PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61N 5/00	A1	WO 92/06739
		(43) International Publication Date: 30 April 1992 (30.04.92)

(21) International Application Number: PCT/US91/07627

(22) International Filing Date: 18 October 1991 (18.10.91)

(30) Priority data:
600,014 18 October 1990 (18.10.90) US

(71) Applicant: THE GENERAL HOSPITAL CORPORATION [US/US]; Office of Technology Affairs, Thirteenth Street, Building 149, Suite 1101, Charlestown, MA 02129 (US).

(72) Inventor: GREGORY, Kenton , W. ; 6 Marlborough Street, Apt. 1A, Boston, MA 02116 (US).

(74) Agent: CLARK, Paul, T.; Fish & Richardson, 225 Franklin Street, Boston, MA 02110-2804 (US).

(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LASER INDUCED PLATELET INHIBITION

(57) Abstract

A laser apparatus arranged to inhibit platelet adhesion to a vascular surface in a mammal. The apparatus comprises a laser arranged to provide a pulse of laser energy having a pulse duration less than the thermal relaxation time of said irradiated vascular surface. The laser energy is delivered to said vascular surface via radiographic contrast material.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU+	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE*	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

+ **Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.**

LASER INDUCED PLATELET INHIBITION

Background of the Invention

This invention relates to laser treatment of vasculature.

Platelets play an important role in treatment strategies for coronary arteries thrombi as well as arterial thrombosis in other portions of the body. Coronary artery re-occlusion following fibrinolysis is often due to platelet-rich thrombi in experimental models (Yasuda, J. Amer. Coll. Cardiology, 1989) and can be prevented by administration of monoclonal anti-platelet antibodies (specific for GP11b/111a) (Gold, Circulation, 1989).

Lasers have been employed as heating sources for metal probes in non-selective ablation of thrombus. Continuous wave blue-green argon ion laser irradiation has been used for selective ablation of thrombus, but the long exposure times inherent with this approach frequently result in damaging vessel walls by heat conduction. Some treatment strategies aimed at platelets, e.g., anticoagulation, or thrombolytic therapy (e.g., administration of t-PA), result in severe bleeding complications.

Summary of the Invention

We have discovered that short-duration pulses of laser irradiation can be used to preferentially treat vascular surfaces, with reduced likelihood of damage to surrounding endovascular tissue, so as to inhibit platelets from adhering or aggregating locally, while not affecting systemic anticoagulation.

In general, in one aspect, the invention features a method for inhibiting platelet adhesion to a surface of the vasculature in a mammal, which includes irradiating the surface with a laser energy pulse having a pulse

duration less than the thermal relaxation time of the irradiated surface, wherein the lasar energy is delivered to the vascular surface via radiographic contrast material. As used herein, "surface" of a vessel refers to the internal surface, i.e., facing the lumen; "radiographic contrast material" refers to a fluid which is transparent to optical wavelengths but opaque to xray irradiation and is injected to opacify blood vessels during xray procedures.

In preferred embodiments, the vascular surface may be an arterial surface or a venous surface; the pulse duration is less than one-half, more preferably less than one-tenth, the thermal relaxation time of the irradiated arterial surface. Preferably, the laser energy is delivered to the artery via a fluid-core laser catheter; more preferably, the radiographic contrast material is delivered through the fluid core laser catheter. Preferably, the radiographic contrast material is mixed with a therapeutic amount of one or more anticoagulants, such as heparin, a thrombolytic agent, e.g., one or both of streptokinase or TPA, or a thrombin inhibitor, e.g., argatropin or hirudin. Preferably, the pulse duration is less than 100 μsec, more preferably less than 2 μsec, still more preferably about 1 μsec or less; the pulse can be generated by a flashlamp-excited dye laser; the surface is irradiated with a succession of laser energy pulses, each having a pulse duration less than the thermal relaxation time of the irradiated surface; the repetition rate of the succession of pulses is less than 100 Hz, more preferably about 20 Hz or less, and preferably not greater than the reciprocal of the thermal relaxation time of the irradiated surface; the relaxation interval between successive pulses is greater than 100 μsec, more preferably greater than one msec, and still

more preferably greater than twice the thermal relaxation time of the irradiated surface.

The method may further include administering a therapeutic amount of a thrombolytic agent to the mammal intravenously, intra-arterially, or through the optical fluid stream.

In various aspects, the method is a method for preventing platelet adhesion to an arterial surface following injury to the arterial surface, particularly following occlusion of the artery by a thrombus; or following angioplasty, unstable angina, or acute myocardial infarction.

A "platelet-containing mass", as used herein, is a mass containing platelets, e.g., a layer of platelets covering the vessel surface, or a clot containing platelets, e.g., a thrombus. A thrombus originates at a site of blockage and is a clot or aggregation of blood factors, primarily platelets and fibrin, with the entrapment of cellular elements. A thrombus can originate in a vein or an artery; such a thrombus can break apart, and fragments of it can move away from the place of origin and become lodged elsewhere in the cardiovascular system as an arterial or venous embolus, forming an obstruction which can include foreign material other than a clot. An embolus which dislodges and travels to the lungs can form a pulmonary embolism.

When the arterial surface is irradiated with laser energy, as for example when laser energy is directed at the inner surface of the artery in the form of a beam, the energy is absorbed by various components of the irradiated portion of the arterial surface as the beam penetrates into the artery, and the energy of the beam is progressively attenuated at greater depths beyond the irradiated surface.

For a circular beam consisting of substantially parallel rays, the irradiated portion of the arterial surface has approximately the form of a cylinder whose axis corresponds to the axis of the beam. For purposes of description, the "irradiated volume" of the irradiated surface is taken as a cylinder whose diameter is the diameter of the beam and whose height is the depth to which 67% of the energy of the beam has been absorbed.

As the beam energy is absorbed, heat is generated, and the temperature of the irradiated portion of the arterial surface rises. Heat dissipates away from the irradiated portion of the surface into the cooler matter surrounding it, raising the temperature of the surrounding matter, from which also the heat dissipates. When the beam is shut off or is moved away from the irradiated portion of the arterial surface, the dissipation of heat continues as the temperature of the irradiated arterial surface falls and the irradiated surface and the surrounding matter approach an equilibrium state.

The rate of dissipation of heat for a particular material varies according to the thermal diffusion constant of the material, expressed as K, and the time required for the temperature of the irradiated mass to fall to a specified temperature depends upon K and upon the dimensions of the arterial surface.

The "thermal relaxation time", expressed as t, is the time required for the temperature at an irradiated surface whose temperature has been increased to $T + \Delta T$ by a pulse of energy to return to a temperature $T + 0.5(\Delta T)$. The thermal relaxation time t is measured from the initiation of the pulse.

The thermal relaxation time t can be measured directly by the use of, for example, a suitable temperature measuring device; or t can be calculated from

a knowledge of the dimensions and thermal characteristics of the irradiated surface. For a uniform surface of small dimensions and for pulses of light energy of short duration, t is related to K and the dimensions of the surface approximately according to the relation

$$t = d^2/2K,$$

where d, expressed in cm, is the smaller of: (1) the diameter of the irradiated volume (taken here to be the diameter of the beam, as described above; conventionally expressed as "D"), or (2) the depth of the irradiated volume (taken here as the depth beyond the surface of the irradiated tissue at which 67% of the incident energy has been absorbed; conventionally expressed as "d"). The thermal diffusion constant for most soft tissues and for platelet-containing masses approximates that of water; that is, K is approximately 0.0013 cm^2/sec.

The above method of calculating t is given for illustration only; where reference is made to the relationship between pulse duration and t, it is the actual thermal relaxation time of the particular tissue that is intended.

A laser energy "pulse", as that term is used here, means a quantity of laser energy, delivered during a time interval in which the rate of energy delivery is high enough that the energy fluency of the pulse [can cause ablation of the mass,] followed by a time interval in which the rate of energy delivery is low enough to permit thermal relaxation of the surface.

It will be appreciated that the process of diffusion of heat away from the irradiated surface into surrounding matter begins at the moment the temperature of the irradiated surface begins to elevate. Where the pulse duration is sufficiently low with respect to the thermal relaxation time of the irradiated surface, an energy fluence can be directed onto the irradiated

surface that is sufficient to alter the character of the surface of the vessel such that platelet adherence is inhibited, yet not so great as to damage surrounding tissues either by direct irradiation or by excessive conductive heating during the relaxation interval.

The "pulse duration" (here expressed in μsec) of a laser energy pulse is the time interval in which the intensity of the radiation is equal to or greater than half its maximum over the entire pulse. The energy fluence delivered (expressed in J/cm^2) by each pulse describes the concentration of energy, or energy per unit area, delivered to the irradiated field.

Where the pulse duration is sufficiently low in comparison to the repetition rate, an interval between pulses occurs, in which the temperature of the irradiated tissue falls as the heat generated during the pulse dissipates into the surrounding matter. The "relaxation interval", as that term is used here, is defined as the difference between the time interval between initiations of succeeding pulses and the pulse duration.

The arterial surface can be irradiated with a series of repeating pulses, and the "repetition rate", as that term is used here, is the rate (expressed in cycles/sec, or Hz) at which pulses are initiated.

The method of the invention provides for the treatment of vascular surfaces with reduced likelihood of damage to surrounding tissues, to prevent platelets from adhering and aggregating locally, while not affecting systemic anticoagulation; that is, with a greater margin of safety to the mammal being treated. The preferential absorption of laser energy by the arterial surface in comparison to surrounding tissues is sufficiently high throughout the visible spectrum that the method can be practiced at wavelengths other than those where absorption maxima occurs. A particular wavelength can be

selected to optimize wavelength dependent criteria, including apparatus-related criteria such as ease of transmission through optical fibers and availability, cost and reliability of various laser systems, and including treatment-related criteria such as the desired depth of ablation per pulse.

The method may be combined with other known techniques. For example, pulsed laser irradiation can be used according to the invention to treat vascular surfaces, and in conjunction with (i.e., concurrently or thereafter the vascular surface can be exposed to) one or more thrombolytic agents such as streptokinase or t-PA. The partial breakdown of the obstruction, and the resulting increase in its surface area, can render it more susceptible to the action of the thrombolytic agent. Alternatively, if the patient has been treated with streptokinase or TPA and failed to respond, the method of the invention could be used to treat the thrombus or platelet covered surface by removing the thrombus or platelets. In fact, streptokinase or TPA do not remove the platelet portion of the thrombus; these agents only remove the fibrin portion of the clot; platelets remaining after streptokinase or TPA treatment are available to form another clot, as well as capable of promoting artheriosclerosis by releasing growth factors.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof and from the claims.

Description of the Preferred Embodiments

Any of a variety of practical considerations can enter into the selection or design of delivery catheters and the choice of laser exposure parameters, including wavelength, pulse duration, relaxation interval, and energy fluence. Consideration can be given, for example, to achieving uniform exposure of the arterial surface to

laser irradiation; to generate a minimum of debris; to minimize thermal injury to normal structures; and to prevent or reduce the likelihood of vascular perforation.

Any laser which can deliver pulses of the desired intensity, duration, and wavelength can be used. A preferred laser is a flashlamp-excited pulsed dye laser (Dymed pulsed dye laser Model 3000). Lasar energy is delivered to the vessel surface via radiographic contrast material; any standard contrast material may be used, e.g., angiovist (Berlex, Wayne, NJ) or hexabrix (Mallincrodt, St. Louis, MO). The fiber optic bundles and auxiliary apparatus by which laser light is delivered to the obstruction can be of any conventional configuration, for example, as described in Choy, U.S. Pat. No. 4,207,874. A second fiber optic bundle can be used for detecting an obstruction, if one exists, and monitoring the progress of ablation of the obstruction.

The fluence (Joules/cm^2) of the laser light should be sufficiently high to treat the arterial surface at the wavelength and pulse duration employed, and not so high as to cause unacceptable damage to surrounding healthy tissue. The requisite fluence range varies with the diameter of the optical fiber used, with smaller diameter fibers requiring higher fluences to compensate for scattering losses at the periphery of the illuminated volume.

Procedure

The method of the invention can be used for selectively treating vascular surfaces to prevent platelets from adhering and aggregating locally in vivo by employing known methods of directing optical energy to irradiate the vascular surface with laser energy having suitable pulse duration, as described generally above.

Example

An animal model of coronary artery thrombosis (developed by Herman Gold and Louise Guerrero, Massachusetts General Hospital) was used to test the method of the invention. In this model, the animal is under anesthesia and the left circumflex or left anterior descending coronary artery is treated. First, the artery is isolated and an external hose clamp plastic connector is placed around the distal coronary artery. Arterial blood flow is decreased with the clamp to reduce flow by 50%, which corresponds to a 90 stenosis. The proximal artery is then damaged by forcep compression, thus effectively removing the endothelium and results in deep tears to the media. A period of 20 min. of perfusion is allowed for platelet adhesion and aggregation and then thrombin in whole blood is injected in a proximal side branch to create a mixed platelet and fibrin thrombus. The thrombus is allowed to mature for 3 hours before laser treatment is accomplished.

Materials

Laser energy deposition is performed with a Dymed pulse dye laser or a candela pulse dye laser (Candela Corp., Wayland, MA) emitting light pulses. This laser generated 1 μsec-long pulses at a repetition rate of 3-5 hertz. Approximately 3-10 joules/cm^2 is used in a 1 mm^2 irradiation area. Laser output spectrum was measured with a monochromator, and ranged from 480 to 580 nm with the maximum at 482 nm. Pulse width was measured with a reverse biased silicon photodiode (EG&G, Salem, MA). The laser radiation was focused with a 2.5 cm focal length quartz lens into a 320 μm core diameter quartz optical fiber (Spectran Corp., Sturbridge, MA). The delivered energy per pulse was measured with an energy meter (Scientech, Boulder, CO.) or a power meter (Coherent, Palo Alto, CA), and varied ± 5%. Approximately 100-1000 laser pulses are needed in this experimental model.

The laser energy is delivered to the circumflex or left anterior descending coronary arteries via a fluid core laser catheter. The fluid core laser catheter is introduced into the coronary artery with conventional angioplasty guidewire and guiding catheter techniques. A power injector is connected to the fluid core catheter and radiographic contrast media is injected to carry the light to the coronary artery under fluoroscopic guidance.

Results

The method of the invention was tested by performing the above-described animal test on 22 dogs. The left anterior descending or left circumflex coronary artery in each dog was damaged by forcep compression and a mixed platelet and fibrin thrombus allowed to form before the artery was exposed to laser irradiation. All 22 arteries achieved reprofusion; of these, 2 became reoccluded within 30 min. and 2 demonstrated cyclic reocclusion; the remaining 18 remained patent for a mean of 1.4 hr. Thus, the method of the invention gives an 80% patency rate. Four control arteries which did not receive laser treatment also did not achieve reperfusion and were occluded at the time of evaluation. Compared to arteries treated with recombinant TPA, which show a 20% patency rate at 10 min., the above-irradiated arteries show an 80% patency rate at a mean of 1.4 hr.

Histology and Electron Microscopy

Fresh specimens of coronary artery were obtained from the above-described test dogs. The specimens were processed for routine histology with hematoxylin and eosin staining.

Histologic evaluation of coronary arteries which had been previously occluded and laser treated to remove platelets and fibrin revealed a widely patent artery in a tract through which the fiber passed. There was no

evidence of carbonization or thermal alteration of either the embolus or the underlying coronary artery. A high power magnification of one artery showed a clean arterial surface with no platelet deposition. Histologic evaluation of an artery which was comparatively treated with T-PA showed a patent artery at 7 1/2 min. and the absence of subendothelial structures. However, deep layers of platelets and fibrin were evident with platelet monolayers as well as aggregates.

The specimens were also processed for scanning electron microscopy of the laser irradiated arteries which showed deep medial tears resulting from forceps denudation, but no platelet deposition. Laser-treated surfaces were notable in that they showed either the complete absence of adhering platelets or a markedly reduction in platelet adherence compared to control dogs or dogs treated with TPA or streptokinase. A transmission electron micrograph of a laser treated vessel following forceps trauma revealed dead and dying smooth muscle cells, no endothelial cells, no internal elastic lumen, and no base membrane. Undenatured collagen fibrils were covered by an electron dense layer which might prevent platelets from recognizing collagen receptors and, thus, inhibit platelet adhesion.

Use

Pulsed laser radiation can be employed with a wide margin of safety to a previously occluded vessel to prevent reocclusion, or to a vessel that is sub-occluded by platelet or thrombus adherence. A wide range of wavelengths may be used to treat the vessel surface; wavelength-dependent criteria which may be considered are depth of optical penetration, desired depth of ablation per laser pulse, ease of transmission through optical fibers, and cost and reliability of various laser systems.

The method of the invention may also be used for canalization, disruption, or ablation of a platelet-containing mass; e.g., for treatment of acute and chronic coronary artery thrombotic syndromes, as well as arterial thrombosis in other organs; for treatment of acute myocardial infarction; for prevention of thrombosis and restenosis following enterectomy or balloon angioplasty; and for treatment of unstable angina. Laser irradiation can advantageously be combined for example with infusion, according to conventional techniques, of a thrombolytic agent such as streptokinase or t-PA for safe and efficient removal of a mass.

The inventive method can also be used for the selective ablation of thrombus and prevention of reocclusion in a graft of the kind used, for example, in bypass surgery for diverting blood around blockages in the arterial systems. The invention can be used in tissue grafts or in grafts made from a prosthetic material, and the pulse widths and energy fluencies can be adjusted to provide efficient treatment of the arterial surface without damaging the graft.

Other embodiments are within the following claims.

Claims

1. Laser apparatus arranged to inhibit platelet adhesion to a vascular surface in a mammal, characterized in that said apparatus comprises a laser arranged to provide a pulse of laser energy having a pulse duration less than the thermal relaxation time of said irradiated vascular surface, wherein said laser energy is delivered to said vascular surface via radiographic contrast material.

2. The laser apparatus of claim 1, wherein said laser is arranged to provide pulsed laser energy to a platelet-containing mass on said vascular surface and the laser energy radiation is arranged to prevent re-occlusion of the vascular surface.

3. The laser apparatus of claim 1, wherein said laser is arranged to provide a pulse duration of less than one-half said thermal relaxation time.

4. The laser apparatus of claim 3 wherein said laser is arranged to provide a repetition rate of a succession of pulses which is less than 100 Hz.

5. The laser apparatus of claim 4 wherein said laser is arranged to provide a repetition rate of a succession of pulses which is less than about 20 Hz.

6. The laser apparatus of claim 4 wherein said laser is arranged to provide a relaxation interval between successive pulses greater than 1 msec.

7. The laser apparatus of claim 6 wherein said laser is arranged to provide a relaxation interval between successive pulses greater than about 100 μsec.

8. The laser apparatus of claim 1, characterized in that said apparatus further comprises a fluid core laser catheter arranged to direct laser energy and radiographic contrast material to said vascular surface.

9. The laser apparatus of claim 8, further characterized in that said apparatus is arranged to mix one or more anticoagulants with said radiographic contrast material and to provide said mixture to said vascular surface via said fluid core laser catheter.

10. The laser apparatus of claim 9, said one or more anticoagulant being heparin, a thrombolytic agent, or a thrombin inhibitor.

11. A laser apparatus for treatment of arteries involved in acute myocardial infarction, unstable angina or arterial occlusion following balloon angioplasty, characterized in that said apparatus comprises a laser arranged to provide a pulse of laser energy having a pulse duration less than the thermal relaxation time of said irradiated vascular surface.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/07627

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61N 5/00

U.S.Cl.: 128/395

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
US Cl.	128/395-398 604/20 606/2,3,7,8,10,11

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 4,829,262 (FURUMOTO) 09 May 1989 See the entire document.	1-7, 11
X	US, A, 4,556,057 (HIRUMA ET AL.) 03 December 1985 See the entire document.	1-7, 11
P,Y	US, A, 5,019,075 (SPEARS ET AL.) 28 May 1991 See the entire document.	8-10
Y	US, A, 4,870,953 (DON MICHAEL ET AL.) 03 October 1989 See the entire document.	8-10
P,Y	US, A, 5,040,548 (YOCK) 20 August 1991 See the entire document.	8-10
P,Y	US, A, 4,966,596 (KUNTZ ET AL.) 30 October 1990 See the entire document.	8-10

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 February 1992	17 MAR 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Mark S. Graham

Form PCT/ISA/210 (second sheet) (Rev.11-87)