in our laboratory

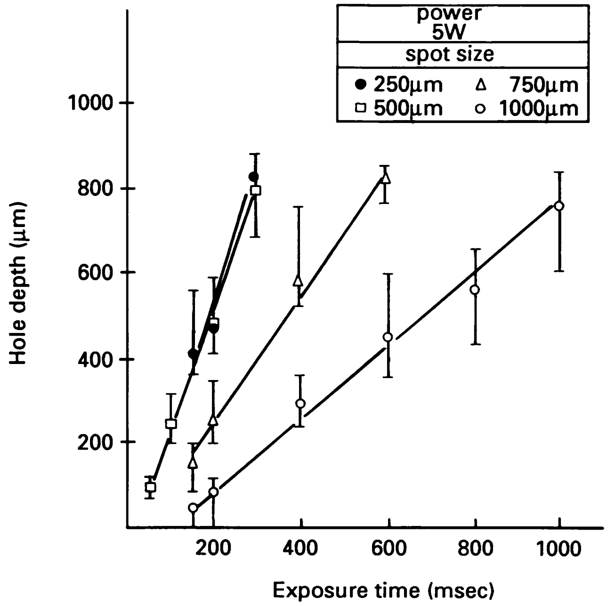

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Fig. 10 Ablation depth as a function of spotsize.

(From Cothren RM, et al,[2] with permission from IEEE J Quantum Electronics.)

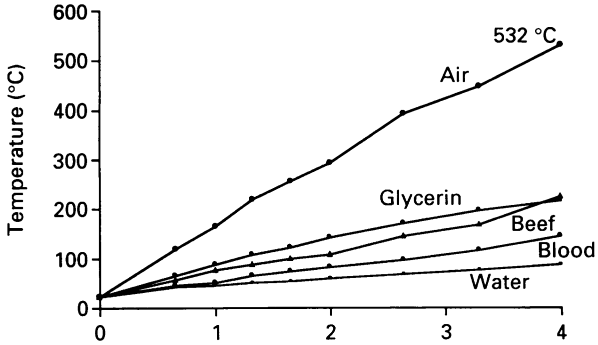

Fig. 11 *Hot-tip laser temperature/power relationships with different environments.*

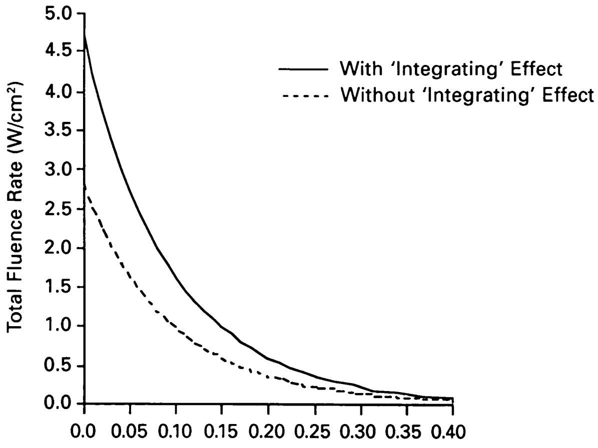

Fig. 12 *Fluence rate (W/cm²) of intravascular light during laser-balloon angioplasty.*

have been white; with white plaque, the selectivity curve is virtually reversed. We have found that it takes far more energy to ablate whitish atheromata than normal tissue.

The Food and Drug Administration has approved the use of angioplasty with hot-tip probes heated by laser light, and these devices are widely used in the peripheral arteries. During this procedure, the probe's entire tip becomes hot, and heat is transferred to the atheromata. The probe's performance depends upon the surrounding medium. If the vessel contains blood, a higher temperature increase will occur than if it contains saline. This is illustrated in Figure 11, which depicts the temperature/power relationships in different environments. In air, the probe reaches extremely high temperatures, because the air acts as an insulator around the probe and prevents heat from escaping as rapidly. When the probe is heated in the presence of blood, there is an interesting sequence of events: if the power is increased, there is a certain temperature at which the blood carbonizes and acts as an insulator with respect to the probe, thereby causing a rapid increase in the probe's temperature. Movement prevents coagulation on the probe, or, if coagulation does occur, coagulated material is rubbed off the tip so that movement may improve the probe's efficiency. During probe ablation in air, the temperatures produced in the tissue have been measured with a thermal camera and have been found to exceed 100 °C (often rising to between 150 and 180 °C).

Laser-Balloon Angioplasty. Laser-balloon angioplasty* is a somewhat different application that does not involve ablation. Once a lumen has been opened by means of standard balloon angioplasty, laser light is directed from within the balloon into the lumen in order to weld the fractured plaque matrix together and prevent tissue from dropping back into the lumen. This system, which was developed by Richard Spears,[1] uses an Nd:YAG laser (1060 nm) as the heating source.

What optical and thermal events are associated with laser-balloon angioplasty? This therapeutic mode presents an especially interesting optical problem because of the closed cavity created by the inflated balloon and the surrounding tissues, as well as the high degree of scattering associated with the 1060-nm wavelength. What happens to the light? What temperature is produced? Figure 12 shows the results of an analysis of the light distribution. For computational convenience, the direct diffuse laser irradiation of the surface of the balloon is arbitrarily set at 100 W/cm². This light enters the tissue and is scattered. The back-scattered light that leaves the tissue becomes a secondary irradiance as it falls onto another section of the balloon. Just below the surface of the tissue, there is 4 ½ times more light than the direct irradiance delivered by the laser. If light coming back into the balloon strikes another portion of the wall and is not considered, there is a factor of 2 ½ times more light (W/cm²) on the inner surface of the tissue than is being delivered by the direct laser source. This factor reveals the importance of considering the effects of backward and forward scattering when absorption is low and the closed-cavity geometry almost doubles again the noncavity light fluence rate in tissue .

Laser Anastomosis. Stewart Fleming, of England, performed a series of rat femoral anastomoses at our institution with a CO_2 laser, using a spotsize of 400 to 500 μm and 80 to 120 milliwatts, for an irradiation time of 0.05 to 0.25 seconds. Temperatures were measured with a thermal camera. The results showed that, during vessel welding, if the "shots" are too close

*Not to be confused with "laser-assisted balloon angioplasty," as used elsewhere in this issue.–*ed.*

together, a superposition of temperatures may occur. As a consequence, vessel temperature may exceed 120 °C rather than staying below, or at, the desired level of 80 °C achieved with a single laser pulse, even though the same irradiation parameters are used for each pulse. With continued irradiation, the tissue will dehydrate, and vacuolization will take place.

Many of the topics mentioned in this article (absorption/scattering properties, fluorescence, and the temperature increase that can lead to ablation) are discussed in further detail elsewhere in this issue.

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