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(54) **TISSUE TREATMENT**

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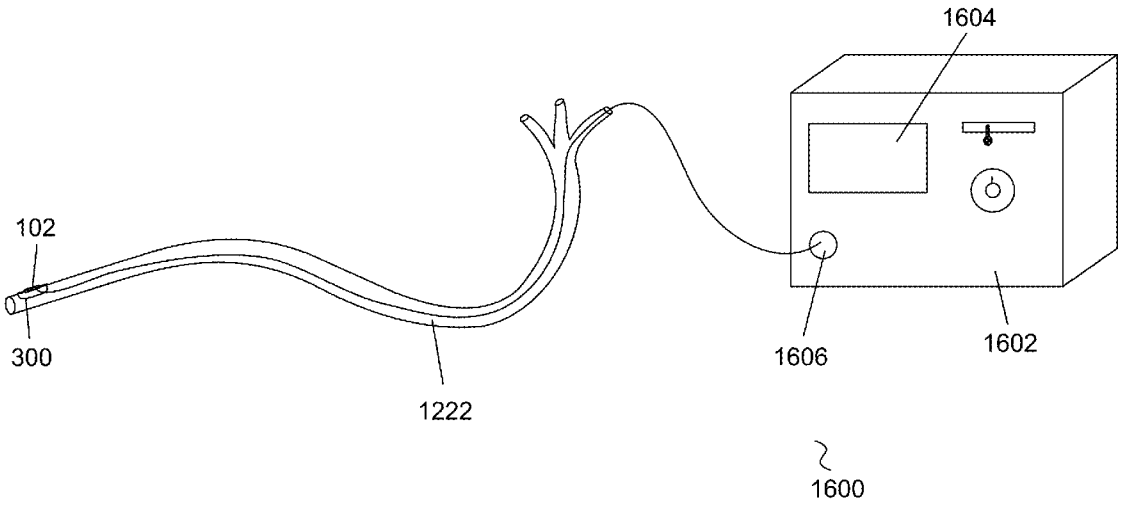
CPC ***A61B 17/320068*** (2013.01)
USPC **606/28**

(57) **ABSTRACT**

There is provided in accordance with an exemplary embodiment of the a method of selectively treating tissue using non-focused ultrasound energy delivered intrabody comprising: selectively determining a target tissue in a wall of a lumen or cavity; selecting parameters sufficient to provide a desired effect in the target tissue; and applying the parameters to treat the target tissue using non-focused ultrasound to achieve the desired effect.



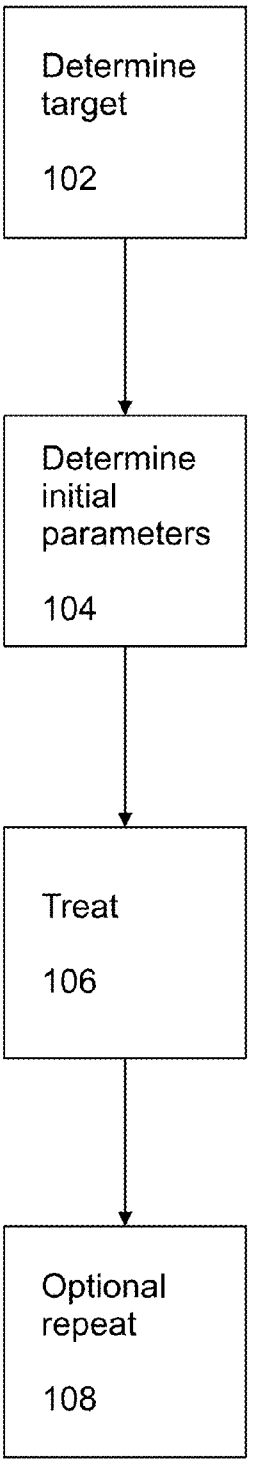

Determine target
102
Determine initial parameters
104
Treat
106
Optional repeat
108

FIG. 1A

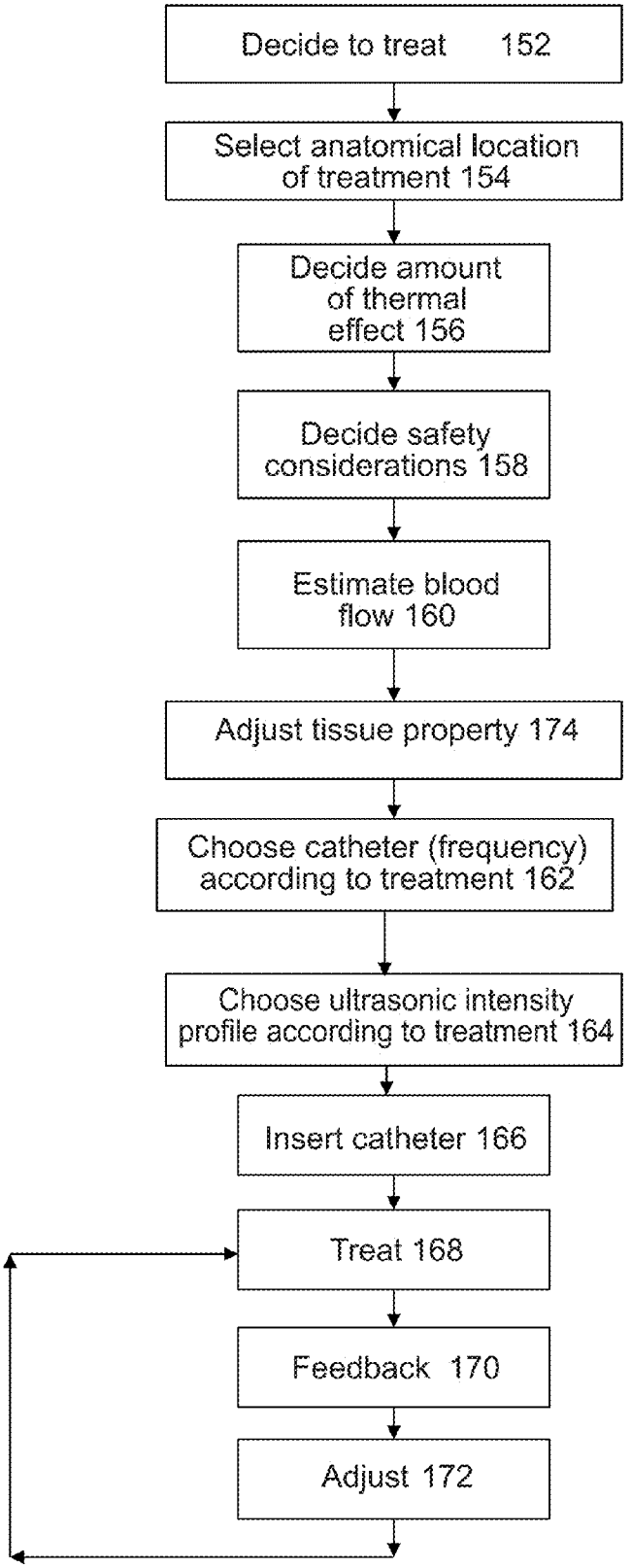

Decide to treat 152
Select anatomical location of treatment 154
Decide amount of thermal effect 156
Decide safety considerations 158
Estimate blood flow 160
Adjust tissue property 174
Choose catheter (frequency) according to treatment 162
Choose ultrasonic intensity profile according to treatment 164
Insert catheter 166
Treat 168
Feedback 170
Adjust 172

FIG. 1B

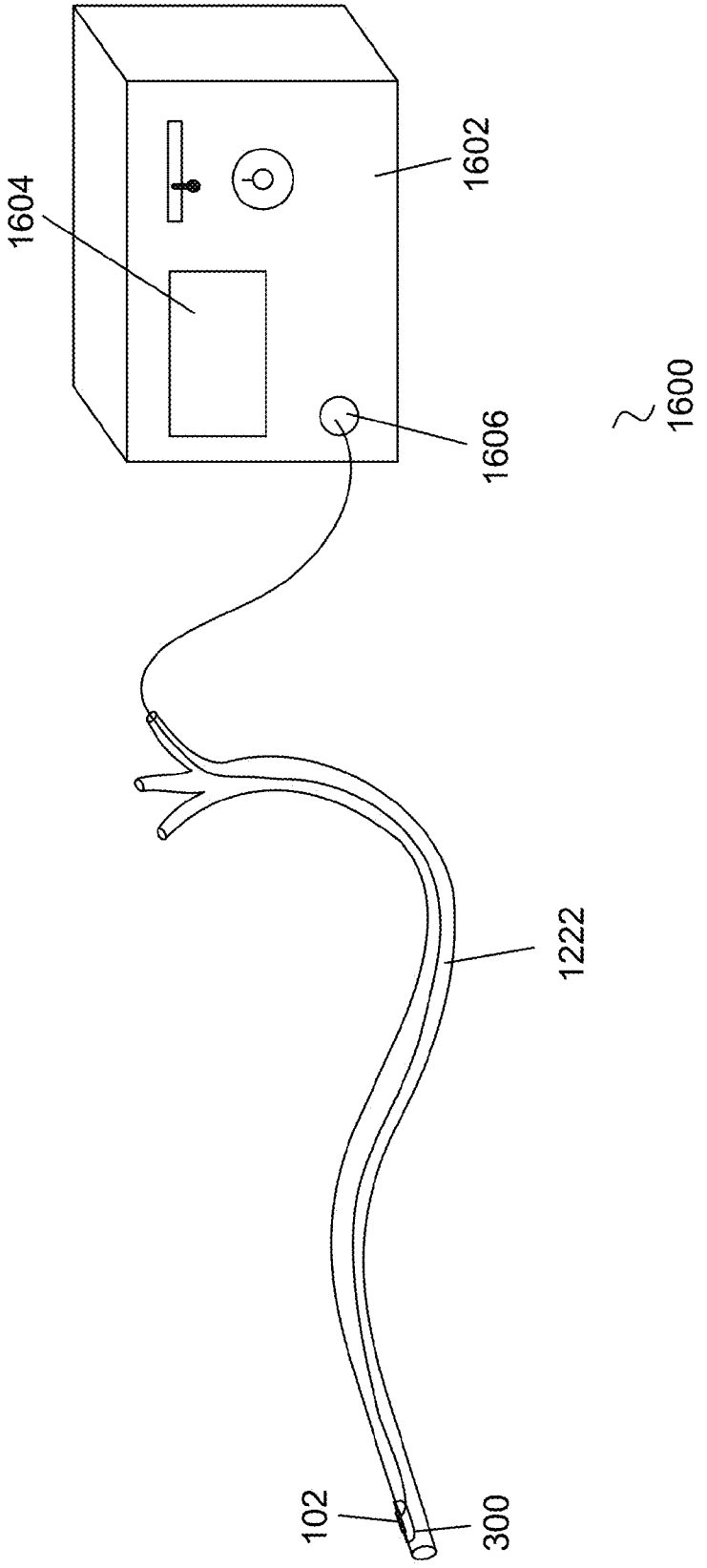


FIG. 2

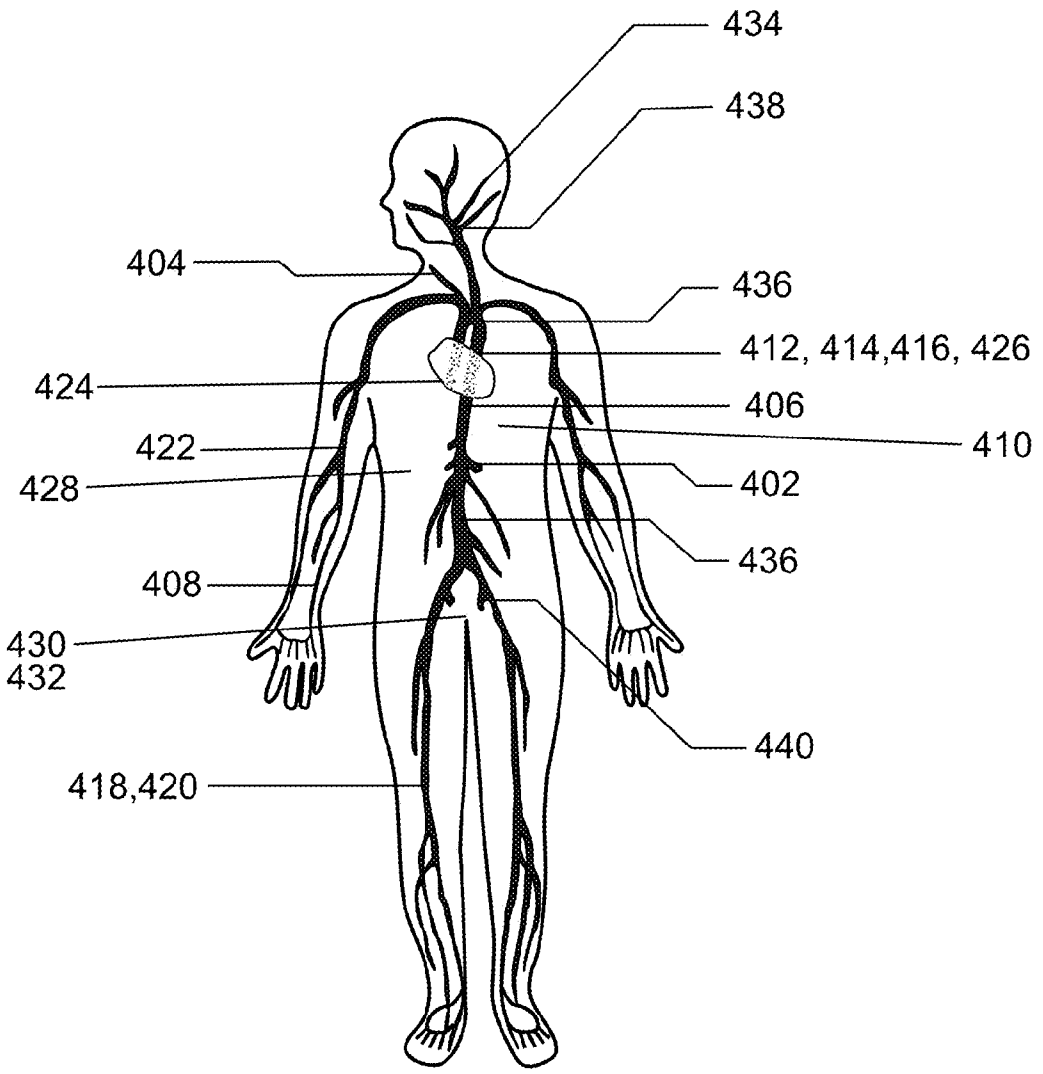

434
438
404
436
412, 414,416, 426
424
406
410
422
428
402
436
408
430
432
440
418,420

FIG. 3

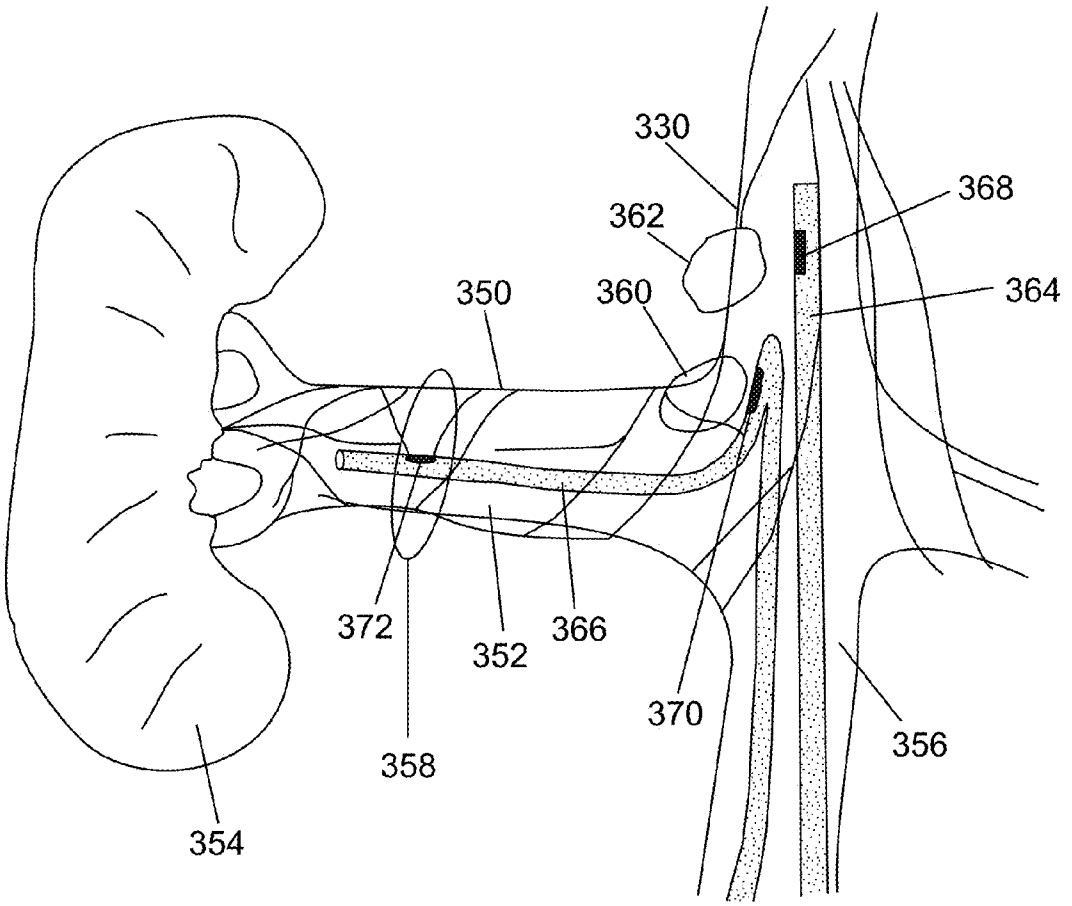


FIG. 4

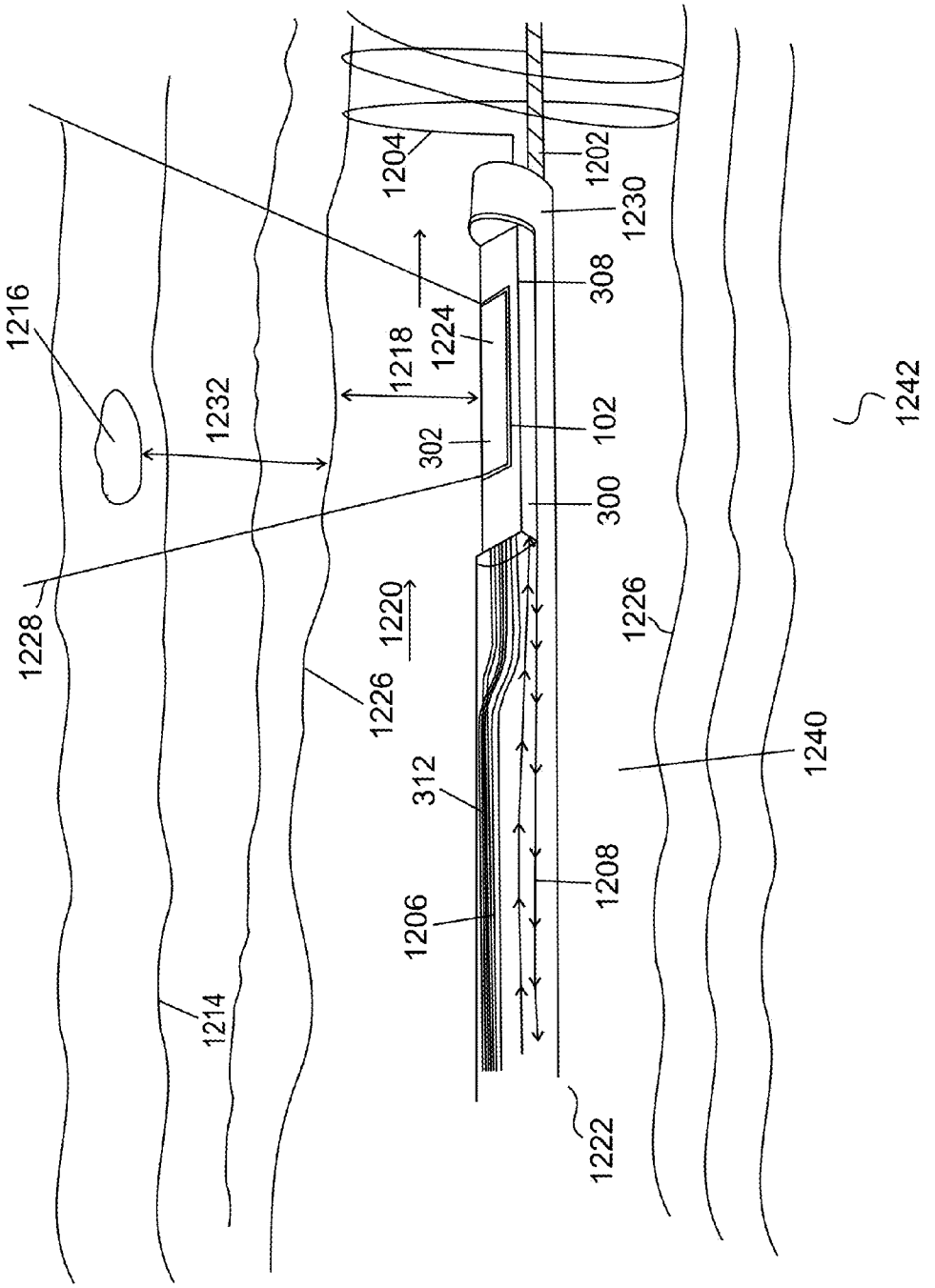

1216
1232
1228
1214
1226
1220
1218
1224
302
102
300
308
1230
1202
1204
312
1206
1208
1222
1240
1242

FIG. 5

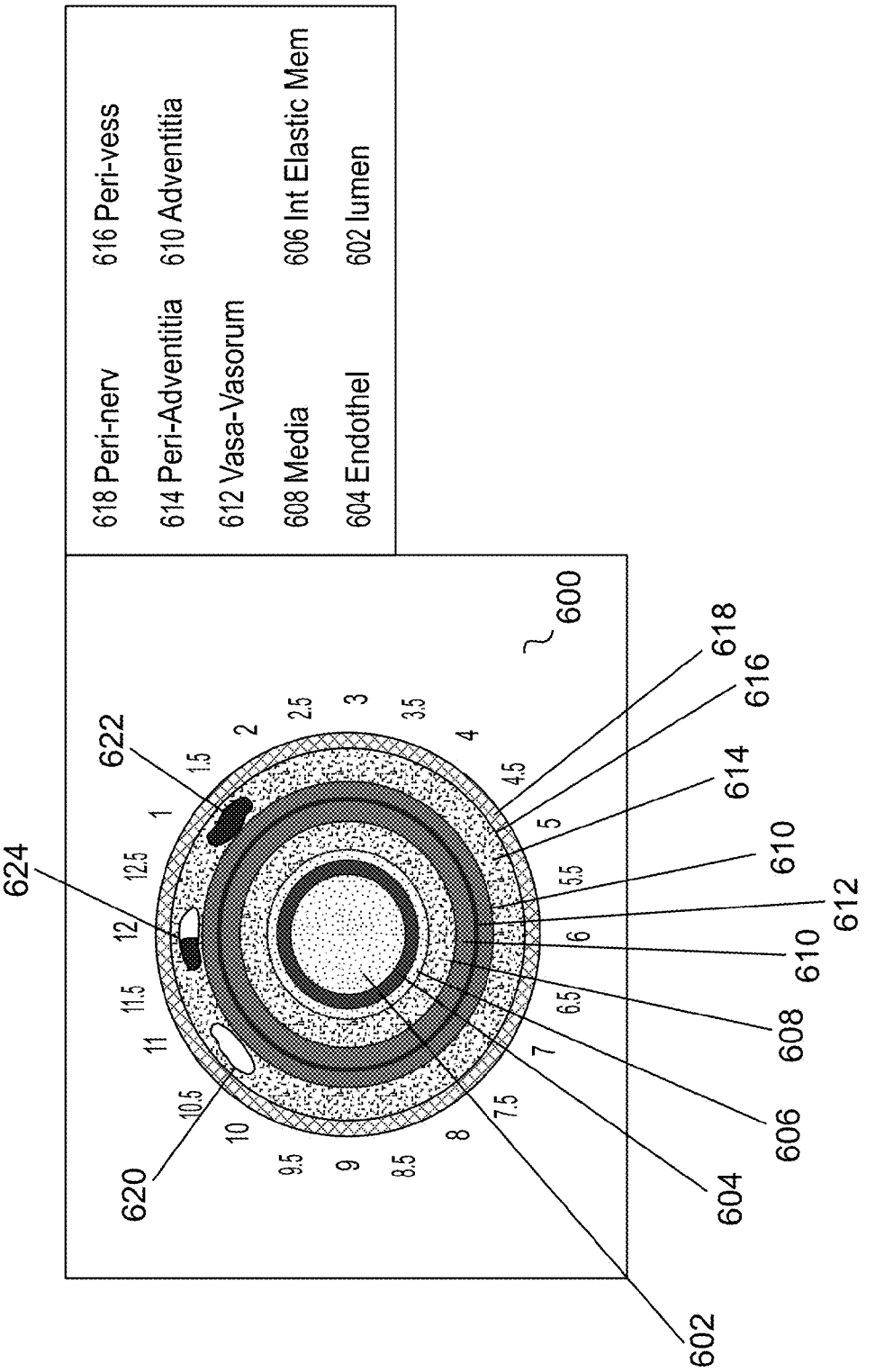

618 Peri-nerv
614 Peri-Adventitia
612 Vasa-Vasorum
608 Media
604 Endothel
616 Peri-vess
610 Adventitia
606 Int Elastic Mem
602 lumen
600
622
624
620
602
604
606
608
610
612
614
616
618

FIG. 6A

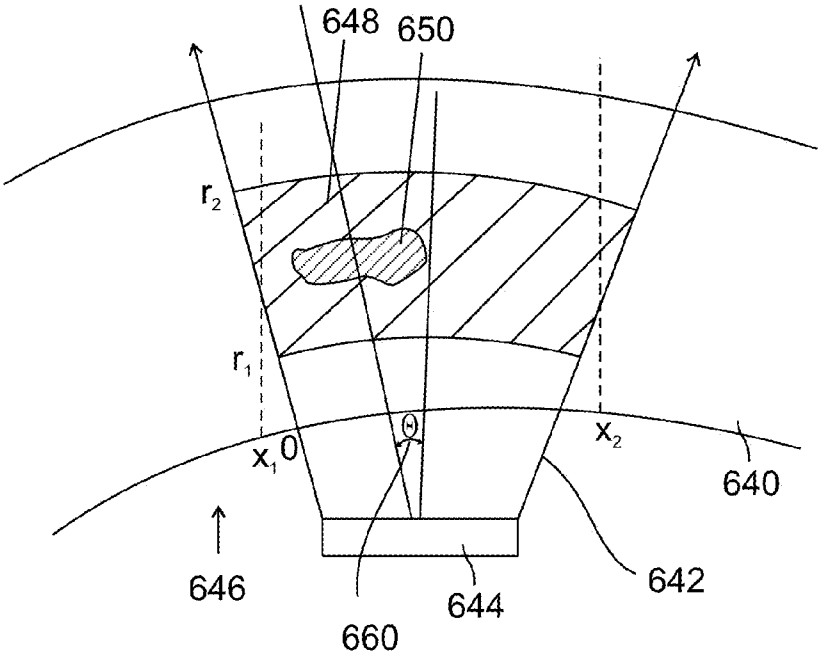

648
650
r_2
r_1
x_1 0
x_2
640
646
644
642
660

FIG. 6B

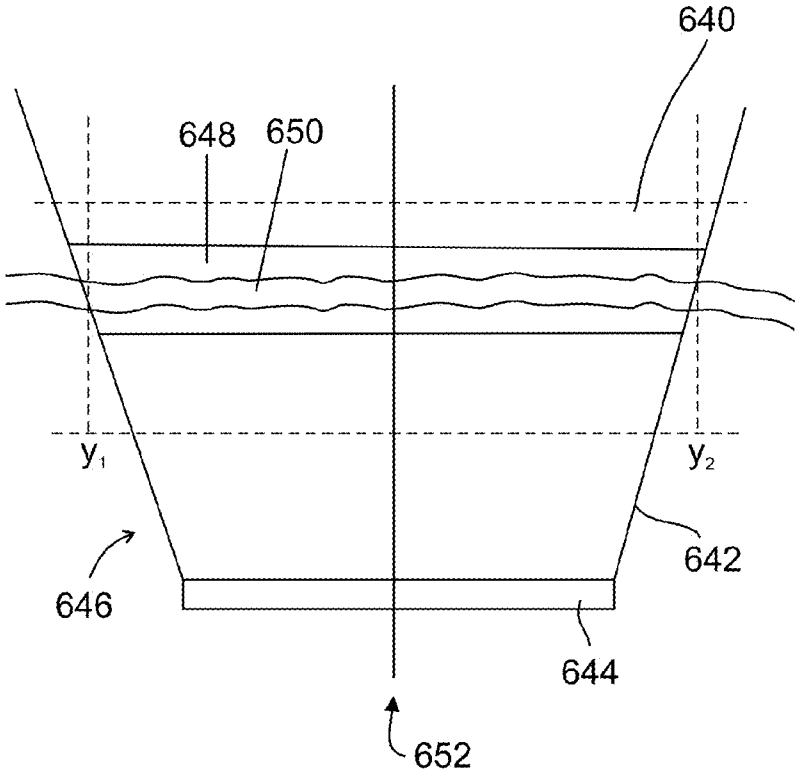

640
648
650
y_1
y_2
642
646
644
652

FIG. 6C

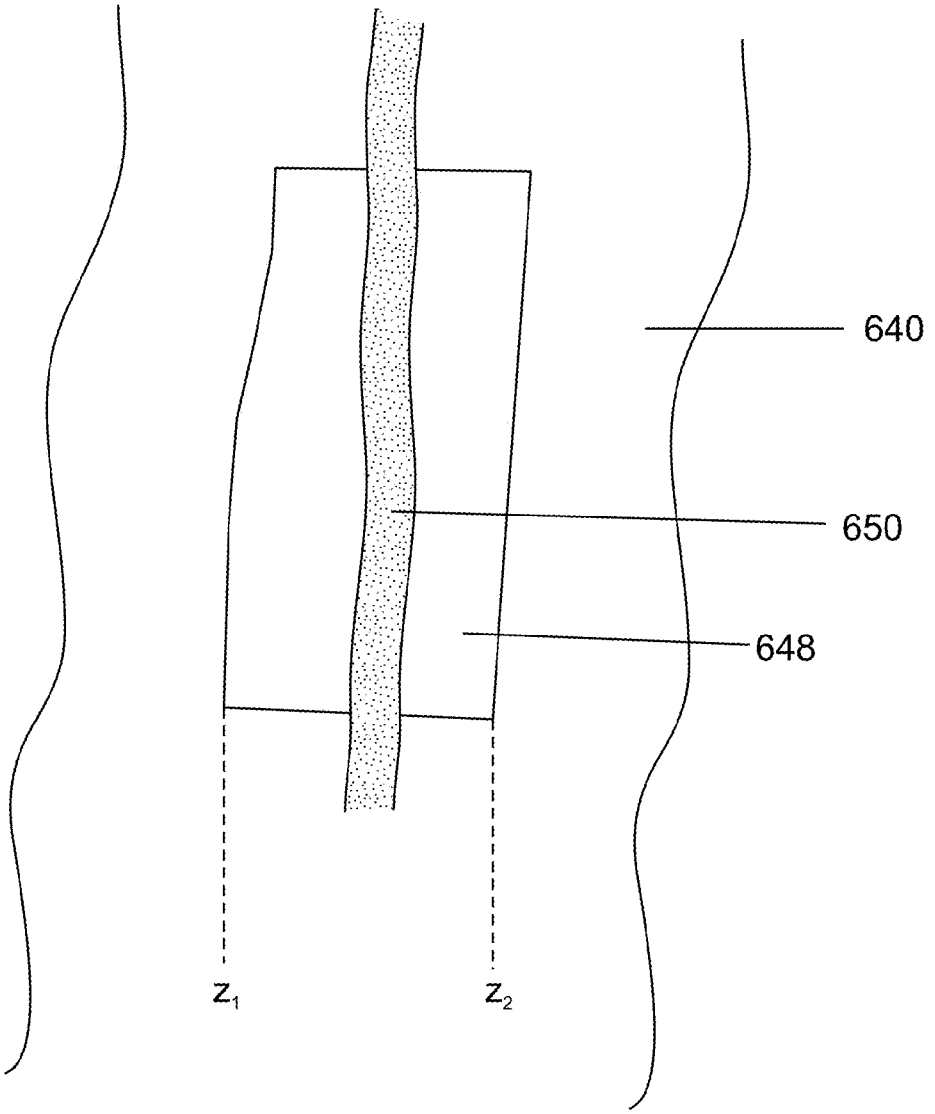


FIG. 6D

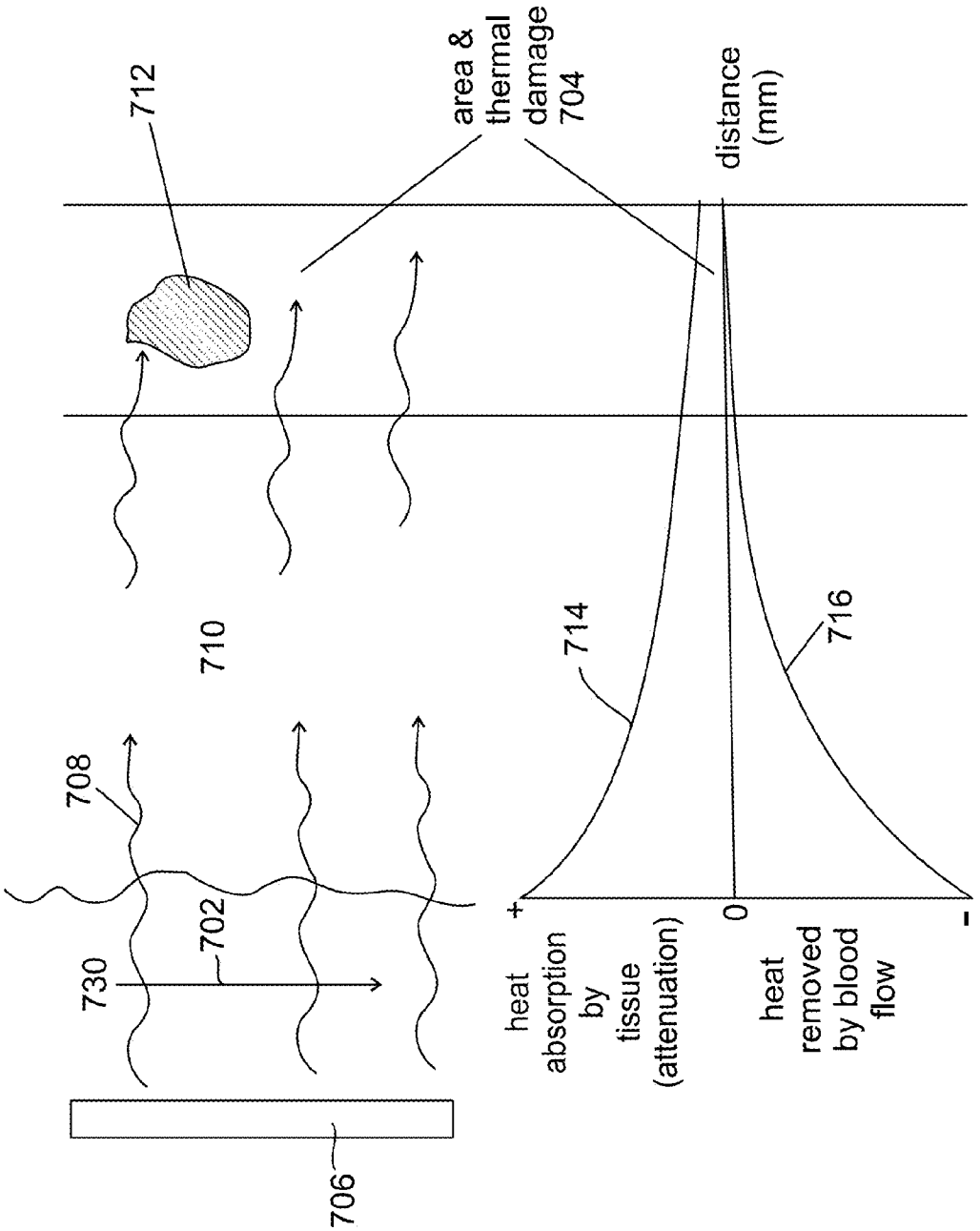

712
area & thermal damage 704
distance (mm)
710
708
702
730
706
714
716
+
0
-
heat absorption by tissue (attenuation)
heat removed by blood flow

FIG. 7A

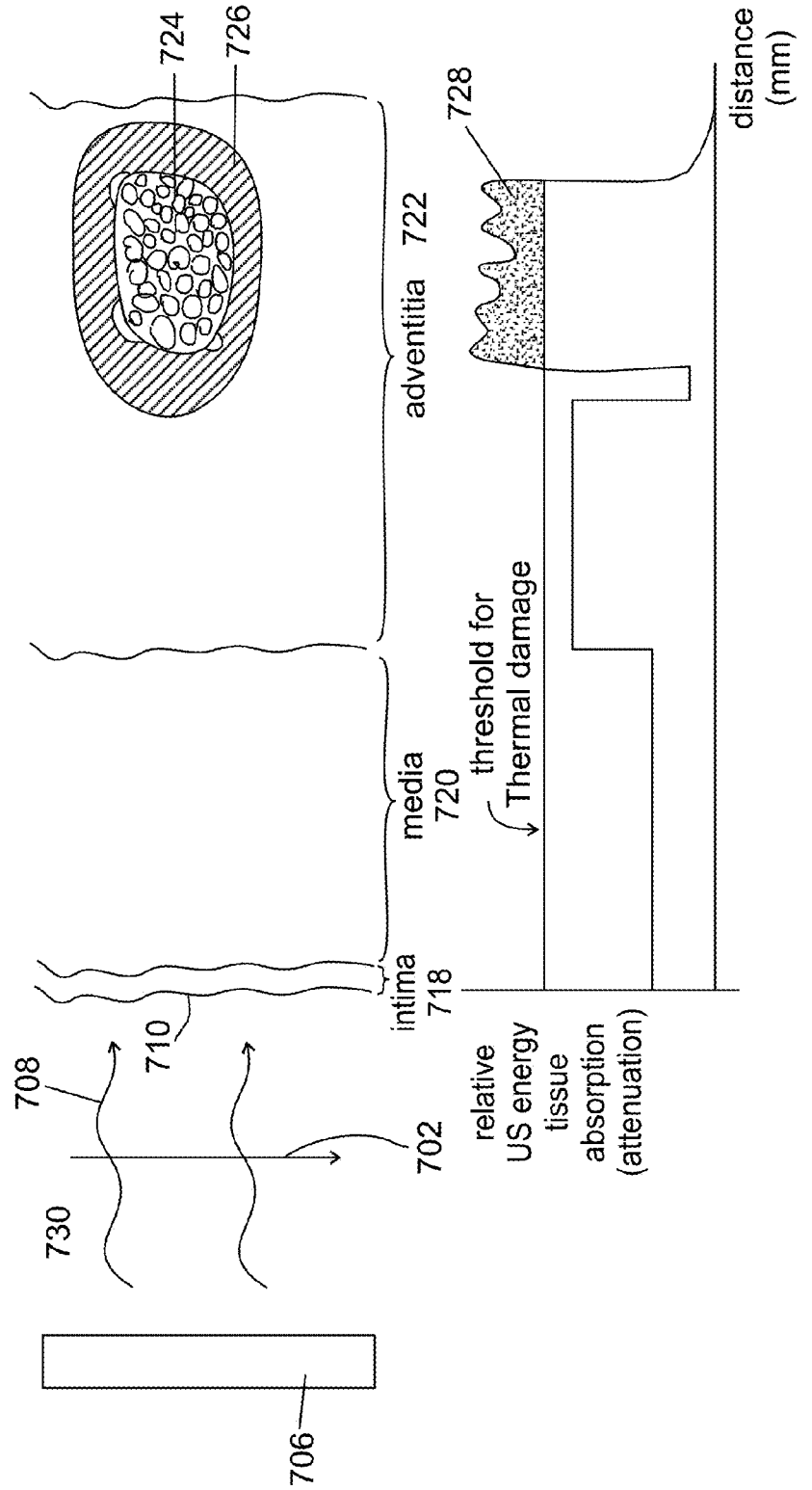

724
726
728
adventitia 722
media 720
intima 718
threshold for Thermal damage
distance (mm)
relative US energy tissue absorption (attenuation)
708
710
730
702
706

FIG. 7B

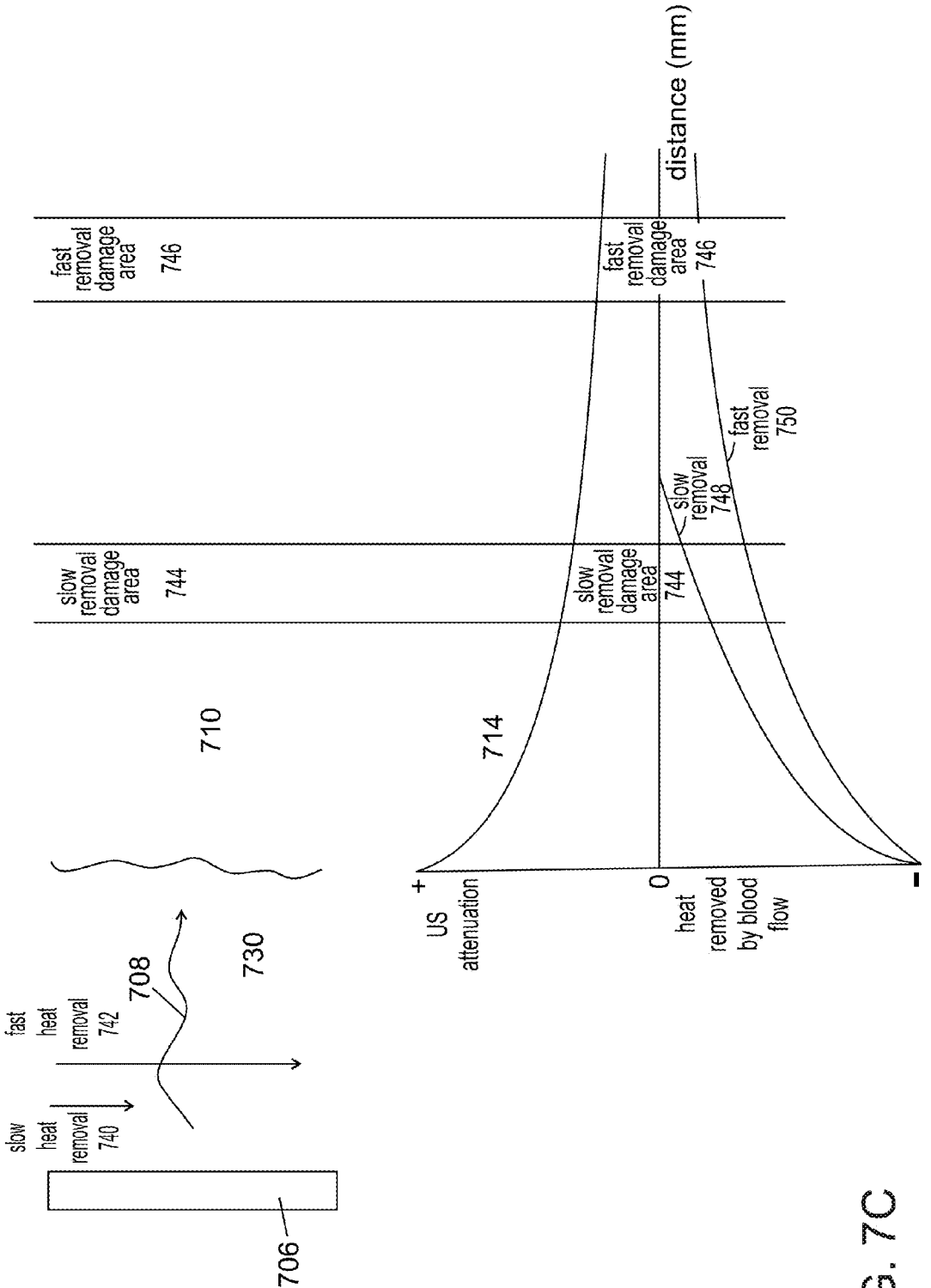

fast removal damage area 746
slow removal damage area 744
710
714
730
708
fast heat removal 742
slow heat removal 740
706
distance (mm)
fast removal damage area 746
slow removal damage area 744
slow removal 748
fast removal 750
+
US attenuation
0
heat removed by blood flow
-

FIG. 7C

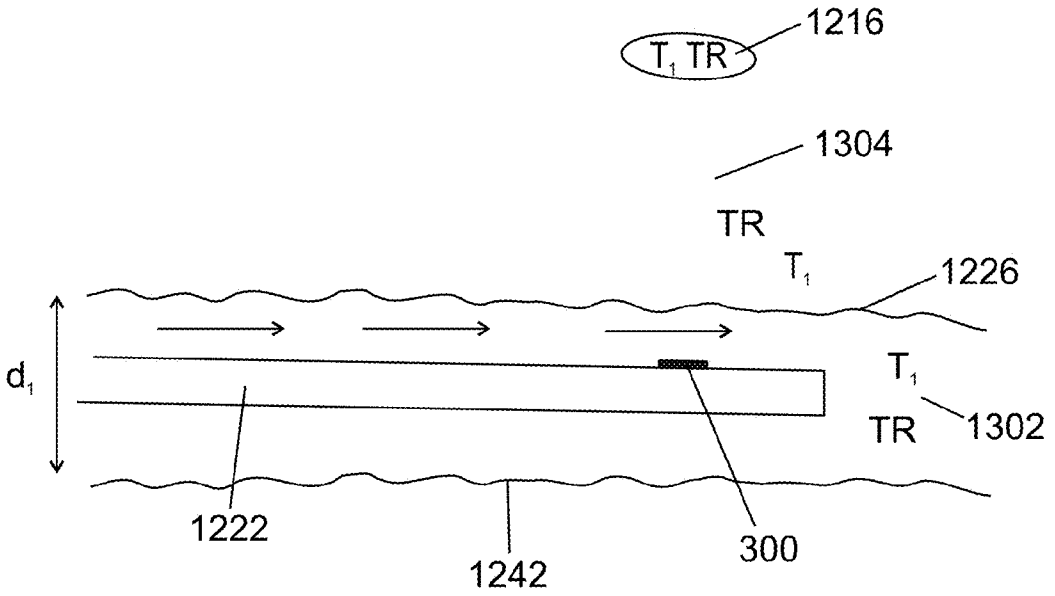

1216
T1 TR
1304
TR
T1
1226
d1
T1
TR
1302
1222
1242
300

FIG. 7D

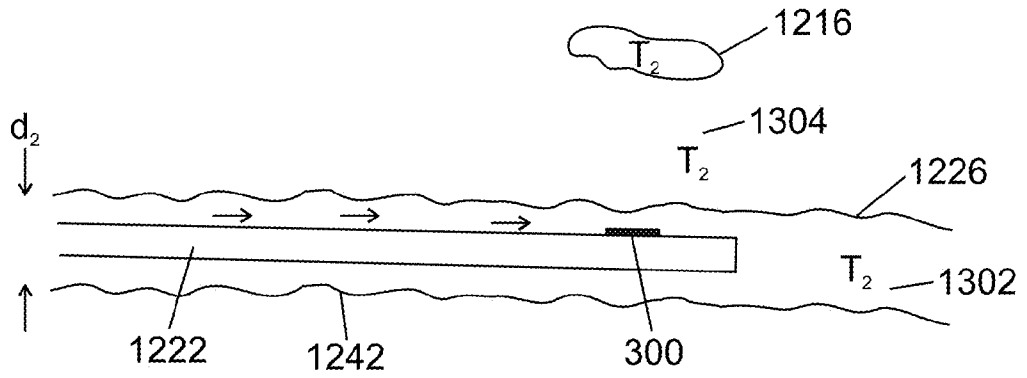

1216
T2
d2
1304
T2
1226
T2
1302
1222
1242
300

FIG. 7E

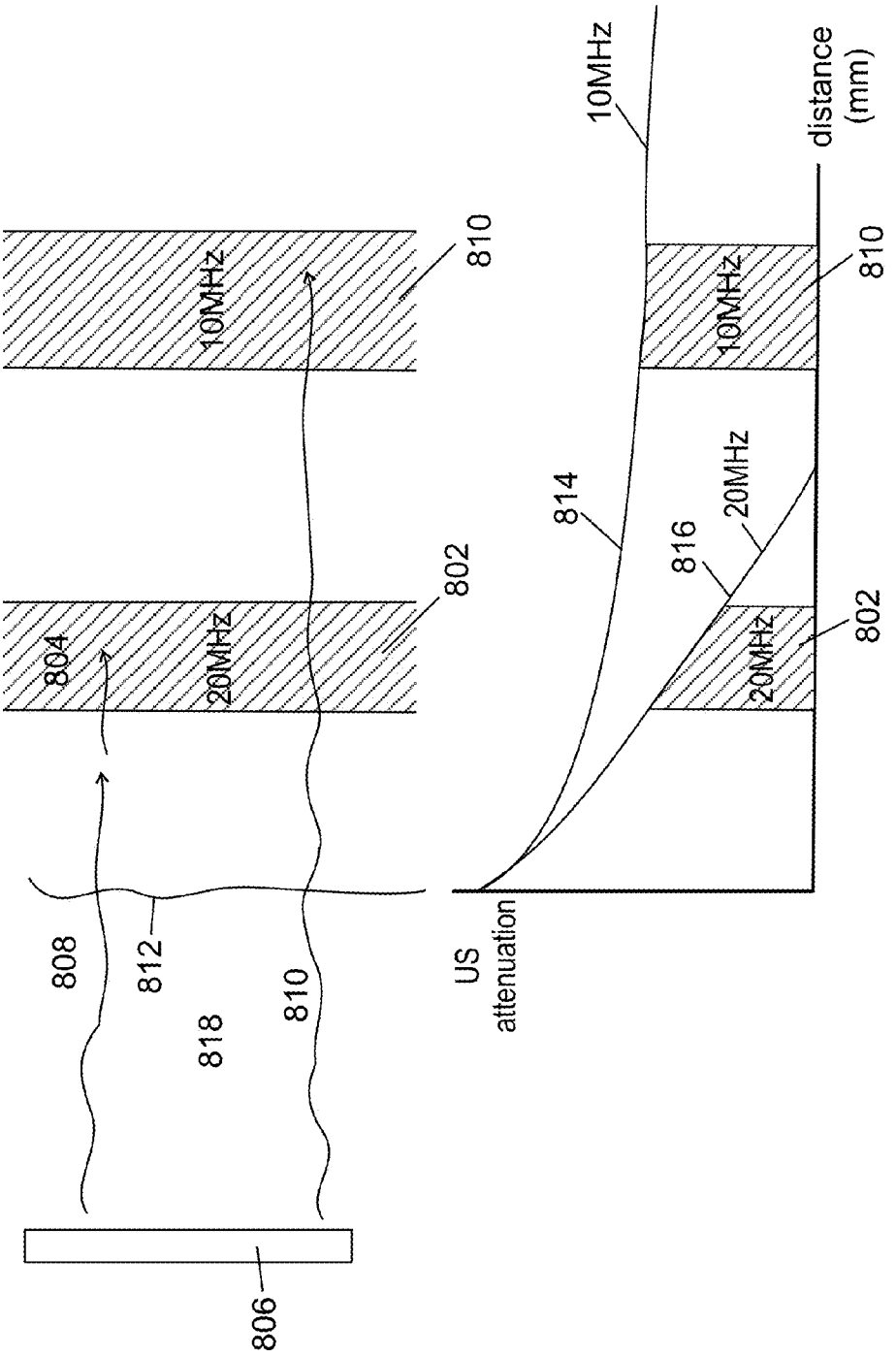

10MHz
20MHz
804
802
810
808
812
818
806
US attenuation
distance (mm)
814
816

FIG. 8

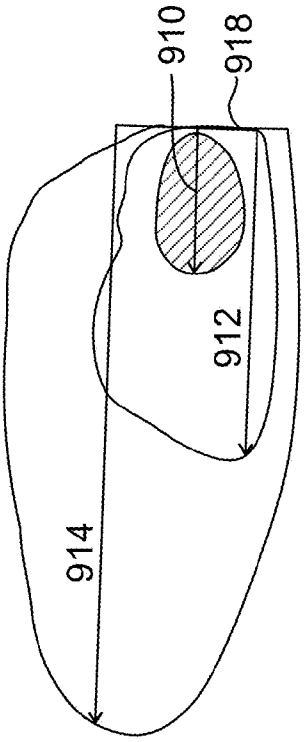
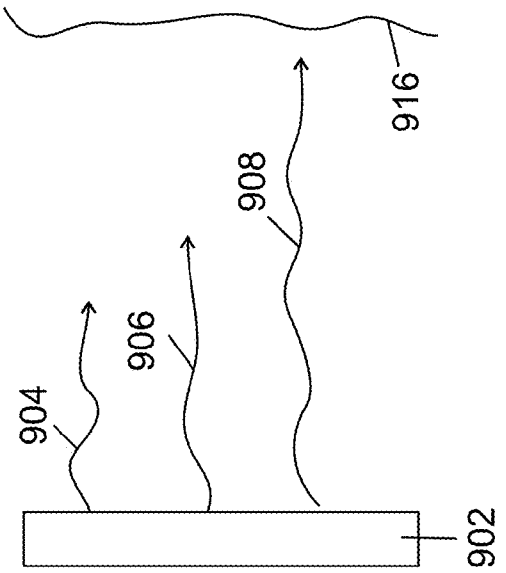


FIG. 9



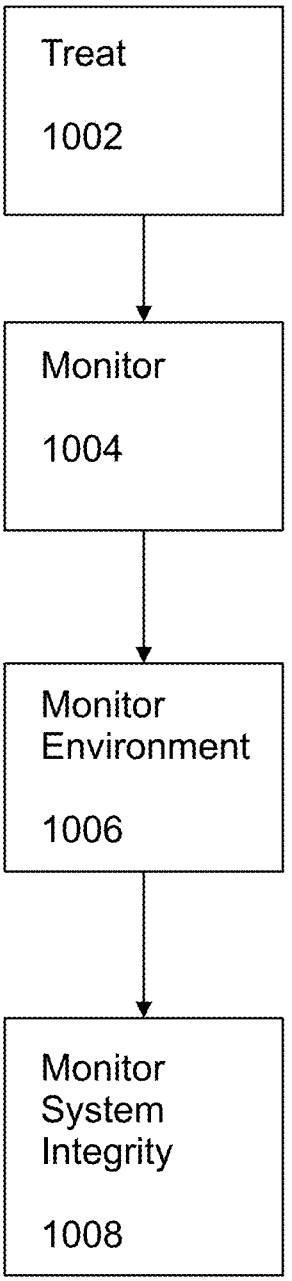

Treat
1002
Monitor
1004
Monitor Environment
1006
Monitor System Integrity
1008

FIG. 10

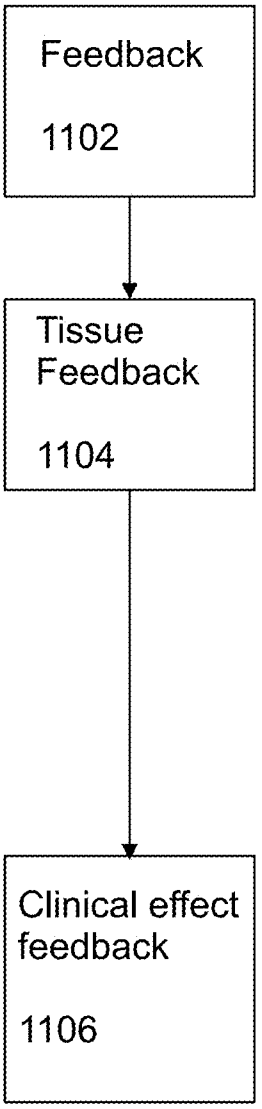

Feedback
1102
Tissue Feedback
1104
Clinical effect feedback
1106

FIG. 11

CAROTID

10 MHz						
w/cm^2	1-10	11-20	21-30	31-40	41-50	51-60
AREA			PA	M		M
DAMAGE			S	S		L
NERVE			N	N		Y
pig			7	7		8
point			6	7		6

15 MHz						
w/cm^2	1-10	11-20	21-30	31-40	41-50	51-60
AREA			M			
DAMAGE			L			
NERVE			Y			
pig			9			
point			4			

20 MHz				
w/cm^2	1-10	11-20	21-30	>31
AREA	PA	PA	M	IEL
DAMAGE	L	L	L	S
NERVE	N	Y	Y	Y
pig	7	7	7	7
point	2	3	5	8

RENAL

10 MHz					
w/cm^2	1-10	11-20	21-30	31-40	>40
AREA			PA	PA	M
DAMAGE			S	M	L
NERVE			Y	Y	Y
pig			5	8	8
point			5	2	2

15 MHz							
w/cm^2	1-10	11-20	21-30	31-40	41-50	51-60	>60
AREA							M
DAMAGE							L
NERVE							Y
pig							9
point							1

20 MHz								
w/cm^2	1-10	11-20	21-30	31-40	41-50	51-60	51-60	51-60
AREA					M	M	M	IEM
DAMAGE					M	M	M	S
NERVE					Y	Y	Y	N
pig					7	7	7	6
point					1	1	1	2

FIG. 12A

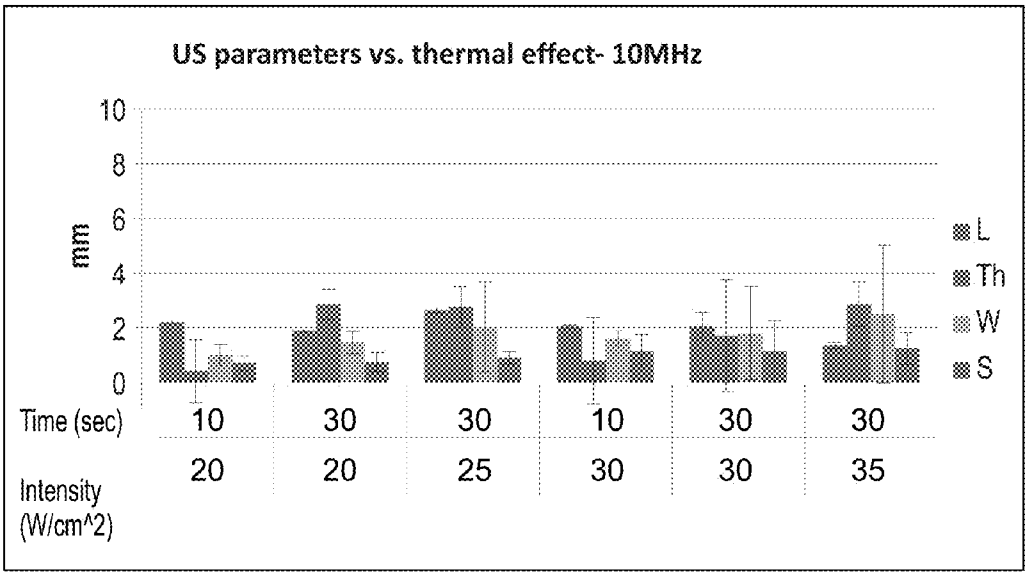
FIG.12B: US parameters vs Thermal effects for 10 Mhz

Pig no.	R/L	F	I	T	slide no.	Location (mm)	loc no.	Med	L	Th	W	S
25	R	10	20	10	RR5+10	13	2	0.66	1.49	1	2.78	1
					RR6+10	16	2	0.66	2.29	0.06	0.06	0.5
								0.66	1.73	0.17	0.48	0.5
25	L	10	20	10	RL2+15	4.5	1	0.78	4.18	0.64	1.27	1
					RL3+10	7	1	0.62	1.32	0.19	0.89	0.5
							average	0.676	2.202	0.412	0.996	0.7
							stdev	0.060663004	1.16489055	0.39869888	1.0917097	0.27386128
24	R	10	20	30	RR2+05	3.5	1	0.53	2.27	2.56	0.53	0.5
24	L	10	20	30	RL2+10	4	1	0.48	1.49	3.14	2.38	1
							average	0.505	1.88	2.85	1.455	0.75
							stdev	0.035355339	0.55154329	0.41012193	1.3081475	0.35355339
30	R	10	25	30	RR2+00	3	1	0.59	2.8	2.79	1.48	1
					RR5+00	12	3	0.53	3.38	0.25	0.45	0.5
30	L	10	25	30	RL2+10	4	1	0.65	2.42	2.64	1.75	1
					RL3+05	6.5		0.76	1.47	3.32	3.28	1
					RL4+05	9.5	2	0.55	3.12	4.8	3.14	1
							average	0.616	2.638	2.76	2.02	0.9
							stdev	0.092628289	0.74513086	1.64245243	1.1907351	0.2236068
38	R	10	30	10	RR2+10	4	1	0.48	3.84	0.7	0.46	0.5
					RR2+15	4.5	1	0.44	2.12	0.86	1.38	1
					RR3+00	6	1	0.56	0	0.44	1.6	2
					RR5+10	13	2	0.49	2.22	1.15	3	1
							average	0.4925	2.045	0.7875	1.61	1.125
							stdev	0.049916597	1.57483332	0.2972513	1.0500159	0.62915287
32	R	10	30	30	RR2+15	4.5	1	0.5	1.56	0.47	0.54	0.5
								0.5	3.33	0.6	1.39	1
								0.5	0.34	2.29	4.08	2
					RR3+05	6	1	0.44	1.4	2.26	1.37	1
								0.44	1.63	1.18	1.03	0.5
								0.44	0	0.54	1.43	2
								0.44	0	1.65	0.74	2
								0.44	0	0.29	0.25	2
								0.44	4.12	1.26	3.01	1
					RR4+15	10.5	2	0.46	1.27	1.92	2.31	1
								0.46	2.03	1.06	1.93	1
								0.46	0	0.5	0.5	2
32	L	10	30	30	RL3+00	6	1	0.53	6.01	3.1	4.1	1
						9.5	2	0.43	1.81	2.73	3.88	1
								0.43	2.33	0.3	2.56	1
								0.43	1.6	3.71	4.86	1
								0.43	1.12	3.81	2.04	1
23	R	10	30	30	RR2+15	4.5	1	0.55	1.11	2.21	1.16	1
					RR3+10	7	2	0.51	0.88	0.54	0.4	1
								0.51	1.65	1.47	0.64	1
					RR4+00	9	2	0.67	1.54	1.67	1.78	1
					RR4+15	10.5	2	0.54	3.31	2.42	0.27	0.5
23	L	10	30	30	RL2+05	3.5	1	0.66	3.44	1	0.45	1
								0.66	4.29	4.92	4.16	1
					RL2+15	4.5	1	0.84	4.01	1.5	1.68	1
					RL3+00	6	1	0.56	3.48	2.28	1.45	1
								0.56	2.95	0.41	0.7	1
							average	0.512222222	2.04481481	1.70703704	1.8040741	1.12962963
							stdev	0.998071141	1.54292273	1.20306281	1.3761185	0.45133547

Pig no.	R/L	F	I	T	slide no.	Location (mm)	loc no.	Med	L	Th	W	S
31	R	10	35	30	RR2+15	4.5	1	0.59	1.81	2.81	4.87	1
							1	0.59	1.64	1.06	0.68	1
							1	0.50	1.8	1.44	1.18	1
					RR3+10	7	1	0.48	0.28	2.82	4.11	2
							1	0.48	0.5	2	2.18	1
					RR4+10	10	2	0.62	1.72	0.1	0.1	0.5
					RR4+15	10.5	2	0.7	0.44	4.87	3.99	2
							2	0.7	2.67	0.37	0.61	0.5
							2	0.7	0.14	0.44	0.54	2
31	R	10	35	30	RL3+15	7.5	1	0.53	1.64	3.9	3.47	1
					RL4+05	9.5	2	0.81	1.6	7.64	5.1	1
							2	0.81	2	6.89	3.21	2
							average	0.633333333	1.35333333	2.86166667	2.5033333	1.25
							stdev	0.112519359	0.80374502	2.52055489	1.833151	0.58387421

FIG.12C: US parameters vs Thermal effects for 20 Mhz

Pig no.	R/L	F	I	T	slide no.	Location (mm)	loc no.	Med	L	Th	W	S
34	R	20	10	30	RR5+05	12.5	1	0.47	1.24	0.74	1.64	0.5
								0.47	1.03	0.26	0.87	0.5
					RR5+15	13.5		0.6	2.49	0.61	0.55	1
								0.6	1.81	2.81	0.8	1
							average	0.535	1.6425	1.105	0.965	0.75
							stdev	0.0750555	0.6540833	1.1545995	0.4704962	0.2886751
29	R	20	20	10	RR1+10	1	1	0.6	1	1.52	3.49	1
					RR2+05	3.5	1	0.65	0.28	2.3	3.72	2
					RR4+15	10.5	2	0.62	1.36	0.23	0.17	0.5
								0.62	2.74	0.3	0.44	0.5
					RR5+10	13	2	0.54	1.35	3.7	2.7	1
								0.54	1.53	0.27	0.31	0.5
29	R	20	20	10	RL1+05	0.5	1	0.73	0.91	1.57	1.63	1
					RL1+15	1.5	1	0.67	1.03	3.93	2.79	1
					RL3+10	7	1	0.54	5	0.26	0.94	0.5
40	R	20	20	10	RR6+05	15.5	1	0.52	0.3	2.7	3.36	2
								0.52	0.2	3.51	2.18	2
								0.52	0.23	3.14	2.86	2
							average	0.5891667	1.3275	1.9525	2.0491667	1.1666667
							stdev	0.0698646	1.3659437	1.4524658	1.3067758	0.6513389
27	L	20	20	30	RL2+15	4.5	1	0.6	0.42	3.79	5.75	2
					RL3+00	6	1	0.6	0.42	2.1	1.73	2
					RL3+05	6.5	1	0.63	0.12	1.67	2.6	2
								0.63	2.64	0.21	0.18	0.5
								0.63	2.23	4.47	5.73	1
27	R	20	20	30	RR2+00	3	1	0.5	0	3.85	2.68	2
								0.5	7.16	2.15	3	1
								0.5	1.49	2.16	1.97	1
					RR2+10	4	1	0.48	0	2.54	2.07	2
								0.48	0.88	1.39	3.15	1
							average	0.555	1.536	2.433	2.884	1.45
							stdev	0.0677003	2.1852241	1.2861402	1.7214348	0.5986095
Pig no.	R/L	F	I	T	slide no.	Location (mm)	loc no.	Med	L	Th	W	S
33	L	20	30	10	RL3+05	6.5	1	0.72	1.17	3.95	1.42	1
33	R	20	30	10	RR3+15	7.5	1	0.65	0	3.34	1.88	2
					RR4+10	10	2	0.67	1.06	2.13	4.53	1
								0.67	0.31	6.81	4.56	2
					RR5+10	13	2	0.58	1.5	0.54	0.12	0.5
							average	0.658	0.808	3.354	3.302	1.3
							stdev	0.0506952	0.6273516	2.3300279	1.5267351	0.6708204


US parameters vs. thermal effect- 10MHz
mm
10
8
6
4
2
0
L
Th
W
S
Time (sec)
10
30
30
10
30
30
Intensity (W/cm^2)
20
20
25
30
30
35

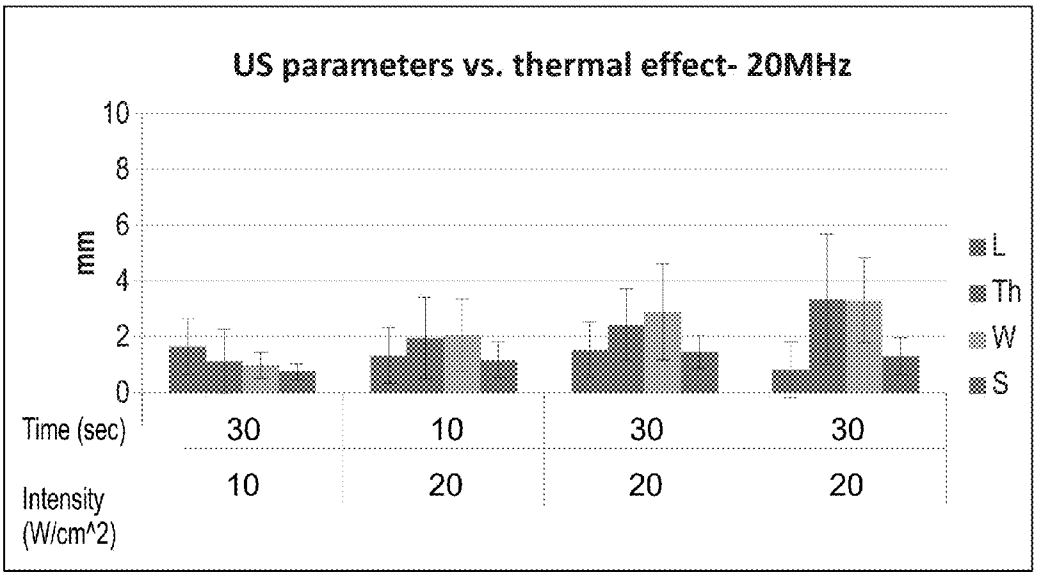

US parameters vs. thermal effect- 20MHz
mm
10
8
6
4
2
0
L
Th
W
S
Time (sec)
30
10
30
30
Intensity (W/cm^2)
10
20
20
20

FIG. 12D

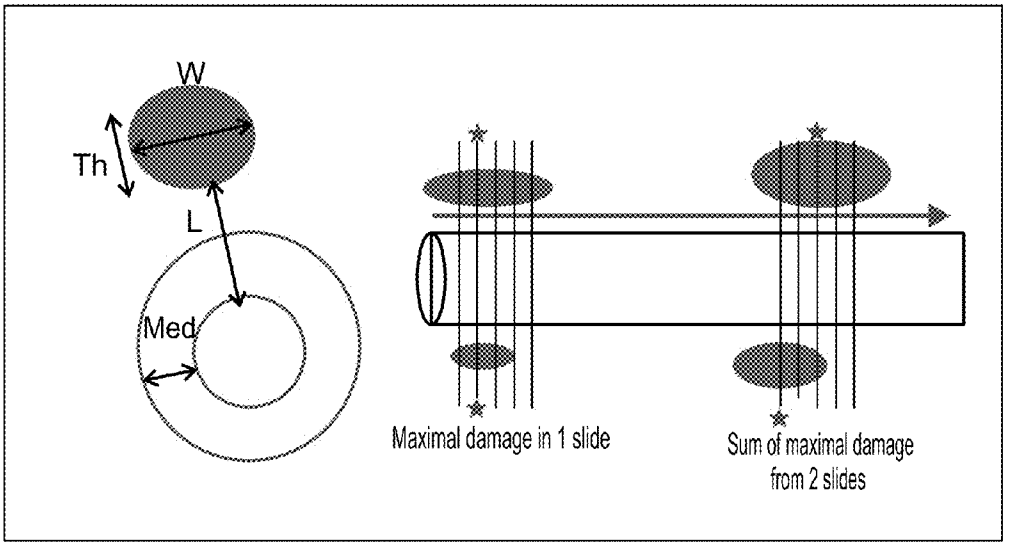
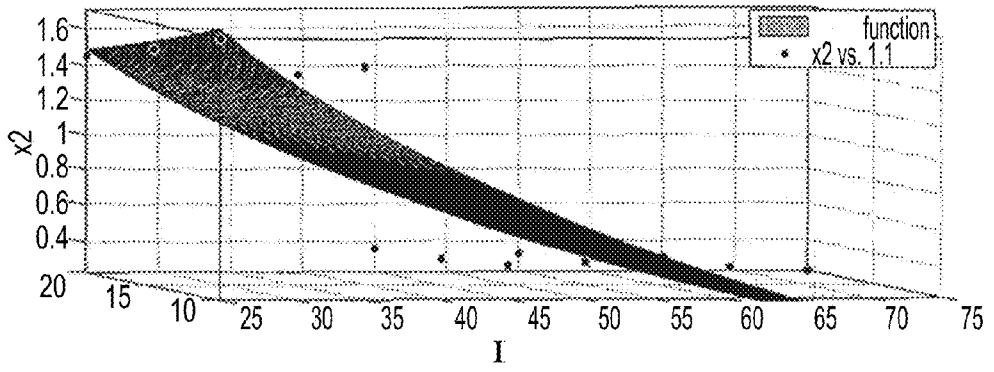

W
Th
L
Med
Maximal damage in 1 slide
Sum of maximal damage
from 2 slides

FIG. 12E

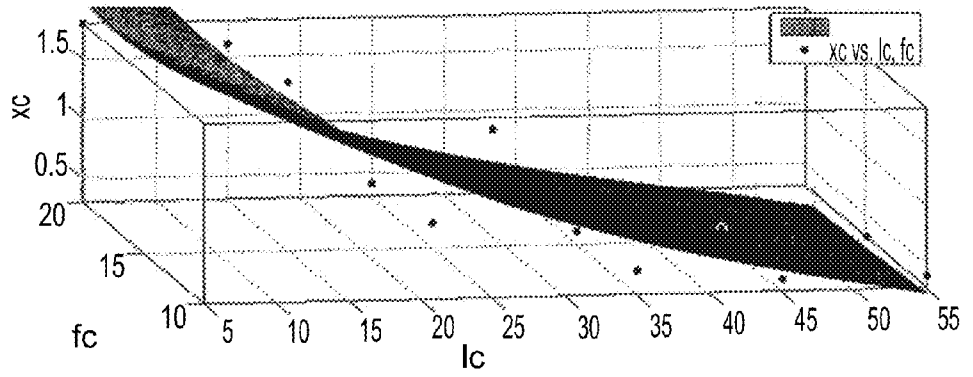
For the renal arteries:



C1 = 435.9
C2 = 92.47
C3 = 1.491
C4 = 1
C5 = 47.84

FIG. 13A

For the carotid arteries:



C1 = 483.2
C2 = 93
C3 = 2.613
C4 = 3.748
C5 = 47

FIG. 13B

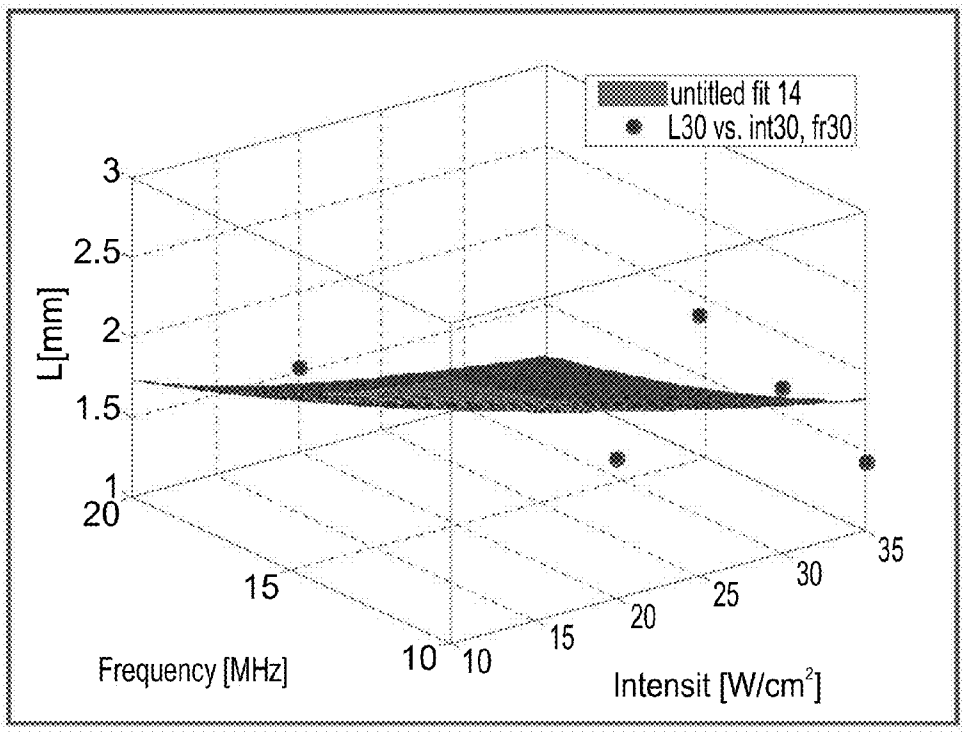


FIG. 13C

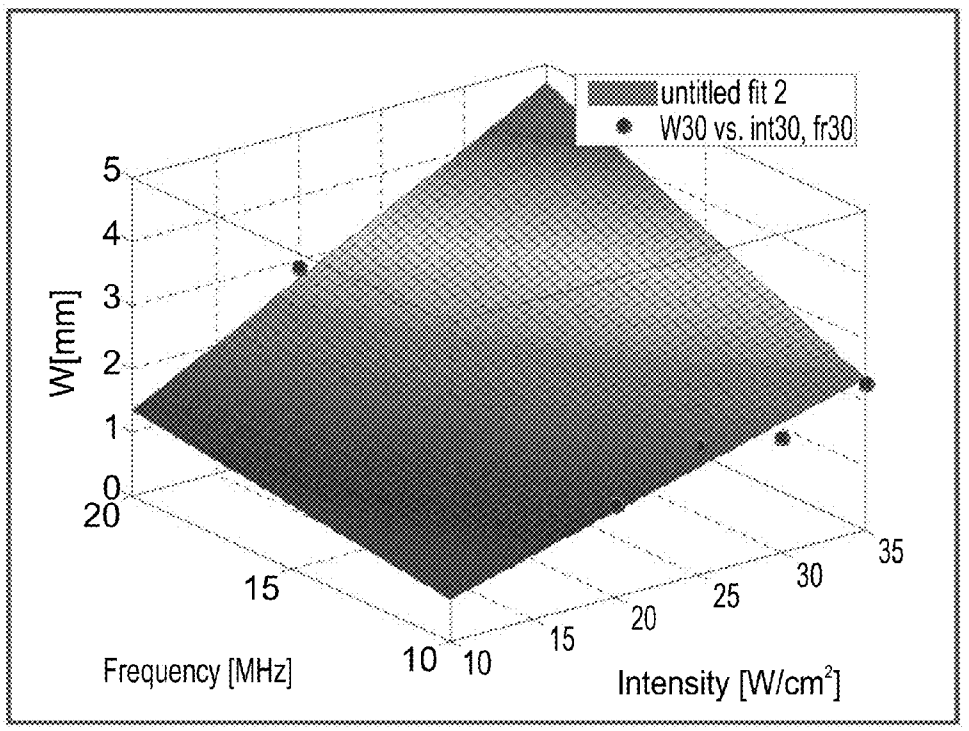


FIG. 13D

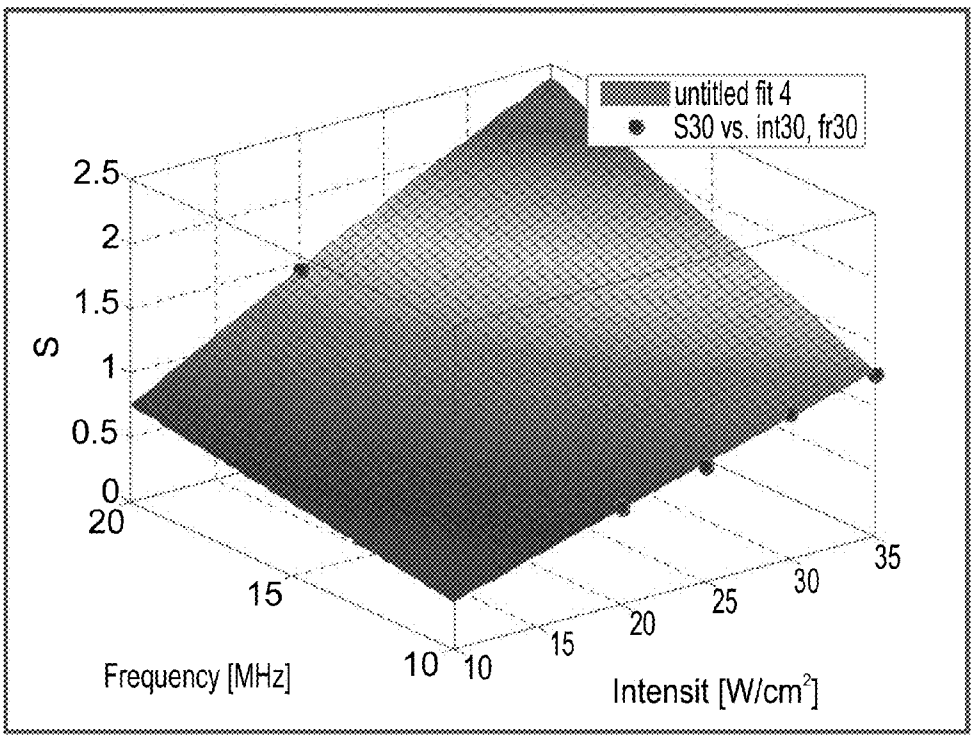


FIG. 13E

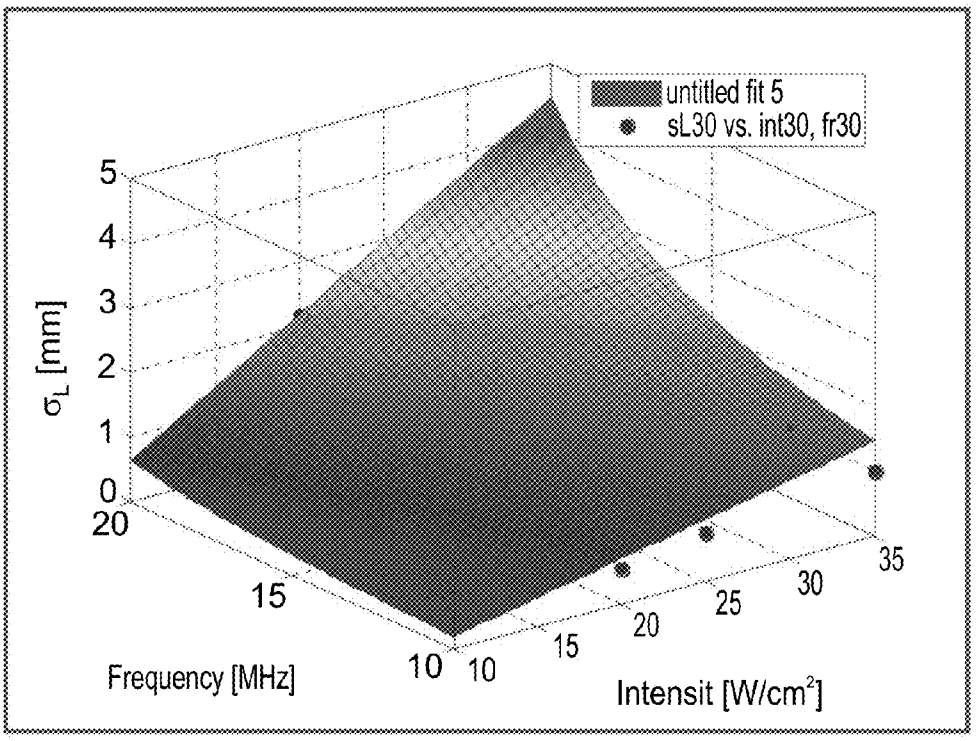


FIG. 13F

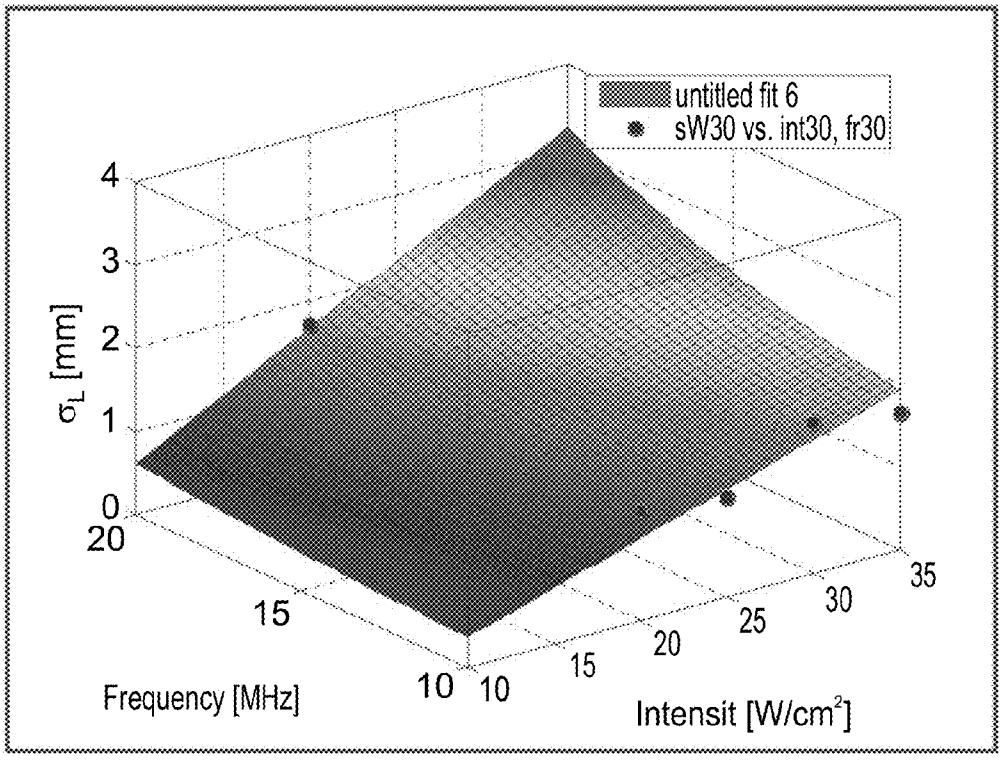


FIG. 13G

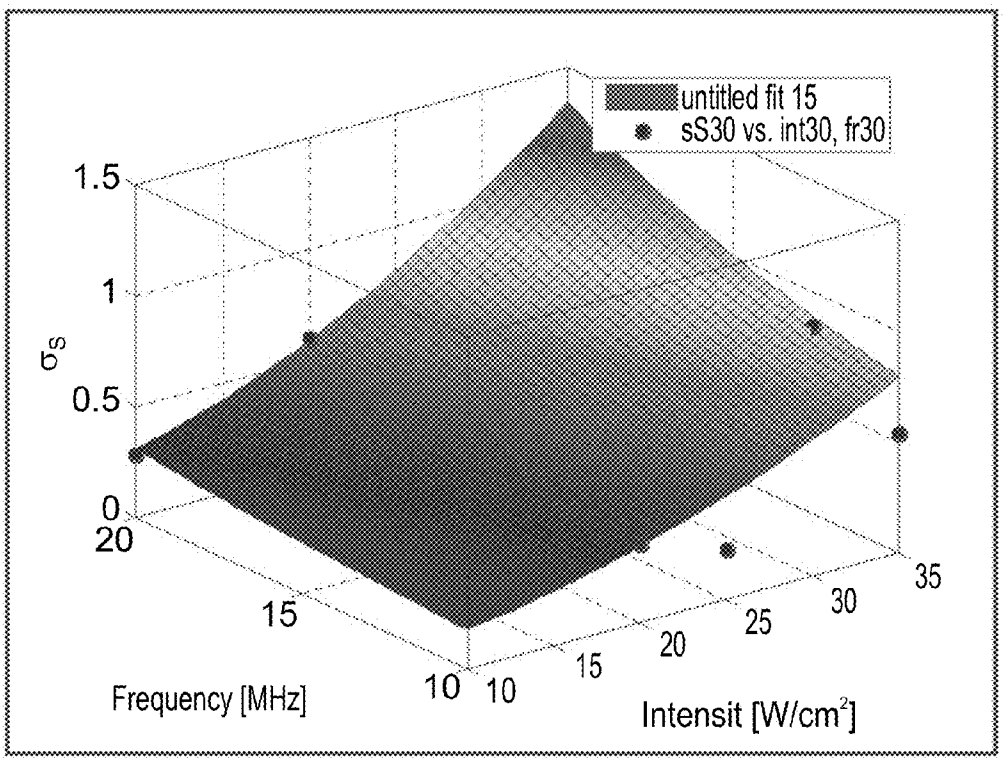


FIG. 13H

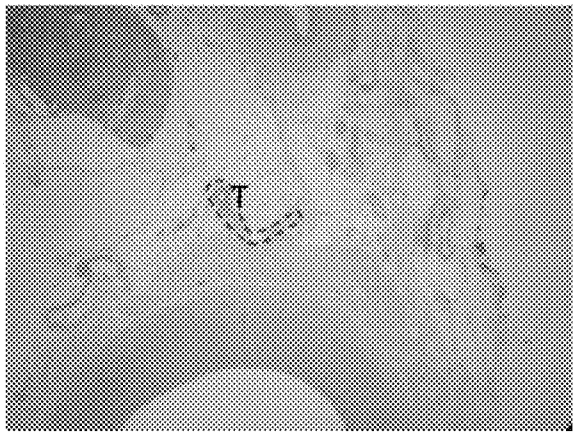


FIG. 14A

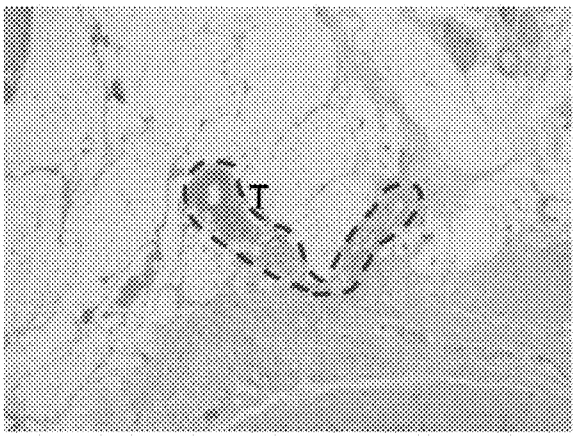


FIG. 14B

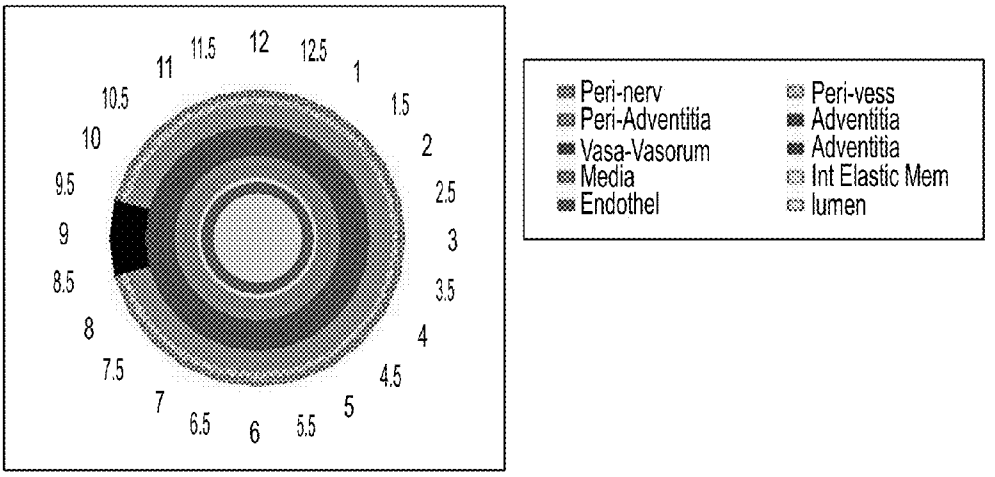


FIG. 14C

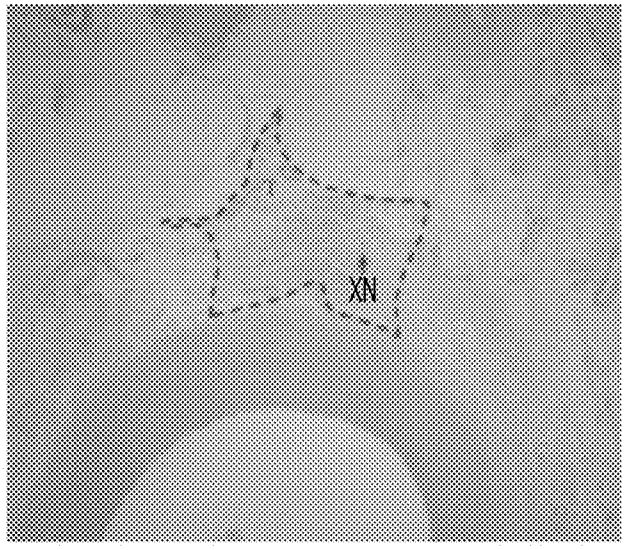


FIG. 15A

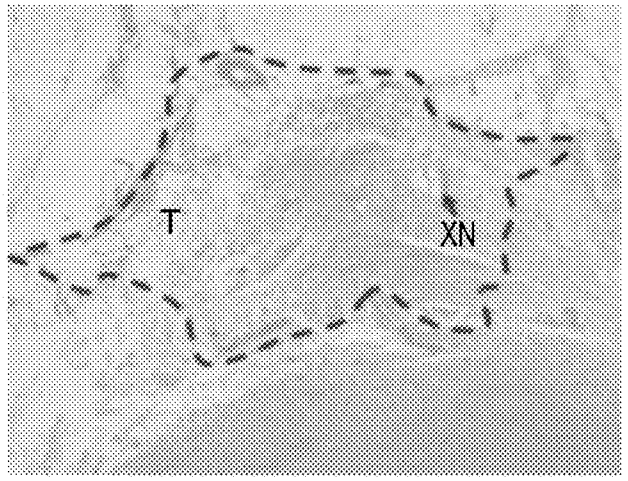


FIG. 15B

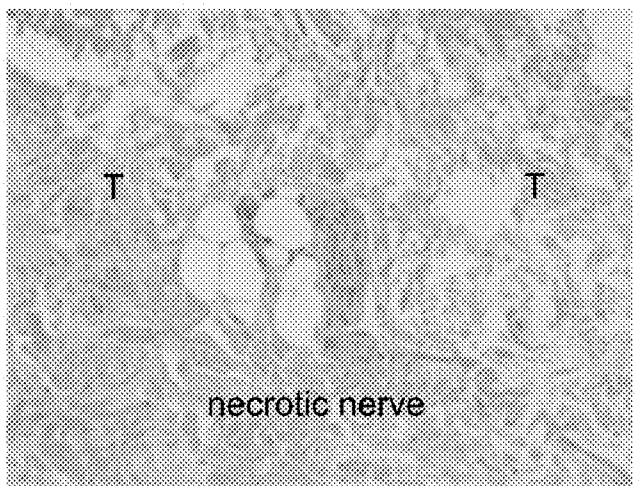
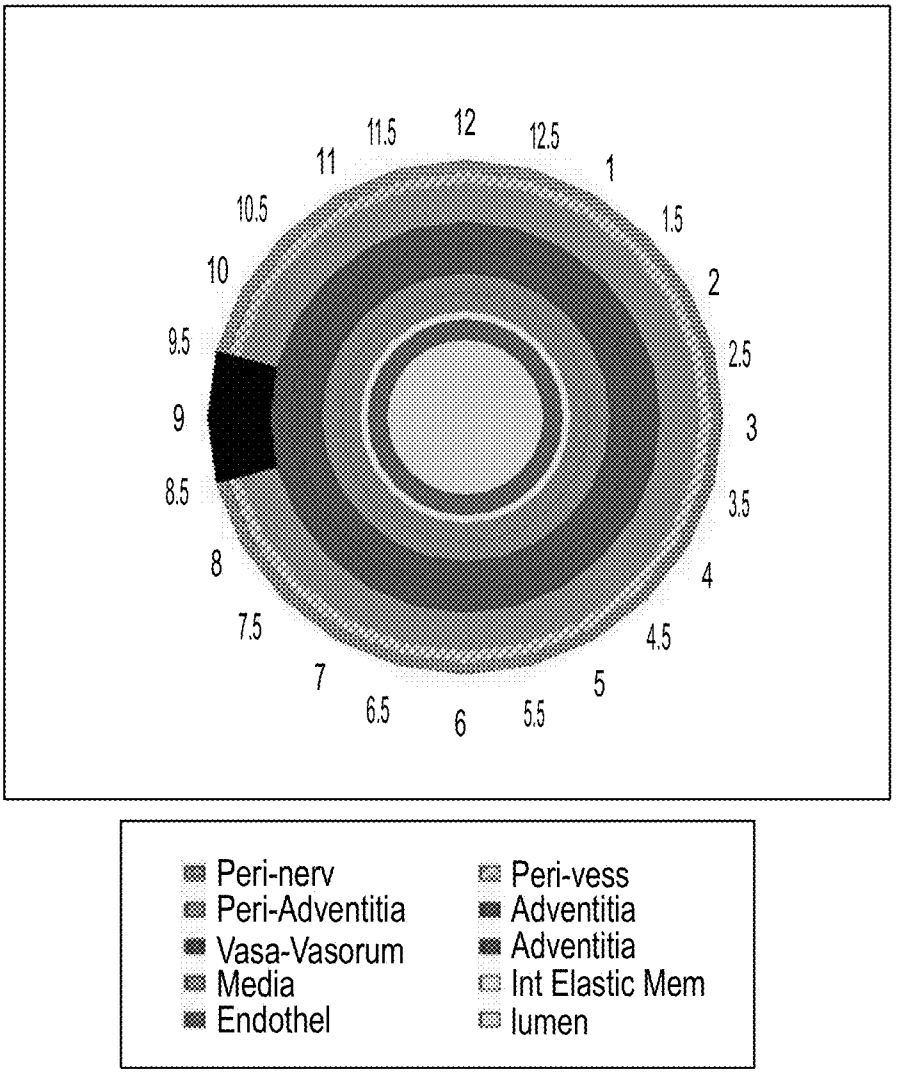


FIG. 15C


12
12.5
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6.5
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7.5
8
8.5
9
9.5
10
10.5
11
11.5
Peri-nerv
Peri-Adventitia
Vasa-Vasorum
Media
Endothel
Peri-vess
Adventitia
Adventitia
Int Elastic Mem
lumen

FIG. 15D

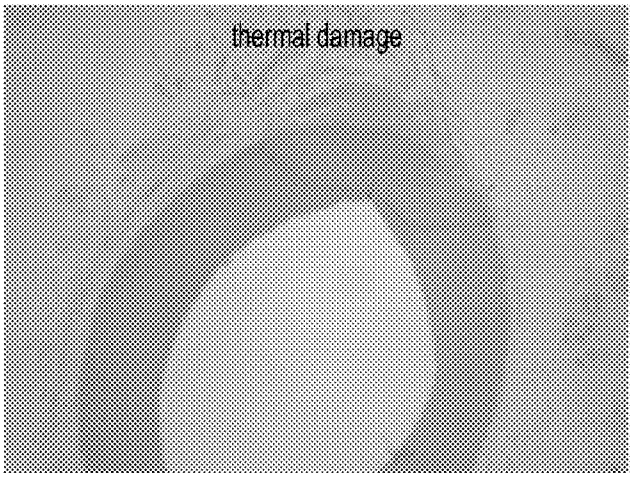


FIG. 16A

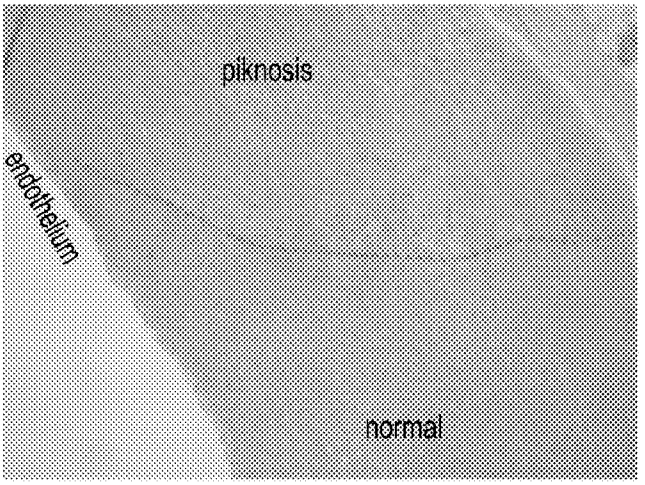


FIG. 16B

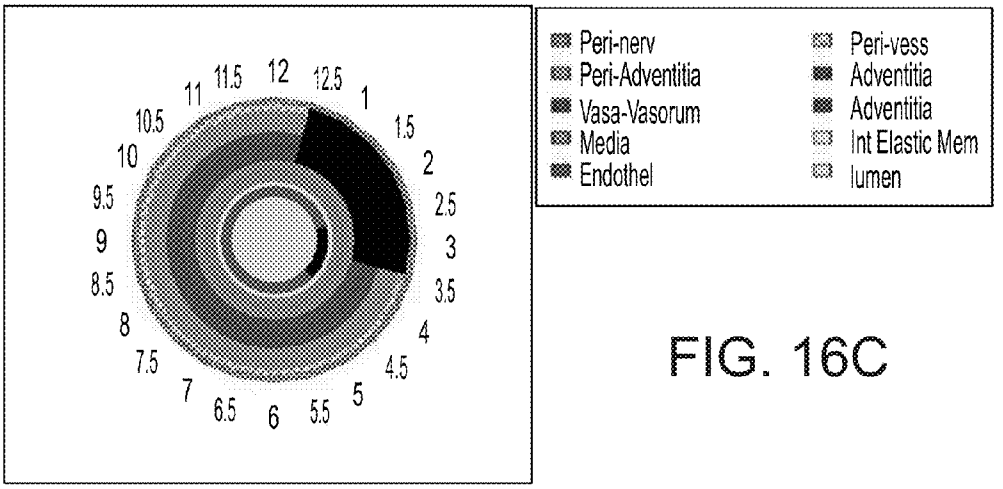


FIG. 16C

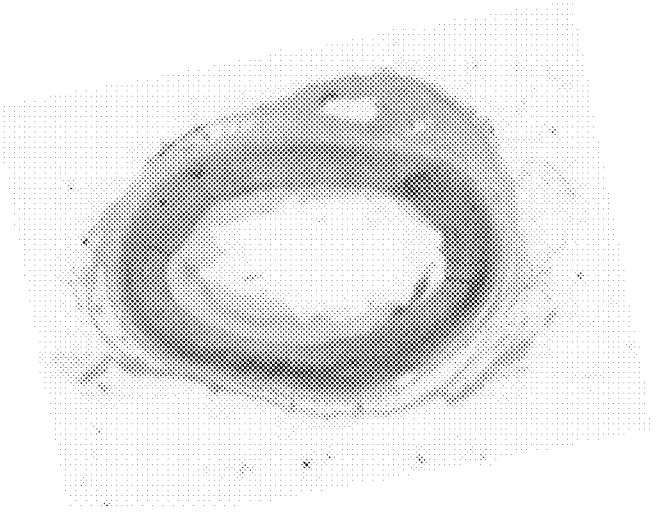


FIG. 17A

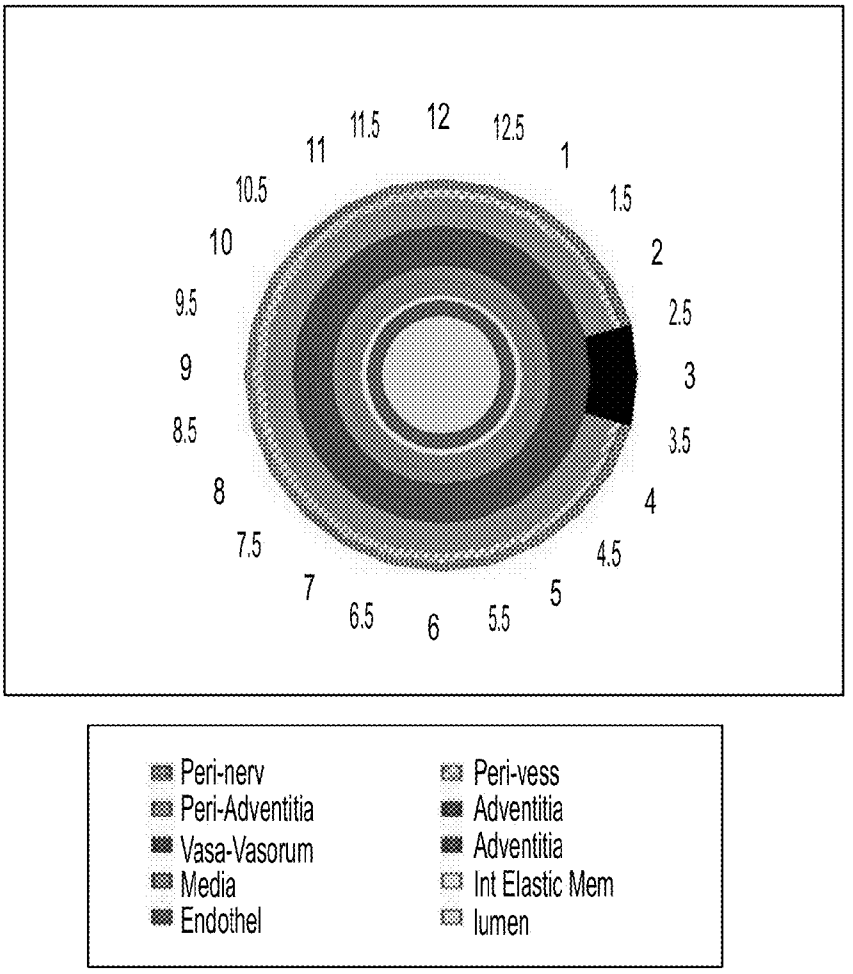


FIG. 17B

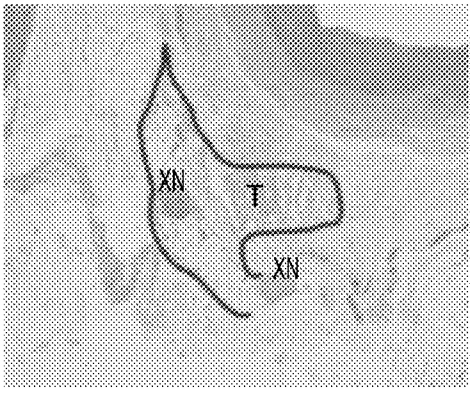


FIG. 18A

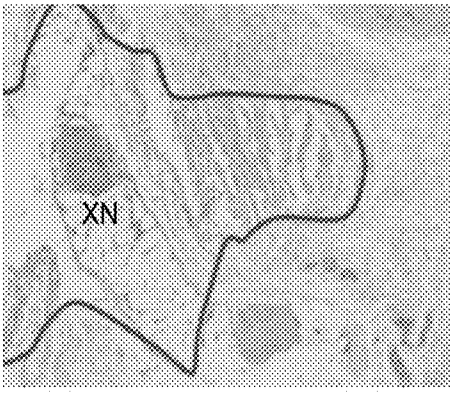


FIG. 18B

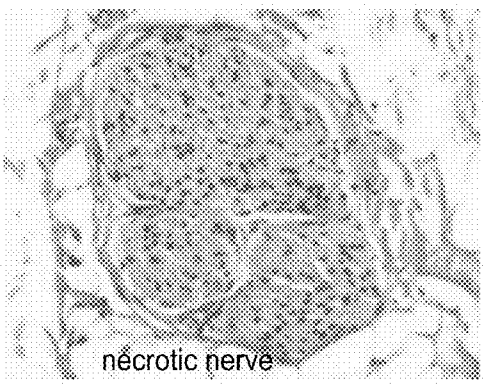


FIG. 18C

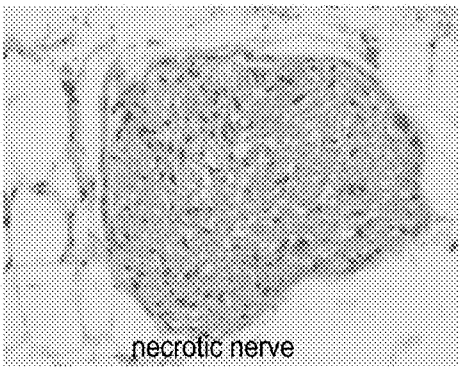


FIG. 18D

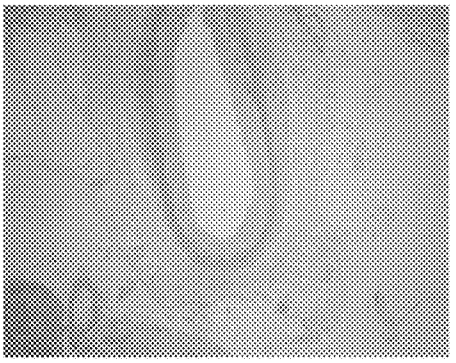


FIG. 18E

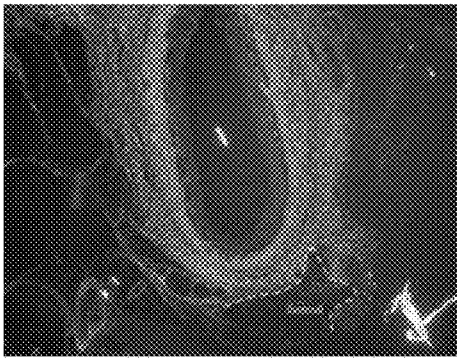
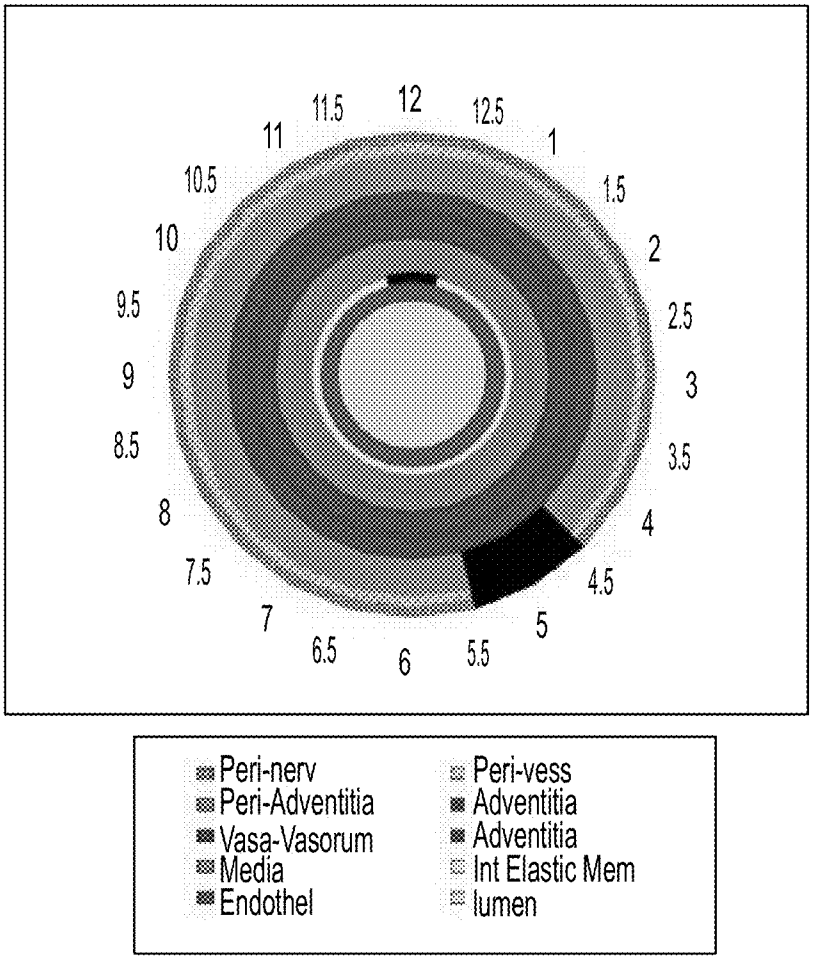


FIG. 18F


12
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9.5
10
10.5
11
11.5
Peri-nerv
Peri-Adventitia
Vasa-Vasorum
Media
Endothel
Peri-vess
Adventitia
Adventitia
Int Elastic Mem
lumen

FIG. 18G

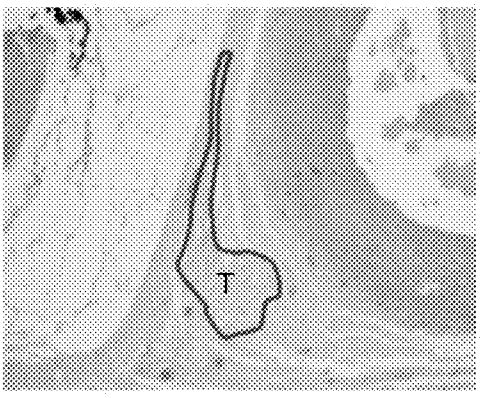

FIG. 19A

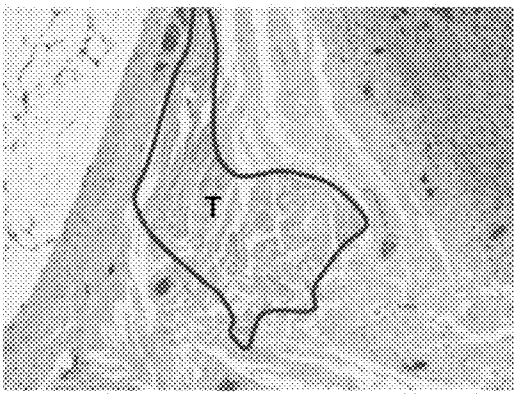

FIG. 19B

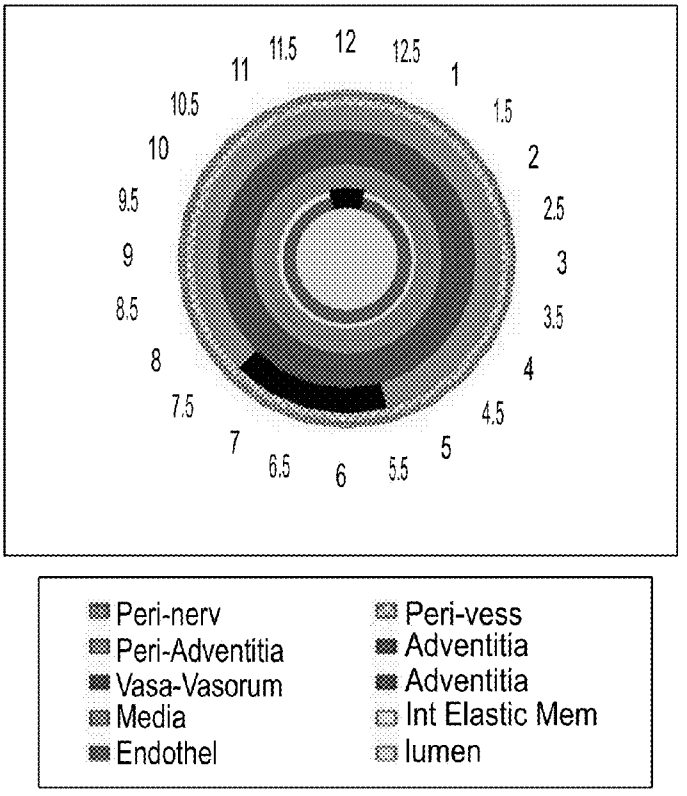

FIG. 19C

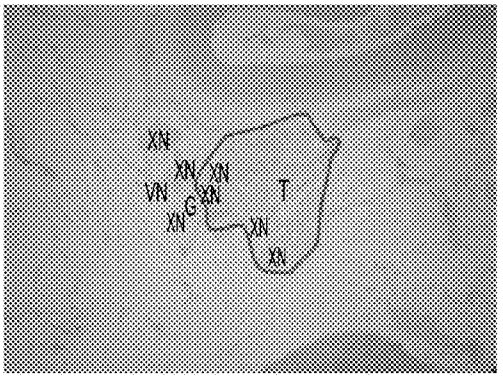

FIG. 20A

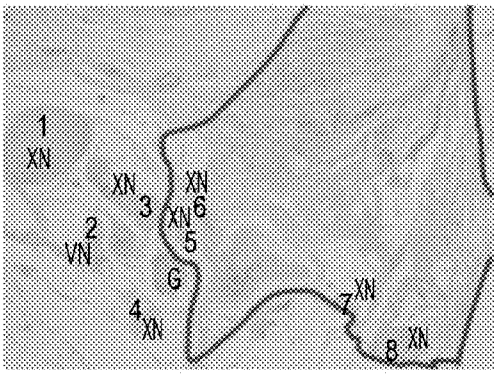

FIG. 20B

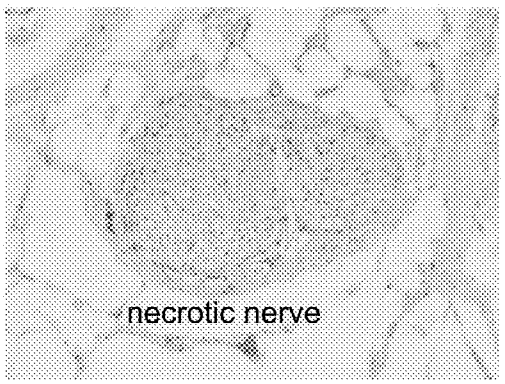

FIG. 20C

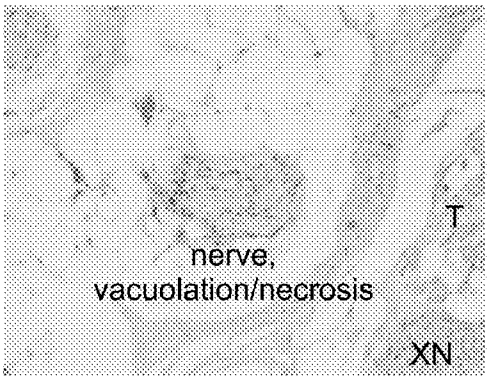

FIG. 20D

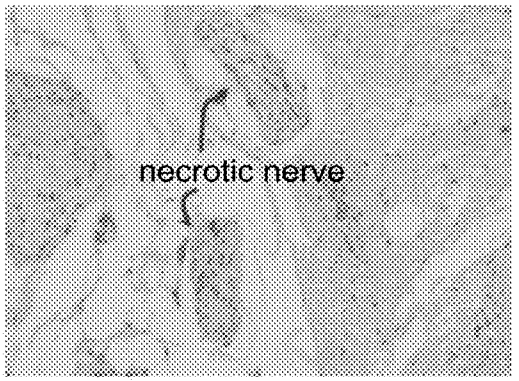

FIG. 20E

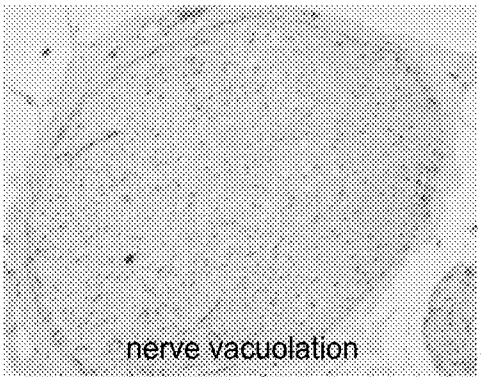

FIG. 20F

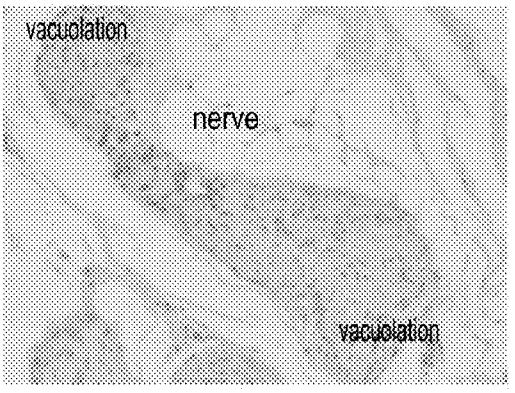

FIG. 20G

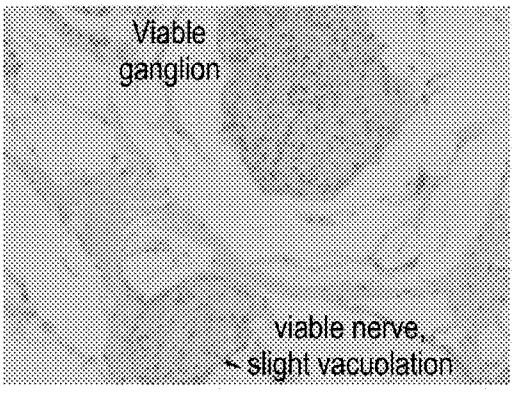

FIG. 20H

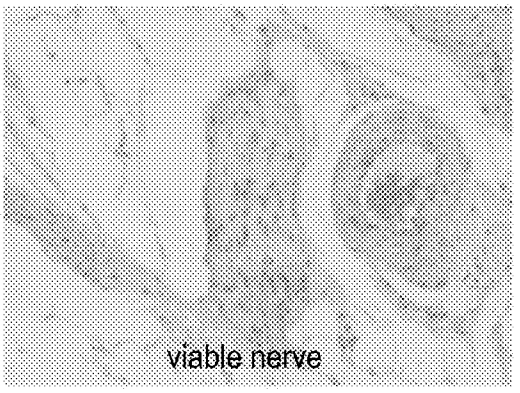

FIG. 20I

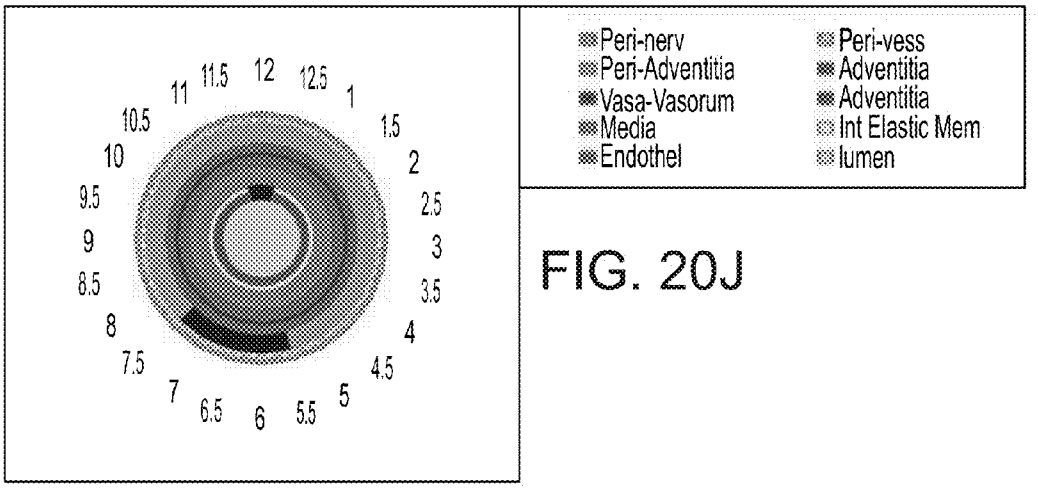

FIG. 20J

TISSUE TREATMENT

RELATED APPLICATIONS

[0001] This is a PCT application which claims the benefit of priority of U.S. Provisional Patent Applications No. 61/393,947 filed Oct. 18, 2010, and No. 61/453,239 filed Mar. 16, 2011, the contents of which are incorporated herein by reference in their entirety.

[0002] The present application is related to co-filed, co-pending and co-assigned patent applications entitled:

[0003] "THERAPEUTICS RESERVOIR" (attorney docket no. 52341), which teaches an apparatus and a method for forming a drug reservoir as a possible application of the ultrasound energy application described herein;

[0004] "AN ULTRASOUND TRANSCEIVER AND CONTROL OF A THERMAL DAMAGE PROCESS" (attorney docket no. 52342), which teaches an apparatus and method for performing ultrasonic imaging, such as to provide feedback about the effect of treatment on tissues as described herein;

[0005] "ULTRASOUND EMISSION ELEMENT" (attorney docket no. 52344), which teaches an apparatus for generating relatively high intensity ultrasound, such as to apply energy to cause the desired effects in tissue as described herein;

[0006] "AN ULTRASOUND TRANSCEIVER AND USES THEREOF" (attorney docket no. 52345), which teaches a method for feedback and control of the ultrasonic emission element, such as to use the same ultrasonic element for treatment and imaging, potentially useful when treating and imaging as described herein;

[0007] "AN ULTRASOUND TRANSCEIVER AND COOLING THEREOF" (attorney docket no. 52346), which teaches a method for cooling of the ultrasonic emission element, potentially useful when applying energy as described herein;

[0008] "SEPARATION DEVICE FOR ULTRASOUND ELEMENT" (attorney docket no. 52348), which teaches a device to prevent the ultrasonic emission element from touching the blood vessel wall, potentially useful for preventing damage to the intima layer when applying energy as described herein;

[0009] the disclosures of which are incorporated herein by reference.

FIELD AND BACKGROUND OF THE INVENTION

[0010] The present invention, in some embodiments thereof, relates to a method of treatment of tissue and, more particularly, but not exclusively, to a method of selectively targeting and treating tissue using unfocused ultrasound energy.

[0011] Sverdlik et al, in PCT/IL2008/000234, filed FEB **21, 2008** disclose:

"Described is a method of stabilizing blood vessel wall abnormality. The method includes ultrasonically heating at least a portion of the blood vessel wall having the abnormality; monitoring a parameter related to a property of at least a portion of the heated portion of the blood vessel wall; and stopping the heating when the monitored parameter changes by a predetermined factor or after the monitored parameter changes in a slow enough rate."

[0012] Additional background art includes:

[0013] EP 1769759

[0014] U.S. Pat. No. 5,699,804

[0015] U.S. Pat. No. 7,410,486

[0016] U.S. Pat. No. 7,621,929

[0017] U.S. Pat. No. 7,717,948

[0018] U.S. Pat. No. 7,771,372

[0019] US patent application 2008228111

[0020] US patent application 2009216246

[0021] US patent application 2010091112

[0022] Xu, D. S., & Pollock, M. (1994). Experimental nerve thermal-injury. Brain, 117, 375-384.

[0023] Katholi et al. "Renal nerves in the maintenance of hypertension: a potential therapeutic target" Curr Hypertens Rep. 2010 June; 12(3):196-204.

[0024] Lele, P. P. (1963). Effects of Focused Ultrasonic Radiation on Peripheral Nerve, With Observations On Local Heating. Experimental Neurology, 8(1), 47-83.

[0025] Fung L C et al. Effects of temperature on tissue thermal injury and wound strength after photothermal wound closure. Lasers Surg Med. 1999; 25(4):285-90.

[0026] Worthington, A. E., et al, Ultrasound in Med. & Biol., Vol. 28, No. 10, pp. 1311-1318, 2002.

[0027] Damianou et al, J Acoust Soc Am. 1997 July; 102 (1):628-34.

SUMMARY OF THE INVENTION

[0028] An aspect of some embodiments of the invention relates to a method of selectively treating a volume of tissue using unfocused ultrasound energy having an acoustic intensity profile of over 1 Watt per square centimeter.

[0029] There is provided in accordance with an exemplary embodiment of the invention a method of setting up a treatment system for non-focused ultrasound energy delivered intrabody comprising:

[0030] selectively determining a target tissue in a wall of a lumen or cavity;

[0031] selecting parameters sufficient to provide a desired therapeutic effect in said target tissue; and

[0032] setting up a treatment system using said parameters

[0033] In an exemplary embodiment of the invention, the method comprises deciding an amount of desired thermal damage. Optionally, said amount of thermal damage comprises a volume where thermal damage is desired. Optionally or alternatively, said amount of thermal damage comprises the degree of thermal damage.

[0034] In an exemplary embodiment of the invention, the method comprises selecting an anatomical location from which to treat said target tissue. Optionally, said anatomical location comprises a renal artery and said target tissue comprises renal artery nerves. Optionally or alternatively, said anatomical location comprises an aorta and said target tissue comprises renal nerves. Optionally or alternatively, said anatomical location comprises a carotid artery and said target tissue comprises nerves.

[0035] In an exemplary embodiment of the invention, selecting comprises taking blood cooling into account.

[0036] In an exemplary embodiment of the invention, selecting comprises selecting in a manner which avoids significant stenosis.

[0037] In an exemplary embodiment of the invention, selecting comprises selecting in a manner which avoids significant damage to non-target tissue.

[0038] In an exemplary embodiment of the invention, selecting comprises selecting in a manner which avoids significant shrinkage in target tissue.

[0039] In an exemplary embodiment of the invention, said desired effect comprises denaturing at least some of said target tissue. Optionally, the method comprises applying said ultrasound energy so as to not denature at least some part of said target tissue.

[0040] In an exemplary embodiment of the invention, said target tissue and said parameters are preselected so that said parameters have said desired effect on said target.

[0041] In an exemplary embodiment of the invention, selecting comprises determining according to an attenuation coefficient of tissues.

[0042] In an exemplary embodiment of the invention, the method comprises selecting a margin of safety. Optionally, said selecting a margin of safety comprises selecting an allowed amount of thermal damage to tissues surrounding said target tissue. Optionally or alternatively, selecting a margin of safety comprises reducing or preventing contraction of said lumen or said cavity.

[0043] In an exemplary embodiment of the invention, selectively determining said target tissue comprises selecting a type of tissue. Optionally, said type of tissue comprises nerve tissue. Optionally or alternatively, said target tissue is selected from tissue located at a tissue layer selected from the group comprising peri-adventitia, adventitia, media, intima.

[0044] In an exemplary embodiment of the invention, said target tissue is located less than 10 mm from a renal ostium.

[0045] In an exemplary embodiment of the invention, said determining initial parameters comprises determining according to a distance of said target tissue from an intima. Optionally, said target tissue is outside said wall of said lumen or said cavity.

[0046] In an exemplary embodiment of the invention, the method comprises selecting a frequency of treatment in the range of 8-25 Mhz.

[0047] In an exemplary embodiment of the invention, the method comprises selecting an ultrasound intensity in the range of 1-100 Watt/square centimeter.

[0048] In an exemplary embodiment of the invention, said target tissue is a renal nerve, and said parameters are an applied frequency of 10[MHz]-22[MHz], and an intensity of 10-40 [W/cm^2].

[0049] In an exemplary embodiment of the invention, a duration of said treatment is 5-30 seconds.

[0050] In an exemplary embodiment of the invention, a length of said lumen or cavity is less than 20 mm.

[0051] In an exemplary embodiment of the invention, the method comprises applying said parameters to selectively treat said target tissue using non-focused ultrasound to achieve said desired effect. Optionally, the method comprises obtaining feedback associated with said treatment. Optionally, the method comprises adjusting said parameters according to said feedback and retreating said target tissue.

[0052] In an exemplary embodiment of the invention, the method comprises a controlled adjustable treatment according to online measurements including at least one of the following group of measurements: flow measurements, current measurement, voltage measurement, power measurement, acoustic backscatter measurements, temperature measurements, pressure measurements.

[0053] In an exemplary embodiment of the invention, treating comprises applying said ultrasound away from said wall but inside a body.

[0054] In an exemplary embodiment of the invention, applying so that a desired effect comprises temporary change in tissue functionality is achieved.

[0055] In an exemplary embodiment of the invention, said applying said parameters comprises applying said parameters in an open loop manner.

[0056] In an exemplary embodiment of the invention, applying comprises applying said ultrasound energy so as to not denature most of the tissue between said target tissue and an edge of said wall.

[0057] In an exemplary embodiment of the invention, applying comprises maintaining blood in said lumen at a temperature below 50 degrees Celsius.

[0058] In an exemplary embodiment of the invention, applying comprises maintaining blood in said lumen at a temperature below 43 degrees Celsius.

[0059] In an exemplary embodiment of the invention, applying comprises heating a nerve while not heating tissue outside of a fat sheath surrounding said nerve.

[0060] In an exemplary embodiment of the invention, applying comprises localizing heating by having a gradient of cooling from blood and a gradient of heating from a distance.

[0061] In an exemplary embodiment of the invention, applying comprises heating nerves sufficiently to reduce renal norepinephrine levels by at least 50%.

[0062] In an exemplary embodiment of the invention, applying comprises heating a part of a nerve to necrosis while not heating another part of said nerve in a same axial location along said nerve to necrosis.

[0063] In an exemplary embodiment of the invention, the method comprises adjusting a property of at least one of said target tissue, said wall and blood in said lumen to provide said desired effect. Optionally, said property comprises a rate of heat removal. Optionally or alternatively, said property comprises a flow rate of said blood. Optionally or alternatively, said property comprises a temperature.

[0064] In an exemplary embodiment of the invention, applying comprises applying said ultrasound energy so as to treat a patient suffering from hypertension.

[0065] In an exemplary embodiment of the invention, applying comprises applying said ultrasound energy so as to prevent signals from propagating through at least one renal nerve.

[0066] In an exemplary embodiment of the invention, applying comprises applying said ultrasound energy so as to position said treatment area with an accuracy of better than 0.2 mm along an axis perpendicular to said wall.

[0067] There is provided in accordance with an exemplary embodiment of the invention a system configured for carrying out the method as described herein.

[0068] There is provided in accordance with an exemplary embodiment of the invention a system for treating a blood vessel wall comprising:

[0069] a catheter;

[0070] at least one ultrasound emitter mounted on the catheter and adapted for emitting unfocused ultrasound at a frequency of 10-40 Mhz at a target tissue located a distance from an intima of the blood vessel wall with a power setting sufficient to heat said target tissue; and

[0071] a controller,

[0072] wherein the controller is configured to deliver enough power to heat said target tissue to a selected size and to a desired thermal effect. Optionally, said target tissue comprises nerves, and said desired thermal effect comprises

reducing signals through said nerves by at least 50%. Optionally or alternatively, said catheter is configured so that said emitter does not contact said wall. Optionally or alternatively, said controller is configured to selectively treat a volume of tissue distanced from an intima of a blood vessel wall. Optionally or alternatively, said controller is configured for thermal treatment of renal nerves. Optionally or alternatively, said controller is configured for treatment accuracy of better than 0.5 mm positioning of the treatment area, along a dimension perpendicular to said blood vessel. Optionally or alternatively, said controller is configured for treatment specificity which avoids significant vessel stenosis as an aftermath of said treatment. Optionally or alternatively, said controller is configured to selectively heat nerves within a fat sheath thereof. Optionally or alternatively, said controller is configured with a protocol including a plurality of treatment regions and sufficient to reduce hypertension if applied to renal nerves. Optionally or alternatively, said controller is preconfigured with sets of parameters matching different target tissues and target tissue locations. Optionally or alternatively, said controller includes a feedback circuit for real-time control of settings of said system.

[0073] There is provided in accordance with an exemplary embodiment of the invention a method of setting up a device to selectively treating tissue using non-focused ultrasound energy delivered intrabody comprising:

[0074] setting up said device to be suitable for heating a selected area of tissue at a selected location from an arterial wall.

[0075] There is provided in accordance with an exemplary embodiment of the invention a method of treating a blood vessel wall comprising:

adjusting a said blood vessel during intravascular ultrasound treatment, other than by said treatment. Optionally, said adjusting comprises adjusting blood flow through said blood vessel. Optionally or alternatively, said adjusting comprises adjusting a thickness of said blood vessel wall. Optionally or alternatively, said adjusting comprises adjusting a temperature of at least one of said blood and said blood vessel wall.

[0076] There is provided in accordance with an exemplary embodiment of the invention a method of setting up a device to selectively treating tissue using non-focused ultrasound energy delivered intrabody comprising:

[0077] setting up said device to be suitable for heating nerve tissue while not heating, to a tissue damaging level, tissue outside a fat sheath surrounding said nerve.

[0078] There is provided in accordance with an exemplary embodiment of the invention a method of reducing blood pressure comprising:

[0079] applying unfocused ultrasonic energy to the renal ostium from within a blood vessel, said energy sufficient to disrupt signals propagating through renal nerves.

[0080] There is provided in accordance with an exemplary embodiment of the invention a device for treating blood pressure comprising:

[0081] a catheter configured to position an ultrasonic emission element close to a renal ostium, said element configured to emit unfocused ultrasonic energy to nerves. Optionally, close comprises less than 10 mm.

[0082] There is provided in accordance with an exemplary embodiment of the invention a method for treating a patient experiencing a clinical disorder, the method comprising:

[0083] positioning at least one unfocused ultrasound emitter at an anatomical location proximate to a target tissue;

[0084] selectively delivering unfocused ultrasound energy to the target tissue; and

[0085] selectively causing thermal damage to at least a portion of the target tissue, to provide a desired treatment. Optionally, the target tissue comprises body lumen, fat, nerves, vasa vasora, lymph, tumor, connective tissue, or plaque. Optionally or alternatively, the anatomical location comprises a blood vessel or artery. Optionally, the anatomical location is the renal artery and the target tissue comprises one or more renal artery nerves. Optionally or alternatively, the at least one unfocused ultrasound emitter is configured not to touch the wall of the blood vessel or artery. Optionally or alternatively, the at least one unfocused ultrasound emitter is positioned as to not substantially block blood flow in the blood vessel or artery. Optionally, the at least one unfocused ultrasound emitter, in operation, is cooled by the blood flow.

[0086] In an exemplary embodiment of the invention, the clinical disorder comprises at least one of sleep apnea, obesity, diabetes, end stage renal disease, lesion on a body lumen, contrast nephropathy, heart arrhythmia, congestive heart failure, and hypertension.

[0087] In an exemplary embodiment of the invention, the method comprises determining the distance from the blood vessel or artery wall to the target tissue and selecting the frequency of the unfocused ultrasound energy based upon on said distance of the target tissue.

[0088] In an exemplary embodiment of the invention, the frequency of the unfocused ultrasound energy is 10-22 Mhz.

[0089] In an exemplary embodiment of the invention, the target tissue comprises a treatment region. Optionally, the method comprises determining the treatment region and selecting the intensity of the unfocused ultrasound energy according to the size of the treatment region.

[0090] In an exemplary embodiment of the invention, the method comprises delivering the at least one unfocused ultrasound emitter intrabody within the blood vessel or artery by a delivery catheter and configuring the delivery catheter to prevent the at least one unfocused ultrasound emitter from touching the wall of the blood vessel or artery.

[0091] In an exemplary embodiment of the invention, the method comprises selecting the target tissue using parameters obtained from an equation based upon empirical data. Optionally, the equation is:

$$x(f,I)\ [\mathrm{mm}]=(C6+a*\mathrm{Exp}(\mathrm{flow}*b)-C2*\log(C3*I\ [\mathrm{W/cm\hat{}2}]))/(C4*f\ [\mathrm{MHz}]+C5)$$

Wherein, "I" is excitation intensity [W/cm^2]; "f" is working excitation frequency [MHz]; "x" is minimal radial distance from the artery wall [mm]; and "flow" is blood flow rate in the artery [ml/mm].

[0092] In an exemplary embodiment of the invention, the method comprises receiving feedback indicating the thermal damage to the target tissue. Optionally, the method comprises modifying the parameters in response to said feedback.

[0093] In an exemplary embodiment of the invention, the method comprises selectively delivering the unfocused ultrasound energy in a manner such that there is no significant damage to non-target tissue.

[0094] In an exemplary embodiment of the invention, the method comprises selectively delivering the unfocused ultrasound energy in a manner such that there is no significant stenosis.

[0095] In an exemplary embodiment of the invention, the method comprises delivering unfocused ultrasound energy to at least one treatment region, each treatment region being at a

separate circumferential location. Optionally, the duration that unfocused ultrasound energy is delivered to the target tissue is 5-30 seconds per treatment region. Optionally or alternatively, the treatment comprises between 1 and 8 treatment regions.

[0096] Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

[0097] Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of embodiments of the method and/or system of the invention, several selected tasks could be implemented by hardware, by software or by firmware or by a combination thereof using an operating system.

[0098] For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

BRIEF DESCRIPTION OF THE DRAWINGS

[0099] Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

[0100] In the drawings:

[0101] FIG. **1**A is a flowchart of a treatment method, in accordance with an exemplary embodiment of the invention;

[0102] FIG. **1**B is a flowchart of a more detailed treatment method of FIG. **1**A, in accordance with an exemplary embodiment of the invention;

[0103] FIG. **2** is an illustration of an embodiment of the treatment system for selectively treating tissues, in accordance with an exemplary embodiment of the invention;

[0104] FIG. **3** is an illustration of the human body showing exemplary treatment locations, useful in practicing some embodiments of the invention;

[0105] FIG. **4** is an illustration of the renal artery, showing exemplary treatment locations, in accordance with an exemplary embodiment of the invention;

[0106] FIG. **5** is an illustration of ultrasound energy treating tissues, in accordance with an exemplary embodiment of the invention;

[0107] FIG. **6**A is a cross section of an arterial wall, illustrating selective tissue treatment, in accordance with an exemplary embodiment of the invention;

[0108] FIG. **6**B is a cross sectional view, FIG. **6**C is a side view and FIG. **6**D is a top view illustrating a controllable volume of thermal effect to tissue, in accordance with an exemplary embodiment of the invention;

[0109] FIG. **7**A is an exemplary graph illustrating a temperature profile, useful in practicing some embodiments of the invention;

[0110] FIG. **7**B is an exemplary graph illustrating relative tissue attenuation, useful in practicing some embodiments of the invention;

[0111] FIG. **7**C is an exemplary graph illustrating some associations between heat removal rates and treatment, useful in practicing some embodiments of the invention;

[0112] FIGS. **7**D-**7**E illustrate the adjustment of one or more tissue properties, in accordance with some embodiments of the invention;

[0113] FIG. **8** is an exemplary graph illustrating some associations between frequency and treatment, useful in practicing some embodiments of the invention;

[0114] FIG. **9** is an exemplary graph illustrating some associations between ultrasound intensity profile and treatment, useful in practicing some embodiments of the invention;

[0115] FIG. **10** is a flow chart of monitoring during treatment, in accordance with an exemplary embodiment of the invention;

[0116] FIG. **11** is a flow chart of feedback during treatment, in accordance with an exemplary embodiment of the invention;

[0117] FIG. **12**A is a table summarizing experimental results obtained using some embodiments of the invention;

[0118] FIG. **12**B is a table summarizing experimental results at 10 Mhz, obtained using some embodiments of the invention;

[0119] FIG. **12**C is a table summarizing experimental results at 20 Mhz, obtained using some embodiments of the invention;

[0120] FIG. **12**D illustrates graphs summarizing the values in FIGS. **12**B-**12**C, useful in practicing some embodiments of the invention;

[0121] FIG. **12**E is an image illustrating the variables described in FIGS. **12**B-**12**D, useful in practicing some embodiments of the invention;

[0122] FIGS. **13**A-B are graphs of associations between thermal damage results and ultrasound parameters according to the results of FIG. **12**A, useful in practicing using some embodiments of the invention;

[0123] FIGS. **13**C-H are exemplary graphs of thermal damage results and ultrasound parameters according to the results as shown in FIGS. **12**B-**12**D, useful in practicing some embodiments of the invention;

[0124] FIGS. **14**A-C are images of experimental results in the aorta obtained using some embodiments of the invention;

[0125] FIGS. **15**A-D are images of experimental results in the aorta obtained using some embodiments of the invention;

[0126] FIGS. **16**A-C are images of experimental results in the carotid artery obtained using some embodiments of the invention;

[0127] FIGS. **17**A-B are images of experimental results in the carotid artery obtained using some embodiments of the invention;

[0128] FIGS. **18**A-G are images of experimental results in the renal artery obtained using some embodiments of the invention;

[0129] FIGS. **19**A-C are images of experimental results in the renal artery obtained using some embodiments of the invention; and

[0130] FIGS. **20**A-J are images of experimental results in the renal artery obtained using some embodiments of the invention.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

[0131] The present invention, in some embodiments thereof, relates to a method of treatment of tissue and, more particularly, but not exclusively, to a method of selectively targeting and treating tissue using unfocused ultrasound energy. In an exemplary embodiment of the invention, the tissue is in a mammal, for example, a pig or a human.

[0132] An aspect of some embodiments of the invention relates to a method of selectively treating tissue using ultrasound energy delivered intrabody. Optionally, the ultrasound energy is non-focused.

[0133] In an exemplary embodiment of the invention, tissues can be targeted spatially, for example, a volume of tissue located in a wall of a blood vessel. Optionally, the tissue to be targeted is defined spatially, for example, using x, y, z coordinates.

[0134] In an exemplary embodiment of the invention, target tissues are treated with ultrasound energy, for example, heated using ultrasound energy. Optionally, tissues are thermally damaged, non-limiting examples of damage include; burning, coagulation, denaturation, ablation, necrosis, disruption (e.g., of signal propagation in nerves), degeneration, destruction. Optionally or additionally, tissues are heated sufficiently without causing immediate damage and/or shrinkage.

[0135] In an exemplary embodiment of the invention, target tissues are heated to a selected temperature. For example, about 43, 45, 50, 55, 60, 65, 70, 80, 85, 90, 95 degrees Celsius, or other smaller, intermediate or larger temperatures are used, or subranges thereof.

[0136] In an exemplary embodiment of the invention, the time to reach the peak temperature is selected. For example, about 0.1 seconds, about 1 second, about 3 seconds, about 5 seconds, about 10 seconds, about 15 seconds, about 30 seconds, or other smaller, intermediate or larger values are used.

[0137] In an exemplary embodiment of the invention, the acoustic intensity profile is high intensity, for example, about 11-20, or 21-30 or 31-40, or 41-50 or 51-60 or 61-70 or >=71 Watt/square centimeter, or other smaller, intermediate or larger values are used.

[0138] In an exemplary embodiment of the invention, the initial thermal effect is selected to start away from the intima of the artery, for example, about 0.2 mm away from the intima, or 0.3 mm, 0.5 mm, 1 mm, 2 mm, 3 mm, 4 mm, 5 mm, 7 mm, away, or other smaller, intermediate or larger distances are selected.

[0139] In an exemplary embodiment of the invention, the location, the volume and/or the extent of the thermal effect is selected.

[0140] In an exemplary embodiment of the invention, the treatment is selected to treat only a portion of the target tissue, for example, half of the target tissue. Alternatively, the treatment is selected to treat the entire target tissue.

[0141] In an exemplary embodiment of the invention, the treatment is selected according to safety considerations. Optionally, a safety consideration is treating with a margin of safety around the target tissue, for example, the treatment is selected to treat the target tissue without treating surrounding tissue. Alternatively, the treatment is selected to treat at least some tissue surrounding the target tissue. Alternatively or additionally, a safety consideration is side effects of treatment, for example, treatment is selected to reduce and/or prevent contraction (e.g., stenosis) of the artery, for example, due to scarring of tissue in the arterial wall.

[0142] In an exemplary embodiment of the invention, the treated is selected for a type of tissue. Optionally, the treatment is selected towards nerves in the adventia or peri-adventitia. Optionally or additionally, the treated is selected towards nerves are in the renal artery wall. Alternatively, the treatment is selected towards renal nerves in the aorta. Alternatively, the treatment is selected towards nerves in the carotid artery wall.

[0143] In an exemplary embodiment of the invention, the treatment is selected by taking into account the cooling capacity of the vessel wall, such as a blood flow in the artery.

[0144] In an exemplary embodiment of the invention, the frequency of vibration of the acoustic element of the transducer is selected according to the depth of the target tissue.

[0145] In an exemplary embodiment of the invention, the ultrasonic intensity profile is selected according to the size of the treatment region. Optionally, a relatively low ultrasonic intensity profile treats a relatively small area in the peri-adventitia. Optionally, a relatively higher ultrasonic intensity profile is selected to increase the treatment region from the peri-adventitia towards the intima, for example until the adventia, until the media, or to increase the size of the treatment region in the peri-adventia.

[0146] In an exemplary embodiment of the invention, one or more tissue properties are adjusted, for example, increased and/or decreased. Non-limiting examples of tissues include; target tissue, surrounding tissue, blood flowing in vessel. Optionally, tissue properties are adjusted in accordance with the selected thermal effect, for example, to relatively increase the size of the thermally affected area. Optionally or additionally, tissue properties are adjusted in accordance with the selected safety parameters, for example, to relatively increase the margin of safety. Non-limiting examples of tissues properties that are adjusted include; the temperature of the tissue, the heat removal rate from the tissue, the acoustic energy absorption of the tissue.

[0147] In an exemplary embodiment of the invention, feedback associated with the treatment is obtained. Optionally, the desired result is used as a target, such as in an open-loop manner. For example, initial parameters are set and the tissue is treated to achieve the result. Alternatively or additionally, the desired result is used as feedback of the treatment, such as in a close-loop manner. For example, treatment is applied, imaging of the treatment region is performed to check if the desired result has been met and treatment is reapplied, optionally with adjustments to the treatment.

[0148] In an exemplary embodiment of the invention, the treatment region is defined by a circumferential extent and by a distance extent and also by a starting distance (e.g., from an intima). In an exemplary embodiment of the invention, the distance extent and/or starting distance are controlled with an accuracy of, for example, better than 2 mm, 1 mm, 0.5 mm, or 0.2 mm. Optionally or alternatively, the circumferential extent of treatment is controlled with an accuracy of better than 30 degrees, 10 degrees, or 5 degrees, which can be, for example, 3 mm, 2 mm, 1 mm, 0.5 mm or better or intermediate accuracy.

[0149] In an exemplary embodiment of the invention, the amount, pattern and/or extent of the treated region is selected according to a desired effect and/or a probability of affecting sufficient tissue to be treated (e.g., nerves). Optionally, the amount of treatment is curtailed, for example, to reduce side effects, such as constriction of the lumen caused by too much damage in the lumen wall.

[0150] In an exemplary embodiment of the invention, for a section of treated lumen of, for example, 1-5 cm in length (e.g., axial distance between outermost treatment locations), the percentage of axial locations treated is, for example, 10%, 30%, 50%, 80% or smaller or intermediate or greater percentages.

[0151] In an exemplary embodiment of the invention, when considering the surface area of the intima of such a treated section, and mapping treated regions by "collapsing" them towards the intima, the percentage of area treated can be, for example, 5%, 15%, 30%, 60%, 80% or smaller or intermediate or larger percentages.

[0152] In an exemplary embodiment of the invention, when considering the circumference of the intima of such a treated section at an axial location where treatment is applied, and mapping treated regions by "collapsing" them towards the intima, the percentage of circumference treated can be, for example, 5%, 15%, 30%, 60%, 80% or smaller or intermediate or larger percentages, for example, for between 1 and 8 axial treatment locations.

[0153] A particular feature of some embodiments of the invention is that an extent of treatment in a dimension perpendicular to the lumen wall is affected both by cooling of the lumen wall, e.g., by natural blood flow and by dissipation of energy as the energy penetrates into the tissue. In an exemplary embodiment of the invention, the frequency and/or other properties of the energy affect the absorption per unit distance, which results in reduced energy deposition as distance increases. Optionally or alternatively, cooling effects of nearby tissue reduce energy deposition. Optionally or alternatively, divergence of the beam reduces energy deposition. Optionally or alternatively, tissue properties, for example, insulation of a sheath surrounding nerves, serves to increase the effect of energy deposition at some tissues. Optionally or alternatively, tissue characteristics affect energy deposition thereat.

[0154] A particular feature of some embodiments of the invention is the use of an unfocused energy field, which, in some embodiments, can preserve a uniform definition of its edges for a considerable distance, thereby providing definition of circumferential edges of a treated area.

[0155] A particular feature of some embodiments of the invention relates to the ability to reduce mechanical positioning requirements while maintaining and/or increasing accuracy of spatial selectivity of treatment.

[0156] With respect to a direction perpendicular to the vessel wall, in a focused system, position control is provided by accurate focusing and control of catheter position (e.g., to be in contact with a wall). In an exemplary embodiment of the invention, however, position control in that direction is provided by a tradeoff between cooling by blood flow and energy application. This is not dependent on the catheter position in a blood flow, as there is relatively little loss in the blood, in some embodiments. This means that variations of several millimeters in catheter distance form the wall need not have a significant effect on spatial treatment location. Moreover, not having contact with the vessel wall can ensure, in some embodiments, sufficient cooling to prevent damage at any part of the intima.

[0157] Use of non-focused beams can also help in the circumferential accuracy requirements. In one example, it allows the treated "spot" to be quite large, which means there need not be any scanning of a focal point of a focused beam, which scanning may be complex and/or inaccurate. Optionally, the circumferential profile of the beam is selected so that it provides a gradual cut-off in degree of damage, for example, along a border of, for example, 1-2 mm in width. Alternatively, a sharp cut-off is provided, for example, by suitable selection of emitter design to have a sharp cut-off in intensity profile.

[0158] In an exemplary embodiment of the invention, provision of high power allows the treatment time to be short enough so that, for example, treatment can be applied while blood velocity is constant (e.g., during cardiac disatole) and/or while the vessel wall is not moving (e.g., relative to catheter, which is optionally determined using a distance sensor and/or estimated using a pulse sensor and/or ECG sensor).

[0159] In an exemplary embodiment of the invention, cooling of an ultrasonic emitter by blood flow allows higher power to be used.

Overview of Treatment

[0160] FIG. **1**A is a flow chart of a method of selectively treating tissues using ultrasound energy, in accordance with an exemplary embodiment of the invention. Optionally, the ultrasound energy is applied at a selected frequency. Optionally or additionally, the ultrasound energy is applied at a selected intensity profile (e.g., watts per square centimeters, time of treatment). The method described in the flowchart is non-limiting. For example, some steps are optional. Furthermore, there can be other methods and/or other apparatus used to obtain the results.

[0161] At **102**, a target tissue is optionally determined, for example, to treat a clinical disorder by thermally damaging (e.g., ablating) the target tissue, in accordance with an exemplary embodiment of the invention.

[0162] In an exemplary embodiment of the invention, one or more factors related to the thermal effect are optionally determined (e.g. manually by a physician, automatically by software), for example, the anatomical location (e.g., the blood vessel where the catheter will be inserted) of the lesion, the type of tissue to ablate (e.g. nerve), an extent of the thermal effect (e.g., the entire tissue, part of the tissue), and/or safety considerations.

[0163] At **104**, one or more parameters to result in the desired thermal effect of the target tissue are optionally determined, in accordance with an exemplary embodiment of the invention.

[0164] Optionally, feedback is obtained about the treatment effect, for example, imaging of the target tissues. Alternatively, feedback is not required, as the initial settings are sufficient to achieve the desired treatment effect.

[0165] In an exemplary embodiment of the invention, localization of the treatment effect is optionally provided by one or more factors including, the blood cooling the vessel wall, the ultrasonic beam amplitude attenuation, the ultrasonic beam dispersion, and/or tissue types.

[0166] At **106**, the target tissue as determined in **110** is treated using parameter settings as in **104**, in accordance with an exemplary embodiment of the invention. Optionally, ultrasound energy is delivered by a transducer on a catheter inserted into the body. Optionally, the treatment is monitored.

[0167] Optionally, at **108**, treatment is repeated, for example, immediately and/or at a later point in time. Optionally, treatment is adjusted in response to feedback.

[0168] In an exemplary embodiment of the invention, feedback optionally is related to the parameters used for transmission of ultrasonic energy, for example, associated with the treatment intensity profile. Optionally, feedback is related to the environment, for example, the rate of blood flow. Alternatively or additionally, feedback is related to the impedance of the acoustic element, such as to estimate changes in efficiency that can affect the transmitted acoustic intensity profile.

[0169] In an exemplary embodiment of the invention, feedback is optionally functionally related to the effects of the ultrasonic energy on tissues. Optionally, feedback in the form of imaging is used to detect the effect of treatment on tissues. Alternatively or additionally, feedback in the form of clinical measurements (e.g., blood pressure changes) are used to detect the effect.

[0170] In some embodiments, imaging is optionally used to evaluate the treatment (e.g., thermal damage to target tissue). Alternatively or additionally, the treatment is evaluated using other methods, such as clinical measurements, sometimes over the long term.

Control System

[0171] FIG. **2** illustrates an exemplary ultrasound treatment system **1600** for selectively treating tissues, in accordance with an exemplary embodiment of the invention. System **1600** provides for the control of the ultrasound treatment and/or monitoring of the treatment using catheter **1222**. A transducer **300** comprising an acoustic element **102** to produce ultrasound energy is optionally located on a distal end of catheter **1222**.

[0172] In an exemplary embodiment of the invention, an operator (e.g., physician performing the procedure) programs a controller **1602** (e.g., computer) for treatment using a user interface **1604** (e.g., keyboard, mouse, monitor). Optionally, treatment is monitored, for example, by viewing feedback parameters on interface **1604**.

[0173] In an exemplary embodiment of the invention, a power port **1606** provides electrical power to electrodes across element **102**, causing element **102** to vibrate at the set frequency, outputting a set ultrasound intensity profile.

[0174] In an exemplary embodiment of the invention, one or more functions and/or parameters and/or settings are programmed and/or set into controller **1602** (e.g., automatically determined by software such as according to a treatment plan). Optionally or additionally, one or more functions and/or parameters are selectable (e.g., manually set by a user, automatically selected by software).

[0175] One or more non-limiting examples of settable parameters include:

[0176] Impedance of element **102**.

[0177] Acoustic feedback is feedback obtained by analyzing echoes of a diagnostic ultrasound signal returning from tissues, for example, as will be described in more detail with reference to FIG. **11**.

[0178] Estimated or measured flow rate of blood across the surface of the acoustic element is important for controlling the temperature of the element to prevent overheating. In some embodiments, the flow rate of the blood is adjusted relatively higher or relatively lower, such as to control the temperature.

[0179] Estimated or measured flow rate of blood across the wall of the treatment target (e.g., blood vessel) is important for estimating the cooling capacity of the blood on the tissues of the wall being heated by ultrasound.

[0180] Efficiency is the estimated efficiency of converting electrical energy into ultrasound energy by the acoustic element.

[0181] Temperature control system cools and/or heats the element and/or tissues (e.g., blood vessel wall) to the desired temperature. Optionally, the temperature control system is used in combination with the blood flow. In some embodiments, the blood and/or tissue is preheated, for example, to obtain a relatively larger thermal effect.

[0182] Impulse excitation is the application of an impulse function (e.g., delta function) to the element, causing the element to vibrate with a decreasing amplitude. Impulse excitation is used to estimate a reduction in efficiency, useful as feedback, for example, to determine one or more of, thrombus formation on the element, the element coming in contact with the vessel wall, mechanical damage to the element.

[0183] Navigation system controls the movement and/or positioning and/or orientation of catheter **1222** and/or the transducer.

[0184] Pressure is the pressure caused by sound (e.g., acoustic intensity) during treatment and/or imaging.

[0185] Electric power is the applied power to the transducer.

[0186] Reflected electric power from the transducer back to the controller.

[0187] Voltage is the measured and/or applied voltage on the transducer.

[0188] Current is the measured and/or applied current in the transducer.

[0189] One or more non-limiting examples of selectable parameters include:

[0190] Frequency of the ultrasound energy produced by vibration of the acoustic element.

[0191] Waveform applied to the acoustic element, for example, a sinusoidal wave form.

[0192] Intensity is the produced ultrasound power divided by the surface area of the acoustic element.

[0193] Pulse duration is the length of a pulse of acoustic energy measured in time.

[0194] Duty cycle is the percentage of time in a single pulse that ultrasound energy is transmitted.

[0195] Temperature threshold is the approximate temperature of the element and/or the liquid (e.g., blood, saline) that should not be exceeded.

[0196] Treatment pattern is the spatial and/or temporal combination of one or more of the above variables, for example, a single pulse, a sequence of pulses, a train of pulses.

[0197] Focusing is the setting of non-focused vs. focused ultrasound energy.

[0198] The table below sets out some examples of the selectable parameters, and provides their theoretical limits, an exemplary treatment range, and an exemplary treatment sub range (e.g., most commonly used settings). It is important to note that some selectable parameters can only be selected from a pre-determined set, for example, in some embodiments, catheters are designed to operate at a specific frequency, in which case the user selects the frequency according to the catheter available.

Parameter	Theoretical range	Exemplary Treatment range	Exemplary Treatment sub range
Frequency (MHz):			
Treatment	1-60	8-30	10-22
Imaging	1-60	10-60	10-25
Intensity (Watts/sq cm)	1-200	10-100	10-60
Duty cycle (%)	0.1-100	10-100	50-100
Pulse duration (seconds)	0.01-1000	0.1-4	0.1-2
Duration of treatment (Seconds) per location	0.1-1000	2-120	3-60
Efficiency (%)	1-70%	20-70%	35-70%
Temperature (Celsius)	10-100	15-80	25-80

Some Examples of Expected Effects Associated with Variables

[0199] The following are some non-limiting examples illustrating some parameters under control, and their association with some expected treatment effects, in accordance with an exemplary embodiment of the invention:

[0200] Impedance: a decrease of more than 10% suggests a decrease in efficiency of the acoustic element. The element will heat up more (e.g., requiring more cooling), and/or the acoustic intensity will decrease (e.g., requiring a higher intensity). In some embodiments, the impulse excitation is used to estimate the change in efficiency.

[0201] Acoustic feedback: imaging of the treatment region for the desired thermal effects can be used to decide if to continue treatment, stop treatment or change treatment (e.g., increase or decrease acoustic intensity profile, change positions of catheter).

[0202] Estimated flow rate of blood across acoustic element: a change in blood flow can cause the element to overheat, potentially damaging the element.

[0203] Estimated flow rate of blood across wall of blood vessel: a decrease in flow rate reduces the cooling of tissues, potentially resulting in a larger thermal effect for the given acoustic intensity. An increase in flow increases the cooling of the tissues, potentially resulting in a smaller thermal effect. Alternatively, the location of the thermal effect will be shifted. In some embodiments, the flow rate is controlled to within a predetermined range (e.g., as will be described below). Alternatively or additionally, the acoustic intensity profile is adjusted. Alternatively or additionally, the cooling system is used to maintain the temperature of the element and/or wall within the range.

[0204] Navigation system: imaging feedback can be used to detect if the thermal effect is at the desired location (e.g., to the target tissue). Adjustments in position can be made accordingly.

[0205] Frequency: a relatively lower frequency of ultrasonic energy is able to penetrate relatively deeper into tissue. In some embodiments, relatively lower frequencies are used to achieve thermal effects relatively further away from the blood vessel wall.

[0206] Intensity: a relatively higher intensity of ultrasonic energy is able to penetrate relatively deeper into tissue and/or achieves a relatively higher heating of tissues quicker. In some embodiments, relatively higher intensities are used to achieve relatively larger thermal effects. Alternatively or additionally, thermal effects are further away from the vessel wall.

[0207] Pulse duration: a relatively longer pulse will deliver a relatively larger amount of ultrasonic energy to tissues, achieving a relatively larger thermal effect.

[0208] Duty cycle: a relatively higher duty cycle will deliver a relatively higher amount of ultrasonic energy to tissues, achieving a relatively larger thermal effect. In some embodiments, a relatively short duty cycle acts as a train of short pulses separated by delays, the effect of which is described below with reference to 'treatment pattern'.

[0209] Treatment Pattern: can be applied to achieve various treatment objectives, for example, a pulse of acoustic energy can be applied, followed by a delay period to allow cooling (e.g., by spreading of heat) before applying another pulse of energy. In another example, tissue can be targeted for treatment at one location, followed by a rotation (e.g., 10 degrees), followed by treatment at the second location, followed by a rotation to the first location.

[0210] Focusing: non-focused application of energy does not require precise anatomical positioning of the distance from the transducer to the target tissue throughout treatment, and achieves a relatively larger treatment volume using a relatively lower acoustic intensity. Focused application of energy requires precise positioning of the focal point to the target tissue throughout treatment, and achieves a relatively smaller treatment volume using a relatively higher intensity (e.g., total intensity at focal point).

Exemplary Method of Treatment

[0211] FIG. **1**B is a detailed method of treatment of FIG. **1**A, in accordance with an exemplary embodiment of the invention. It should be noted that the method described in the flowchart is non-limiting. For example, some steps are optional. Furthermore, there can be other methods and/or other apparatus used to obtain the results.

[0212] Optionally, at **152**, a decision to treat is made, for example, as will be described in the section "DECIDING TO TREAT".

[0213] Optionally, at **154**, the anatomical location to treat is selected, for example, as will be described in the section "SELECTING ANATOMICAL LOCATION OF TREATMENT".

[0214] Optionally, at **156**, a decision is made with regards to the amount of thermal damage to cause, for example, as will be described in the section, "DECIDE AMOUNT OF THEMAL EFFECT".

[0215] Optionally, at **158**, a decision is made with regards to tradeoffs related to safety considerations, for example, increasing the margin of safety will result in less damage to surrounding tissue, but may not result in full treatment of the target tissue, for example, as will be described in the section "DECIDE SAFETY CONSIDERATIONS".

[0216] Optionally, at **160**, the rate of blood flow in the artery is estimated, for example, as will be described in the section "ESTIMATE BLOOD FLOW".

[0217] Optionally, at **174**, one or more tissue properties of the target tissue and/or surrounding tissue are adjusted, such as temperature and/or heat removal rate, for example, as will be described in the section "ADJUSTING TISSUE PROPERTIES". In some embodiments, the tissue properties are adjusted according to one or more parameters, such as the amount of thermal effect and/or safety considerations.

[0218] Optionally, at **162**, the frequency of the ultrasound energy to apply is selected, such as by choosing a catheter designed to operate at that frequency, for example, as will be described in the section "CHOOSE CATHETER (FREQUENCY) ACCORDING TO TREATMENT". In some embodiments, the user is limited in the selection of the frequency according to the available frequency. At **164**, the ultrasonic intensity profile is selected according to the treatment (e.g. watts per square centimeter, time of treatment, profile over time) for example, as will be described in the section "CHOOSE ULTRASONIC INTENSITY PROFILE ACCORDING TO TREATMENT".

[0219] Optionally, at **166**, the catheter (e.g., as selected in **162**) is inserted into the body of the patient and threaded to the treatment site (e.g., as selected in **154**), for example, as will be described in the section "INSERT CATHETER".

[0220] At **168**, the patient is treated, for example, as will be described in the section "TREAT".

[0221] Optionally, at **170**, feedback is obtained, for example, as will be described in the section "FEEDBACK".

[0222] Optionally, at **172**, adjustments are made, for example, to one or more parameters, and treatment continues as in **168**, for example, as will be described in the section "ADJUST".

Deciding to Treat

[0223] In an exemplary embodiment of the invention, a decision to treat by thermally damaging target tissue is made, for example, by a physician according to clinical indications.

[0224] Non-limiting examples of clinical applications are listed in the table below. The applications listed in the table are referenced (e.g., according to numbers) to FIG. **3**, which is an illustration of the human body showing the major arteries as reference points, useful in practicing some embodiments of the invention.

Exemplary Clinical Applications

[0225]

#	Application Name	Anatomy	Target
402	Renal sympathetic nerve modulation	Renal artery	Renal sympathetic nerves
404	Carotid sympathetic nerve modulation	Carotid artery	Carotid sympathetic nerves
406	Vagus sympathetic nerve modulation	Aorta	Vagus sympathetic nerve
408	Peripheral sympathetic nerve modulation	Peripheral blood vessels	Peripheral sympathetic nerves
410	Pain nerve modulation	Spinal cord cannel	Pain nerves
412	Restenosis decrease	All relevant arteries	Artery media and adventitia
414	Vulnerable plaque stabilization	All relevant arteries	Artery media and adventitia
416	Atherosclerosis passivation	All relevant arteries	Artery media and adventitia
418	Plaque volume decrease	All relevant arteries	Artery media and adventitia
420	Plaque thrombosis decrease	All relevant arteries	Artery media and adventitia
422	Tetanic limb muscle tonus decrease	Limb arteries or veins	Peripheral motor nerves
424	Atrial fibrillation prevention	Right atria	Pulmonary vain insertion
426	Cardiac arrhythmia prevention	Coronary arteries	Cardiac tissue pathology
428	Liver tumor necrosis	Inferior vena cava	Tumor
430	None-malignant prostate treatment	Urethra	Sick prostate tissue
432	Malignant prostate treatment	Urethra	Sick prostate tissue
434	Artery aneurysms stabilization	All relevant arteries	Aneurysm wall
436	Aortic aneurysms stabilization	Aorta	Aneurysm wall
438	Berry aneurysms sealing	Brain arteries	Aneurysm wall
440	Erectile dysfunction treatment	Internal Iliac	Artery media and adventitia

[0226] A non-limiting method of stabilizing a plaque and/or aneurysm using ultrasound energy is described for example, in Sverdlik et al, in PCT/IL2008/000234, incorporated herein by reference in its entirety.

[0227] In an exemplary embodiment of the invention, nerve tissue is selectable for treatment by ultrasonic energy, for example, as will be described below with reference to FIG. **7**B.

[0228] Some exemplary medical conditions and their proposed treatment by treating nerves (examples not limited to the nerves described, treating other nerves may achieve a similar clinical outcome) in accordance with an exemplary embodiment of the invention include:

[0229] Frozen shoulder—suprascapular nerve.

[0230] Zygapophysial joint pain—cervical medial branch nerves.

[0231] Chronic Pelvic Pain (in women)—uterosacral nerve.

[0232] Glabellar Frowning—facial nerve.

[0233] Phantom Pain—lumbar dorsal root ganglia.

[0234] Trigeminal Neuralgia—branches of the trigeminal nerve.

[0235] Cluster Headache—trigeminal and/or sphenopalatine ganglions.

[0236] Complex Regional Pain Syndrome—stellate ganglion.

[0237] In some embodiments, electrical signals through nerves are reduced by treatment, for example, by damaging some neurons in the nerve bundle. Alternatively or addition-

ally, electrical signals through nerves are prevented from passing through, for example, by damaging the entire nerve bundle.

[0238] In some embodiments, malignant tissues (e.g., in the liver) and/or hypertrophic tissues (e.g., in the prostate) are damaged.

[0239] In some embodiments, the parameters to treat the tissues are obtained from a mathematical model, for example, as described in the section "EXEMPLARY DEVELOPMENT OF AN EQUATION" parts A and/or B.

[0240] Some non-limiting examples of how to achieve various desired effects using some embodiments of the invention are described. The description refers to obtaining the described effect. However, it should be noted that some effects overlap, and so some embodiments achieve one or more effects. In some embodiments, only the desired effect is achieved without other effects.

[0241] Coagulation—In some embodiments, heating tissue including blood to the range of 42-55 or 42-50 or other smaller, intermediate or larger values, results in blood coagulation without damage to surrounding tissues.

[0242] Denaturation—In some embodiments, heating tissue above 50, above 55, above 60 or other smaller, intermediate or larger values results in denaturation of collagen.

[0243] Apoptosis—In some embodiments, tissues are heated to over 85, over 95 degrees Celsius, or other smaller, intermediate or larger values to cause apoptosis, for example, as taught by Fung et al. Tissues affected are located about 0-0.5 mm away from the area of the applied energy.

[0244] Temporary/permanent disruption of nerve signals—In some embodiments, the length of nerve that is disrupted (e.g., burned) is selected to result in temporary or permanent disruption of nerve signals. For example, a relatively short disruption length can allow nerves to regenerate and reconnect, for example, about 0.1 mm, about 0.5 mm, about 1 mm, about 2 mm, about 5 mm, or other smaller, intermediate or larger values are used. Optionally, relatively long disruption lengths prevent nerves from regenerating and reconnecting, for example, about 10 mm, about 15 mm, about 20 mm, about 30 mm, or other smaller, intermediate or larger values are used.

[0245] Destruction—In some embodiments of the invention, tissues are heated to over 100 degrees Celsius to result in tissue destruction. A temperature of over 100 degrees Celsius results in vaporization of water, which can cause cells to burst.

[0246] Burning—In some embodiments, tissues are heated for relatively long periods of time to result in burning of the tissue, for example, over 10, 20, 30, 50, 100 seconds, or other smaller, intermediate or larger time periods. Alternatively or additionally, relatively high intensities are applied to result in the burn.

[0247] Degeneration—In some embodiments, tissues are heated to cause degeneration of the tissue, such as to about 47 degrees Celsius, for example, as taught by Xu & Pollock (see below).

Selecting Anatomical Location of Treatment

[0248] In an exemplary embodiment of the invention, the anatomical location for treatment (e.g., thermal effect) is selected. Optionally, a factor in the selection is the ability to apply ultrasound energy to the target tissue. One or more non-limiting examples of target tissues include, fat, nerves, vasa vasora, lymph, tumor, connective tissue, plaque (e.g., atherosclerotic).

[0249] In an exemplary embodiment of the invention, ultrasonic energy is applied invasively, for example, using a catheter and/or an endoscope. Alternatively, ultrasonic energy is applied non-invasively. Non-limiting examples from which thermal effects can be applied include one or more of, a fluid filled lumen (e.g., blood vessel), a non-fluid filled lumen (e.g., ureter), a fluid filled cavity (e.g., spinal canal), a non-fluid filled cavity (e.g., stomach), from outside the body (e.g., ultrasonic transducer is placed in a liquid such as water, and energy is delivered across the skin).

[0250] In an exemplary embodiment of the invention, a decision on the location of treatment is made from one or more different possible anatomical locations. Optionally, a factor in the selection is the location inside the lumen from which ultrasonic energy is applied, for example some locations are more easily accessed by using a catheter than others. Alternatively or additionally, a factor in the selection is the rate of blood flow in the blood vessel where the catheter will be positioned (e.g., some areas have more uniform flow), potentially important for cooling, for example, as will be described in the section "Estimate blood flow". In some cases, similar clinical effects will be achieved by thermal effects (e.g., damage) of at least one of the different locations.

[0251] For example, a treatment of resistant essential hypertension is renal denervation. Reference is made to FIG. **4**, which is an illustration of the anatomy of renal nerves **350** in relation to a right renal artery **352**. Right renal artery **352** supplies blood to a right kidney **354** from an aorta **356**. Commonly, renal nerves **350** arise from T10-L2 spinal roots, travel along aorta **356** and along renal artery **352** to innervate kidney **354**. In some anatomies, renal nerves **350** primarily lie within the adventia of the renal artery **352** and/or aorta **356**.

[0252] Non-limiting examples of conditions likely to respond to renal denervation:

[0253] Resistant essential hypertension.

[0254] Essential hypertension intolerant to medications.

[0255] Nondipping essential hypertension.

[0256] Resistant renovascular hypertension.

[0257] Hypertension with chronic renal disease (unilateral or bilateral).

[0258] Hypertension with obstructive sleep apnea intolerant to continuous positive airway pressure.

[0259] Congestive heart failure (with reduced or preserved left ventricular systolic function) with cardiorenal syndrome.

[0260] Hypertension in end-stage kidney disease on dialysis with native kidneys.

[0261] Hypertension in renal transplant patients with remaining native kidneys.

Non-limiting examples of potential long-term benefits of renal denervation:

[0262] Attenuation of arterial pressure.

[0263] Stabilization of renal function with attenuation of the rate of decline of estimated glomerular filtration rate and reduction of proteinuria in hypertensive patients.

[0264] Restoration of nocturnal dipping.

[0265] Regression of left ventricular hypertrophy.

[0266] Decreased insulin resistance.

[0267] Slower progression of vascular disease.

[0268] Decreased incidence of congestive heart failure with reduced ventricular hypertrophy, reduced salt and water retention, and improved exercise tolerance.

[0269] Decreased risk of stroke.

[0270] Decreased risk of atrial and ventricular arrhythmias.

[0271] Decreased risk of sudden cardiac death.

[0272] Further details about renal denervation can be found in an article by Katholi et al. "Renal nerves in the maintenance of hypertension: a potential therapeutic target" Curr Hypertens Rep. 2010 June; 12(3):196-204, incorporated herein by reference in its entirety.

[0273] There are one or more exemplary locations for performing the renal denervation procedure, useful in practicing some embodiments of the invention. For example, the procedure can be performed at a renal artery location **358** (e.g., from inside renal artery **352**), at an ostium location **360** (e.g., the branch of renal artery **352** off aorta **356**) and/or at an aorta location **362** (e.g., from inside aorta **356**).

[0274] Non-limiting examples of factors affecting the location (e.g., **358**, **360**, **362**) of treatment include simplicity of access, simplicity of the treatment procedure. For example, at location **358** multiple treatment areas may be required to ablate enough renal nerves **350** to achieve a desired clinical result of lowering blood pressure. For example, at location **360** and/or **362** two treatments can achieve the same effect, as the renal nerves **350** are concentrated together (e.g., afferent and efferent renal nerves travel together).

[0275] In some embodiments, catheters with ultrasound transducers for treatment at specific locations can be custom designed. For example, a straight catheter **364** with a transducer **368** can be designed for treatment at location **362**. For example, a curved catheter **366** can be designed for treatment at location **360** (e.g., by placing a transducer **370** at the curve) and/or at location **358** (e.g., by placing a transducer **372** at the distal end of catheter **366**).

[0276] In an exemplary embodiment of the invention, the ultrasound energy used to treat the target tissues does not need to be applied directly to the vessel wall. Optionally, the ultrasound energy is applied away from the vessel wall, for example, the transducer is not in contact with the wall.

[0277] In an exemplary embodiment of the invention, damage to the intima layer (e.g., endothelium) and/or internal elastic lamina of the vessel wall is prevented and/or reduced. A potential advantage is preventing and/or reducing the risk of adverse clinical outcomes, for example, one or more of, triggering a coagulation cascade, causing a vessel spasm, causing stenosis, blood loss due to injury to the vessel wall.

Exemplary Treatment Device

[0278] FIG. **5** illustrates a target tissue being irradiated with ultrasonic energy, in accordance with an exemplary embodiment of the invention. Shown is catheter **1222** inside a lumen **1240** of a blood vessel **1242** (e.g., artery). Optionally, an acoustic element **102** (e.g., part of transducer **300**) emits a beam **1228** of ultrasound energy towards a target tissue **1216**.

[0279] In an exemplary embodiment of the invention, the ultrasonic emission element and/or transducer **300** is capable of relatively high intensity ultrasound output. Optionally, transducer **300** is gas-backed, such as with a bubble of gas. Non-limiting examples of high intensity ultrasound include at least 20 watts/cm^2, at least 30 watts/cm^2, at least 50 watts/cm^2, at least 100 watts/cm^2 or other smaller, intermediate or larger intensities.

[0280] In an exemplary embodiment of the invention, beam **1228** is unfocused, for example, beam does not converged at a point, for example, beam diverges relatively little.

[0281] In an exemplary embodiment of the invention, the shape of element **102** is rectangular. Optionally, element **102** is planar. Optionally, a length of element **102** is, for example, about 1 mm, about 2 mm, about 4 mm, about 6 mm, about 8 mm, about 10 mm, or other smaller, intermediate or larger lengths are used. Optionally, a width of element **102** is, for example, about 0.2 mm, about 0.6 mm, about 1.0 mm, about 1.4 mm, about 2.0 mm, or other smaller, intermediate or larger widths are used.

[0282] In an exemplary embodiment of the invention, beam **1228** produced by a rectangular acoustic element is relatively straight, spreading an angle of about fifteen degrees relative to the exposed surface of element **102**, when measured along the length.

[0283] In an exemplary embodiment of the invention, target tissue **1216** is located a distance **1232** away from wall **1226**. Non-limiting examples of the maximum distance **1232** of target tissue **1216** that can be treated include 0.5 mm, 1 mm, 2 mm, 5 mm, 10 mm, or other smaller, intermediate or larger distances.

[0284] In an exemplary embodiment of the invention, target tissue **1216** is treated by an ultrasound beam **1228** from transducer **300**. In an exemplary embodiment of the invention, treating comprises a thermal effect (e.g., heating to above 55 degrees Celsius) and/or a cavitation effect.

[0285] The table below illustrates some non-limiting examples of the effect of temperature on nerves over time. The rise in temperature is due to heat sources in general and is not limited to ultrasonic heating.

Article	Temp (° C.)	Follow up	Histological findings - summary
Xu & Pollock, 1994	47	Immediately after treatment	Schwann cells - disrupted cytoplasmic organelles Blood vessels - collapsed; endothelia separated from overlying pericytes; swollen endothelia and perivascular oedema in endoneurial capillaries; Axoplasm - 'watery'
Xu & Pollock, 1994	47	2 hours after thermal injury	Myelinated axons - degenerating
Xu & Pollock, 1994	47	6 hours after thermal injury	Myelin - decrease in diameter Myelinated axons - degenerated Myelinated fibers - distended
Xu & Pollock, 1994	47	1 day after thermal injury	Axons - degenerated Schwann cells - hypertrophied
Xu & Pollock, 1994	58	immediately after treatment	Myelin - widened Schmidt-Lanterman incisures; disruption of myelin lamellae Blood vessels - endothelia separated from overlying pericytes; thrombosed; perivascular oedema Unmyelinated fiber - degenerated Unmyelinated axons - swollen and devoid of organelles
Xu & Pollock, 1994	58	3 days after thermal injury	Nerve fibers - destructed
Lele, 1963	24-48		Axons -fragmented; nodular appearance; continuity interrupted; decreased in length Myelin - vacuolated

[0286] In an exemplary embodiment of the invention, damage and/or treatment to tissues (e.g., normal, healthy) sur-

rounding target tissue **1216** is reduced and/or prevented. Optionally, treatment and/or damage to a volume of tissue between target tissue **1216** and wall **1226** is reduced and/or prevented.

[0287] In some embodiments, contact between an acoustic element **102** of transducer **300** and wall **1226** of vessel **1240**, is reduced and/or prevented, for example, by a separation device **1204**. Optionally, device **1204** maintains a distance **1218** between element **102** and wall **1226** of at least 1 mm. Optionally, a relatively cool liquid (e.g., blood, injected saline) flows in distance **1218**. In an exemplary embodiment of the invention, the liquid cools element **102** and/or wall **1226**.

[0288] In some embodiments, catheter **1222** comprises at least one transducer **300**, positioned for example, on the side, such as inside a window cut into the catheter shaft **1230**.

[0289] In an exemplary embodiment of the invention, element **102** is cooled. Optionally, cooling occurs by transfer of heat from element **102** to a surrounding fluid such as blood **1220**, saline, urine, water, angiography contrast fluids, cerebrospinal fluid, lymph, mucous, stomach acid. Alternatively or additionally, cooling occurs by injection of a volume of a liquid (e.g., saline, radio-opaque dye) through tube **1206**, and/or circulation of a liquid through tube **1208**. Alternatively or additionally, cooling is increased using an active heat flux, such as a thermoelectric cooler. It should be noted, that herein cooling by blood flow also refers to cooling using other fluids (e.g., saline) in addition to blood, or cooling using other fluids as a substitution for blood cooling.

[0290] In an exemplary embodiment of the invention, a temperature sensing element, such as sensor **308**, measures and/or estimates the temperature of element **102**. In an exemplary embodiment of the invention, sensor **308** measures the temperature of blood that has flowed **1220** over a surface **1224** of element **102**. In an exemplary embodiment of the invention, the temperature of the blood that has flowed **1220** over surface **1224** is used as an estimate of the temperature of element **102**.

[0291] In an exemplary embodiment of the invention, a 6 mm long X 1 mm wide transducer emitting ultrasound energy at an intensity of 100 Watts/square centimeter, is calculated to generate about 11-24 Watts of excess heat (variation according to efficiency of operation) for removal. The amount of heat generated varies linearly with the size of the element and/or the intensity of emitted ultrasound energy.

Decide Amount of Thermal Effect

[0292] FIG. **6**A is a schematic diagram of a cross section of an artery **600**, useful in practicing some embodiments of the invention. The layers of the wall of artery **600**, from a lumen **602** outwards are: endothelium **604**, internal elastic media **606**, media **608**, adventia **610** having vasa vosorum **612** embedded therein, peri-adventitia **614**, peri-vess (peri-adventitia blood vessels (capillaries)) **616**, peri-nerv (peri-adventitia nerve fibers) **618**.

[0293] In an exemplary embodiment of the invention, one type of target tissue is nerve tissue **620**. In some anatomies, nerves **620** surrounded by fat are especially well suited for targeted treatment, for example, as will be discussed with reference to FIG. **7**B. Nerve tissue **620** is commonly located in peri-adventitia **614**.

[0294] In an exemplary embodiment of the invention, the extent of thermal damage is selectable and/or controllable. Optionally, thermal damage is selected to include only the target tissue, for example, thermal damaged nerves **622**. Alternatively or additionally, thermal damage is selected to include tissue surrounding the target tissue.

[0295] In an exemplary embodiment of the invention, the portion of the target tissue to treat by thermal effect is selected. Optionally, a portion of the target tissue experiences thermal damage and a portion of the same target tissue does not experience damage, for example, as shown with reference to nerve **624**. The left side of nerve **624** experienced thermal damage and the right side of nerve **624** did not experience thermal damage. In an exemplary embodiment of the invention, the effect of thermal damage to portion of the target tissue is associated with an unfocused ultrasound beam that is relatively high in acoustic intensity, and diverges a relatively small amount. In some embodiments, a portion of the nerve is treated by directing the ultrasound beam to the desired targeted portion of the nerve. Alternatively or additionally, parameters are selected to treat the portion of the nerve, for example, a thermal effect that starts a first distance away from the intima and ends a relatively closer second distance away from the intima, where the target portion of the nerve falls between the first and second distances, and the portion not to be treated falls between the second distance and the intima.

[0296] In an exemplary embodiment of the invention, the extent of the thermal effect to the target tissue is selected, for example, tissues can be partially thermally damaged to the extent that the damage is reversible (e.g., tissue can self regenerate and/or heal).

[0297] In an exemplary embodiment of the invention, the functional result of the thermal effect is selected, for example, to achieve a temporary effect (e.g., reversible effect).

[0298] In an exemplary embodiment of the invention, the spatial profile of the thermal effect is selectable, for example, the volume of the thermal effect.

[0299] FIG. **6**B is a cross sectional view, FIG. **6**C is a side view and FIG. **6**D is a top view illustrating a controllable volume of thermal damage **648** to tissue, for example to a blood vessel wall **640**, in accordance with an exemplary embodiment of the invention. Optionally, thermal damage is caused by an ultrasound beam **642** from a transducer **644**.

[0300] In an exemplary embodiment of the invention, thermal damage is selectable a distance into wall **640** as measured from a lumen **646**, for example, zero is set at the boundary of wall **640** and lumen **646**. Optionally, thermal damage starts at about a distance "r**1**" and ends at about a distance "r**2**", wherein r**1** is greater than or equal to zero and r**2**>r**1**. In some embodiments, r**2** is greater than the thickness of wall **640**, for example, tissues outside of the blood vessel can be thermally damaged.

[0301] In an exemplary embodiment of the invention, the volume of thermal damage **648** is selectable, for example, the volume of thermal damage is an area of about "x**2**−x**1**" (e.g., measured along the cross section of the blood vessel) multiplied by about "y**2**−y**1**" (e.g., measured along the long axis of the blood vessel) multiplied by about "z**2**−z**1**" (e.g., measured parallel to the diameter of the blood vessel). Optionally, the volume of the thermal damage is associated with one or more factors, such as the size and/or area of an acoustic element of transducer **644**, the tissues in the wall (e.g., the tissues from the intima to the target tissue, as well as the target tissue), and/or the interaction between the tissues and the ultrasonic energy (e.g., attenuation).

[0302] In an exemplary embodiment of the invention, the location of thermal damage **648** is selectable. Optionally, an

angular location **660** of thermal damage is selectable, for example, in the range of 0-360 degrees, as determined by an arbitrary reference such as on a fluoroscopic image. Alternatively or additionally, a longitudinal location **652** in the artery is selectable, for example, measured in centimeters, as determined by an arbitrary reference such as distance from an arterial branch. Optionally, angle **660** and/or longitudinal location **652** are selected according to the position of transducer **644**, for example, rotating transducer and/or longitudinal positioning of transducer **644**. Optionally or additionally, the extent of the thermal effect and/or thermal damage is selectable.

[0303] In an exemplary embodiment of the invention, a damage axis (e.g., the volume of thermal damage) is aligned with the tissue axis. For example, to cause a clinical effect in elongated nerves such as by thermally damaging them, it is sufficient to treat a section of the nerve as opposed to the entire nerve.

Partial Denervation

[0304] In some embodiments of the invention, only partial denervation is desired, for example, it may be desired to reduce the function of the nerves by, for example, 20%, 30%, 50%, 80%, 90% or intermediate or larger amounts. In an exemplary embodiment of the invention, the function of the nerves is measured by the effect on the target tissue controlled by the nerves and/or providing signals to the nerves, rather than by the nerves ability to transmit signals.

[0305] In an exemplary embodiment of the invention, it is desirable to maintain some of the natural feedback controls over blood pressure and/or other biological functions, provided by the nerve (e.g., as part of a biological system), albeit, at an attenuated level, for example, to compensate in part or in full and/or overcompensate for a diseased state caused by such feedback. It has, in fact, been found that even partial denervation which only causes a drop of Renal Norepinephrine spillover to about 50% from baseline (e.g., in a diseased patient), still provides a significant drop in blood pressure.

[0306] In greater detail. In the kidney, Norepinephrine (NE) is stored only in the renal sympathetic nerve terminals from where it is released in relation to increases in renal sympathetic nerve activity (renal Norepinephrine spillover (NESO)). Thus, it is reasonable to assume that if renal tissue NE content is decreased, then there is less NE in the renal sympathetic nerve terminals available for release and that renal NESO will be decreased somewhat in proportion to the decrease in renal tissue NE content. Thus, in this way, a rough correlation is to be expected between the renal tissue NE content and renal NESO. It is noted that this relationship is not a precise and/or necessarily a linear relationship.

[0307] In organ physiology, the assumption is made that if a control mechanism exists, then it is meant to fulfill a vital function, even if it is redundant to other control systems. Thus, the efferent renal nerves are involved in controlling certain renal functions (GFR, RBF, sodium handling, renin release, etc.). Activation of these mechanisms in times of volume depletion (hemorrhage, etc.) can be of value in preserving integrity of body fluid volumes and cardiovascular integrity. The afferent renal nerves sense pain (e.g., due to kidney stone) as well as provide other reflex inputs to the central nervous system that influence systemic sympathetic outflow to the periphery. While it believed that efferent renal nerves grow back and that afferent renal nerves do not grow back, the consequences of total (afferent and efferent) renal denervation over a long time future is not clear and it may be desirable to avoid.

[0308] In an exemplary embodiment of the invention, selecting the treatment parameters includes deciding on a desired degree of denervation and/or desired change in NE, for example, a change over time, for example, a change at one day (from denervation), 10 days, 30 days, 90 days and/or intermediate and/or longer times and/or at a plurality of times. Optionally, after a period of time, for example, 1 month or several months, a partial denervation may be repeated (e.g., at one or both kidneys), for example, to achieve a desired results shown by the NE levels (or a marker thereof) not to have been achieved.

Decide Safety Considerations

[0309] In an exemplary embodiment of the invention, a margin of safety is selectable.

[0310] In an exemplary embodiment of the invention, the extent of thermal damage to tissues (e.g., normal and/or healthy) surrounding a target tissue **650** (e.g., nerve) is selectable. Optionally, volume of thermal damage **648** is approximately a volume of target tissue **650**. Alternatively, volume of thermal damage **648** is relatively larger than the volume of target tissue **650**.

[0311] In an exemplary embodiment of the invention, the volume of normal tissue thermally treated (e.g., in volume of thermal damage **648**) surrounding target tissue **650** is selectable, for example, as a margin of safety. A potential advantage is a trade-off between certainty of thermally damaging target tissue **650** and damaging nearby tissue (e.g., healthy and/or normal).

[0312] In an exemplary embodiment of the invention, side effects as a result of treatment are selectively reduced and/or prevented by proper selection of treatment parameters. For example, one or more scarring, shrinking and/or spasm of the blood vessel may be reduced such as by a treatment profile that maintains a temperature sufficiently low to achieve a thermal effect while avoiding side effects (e.g., 55 degrees Celsius) and/or for a time period sufficiently long to achieve the thermal effect while avoiding side effects.

Estimate Blood Flow

[0313] In an exemplary embodiment of the invention, the rate of blood flow is measured and/or estimated, for example, using one or more methods including, a look-up table of estimated blood flow rates in blood vessels, Doppler, flow sensor, temperature measurement downstream of the transducer (e.g., measuring temperature to estimate if blood flow is sufficient). Optionally, the rate of blood flow as a function of time is controlled, for example, by inflating and/or deflating a balloon upstream from the transducer. Alternatively or additionally, a liquid (e.g., saline, radio-opaque dye) is injected to create flow.

[0314] In some embodiments of the invention, the diameter of the catheter is selected according to the desired rate of blood flow. For example, a relatively smaller catheter is selected to provide for relatively greater blood flow, such as a relatively faster rate of blood flow. For example, a relatively larger catheter is selected to provide for relatively slower blood flow. Non-limiting examples of diameters include; 1 mm, 2 mm, 3 mm, 4 mm, 5 mm, or other smaller, intermediate or larger values are used. Optionally, the diameter of the

catheter is selected relative to the diameter of the blood vessel, for example, about 20%, 30%, 40%, 50%, 75% of the vessel diameter, or other smaller, intermediate or larger values are used.

[0315] FIG. **7**A illustrates an exemplary of a simplified estimate of the association between a flow of blood and the location of an area of thermal damage.

[0316] The upper part of FIG. **7**A shows an ultrasound transducer **706** emitting ultrasound energy **708** at a target tissue **712**. Energy **708** travels across a lumen **730** (e.g., of a blood vessel) into a blood vessel wall **710**. Energy **708** causes an area of thermal damage **704**. Blood flows **702** inside lumen **730**.

[0317] Without being bound to theory, the lower part of FIG. **7**A illustrates an exemplary association between blood flow **702** and the resulting area of thermal damage **704**. Thermal damage **704** is hypothesized to occur when the temperature of a tissue reaches 55 degrees Celsius or higher. The temperature in tissues of blood vessel wall **710** is a tradeoff between the tissues being heated by ultrasonic energy **708** (e.g., mechanical friction) and the tissues being cooled by flow of blood **702** (e.g., convection).

[0318] Curve **714** is an exemplary illustration of a simplified estimate of the effect of heating of wall **710** due to ultrasonic energy **708** absorption (e.g., attenuation) as a function of distance away from lumen **730**. As energy **708** travels through wall **710**, it is absorbed, resulting in tissue of wall **710** heating up. Without blood flow **702**, the tissues closest to lumen **730** heat up the most and the tissues furthest away heat up the least.

[0319] Curve **716** is an exemplary illustration of the cooling effect on wall **710** due to blood flow **702** as a function of distance away from lumen **730**. Tissues closest to lumen **730** are cooled relatively more by blood flow **702**, and tissues furthest away are cooled relatively less.

[0320] Without being bound to theory, if heat generated by ultrasonic energy **708** is removed sufficiently quickly by blood flow **702**, the tissues in wall **710** will not heat up enough to achieve a thermal effect. At the point where the heat due to energy **708** is not removed fast enough, the tissue can heat up to 55 degrees, potentially resulting in area of thermal damage **704**.

[0321] In an exemplary embodiment of the invention, blood flow **702** is taken into account to adjust parameters to treat target tissue **712** and/or to set area of thermal damage **704**, for example, by using a look-up table of correlated values and/or using a mathematical formula modeling (e.g., manually by a user, automatically by a software module). Optionally, the intensity profile of energy **708** (e.g., time of treatment, intensity of energy emitted) is selected according to target tissue **712** and/or area of thermal damage **704**. Alternatively or additionally, the frequency of ultrasonic energy **708** is selected.

[0322] FIG. **7**B is an exemplary graph illustrating a simplified estimate of the effects of various tissues absorbing ultrasound energy in obtaining a desired thermal effect, useful in practicing some embodiments of the invention. In an exemplary embodiment of the invention, selecting target tissue for treatment is associated with the ability of the target tissue and/or tissues between the transducer and the target tissues in attenuating ultrasonic energy.

[0323] The table below illustrates the ability of different types of tissues to absorb (e.g., attenuate) ultrasound energy. Tissues having relatively higher coefficients of attenuation, heat relatively more.

[0324] In an exemplary embodiment of the invention, the relatively values as shown in the table are used to prepare a treatment plan to selectively target tissues. For example, to selectively target connective tissue (α=1.57) surrounding muscle (α=1.09), the treatment plan can consist of bursts of ultrasonic energy separated by gaps without energy transmission. During the bursts, the ultrasonic energy will be attenuated relatively more by the connective tissue resulting in a relatively higher temperature. During the gaps, the ultrasonic energy will be dispersed relatively more quickly by the muscle. The net result of the treatment pattern is that connective tissues will be heated to a thermal effect, while the muscle will not achieve a temperature high enough to be thermally affected.

Material	α(dB/(MHz · cm))
Blood	0.2
Fat	0.48
Liver	0.5
Cardiac	0.52
Brain	0.6
Breast	0.75
Muscle	1.09
Connective tissue	1.57
Tendon	4.7
Bone, cortical	6.9

[0325] The top part of FIG. **7**B illustrates transducer **706** emitting ultrasonic energy **708** into arterial wall **710**. The bottom part of FIG. **7**B illustrates relative energy **708** absorption by different tissues.

[0326] Starting from lumen **730**, the layers of wall **710** can be categorized as intima **718**, media **720** and adventitia **722**. As intima **718** is a single layer of endothelial cells, energy **708** absorption can be assumed to be negligible. Media **720** is primarily muscle, having a relatively low level of absorption. Adventitia is primarily connective tissue, having a relatively higher level of absorption. The attenuation of acoustic energy is inversely related to frequency, for example, a relatively higher frequency results in relatively higher attenuation. In an exemplary embodiment of the invention, an area of thermal damage is associated with relatively higher levels of energy **708** absorption by adventitia **722**.

[0327] In an exemplary embodiment of the invention, the relative attenuation of energy **708** by tissues is taken into account when deciding on treatment parameters for the target tissue. In some embodiments, the target tissue is nerve **724**. Nerve **724** is primarily connective tissue, having a relatively higher US attenuation coefficient. In some embodiments, nerve **724** is selectively targeted for thermal damage.

[0328] In some cases, nerve **724** is surrounded by a layer of fat **726**. Fat **726** has a relatively lower level of absorption (e.g., attenuation of the acoustic energy) and relatively low level of thermal conductivity (e.g., doesn't transfer the thermal energy). Inventors hypothesize that fat **726** acts as a thermal insulator for nerve **724**, trapping the US energy absorbed by nerve **724** (e.g., heat), as the heat dissipation outside fat ring **726** is relatively higher (e.g., relatively lower attenuation coefficient), the outside tissues do not heat up as much. In an

exemplary embodiment of the invention, nerve **724** surrounded by fat **726** is selectively targeted for thermal damage. In an exemplary embodiment of the invention, energy **708** causes temperature in nerve **724** surrounded by fat **726** to exceed a threshold, resulting in thermal damage **728** to nerve **724**, while tissues surrounding fat **726** are not thermally affected (e.g., damaged).

[0329] FIG. **7**C is an exemplary graph illustrating a simplified estimate of the effect of the ability of heat removal in obtaining a desired thermal effect, useful in practicing some embodiments of the invention. In an exemplary embodiment of the invention, selecting target tissue for thermal damage is associated with the capacity of heat removal from the target tissues and/or surrounding tissues.

[0330] In an exemplary embodiment of the invention, heat removal from tissues in wall **710** occurs from lumen **730**. Optionally, the rate of heat removal is variable. Alternatively or additionally, the rate of heat removal is controllable.

[0331] In an exemplary embodiment of the invention, heat removal is accomplished by a flow of blood in the lumen. Without being bound to theory, a higher flow of blood results in a higher rate of heat removal. Optionally, the flow of blood in the lumen is selectable and/or controllable, for example, by one or more methods such as, cardiac pacing (e.g., artificially controlling the heart rate), inflating a balloon inside the artery, and/or operating an obstructing structure on the catheter, to at least partially block the flow of blood and/or to direct the flow to the target artery wall.

[0332] In an exemplary embodiment of the invention, heat removal is associated with the temperature of the blood in the lumen. Without being bound to theory, a lower blood temperature results in a higher rate of heat removal. Optionally, the temperature of blood is selectable and/or controllable, for example, by injection of a relatively cold liquid upstream from the treatment area (e.g. saline, radio-opaque dye, patient's own blood that has been cooled).

[0333] For illustrative purposes, FIG. **7**C shows a relatively slow heat removal **740** and a relatively fast heat removal **742** in lumen **730**. In some embodiments, slow heat removal **740** results in a thermal damage area **744** that is relatively closer to lumen **730**. In some embodiments, fast heat removal **742** results in a thermal damage area **746** that is relatively further away from lumen **730**.

[0334] Without being bound to theory, the bottom part of FIG. **7**C shows that for the same ultrasound attenuation curve **714** (e.g. ultrasound energy **708** produced by transducer **706**), a slow removal curve **748** causes thermal damage area **744** relatively closer to lumen **730** as compared with a fast removal curve **750** that causes thermal damage area **746** relatively further from lumen **730**.

Adjusting Tissue Properties

[0335] In some embodiments of the invention, one or more tissue parameters are adjusted. Optionally, the tissue is adjusted (which affects the tissue parameters) in accordance with one or more treatment parameters, for example, the selected safety profile and/or selected amount of thermal effect. Optionally, parameters are adjusted relatively higher or relatively lower.

[0336] In an exemplary embodiment of the invention, adjustment is provided by the controller, optionally using the catheter, for example, to deliver an electrical current or a drug to the artery and/or to the heart and/or other tissue, such as tissue near the artery. Alternatively a separate application device is provided. In an exemplary embodiment of the invention, the adjustment is automatic. Alternatively, the adjustment is in response to a manual control. Optionally, the adjustment is semi automatic, with the controller, for example, modifying the adjustment means to maintain a user-indicated result, such as vessel diameter. In an exemplary embodiment of the invention, the treatment is modified (e.g., automatically, by the controller) in realtime to match the modification and/or so it is applied when the blood vessel properties are within a given window (e.g., timed to thickness changes associated with the pulse wave), even if no intentional adjustments is applied.

[0337] FIGS. **7**D and **7**E illustrate non-limiting examples of adjustments of tissue parameters, in accordance with some embodiments of the invention. FIG. **7**D illustrates a relative decrease in tissue parameters; temperature, thickness of vessel wall, diameter of blood vessel, rate of blood flow. FIG. **7**E illustrates a relative increase in tissue parameters; temperature, thickness of vessel wall, diameter of blood vessel, rate of blood flow. Catheter **1222** having ultrasonic emission element **300** is located inside blood vessel **1242**. Ultrasound is used to treat target tissue **1216** surrounded by tissue **1304**. Blood **1302** is flowing through vessel **1342**.

[0338] In some embodiments of the invention, the temperatures of one or more of blood **1302**, surrounding tissue **1304** and/or target tissue **1216** are adjusted, for example, to one or more different temperatures. Optionally, the temperature of one or more tissues is relatively increased (shown as T**1**), for example, by 0.2 degrees Celsius, or 0.5 or 1 or 2 or 5 or 10 degrees Celsius above body temperature, or other smaller, intermediate or larger values are used. Alternatively or additionally the temperature of one or more tissues is relatively reduced (shown as T**2**), for example, by 0.2 degrees, Celsius, or 0.5 or 1 or 2 or 5 or 10 or 20 or 30 or 35 degrees Celsius below body temperature or other smaller, intermediate or larger values are used. Non-limiting options of adjusting the temperature include: inserting the patient and/or region of the body into a solution of relatively cooler or relatively hotter liquid, blowing cold or hot gas (e.g., room air) on the patient, infusing relatively cold or relatively hot liquid (e.g., saline) into the patient. Exemplary reasons for changing the temperature of tissues will be described below.

[0339] In some embodiments of the invention, the thickness of the arterial wall is adjusted. Optionally, the arterial wall is maintained and/or expanded (if in a contracted state). Optionally or alternatively, the arterial wall is contracted, for example, by about 10%, about 20%, about 30%, or other smaller, intermediate or larger values. The rate of evacuation of heat from surrounding tissues **1304** and/or target tissue **1216** can be related to contraction and/or expansion of the arterial wall. For example, expanding and/or relaxing the arterial wall can cause a dilation of the vasa vasorum, thereby increasing blood flow and the evacuation of heat. For example, contraction of the arterial wall can cause contraction of the vasa vasorum, thereby decreasing blood flow and the evacuation of heat.

[0340] In some embodiments, the entire circumference of the vessel is adjusted. Alternatively, an arc of the circumference of the vessel is adjusted, for example, about 10, 15, 30, 45, 60, 90 degrees, or other smaller, intermediate or larger values are adjusted. One part (e.g., arc) of the vessel around the circumference is adjusted, for example, 2, 3, 4 or other

smaller, intermediate or larger numbers of areas around the circumference. Optionally, the adjusted areas correspond to the treatment areas.

[0341] In some embodiments, a portion of the blood vessel length is adjusted. For example, about 5 mm, about 10 mm, about 20 mm, about 30 mm, about 50 mm, about 100 mm, or other smaller, intermediate or larger values are used. Alternatively, areas substantially larger than the blood vessel itself are affected, for example, an organ, a limb, the entire body, the entire vasculature.

[0342] In some embodiments, the volume of the adjusted tissue corresponds to the selected volume of the desired thermal effect. Optionally, the target tissue is within the adjusted tissue. For example, the volume of adjusted tissue is about 100%, 150%, 200%, 500%, 1000%, 10000% of the volume of the desired thermal effect, or other smaller, intermediate or larger values are used.

[0343] In some embodiments of the invention, the rate of evacuation of heat from one or more of blood **1302**, surrounding tissues **1304** and/or target tissue **1216** are adjusted, for example, by varying amounts. Optionally, the rate of evacuation of heat is relatively increased. Alternatively or additionally, the rate of evacuation of heat is relatively decreased.

[0344] In some embodiments of the invention, flow of blood **1302** through vessel **1242** is adjusted. Optionally, a relatively higher rate of blood flow **1302** (shown as long arrows) relatively increases the rate of heat removal. Optionally or additionally, a relatively lower rate of blood flow **1302** (shown as short arrows) relatively reduces the rate of heat removal. The effect of heat removal, such as on the area of thermal damage, has been described with reference to FIGS. **7**A-**7**C.

[0345] Non-limiting examples of methods to adjust the rate of blood flow **1302** include:

[0346] Increasing or decreasing the cardiac output, for example, by artificially pacing the heart (e.g., external pacemaker) to a relatively higher or relatively lower rate, for example, to 120, 150, 180, 200 beats per minute or other smaller, intermediate or larger values.

[0347] Dilating blood vessel **1242** (shown as d**1**), such as by administration (e.g., into the vasculature) of vasodilatory agents such as nitrates (e.g., nitroglycerin) and/or agents to relax the muscles of arterial wall **1242**, such as muscle paralyzing agents such as botulinum (blocks release of acetylcholine). Agents can be delivered locally and/or systemically. Electricity can also be applied in a pattern and/or settings (e.g., long DC signal) that relaxes the arterial wall.

[0348] Constricting blood vessel **1242** (shown as d**2**), such as by administration of vasoconstricting agents such as alpha-1 agonists (e.g., phenylephrine), by applying an electrical current to cause muscle contraction in arterial wall **1242**, and/or by mechanically agitating tissues (e.g., traumatizing) to cause constriction.

[0349] In some embodiments of the invention, the absorption to applied ultrasound energy of one or more of blood **1302**, surrounding tissues **1304** and/or target tissue **1216** are adjusted, for example, by varying amounts. Optionally, the absorption is relatively increased (shown as TR). A non-limiting example of relatively increasing the absorption to ultrasound is by injecting a material that absorbs ultrasound energy to a relatively higher degree, such as microbubbles.

[0350] In some embodiments of the invention, tissue properties are adjusted in accordance with the selected safety parameters, for example, to relatively increase the margin of safety. Optionally, the rate of heat removal from surrounding tissues **1304** is relatively increased, for example, as described herein. Alternatively or additionally, the temperature of tissues **1304** is relatively reduced, for example, as described herein. A potential advantage of increasing the rate of heat removal and/or reducing the temperature is reducing thermal damage to surrounding tissues **1304**, for example, as described with reference to FIGS. **7**A-**7**C.

[0351] In some embodiments of the invention, tissue properties are adjusted in accordance with the selected thermal damage profile, for example, to relatively increase the area of thermal damage. Optionally, the ability of surrounding tissues **1304** to absorb ultrasound energy is relatively increased, for example, as described herein. Alternatively or additionally, the temperature of tissues **1304** is relatively increased. A potential advantage of increasing the temperature and/or acoustic absorption is increasing the thermal effect of the applied ultrasonic energy, for example, as described with reference to FIGS. **7**A-**7**C and/or FIG. **9**. For example, if the tissue temperature is increased and/or the rate of heat removal is decreased, the thermal effects resulting from an amount of acoustic energy can be relatively increased.

Selecting parameters—example of choosing catheter (Frequency) According to Treatment

[0352] FIG. **8** is an exemplary illustration of a simplified estimate of the effect of frequency of ultrasound energy on an area of thermal damage, in accordance with an exemplary embodiment of the invention.

[0353] The top part of FIG. **8** illustrates an ultrasound transducer **806** emitting ultrasound energy towards an arterial wall **812**. Non-limiting examples of the ultrasound energy include 20 Mhz ultrasound energy **808** and/or 10 Mhz ultrasound energy **810**.

[0354] The bottom part of FIG. **8** illustrates the attenuation of energy **808** and/or **810** by the tissues of wall **812**. As illustrated by the table in the section "ESTIMATE BLOOD FLOW", attenuation of ultrasound energy by tissue is inversely proportional to frequency. An exemplary attenuation graph for 20 Mhz **816** shows relatively higher attenuation relatively closer to a lumen **818**. In some embodiments, an area of thermal damage **802** is relatively closer to lumen **818**. An exemplary attenuation graph for 10 Mhz **814** shows relatively lower attenuation as a function of distance from lumen **818**. In some embodiments, an area of thermal damage **810** is relatively further from lumen **810**.

[0355] In an exemplary embodiment of the invention, the frequency of ultrasound energy used for selectively targeting tissue is selected according to the treatment plan. For example, target tissue relatively further from the lumen and/or from the intima layer is selectively treated by using a relatively lower frequency of ultrasound energy.

[0356] In an exemplary embodiment of the invention, the frequency of the ultrasound energy used for treatment is selected, for example to be about 5 Mhz, about 8 Mhz, about 10 Mhz, about 15 Mhz, about 8 Mhz-15 Mhz, about 20 Mhz, about 10 Mhz-20 Mhz, about 30 Mhz, or other smaller, intermediate or larger frequencies. IN some cases, et frequncy will be substantially narrow band, for example, les sthan 30%, 20%, 10%, 5% of the application frequency. Optionally or alternatively, a wide band or multi frequency signal is used, for example, with 2, 3, 4, 5 or more discrete frequencies and/or with a range of, for example, 1 Mhz, 3 Mhz, 5 Mhz or smaller or intermediate widths.

[0357] In an exemplary embodiment of the invention, for example for renal denervation, a lower frequency may be used to achieve a higher reduction in norepinephrine levels.

[0358] In an exemplary embodiment of the invention, the signal parameters are selected according to a desired functional effect, in addition to or instead of according to a desired structural effect (e.g., tissue ablation).

[0359] In an exemplary embodiment of the invention, a catheter is selected according to the frequency of the selected ultrasound energy. Optionally, the acoustic element on the transducer is designed to vibrate at the treatment frequency. For example, the thickness of the acoustic element is related to the expected frequency of vibration of element, optionally linearly related, for example, a thickness of 100 micrometers for a frequency of 20 Mhz, a thickness of 200 micrometers for a frequency of 10 Mhz.

Selecting Parameters—Choosing an Ultrasonic Intensity Profile According to Treatment

[0360] FIG. **9** is an exemplary illustration of a simplified estimate of the association between an ultrasonic intensity profile and thermally damaged areas, useful in practicing some embodiments of the invention.

[0361] In an exemplary embodiment of the invention, the ultrasonic intensity profile for treatment is selected. Optionally, the ultrasonic intensity profile is related to the ultrasonic intensity emitted by the acoustic element (e.g., in watts per square centimeter) over time (e.g., in seconds), for example, relatively longer times relatively increase the ultrasonic intensity profile, for example, relatively higher acoustic intensities relatively increase the ultrasound intensity profile. Optionally or additionally, the ultrasonic profile is selected to vary over time. In some embodiments, the ultrasonic profile is associated with the total amount of ultrasonic energy delivered to the tissues. In some embodiments, the profile is substantially a temporal square wave. Optionally or alternatively, the profile is substantially a spatial square wave (e.g., sharp cut-offs at the edges of the beam), in one or two dimensions.

[0362] FIG. **9** shows an ultrasound transducer **902**, emitting ultrasonic energy at various intensity profiles, for example, a relatively low intensity profile **904**, a relatively medium intensity profile **906** and/or a relatively high intensity profile **908**.

[0363] In some embodiments, the area of thermal damage begins relatively far from an intima **916**, for example, at a peri-adventitia **918**. In some embodiments, the area of thermal damage increases towards the intima with relatively increased ultrasonic intensity profiles.

[0364] In an exemplary embodiment of the invention, tissues relatively closer to the blood cool relatively faster. In an exemplary embodiment of the invention, a treatment plan comprising of a series of pulses with a delay between the pulses will have a greater cumulative effect away from the wall. In an exemplary embodiment of the intervention, a treatment plan of pulses with delays causes a thermal effect to tissues relatively further away from the wall, without causing a thermal effect to tissues relatively closer to the wall.

[0365] In an exemplary embodiment of the invention, the extent of thermal damage is settable according to the ultrasound intensity profile, such as **904**, **906** and/or **908**. For example, thermal damage is localized to target tissue **910** (e.g., no damage to surrounding tissue). For example, an area of thermal damage **912** extends somewhat beyond target tissue **910**. For example, a relatively large area of thermal damage **914** extends a relatively larger area beyond target tissue **910**.

[0366] In an exemplary embodiment of the invention, the extent of thermal damage is selected to not reach intima **916**.

Insert Catheter

[0367] In an exemplary embodiment of the invention, catheter **1222** (e.g., as shown in FIG. **5**) in inserted into the body of a patient. Standard vascular access methods can be used, for example, from the femoral artery. Optionally, catheter **1222** is threaded using a guidewire **1202** (e.g., over the wire, rapid exchange, "buddy" wire) to the target treatment site (e.g., an artery such as the iliac, renal, carotid, aorta) under image guidance, such as fluoroscopy. Alternatively or additionally, catheter **1222** is directed inside a guiding sheath, for example to protect the ultrasound transducer from mechanical damage during delivery to the target site. Alternatively or additionally, catheter **1222** is directed inside a guiding catheter.

[0368] In an exemplary embodiment of the invention, catheter **1222** is guided during delivery using imaging, for example fluoroscopic image.

[0369] Referring back to FIG. **5**, in an exemplary embodiment of the invention, element **102** on catheter **1222** is prevented from contacting vessel wall **1226**, for example, by using separation device **1204**. Details about separation device are provided with reference to attorney docket number 50824, incorporated herein by reference in its entirety. Optionally, element **102** contacts wall **1226** if treatment parameters are set and/or adjusted accordingly, for example, if element **102** is sufficiently cooled and/or if the intensity profile is reduced.

[0370] In an exemplary embodiment of the invention, distance **1218** (between element **102** and wall **1226**) does not have to be taken into account for setting treatment parameters. Optionally distance **1218** varies during treatment. In some embodiments, the attenuation of ultrasonic beam **1228** by blood flow **1220** is relatively insignificant.

[0371] A potential advantage of preventing contact between element **102** and wall **1226** is reducing or preventing thermal damage to the endothelium, basal membrane and/or internal elastic lamina.

[0372] In some embodiments of the invention, catheter **1222** includes one or more elements to move transducer **300**. Optionally, the element is a piezoelectric element that can be vibrated by applying electrical power. Alternatively or additionally, the element moves transducer **300** for relatively fine positioning, for example, an electrically controlled motor. In some embodiments, the element vibrates and/or moves transducer **300** to position the strongest part of the ultrasound beam at the target tissue.

[0373] In some embodiments the controller can be calibrated according to the expected intensity profile of the produced ultrasound beam, for example, the controller vibrates and/or moves transducer **300** in order to obtain a desired position for thermally affecting the tissues.

Treat

[0374] FIG. **10** is a flow chart of monitoring during treatment, in accordance with an exemplary embodiment of the invention. In some embodiments, monitoring is a type of feedback associated with the parameters affecting treatment.

[0375] At **1002**, the target tissue is treated. The ultrasound transducer emits ultrasound energy towards the target tissue at the selected acoustic intensity profile and/or at the selected frequency.

[0376] In an exemplary embodiment of the invention, the target tissue can be treated according to the selected treatment plan (e.g., acoustic intensity profile, frequency) without requiring monitoring and/or feedback.

[0377] Optionally, at **1004**, monitoring of the treatment is performed.

[0378] In some embodiments of the invention, monitoring occurs at the same time as treatment is occurring (e.g., in parallel with the treatment). Alternatively or additionally, treatment (e.g., transmission of ultrasonic energy) occurs in pulses separated by a delay, with the monitoring occurring during the delay. Optionally, monitoring is carried out continuously during the entire treatment.

[0379] Optionally, at **1006**, the environment surrounding the treatment procedure is monitored. In some embodiments, changes in environmental conditions affect the treatment if the treatment parameters remain unchanged. For example, if blood flow is increased without changing the treatment parameters, the treatment may not be effective due to the increased rate of cooling. In some embodiments, changes in environmental conditions are taken into account when adjusting treatment parameters, for example, if an increase in blood flow is detected, the intensity profile is increased accordingly to achieve the desired effect in the selected tissues.

[0380] In some embodiments, the temperature of the blood flow is monitored, for example, by a sensor placed downstream from the transducer.

[0381] Optionally, at **1008**, the integrity of the transducer is monitored. In some embodiments, changes in the integrity suggest one or more causes such as blood clots on the transducer, overheating of the transducer, mechanical damage. In some embodiments, changes in the integrity of the transducer are monitored to prevent adverse events. Optionally, the treatment parameters are adjusted according to the integrity. For example, if the transducer comes closer to the wall or contacts the wall, potentially the intima can overheat, resulting in thermal damage to the intima if the treatment parameters are not adjusted accordingly (e.g., increased cooling, reducing the intensity profile).

[0382] In some embodiments, the integrity of the transducer is monitored by measuring changes in the impedance, for example, a change greater than 3%, 5%, 10%, 20%, or other smaller, intermediate or larger percent changes.

[0383] In some embodiments, the integrity of the transducer is monitored by measuring the distance from the transducer to the arterial wall (e.g. to the intima). Optionally, the distance is measured by a returning echo. Alternatively or additionally, the distance is measured on x-ray images.

Feedback

[0384] In some embodiments of the invention, acoustic energy is applied to the target tissue in an open loop manner. For example, the target is set and the target is met, without using feedback. Alternatively, acoustic energy is applied to the target tissue in a closed loop manner, such as with feedback.

[0385] In some embodiments, feedback is a measure of the physical effect of the treatment on the tissue. Optionally or alternatively, feedback is a functional measurement. In some embodiments, feedback is provided on the transmission of the energy and/or parameters of the emitter and/or catheter (e.g., distance), in addition to or instead of on the target tissue. While, in an exemplary embodiment of the invention, feedback is during the procedure, possibly during a single application of energy (e.g., within less than 30 seconds), in some embodiments, feedback is on longer time scales, such as 1-3 minutes (e.g., between applications and/or after a set of applications is provided) or days or more.

[0386] FIG. **11** is a flow chart showing optional functional feedback associated with treatment, in accordance with an exemplary embodiment of the invention.

[0387] Optionally, at **1102** feedback is obtained about the results of the treatment.

[0388] Optionally, at **1104**, functional feedback is obtained about the effect of treatment on tissues. Optionally, imaging is performed of the target tissue to detect and/or estimate the extent of therapy. Alternatively or additionally, imaging is performed of the surrounding tissue to detect and/or estimate the extent of damage (e.g., margin of safety). In some embodiments, some changes (e.g., due to denaturation of collagen) are detected as they happen. In some embodiments, some changes are detected after a period of time (e.g., several days), for example, anatomical changes secondary to the inflammatory response, such as fibrosis.

[0389] In some embodiments, imaging is performed by the using the same ultrasound transducer used for treatment, for example, by treating at a first treatment frequency for a period of time, then imaging at a second diagnostic frequency for another period of time (e.g., analyzing the ultrasonic echoes returning from the tissues). Alternatively or additionally, the same ultrasound transducer is used, but with different electrodes which separate the transducer into an imaging region and a treatment region. Alternatively or additionally, one or more acoustic elements are used, for example, one element for imaging and one element for treatment.

[0390] In some embodiments, one or more other imaging modalities are used instead or in addition to the element, such as CT, MRI, x-ray.

[0391] One or more non-limiting examples of ultrasound imaging methods for feedback include,

[0392] Measuring the ultrasonic attenuation of the target tissues, for example, as described by Damianou et al, J Acoust Soc Am. 1997 July; 102(1):628-34, incorporated herein by reference in its entirety. Damianou found that the rate at which the thermal dose was applied was associated with the total attenuation absorption, for example, relatively lower thermal dose rates resulted in relatively larger attenuation coefficients. In some embodiments, the intensity profile that is applied to the target tissues is estimated by measuring the attenuation coefficient and/or the absorption. Optionally, the measurements are compared to expected values according to the set intensity profile. Optionally or additionally, the intensity profile is adjusted relatively higher or relatively lower according to the comparison, for example, to achieve the resulting thermal damage to the target tissue.

[0393] Measuring the ultrasound attenuation coefficient and/or backscatter power for example, as described by Worthington, A. E., et al, Ultrasound in Med. & Biol., Vol. 28, No. 10, pp. 1311-1318, 2002, incorporated herein by reference in its entirety. Worthington found that the attenuation coefficient and/or backscatter power increased with relatively higher temperatures. In some embodiments, the temperature of the target tissues is estimated according to the attenuation coefficient and/or backscatter power. Optionally, the temperature

of the tissue is compared to the temperature range and/or threshold required to achieve a desirable effect in the tissues (e.g., collagen denaturation above 55 degrees Celsius). Optionally or additionally, the intensity profile is adjusted relatively higher or relatively lower according to the comparison, for example, to achieve the target temperature in the target tissue.

[0394] Optionally, at **1106**, feedback consists of clinical effects, for example, desired clinical effects, adverse clinical effects, lack of clinical effects.

[0395] In some embodiments, clinical measurements are used as feedback. For example, the results of renal denervation to treat persistent hypertension can be measured by one or more of, blood pressure, norepinephrine spillover, norepinephrine levels, renal artery blood flow.

[0396] In some embodiments of the invention, the distance from the acoustic element to the arterial wall is measured, optionally continuously measured. Optionally, the distance is measured using the acoustic element itself, for example, as described in co-filed PCT applications attorney docket numbers 52345 and/or 52342, incorporated herein entirely by reference. In some embodiments, the distance is used as feedback to prevent high power operation of the acoustic element while touching the arterial wall, for example, if the distance is measured to be zero (e.g., contact) or relatively close to contact (e.g., 0.1 mm, 0.3 mm or other smaller, intermediate or larger distances), the power to the transducer can be reduced and/or shut off. A potential advantage of measuring the distance using the element is a relatively more accurate measurement of the distance as compared with measuring the distance from angiographic images.

Adjust

[0397] In some embodiments of the invention, monitoring of the treatment and/or feedback of the treatment can increase the level of control of the treatment (e.g., in real time, overall effect over several treatment sessions). Optionally, desired clinical results are achieved by the treatment.

[0398] In some embodiments, data from feedback and/or monitoring is used to adjust treatment parameters (e.g., frequency, ultrasonic intensity profile), for example, by a look-up table (e.g., stored in a memory), calculations, trial and error (e.g., slowly changing a parameter and/or monitoring changes). Optionally, parameters are adjusted manually (e.g., by a user) using an interface coupled to a controller. Alternatively or additionally, parameters are automatically adjusted, such as by a software module of controller.

[0399] One or more non-limiting examples of adjustments include, increasing the treatment, reducing the treatment, stopping the treatment.

[0400] A non-limiting example to illustrate the concept of adjusting variables according to measurements is provided:

[0401] A patient with resistant essential hypertension was proposed treatment by a renal denervation procedure. A renal nerve surrounded by fat located about 4 mm away from the renal vessel wall in the peri-adventitia was targeted for thermal effect. A catheter designed for a frequency of 10 Mhz was selected (e.g., due to the relative distance away from the wall) and an initial intensity of 30 watt/cm^2 was selected based on standard blood flow rates expected (e.g., according to a look-up table of patient profiles). The catheter was inserted into the renal artery. A pulse of duration 1 second was used to initially treat the vessel wall for calibration purposes. Imaging results indicated that the area of thermal effect was located 15 degrees clockwise, and 5 mm away from the wall. Based on the results, the catheter was manually rotated 15 degrees towards the target. Treatment started again, using a pulse of 30 seconds duration. About 5 seconds into treatment, the cardiac output of the patient suddenly increased, causing a 50% increase in the rate of blood flow through the renal artery. The controller automatically increased the intensity profile to 40 watt/cm^2 to offset the increased cooling rate of the tissue wall by the blood. Another calibration pulse of 1 second was applied. Imaging indicated that the nerve was being thermally damaged. Treatment was stopped after 22 seconds, once imaging results indicated that the nerve was fully damaged, along with a tissue margin around the nerve of at least 0.5 mm. The patient was followed in clinic for several weeks to verify the expected treatment effect of a reduction in blood pressure.

[0402] In some embodiments of the invention, treatment is synchronized (e.g., at a same time or otherwise timed thereto, such as at a delay after or before) to the adjustments, for example, as will be described at the end of the section "EXEMPLARY DEVELOPMENT OF AN EQUATION—Part B"

Examplary Treatment Protocols

[0403] The table below describes some possible treatment protocols, in accordance with some embodiments of the invention. Optionally, the 'Thermal Effect Location' and/or related 'Information" is determined by imaging, for example, as described in the section "FEEDBACK". Optionally, action is taken, such as based on the "Information", for example, by the 'Cardiologist' and/or by the 'System' (for example, the controller, such as using software stored thereon containing the 'algorithm'). Details related to 'Action' can be found for example in the section "ADJUST".

Table of Some Possible Treatment Protocols

[0404]

Thermal effect location	Criteria	Subject	Information	Action: Cardiologist	Action: System/algorithm
Minimal distance of thermal effect from artery lumen	Minimal 1 mm	Thermal effect location during treatment	Thermal effect area/volume	Reduce energy-change treatment parameters or duration	If distance <1- system stops excitation If distance >10- system alerts- thermal effect is too far
Maximal distance of thermal effect from artery lumen	Maximal 15 mm	Thermal effect location during treatment	Thermal effect area/volume		If distance >15- system stops excitation

-continued

Thermal effect location	Criteria	Subject	Information	Action: Cardiologist	Action: System/algorithm
Rate of thermal effect formation		Thermal effect location during treatment	Rate of thermal effect formation	Reduce energy-change treatment parameters or duration	If (maximal – minimal distance) difference is higher than 2 mm/sec-system stops excitation
				Enable treatment	If (maximal – minimal distance) difference is lower than 2 mm/sec-system enables excitation
Location along the artery		Thermal effect location post treatment	Thermal effect width in artery length	Decision-Continue Adjust Sufficient	Up to 50% of artery length-system alert for cardiologist decision
Location in the artery circumference		Thermal effect location post treatment	Thermal effect width in artery circumference	Decision-Continue Adjust Sufficient	Up to 50% of artery circumference -system alert for cardiologist decision
Minimal distance of thermal effect from artery lumen	Minimal 1 mm	Thermal effect location post treatment	Thermal effect area/volume	Decision-Repeat Adjust Sufficient	If thermal effect is too close to lumen (<1 mm)-system suggests cardiologist to add extra anti-coagulation treatment
Maximal distance of thermal effect from artery lumen	Maximal 15 mm	Thermal effect location post treatment	Thermal effect area/volume		

[0405] The following table shows exemplary activities by the controller and/or operator in various conditions, in accordance with some embodiments of the invention, base on the distance between the ultrasound emitter and the wall. Such distance can be measured, for example, using an external system (e.g., angiography or ultrasound), by processing signals received by the emitter or by a separate ultrasonic element.

Distance (calculated/ measured)	Value (mm)	Subject	Criterion	Cardiologist	System/ algorithm
Distance measurement before treatment	<1.4	Catheter position before treatment	>1	* Change GC (guide catheter) position * Change US transducer angle * Change US transducer position along the artery	* System alert-short distance * System disables excitation until distance is changed according to criterion
	>1	Catheter position before treatment	>1	Enable excitation	Enable excitation
	>5	Catheter position before treatment	1 < x < 5	Too large distance: Confirm possible bifurcation or dislocation with contrast injection and angiography and move US transducer	System alert-bifurcation, change US transducer position
	1 > x > 1.3 Angle between US transducer and artery wall is larger than 10°	Catheter position before treatment	>1	Unreliable distance-Confirm US transducer angle with contrast injection and angiography: Change GC position	

-continued

Distance (calculated/ measured)	Value (mm)	Subject	Criterion	Cardiologist	System/ algorithm
	>1.3 Angle between US transducer and artery wall is larger than 10° (diagonal)	Catheter position before treatment	>1	Enable excitation	Enable excitation
Distance measurement during treatment	<1	Catheter position during treatment	>1	Change GC position and complete treatment	* System alerts- short distance * System stops excitation until distance is changed according to criterion
	0.7 < x < 1	Catheter position during treatment	>1	Consider to stop excitation and improve position before completing treatment	System alert- shortening distance
	1 < x < 5	Catheter position during treatment	>1	Enable excitation to end	Enable excitation to end
	Decreasing distance	Catheter position during treatment	>1	Possible blood vessel constriction due to treatment- consider stop and nitroglycerin infusion	System alert- decreased distance
	>5 Sudden movement	Catheter position during treatment	>1		System disabled
Vessel blood pulsation analysis	Repetitive changes- Maximal position to minimal position	Pulsation detection before treatment			Calculated blood pulsation: If normal, enable excitation
	No differences between Maximal position to minimal position	Pulsation detection before treatment		Possible no circulation: * Validate flow by contrast injection and angiography * If needed- infuse with nitroglycerin or cold saline	System alert- no pulsation, possible constriction
	distance >1 But no pulsation detection	Pulsation detection before treatment	>1	* Validate flow by contrast injection and angiography * If needed- infuse with nitroglycerin or cold saline	System alert- no pulsation, possible constriction
Distance measurement, rotate 180°, distance measurement	1^{st}- <1 2^{nd}- <1	Artery diameter evaluation		Possible constriction: * Confirm by contrast injection and angiography * If needed- inject nitroglycerin and treat	System alert- possible constriction: Disable excitation
Distance measurement in 4 angles (90°)- artery diameter calculation	<3	Artery diameter evaluation		* Check if US transducer is located in the correct artery- using contrast injection and angiography * Check for local constriction * Possible- Nitroglycerin injection	System alert- possible constriction: Disable excitation
	3 < x < 8	Artery diameter evaluation		Enable excitation	Enable excitation

[0406] In an exemplary embodiment of the invention, both kidneys (e.g., renal arteries, renal nerves) are treated. However, this need not be the case. For example, in a follow-up treatment, possibly only a single kidney is treated. Optionally or alternatively, if one kidney is known to be more diseased, that is treated more (e.g., this is a reason for providing a treatment which is asymmetrical between kidneys, this may be done for other reasons as well). Optionally or alternatively, different kidneys are treated a different amount. Optionally, one kidney is intentionally undertreated so as to allow increasing treatment thereof, at a later time.

Potential Advantages of Some Embodiments

[0407] Further details of the system described herein can be found in the related applications. For example, "ULTRASOUND EMISSION ELEMENT" (attorney docket no. 52344) describes an ultrasound emission element. For example, "AN ULTRASOUND TRANSCEIVER AND USES THEREOF" (attorney docket no. 52345) describes a method for feedback and control. For example, "AN ULTRASOUND TRANSCEIVER AND COOLING THEREOF" (attorney docket no. 52346) describes cooling of the ultrasonic element. For example, "SEPARATION DEVICE FOR ULTRASOUND ELEMENT" (attorney docket no. 52348) describes preventing contract between the ultrasonic element and the blood vessel wall. For example, "ULTRASOUND TRANSCEIVER AND USES IN DETECTION" (attorney docket no. 52342) describes ultrasonic imaging.

Some embodiments have one or more of the following exemplary advantages:

[0408] Relatively faster treatment, for example, a treatment duration of 5-30 seconds per treatment region, or other smaller, larger or intermediate ranges can be used.

[0409] Relatively small number of treatment regions per artery for renal denervation, for example, 1 treatment region, 3 treatment regions, 4 treatment regions, 6 treatment regions, 8 treatment regions or other smaller, intermediate or larger number of regions are used.

[0410] Remote and/or localized effect, for example,

[0411] Accurate control of the thermal effect and/or location, such as good control on the location and/or size of the artery tissue damage by therapeutic parameters.

[0412] Ability to treat relatively large continuous areas in the arterial wall.

[0413] A treatment option for short artery stumps and/or for short total treatment durations (e.g., 5-10 minutes vs 20 minutes for RF treatments).

[0414] The thermal effect volume in the tissue is relatively far from the transducer face (e.g, media, adventitia, vasa-vasorum, peri-adventitia, adventitia nerves, peri-adventitia nerves, peri-adventitia capillaries).

[0415] Targeting tissues in varying distances from the transducer face according to treatment parameters. For example, applying the thermal effect in tissues located about 5 mm or more from the lumen wall (e.g., intima layer). A relatively far effect is relevant for example, for achieving peripheral nerves blocks from inside the peripheral arteries.

[0416] Non-targeted tissues on the beam path to the target tissue are not damaged and/or are selectively damaged (e.g. according to a margin of safety), for example, the endothelium, basal membrane and/or internal elastic lamina.

[0417] Possibility for varying levels of thermal modulation of the target tissue. For example, partial damage to nerves and/or other target tissues, in a controlled manner and different effect levels. Potentially, partial nerve injury can be controlled, that might lead to nerve recovery, either partially or entirely.

[0418] Tissue selectivity, for example, highly selective remote thermal effect in nerve bundles, such as nerves that are covered with thick fat tissue. For example as used in a Renal Denervation procedure in the Renal Artery ostium.

[0419] Treatment features suitable for Renal Denervation include:

[0420] The ability to work very close to the renal artery ostium, for example, <10 [mm], or other smaller, intermediate or larger values.

[0421] The ability to work in short arteries, for example, <20 [mm], or other smaller, intermediate or larger values

[0422] The ability to work in small arteries, for example, 4-3 [mm], or other smaller, intermediate or larger values

[0423] Safety issues

[0424] Relatively safer treatment.

[0425] The temperature of the blood that flows over the ultrasonic transducer can be controlled to not exceed a temperature threshold of 50 degrees Celsius (or other smaller, intermediate or larger numbers) while working in the maximal allowed operation intensity level, for example, 50 [W/cm^2], or other smaller, intermediate or larger intensity levels.

[0426] The temperature of the blood that flows over the ultrasonic transducer can be controlled to not exceed a temperature threshold of over 43 degrees Celsius (or other smaller, intermediate or larger numbers), for example, while working in the therapeutic operation intensity level 30 [W/cm^2], or other smaller, intermediate or larger intensity levels. In some embodiments, there is no need to add external cooling such as by saline injection.

[0427] The therapeutic treatment on the blood vessel wall is done with no mechanical contact with the vessel wall, thereby reducing or eliminating the danger of damaging the vessel wall or disrupting any pathologies on the wall (e.g., atherosclerotic plaques). For example, reducing the risk of arterial perforation and/or mechanical damage that might cause a narrowing in the vessel, plaque tear and/or emboli.

[0428] Localized and/or controlled effects specifically in the targeted treatment volume, preventing and/or reducing non-controlled energy effects in other tissues.

[0429] Blocking of the blood flow during the treatment is optional, and in some embodiments, is not required.

[0430] Treatment of a single artery location (e.g., longitudinally) in one or more circumferential directions, potentially, significantly reducing and/or preventing stenosis.

[0431] Preventing and/or reducing damage to the artery due to repeating treatment 2-3 times (or more) at the same axial position/radial direction, such as due to a mistake.

[0432] Prevent and/or reduce interference with implanted electronic medical devices (e.g., pacemakers, defibrillators).

[0433] Clinical implications, for example, relatively lower pain during treatment as a result of relatively faster blocking of nerves, with no electric excitation of the target nerve and/or no effect on other nerves. Potentially reducing sedation and/or anesthesia.

[0434] Relatively shallow learning curve, as leverages existing operator skill sets.

[0435] Many applications and/or ability to treat a wide range of clinical disorders.

[0436] Treatment option for a wide range of patients, such as high risk populations, for example as those suffering from vascular pathologies. Ability to treat in arteries with plaques and/or stents.

[0437] Ability to obtain a partial clinical effect (vs. complete effect). Potentially suitable for patients with milder disease, such as mild hypertension.

[0438] Feedback availability during treatment, such as information on the direction and location of the applied energy, catheter and the therapeutic catheter tip:

[0439] Easy control capability and a clear direction and location of the ultrasonic ray and/or catheter location to carry out treatment, such as according to the ultrasonic echo reflection analysis.

[0440] Ability to control the circumferential direction of the artery tissue damage.

[0441] Continues information (e.g., ultrasonic measurement) on the position of the catheter tip, such as from the artery wall during treatment.

[0442] Automatic detection of unwanted and/or risky movement of the catheter during treatment.

Alternative Ways to Determine Desirable Parameters

[0443] In some embodiments of the invention, trial and error is used to figure out at least some parameters. For example, an initial set of parameters estimated to cause a relatively small area of thermal damage can be applied to the target tissue. Alternatively, thermal damage is applied to a region that would not be affected by the small area of thermal damage. Based on the resulting area and/or volume of thermal damage caused by the parameter settings (e.g., according to imaging), one or more settings can be adjusted to achieve a desired effect in the target tissues. Such a process can be followed iteratively until the desired effect is achieved. Such a process is potentially useful in certain situations, for example, if the rate of blood flow is unclear.

[0444] In some embodiments of the invention, one or more equations (e.g., a simplified physical and/or mathematical model) are developed for obtaining at least some parameters, for example, as described in detail in the sections "EXEMPLARY DEVELOPMENT OF AN EQUATION" parts A and/or B. In some embodiments, the equations are used to derive parameters according to experimental results. In some embodiments, different equations are developed for different experiments, such as for targeting different types of tissues in different anatomical areas. In some embodiments, parameters are extrapolated based on experimental results.

Exemplary Development of an Equation—Part A

[0445] Inventors followed the process as described in FIGS. **1**A and/or **1**B to conduct experiments in 10 pigs (e.g., results displayed with reference to FIG. **12**A). Experiments were performed using a catheter having a diameter of 3 mm. The data collected from the process was analyzed and turned into parameters that affect treatment; the intensity of ultrasound energy, the frequency of ultrasound energy, and the flow rate of blood in the artery. An equation was developed associating the parameters with the resulting area of thermally damaged tissue, such as the minimum radial distance from the artery wall.

[0446] The equation is based on the results of the conducted experiments that showed the thermal effect initiating about 3 mm from the intima, in the most distant location of the periadventitia. As the acoustic intensity profile increased, the thermal effect increased towards the intima. The experiments were conducted for a period of about 30 seconds. The equation can be adapted for other time periods in a similar manner.

[0447] The function that associates the radial distance (the distance from the arterial wall to the start of the thermally damaged area) to the ultrasound treatment parameters is:

$$x(f,I)\ [\mathrm{mm}]=(C6+a*\mathrm{Exp}(\mathrm{flow}*b)-C2*\log(C3*I\ [\mathrm{W/cm^2}]))/(C4*f\ [\mathrm{MHz}]+C5)$$

[0448] Where:

[0449] I=Excitation intensity [w/cm^2]

[0450] f=Working excitation frequency [MHz]

[0451] x=Minimal radial distance from the artery wall [mm]

[0452] flow=blood flow rate in the artery [ml/min]

[0453] Calculated coefficients in order to adjust the model assumptions, neglects and unknown variables to the experimental results:

[0454] a=3.7 (2 . . . 4)

[0455] b=−1134(−2500 . . . 0)

[0456] C2=93 (90 . . . 100)

[0457] C3=2.2 (1 . . . 4)

[0458] C4=2.1 (1 . . . 4)

[0459] C5=47.4 (45 . . . 50)

[0460] C6=400 (0 . . . 1000)

[0461] *the numbers in (. . .) are the limits of the parameters estimation based on the results of the experiments conducted.

[0462] The physical model (for parts A and/or B, below) is based on several assumptions and/or simplifications. The Arrhenius thermal damage equation was used as the basis for estimating the thermal damage area in the artery wall, using a time value of 30 seconds and an effective temperature higher than 55 degrees Celsius. The blood flow in the artery was assumed to be exponentially related to cooling of the artery wall by convection.

[0463] The equations were developed by plotting the experimental results (e.g., as summarized in FIG. **12**A for the renal arteries (shown in FIG. **13**A) and for the carotid arteries (shown in FIG. **13**B). The plots graphically illustrate the extent of thermal damage (e.g., the distance from the intima to the start of the damage on the 'y-axis) as a function of the intensity of the applied acoustic energy (on the 'x-axis) and as a function of the frequency of the applied acoustic energy (on the 'z-axis'). The coefficients of the equation were adjusted in order to align the equation to the plots.

Exemplary Development of an Equation—Part B

[0464] In another set of experiments, inventors followed the process as described in FIGS. **1**A and/or **1**B to conduct experiments in **12** pigs (e.g., results shown in FIGS. **12**B-

12D). Experiments were performed using a catheter having a diameter of 2 mm, at frequencies of 10 Mhz and/or 20 Mhz. Ultrasound was emitted at intensities ranging from 10-35 watt/cm^2, for time periods ranging from 10-30 seconds. The anatomical target sites were the left and/or right renal arteries.

[0465] FIG. **12**B summarizes the experimental data for an ultrasound emission frequency of 10 Mhz. FIG. **12**C summarizes the experimental data at 20 Mhz. FIG. **12**D shows graphs visually displaying the data of FIGS. **12**B-**12**C.

[0466] FIG. **12**E illustrates variables describing the resulting area of thermally damaged tissue, useful in helping to understand the results shown in FIGS. **12**B-**12**D. The left side of the figure illustrates a cross section of an artery (all measurements in millimeters). 'MED' represents the thickness of the media layer of the arterial wall. 'L' represents the minimum distance of the thermally affected region from the lumen wall. 'W' represents the maximal width of the thermally effected region. 'Th' represents the thickness of the thermally affected region. 'S' represents the severity of the thermally affected region (e.g., as defined by a trained professional), defined as: 0=no thermal damage, 0.5=thermal damage to nerves only, 1=thermal damage to connective tissue in surrounding artery, 2=thermal damage to media (represents possible future risk of arterial stenosis).

[0467] Equations associating the parameters of ultrasound energy (frequency and intensity) to the thermal effect in tissue were developed by fitting the thermal damage parameters based on the histological analysis. Exemplary graphs are shown in FIGS. **13**C-**13**H. Exemplary fitting coefficients (e.g., for duration of 30 seconds) are shown in the table below. Although coefficients correspond to a duration of 30 seconds, this is not intended to be limiting, and a similar analysis can be conducted for any other data points. It is emphasized that the coefficients in the table cannot be compared with each other. Each coefficient is distinct with reference to each formula. For example, the coefficient 'b_1' in formula 2 is different than the coefficient 'b_1' in formulas 3-7.

[0468] One possible function that associates the radial distance 'L' to the ultrasound treatment parameters of intensity (watt/cm^2) and frequency (Mhz) is shown as:

$$L(I, f) = \frac{c_1 - c_2 \log(c_3 I)}{c_4 f + c_5} \qquad \text{equation (1)}$$

[0469] Equation 1 contains 5 unknowns, but can be simplified to only 3 independent values, such as shown in equation 2. Some relationships represented by equation 2 are graphically illustrated by FIG. **13**C.

$$L(I, f) = \frac{b_1 - \log(I)}{b_2 f + b_3}. \qquad \text{equation (2)}$$

[0470] The relatively stronger flow of blood related to the relatively smaller diameter catheter in this group of experiments (2 mm vs 3 mm) is taken into consideration automatically by the proper choice of the first parameter in equation (2).

[0471] One possible function that associates the width 'W' to intensity and frequency is represented by equation 3. Some relationships represented by equation 3 are graphically illustrated by FIG. **13**D.

$$W(I,f)=(b_1+b_2f)I+(b_3+b_4f)I^2 \qquad \text{equation (3)}$$

[0472] One possible function that associates the severity of the thermal effect 'S' to intensity and frequency is represented by equation 4. Some relationships represented by equation 4 are graphically illustrated by FIG. **13**F.

$$W(I,f)=(b_1+b_2f)I+(b_3+b_4f)I^2 \qquad \text{equation (4)}$$

[0473] Some possible functions that associate the standard deviations of 'L', 'W' and 'S' to intensity and frequency include respective equations 5-7. Some relationships represented by equations 5-7 are graphically illustrated by respective FIGS. **13**F-H.

$$\sigma_L(I, f) = \frac{b_1 + b_2 I}{b_3 f + b_4}. \qquad \text{equation (5)}$$

$$\sigma_W(I, f) = \frac{b_1 + b_2 I}{b_3 f + b_4}. \qquad \text{equation (6)}$$

$$\sigma_S(I, f) = \frac{b_1 + b_2 I^2}{b_3 f + b_4}. \qquad \text{equation (7)}$$

Parameter	Formula	b_1	b_2	b_3	b_4
L	(2)	6.22	0.080	0.665	—
W	(3)	0.1374	−0.0044	−0.0065	0.00056
S	(4)	−0.0082	0.0039	0.00014	$-1.9 \cdot 10^b$
L	(5)	−0.069	0.012	−0.016	0.40
W	(6)	−1.87	0.45	−0.29	10.13
S	(7)	1.66	0.0070	−0.53	18.18

Table of Exemplary Coefficients Corresponding to Exemplary Equations 2-7

[0474] The equations (parts A and B) illustrate that the frequency can be adjusted to control the area of thermal effect. For example, a relative increase in frequency can result in one or more of: the thermal effect being relatively closer to the wall edge, the width of the thermal effect being relatively increased, the severity of the thermal damage being relatively increased. The relative decrease in frequency can result in one or more of: the thermal effect being relatively further to the wall, the width is relatively reduced, the severity of the thermal damage is relatively reduced.

[0475] The equations further illustrate that the intensity can be adjusted to control the area of thermal effect. For example, a relatively increase in intensity can result in one or more of: the thermal effect being relatively further closer to the wall edge, the width of the thermal damage being relatively increased, the severity of the thermal damage being relatively increased. The relative decrease in intensity can result in one or more of: the thermal effect being relatively further from the wall, the width is relatively reduced, the severity of the thermal damage is relatively reduced.

[0476] As can be seen, various application times can be used as well.

[0477] In an exemplary embodiment of the invention equations can be used to calibrate the system. For example, the system can use the equations to provide an initial set of parameters. Optionally, treatment is synchronized to adjustments. For example, a thermal effect can be applied to a test

region, or a small part of the target region. Feedback such as imaging can be performed to estimate the distance from the treated region to the arterial wall, the width of the region and/or the severity of the thermal effect (e.g., as described in co-filed PCT application with attorney docket number 52342). The actual measured values can be compared to the expected values. One or more parameters such as frequency and/or intensity can be adjusted relatively higher or relatively lower. The process can be repeated in a feedback-loop, thereby achieving the desired thermal effect to the desired area of tissue at the desired location.

Experimental Results

[0478] FIG. **12**A is a table summarizing experimental results of selective thermal effects (e.g., damage) to arterial wall tissues, performed by the inventors, in accordance with some embodiments of the invention.

[0479] Experiments were performed in a total of 10 pigs, with multiple locations treated in the carotid and renal arteries. The pigs were under general anesthesia. The frequencies of ultrasound used were 10 Mhz, 15 Mhz and 20 Mhz. The intensity of acoustic ultrasound applied to the target tissue ranged from 1-10 watts/square centimeter to over 71 watts/square centimeter. The treatment duration was 30 seconds per location. The ultrasonic catheter used had a transducer with dimensions of 1.5 mm×6 mm×0.8 mm. The size of the catheter was 9 French. The length of the catheter was 55 cm when inserted into the renal artery, and a catheter having a length of 95 cm was used for the carotid artery.

[0480] In the set of experiments performed, the acoustic intensity was applied for about 30 seconds.

[0481] In the set of experiments performed, the thermal damaged initiated in the peri-adventitia, increasing towards the intima. The tables illustrate that the area of damage from the peri-adventitia inwards, for example, PA=damage localized to the peri-adventitia, M=damage from the peri-adventitia to the media, IEM=damage from the peri-adventitia to the internal elastic media. The area damaged (e.g., on a cross sectional histological slide through the artery) was summarized as S=small, M=medium and L=large. The definition of the damage (S, M, L), reflects the percentage of tissue with thermal effect in the relative sector with the pathology; S=1-20% thermal effect, M=21-60% thermal effect, L=>61% of thermal effect. The thermal effect was localized by sectors in a clockwise manner. The percentage effect represents the proportion of the thermal effect inside the defined sector. For example, "S" represents a string-like thermal zone, while "L" represents that most or all of the sector area was affected.

[0482] In the experiments performed, nerves in the peri-adventitia were thermally damaged, for example, Y=thermally damaged nerve, N=no thermally damaged nerves. The extent of thermal damage and/or the identification of thermally damaged nerves was conducted by a trained pathologist. In the experiments performed, the location of thermal damage in the arterial wall was selective. "Points" refers to the location (e.g., center of a treatment region) in the arterial wall by using an arbitrary clock as measurement, for example, 12 o'clock=0 degrees, 6 o'clock=180 degrees. The transducer was directed towards the affected sector.

[0483] In the experiments performed, multiple lesions were selectively made in a single blood vessel in a pig.

Experiment in the Aorta #1

[0484] Study subject: a female domestic pig, 71.7 Kg had been treated with an ultrasonic treatment system on its renal left artery.

Anatomical target: nerves in the surrounding of the ostium of the right renal artery.

Anatomical position of catheter: aorta artery, proximity to the ostium of right renal artery.

Length of ultrasonic treatment catheter: 55 cm

Transducer frequency: 20 MHz

Time component of intensity profile: 30 seconds

Acoustic intensity component of intensity profile: 52 Watts/cm^2

Results: mild thermal effect was demonstrated at the peri adventitia.

[0485] FIG. **14**A represents a 2× magnification of the location at the aorta artery circumference that was treated with the ultrasonic system, 6.0 mm proximal from the renal right ostium artery. The marked area represents the border of the thermal effect seen in the priadventitia, which manifests in an irreversible tissue, and vessels necrosis, (T=Thermal).

[0486] FIG. **14**B represents a 4× magnification of the thermal area.

[0487] Schematic Description of Pathology Analysis:

FIG. **14**C represents a top view of all the artery layers (see index box as follows), at the relevant depth (6.0 mm from the renal right ostium). The artery is planned clockwise for the pathology definition.

[0488] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 9.

Experiment in the Aorta #2

[0489] Study subject: a female domestic pig, 71.7 Kg had been treated with an ultrasonic treatment system on its renal left artery.

Anatomical target: nerves in the surrounding of the ostium of the right renal artery.

Anatomical position of catheter: aorta artery, proximity to the ostium of right renal artery.

Length of ultrasonic treatment catheter: 55 cm

Transducer frequency: 20 MHz

Time component of intensity profile: 30 seconds

Acoustic intensity component of intensity profile: 67 Watts/cm^2

Results: nerves at the ostium of the aorta were treated.

[0490] FIG. **15**A represents a 2× magnification of the location at the aorta artery circumference that was treated with the ultrasonic system, 6.5 mm proximal from the renal right ostium artery. The marked area represents the border of the thermal effect seen in the priadventitia, which manifests in an irreversible tissue, and vessels necrosis, (T=Thermal). Furthermore the nerve which was affected by the ultrasonic treatment is marked with XN, which represents unviable nerves, expressed by necrosis of the nerve.

[0491] FIG. **15**B represents a 4× magnification of the thermal area and the localization of the thermal necrotic nerve.

[0492] FIG. **15**C represents a 10× magnification of the necrotic nerve surrounded by tissue with thermal effect.

Schematic Description of Pathology Analysis:

[0493] FIG. **15**D represents top view of all the artery layers (see index box as follows), at the relevant depth (6.5 mm from the renal right ostium). The artery is planned clockwise for the pathology definition.

[0494] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 9.

Experiment in the Carotid Artery #1

[0495] Study subject: a female domestic pig, 72.8 Kg had been treated with an ultrasonic treatment system on its carotid left artery.

Anatomical target: nerves in the wall of the right common carotid artery.

Anatomical position of catheter: Right common carotid artery.

Length of ultrasonic treatment catheter: 95 cm

Transducer frequency: 20 MHz

Time component of intensity profile: 30 seconds

Acoustic intensity component of intensity profile: 34 Watts/cm^2

Results: thermal effect was demonstrated from the media layer throughout the priadventitia of the right common carotid artery.

[0496] FIG. **16**A represents a 2× magnification of the location of the thermal effect at the circumference of the right common carotid artery. The marked area represents the border of the thermal effect seen in the media throughout the priadventitia layer, which manifests in pyknosis of the smooth muscle cells and focal collagen condensation.

[0497] FIG. **16**B represents a 4× magnification of the thermal area

Schematic Description of Pathology Analysis:

[0498] FIG. **16**C represents top view of all the artery layers (see index box as follows), at the relevant depth. The artery is planned clockwise for the pathology definition.

[0499] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 1-3.

Experiment in the Carotid Artery #2

[0500] Study subject: a female domestic pig, 78.0 Kg had been treated with an ultrasonic treatment system on its carotid left artery.

Anatomical target: nerves in the wall of the left common carotid artery.

Anatomical position of catheter: left common carotid artery.

Length of ultrasonic treatment catheter: 95 cm

Transducer frequency: 20 MHz

Time component of intensity profile: 30 seconds

Acoustic intensity component of intensity profile: 13.2 Watts/cm^2

Results: nerves surrounding the left common carotid artery were treated

[0501] FIG. **17**A represents a digital scan of the 28.5 mm from the aorta arch slide. The thermal effect is manifested in an irreversible tissue, and vessels necrosis in less than 25% of the peri adventitia in the artery circumference. Furthermore nerves which were affected by the ultrasonic treatment are found to be necrotic.

Schematic Description of Pathology Analysis:

[0502] FIG. **17**B represents top view of all the artery layers (see index box as follows), at the relevant depth (6.5 mm depth from the aorta). The artery is planned clockwise for the pathology definition.

[0503] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 3.

Experiment in the Renal Artery #1

[0504] Study subject: a female domestic pig, 68.2 Kg had been treated with an ultrasonic treatment system on its renal left artery.

Anatomical target: nerves in the wall of the left renal artery.

Anatomical position of catheter: left renal artery.

Length of ultrasonic treatment catheter: 55 cm

Transducer frequency: 10 Mhz

Time component of intensity profile: 30 seconds

Acoustic intensity component of intensity profile: 26 Watts/cm^2

Results: nerves surrounding the left renal artery were treated

[0505] FIG. **18**A represents a 2× magnification of the 6.5 mm depth from the aorta slide. The marked area represents the border of the thermal effect seen in the priadventitia, which manifests in an irreversible tissue, and vessels necrosis, (T=Thermal). Furthermore the nerves which were affected by the ultrasonic treatment are marked with XN, which represents unviable nerves. Both nerves in the surrounding of thermal area are necrotic.

[0506] FIG. **18**B represents a 4× magnification of the thermal area, and the localization of the thermal necrotic nerves.

[0507] FIG. **18**C represents a 10× magnification of the necrotic nerves inside the thermal effect zone.

[0508] FIG. **18**D represents a 10× magnification of the necrotic nerve outside the thermal effect zone. Both nerves' necrosis caused by the thermal ultrasonic treatment.

[0509] FIG. **18**E represents a 2× magnification of the 6.5 mm depth from the aorta slide stained in PSR, before applying the polarizer lens.

[0510] FIG. **18**G represent a 2× magnification of the 6.5 mm depth from the aorta slide, examined under polarizer light, representing a distinctive negative birefringence caused by collagen denaturation as consequence of the ultrasonic treatment. The marked area represents the border of the thermal effect seen in the priadventitia.

Schematic Description of Pathology Analysis:

[0511] FIG. **18**G represents top view of all the artery layers (see index box as follows), at the relevant depth (6.5 mm depth from the aorta). The artery is planned clockwise for the pathology definition.

[0512] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 5.

Pathology Analysis: Pathology Report Prepared by a Trained Pathologist

[0513] The table below represents the pathology report for the experiment. The table contains columns with the artery layers, different potential pathologies relevant to the artery layer, slide ID with a categorical scoring of lesions (as

detailed below), and a sector (S) column for the localization of the pathology damage in clockwise manner.

Slide ID: PIG No.	N05-R-L3	N05-R-L3 + 0.5	Sector	Status
Lumen	Free thrombus	0		
Endothelium	Pyknosis	0		
Endothelium	Attached thrombus	0		
Endothelium	Fibrin deposition	0		
Endothelium	Erosion	4	1-12	
Int. Elastic Lamina	Distorted	0		
Int. Elastic Lamina	Rupture	1	11-1	
Media	Inflammation	0		
Media	Pyknosis*	1	11-1	
Media	Necrosis	0		
Media	Damage width (%)	40-	11-1	
Vasa-Vasorum	Thrombus	0		
Vasa-Vasorum	Fibrin	0		
Vasa-Vasorum	Necrosis	0		
Adventitia	Pyknosis	0		
Adventitia	Necrosis	0		
Adventitia	Inflammation	0		
P. Adventitia vessels	Necrosis	1	5	THERMAL
P. Adventitia vessels	Thrombus	0		
Peri Adventitia	Inflammation	0		
Peri Adventitia	Necrosis	1	5	
P. Adventitia nerves	Degeneration/ vacuolation	0		
P. Adventitia nerves	Inflammation	0		
P. Adventitia nerves	Necrosis	1	5	

For lesion scoring:

0: Normal	Media damage width (%, maximum width given):
1: Minimal or involving 0-25% of the vessel circumference	X−: damage from the lumen towards the periphery of the vessel
2: Mild or involving 25-50% of the vessel circumference	X+: damage from the periphery towards the lumen of the vessel
3: Moderate or involving 50-75% of the vessel circumference	A: Artifact on histological processing
4: Marked/Severe or involving 75-100% of the vessel circumference	S-Clockwise sector

Experiment in the Renal Artery #2

[0514] Study subject: a female domestic pig, 65.7 Kg had been treated with an ultrasonic treatment system on its renal left artery.

Anatomical target: nerves in the wall of the right renal artery.

Anatomical position of catheter: right renal artery.

Length of ultrasonic treatment catheter: 55 cm

Transducer frequency: 20 Mhz

Time component of intensity profile: three times for a period of 30 second each

Acoustic intensity component of intensity profile: 53 Watts/cm^2, 59 Watts/cm^2 and 66 Watts/cm^2 respectively.

Results: thermal effect was demonstrated at the peri adventitia of the right renal artery.

[0515] FIG. **19**A represent a 2× magnification of the 6.5 mm depth from the aorta slide. The marked area represents the border of the thermal effect seen in the priadventitia, which manifests in an irreversible tissue necrosis, (T=Thermal).

[0516] FIG. **19**B represents a 4× magnification of the thermal area. No nerves were affected at this treatment.

Schematic Description of Pathology Analysis:

[0517] FIG. **19**C represents top view of all the artery layers (see index box as follows), at the relevant depth (6.5 mm depth from the aorta). The artery is planned clockwise for the pathology definition.

[0518] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 6-7.

Pathology Analysis: Pathology Report Prepared by a Trained Pathologist

[0519] The table below represents the pathology report for the experiment. The table contains columns with the artery layers, different potential pathologies relevant to the artery layer, slide ID with a categorical scoring of lesions (as detailed below), and a sector (S) column for the localization of the pathology damage in clockwise manner.

Slide ID: PIG No.	N06-R-R4	N06-R-R4 + 0.5	Sector
Lumen	Free thrombus	0	
Endothelium	Pyknosis	0	
Endothelium	Attached thrombus	0	
Endothelium	Fibrin deposition	1	12
Endothelium	Erosion	2	9-3
Int. Elastic Lamina	Distorted	0	
Int. Elastic Lamina	Ruptured	1	12
Media	Inflammation	0	
Media	Pyknosis*	1	12
Media	Necrosis	0	
Media	Damage width (%)	<10-	12
Vasa-Vasorum	Thrombus	0	
Vasa-Vasorum	Fibrin	0	
Vasa-Vasorum	Necrosis	0	
Adventitia	Pyknosis	0	
Adventitia	Necrosis	0	
Adventitia	Inflammation	0	
P. Adventitia vessels	Necrosis	0	
P. Adventitia vessels	Thrombus	0	
Peri Adventitia	Inflammation	0	
Peri Adventitia	Necrosis	1	6-7
P. Adventitia nerves	Degeneration/ vacuolation	0	
P. Adventitia nerves	Inflammation	0	
P. Adventitia nerves	Necrosis	0	

For lesion scoring:

0: Normal	Media damage width (%. maximum width given):
1: Minimal or involving 0-25% of the vessel circumference	X−: damage from the lumen towards the periphery of the vessel

-continued

For lesion scoring:	
2: Mild or involving 25-50% of the vessel circumference	X+: damage from the periphery towards the lumen of the vessel
3: Moderate or involving 50-75% of the vessel circumference	A: Artifact on histological processing
4: Marked/Severe or involving 75-100% of the vessel circumference	

Experiment in the Renal Artery #3

[0520] Study subject: a female domestic pig, 65.7 Kg had been treated with an ultrasonic treatment system on its renal left artery.

Anatomical target: nerves in the wall of the right renal artery.

Anatomical position of catheter: right renal artery.

Length of ultrasonic treatment catheter: 55 cm

Transducer frequency: 20 MHz

Time component of intensity profile: twice for a period of 30 second each

Acoustic intensity component of intensity profile: 40 Watts/cm^2 and 53 Watts/cm^2

Results: nerves surrounding the right renal artery were treated

[0521] FIG. **20**A represents a 2× magnification of the 10.5 mm depth from the aorta slide. The marked area represents the border of the thermal effect seen in the priadventitia, which manifests in an irreversible tissue, and vessels necrosis, (T=Thermal). Furthermore the nerves which were affected by the ultrasonic treatment are marked with XN, which represents unviable nerves, and VN, which represent viable nerves. In the surrounding of thermal area are present 8 nerves, including 7 unviable.

[0522] FIG. **20**B represents a 4× magnification of the thermal area.

[0523] FIGS. **20**C-E represents a 10× magnification of the necrotic and/or vacuolated nerves inside the thermal effect zone.

[0524] FIGS. **20**E-I represents a 10× magnification of the necrotic and/or vacuolated and viable nerves outside the thermal effect zone.

Schematic Description of Pathology Analysis:

[0525] FIG. **20**J represents top view of all the artery layers (see index box as follows), at the relevant depth (10.5 mm depth from the aorta). The artery is planned clockwise for the pathology definition.

[0526] The thermal effect seen in the artery is represented by the black area in the peri-adventitia, at sector 4-5.

Renal Denervation Study

Goal:

[0527] Inventors performed a controlled study to evaluate the clinical feasibility and/or safety of performing a renal denervation procedure in a chronic swine model, in accordance with some embodiments of the invention.

Study End Points

[0528] Primary: A significant decrease in norepinephrine levels at **30** days following the procedure, in the treatment group compared to the control group.

[0529] Secondary: Lack of procedure related stenosis in the treated renal arteries at **30** days following the procedure.

Experimental Materials

[0530] Equipment: An ultrasound emission element, catheter and control system as described herein and/or in the related applications was used to perform the treatments. A 10 Mhz ultrasound emission element was used in the first set of experiments. A 20 Mhz element was used in the second set of experiments.

[0531] Animals and preparation: All aspects of the study were approved by the Animal Research Committee. A total of 10 Yorkshire domestic swine (weight 70-75 Kg) were used for the first set of experiments, 4 underwent the renal denervation procedure and 6 served as control. 5 additional pigs were used for the second set of experiments, all underwent the procedure.

[0532] Animal preparation: Anatomic eligibility was confirmed by angiography prior to the treatment. No animals were disqualified. The experiment was performed under general anesthesia. Intravenous heparin was administered to achieve an intraprocedural activated clotting time (ACT)>250 seconds. At the end of the procedure the animals were euthanized.

Experimental Protocol

Ultrasonic Treatment:

[0533] In the experimental swine group, the catheter was advanced via a femoral approach to access the renal arteries. Ultrasound treatment, in accordance with some embodiments of the invention, was administered at the main arterial trunks in one or more locations. In each location, the ultrasound energy was directed in up to 4 angles of the arterial circumference (e.g., 0°, 90°, 180°, 270°—equivalent to 12, 3, 6, 9 hours in a clock model). Ablation of neural tissue was performed by ultrasonic excitation of 10 or 30 seconds in each treatment location. In actual practice, a smaller or larger number of angle may be used.

[0534] The catheter distance from the artery wall was measured using ultrasonic imaging of the system, prior to ultrasonic excitation, in accordance with some embodiments of the invention. If needed, a distancing device (e.g., as described with reference to co-filed PCT application "Separation device for ultrasound transducer", attorney docket number 52348) was deployed, such as a part of the safety mechanism.

[0535] Control:

[0536] No ultrasonic energy was applied to the 6 swines in the control group. One control animal was cannulated and the catheter was introduced to the renal arteries without ultrasonic energy delivery.

[0537] Angiography:

[0538] Angiography was performed during three time periods; prior to the procedure, immediately at the end of procedure, and at 30 days+2 days. Under angiography, each renal artery was examined by a trained physician for stenosis, constriction and/or any abnormalities in blood flow.

[0539] Biopsy:

[0540] All experimental and control animals were biopsied. In vivo, open bilateral renal cortex biopsies were conducted in order to perform a norepinephrine (NE) quantitative analysis. The biopsy was taken from the cranial and caudal poles of the kidney under direct vision. Samples were sent to analysis of NE levels in the tissue using HPLC.

[0541] Histology:

[0542] The renal arteries and kidneys were perfused, dissected and immersed in 4% formalin prior to histological processing. Pathological examination for any thermal or mechanical damage to the renal arteries and connective tissue, including nerves.

Procedure Parameters

[0543] Procedure parameters are described for the first set of experiments.

[0544] An average of about 6.5+0.5 ultrasonic treatments were performed in the right renal artery in two locations along the artery, and about 4.5+1.0 ultrasonic treatments were performed in the left artery, in 1-2 focal locations along the artery. In an exemplary embodiment of the invention, a number of treatments can be performed in a number of locations. For example, 1, 2, 4, 8 or other smaller, intermediate or larger treatment locations are available. For example, 1, 2, 4, 6, 8, 12 or other smaller, intermediate or larger numbers of treatments can be performed in an artery.

[0545] Ultrasonic ablations were applied in one of two time durations, 10 seconds or 30 seconds. In an exemplary embodiment of the invention, the treatment time is about 1 second, about 5, 10, 15, 20, 25, 30, 35, 50, 60, 100 seconds or other smaller, intermediate or larger time periods are used.

[0546] The average total procedure time was about 35.2+13.3 minutes. The maximal temperature measured by the sensor close to the ultrasonic transducer was about 44.25+1.0 degrees Celsius in the right renal artery, and about 45.2+3.4 degrees Celsius in the left renal artery. The temperatures are considered safe.

Table Summarizing the Treatment Parameters

[0547]

Animal ID	Number of excitations in right renal artery	Number of treated locations in right renal artery	Number of excitations in left renal artery	Number of treated locations in left renal artery	Duration of treatment (seconds)
7917	6	2	4	1	30
7918	7	2	6	2	30
7920	6	2	4	1	10
7921	7	2	4	1	10

Results

[0548] Norepinephrine (NE):

[0549] Renal tissue NE content was used as a chemical marker of the sympathetic nervous system activity. Denervation of the sympathetic nervous system potentially causes a reduction in NE release from the sympathetic nerves terminals, indicating reduced sympathetic activity.

[0550] The mean reduction in NE concentration (normalized and averaged over different parts of the kidney) in renal tissue in the treated animals in comparison to the control group was, on the average, greater than 50% after 30 days. Longer treatment durations generally caused a greater reduction.

[0551] Angiography:

[0552] Neither perfusion defects nor artery constriction were depicted in the treatment group of animals, neither at the treatment time point, nor at the 30 day follow up. Mild spasm had occurred coincidentally during the treatment, with no sign of permanent spasm or abnormalities remaining or forming de-novo in the 30 days following treatment.

[0553] Histopathology:

[0554] There was no stenosis in any of the renal artery vessels in all levels. All vessels were potent in all levels.

CONCLUSION

[0555] As illustrated by the decrease in NE levels, all 10 pigs were successfully treated by renal denervation using ultrasound energy, in accordance with some embodiments of the invention. A relatively longer treatment (e.g., 30 seconds vs. 10 seconds) resulted in a relatively larger decrease of NE levels, suggesting that longer treatment times disrupt a larger number of nerves and/or nerves to a greater degree. Furthermore, some embodiments as described herein have been shown to be safe, as no abnormalities occurred to the renal arties during and immediately post treatment, as well as at **30** days.

[0556] Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

[0557] All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

GENERAL

[0558] It is expected that during the life of a patent maturing from this application many relevant ultrasound transducers will be developed and the scope of the term transducer is intended to include all such new technologies a priori.

[0559] As used herein the term "about" refers to ±10%

[0560] The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

[0561] The term "consisting of" means "including and limited to".

[0562] The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional

ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

[0563] As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

[0564] Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0565] Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

[0566] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

[0567] Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non limiting fashion.

1. A method of setting up a treatment system for non-focused ultrasound energy delivered intrabody comprising:

selectively determining a target tissue in a wall of a lumen or cavity;

selecting parameters sufficient to provide a desired therapeutic effect in said target tissue and which start a thermal damage effect only at a distance of at least 0.2 mm from an inner side of said wall; and

setting up a treatment system using said parameters.

2. A method according to claim **1**, further comprising deciding an amount of desired thermal damage.

3. A method according to claim **2**, wherein said amount of thermal damage comprises a volume where thermal damage is desired.

4. A method according to claim **2**, wherein said amount of thermal damage comprises the degree of thermal damage.

5. A method according to claim **1**, further comprising selecting an anatomical location from which to treat said target tissue.

6. A method according to claim **5**, wherein said anatomical location comprises a renal artery and said target tissue comprises renal artery nerves.

7. A method according to claim **5**, wherein said anatomical location comprises an aorta and said target tissue comprises renal nerves.

8. A method according to claim **5**, wherein said anatomical location comprises a carotid artery and said target tissue comprises nerves.

9. A method according to claim **1**, wherein selecting comprises taking blood cooling into account.

10. A method according to claim **1**, wherein selecting comprises selecting in a manner which avoids significant stenosis.

11. A method according to claim **1**, wherein selecting comprises selecting in a manner which avoids significant damage to non-target tissue.

12. A method according to claim **1**, wherein selecting comprises selecting in a manner which avoids significant shrinkage in target tissue.

13. A method according to claim **1**, wherein said desired effect comprises denaturing at least some of said target tissue.

14. A method according to claim **13**, further comprising applying said ultrasound energy so as to not denature at least some part of said target tissue.

15. A method according to claim **1**, wherein said target tissue and said parameters are preselected so that said parameters have said desired effect on said target.

16. A method according to claim **1**, wherein said selecting comprises determining according to an attenuation coefficient of tissues.

17. A method according to claim **1**, further comprising selecting a margin of safety.

18. A method according to claim **17**, wherein said selecting a margin of safety comprises selecting an allowed amount of thermal damage to tissues surrounding said target tissue.

19. A method according to claim **17**, wherein said selecting a margin of safety comprises reducing or preventing contraction of said lumen or said cavity.

20. A method according to claim **1**, wherein said selectively determining said target tissue comprises selecting a type of tissue.

21. A method according to claim **20**, wherein said type of tissue comprises nerve tissue.

22. A method according to claim **20**, wherein said target tissue is selected from tissue located at a tissue layer selected from the group comprising peri-adventitia, adventitia, media, intima.

23. A method according to claim **1**, wherein said target tissue is located less than 10 mm from a renal ostium.

24. A method according to claim **1**, wherein said determining initial parameters comprises determining according to a distance of said target tissue from an intima.

25. A method according to claim **24**, wherein said target tissue is outside said wall of said lumen or said cavity.

26. A method according to claim **1**, further comprising selecting a frequency of treatment in the range of 8-25 Mhz.

27. A method according to claim **1**, further comprising selecting an ultrasound intensity in the range of 1-100 Watt/square centimeter.

28. A method according to claim **1**, wherein said target tissue is a renal nerve, and said parameters are an applied frequency of 10[MHz]-**22**[MHz], and an intensity of 10-40 [W/cm^2].

29. A method according to claim **1**, wherein a duration of said treatment is 5-30 seconds.

30. A method according to claim **1**, wherein a length of said lumen or cavity is less than 20 mm.

31. A method according to claim **1**, comprising applying said parameters to selectively treat said target tissue using non-focused ultrasound to achieve said desired effect.

32. A method according to claim **31**, further comprising obtaining feedback associated with said treatment.

33. A method according to claim **32**, further comprising adjusting said parameters according to said feedback and retreating said target tissue.

34. A method according to claim **31**, further comprising a controlled adjustable treatment according to online measurements including at least one of the following group of measurements: flow measurements, current measurement, voltage measurement, power measurement, acoustic backscatter measurements, temperature measurements, pressure measurements.

35. A method according to claim **31**, wherein treating comprises applying said ultrasound away from said wall but inside a body.

36. A method according to claim **31**, applying so that a desired effect comprises temporary change in tissue functionality is achieved.

37. A method according to claim **31**, wherein said applying said parameters comprises applying said parameters in an open loop manner.

38. A method according to claim **31**, wherein applying comprises applying said ultrasound energy so as to not denature most of the tissue between said target tissue and an edge of said wall.

39. A method according to claim **31**, wherein applying comprises maintaining blood in said lumen at a temperature below 50 degrees Celsius.

40. A method according to claim **31**, wherein applying comprises maintaining blood in said lumen at a temperature below 43 degrees Celsius.

41. A method according to claim **31**, wherein said applying comprises heating a nerve while not heating tissue outside of a fat sheath surrounding said nerve.

42. A method according to claim **31**, wherein said applying comprises localizing heating by having a gradient of cooling from blood and a gradient of heating from a distance.

43. A method according to claim **31**, wherein applying comprises heating nerves sufficiently to reduce renal norepinephrine levels by at least 50%.

44. A method according to claim **31**, wherein applying comprises heating a part of a nerve to necrosis while not heating another part of said nerve in a same axial location along said nerve to necrosis.

45. A method according to claim **31**, further comprising adjusting a property of at least one of said target tissue, said wall and blood in said lumen to provide said desired effect.

46. A method according to claim **45**, wherein said property comprises a rate of heat removal.

47. A method according to claim **45**, wherein said property comprises a flow rate of said blood.

48. A method according to claim **45**, wherein said property comprises a temperature.

49. A method according to claim **31**, wherein said applying comprises applying said ultrasound energy so as to treat a patient suffering from hypertension.

50. A method according to claim **31**, wherein said applying comprises applying said ultrasound energy so as to prevent signals from propagating through at least one renal nerve.

51. A method according to claim **31**, wherein said applying comprises applying said ultrasound energy so as to position said treatment area with an accuracy of better than 0.2 mm along an axis perpendicular to said wall.

52. A system for treating a blood vessel wall comprising:

a catheter;

at least one ultrasound emitter mounted on the catheter and adapted for emitting unfocused ultrasound at a frequency of 10-40 Mhz at a target tissue located a distance from an intima of the blood vessel wall with a power setting sufficient to heat said target tissue; and

a controller,

wherein the controller is configured to deliver enough power to heat said target tissue to a selected size and to a desired thermal effect, said thermal effect starting only after at least a distance of 0.2 mm from said wall.

53. A system according to claim **52** wherein said target tissue comprises nerves, and said desired thermal effect comprises reducing signals through said nerves by at least 50%.

54. A system according to claim **52**, wherein said catheter is configured so that said emitter does not contact said wall.

55. A system according to claim **52**, wherein said controller is configured to selectively treat a volume of tissue distanced from an intima of a blood vessel wall.

56. A system according to claim **52**, wherein said controller is configured for thermal treatment of renal nerves.

57. A system according to claim **52**, wherein said controller is configured for treatment accuracy of better than 0.5 mm positioning of the treatment area, along a dimension perpendicular to said blood vessel.

58. A system according to claim **52**, wherein said controller is configured for treatment specificity which avoids significant vessel stenosis as an aftermath of said treatment.

59. A system according to claim **52**, wherein said controller is configured to selectively heat nerves within a fat sheath thereof.

60. A system according to claim **52**, wherein said controller is configured with a protocol including a plurality of treatment regions and sufficient to reduce hypertension if applied to renal nerves.

61. A system according to claim **52**, wherein said controller is pre-configured with sets of parameters matching different target tissues and target tissue locations.

62. A system according to claim **52**, wherein said controller includes a feedback circuit for real-time control of settings of said system.

63. A method of setting up a device to selectively treating tissue using non-focused ultrasound energy delivered intrabody comprising:

setting up said device to be suitable for heating a selected area of tissue at a selected location from an arterial wall.

64-67. (canceled)

68. A method of setting up a device to selectively treating tissue using non-focused ultrasound energy delivered intrabody comprising:

setting up said device to be suitable for heating nerve tissue while not heating, to a tissue damaging level, tissue outside a fat sheath surrounding said nerve.

69. A method of reducing blood pressure comprising:

applying unfocused ultrasonic energy to the renal ostium from within a blood vessel, said energy sufficient to disrupt signals propagating through renal nerves.

70-71. (canceled)

72. A method for treating a patient experiencing a clinical disorder, the method comprising:

positioning at least one unfocused ultrasound emitter at an anatomical location proximate to a target tissue;

selectively delivering unfocused ultrasound energy to the target tissue; and

selectively causing thermal damage to at least a portion of the target tissue, to provide a desired treatment, no significant thermal damage being caused closer than 0.2 mm to said wall.

73. The method of claim **72** wherein the target tissue comprises body lumen, fat, nerves, vasa vasora, lymph, tumor, connective tissue, or plaque.

74. The method of claim **72** wherein the anatomical location comprises a blood vessel or artery.

75. The method of claim **74** wherein the anatomical location is the renal artery and the target tissue comprises one or more renal artery nerves.

76. The method of claim **74** wherein the at least one unfocused ultrasound emitter is configured not to touch the wall of the blood vessel or artery.

77. The method of claim **74** wherein the at least one unfocused ultrasound emitter is positioned as to not substantially block blood flow in the blood vessel or artery.

78. The method of claim **77** wherein the at least one unfocused ultrasound emitter, in operation, is cooled by the blood flow.

79. The method of claim **72** wherein the clinical disorder comprises at least one of sleep apnea, obesity, diabetes, end stage renal disease, lesion on a body lumen, contrast nephropathy, heart arrhythmia, congestive heart failure, and hypertension.

80. The method of claim **74** further comprising determining the distance from the blood vessel or artery wall to the target tissue and selecting the frequency of the unfocused ultrasound energy based upon on said distance of the target tissue.

81. The method of claim **72** wherein the frequency of the unfocused ultrasound energy is 10-22 Mhz.

82. The method of claim **72** wherein the target tissue comprises a treatment region.

83. The method of claim **82** further comprising determining the treatment region and selecting the intensity of the unfocused ultrasound energy according to the size of the treatment region.

84. The method of claim **77** further comprising delivering the at least one unfocused ultrasound emitter intrabody within the blood vessel or artery by a delivery catheter and configuring the delivery catheter to prevent the at least one unfocused ultrasound emitter from touching the wall of the blood vessel or artery.

85. The method of claim **72** further comprising selecting the target tissue using parameters obtained from an equation based upon empirical data.

86. The method of claim **85** wherein the equation is:

$$x(f,I)\ [\mathrm{mm}]=(C6+a*\mathrm{Exp}(\mathrm{flow}*b)-C2*\log(C3*I\ [\mathrm{W/cm^2}]))/(C4*f\ [\mathrm{MHz}]+C5)$$

Wherein, "I" is excitation intensity [W/cm^2]; "f" is working excitation frequency [MHz]; "x" is minimal radial distance from the artery wall [mm]; and "flow" is blood flow rate in the artery [ml/mm].

87. The method of claim **72** further comprising receiving feedback indicating the thermal damage to the target tissue.

88. The method of claim **87** further comprising modifying the parameters in response to said feedback.

89. The method of claim **72** further comprising selectively delivering the unfocused ultrasound energy in a manner such that there is no significant damage to non-target tissue.

90. The method of claim **72** further comprising selectively delivering the unfocused ultrasound energy in a manner such that there is no significant stenosis.

91. The method of claim **72** further comprising delivering unfocused ultrasound energy to at least one treatment region, each treatment region being at a separate circumferential location.

92. The method of claim **91** wherein the duration that unfocused ultrasound energy is delivered to the target tissue is 5-30 seconds per treatment region.

93. The method of claim **91** wherein the treatment comprises between 1 and 8 treatment regions.

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