(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 April 2008 (24.04.2008)

PCT

(10) International Publication Number
WO 2008/049082 A2

(51) International Patent Classification:
A61B 18/14 (2006.01)

(21) International Application Number:
PCT/US2007/081845

(22) International Filing Date: 18 October 2007 (18.10.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/852,787	18 October 2006 (18.10.2006)	US
60/921,973	4 April 2007 (04.04.2007)	US
60/976,752	1 October 2007 (01.10.2007)	US

(71) Applicant *(for all designated States except US)*: **MINNOW MEDICAL, INC.** [US/US]; 10911 Technology Place, San Diego, CA 92127 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **STONE, Corbett W.** [US/US]; c/o Minnow Medical, Inc., 10911 Technology Place, San Diego, California 92127 (US). **HOEY, Michael F.** [US/US]; c/o Minnow Medical, Inc., 10911 Technology Place, San Diego, California 92127 (US). **GUSTUS, Rolfe Tyson** [US/US]; c/o Minnow Medical, Inc., 10911 Technology Place, San Diego, California 92127 (US). **PERRY, Mike** [US/US]; c/o Minnow Medical, Inc., 10911 Technology Place, San Diego, California 92127 (US). **BLANCK, Arthur G.** [US/US]; c/o Minnow Medical, Inc., 10911 Technology Place, San Diego, California 92127 (US). **KUNSTMANAS, Linas R.** [US/US]; c/o Minnow Medical, Inc., 10911 Technology Place, San Diego, California 92127 (US).

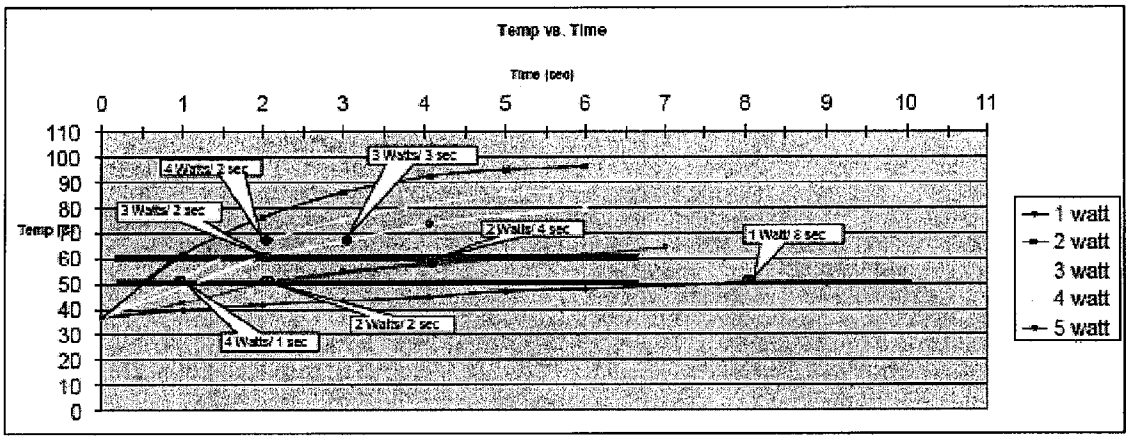
(74) Agents: **SHEVLIN, Michael** et al.; TOWNSEND AND TOWNSEND AND CREW LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) **Title:** INDUCING DESIRABLE TEMPERATURE EFFECTS ON BODY TISSUE



(57) **Abstract:** Methods and systems are disclosed for treating diseased tissue by gentle heating. The method induces vasodilation on tissue disposed about an lumen having both healthy tissue and diseased tissue. The method includes coupling a probe surface to the luminal tissue at a target location and transmitting desired quantities of tissue remodeling energy from the coupled probe into each of a plurality of discrete remodeling zones in the luminal tissue so that the tissue remodeling energy heats the plurality of remodeling zones, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

WO 2008/049082 A2

INDUCING DESIRABLE TEMPERATURE EFFECTS ON BODY TISSUE

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 USC 119(e) of U.S. Provisional Application No. 60/852,787, filed on October 18, 2006, and entitled "Tuned RF Energy And Electrical Tissue Characterization For Selective Treatment Of Target Tissues"; U.S. Provisional Application No. 60/921,973, filed on April 4, 2007, and entitled "Tuned RF Energy And Electrical Tissue Characterization For Selective Treatment Of Target Tissues", and U.S. Provisional Application No. 60/976,752, filed on October 1, 2007, entitled "Inducing Desirable Temperature Effects On Body Tissue", the full disclosures of which are incorporated herein by reference.

[0002] This application is related to U.S. Patent Application No. 11/392,231, filed on March 28, 2006, entitled "Tuned RF Energy for Selective Treatment of Atheroma and Other Target Tissues and/or Structures"; US Patent Application No. 10/938,138, filed on September 10, 2004, and entitled "Selectable Eccentric Remodeling and/or Ablation of Atherosclerotic Material"; U.S. Patent Application No. 60/852,787, filed on October 18, 2006, entitled "Tuned RF Energy And Electrical Tissue Characterization For Selective Treatment Of Target Tissues"; U.S. Provisional Application No. 60/921,973, filed on April 4, 2007, entitled "Tuned RF Energy And Electrical Tissue Characterization For Selective Treatment Of Target Tissues"; and U.S. Provisional Application No. 60/976,733, filed on October 1, 2007, entitled "System for Inducing Desirable Temperature Effects on Body Tissue", the full disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0003] 1. Field of the Invention

[0004] The present invention is generally related to medical devices, systems, and methods. In exemplary embodiments, the invention provides catheter-based treatment for luminal diseases, particularly for atherosclerotic plaque, vulnerable or "hot" plaque, and the like. The structures of the invention allow remodeling artery tissue using heat.

[0005] Physicians use catheters to gain access to and repair interior tissues of the body, particularly within the lumens of the body such as blood vessels. For example, balloon

angioplasty and other catheters often are used to open arteries that have been narrowed due to atherosclerotic disease.

[0006] Balloon angioplasty is often effective at opening an occluded blood vessel, but the trauma associated with balloon dilation can impose significant injury, so that the benefits of balloon dilation may be limited in time. Stents are commonly used to extend the beneficial opening of the blood vessel.

[0007] Stenting, in conjunction with balloon dilation, is often the preferred treatment for atherosclerosis. In stenting, a collapsed metal framework is mounted on a balloon catheter which is introduced into the body. The stent is manipulated into the site of occlusion and expanded in place by the dilation of the underlying balloon. Stenting has gained widespread acceptance, and produces generally acceptable results in many cases. Along with treatment of blood vessels (particularly the coronary arteries), stents can also be used in treating many other tubular obstructions within the body, such as for treatment of reproductive, gastrointestinal, and pulmonary obstructions.

[0008] Restenosis or a subsequent narrowing of the body lumen after stenting has occurred in a significant number of cases. More recently, drug coated stents (such as Johnson and Johnson's Cypher™ stent, the associated drug comprising Sirolimus™) have demonstrated a markedly reduced restenosis rate, and others are developing and commercializing alternative drug eluting stents. In addition, work has also been initiated with systemic drug delivery (intravenous or oral) which may also improve the procedural angioplasty success rates.

[0009] While drug eluting stents appear to offer significant promise for treatment of atherosclerosis in many patients, there remain many cases where stents either cannot be used or present significant disadvantages. Generally, stenting leaves an implant in the body. Such implants can present risks, including mechanical fatigue, corrosion, and the like, particularly when removal of the implant is difficult and involves invasive surgery. Stenting may have additional disadvantages for treating diffuse artery disease, for treating bifurcations, for treating areas of the body susceptible to crush, and for treating arteries subject to torsion, elongation, and shortening.

[0010] A variety of modified restenosis treatments or restenosis-inhibiting treatment modalities have also been proposed, including intravascular radiation, cryogenic treatments, ultrasound energy, and the like, often in combination with balloon angioplasty and/or stenting. While these

and different approaches show varying degrees of promise for decreasing the subsequent degradation in blood flow following angioplasty and stenting, the trauma initially imposed on the tissues by angioplasty remains problematic.

[0011] A number of alternatives to stenting and balloon angioplasty so as to open stenosed arteries have also been proposed. For example, a wide variety of atherectomy devices and techniques have been disclosed and attempted. Despite the disadvantages and limitations of angioplasty and stenting, atherectomy has not gained the widespread use and success rates of dilation-based approaches. More recently, still further disadvantages of dilation have come to light. These include the existence of vulnerable plaque, which can rupture and release materials that may cause myocardial infarction or heart attack.

[0012] In light of the above, it would be advantageous to provide methods and systems for inducing vasodilation on artery tissue and remodeling of the lumens of the body. It would further be desirable to avoid significant cost or complexity while providing structures which could remodel body lumens without having to resort to the trauma of extreme dilation, and to allow the opening of blood vessels and other body lumens which are not suitable for stenting.

BRIEF SUMMARY OF THE INVENTION

[0013] The present invention generally provides methods and systems for inducing desirable temperature effects on artery tissue, particularly, diseased tissue.

[0014] In one embodiment, a method is disclosed for inducing vasodilation on artery tissue disposed about an arterial lumen having both healthy tissue and diseased tissue. The method includes coupling a probe surface to the artery tissue at a target location and transmitting desired quantities of energy intended to remodel the tissue ("tissue remodeling energy") from the coupled probe into each of a plurality of discrete tissue volumes ("remodeling zones") in the artery tissue so that the tissue remodeling energy heats the plurality of remodeling zones, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen..

[0015] In another embodiment, a method is disclosed for remodeling artery tissue disposed about an arterial lumen using heat assisted balloon angioplasty. The method includes expanding a catheter balloon within the artery lumen in contact with the artery tissue, wherein a plurality of electrodes are disposed about the catheter balloon and coupled with the artery tissue so as to define a plurality of remodeling zones in the artery tissue when the balloon is in contact with the

artery tissue. The plurality of electrode pairs are then energized with associated desired quantities of bipolar tissue remodeling energy so as to heat each of the plurality of remodeling zones with the associated desired tissue remodeling energy, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

[0016] In still another embodiment, a method is disclosed for treating a treatment area within a blood vessel. The method includes providing a catheter having an energy delivery portion, inserting the energy delivery portion of the catheter into said blood vessel and positioning said catheter portion within the treatment area, using the catheter portion to deliver energy to the vessel at a plurality of energy delivery zones within the treatment area, each of which is small compared to the treatment area. Said delivery of energy comprises delivering energy from the catheter portion, such that in an eccentrically diseased vessel, the energy will heat both healthy tissue and diseased tissue, and using the energy to heat diseased tissue to a temperature sufficient to efficaciously alter the diseased tissue without causing sufficient thermal damage to the healthy tissue so as to induce a long-term occlusive response.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Fig. 1 shows temperature vs. time curves of various electrode energy settings to achieve surface temperatures between 50°C and 65°C.

[0018] Fig. 2 shows time vs. temperature curves from a FEA computer modeling simulation compared with the curves of Fig. 1.

[0019] Figs. 3 and 4 show finite element model composition.

[0020] Fig. 5 shows finite element model results of treatment power 0.5 Watts for 30 seconds into healthy tissue (Peak = 51°C).

[0021] Fig. 6 shows finite element model results of treatment power 0.5 Watts for 30 seconds into vulnerable plaque (Peak = 61°C).

[0022] Fig. 7A illustrates diffuse atherosclerotic disease in which a substantial length of multiple blood vessels has limited effective diameters.

[0023] Fig. 7B illustrates vulnerable plaque within a blood vessel.

[0024] Fig. 7C illustrates the sharp bends or tortuosity of some blood vessels.

[0025] Fig. 7D illustrates atherosclerotic disease at a bifurcation.

[0026] Fig. 7E illustrates a dissection within a blood vessel.

[0027] Fig. 7F illustrates an artery wall around a healthy artery.

[0028] Fig. 7G illustrates a restenosed artery.

[0029] Fig. 8 schematically illustrates a balloon catheter system according to the present invention.

[0030] Fig. 9 schematically illustrates placement of electrode pairs for use in bipolar energy treatment.

[0031] Fig. 10 schematically illustrates placement of electrodes for use for monopolar energy treatment.

[0032] Figs. 11A-11C illustrate a method of using a balloon catheter system treating artery tissue.

[0033] Fig. 12 illustrates frequency targeting of tissues.

[0034] Fig. 13 shows histological results for the application of 1 Watt for 8 seconds at seven days.

[0035] Fig. 14 shows histological results for the application of 2 Watts for 2 seconds at eight days.

[0036] Figs. 15A and 15B show histological results for the application of 4 Watts for 1 second at seven days.

[0037] Fig. 15C shows histological results for the application of 4 Watts for 1 second at thirty days.

[0038] Figs. 16A and 16B show histological results for the application of 2 Watts for 4 seconds at seven days.

[0039] Fig. 16C shows histological results for the application of 2 Watts for 4 seconds at thirty days.

[0040] Fig. 17A shows histological results for the application of 3 Watts for 2 seconds at seven days.

[0041] Fig. 17B shows histological results for the application of 3 Watts for 2 seconds at thirty days.

[0042] Figs. 18A-18G show results of bench top testing.

[0043] Fig. 19 graphically illustrates advantageous treatment power and time ranges for different electrode geometries, for use in embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0044] The present invention provides systems and methods to affect vessel plaque with a controlled amount of thermal energy to reduce plaque burden, increase lumen blood flow, and decrease plaque embolic vulnerability. In eccentric disease with non-targeted plaque, a lower temperature may be used to concomitantly treat both plaque ("diseased tissue") and non-diseased artery tissue ("healthy tissue"). In this scenario, a thermal therapy must be applied that reduces or eliminates recoil from balloon expansion or future vessel contraction. However, it must also impart enough thermal perturbation to promote tissue remodeling, debulking and stabilization without immediate collagen shrinkage and stenosis. You can render the smooth muscle contraction ineffective without actually killing or ablating it by heating it to 47-48°C. The actin and myosin proteins become denatured but vital oxidative metabolic enzymes remain intact. This can promote luminal dilation or at minimum, prevent constriction (i.e. angioplasty balloon expansion vessel recoil or vasospasms often linked as a contributor to acute anginal attacks). Also, thermal energy must be low enough to prevent "thermal fixation". In this case, tissue is "fixed" analogous to formalin fixation that prevents a desired immune system activated tissue debulking. As a general guide to tissue-temperature effects, below is a list of correlations that fall within the 2-10 second duration range:

42°C = protein denaturation
41°-44°C = DNA susceptibility
43°C = spontaneous depolarizations
45°C = mitochondrial breakdown
47.5°C = contractile protein breakdown
48°C = depolarization incapable
50°C = blood cells become amorphous
50°C = intracellular toxicity
50°C = irreversible cell death
>50°C = oncosis

[0045] In the case of therapy for non-targeted eccentric disease, it can be deduced that most of the above tissue-temperature effects below 50°C would be advantageous. While inducing a

therapeutic temperature with radiofrequency energy (RF) for even a second can result in tissue temperatures with a longer duration of elevated temperatures due to the built-up "sensible" heat that continues to thermally diffuse into surrounding tissue. Irreversible cell death temperatures are suggested above but in reality comprise a wide range of temperatures capable of such effect. These temperatures can mathematically be described by a "line-fit" algorithm of ($y = ^{-}0.011x + 55.01$), whereas the y-axis is temperature in (°C) and the x-axis is in time in (sec). This demonstrates irreversible cell death as a relationship of temperature vs. time with the above described slope starting from 55°C at 1 second to 45°C at 1000 seconds. At temperatures higher than 55°C, time for cell death is too short to be effectively measured, and below 45°C the time required is too long to be useful.

[0046] There are other tissue-temperature effects that occur at higher temperatures but should be applied only to known and targeted diseased plaque without application to surrounding healthy tissue. Tissue temperatures above 60°C become capable of immediate tissue debulking in plaque but could render healthy vessel stenosed, charred, perforated or vaporized. Examples of these tissue-temperature effects are:

72°-86°C = type 1 collagen breakdown
85°C = blood coagulation/clumping
82-96°C = type 3 collagen breakdown
100°C = intracellular/interstitial fluid phase change – "popping"
>100°C = tissue desiccation
100°-200°C = tissue glucose sticks to electrode
>200°C = rapid vaporization/cell explosions (cutting), carbonization

[0047] Some fats begin melting at a temperature as low as 51°C while other fats require temperatures up to 90°C. Therefore, some fat can be melted and remodeled at the low temperature therapy while all of the fat can be melted at the high temperature.

[0048] Plaque that has a thin fibrous cap surrounding a larger lipid core (vulnerable plaque) should respond to a temperature around 50-55°C and the tissue should be rendered irreversibly damaged without removing it. The consequent immune system response should be phagocytic tissue debulking and scar tissue genesis. Theoretically this could protect vulnerable plaque from future rupture and resultant cascade events leading to thrombus or acute myocardial infarction. This treatment also has the potential to open up the lumen to a modest degree via the debulking and remodeling processes.

[0049] Heat Shock proteins may play a role in tissue debulking after thermal therapy by activation of Heat Shock Proteins (HSP's). First, HSPs are proteins that exist in most living cells i.e. mammals, plants, and yeast. They often act like "chaperones" to ensure that a cell's normal functional proteins are in the right place at the right time. Their concentrations can increase in response to stress, such as heat, cold or lack of oxygen. Their increased presence can be a signal to the immune system for sick or necrotic cells that require removal, and therefore play a role in tissue debulking after a thermal treatment.

[0050] The present invention will be particularly useful for remodeling materials along a partially occluded body lumen or artery in order to open the lumen and increase blood flow. The devices, systems, and methods disclosed herein may be used in any body lumen, for example, artery lumens such as the femoral, popliteal, coronary and/or carotid arteries. While the disclosure focuses on the use of the technology in the vasculature, the technology would also be useful for any luminal obstruction. Other anatomical structures in which the present invention may be used are the esophagus, the oral cavity, the nasopharyngeal cavity, the auditory tube and tympanic cavity, the sinus of the brain, the arterial system, the venous system, the heart, the larynx, the trachea, the bronchus, the stomach, the duodenum, the ileum, the colon, the rectum, the bladder, the ureter, the ejaculatory duct, the vas deferens, the urethra, the uterine cavity, the vaginal canal, and the cervical canal.

[0051] Some embodiments described herein may be used to treat atherosclerotic disease by gentle heating in combination with gentle or standard dilation. (Gentle heating and dilatation to be defined below.) For example, an angioplasty balloon catheter structure having electrodes disposed thereon might apply electrical potentials to the vessel wall before, during, and/or after dilation, optionally in combination with dilation pressures which may allow significantly lower than standard, unheated angioplasty dilation pressures. Where balloon inflation pressures of 10-16 atmospheres may, for example, be appropriate for standard angioplasty dilation of a particular lesion, modified dilation treatments combined with appropriate electrical potentials may be effected with pressures of 6 atmospheres or less, and possibly as low as 1 to 2 atmospheres. One example of a suitable balloon catheter device is disclosed U.S. Provisional Application No. 60/976,733, filed on October 1, 2007, entitled "System for Inducing Desirable Temperature Effects on Body Tissue", the full disclosures of which are incorporated herein by reference.

[0052] In many embodiments, gentle heating energy added before, during, and/or after dilation of a blood vessel may increase dilation effectiveness while lowering complications. In some

embodiments, such controlled heating with a balloon may exhibit a reduction in recoil, providing at least some of the benefits of a stent-like expansion without the disadvantages of an implant. Benefits of heating the artery may be enhanced (and/or complications inhibited) by limiting heating of the adventitial layer below a deleterious response threshold. Such heating of the intima and/or media may be provided using heating times of less than about 10 seconds, often being less than 3 (or even 2) seconds.

[0053] Remodeling of the tissue in the present invention is done in remodeling zones with the application of tissue remodeling energy, typically in the form of RF, microwave and/or ultrasound energy to tissue between electrode pairs. This energy will be controlled so as to limit a surface or bulk temperature of target and/or collateral tissues, for example, limiting the heating of a fibrous cap of a vulnerable plaque or the intimal layer of an artery structure to a maximum temperature in a range somewhere between 47°C and 99°C; more specifically described as follows. This temperature range may be divided into two dose treatment ranges, low or "gentle" surface temperature treatment between 50°C to 65°C, and high surface temperature treatment between 65°C to 99°C ranges. The intent of low temperature treatment is to create a surface temperature between 50°C to 65°C, such that the bulk tissue temperature remains mostly below 50°C - 55°C, which will not severely damage healthy tissue found in eccentric disease. The intended result is to reduce the recoil due to the balloon expansion. This low temperature treatment dose is safe for all tissues without the use of selectivity. The intent of high surface temperature treatment between 65°C to 99°C is to shrink, melt, and debulk the disease tissue. The intended result is to reduce and melt the plaque burden. This high temperature treatment dose is only intended to be used when selectivity of treatment site is available.

[0054] Limiting heating of a lipid-rich pool of a vulnerable plaque sufficiently to induce melting of the lipid pool while inhibiting heating of other tissues (such as an intimal layer or fibrous cap) to a surface temperature in a range from about 50°C to about 65°C may minimize or inhibit an immune response that might otherwise lead to restenosis, or the like, and may be sufficient to denature and break protein bonds during treatment, immediately after treatment, and/or more than one hour, more than one day, more than one week, or even more than one month after the treatment through a healing response of the tissue to the treatment so as to provide a bigger vessel lumen and improved blood flow.

[0055] To keep surface temperatures of the tissue in a range from about 50°C to about 65°C, power is applied to remodeling zones (tissue between electrode pairs) using combinations of

power and time that are calibrated to remain in this zone. Fig. 1 shows some results of testing done on a cadaver aorta showing various electrode energy settings and surface temperatures achieved versus time. By ranging the average power between 1 and 5 Watts for between 0.5 and 10 seconds, the surface temperature reached was between 50°C and 65°C. Sample doses are shown below in Table 1.

Average power	Time	Approx. Surface Temp
1 Watt	8 sec	50°C
2 Watt	2 sec	50°C
3 Watt	1.3 sec	50°C
4 Watt	1 sec	50°C
5 Watt	.5 sec	50°C
2 Watt	4 sec	60°C
3 Watt	2 sec	60°C
4 Watt	1.5 sec	60°C
5 Watt	1 sec	60°C
3 Watt	3 sec	65°C
4 Watt	2 sec	65°C

Table 1

[0056] Fig. 2 shows time vs. temperature curves of a computer simulation of the system showing a strong correlation between the bench top data (shown in Fig. 1) and a FEA computer model. The higher power settings show a stronger correlation than the lower power settings. This is believed to be attributed to the absence of longitudinal heat transfer in the 2D model and the bio-cooling effect that is also not included in the computer simulation of Fig. 2. Both modes would have a larger cooling effect at the lower power settings. Nonetheless, the correlation between the FEA models and the bench top experiments is very good.

[0057] The methods and systems described herein are accomplished with or without knowing the tissue type and can be used for treatment of both concentric and eccentric atherosclerosis. This non selective treatment is a particular advantage because atherosclerosis may be eccentric relative to an axis of the blood vessel over 50% of the time, possibly in as much as (or even more than) 75% of cases. The present invention may additionally take advantage of the differences in tissue properties. If one tissue has a better thermal conductivity (k) than another type of tissue, it will conduct heat away more rapidly. If one tissue has a lower specific heat capacity (c_p) than another type of tissue, its temperature will increase more given the same amount of energy applied to the same mass (and volume, assuming relatively similar tissue density). If one type of

tissue has denser vasculature, or is reliably in closer proximity to well-perfused areas, it will conduct heat away more rapidly.

[0058] The present invention allows one to preferentially heat a type of tissue that has one or more of the following characteristics: Relatively poor (lower) thermal conduction, lower specific heat capacity, less inate blood perfusion, and/or relatively larger distance away from well-perfused areas. Very importantly, the invention allows preferential heating to be accomplished without knowing the location of the different tissues.

[0059] In the case of artery disease, all of the above characteristics apply. The disease is generally comprised of lipidic fat-like diseased tissue and/or fibrous collagen-like tissue. Both have a lower specific heat capacity and lower thermal conductivity than healthy vascular tissue. Healthy vascular tissue also has more microvasculature, and is in closer proximity to well-perfused tissue, therefore healthy tissue can sink heat away more effectively.

[0060] One advantage of non selective treatment is that energy preferentially/selectively accumulates in a desired type of tissue because of innate differences between the diseased and healthy tissue, for example, "thermal inertia" and perfusion.

[0061] "Thermal inertia" is a concept mainly used in geology to describe how the temperature of rocks changes over time. Matter with a high thermal inertia takes longer to heat and cool, and vice-versa. The quantity is also known as the "thermal effusivity" and is defined as $(k \rho c_p)^{\wedge}\frac{1}{2}$, where k is the specific thermal conductivity, c_p is the specific heat capacity, and ρ is the mass density.

[0062] This same concept may be applied to tissue. Diseased arterial tissue has a lower k, c_p, and ρ, compared to healthy artery tissue. Therefore, with all three quantities being lower, the thermal inertia is significantly lower for the diseased tissue, particularly fatty vulnerable plaque. (See Table 2.)

Material	Specific Thermal Conductivity (W/m/K)	Specific Heat (J/kg/K)	Density (kg/m^3)	Thermal Inertia (J/m^2/K/s^1/2)
Intima	0.44 (1)	3587 (1)	1064 (1)	1288
Media (muscle)	0.59 (2)	3900 (1)	1060 (1)	1555
Adventitia (collagen)	0.49 (1)	3146 (1)	1162 (1)	1341
Adipose (fat)	0.23 (3,6)	2300 (6)	900 (6,8)	682
Vulnerable Plaque (fat)	0.23 (3,6)	2300 (6)	900 (6,8)	682
Fibrous Cap (collagen)	0.49 (1)	3146 (1)	1162 (1)	1341
Blood	0.51 (4)	3925 (1)	1018 (1)	1420
Saline/PBS	0.63 (5)	4178 (7)	998 (7)	1618

Table 2: Thermal Properties of Tissue and Related Components

[0063] The difference in the thermal inertia between healthy arterial tissue (e.g. media and adventitia) and diseased tissue (e.g. vulnerable plaque), is significant – about a factor of 2 lower.

[0064] This concept of thermal "inertia" can also be thought of as a "thermal time constant". The term "thermal time constant" is derived from an equivalent RC circuit's time constant. An RC circuit, one with a resistor and a capacitor in series, is one with a stored charge of energy and a dissipation mode (the resistor that turns electric current into heat). The example with tissue is an analogous case.

[0065] If one were to calculate a thermal resistance using the specific thermal resistivity of the material, along with approximate dimensions through which the conduction is happening, one can calculate an approximate R value. The capacitance is the stored energy, and can also be calculated using the specific heat capacity and an approximate volume or mass. This gives a value in seconds that is directly proportional to the thermal conductivity, specific heat capacity, and density of the material. And, this value can be compared relatively between two sets of properties without worrying about what exact dimensions were assumed, because the dimensions can be held constant while the tissue properties are varied.

[0066] The thermal inertia formula is similar, except it assumes no physical dimensions. It's therefore a "specific" thermal inertia – one that does not vary with geometry. In order to get the "thermal time constant" from the thermal inertia, one would need to square the thermal inertia term and multiply in a specified volume and dimensions for a thermal conduction path. These

initial approximations have suggested healthy tissue and diseased arterial tissue to have thermal time constants of 7 and 14 seconds, respectively.

[0067] In addition to advantages in the thermal properties of the different tissues themselves, healthy vascular tissue also has more microvasculature, and is in closer proximity to well-perfused tissue, therefore healthy tissue can sink heat away more quickly. The difference in vascular perfusion between healthy and diseased arterial tissue is shown in Table 3, and its effect is quantified by the biological thermal transport equation by Pennes, shown in Equations 1 and 2.

Organ	Blood flow (mL/min/g)
Left ventricle (pig)	1.45 (9)
Fat (pig)	0.21 (9)

Table 3: Perfusion Properties

$$\rho c \frac{\partial T}{\partial t} = \nabla(k \nabla T) + q_s + q_p + q_m$$

Equation 1: Penne's Bio-Heat Equation

$$q_p = -\omega_b \rho_b c_b \rho (T - T_a)$$

Equation 2: Blood Perfusion Term

[0068] The blood perfusion omega is approximately 7 times larger in healthy tissue. And, when the tissue reaches slightly elevated temperatures such as 43°C, they will dilate and improve blood flow further. This is an added benefit that makes healthier tissue more able to dissipate heat faster.

[0069] Several models were created to evaluate the potential advantages of this technology. Additional work may be done in order to optimize the heating parameters (power vs. time, possible inclusion of PWM, etc.). And, none of the models include cooling from blood perfusion. In the mean time, these models show a distinct advantage without optimization. Pulse width modulation (PWM) where the power is switched on and off at a rate referred to as duty cycle, or the ratio of on time to off time. This could reduce the chance of over heating, and allow for a more controlled dosing rate.

[0070] The FEA model composition is shown in Figs. 3 and 4. In Fig. 5 shows a treatment power of 0.5 Watts for 30 seconds into healthy tissue (Peak = 51°C). Fig. 6 shows a treatment power of 0.5 Watts for 30 seconds into vulnerable plaque (Peak = 61°C). We can see the temperature differential between healthy tissue and vulnerable plaque. The difference in peak temperature is 10°C. This shows that a volume of tissue heated with the same energy reaches temperatures much higher in the diseased tissue than in the healthy tissue.

[0071] Note that these models do not adequately take advantage of differences in cooling or perfusion, only in heating. In a 3D model, the effect of higher thermal conductivity in the healthy tissue should be amplified due to increased losses down the artery's longitudinal direction.

[0072] Another important aspect of this technology is the relationship between time and temperature and how they affect cell death. The time-temperature relationship discovered is an exponential such that, as a general rule, for every 1°C of increase in temperature, the amount of time required to cause cell death is half as long. For instance, at 45°C it would require roughly 1000 seconds to cause cell death. At 55°C, it takes only 1 second. Therefore, a differential of 10°C hotter is actually 1000x more effective.

[0073] Distinction from Prior Art

[0074] There is an important distinction to be made between the present invention and previous attempts at using thermal balloons. The present invention is administered in discrete doses in a localized manner and the energy is created within the tissue rather than simply applied to the surface, such as with a thermal balloon. As discussed here, the present invention uses the insulative properties of arterial disease (fat) as an advantage rather than a disadvantage. Previous attempts at thermal balloon angioplasty failed because they were attempting to push heat preferentially into an insulator (the fat that has poor conductivity). Instead of thermally conducting into the disease, the heat administered by previous thermal balloons was either indiscriminant or preferentially conducted into the healthy tissue.

[0075] While the present invention may be used in combination with stenting, and/or to treat in-stent restenosis, it is particularly well suited for increasing the open diameter of blood vessels in which stenting is not a viable option. Potential applications include treatment of diffuse disease, in which atherosclerosis is spread along a significant length of an artery rather than being localized in one area. The invention may also find advantageous use for treatment of

tortuous, sharply-curved vessels, as no stent need be advanced into or expanded within the sharp bends of many blood vessel. Still further advantageous applications include treatment along bifurcations (where side branch blockage may be an issue) and in the peripheral extremities such as the legs, feet, arms, neck, abdomen (where crushing and/or stent fracture failure may be problematic).

[0076] Diffuse disease and vulnerable plaque are illustrated in Figs. 7A and 7B, respectively. Fig. 7C illustrates vascular tortuosity. Fig. 7D illustrates atherosclerotic material at a bifurcation.

[0077] Arterial dissection and restenosis may be understood with reference to Figs. 7E through 7G. The artery comprises three layers, an endothelial layer, a medial layer, and an adventitial layer. During traditional angioplasty, the inside layer may delaminate or detach partially from the wall so as to form a dissection as illustrated in Fig. 7E. Such dissections divert and may obstruct blood flow. As can be understood by comparing Figs. 7F and 7G, traditional angioplasty is a relatively aggressive procedure which may injure the tissue of the blood vessel. In response to this injury, in response to the presence of foreign substances, such as a stent, and/or in the continuing progression of the original atherosclerotic disease, the opened artery may restenose or subsequently decrease in diameter as illustrated in Fig. 7G. While drug eluting stents have been shown to reduce restenosis, the efficacy of these new structures several years after implantation has not be fully studied, and such drug eluting stents are not applicable in many blood vessels.

[0078] To avoid some of the problems associated with traditional angioplasty, such as those shown in Figs. 7E through 7G, the present invention discloses a method for remodeling artery tissue using a catheter system that uses mild heat to provide tissue surface temperatures in a range between about 50°C and 65°C to gently remodel the tissue, that may allow arteries to be opened. The method includes expanding a catheter balloon within the artery lumen with a first pressure that brings the balloon in contact with the artery tissue. The plurality of electrodes are coupled with the artery tissue so as to define a plurality of remodeling zones in the artery tissue when the balloon is in contact with the artery tissue. The plurality of electrode pairs are then energized with associated desired quantities of bipolar tissue remodeling energy so as to heat each of the plurality of remodeling zones with the associated desired tissue remodeling energy, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

[0079] In some instances, it may be desirable to obtain baseline measurements of the tissues to be treated (which may be characterized via intravascular ultrasound, optical coherence tomography, or the like) may be taken to help differentiate adjacent tissues, as the tissue signatures and/or signature profiles may differ from person to person. Additionally, the tissue signatures and/or signature profile curves may be normalized to facilitate identification of the relevant slopes, offsets, and the like between different tissues. Any of the techniques disclosed in U.S. Patent Application No. 60/852,787, entitled "Tuned RF Energy And Electrical Tissue Characterization For Selective Treatment Of Target Tissues"; and U.S. Provisional Application No. 60/921,973, filed on April 4, 2007, entitled "Tuned RF Energy And Electrical Tissue Characterization For Selective Treatment Of Target Tissues", the full disclosures of which are incorporated herein by reference, may be combined with the present invention.

[0080] One embodiment of a catheter system for use in the present invention is shown in Fig. 8 and includes an angioplasty catheter with electrical contacts mounted on the exterior of a angioplasty balloon. A radiofrequency controller, generator or power source, and connecting cable provide energy to the catheter. Catheters are approximately 135 cm in length and initially are provided in 3.0 mm, 4.0 mm, 5.0 mm and 6.0 mm balloon diameters to accommodate the most common sizes of human femoral and popliteal arteries first. The catheter uses mechanical and radiant energy intended to modify arterial plaque and decrease plaque burden, resulting in a larger artery lumen. The temperature that is generated is low and the total application time is shorter than most angioplasty procedures performed today. The catheter device is compatible with standard angioplasty equipment, thereby allowing access of lower extremity peripheral vasculature via contralateral or ipsilateral common femoral approach using conventional angioplasty techniques.

[0081] Fig. 8 shows one embodiment of a catheter system 10 for inducing desirable temperature effects on artery tissue. The catheter system 10 includes a balloon catheter 12 having a catheter body 14 with a proximal end 16 and a distal end 18. Catheter body 14 is flexible and defines a catheter axis 15, and may include one or more lumens, such as a guidewire lumen and an inflation lumen. Still further lumens may be provided if desired for other treatments or applications, such as perfusion, fluid delivery , imaging, or the like. Catheter 12 includes an inflatable balloon 20. Housing 29 includes a first connector 26 in communication with guidewire lumen 22 and a second connector 28 in fluid communication with inflation lumen 24. Inflation lumen 22 extends between balloon 20 and second connector 28. Both first and

second connectors 26, 28 may optionally comprise a standard connector, such as a Luer-Loc™ connector. Housing 29 also accommodates an electrical connector 38 electrically coupled to electrodes 34 via conductors 36. This allows electrodes 34 to be easily energized, the electrodes often being energized by a controller 40 and power source 42, such as bipolar or monopolar RF energy, microwave energy, ultrasound energy, or other suitable energy sources. In one embodiment, electrical connector 38 is coupled to an RF generator via a controller 40, with controller 40 allowing energy to be selectively directed to electrodes 38. When monopolar RF energy is employed, patient ground may (for example) be provided by an external electrode or an electrode on catheter body 14.

[0082] Electrodes 34 are mounted on a surface of balloon 20, with associated conductors 36 extending proximally from the electrodes. Electrodes 34 may be arranged in many different patterns or arrays on balloon 20. The system may be used for monopolar or bipolar application of energy. For delivery of monopolar energy, a ground electrode is used, either on the catheter shaft, or on the patients skin, such as a ground electrode pad. For delivery of bipolar energy, adjacent electrodes are spaced around the circumference to allow bipolar energy to be directed between adjacent electrodes. In other embodiments, electrodes may be arranged in bands around the balloon to allow bipolar energy to be directed between adjacent distal and proximal electrodes.

[0083] Fig. 9 schematically illustrates bipolar treatment of diseased tissue. Balloon 20 having electrode pairs 34A and 34B is positioned within an artery lumen having fatty disease/necrotic core 48, fibrous disease/fibrous cap 44, healthy tissue 45. Treatment is done to healthy tissue 45 and the fatty disease/necrotic core 48, fibrous disease/fibrous cap 44 by using bipolar energy between pairs 34A and 34B. The electrode pairs may be any electrode pairs on the balloon, for example, in some embodiments, the electrode pairs may be 34A and 34C, or 34A and 34D, or any combination of 34A-34D. This arrangement creates an energy path 50 through the tissue that delivers energy or heat ("tissue remodeling energy") in particular treatment zones or segments 52 to the artery tissue between the electrode pairs ("remodeling zones") having a volume between the electrode pairs at a specific depth. Using different combinations of electrode pairs may reduce or eliminate gaps between the remodeling zones by using overlapping pairs. Using electrode pairs with bipolar energy may avoid some potential issues of the monopolar approach. Diseased artery tissue 48 has a higher electrical resistivity than healthy artery tissue. By using pairs of electrodes 34A, 34B in a bipolar system, tissue remodeling

energy will go through the healthy tissue, diseased tissue, or a combination of both healthy and diseased tissues between the electrode pairs in the remodeling zones. Any number of electrode pairs may be used in different patterns or arrays to create a number of remodeling zones. The controller may apply either constant power, constant current, or constant voltage, whichever has the most advantage.

[0084] Fig. 10 shows one embodiment of balloon catheter system for use for monopolar treatment of diseased tissue. Balloon 20 having electrode pairs 34A and 34B is positioned within an artery lumen having fatty disease/necrotic core 48, fibrous disease/fibrous cap 44, healthy tissue 45 and one or more electrical ground are used, such as positioned on the patients skin. When power is applied to the multiple monopolar electrodes 34 arranged around the circumference of the artery lumen, energy 54 is directed radially outward through the artery wall and treats both diseased and healthy artery tissue.

[0085] The use of catheter system 10 for remodeling artery tissue by heating can be understood with reference to Figs. 11A-11C. As seen in Fig. 11A, accessing of a treatment site will often involve advancing a guidewire 56 within a blood vessel 58 at a target region of diseased tissue 48. Location of balloon 20 may be facilitated by radiopaque markers or by radiopaque structure (or corresponding radiopaque markers placed on or near) balloon 20, and/or by the use of radiopaque electrodes 34. Guidewire 56 may be positioned under fluoroscopic (or other) imaging.

[0086] Catheter 12 is advanced distally over guidewire 56 and positioned adjacent to atherosclerotic material 48. Balloon 20 expands radially within the lumen of the blood vessel so that electrodes 34, or electrodes 34A and 34B, radially engage artery tissue. As diseased tissue 48 may be distributed eccentrically about catheter 12, electrodes 34 may engage diseased tissue 48, healthy tissue 60, or a combination of both tissues, as can be understood with reference to Figs. 9 and 10.

[0087] As discussed above, electrodes 34 are positioned circumferentially around the balloon 20. Energy, such as RF energy, is directed to electrodes 34, or adjacent pairs of electrodes 34A and 34B, treating both diseased tissue 48 and the healthy tissue 60. The controller 40 may energize the electrodes with about 0.25 to 5 Watts average power for 1 to 180 seconds, or with about 4 to 45 Joules. Higher energy treatments are done at lower powers and longer durations, such as 0.5 Watts for 90 seconds or 0.25 Watts for 180 seconds. Most treatments in the 2 to 4 Watt range are performed in 1 to 4 seconds. Using a wider electrode spacing, it would be

appropriate to scale up the power and duration of the treatment, in which case the average power could be higher than 5 Watts, and the total energy could exceed 45 Joules. Likewise, using a shorter or smaller electrode pair would require scaling the average power down, and the total energy could be less than 4 Joules. The power and duration are calibrated to be less than enough to cause severe damage, and particularly less than enough to ablate diseased tissue 48 within a blood vessel. The mechanisms of ablating atherosclerotic material within a blood vessel have been well described, including by Slager et al. in an article entitled, "*Vaporization of Atherosclerotic Plaque by Spark Erosion*" in J. of Amer. Cardiol. (June, 1985), on pp. 1382-6; and by Stephen M. Fry in "*Thermal and Disruptive Angioplasty: a Physician's Guide;*" Strategic Business Development, Inc., (1990) the full disclosures of which are incorporated herein by reference.

[0088] Referring now to Fig. 11C, as described above, balloon 20 may be an angioplasty balloon that combines heating with opening the artery lumen. In some embodiments, injury caused to the atherosclerotic material with the energized electrodes or other energy directing surfaces may result in subsequent resorption of the injured tissue lesions so as to provide further opening of the vessel after termination of treatment as part of the healing process.

[0089] In some embodiments, balloon 20 may be repeatedly contracted, axial movement of the catheter 12 employed to reposition balloon 20, with subsequent expansion of balloon 20 at each of a plurality of treatment locations along diseased tissue.

[0090] Frequency targeting of tissues is illustrated in Fig. 12. Different tissue types have different characteristic electrical impedances that cause the tissue to absorb energy of certain frequencies or frequency ranges more readily than others. By applying energy at the specific frequency or range of frequencies that the tissue is more conductive, energy penetrates the tissue more readily. In general, it has been shown that samples of diseased tissue exhibit higher impedance characteristics than samples of healthy tissue. As illustrated in Fig. 12, in the case where a diseased area of tissue 78 is surrounded by relatively healthy tissue 80, the healthy tissue is likely to shield the diseased tissue from electrical current flow due to the lower impedance of the healthy tissue. Hence, minimal (or less than the desired) current flow 82 may pass through diseased tissue 78, and heavier current flow 84 may be seen in low impedance healthy tissue 80 when bipolar current is transmitted between electrodes 34A and 34B. Typically, the frequency ranges in which tissue impedance varies to a useful degree occur between 30 kilohertz and 30 Megahertz.

[0091] Frequency targeting seeks to deliver more energy to the diseased tissue by determining the frequency or range of frequencies at which the impedance of the diseased tissue is equal to or greater than that of the healthy tissue, such as by operation at or below a threshold frequency. Energy delivered at the specified frequency or range of frequencies will cause more heat to be dissipated in the diseased tissue than energy delivered outside of those specific frequencies.

[0092] Figs. 13-17B show histological results of testing done in animal studies. Fig. 13 shows the application of 1 Watt for 8 seconds at seven days, which had a maximum surface temperature of 50°C in bench top testing, showing mild shortening of smooth muscle at the sites of inserted arrows. Fig. 14 shows the application of 2 Watts for 2 seconds at eight days, which also had a maximum surface temperature of 50°C in bench top testing. Figs. 15A, 15B show the application of 4 Watts for 1 second at seven days and Fig. 15C at thirty days. There are obvious thermal applications corresponding to each electrode (black arrows). There also appears to be thermal alterations to some of the collagenous areas of the vessel wall. This suggests bulk tissue temperatures just slightly over 60°C. Figs. 16A, 16B show the application of 2 Watts for 4 seconds at seven days and Fig.16C at thirty days. The slide shows heat therapy at each electrode-tissue interface (black arrows show edges of treatment zones). There is also a corresponding thermal effect deep into the collagenous areas, and gross observations of tissue shrinkage. The figures also show some thermal diffusion into the tissue in-between treatment zones that also resulted in collagen denaturing. This indicates that the local areas of heat deposition under the electrodes may have reached 70°C or higher. Of course, there is a temperature gradient that slopes off in-between electrodes and radially away from the electrodes, and deeper into the vessel and surrounding tissue. Fig. 17A shows the application of 3 Watts for 2 seconds at seven days and Fig. 17B at thirty days.

[0093] Figs. 18A-18G show some results of bench top testing was conducted on a freshly excised human popliteal artery, 5 cm in length with an occlusion at the distal end. The artery was connected into a flow tank followed by a pre-treatment baseline IVUS scan of the entire artery to locate a suitable lesion for treatment, shown in Figs 18A and 18B. A site was chosen which had a luminal area of 4.5 mm^2 with a minimum and maximum luminal diameter of 2.2 mm and 2.4 mm respectively and a native vessel area of 32.7 mm^2 with a minimum and maximum diameter of 5.8 mm and 6.8 mm respectively.

[0094] For this experiment a catheter system having a 4mm balloon for inducing desirable temperature effects on artery tissue was used. The catheter was inserted into the artery at the

desired location and inflated to 6 atmospheres. The treatment was performed, and the catheter was deflated and removed from the artery. The treatment was applied at 4 Watts for 2 seconds. A post-treatment scan of the entire artery was then performed, shown in Figs 18C and 18D, which showed an increase in luminal area to 20.5 mm^2 with a minimum and maximum diameter of 4.6 mm and 5.5 mm respectively, and a vessel area of 37.2 mm^2 with a minimum and maximum diameter of 6.5 mm and 7.3 mm respectively. If this were a clinical situation rather than a bench top study, a 6 mm balloon would have been implemented to better match the native vessel diameter resulting in a greater luminal opening.

[0095] Following treatment, the artery was then stained, fixed in formalin, sectioned and photographed, shown in Figs. 18E-18G. Fig. 18E is a control section taken proximal to the treatment area. Figs. 18F and 18G are sections of the treatment area approximately 4 mm and 8 mm into the treatment area, respectively and show images of the sectioned artery after treatment, TTC staining and fixation.

[0096] Referring now to Fig. 19, suitable power ranges for providing the desired heating of the target tissue, and/or for limiting of heating to collateral tissues, may depend at least in part on the time for which energy is applied, on the electrode (or other energy transmitting surface) geometry, and the like. First, when applying the treatments described herein to tissues with electrodes, there may be preferred a load impedance range of the tissues within the circuit so as to avoid having to apply voltages and/or currents that are outside desirable ranges, particularly when applying powers within ranges described herein. Suitable load impedance ranges would generally be within a range from about 20 Ohms to about 4500 Ohms, more typically being in a range from about 40 Ohms to about 2250 Ohms, and preferably being in a range from about 50 to about 1000 Ohms.

[0097] The load impedance of the tissue within the circuit may depend on the characteristics of the tissue, and also (for example) on the geometry of a bipolar pair of electrodes that engage the tissue, as the electrodes geometries influence the geometry of the tissue effectively included within the circuit. The tissue to which energy is directed may have a specific conductivity in a range from about 0.2 Siemens per meter to about 0.5 Siemens per meter. Different types of diseased tissues may have specific conductivities in different ranges, with some types of diseased tissues having specific conductivities in a range from about 0.2 Siemens per meter to about 0.35 Siemens per meter, while others fall within a range from about 0.35 Siemens per to about 0.5 Siemens per meter. The spacing between the pair of electrodes and the length of electrodes

(transverse to their spacing) will both have effects on the load impedance, with most embodiments having electrode pair spacings (adjacent edge-to-edge) of between 0.25 mm and 2.50 mm, exemplary embodiments having electrode pair spacing of between 0.50 and 2.00 mm, and preferred embodiments having electrode pair spacing of between 0.75 and 1.50 mm.

[0098] Regarding the length and spacing of the electrodes within a particular pair, these factors are inter-related with the power and impedance. As the length of the electrodes decreases, the impedance seen by the generator will go up, but the volume of tissue will go down, so that the power setting on the generator may be decreased. As the gap between the electrodes widens, the impedance seen by the generator will also go up, but the volume of tissue will go up as well, so that the power setting on the generator should be increased. Hence, there are roughly opposed effects on load impedance when you decrease electrode length and electrode spacing.

[0099] Desired power, energy, and time of the treatment are likewise inter-related, and may also be at least related with electrode geometry. Speaking very generally, lower power treatments applied for long times tends to result in treatments with relatively higher total energies, while higher power treatments for shorter times tends to result in lower energy treatments. More specifically, at relatively low average power (1W or less) the total energy delivery per treatment may range from 8 to 45 Joules. At higher power (more than 1W), the total energy delivery per treatment may range from 4 to 15 Joules. If the electrode spacing were doubled, power may increase by four times. The power transmitted into the tissue can be calibrated and scaled to the particular electrode configuration, often in order to keep the power and energy density in a desirable range. Exemplary power ranges may be, for example from about 1 to 5 Watts. The duration is longer for the lower power settings, and typically varies from about 1 to 8 seconds. Very low power settings less than 1 Watt are also possible, using durations much longer than 10 seconds.

[0100] It is also possible to scale the power settings significantly by varying the electrode configuration. If, for instance, the inner edge-to-edge spacing of the electrodes were doubled, roughly 4 times the power may be applied because the volume of tissue becomes roughly 4 times larger. As such, an electrode configuration that is somewhat different from the exemplary embodiments described herein could be used within a power range of roughly 4 to 20 Watts. Shortening the electrodes, and thus shortening and reducing the volume of the remodeling zones, would also affect the magnitude of the power that is appropriate to apply to the tissue volume.

[0101] Referring still to Fig. 19, in order to quantify this complex set of relationships, and bound the space within which the exemplary treatment device can operate, an empirical relationship between safe values of several of these parameters may be generated and provided graphically, in table form, or by a mathematical relationships. An exemplary equation describing a particularly advantageous relationship is:

power = b * x^2 * L * (t^(-0.59))

where b is a parameter in the range of 0.2 to 0.6, x is the inner edge-to-edge spacing of the electrodes in millimeters, L is the length of the electrodes in millimeters (and also the approximate length of the remodeling zone), the power is in Watts, and t is time in seconds. b has units of Watts/(mm^3)*(seconds^ 0.59). Exemplary treatments in the range described by this equation includes treatments such as 4 Watts for 2 seconds, 3 Watts for 3 seconds, 2 Watts for 4 seconds, and 1 Watt for 12 seconds with the exemplary electrode geometries described herein. Additionally, very low power long duration treatments such as 0.25 Watts for 180 seconds are covered as well. Alternative suitable treatment range falls within or near the set of curves shown in Fig. 19, which shows approximate numbers for maximum power and time by electrode dimensions. Still further alternative treatment parameter values can be understood with reference to Table 4, which shows total energies for different combinations of power and time for a few different electrode pair geometries.

Exemplary Peripheral Treatment Catheter			**Alternative I Peripheral Treatment Catheter**			**Alternative II Peripheral Treatment Catheter**			**Exemplary Coronary Treatment Catheter**		
X=1mm, L=16mm		Total	X=2mm, L=16mm		Total	X=2mm, L=8mm		Total	X=0.5mm, L=8mm		Total
Time (s)	Power (W)	Energy (J)	Time (s)	Power (W)	Energy (J)	Time (s)	Power (W)	Energy (J)	Time (s)	Power (W)	Energy (J)
1	5	5	1	20	20	1	10	10	1	0.625	0.625
2	4	8	2	16	32	2	8	16	2	0.5	1
3	3	9	3	12	36	3	6	18	3	0.375	1.125
4	2	8	4	8	32	4	4	16	4	0.25	1
12	1	12	12	4	48	12	2	24	12	0.125	1.5
30	0.5	15	30	2	60	30	1	30	30	0.0625	1.875
180	0.25	45	180	1	180	180	0.5	90	180	0.03125	5.625

Table 4

[0102] As the energies and powers for characterizing and/or treating tissues are relatively low, the power source may optionally make use of energy stored in a battery, with the power source and/or associated controller optionally being contained within a hand-held housing. Use of such battery-powered systems may have benefits within crowded operating rooms, and may also help avoid inadvertent over treatment. The batteries may be disposable structures suitable to be included in a kit with a single-use catheter, while the processor circuitry may be re-useable. In other embodiments, the batteries may be rechargeable.

[0103] Remodeling of atherosclerotic materials may comprise shrinkage, melting, and the like of atherosclerotic and other plaques. Atherosclerotic material within the layers of an artery may be denatured, melted and/or the treatment may involve a shrinking of atherosclerotic materials within the artery layers so as to improve blood flow. The invention may also provide particular advantages for treatment of vulnerable plaques or blood vessels in which vulnerable plaque is a concern, which may comprise eccentric lesions. The invention will also find applications for mild heating of the cap structure (to induce thickening of the cap and make the plaque less vulnerable to rupture) and/or heating of the lipid-rich pool of the vulnerable plaque (so as to remodel, denature, melt, shrink, and/or redistribute the lipid-rich pool).

[0104] While the exemplary embodiments have been described in some detail, by way of example and for clarity of understanding, those of skill in the art will recognize that a variety of modification, adaptations, and changes may be employed. Hence, the scope of the present invention should be limited solely by the appending claims.

WHAT IS CLAIMED IS:

1. A method of inducing vasodilation on body tissue disposed about a body lumen having both healthy tissue and diseased tissue, the method comprising:

coupling a probe surface to the body tissue at a target location; and

transmitting desired quantities of tissue remodeling energy from the coupled probe into each of a plurality of discrete remodeling zones in the body tissue so that the tissue remodeling energy heats the plurality of remodeling zones, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

2. The method of claim 1, wherein the plurality of remodeling zones include healthy tissue, diseased tissue, or a combination of both healthy and diseased tissues, wherein at least one of the remodeling zones includes healthy tissue, and wherein the heating of the healthy tissue is sufficiently to inhibit acute constriction of the lumen by the healthy tissue and is sufficiently limited to inhibit healing response-induced occlusion of the lumen by the healthy tissue.

3. The method of claim 2, wherein a plurality of energy transmitting surfaces are coupled to the tissue, each remodeling zone associated with at least one energy transmitting surface, wherein at least one of the plurality of remodeling zones includes diseased tissue, wherein the desired energies for the plurality of remodeling zones are within a common desired energy range so that the heating is applied without identifying the energy transmitting surfaces associated with the at least one diseased tissue remodeling zone and the at least one healthy tissue remodeling zone.

4. The method of claim 3, wherein the energy transmitting surfaces comprise a plurality of bipolar electrode pairs, the electrode pairs mounted to a balloon and urged radially outwardly by inflating the balloon into coupling engagement with the tissue, each electrode pair at least in part defining an associated remodeling zone, and wherein the desired energy for each discrete remodeling zone is transmitted by applying the common desired quantity of energy between the electrodes of the pair.

5. The method of claim 2, wherein the remodeling zones are separated by zones of substantially untreated tissue.

6. The method of claim 1, wherein the diseased tissue has a lower specific thermal conductivity, lower specific heat capacity, and/or lower mass density than the healthy tissue, and wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating at least some of the diseased tissue in the remodeling zones to a diseased tissue treatment temperature and heating the healthy tissue in the remodeling zones to a healthy tissue temperature that is lower than the diseased tissue treatment temperature.

7. The method of claim 6, wherein the healthy tissue temperature exceeds a temperature at which healthy tissue can dissipate the heat in a steady state.

8. The method of claim 1, wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating to a temperature which denatures actin and myosin proteins of the tissue that enable recoil.

9. The method of claim 1, wherein a depth of heating in the tissue is limited by limiting the tissue remodeling energy, by limiting a tissue heating time, and/or by a configuration of the at least one energy transmitting surface.

10. The method of claim 1, wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating the tissue between bipolar electrode pairs to between 50 and 65°C.

11. The method of claim 1, wherein energizing the plurality of electrode pairs includes energizing each electrode pairs between 4 and 15 Joules for a remodeling treatment zone having a volume between the electrode pairs at a specific depth.

12. The method of claim 1, further comprising energizing a plurality of electrode pairs of the probe, each electrode pair being energized with an average power of 1 to 5 Watts for 0.1 to 10 seconds.

13. The method of claim 1, wherein heating the plurality of remodeling zones with the tissue remodeling energy is done for less than 60 seconds.

14. The method of claim 1, wherein the plurality of remodeling zones are longitudinal remodeling zones distributed about an axis of the probe.

15. A method for remodeling body tissue disposed about a body lumen using heat assisted balloon angioplasty, the method comprising:

expanding a catheter balloon within the lumen with a pressure, the pressure inflating the catheter balloon in contact with the tissue, wherein a plurality of electrodes are disposed about the catheter balloon and coupled with the tissue so as to define a plurality of remodeling zones in the tissue when the balloon is in contact with the tissue; and

energizing the plurality of electrode pairs with associated desired quantities of bipolar tissue remodeling energy so as to heat each of the plurality of remodeling zones with the associated desired tissue remodeling energy, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

16. The method of claim 15, wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating the artery tissue between bipolar electrode pairs to between 50 and 65°C.

17. The method of claim 15, wherein energizing the plurality of electrode pairs includes energizing the electrode pairs between 4 and 15 Joules.

18. The method of claim 15, wherein energizing the plurality of electrode pairs includes energizing the electrode pairs with 1 to 5 Watts for 0.1 to 10 seconds.

19. The method of claim 15, wherein heating the plurality of remodeling zones with the tissue remodeling energy is done for less than 10 seconds in each zone.

20. A method of treating a treatment area within a body lumen, comprising:

providing a catheter having an energy delivery portion;

inserting the energy delivery portion of the catheter into said body lumen and positioning said catheter portion within the treatment area;

using the catheter portion to deliver energy to the body lumen at a plurality of energy delivery zones within the treatment area, each of which is small compared to the treatment area, said delivery of energy comprising delivering energy from the catheter portion, such that in an eccentrically diseased body lumen, the energy will heat both healthy tissue and diseased tissue; and

using the energy to heat diseased tissue to a temperature sufficient to efficaciously alter the diseased tissue without causing sufficient thermal damage to the healthy tissue so as to induce a long-term occlusive response.

21. The method of claim 20, wherein the energy is delivered so as to cause the healthy tissue to attain a maximum temperature that is significantly lower that the maximum temperature attained by the diseased tissue during the treatment.

22. The method of claim 20, wherein said energy is introduced into tissue such that heat is generated volumetrically in the tissue, beneath the surface of the tissue.

23. The method of claim 20, wherein the delivered energy is sufficiently low that differences in tissue properties, including thermal conduction, heat capacity, innate blood perfusion, and distance from well perfused tissue, cause heat to be drawn from the healthy tissue at a rate that avoids significant thermal damage to the healthy tissue, while allowing heat to build up in diseased tissue.

24. The method of claim 20, wherein the differences in temperature are due at least in part to differences in thermal time constant between healthy and diseased tissue.

25. The method of claim 20, wherein said energy is delivered in the form of pulses.

26. The method of claim 20, wherein the average rate of energy delivery to the treatment area is on the same order of magnitude as the rate of energy dissipation by healthy tissue.

27. A system for inducing vasodilation on body tissue disposed about a body lumen having both healthy tissue and diseased tissue, the system comprising:

an endovascular catheter having an energy delivery portion coupleable with the tissue at a target location, the energy delivery portion having a plurality of energy delivery regions; and

an energy source coupleable with the catheter, the energy source configured to deliver controlled quantities of energy to each portion in response transmitting desired quantities of tissue remodeling energy to each of the energy delivery regions in response to

an input such that the energy heats a plurality of remodeling zones of the tissue, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

28. A method of inducing dilation on body tissue disposed about a body lumen, the method comprising:

coupling a probe surface to the tissue at a target location; and

transmitting desired quantities of tissue remodeling energy from the coupled probe into each of a plurality of discrete remodeling zones in the tissue so that the tissue remodeling energy heats the plurality of remodeling zones, the remodeling energy being configured to avoid muscular contraction and inhibit both acute and long-term occlusion of the lumen.

29. The method of claim 28, wherein the plurality of remodeling zones include healthy tissue, diseased tissue, or a combination of both healthy and diseased tissues, wherein at least one of the remodeling zones includes healthy tissue, and wherein the heating of the healthy tissue is sufficiently to inhibit acute constriction of the lumen by the healthy tissue and is sufficiently limited to inhibit healing response-induced occlusion of the lumen by the healthy tissue.

30. The method of claim 28, wherein a plurality of energy transmitting surfaces are coupled to the tissue, each remodeling zone associated with at least one energy transmitting surface, wherein at least one of the plurality of remodeling zones includes diseased tissue, wherein the desired energies for the plurality of remodeling zones are within a common desired energy range so that the heating is applied without identifying the energy transmitting surfaces associated with the at least one diseased tissue remodeling zone and the at least one healthy tissue remodeling zone.

31. The method of claim 30, wherein the energy transmitting surfaces comprise a plurality of bipolar electrode pairs, the electrode pairs mounted to a balloon and urged radially outwardly by inflating the balloon into coupling engagement with the body lumen tissue, each electrode pair at least in part defining an associated remodeling zone, and wherein the desired energy for each discrete remodeling zone is transmitted by applying the common desired quantity of energy between the electrodes of the pair.

32. The method of claim 28, wherein the remodeling zones are separated by zones of substantially untreated tissue.

33. The method of claim 28, wherein the diseased tissue has a lower specific thermal conductivity, lower specific heat capacity, and/or lower mass density than the healthy tissue, and wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating at least some of the diseased tissue in the remodeling zones to a diseased tissue treatment temperature and heating the healthy tissue in the remodeling zones to a healthy tissue temperature that is lower than the diseased tissue treatment temperature.

34. The method of claim 33, wherein the healthy tissue temperature exceeds a temperature at which healthy tissue can dissipate the heat in a steady state.

35. The method of claim 28, wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating to a temperature which denatures actin and myosin proteins of the body lumen tissue that enable recoil.

36. The method of claim 28, wherein a depth of heating in the tissue is limited by limiting the tissue remodeling energy, by limiting a tissue heating time, and/or by a configuration of the at least one energy transmitting surface.

37. The method of claim 28, wherein heating the plurality of remodeling zones with the tissue remodeling energy includes heating the tissue between bipolar electrode pairs to between 50 and 65°C.

38. The method of claim 28, wherein energizing the plurality of electrode pairs includes energizing each electrode pair between 4 and 15 Joules for a remodeling treatment zone having a volume between the electrode pairs at a specific depth.

39. The method of claim 28, further comprising energizing a plurality of electrode pairs of the probe, each electrode pair being energized with an average power of 1 to 5 Watts for 0.1 to 10 seconds.

40. The method of claim 28, wherein heating the plurality of remodeling zones with the tissue remodeling energy is done for less than 10 seconds in each zone.

41. The method of claim 28, wherein the plurality of remodeling zones are longitudinal remodeling zones distributed about an axis of the probe

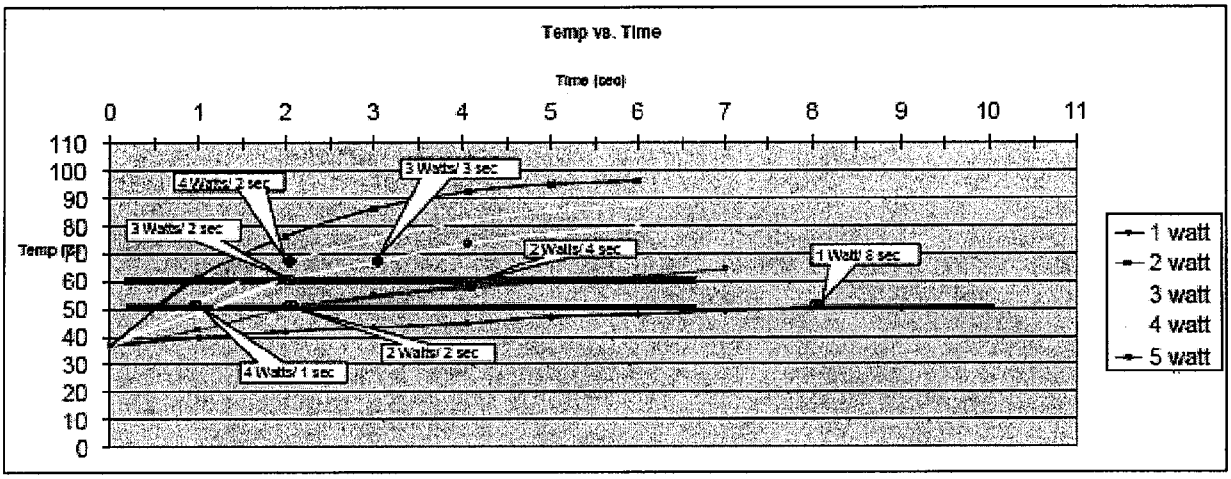

Temp vs. Time
Time (sec)
0 1 2 3 4 5 6 7 8 9 10 11
110 100 90 80 70 60 50 40 30 20 10 0
Temp (C)
4 Watts/ 2 sec
3 Watts/ 3 sec
3 Watts/ 2 sec
2 Watts/ 4 sec
1 Watt/ 8 sec
2 Watts/ 2 sec
4 Watts/ 1 sec
1 watt
2 watt
3 watt
4 watt
5 watt

FIG. 1

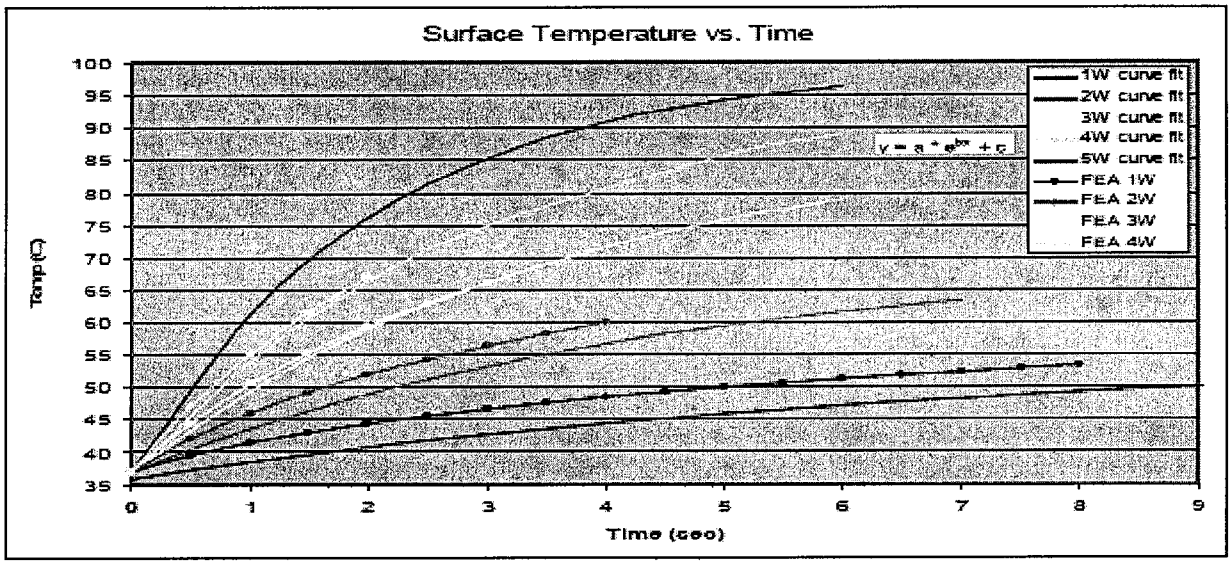

Surface Temperature vs. Time
100 95 90 85 80 75 70 65 60 55 50 45 40 35
Temp (C)
0 1 2 3 4 5 6 7 8 9
Time (sec)
1W curve fit
2W curve fit
3W curve fit
4W curve fit
5W curve fit
FEA 1W
FEA 2W
FEA 3W
FEA 4W

FIG. 2

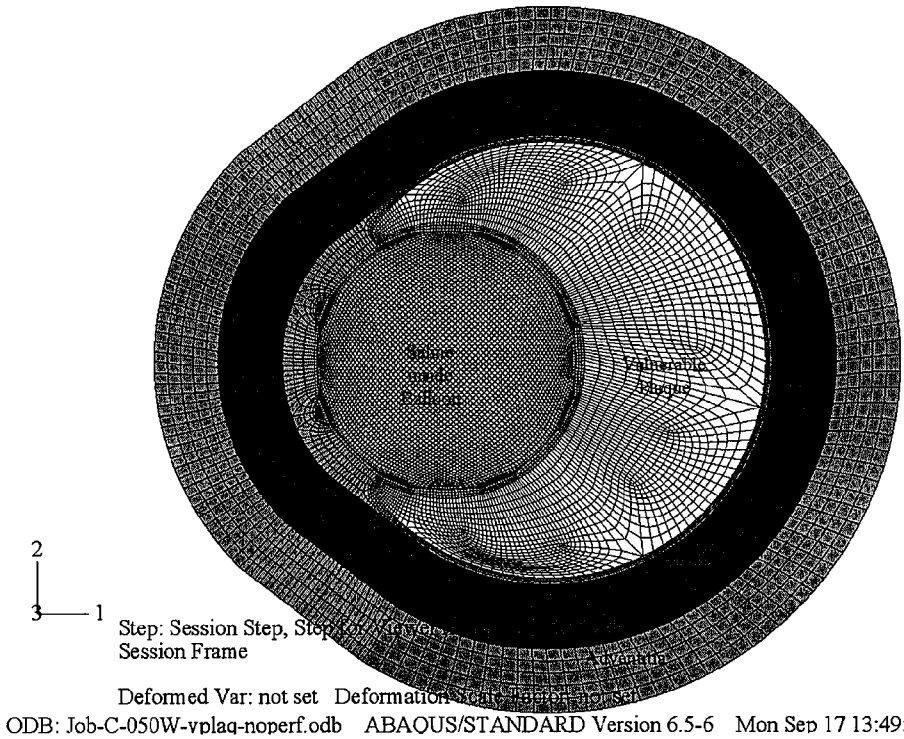


FIG. 3 - Model Composition

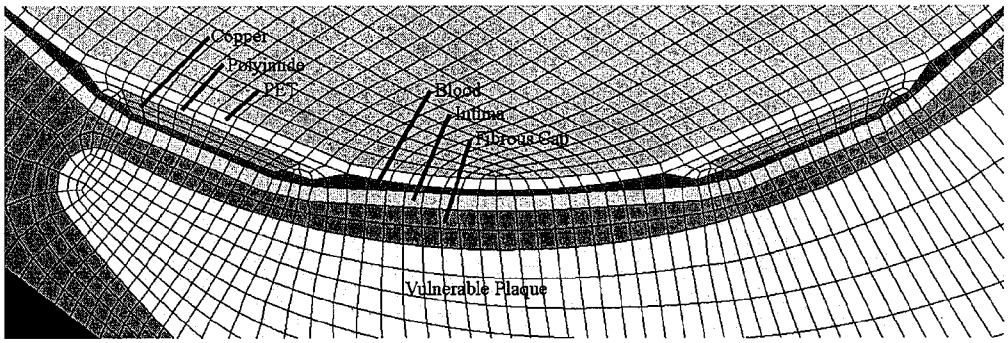


FIG. 4 - Model Composition Detail

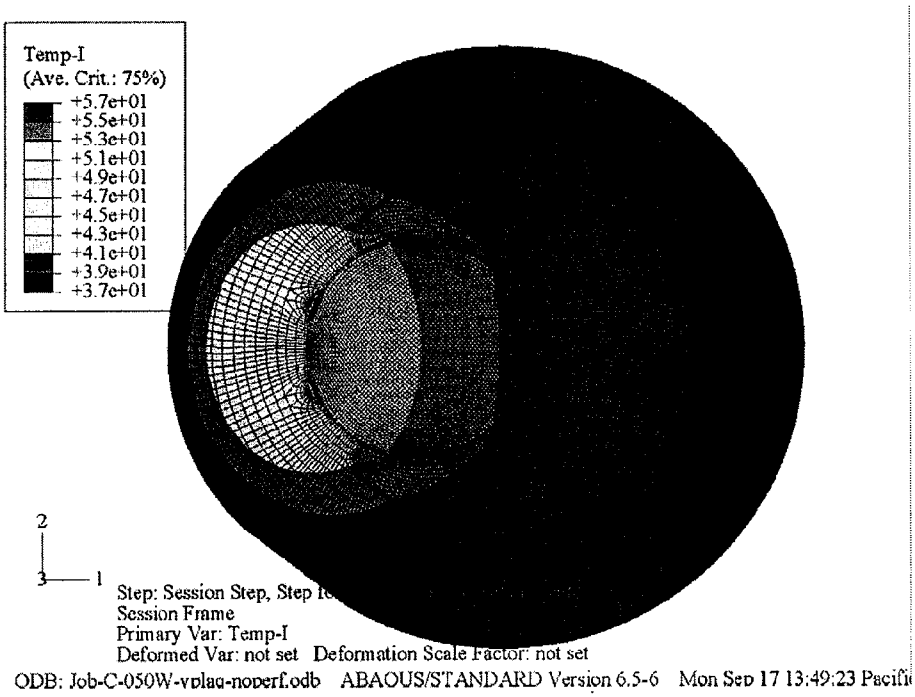


FIG. 5 - Treatment Power 0.5 W for 30 seconds into Healthy Tissue (Peak = 51°C)

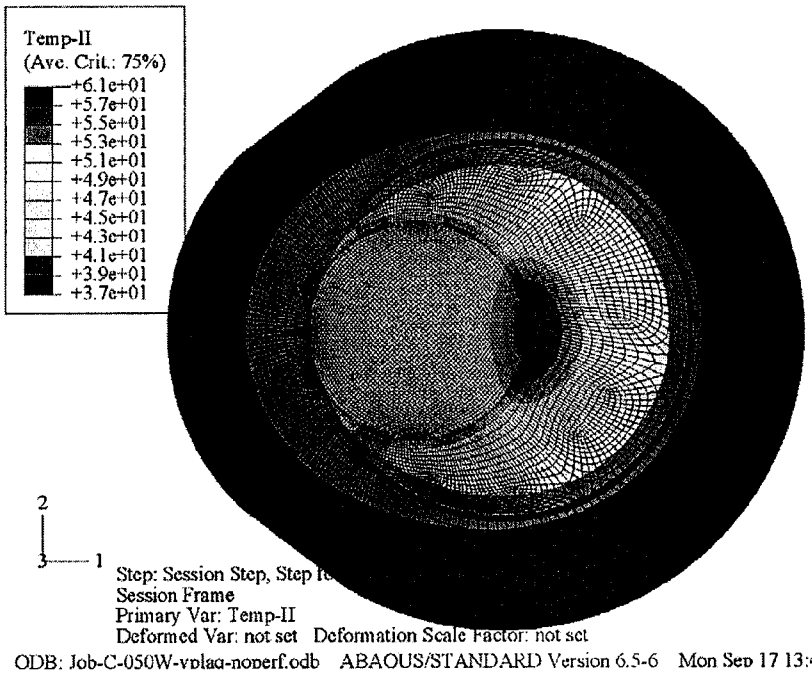


FIG 6.: Treatment Power 0.5 W for 30 seconds into Vulnerable Plaque (Peak = 61°C)

FIG. 7A

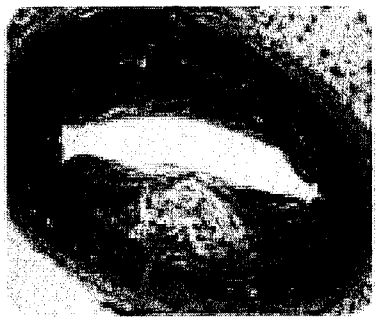


FIG. 7B

FIG. 7C

FIG. 7D

FIG. 7E

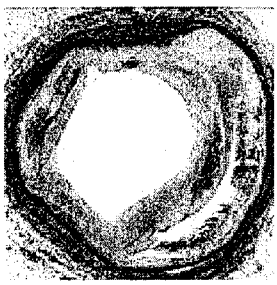


FIG. 7F

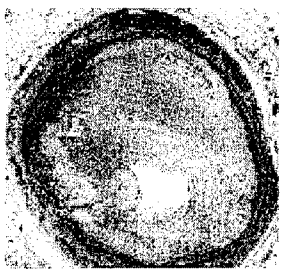


FIG. 7G

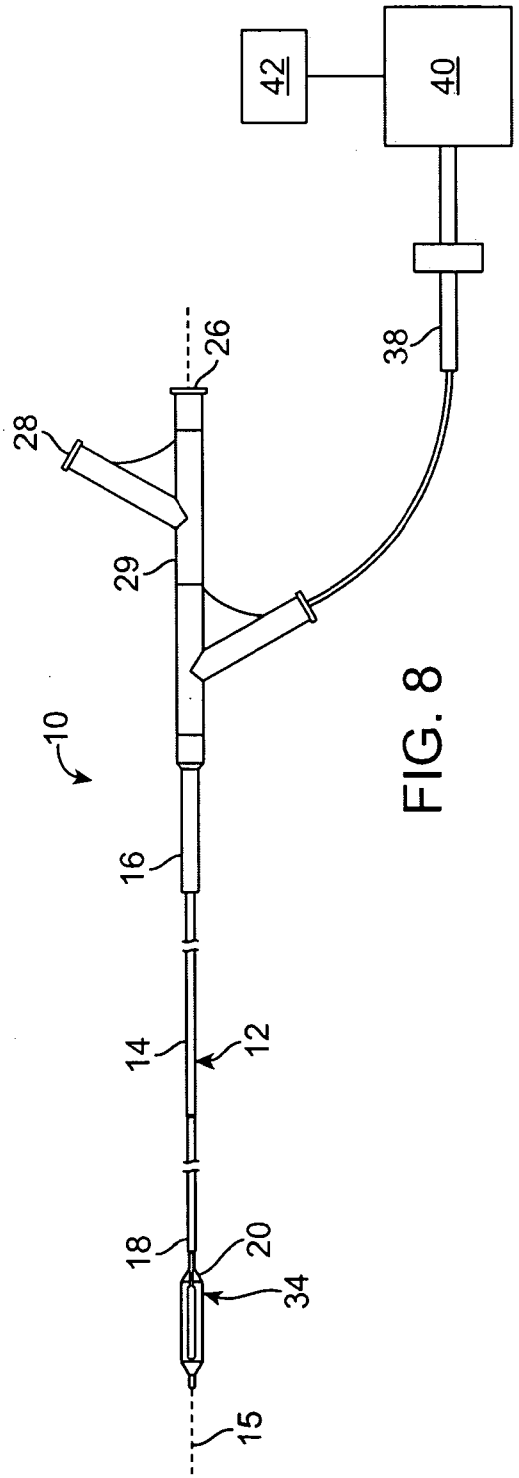


FIG. 8

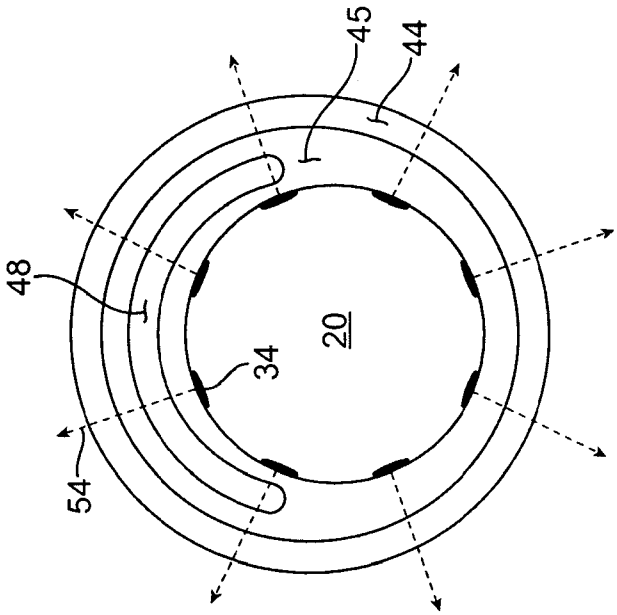


FIG. 10

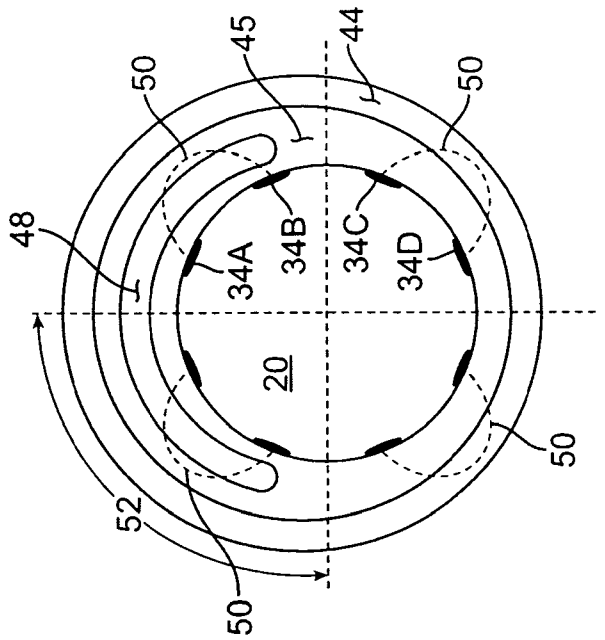


FIG. 9

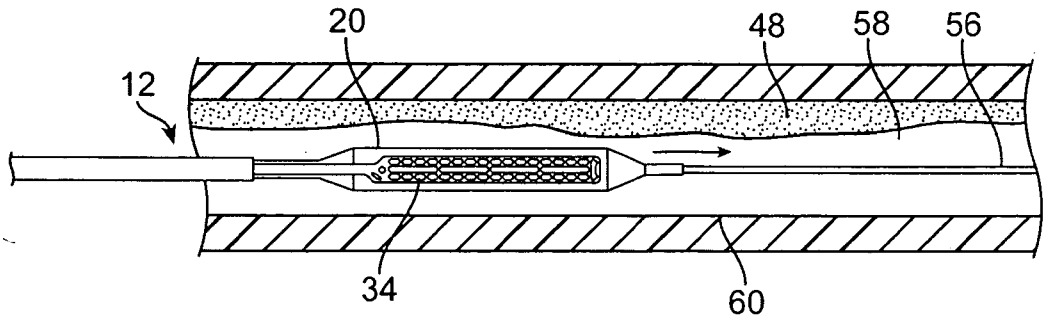


FIG. 11A

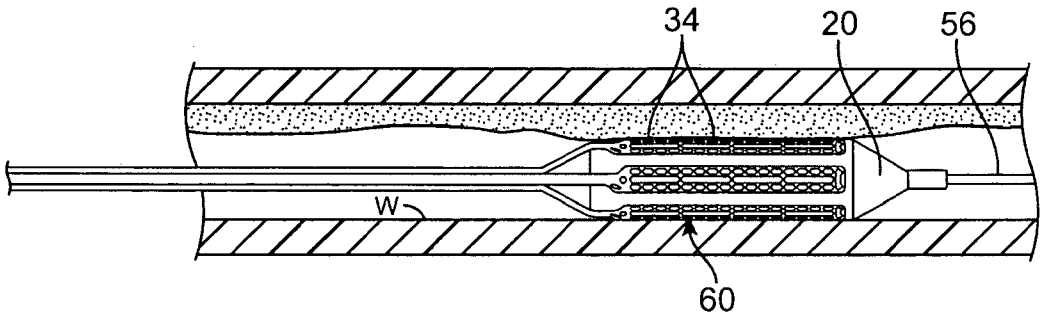


FIG. 11B

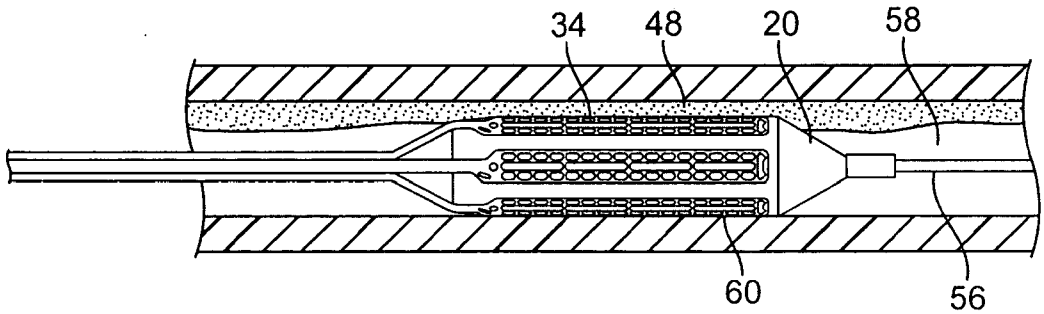


FIG. 11C

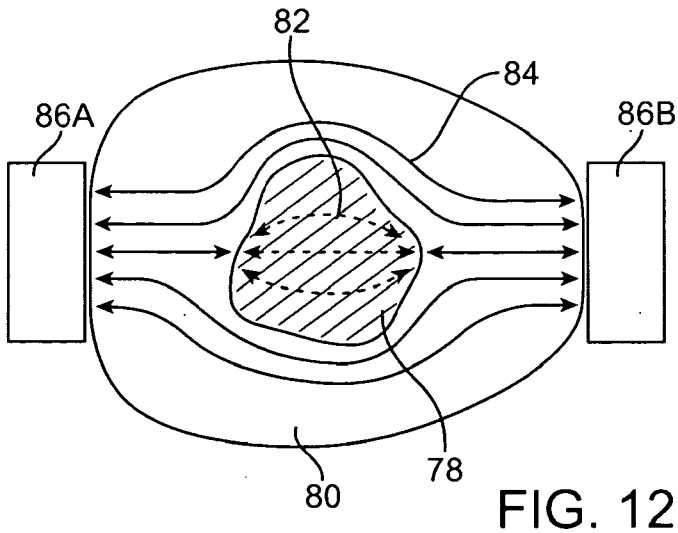


FIG. 12

Dose #1: (1 Watts / 8 Seconds),
7 Day, 144H

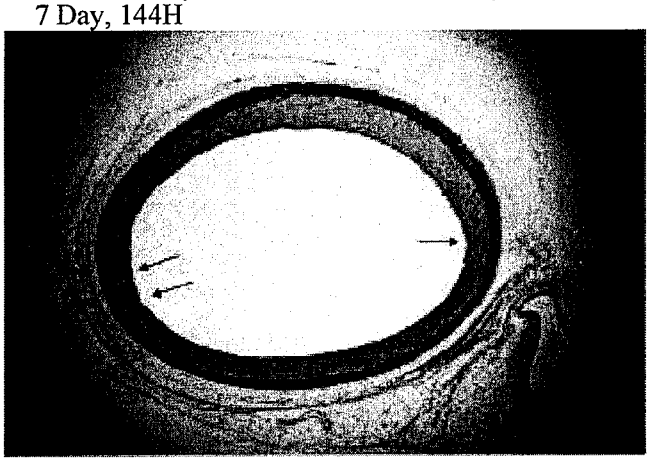


FIG. 13

Dose #2: (2 Watts / 2 Seconds),
8 Day' 145c2

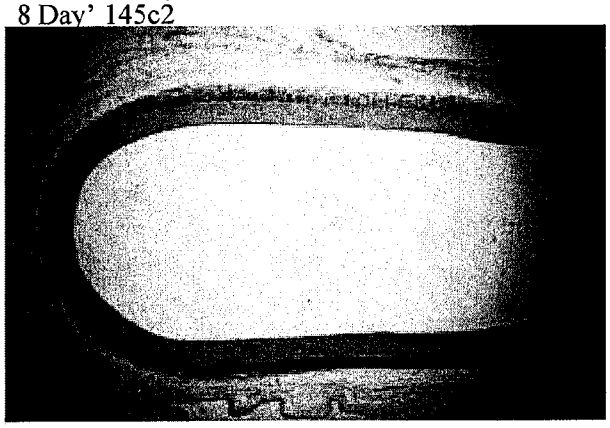


FIG. 14

Dose #3: (4 Watts / 1 Seconds),
7 Day, 146f

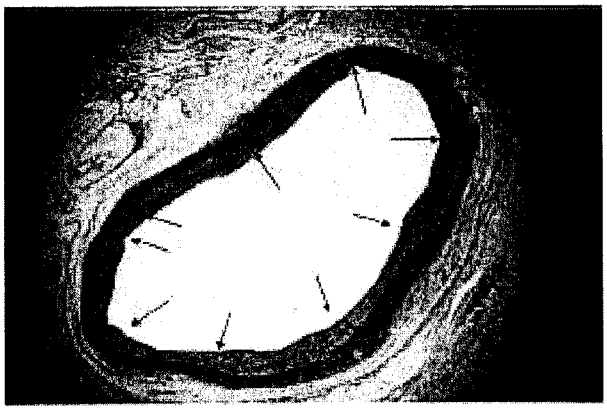


FIG. 15A

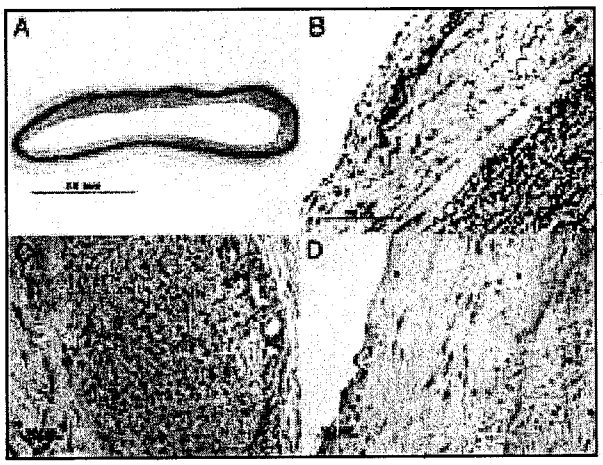


FIG. 15B

(4 Watts / 1 Second), 30 Day

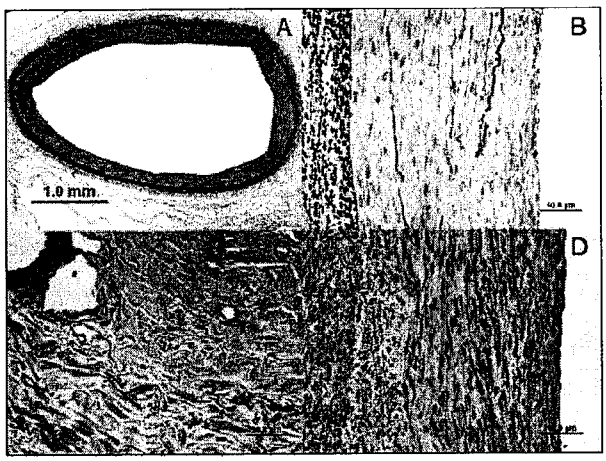


FIG. 15C

Dose #4: (2 Watts / 4 Seconds),
7 Day, 145B

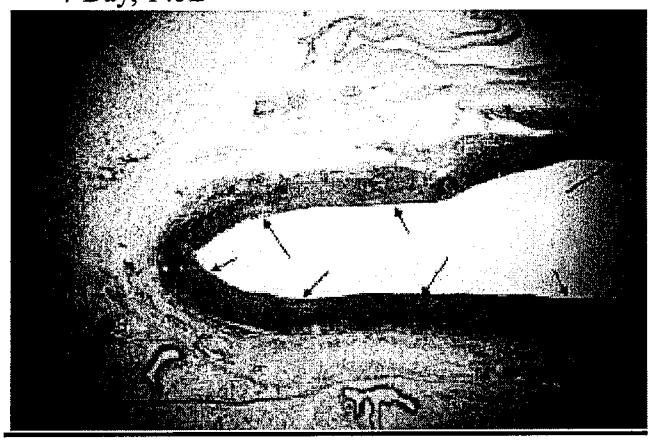


FIG. 16A

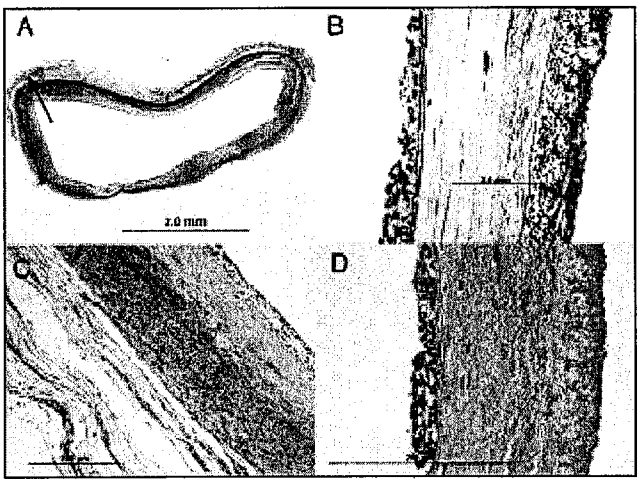


FIG. 16B

(2 Watts / 4 Seconds), 30 Day, 145b

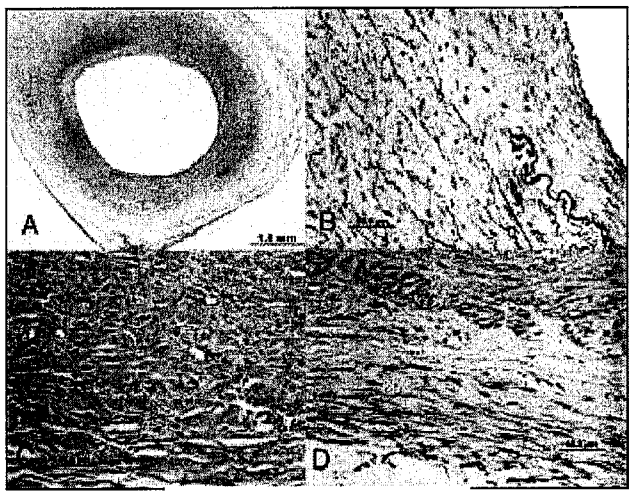


FIG. 16C

Dose #5: (3 Watts / 2 Seconds),
7 Day,

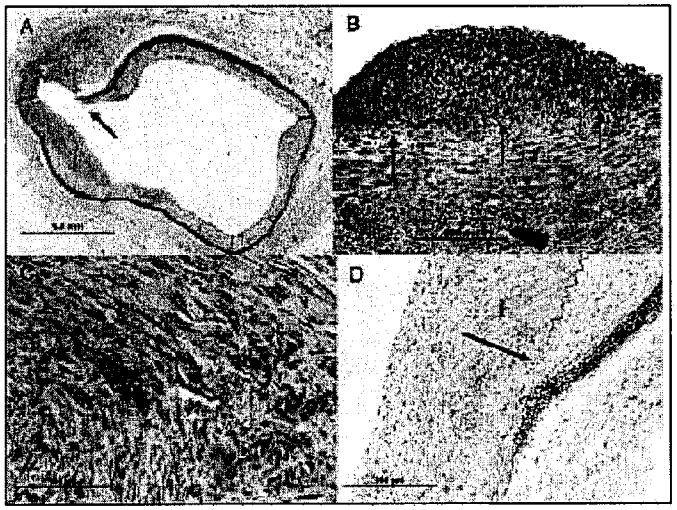


FIG. 17A

(3 Watts / 2 Seconds), 30 Day

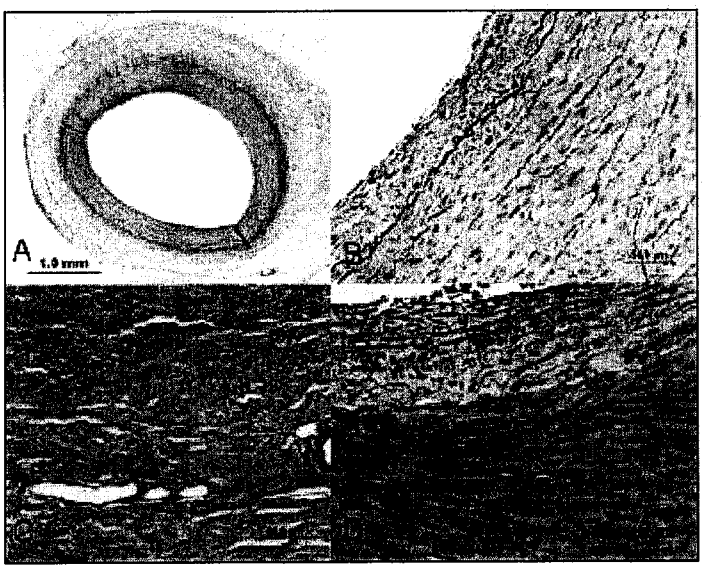


FIG. 17B

Pre-treatment baseline gray-scale IVUS scan

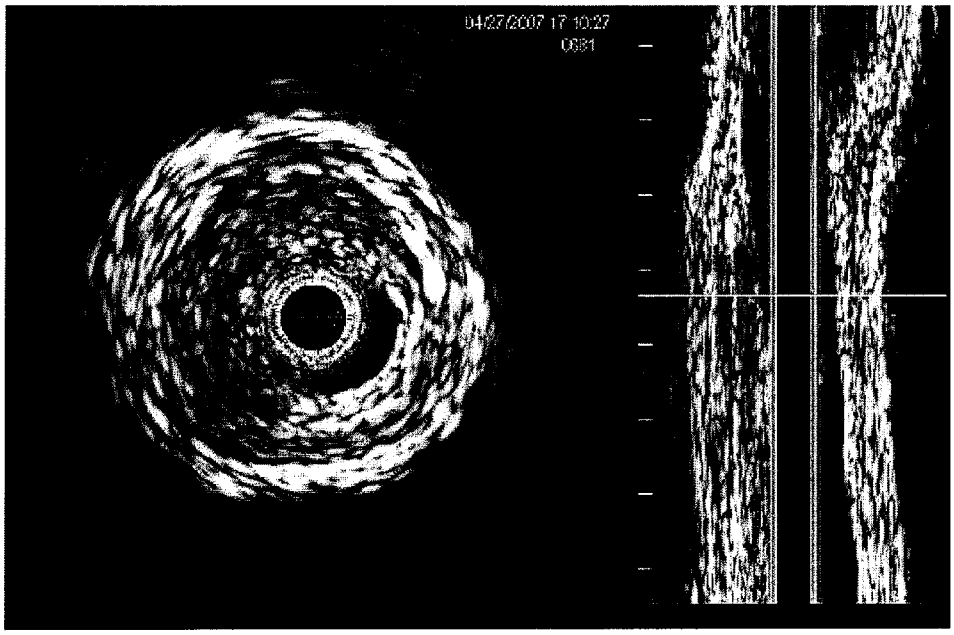


FIG. 18A

Pre-treatment baseline scan w/ VH enabled

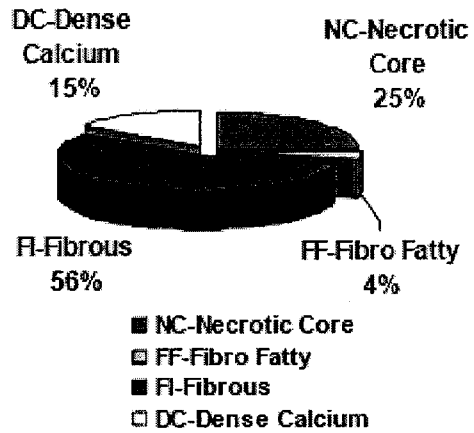


FIG. 18B

Post treatment gray-scale IVUS scan

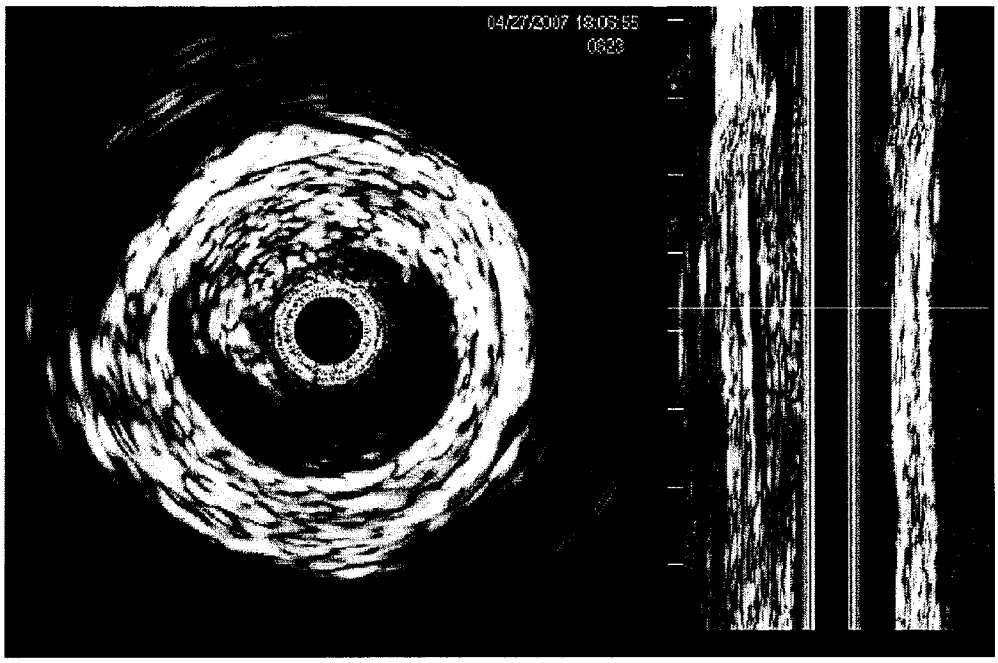
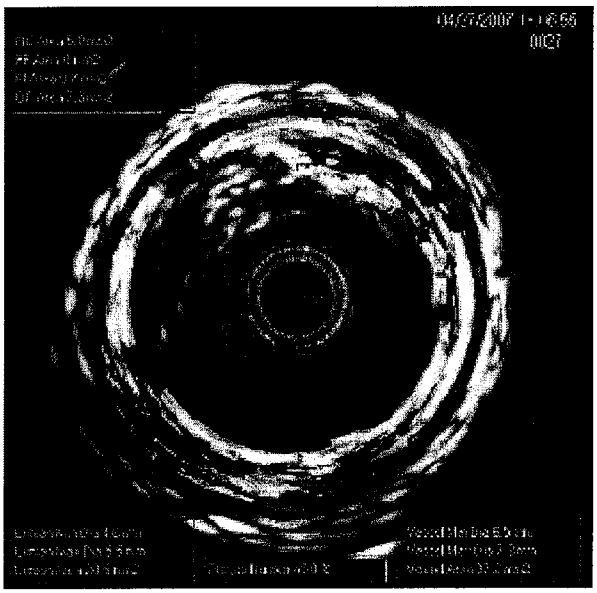


FIG. 18C

Post treatment scan w/ VH enabled



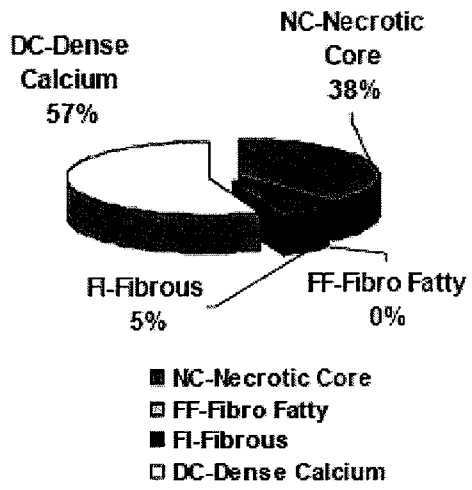


FIG. 18D

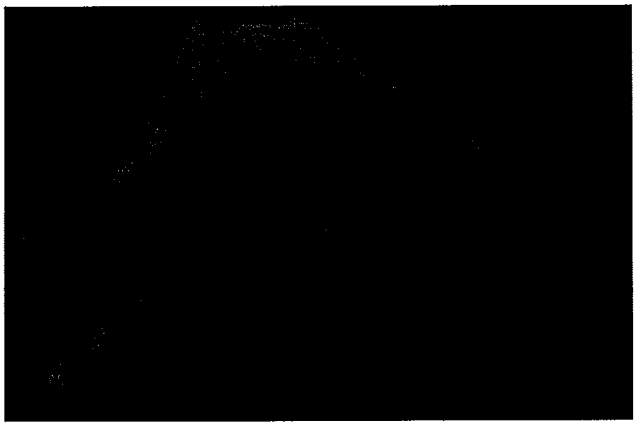


FIG. 18E

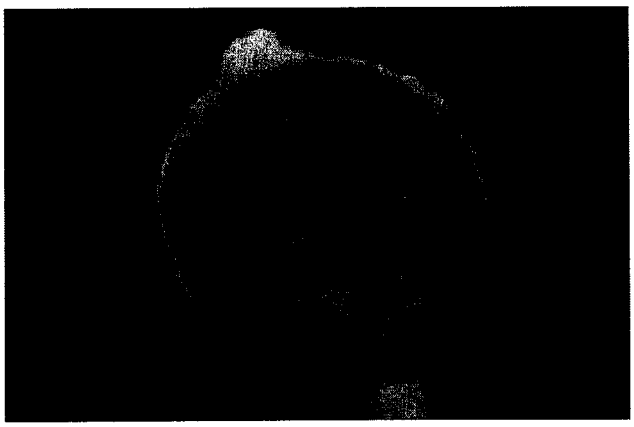


FIG. 18F

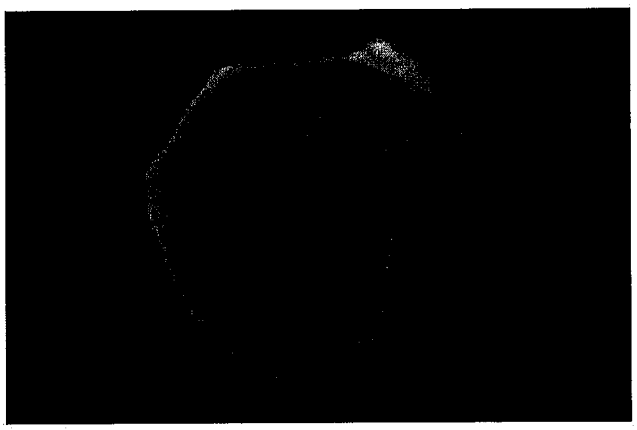


FIG. 18G

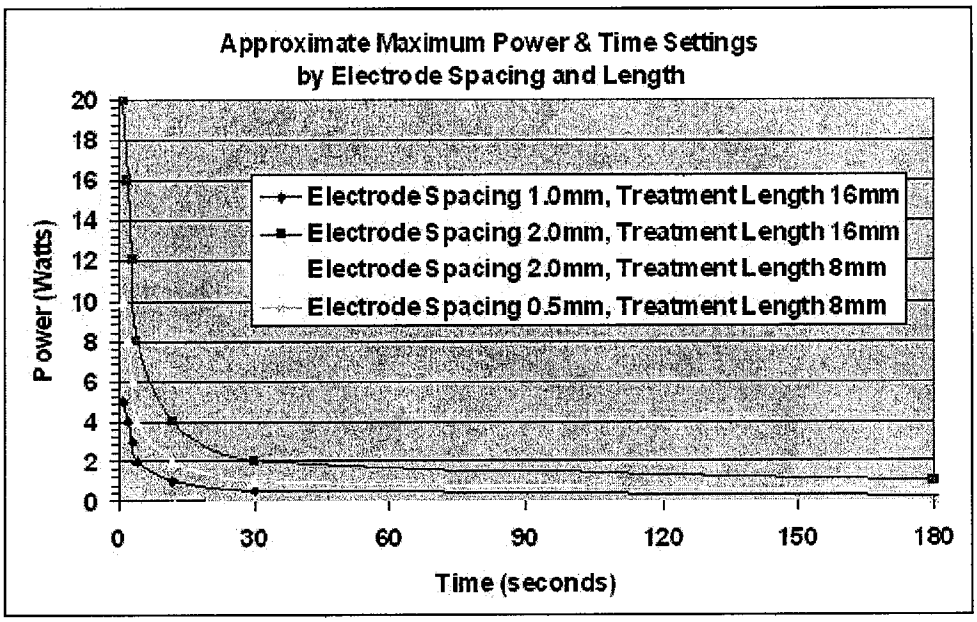

Approximate Maximum Power & Time Settings
by Electrode Spacing and Length
Power (Watts)
20
18
16
14
12
10
8
6
4
2
0
0
30
60
90
120
150
180
Time (seconds)
Electrode Spacing 1.0mm, Treatment Length 16mm
Electrode Spacing 2.0mm, Treatment Length 16mm
Electrode Spacing 2.0mm, Treatment Length 8mm
Electrode Spacing 0.5mm, Treatment Length 8mm

FIG. 19