

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 199959485 B2**
(10) Patent No. **756217**

(54) Title
Therapeutic prostatic thermotherapy

(51)⁶ International Patent Classification(s)
A61N 005/02

(21) Application No: 199959485 (22) Application Date: 1999.04.30

(87) WIPO No: W099/58194

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/084714	1998.05.08	US
09/130708	1998.08.06	US

(43) Publication Date : 1999.11.29

(43) Publication Journal Date : 2000.02.10

(44) Accepted Journal Date : 2003.01.09

(71) Applicant(s)
Thermatrix, Inc.

(72) Inventor(s)
Charles F. Manker; Aaron P. Perlmutter; Theron N.
Schaefermeyer ; Dixie T. Sells; Paul F. Turner

(74) Agent/Attorney
PIZZEYS,GPO Box 1374,BRISBANE QLD 4001

(56) Related Art
US 5480417
US 5895356
WO 97/01374

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



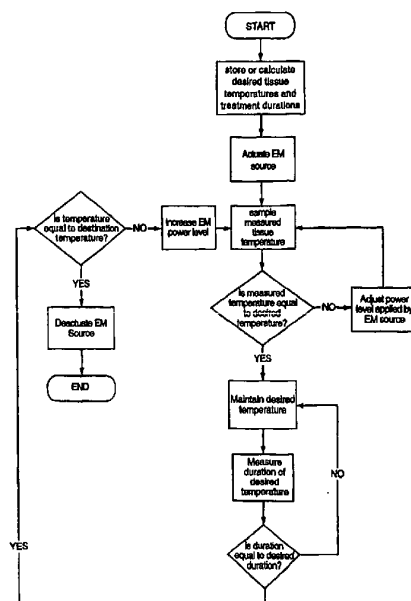
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61N 5/02		(11) International Publication Number: WO 99/58194
A1		(43) International Publication Date: 18 November 1999 (18.11.99)
(21) International Application Number: PCT/US99/09416		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 30 April 1999 (30.04.99)		
(30) Priority Data: 60/084,714 8 May 1998 (08.05.98) US 09/130,708 6 August 1998 (06.08.98) US		
(71) Applicant: THERMATRX, INC. [US/US]; 2211-B Lakeside Drive, Bannockburn, IL 60015 (US).		
(72) Inventors: MANKER, Charles, F.; 35 North Green Bay Road, Lake Forest, IL 60045 (US). PERLMUTTER, Aaron, P.; 525 East 89th Street #5A, New York, NY 10128 (US). SCHAEFERMEYER, Theron, N.; 851 East Eaglewood Drive, North Salt Lake, UT 84054 (US). SELLS, Dixie, T.; 2934 East Cobblemoor Lane, Sandy, UT 84093 (US). TURNER, Paul, F.; 762 Lacey Way, North Salt Lake, UT 84054 (US).		
(74) Agents: GAGALA, Bruce, M. et al.; Leydig, Voit & Mayer, Ltd., Two Prudential Plaza, Suite 4900, 180 North Stetson, Chicago, IL 60601-6780 (US).		Published With international search report.

(54) Title: THERAPEUTIC PROSTATIC THERMOTHERAPY

(57) Abstract

The present invention provides a method of treating a prostate in a patient in need thereof and a heating catheter, or an electromagnetic radiation applicator, system suitable for effecting the present inventive method. The present inventive method provides for substantial unexpected improvement in patient outcome by providing, inter alia, a preferred therapeutic temperature for thermotherapy of the prostate and a method of decreasing a patient's intolerance due to pain. The present inventive system provides for, inter alia, automatic implementation of the present inventive method.



THERAPEUTIC PROSTATIC THERMOTHERAPY

TECHNICAL FIELD OF THE INVENTION

The present invention relates to the heat treatment
5 of prostate disorders, including, but not limited to,
benign prostatic hyperplasia, prostatitis, and prostatic
malignancy.

BACKGROUND OF THE INVENTION.

10 Use of heating or energy radiating devices,
particularly microwave radiating devices, to administer
heat for the treatment of various diseases of the
prostate have been demonstrated to provide efficacious
treatment of various prostate conditions (Devonec et al.,
15 Monographs in Urology, 13, 77-95 (1992); De La Rosette et
al., J. Urology, 157, 430-438 (1997); Devonec et al., J.
Endourology, 5, 129-135 (1991); Bernier et al., Curr.
Opin. Urol., 7, 15-20 (1997)). Research has indicated
20 that the cellular transformations brought about by
raising tissue temperatures above certain levels can be
used therapeutically. At temperatures above 45°C,
thermal damage has been found to occur to cells, even
when the exposure to the elevated temperatures lasts for
even a short period of time. Thermal therapy has been
25 defined as the process of heating tissue to greater than
45°C to create necrosis. Both normal and abnormal cells
respond to thermal exposure. Accordingly, therapies
using heat have relied on healthy tissue regeneration
after the delivery of a "thermal dose." A thermal dose
30 is a quantity which is indicative of the biological
impact of elevated temperature maintained for a period of
time. For the purposes of the present invention, thermal
dosages can be calculated according to the method of
Sapareto et al., International Journal of Radiation
35 Oncology, Biology, Physics, 10, 787-800 (1984), except

that the breakpoint of 45°C, rather than 43°C is used for non-malignant tissues. That is, for the purposes of the present invention, thermal dose measured in Equivalent 45°C hours is equal to the sum of the products of one-half of the treatment temperature in excess of 45°C times the duration at that time, or

$$\sum_{t=0}^{t=\text{final}} 0.5^{(45-T)} \Delta t,$$

wherein T is temperature in degrees centigrade and t is time in hours.

A variety of different methods have been developed to deliver therapeutically effective quantities of heat to the prostate, including ultrasound delivery devices, RF delivery devices and hot water-recirculating catheters. One such device is the "WITT" hot water recirculating catheter, which is manufactured by ArgoMed, Inc. of Parsippany, New Jersey (USA). Another such device is the "Thermex II", which is manufactured by Direx Systems, Ltd. While hot water recirculating catheters are useful in the context of the present invention, a significant drawback is that it is difficult to apply an accurate thermal dose to the prostatic urethra while simultaneously avoiding delivery of a therapeutic dose of heat to non-target tissues such as the penis. Moreover, the design of hot water recirculating catheters can make accurate placement of the heating zones within the patient more difficult. A limitation to the usage of RF applicators is their relatively poor ability to penetrate tissue, often resulting in superficial treatment of the prostatic tissue.

A more preferred method to deliver thermotherapy in the context of the present invention is via a urethrally-

inserted catheter with an imbedded microwave antenna. A cooling device is typically incorporated into microwave emitting catheters so that urethral tissue proximal to the microwave antenna is cooled. The addition of this feature has been directed at preserving the prostatic urethra, thereby reducing treatment discomfort and post-treatment recovery time. A temperature or energy measurement device can be used during treatments so that a thermal dose can be measured. Treatments utilizing this approach include TransUrethral Microwave Thermotherapy (TUMT). One disease currently treated by TUMT is Benign Prostatic Hyperplasia (BPH). The therapeutic effect of such therapies can be measured in any suitable manner. For example, therapy can be measured by an improvement in the AUA symptom score, or by an improvement in the Madsen-Iversen score, an improvement in urine flow, an improvement in urethral diameter, or the like.

The objective of TUMT of BPH is to destroy a portion of the prostatic tissue, while preserving the tissue immediately adjacent to the prostatic urethra and the tissue immediately adjacent to the same. Current opinion in the field is that the greater the tissue destruction in the prostate, the more beneficial the treatment (De La Rosette et al., *supra*). Therefore, current device and therapy design is directed at improving the maximum heat dose over the shortest period of time. In that regard, typical maximum temperatures frequently reach 65°C or greater within the prostate. Unfortunately, this has a number of undesirable side-effects. For example, with prior art TUMT methods, hematuria rates typically exceed 30%, rates of urinary retention requiring long term catheterization usually exceeds 20%, rates of urethral bleeding not merely due to catheterization exceed 5%, and rates of urinary tract infection, ejaculatory

disturbances, inflammation in the urethra, chronic incontinence, and impotence are all statistically significant and exceed about 1.5%.

There are, however, other delivery methods which
5 utilize non-cooled radiation applicators and require the delivery of multiple treatments at relatively low temperatures (45°C - 47°C and lower). The objective of these methods is to obtain a therapeutic benefit while avoiding temperature ranges that are commonly thought to
10 cause patient intolerance and give rise to significant side effects. The problem with these methods is that the data suggest, and current published opinion in the art states, that efficacy is reduced. In addition, multiple treatment sessions are required at these relatively low
15 temperatures which is inconvenient and uncomfortable for the patient and economically disadvantageous for the physician.

One significant drawback to other TUMT devices and therapies is that they are frequently painful for the
20 patient and require the use of narcotic analgesics to control pain. This makes current TUMT inconvenient, limits the use of the therapy, adds to the expense and recovery time, and can potentially result in patient loss.

25 A further drawback to other TUMT devices is the requirement for multiple treatment sessions and its limited efficacy. Thus, the economics of the treatment are severely limited.

The electromagnetic radiation applicator systems
30 developed for the treatment of BPH have limited the ability of the skilled artisan to control urethral and prostate temperatures. Many prior art radiation applicator devices have controlled the heating of the prostate by simply controlling the power supplied to the
35 heating unit. This method of controlling the heating is

typically necessary when the catheter system is used in conjunction with a surface cooling device, because the surface cooling device alters measured temperatures. Non-cooled catheter systems (see, e.g., U.S. Patent 5 4,967,765 to Turner et al.) have the ability to monitor surface temperatures more accurately than cooled catheter systems. However, these devices have also been constructed in a manner to limit complexity and cost. Accordingly, prior art catheter systems have been capable 10 of heating tissue to a pre-selected temperature and maintaining the tissue at that temperature, but have not incorporated the more advanced features of the present invention. Other catheter designs useful in the context of the present inventive system have been commercially 15 developed, e.g., by EDAP/Technomed and Urologix. While these other catheter designs are well known in the art, other examples are disclosed, e.g., by U.S. Patents 4,620,480 and 5,628,770.

In view of the foregoing problems, there is a need 20 for prostatic thermotherapy, particularly for BPH that is cost-effective, eliminates the use of general anesthesia and obviates the need for a cooled catheter. There is also a need for a prostatic thermotherapy that reduces non-beneficial side effects of previous methods.

25 The present invention provides such a method and related devices. These and other advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

30

BRIEF SUMMARY OF THE INVENTION

The present invention provides a method of heat treating a patient's prostate tissue and devices, programs, and systems useful in practicing the present 35 inventive method.

5A

This invention in one aspect resides in a method of treating a prostate of a patient for benign prostatic hyperplasia comprising

inserting a catheter, having an attached applicator,
5 into prostatic urethra tissue of a urethra, wherein said urethra tissue is surrounded by prostate tissue of a prostate;

applying energy through the applicator to said urethra tissue and prostate tissue;

10 sensing the temperature of said urethra tissue;

increasing the energy applied based on the sensed temperature so that the urethra tissue temperature increases in specified incremental rates;

15 maintaining each specified incremental rate for a time sufficient to acclimatize a patient to said incremental rate; and

regulating the energy applied to simultaneously maintain said urethra tissue at a higher temperature than the prostate tissue, and at a destination temperature, within a
20 range of from about 49°C to about 57°C, for a time sufficient to achieve a therapeutic effect on said prostate.



Surprisingly, it has now been found that the maximum urethral temperature that can be tolerated by patients to whom narcotic analgesics or general anesthesia have not been administered exceeds the previously art-accepted maximum of 45°C - 47°C, under selected conditions. It has also now been found that the side-effects which have been reported to accompany high temperature treatment of the prostate are substantially reduced by use of the method of the present invention when the maximum urethral temperature is kept below about 57°C. Moreover, it has been surprisingly discovered that preservation of the prostatic urethra is not an important parameter of the thermotherapy of the prostate. On the contrary, the urethra and the urethrally proximal portions of the prostate are the tissues in which heating is desired in the present inventive method. Thus, the present invention provides a method of heat treating a patient's prostate tissue wherein the temperature of the prostate tissue is raised from an initial temperature below the destination temperature, to a destination temperature in the range of from 49°C to almost 57°C. The destination temperature is maintained for a period of time sufficient to administer a sufficient amount of heat to achieve a therapeutic effect on the prostate.

It has now been found that by allowing a patient to acclimatize to elevated urethral temperatures the patient's threshold of pain, with or without antiinflammatory analgesics, is elevated to about 60°C. Thus, the present invention provides a method of prostatic thermotherapy wherein the maximum urethral temperature is raised to an elevated temperature which exceeds the previous art-accepted maximum by elevating the method temperature in such a manner so as to allow the patient to acclimatize the temperature elevation procedure. The rate at which the temperature can be

raised from 37°C to the range of about 42°C and 46°C can be relatively rapid. In keeping with the inventive method, it is desirable for the rate at which temperature is elevated from about 44°C to the destination temperature to occur more slowly.

- 5 Further, the rate of rise in temperature preferably decreases as the maximum urethral temperature approaches the destination temperature. In general, the rate of increase in temperature according to the present invention varies between 1°C per 0.5 minutes to 1°C per 15 minutes. In order to allow better
- 10 patient acclimatization, the rate of change in the temperature preferably does not exceed 1°C per minute, and more preferably does not exceed 1°C per 2 minutes. However, it is desirable to physician and patient to minimize the amount of time required for therapy. In order to reduce the amount of time required
- 15 to acclimate the patient to elevated urethral temperatures, the rate of temperature rise can be increased to 1°C per 10 minutes near the destination temperature and to about 1°C per 2 minutes at the lower temperatures. The total time to raise the urethral temperatures from 37°C to the destination
- 20 temperature preferably ranges from 15 minutes to 2 hours, and more preferably is from 20 to 45 minutes. Moreover, it will be appreciated that the temperature rise can be continuous or discontinuous (i.e., "stepped").

- In a further aspect, this invention resides in a method
- 25 method of treating a prostate of a patient for benign prostatic hyperplasia comprising

inserting a heated catheter system into prostatic urethra tissue of a urethra, wherein said urethra tissue is surrounded by prostrate tissue of a prostate;

- 30 supplying energy to said heated catheter system sufficient to raise the temperature of said urethra tissue; increasing the energy applied so that the urethra tissue temperature increases in specified incremental rates;



maintaining each specified incremental rate for a time sufficient to acclimatize a patient to said incremental rate; and

regulating the energy applied to simultaneously
 5 maintain said urethra tissue at a higher temperature than the prostate tissue, and at a destination temperature within a range of from about 49°C to about 57°C, for a time sufficient to achieve a therapeutic effect on said prostate.

wherein said heated catheter system comprises:

10 a non-cooled catheter for insertion into said urethra,
 a heat applicator attached to said catheter, and a connector for connecting said heat applicator to a source of energy sufficient to elevate the temperature of tissue
 15 surrounding said heat applicator to said therapeutic temperature and for maintaining said therapeutic temperature for a time sufficient to effect therapy of said prostate; and
 a temperature sensor support attached to said catheter for supporting a temperature sensor for sensing the
 20 temperature of said urethra surrounding said applicator.

In a still further aspect, this invention resides in a method of treating a prostate of a patient for benign prostatic hyperplasia comprising:

applying energy to prostatic urethra tissue of a
 25 urethra and surrounding prostate tissue of a prostate to elevate the temperature of the urethra tissue;

increasing the energy applied so that the urethra tissue temperature increases in specified incremental rates;

maintaining each specified incremental rate for a
 30 time sufficient to acclimatize a patient to said incremental rate; and

regulating the energy applied to simultaneously maintain said urethra tissue at a higher temperature than the prostate tissue, and at a destination temperature within a



7B

range of from 49°C to about 57°C for a time sufficient to achieve a therapeutic effect on said prostate.

The invention can best be understood with reference to the accompanying drawings and in the following detailed
5 description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a block diagram of a urethral insertable electromagnetic radiation applicator system according to an
10 embodiment of the present invention.



Figure 2 is a block diagram of the temperature control system and the microwave applicator of the system illustrated in Figure 1.

Figure 3 is a flow chart of a temperature control program for regulating the temperature of body tissue heated by the microwave applicator of Figure 2.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method of heat treating a patient's prostate tissue and devices, programs, and systems useful in practicing the present inventive method.

Surprisingly, it has now been found that the maximum urethral temperature that can be tolerated by patients to whom narcotic analgesics or general anesthesia have not been administered exceeds the previously art-accepted maximum of 45°C - 47°C, under selected conditions. It has also now been found that the side-effects which have been reported to accompany high temperature treatment of the prostate are substantially reduced by use of the method of the present invention when the temperature is kept below about 57°C. Moreover, it has been surprisingly discovered that preservation of the prostatic urethra is not an important parameter of the thermotherapy of the prostate. On the contrary, the urethra and the urethrally proximal portions of the prostate are the tissues in which heating is desired in the present inventive method. Thus, the present invention provides a method of heat treating a patient's prostate tissue wherein the temperature of the prostate tissue is raised from an initial temperature below the destination temperature, to a destination temperature in the range of from 49°C to almost 57°C. The destination temperature is maintained for a period of time sufficient

to administer a sufficient amount of heat to achieve a therapeutic effort on the prostate.

It has now been found that by allowing a patient to acclimatize to elevated urethral temperatures the patient's threshold of pain, with or without antiinflammatory analgesics, is elevated to about 60°C. Thus, the present invention provides a method of prostatic thermotherapy wherein the maximum urethral temperature is raised to an elevated temperature which exceeds the previous art-accepted maximum by elevating the method temperature in such a manner so as to allow the patient to acclimatize the temperature elevation procedure. The rate at which the temperature can be raised from 37°C to the range of about 42°C and 46°C can be relatively rapid. In keeping with the inventive method, it is desirable for the rate at which temperature is elevated from about 44°C to the destination temperature to occur more slowly. Further, the rate of rise in temperature preferably decreases as the maximum urethral temperature approaches the destination temperature. In general, the rate of increase in temperature according to the present invention varies between 1°C per 0.5 minutes to 1°C per 15 minutes. In order to allow better patient acclimatization, the rate of change in the temperature preferably does not exceed 1°C per minute, and more preferably does not exceed 1°C per 2 minutes. However, it is desirable to physician and patient to minimize the amount of time required for therapy. In order to reduce the amount of time required to acclimate the patient to elevated urethral temperatures, the rate of temperature rise can be increased to 1°C per 10 minutes near the destination temperature and to about 1°C per 2 minutes at the lower temperatures. The total time to raise the urethral temperatures from 37°C to the destination temperature

preferably ranges from 15 minutes to 2 hours, and more preferably is from 20 to 45 minutes. Moreover, it will be appreciated that the temperature rise can be continuous or discontinuous (i.e., "stepped").

5 The total amount of heat delivered to the patient is also an important parameter of the present inventive method. While patients are able to acclimate to temperatures up to about 60°C if the rate of tissue temperature increase is controlled, it is desirable to control the total amount of heat administered to ensure both effective therapy and minimization of side effects. The administration of heat can be quantified by any suitable measurement, however, it is preferable to approximate the quantity of heat administered using the method of Sapareto et al., International Journal of Radiation Oncology, Biology, Physics, 10, 787-800 (1984), modified such that the breakpoint of 45°C, rather than 43°C is used for non-malignant tissues. Thus, while it is only an approximation of the actual thermal dose administered, for the purpose of the present invention, thermal dose measured in equivalent 45°C hours (or equivalent 45°C minutes) is equal to the sum of the products of one-half raised to the result of 45 minus the treatment temperature times the duration of time at that temperature, or

$$\sum_{t=0}^{t=\text{final}} 0.5^{(45-T)} \Delta t,$$

30 wherein T is temperature in degrees centigrade and t is time in hours (or minutes). For purpose of the present invention, the contribution of temperatures to the thermal dose below 45°C can be ignored.

Table 1, below, illustrates several heating protocols, (utilized after heating to about 44°C) that are suitable in the context of the present invention. Each protocol is identified by a letter, A through H.

- 5 Protocol A defines one preferred embodiment. Protocols B and C define embodiments in which the destination temperature is held for a shorter periods of time, while in the embodiment of protocols D and E the final destination temperature is held for a longer period of
- 10 time (relative to protocol A). Protocol F defines an embodiment in which the destination temperature is the lowest amongst the illustrated embodiments. Protocol G defines an embodiment in which the destination temperature is higher than the destination temperature of
- 15 Protocols A-F. Protocol H, which is an operable, but not preferred embodiment of the present invention, illustrates that it is difficult to achieve both pain tolerance (through the use of tolerable rates of temperature increase) and to avoid delivering a thermal
- 20 dose in excess of about 30,000 equivalent 45°C minutes (about 500 equivalent 45°C hours). This is because 1 minute at 60°C is equivalent to 16,384 equivalent 45°C minutes, without calculating any temperature ramp time between body temperature and 60°C.

Table 1.

Measured Urethral Temperature in Celsius	Time at Measured Temperature in Minutes							
	A	B	C	D	E	F	G	H
	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2
Protocol:								
44.0	1	1	1	1	1	1	1	1
45.0	1	1	1	1	1	1	1	1
45.5	1	1	1	1	1	1	1	1
46.0	2	2	2	2	2	2	2	2
46.5	1	1	1	1	1	1	1	1
47.0	2	2	2	2	2	2	2	2
47.5	2	2	2	2	2	2	2	2
48.0	2	2	2	2	2	2	2	2
48.5	2	2	2	2	2	2	2	2
49.0	3	3	3	3	3	100	3	3
49.5	2	2	2	2	2		2	2
50.0	3	3	3	3	3		3	3
50.5	2	2	2	2	2		2	2
51.0	45	20	30	75	90		3	3
51.5							3	3
52.0							3	3
52.5							3	3
53.0							4	4
53.5							3	3
54.0							4	4
54.5							3	3
55.0							4	4
55.5							4	4
56.0								4
56.5							.	5
57.0							.	4
57.5								4
58.0								5
58.5								4
59.0								5
59.5								4
60.0								5
Approximate Thermal	54	27	38	86	102	28	300	4160
Dose (eqv. 45°C hrs.):								
Approximate Thermal	3230	1630	2270	5150	6110	1670	40600	249,600
Dose (eqv. 45°C min.):								

- Preferably, the gradual increase in temperature is automatically regulated. Accordingly, for electromagnetic radiating catheters, it is preferable for the power source that provides the energy to the radiation applicator be in operable association with urethral temperature sensors by way of a microprocessor, computer, or the like. Similarly, for heating catheters (e.g., hot water heaters)

SUBSTITUTE SHEET (RULE 26)

it is preferable for an automatic regulator to control the temperature of the catheter positioned in the prostatic urethra.

The present invention also provides a surprisingly effective form of thermotherapy of the prostate. Prior art methods have called for maximum treatment temperatures at about 47°C or lower ("low temperature treatments") or at temperatures well in excess of 60°C ("high temperature treatments"). However, thermotherapy according to the present invention is advantageously conducted at a temperature of from 49°C to about 57°C, and preferably, at a temperature of from about 50°C to about 55°C. It will be appreciated that in a prostate in which the tissue temperature sensor measures a temperature of 51°C to 52°C that the actual range of temperatures in the heated tissue will vary and in isolated places can reach temperatures as high as 55°C. Tissue temperature variation is consequence of uneven dispersion of energy from the antenna or heating portion of the catheter, differential absorption of the dispersed energy by the targeted tissue, and variations in blood perfusion through the target tissue. Blood, of course, will be about 37°C in a human and acts as coolant. Preferably patient tissue is heated to a maximum average sensed temperature of about 51°C to about 52°C.

Thermotherapy conducted in this temperature range is more effective than that conducted at the lower temperature ranges and is not accompanied by an increase in side-effects (except for the need to anesthetize the patient with medication or acclimate the patient by gradually increasing urethral temperatures). Moreover, thermotherapy of the prostate performed in accordance with the present invention is accompanied by substantially fewer side effects such as, for example, hematuria, dysuria, tissue slough, retrograde ejaculation, extended catheterization and the like; see De La Rosette et al.,

supra than thermotherapy performed at temperatures exceeding 60°C .

The temperature of the prostate is maintained at the destination temperature (regardless of whether the temperature is gradually or rapidly increased to the destination temperature) for a period of time suitable to effect a therapeutic result (e.g., a decrease in the AUA symptom score). Suitable times at the treatment temperature can be as short as about 0.5 minutes, but are preferably at least 30 minutes. Suitable times at the treatment temperature can be as long as desired, but in order to avoid overdosage of heat, undesirable side-effects, and loss of time, the time at the treatment temperature can be as long as about 4 hours, but preferably is not longer than about 2 hours, and more preferably is not longer than about 1 hour. Treatment time should take into account the thermal dose that is administered.

Heat treatment according to the present invention preferably provides the urethra proximal tissues with a heat dose that is sufficient to provide a therapeutic effect, but which is low enough to avoid excessive undesired side-effects. For example, treatment according to the present invention provides at least an estimated minimum cumulative thermal dose of at least about 1500 equivalent 45°C minutes (i.e., 25 equivalent 45°C hrs.). More preferably, treatment according to the present invention provides at least about 2000 equivalent 45°C minutes. Treatment according to the present invention preferably provides an estimated maximum cumulative thermal dose which does not exceed about 30,000 equivalent 45°C minutes, and more preferably does not exceed about 20,000 equivalent 45°C minutes, and yet more preferably does not exceed about 7000 equivalent 45°C minutes.

The present inventive method is specifically designed to provide the highest temperatures in the prostatic urethra consistent with minimizing side effects and patient discomfort. The method is preferably accomplished in a straightforward method by not using a cooled catheter. A cooled catheter causes the peak temperatures to occur a well within the prostate away from the urethral walls. When a cooled catheter is used, measured tissue temperatures decline rapidly as the urethra is approached, such that the 2 mm of prostate tissue proximal to the urethra typically do not receive therapeutic quantities of heat. However, rather than attempting to insulate these tissues, the present invention seeks to directly treat these tissues. When a heating catheter or non-cooled electromagnetic-radiating catheter is used the highest temperatures are reached in the urethra. Temperature declines deeper into the prostate tissue away from the catheter. Surprisingly, this heating pattern provides substantially more effective treatment.

Moreover, high temperature prior art techniques have focused on ablation of deep prostate tissue with the idea that eliminating deep prostatic tissue mass would decrease the pressure on the urethra allowing better urine flow and other benefits. In contrast, the present inventive method does not have the goal of decreasing prostate volume or mass and substantial changes in prostate volume or mass are not an expected outcome of the present inventive therapy. While applicants do not wish to be bound to any particular theory, it is believed that the application of an appropriate dose of heat to the prostatic urethra and the urethrally proximal prostate tissue causes a change in sensation. It is not known whether this change in sensation is accompanied by physical changes to the nerve bundles extending along the urethra through the prostate, but it is conceivable that these neurons are the true

targets of the thermotherapy. In any event, while it is possible to use a catheter with a cooling device to practice the present invention, there is not a compelling medical reason to do so.

5 By limiting all tissue temperatures to less than about 57°C, and preferably less than about 55°C, the substantial side-effects accompanying very high temperature thermal therapy are advantageously avoided. Treatment according to the present invention is not unduly
10 or intolerably painful. However, pain relieving medication can be optionally administered. Preferably, treatment according to the present invention does not require narcotic analgesics, however, the use of antiinflammatory analgesics and mild anxiolytics can be
15 administered according to the judgement of the skilled clinician.

One aspect of the present invention provides a urethral insertable electromagnetic radiation applicator system suitable for implementing the present inventive
20 method. Figure 1 provides a block diagram of an example of a urethral insertable electromagnetic radiation applicator system according to an embodiment of the present invention. The system includes a catheter 1 for insertion into the urethra. The catheter 1 generally is
25 adapted to enclose a microwave applicator 2. As illustrated in Figure 2, the microwave applicator includes an antenna 10 for radiating electromagnetic energy through the wall of the catheter to body tissue, particularly a prostate gland undergoing treatment.

30 In this embodiment, the catheter 1 and the microwave applicator 2 may be variously configured, and can be similar to the catheter and the applicator disclosed in U.S. Patent Number 4,967,765, the disclosure of which is hereby incorporated by reference in its entirety. In the
35 referenced document, the microwave applicator includes a

helical coil antenna mounted inside a urethral catheter. A suitable electrical connector, such as a coaxial cable connects the antenna to external excitation electronics. The antenna delivers electromagnetic radiation through the wall of the catheter to heat tissue adjacent to the catheter. Using a helical coil antenna is preferred to provide substantially uniform heating along the length of the antenna.

According to an important aspect of the invention, the applicator system includes a temperature control system 3 for regulating the temperature of tissue heated by the microwave applicator 2. Although the temperature control system may be an open loop system or a closed loop system, in a preferred embodiment, the temperature control system 3 comprises a closed loop system. In a most preferred embodiment, the temperature control system senses the temperature of tissue to being heated by the microwave applicator and regulates the electromagnetic energy output by the microwave applicator based on the sensed tissue temperature. Regulating the electromagnetic energy output by the microwave applicator based on the sensed tissue-temperature is preferred, because the tissue temperature may be a non-linear function of applied electromagnetic energy. More particularly, when electromagnetic energy is applied to tissue, such as the tissue of the prostate gland, the resulting temperature of the tissue depends on a variety of factors, for example, the blood flow to the tissue. Moreover, the relationship between temperature and applied electromagnetic energy may vary from one patient to the next. In conventional systems, the power applied to microwave applicators was simply increased in fixed power increments. For example, the power was increased by x watts every y minutes. Such a system is less preferred because of the variable relationship between applied electromagnetic energy and

tissue temperature. Thus, by controlling the applied electromagnetic energy based on an accurately sensed temperature, embodiment of the present invention are capable of accurately regulating tissue temperature, while
5 accounting for variations in the tissue being heated.

Figure 2 illustrates an example of a block diagram of the temperature control system 3 and the microwave applicator 2 according a preferred embodiment of the invention. In the illustrated embodiment, the temperature
10 control system 3 comprises a temperature sensor 4 capable of sensing tissue temperature, signal conditioning circuitry 5 for conditioning the output signal from the temperature sensor 4, a microcontroller 6 for producing a temperature control signal based on the output signal from
15 the temperature sensor 4, and an electromagnetic energy source 8 for applying electromagnetic energy to the antenna 10. The components illustrated in Figure 2 cooperate to control the temperature of tissue being treated in response to the sensed tissue temperature.

20 The temperature sensor 4 may be variously configured. For example, the temperature sensor 4 may comprise a thermistor or thermocouple capable of sensing the temperature of tissue, such as the tissue of the prostate gland. In an alternative embodiment, the temperature
25 sensor 4 may comprise a resistance temperature difference (RTD) sensor. The temperature sensor 4 preferably produces an output signal, e.g., a voltage, indicative of the tissue temperature.

The signal conditioning circuitry preferably receives
30 the output signal from the temperature sensor and conditions the signal for processing by the microcontroller 6. For example, the signal conditioning circuitry may include a low-pass filter for filtering noise from the signal from the temperature sensor 4. The
35 signal conditioning circuitry may also include an

amplifier, such as an operational amplifier, for amplifying the signal output from the temperature sensor 4. The gain of the operational amplifier is preferably selected so that the voltage range of the output signal of the signal conditioning circuitry matches the input voltage range of the microcontroller 6.

The microcontroller 6 may be variously configured. For example, the microcontroller 6 may comprise a microprocessor including internal memory circuits and analog to digital conversion circuitry, for processing the output signal from the signal conditioning circuitry and producing the temperature control signal. Although the illustrated embodiment depicts a microcontroller having an internal analog to digital converter, the present invention is not limited to such an embodiment. For example, the analog to digital converter may be external to the microcontroller 6. A temperature control program controls the microcontroller to output the temperature control signal based on the sensed tissue temperature. The temperature control program may be stored in memory internally or externally to the microcontroller. In an alternative embodiment, the temperature control program may be stored in a portable computer-readable storage medium, such as a magnetic disk or an optical disk. Utilizing a temperature control program to produce the control signal is preferred because the program can be updated as treatment protocols, e.g., treatment temperatures and/or durations, change.

The present invention is not limited to utilizing a microcontroller 6 to produce the temperature control signal. For example, analog or digital circuitry that performs equivalent functions to the microcontroller or the temperature control program is within the scope of the invention.

An electromagnetic energy source 8 receives the temperature control signal from the microcontroller and applies electromagnetic energy to the antenna. In a preferred embodiment, the electromagnetic energy source comprises an oscillator. The frequency of oscillation of the oscillator is preferably selected for optimal heating of tissue within FCC regulations. The oscillation frequency of the electromagnetic energy source is preferably selected to be about 915 MHz or about 12, in accordance with present FCC regulations. However, the present invention is not limited an oscillation frequency of 915 MHz. For example, if another frequency is determined to be more therapeutically beneficial and/or FCC regulations change, the preferred frequency of oscillation may change accordingly.

The antenna 10 receives the electromagnetic energy from the source 8 and radiates the energy to the tissue being treated. As stated above, the antenna preferably comprises a helical coil antenna. However, the present invention is not limited to helical coil antennas. Any antenna that produces a substantially uniform radiation pattern over a desired area of treatment is within the scope of the invention.

Figure 3 is a flow chart of an example of a temperature control program according to an embodiment of the present invention. Once the catheter 1 is inserted into the urethra and the antenna is positioned near the prostate gland, the electromagnetic energy source is actuated. In order to avoid having to anesthetize the patient, the program preferably increases the temperature in predetermined or specified increments and maintains the temperature at each increment for a predetermined or specified duration. The temperature control program may store or calculate a plurality of desired prostatic tissue temperatures and a treatment duration corresponding to

each temperature. The temperature sensor measures the tissue temperature. The control program may sample the measured temperature and store the measured temperature in memory. The program determines whether a first desired
5 temperature level for treatment has been reached, i.e., by comparing the measured temperature stored in memory to one of desired treatment temperatures. If the first temperature has not been reached, the microcontroller continues increasing the temperature. Once the first
10 temperature has been reached, the microcontroller adjusts the temperature control signal to maintain the first temperature. In order to maintain the first temperature, the microcontroller adjusts the temperature control signal based on the output signal from the temperature sensor,
15 i.e., by sampling and comparing the measured temperature to the first desired temperature.

According to a preferred embodiment, the microcontroller also measures and controls the duration of treatment at each desired temperature. This measurement
20 may be performed by executing a timer routine once each desired temperature is reached. The timer routine records the duration of the treatment at each desired temperature. The program compares the recorded duration to a desired duration. Once the desired duration has been reached, the
25 program continues to the next processing step. In an alternative embodiment, an external timer circuit may be coupled to the microcontroller to measure treatment duration.

Once treatment occurs at a first desired temperature
30 for a first desired time period, the control program determines whether the first temperature is the final or destination temperature in the processing routine. If the first temperature is the final or destination temperature, the program deactuates the electromagnetic energy source
35 and ends. However, because the treatment preferably

occurs at a plurality of different temperature levels, the temperature control program preferably increases the power level after the treatment at the first temperature so that treatment can occur at a second at a second temperature, preferably higher than the first temperature. The control program preferably repeats these steps, i.e., increasing the temperature until a desired temperature is reached, maintaining the temperature at the desired temperature for a desired duration, then increasing the temperature to the next level. Because the power level is controlled based on the sensed tissue temperature, the control program automatically tailors itself to each patient.

As stated above, the control program preferably steps through a plurality of temperature levels with predetermined or specified durations. The predetermined or specified durations may be fixed or variable. The number of levels, the temperature at each level, and the duration of each level are preferably selected to reduce patient discomfort and increase the effectiveness of treatment. In a most preferred embodiment, the temperature levels and durations are selected as shown in Table 1 above.

As illustrated in Table 1, a preferred embodiment of the treatment protocol begins at 44°C. In order to reach a tissue temperature of 44°C, the control program may actuate the electromagnetic source at an initial level until 44°C is reached. The program may increase the temperature in predetermined or specified steps, as illustrated in Figure 3 in order to reach 44°C. In an alternative embodiment, since the low temperature portion, e.g., between about 37°C and about 44°C, of the treatment protocol is not as important, the control program may actuate the electromagnetic energy source such that the antenna delivers one watt during each 30 second time

internal until 44°C is reached. Once 44°C is reached, the temperature control program preferably controls the energy applied by the antenna based on the sensed tissue temperature as illustrated in Table 1. For example, when
5 the tissue temperature measured by the temperature sensor is 44°C, the microcontroller executes a timer routine. When the timer routine reaches 1 minute, the microcontroller preferably increases the power applied by the electromagnetic energy source to increase the tissue
10 temperature to the next level, e.g., 44.5°C. When the tissue temperature measured by the temperature sensor reaches 44.5°C, the microcontroller preferably maintains that level and re-executes the timer routine. In this manner, the microcontroller and the temperature sensor
15 step through the desired treatment protocol. Because the temperature increments according to Table 1 are relatively small, e.g., about 0.5 degrees, the patient is able to acclimate to the elevated temperatures, discomfort is minimized, and the need for narcotic analgesics and/or
20 general anesthesia is attenuated or eliminated.

Once the destination temperature is reached and maintained for a desired time period, the control program deactuates the electromagnetic energy source and ends. According to Table 1, the destination temperature is
25 preferably 51°C and the treatment duration at that temperature is 45 minutes. However, the present invention is not limited to a destination temperature of 51° for a duration of 45 minutes. For example, the destination temperature is preferably between 49°C and about 57°C, and
30 more preferably between about 50°C and about 55°C. Also, the average maximum sensed temperature is between about 51°C and about 52°C. The treatment duration at the destination temperature preferably does not exceed about 60 minutes.

The present invention is not limited to the temperature below the destination temperature or the durations at these temperatures illustrated in Table 1. For example, the control program may control the tissue temperatures such that the temperature is increased in increments of about 1°C. The treatment duration at each temperature is preferably selected to range from no less than about 30 seconds to no more than about 15 minutes, and more preferably no less than about 1 minute to no more than about 10 minutes, and even more preferably no less than about 2 minutes to no more than about 5 minutes. The longer the duration at each temperature, the lower the discomfort level of the patient. On the other hand, increasing the duration also increases treatment time. Thus, the upper limit of about 15 minutes per degree is preferably not exceeded.

Although increasing the temperature in predetermined or specified steps is preferred, the present invention is not limited to such an embodiment. For example, the control program may implement a slow ramping function from an initial temperature to a destination temperature. The initial temperature may be about 37°C. The destination temperature may be about 51°C. In order to implement the ramping function the temperature control program may actuate the electromagnetic energy source. The temperature sensor measures the tissue temperature. The temperature control program may sample and store values corresponding to the measured temperature. The control program may determine the rate of change of the temperature signal, i.e., by differentiating the temperature signal utilizing the stored values. The control program may compare the calculated rate of change to a desired rate of change. If the rate of change in temperature is greater than the desired rate of change,

the temperature sensor decreases the energy supplied by the electromagnetic energy source. If the rate of change in temperature is less than the desired rate of change, the temperature sensor decreases the power supplied by the electromagnetic energy source. If the rate of change is less than a desired rate of change, the temperature control program increases the energy supplied by electromagnetic energy source. The desired rate of increase in temperature may be fixed or variable. Once the destination temperature is reached, the temperature control program preferably maintains the destination temperature for a predetermined or specified time period, as described above.

15 All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating a prostate of a patient for benign prostatic hyperplasia comprising inserting a catheter, having an attached applicator,
5 into prostatic urethra tissue of a urethra, wherein said urethra tissue is surrounded by prostate tissue of a prostate;

applying energy through the applicator to said urethra tissue and prostate tissue;

10 sensing the temperature of said urethra tissue;
increasing the energy applied based on the sensed temperature so that the urethra tissue temperature increases in specified incremental rates;

15 maintaining each specified incremental rate for a time sufficient to acclimatize a patient to said incremental rate; and

20 regulating the energy applied to simultaneously maintain said urethra tissue at a higher temperature than the prostate tissue, and at a destination temperature, within a range of from about 49°C to about 57°C, for a time sufficient to achieve a therapeutic effect on said prostate.

2. The method of claim 1, wherein said destination temperature is in the range of about 50°C to about 55°C.

25

3. The method of claim 1, wherein said temperature is measured by said sensor as a maximum average temperature of about 51°C to about 52°C.

30 4. The method of any one of claims 1 to 3, wherein said energy is hot water.



5. The method of any one of claims 1 to 3, wherein said energy is microwave.

6. The method of any one of claims 1 to 3, wherein said energy is ultrasonic energy or radiofrequency (RF) energy.

7. The method of any one of claims 1 to 6, wherein said time sufficient to effect therapy of said prostate is from about 5 minutes to about 4 hours.



10

8. The method of any one of claims 1 to 6, wherein said time sufficient to effect therapy of said prostate includes from about 20 minutes to about 90 minutes at the destination temperature.

15



9. The method of any one of claims 1 to 8, said method comprising

a first heating step of warming tissue proximal to said applicator up to critical temperature, said critical

20 temperature being in the range of about 42°C to about 46°C,

followed by a second heating step, said second heating step comprising gradually increasing the temperature of said tissue proximal to said applicator to said therapeutic temperature such that the mean rate of increase in temperature

25 is from about 0.5 minute/°C to about 15 minute/°C.

10. The method of claim 9, wherein said mean rate of increase in temperature, during said second step, is from about 1.0 minute/°C to about 10 minute/°C.

30



11. The method of claim 10, wherein said mean rate of increase in temperature, during said second step, is selected such that from about 15 minutes to about 2 hours separate the time points when said tissue surrounding said applicator rises

from said critical temperature to said therapeutic temperature.

12. The method of claim 11, wherein said mean rate of increase in temperature is selected such that from about 15 minutes to about 45 minutes separate the time points when said tissue surrounding said applicator rises from said critical temperature to said therapeutic temperature.

13. The method of claim 9, wherein said second heating step is controlled by a microcontroller, such that said second step occurs independent of direct human intervention after the initiation of said second step.

14. The method of any one of claims 1 to 13, wherein said method is tolerable to said patient such that it is not necessary to administer a narcotic analgesic to said patient.

15. A method of treating a prostate of a patient for benign prostatic hyperplasia comprising
 inserting a heated catheter system into prostatic urethra tissue of a urethra, wherein said urethra tissue is surrounded by prostate tissue of a prostate;
 supplying energy to said heated catheter system
 sufficient to raise the temperature of said urethra tissue;
 increasing the energy applied so that the urethra tissue temperature increases in specified incremental rates;
 maintaining each specified incremental rate for a time sufficient to acclimatize a patient to said incremental rate; and

regulating the energy applied to simultaneously maintain said urethra tissue at a higher temperature than the prostate tissue, and at a destination temperature within a



range of from about 49°C to about 57°C, for a time sufficient to achieve a therapeutic effect on said prostate.

wherein said heated catheter system comprises:

- a non-cooled catheter for insertion into said urethra,
- a heat applicator attached to said catheter, and a connector for connecting said heat applicator to a source of energy sufficient to elevate the temperature of tissue surrounding said heat applicator to said therapeutic temperature and for maintaining said therapeutic temperature for a time sufficient to effect therapy of said prostate; and
- a temperature sensor support attached to said catheter for supporting a temperature sensor for sensing the temperature of said urethra surrounding said applicator.

15

- 16. The method of claim 15, comprising (a) inserting a electromagnetic radiation applicator system into said urethra, (b) supplying energy to said electromagnetic radiation applicator system sufficient to raise the temperature of said prostate to a therapeutic temperature, and (c) maintaining said therapeutic temperature for a time sufficient to effect therapy of said prostate,

wherein said electromagnetic radiation applicator system comprises

- a non-cooled catheter for insertion into said urethra;
- an energy radiating applicator attached to said catheter and a connector for connecting said applicator to a source of electromagnetic energy sufficient to elevate the temperature of tissue surrounding said applicator to said therapeutic temperature and for maintaining said therapeutic temperature for a time sufficient to effect therapy of said prostate



a temperature sensor support attached to said catheter for supporting a temperature sensor for sensing the temperature of said urethra surrounding said applicator,

wherein said therapeutic temperature in the tissue
 5 immediately adjacent to the applicator is from 49°C to about 57°C, and

wherein said time sufficient to effect therapy of said prostate is from about 20 minutes to about 4 hours.

10 17. A method of treating a prostate of a patient for benign prostatic hyperplasia comprising:

applying energy to prostatic urethra tissue of a urethra and surrounding prostate tissue of a prostate to elevate the temperature of the urethra tissue;

15 increasing the energy applied so that the urethra tissue temperature increases in specified incremental rates;

maintaining each specified incremental rate for a time sufficient to acclimatize a patient to said incremental rate; and

20 regulating the energy applied to simultaneously maintain said urethra tissue at a higher temperature than the prostate tissue, and at a destination temperature within a range of from 49°C to about 57°C for a time sufficient to achieve a therapeutic effect on said prostate.

25 18. The method of claim 17, wherein said destination temperature is in the range of from about 50°C to about 55°C.

30 19. The method of claim 17 or claim 18, wherein said temperature of the urethra tissue is elevated by an electromagnetic radiation applicator.



20. The method of claim 17 or claim 18, wherein said temperature of the urethra tissue is elevated by a heated catheter.

5 21. The method of claim 20, wherein said heated catheter is heated by hot water.

22. The method of any one of claims 19 to 21, wherein said catheter is a non-cooled catheter.

10

23. The method of any one of claims 17 to 22, said method comprising

a first heating step of warming said urethra tissue up to critical maximum temperature, said critical maximum temperature being in the range of about 42°C to about 46°C,

15 followed by a second heating step, said second heating step comprising gradually increasing said maximum temperature of said urethra tissue to said destination temperature such that the mean rate of increase in temperature is from about 0.5 minute/°C to about 15 minute/°C.

20

24. The method of claim 23, wherein said mean rate of increase in temperature, during said second step, is from about 1.0 minute/°C to about 10 minute/°C.

25

25. The method of any one of claims 17 to 24, wherein said method does not comprise the administration of a narcotic analgesic to said patient.

30

26. A method of treating a prostate of a patient for benign prostatic hyperplasia according to any one of claims 1 to 25 substantially as hereinbefore described with reference to the Detailed Description of the Preferred Embodiments and the Figures.



DATED THIS THIRTY-FIRST DAY OF OCTOBER 2002

THERMATRX, INC.

BY

5 PIZZEYS PATENT AND TRADE MARK ATTORNEYS

0
0
0
0

0
0
0
0



1/3

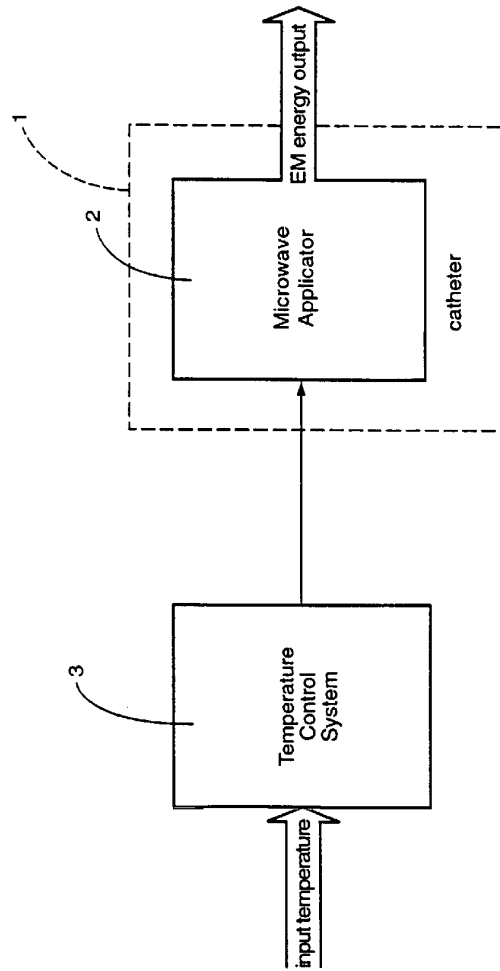


FIG. 1

SUBSTITUTE SHEET (RULE 26)

2/3

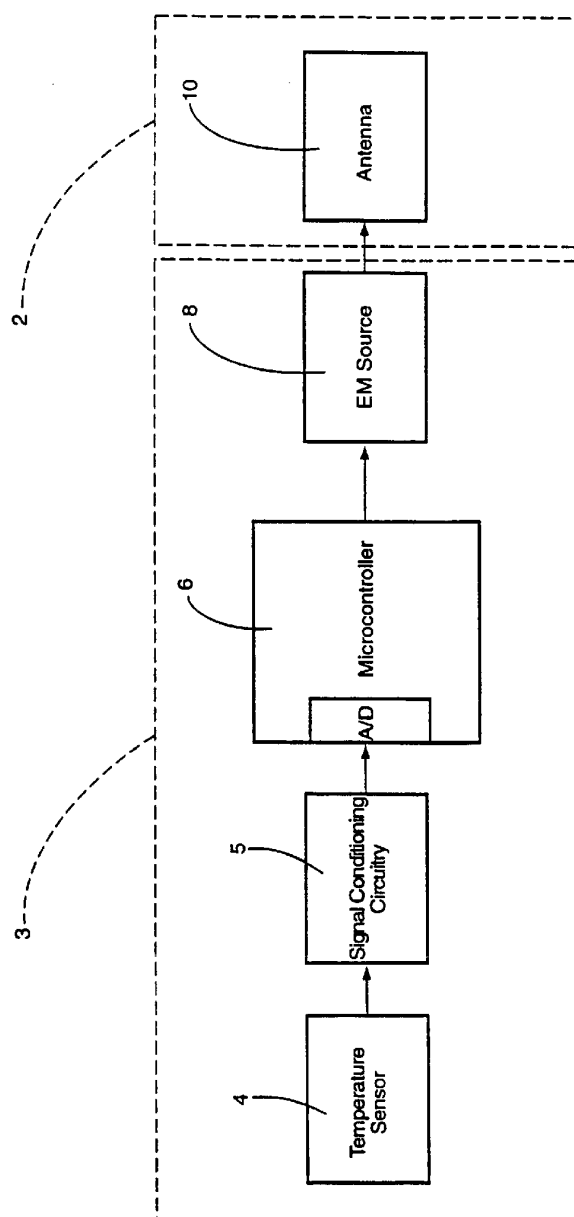


FIG. 2

SUBSTITUTE SHEET (RULE 26)

3/3

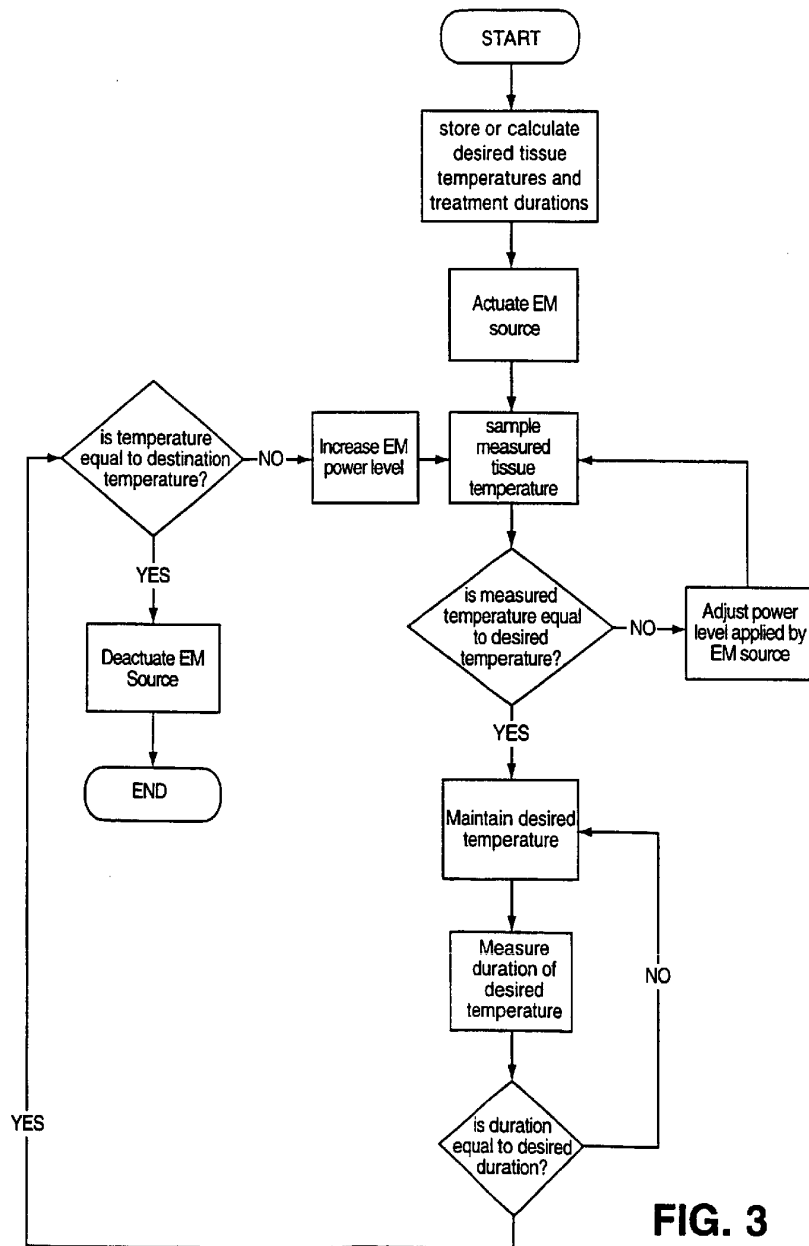


FIG. 3

SUBSTITUTE SHEET (RULE 26)