IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Demarais et al.
U.S. Patent No.:	7,717,948
Issue Date:	May 18, 2010
Serial No.:	11/840,142
Filing Date:	August 16, 2007
Title:	Methods and Apparatus for Thermally-Induced Renal Neuromodulation

Mail Stop *Inter Partes* Reexamination
Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR INTER PARTES REEXAMINATION UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 1.913

Reexamination under 35 U.S.C. § 311 and 37 C.F.R. § 1.913 is requested for claims 1, 5, 7, 12, 20 and 21 of U.S. Patent No. 7,717,948 (the ’948 patent) which issued on May 18, 2010 to Demarais et al.

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I. INTRODUCTION

U.S. Patent No. 7,717,948 claims techniques for thermally modulating or destroying (ablating) the nerves that run along the outside of the artery that feeds the kidney, known as the renal artery, to treat a cardiovascular condition such as high blood pressure, commonly referred to as hypertension.[1]

The independent claims of the '948 patent are broad enough to literally cover[2] procedures disclosed in at least three references that were not before the Examiner: Kompanowska, E., et al. "Early effects of renal denervation in the anaesthetised rat: Natriuresis and increased cortical blood flow." *J Physiol*, 531.2:527-534 (2001) (App. B); Stella, A., et al. "Effects of reversible renal denervation on haemodynamic and excretory functions of the ipsilateral and contralateral kidney in the cat." *J Hypertension*, 4:181-188 (1986) (App. C); and Han, Y.-M., et al. "Renal artery embolization with diluted hot contrast medium: An experimental study." *J Vasc Interv Radiol*, 12:862-868 (2001) (App. D). Each of these three references would anticipate the independent claims but for the recitation in the preamble that the method is used to treat a human patient.[3]

While the above references discussed studies on animal models, the motivation to use this procedure to treat high blood pressure in humans was provided by additional prior art that was not before the Examiner. For example, Weinstock, M., et al. "Renal denervation prevents sodium retention and hypertension in salt-sensitive rabbits with genetic baroreflex impairment." *Clin Sci*, 90:287-293 (1996) (App. E), specifically teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) <u>in humans</u>. Whereas the prior art of record[4] showed that destruction or ablation of the renal nerves could delay or alleviate hypertension in various animals, Weinstock went further and explicitly stated that <u>renal denervation was expected to treat hypertension in humans</u>.[5] Additional references discussed herein also show that there was a clear suggestion to treat hypertension in humans by inhibiting neural communication prior to the earliest claimed priority date of the '948 patent.

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[1] Claim 1 reads as follows:

> 1. A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising:
>
> delivering a device to a vicinity of a neural fiber associated with renal function; and
> thermally inhibiting neural communication along the neural fiber with the device.

[2] Under the broadest reasonable construction.

[3] To circumvent debate on application of animal models to humans, these references are presented in obviousness rejections.

[4] But not specifically considered or discussed.

[5] It should be noted that skilled artisans would in fact have understood the art of record to teach that which Weinstock states expressly.

Further, given the prior art teaching that renal denervation may be an effective therapy for hypertension in humans, it would have been natural for a person of ordinary skill in the art to have utilized thermal ablation to achieve the denervation. There was a distinct trend in the medical device industry throughout the 1980s and 1990s to move from invasive surgical procedures (those in which tissue is cut with a scalpel) to much less invasive intravascular techniques. The less invasive intravascular techniques utilized ablative catheters introduced into the femoral artery or vein and advanced to the treatment site intravascularly. In the early 2000s a skilled artisan without question would have considered intravascular ablation to be a leading candidate for a transvascular denervation procedure.

It would have been natural to use the type of intravascular catheter that had been used throughout the 1990s to ablate cardiac tissue and neural tissue in the accessory pathways of the heart, especially in light of the fact that arterial tissue and certain cardiac tissues are of similar toughness. Many such catheters would have been considered particularly well suited to achieve the desired denervation and would have been used for such procedures with little or no modification. References such as Webster, W. W., Jr., et al. "Method and apparatus for transvascular treatment of tachycardia and fibrillation." *U.S. Patent No.* 6,292,695 ("Webster '695") (App. J) and Schauerte, P., et al. "Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation." *Circulation*, 102:2774-2780 (2000) (App. K) disclose that intravascular electrode-tipped catheters can be used to ablate sympathetic nerve tissue from within a vessel. The prior art references describing these cardiovascular sympathectomy (or nerve removal) procedures explain that the devices could be used to perform sympathectomies in any vessel.

The fact that cardiovascular catheters could be used essentially "off the shelf" for ablation of renal arterial nerves is highlighted by the '948 patent's failure to provide any specific teaching concerning the physical properties of the catheter when it describes utilizing a radiofrequency device to achieve ablation. The '948 patent says nothing specific about catheter dimensions, electrode size, steerability requirements, electrical parameters, materials, etc. Rather, the applicants merely stated that previously known cardiovascular ablation catheters were suitable for the described renal denervation technique.[6]

In related proceedings in the United States and Europe the patent owner has pointed primarily to three things in an attempt to establish that a skilled artisan would not have attempted to use such intravascular ablative catheters to perform a renal denervation: (i) skilled artisans did not expect that renal denervation would treat hypertension in humans, (ii) the risk of damage to the renal arterial wall, and (iii) the need for the catheter to be small and highly maneuverable. The first is plainly taught by the Weinstock reference and other similar references discussed herein; the latter two are easily dismissed.

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[6] Gelfand, M., et al., "Treatment of renal failure and hypertension," *U.S. Patent Application No.* 60/442,970, filed on Jan 29, 2003, p. 13 (App. L).

With respect to the risk of damage to the wall of the renal artery, cardiac vessels were routinely ablated without stenosis. Moreover, in the 1990s various techniques to avoid stenosis, such as using lower power levels and irrigation, were widely reported and embodied in commercial ablative catheters. Skilled artisans would have expected that those techniques would be effective in the renal artery as well, and history shows that those techniques did in fact prove effective.

With respect to the requirement that the catheter be small and highly maneuverable, the reality is that various off-the-shelf cardiovascular catheters could have been used for renal sympathectomies (or nerve removal). Here again, the ‘948 patent teaches nothing about the catheter dimensions, electrode size, steerability, electrical parameters, or materials. That is primarily because modifying catheters to provide appropriate dimensions and maneuverability for a given procedure was routine in the industry long before the earliest claimed priority date.

In summary, the ‘948 patent is broad enough to literally cover[7] the methods disclosed in several prior art references which were not before the Examiner. With respect to the intravascular ablative catheter embodiment (to which the relevant dependent claims are directed), this was the most apparent and natural way to perform the renal denervation procedure specifically suggested by the Weinstock reference.

In the sections which follow Requester provides detailed comparisons of new and noncumulative prior art references to claims 1, 5, 7, 12, 20 and 21 of the ’948 patent.

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[7] Under the broadest reasonable construction.

II. DECLARATIONS OF PROFESSORS WEBSTER, PAPADEMETRIOU AND HAEMMERICH

This Request is supported by the declarations of Professor John G. Webster PhD (App. G), Professor Vasilios Papademetriou MD (App. H) and Professor Dieter Haemmerich PhD (App. I). Each offers his opinion with respect to the content and state of the prior art pursuant to 37 C.F.R. 1.915.

Dr. Webster is a Professor Emeritus of Biomedical Engineering at the University of Wisconsin-Madison.[8] He has published in excess of two hundred (200) referenced publications in academic journals and patents and has developed twenty-three (23) textbooks on medical device design.[9] Many of his publications and several of his textbooks relate to radiofrequency ablation, microwave ablation and cryoablation.[10] For instance, he edited the book Webster, J. G. "*Medical instrumentation: Application and design*." 4th ed. John Wiley & Sons, Hoboken, NJ (2009), which describes device design to measure nerves, and device design using ablation.[11] He also edited a book: Webster, J. G. "*Bioinstrumentation*." John Wiley & Sons, Hoboken, NJ (2004), which describes device design for measurements and treatment of kidneys.[12] He was recently invited by the government of Saudi Arabia to give lectures at its leading university. Dr. Webster is one of the world's foremost authorities on medical device design.

Dr. Papademetriou is a Professor of Medicine at Georgetown University School of Medicine and the Director of Hypertension and Cardiovascular Research, and Co-Director of the Cardiac Catheterization Laboratory at the Veterans Affairs Medical Centre in Washington, DC.[13] Because of his expertise in the field of cardio-renal medicine, Dr. Papademetriou was recently honored with an invitation to serve as a Member of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration.[14] Dr. Papademetriou has published over 200 peer-reviewed research papers, review articles, editorials, and book chapters and presented over 400 abstracts at national and international meetings.[15] Dr. Papademetriou has performed intravascular cardiovascular procedures (both diagnostic and interventional) almost daily for the last 25 years and likewise has performed renal imaging and interventional procedures.[16] He has performed over 8,000 intravascular cardiac procedures.[17]

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8 *CV of Webster*.

9 *Webster Dec.*, ¶ 2; *CV of Webster*.

10 *Id.*

11 *Id.* at ¶ 4.

12 *Id.*

13 *Papademetriou Dec.*, ¶ 1; *CV of Papademetriou*.

14 *Id.* at ¶ 6.

15 *Id.* at ¶ 4.

16 *Id.* at ¶ 7.

Dr. Haemmerich is an Associate Professor in the Division of Pediatric Cardiology at the Medical University of South Carolina, Director of the Pediatric Cardiology Bioengineering Program within the Division of Pediatric Cardiology, and an Adjunct Associate Professor in the Department of Bioengineering at Clemson University.[18] He is currently President of the Society for Thermal Medicine and a Fellow of the Heart Rhythm Society.[19] Professor Haemmerich is listed as an inventor on several patents, including patents related to radiofrequency ablation.[20] Professor Haemmerich also has written several written book chapters concerning ablative tissue therapies.[21] Professor Haemmerich has published over 100 peer-reviewed journal articles, many of which concern ablation modalities.[22]

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[17] *Id.*

[18] *Haemmerich Dec.*, ¶ 1; *CV of Haemmerich*.

[19] *Id.* at ¶ 4.

[20] *Id.* at ¶ 23.

[21] *Id.* at ¶ 21.

[22] *Id.* at ¶ 19.

III. TECHNICAL BACKGROUND AND STATE OF THE ART

The '948 patent is generally directed to stimulating or ablating the nerves which run along the outside of the artery leading into the kidney, called the renal artery.[23] The renal artery carries blood from the heart to the kidney. The kidney is responsible for filtering the blood by removing impurities and sending them to the bladder.[24] The sympathetic nerves which run along the renal artery communicate bidirectionally with the heart.[25] Efferent renal nerves carry nerve impulses away from the central nervous system to the kidneys.[26] Afferent renal nerves carry nerve impulses in the opposite direction.[27]

A. It Was Well Known that Renal Denervation Prevents or Alleviates Hypertension in Virtually All Animal Models

Starting in the middle of the 20th century, a significant number of authors reported on the interaction between renal nerve activity and cardiovascular conditions such as hypertension and congestive heart failure.[28] DiBona, G. F., et al. "Neural control of renal function." *Physiol Rev*, 77:75-197 (1997) (App. M) summarized the findings reported in hundreds of journal articles concerning the implications of renal neural activity and treatments associated with renal nerves.[29]

As can be appreciated from a perusal of DiBona 1997's table of contents, skilled artisans understood that stimulation or removal of renal nerves effected renal function (Chapter VI) and hypertension (Chapter VII).[30]

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[23] As discussed in Section V, below, the claim term "modulate" encompasses both stimulation and ablation under the broadest reasonable interpretation. See also *Papademetriou Dec.*, ¶ 10.

[24] *Id.*

[25] *Id.*

[26] *Id.*

[27] *Id.*

[28] *Papademetriou Dec.*, ¶ 12; *Haemmerich Dec.*, ¶ 37; *Webster Dec.*, ¶ 9.

[29] *Papademetriou Dec.*, ¶ 57; *Haemmerich Dec.*, ¶ 30; *Webster Dec.*, ¶ 13.

[30] *DiBona 1997*, 75.

DiBona 1997 explained that at least twenty five journal articles had reported that hypertension could be treated by removing the nerves which run along the outside of the renal artery. DiBona 1997's Table 9[31] summarizes various types of hypertension that were prevented or delayed by renal denervation:

[31] *DiBona 1997*, 144.

TABLE 9. ***Models of experimental hypertension in which renal denervation prevents or delays the development of hypertension***

Models	Reference No.
Spontaneously hypertensive rat (SHR)	832, 946, 1150, 1383, 1540, 1674
Borderline hypertensive rat	932
SHR stroke prone	1112
New Zealand SHR	373
Goldblatt 1K, 1C (rat)	798, 1149
Goldblatt 2K, 1C (rat)	798
Aortic coarctation (dog)	1663
Aortic nerve transection (rat)	834, 1354
DOCA-NaCl (rat)	796, 1150, 1539
DOCA (pig)	1168
Grollman renal wrap (rat)	464, 831
Low sodium, 1K hypertension (rat)	1622
Angiotensin II hypertension (rat)	1623
Obesity hypertension (dog)	791
NaCl (baroreflex-impaired rabbit)	1658

1K, 1C, one kidney, one clip; 2K, 1C, two kidney, one clip; DOCA, deoxycorticosterone acetate.

A later DiBona article summarizes the state of the art concerning renal denervation procedures as of the earliest claimed priority date (April 2002). DiBona, G. F. "Sympathetic nervous system and kidney in hypertension." *Nephrol and Hypertension*, 11:197-200 (2002) (App. N) reviews the findings of the DiBona 1997 paper and reports the relevant state of the art as follows:

> There is growing evidence that an important cause of the defect in renal excretory function in hypertension is an increase in renal sympathetic nerve activity (RSNA). First, increased RSNA is found in animal models of hypertension and hypertensive humans. Second, renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[32]

Similar findings are reported in Huang, W. C., et al., "Renal denervation prevents and reverses hyperinsulinemia-induced hypertension in rats." *Hypertension*, 32:249-254 (1998). Huang reports that bilateral renal denervation prevented the development of hypertension and treated existing hypertension by lowering the blood pressure.

> Bilateral renal denervation depleted renal norepinephrine stores and prevented the development of hyperinsulinemia-induced hypertension. After hyperinsulinemia-induced hypertension had been fully established (from 134±2 to 157±2 mm Hg), bilateral

[32] *DiBona 2002*, Abstract (Emphasis added).

renal denervation reversed the elevated systolic blood pressure to normotensive levels within 2 weeks.[33]

The results of renal denervation in Huang are shown quite clearly in one of the figures, wherein the blank diamonds show a significant effect from bilateral renal denervation performed 28 days after insulin infusion was begun in rats and hypertension was induced:[34]

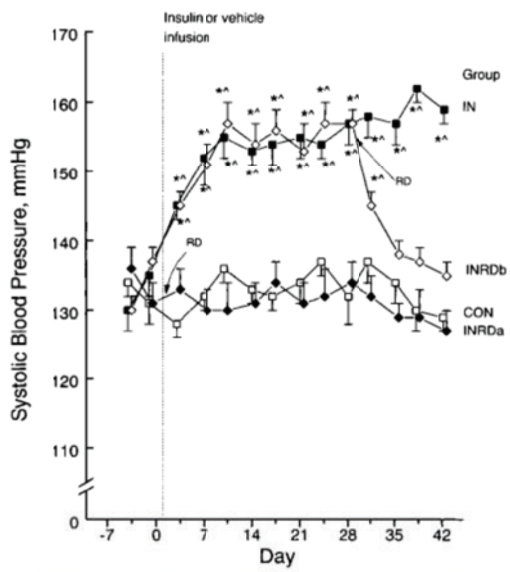

Figure 1. Changes in systolic blood pressure in control rats and insulin-infused rats with and without bilateral renal denervation. Control rats (CON) received vehicle alone. Insulin was administered via subcutaneous osmotic minipump (3 mU/kg per minute). —□— indicates control rats, n=8; —■—, insulin infusion alone (IN), n=8; —◆—, concurrent insulin administration and bilateral renal denervation (INRDa), n=8; and —◇—, insulin administration and bilateral renal denervation performed 4 weeks later (INRDb), n=8. RD indicates bilateral renal denervation. ⋆ and ^ denote $P<0.05$ vs preinsulin period and vs control rats, respectively.

Huang states that "numerous studies have provided strong inferential evidence that positively associates hypertension with insulin resistance and hyperinsulinemia in humans and some genetically hypertensive rats."[35]

The renal denervation procedures in the animal models were normally performed via ablation or surgical resection.[36] Most commonly the renal nerves near the surface of the adventitia were physically separated from the renal artery and that portion of the renal nerve bundle was cut with a scalpel.[37]

[33] *Huang 1998*, Abstract (Emphasis added).

[34] *Id.* at 250.

[35] *Id.* at 249.

[36] See, e.g., *Haemmerich Dec.*, ¶¶ 28, 31; *Papademetriou Dec.*, ¶ 12.

[37] *Id.*

Thereafter, a mixture of phenol in ethanol was typically painted on the remaining renal nerves in order to destroy them.[38] With respect to surgical resection techniques, sometimes an electrocautery device was used to cut, or resect, the nerves instead of a standard scalpel.[39]

Accordingly, those skilled in the art had an understanding that renal denervation prevents or alleviates hypertension – or high blood pressure – in virtually all animal models.[40]

B. Starting in the 1980s Surgical Methods Were Consistently Being Displaced by Minimally Invasive Intravascular Catheter Procedures

In the years leading up to the filing date of the earliest claimed priority application for the '948 patent, numerous cardiac procedures evolved from surgical methods (in which tissue is cut with a scalpel) to much less invasive intravascular procedures.[41] Intravascular cardiac procedures utilized ablative catheters that were introduced into the femoral artery or vein and then advanced intravascularly to the treatment site.[42] Three of the most prolific cardiovascular surgeries that underwent this transition from surgical-to-intravascular involved treatments for atrial fibrillation (AF), Wolff-Parkinson-White (WPW) syndrome, and atrioventricular node reentry tachycardia (AVNRT).[43] Each of these conditions had previously been treated surgically in an open-heart procedure wherein the surgeon cut the affected heart tissue with a scalpel.[44] By the filing date of the earliest claimed priority application for the '948 patent these procedures were routinely performed intravascularly.[45]

The treatment for WPW was the first of the three to transition to an intravascular procedure.[46] WPW is caused by abnormal electrical pathways in the heart.[47] WPW had been sometimes treated by open heart surgery to create scar tissue that blocks the abnormal electrical pathways.[48] In 1985 Cohen received a patent on an intravascular catheter for locating and ablating cardiovascular conduction

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[38] *Id.*

[39] *Kompanowska*, 527; *Webster Dec.*, ¶ 12; *Papademetriou Dec.*, ¶ 12.

[40] *Webster Dec.*, ¶ 16; *Haemmerich Dec.*, ¶¶ 28, 30, 31, 88.

[41] *Webster Dec.*, ¶¶ 24-41; *Haemmerich Dec.*, ¶¶ 39-52; *Papademetriou Dec.*, ¶¶ 21-36.

[42] *Id.*

[43] *Id.*

[44] *Id.*

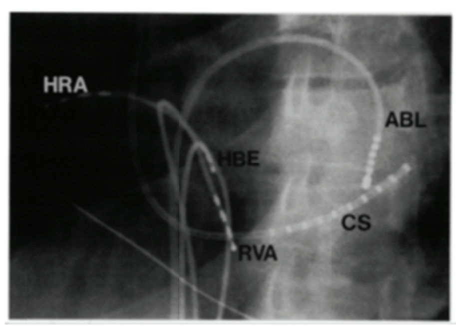
[45] *Id.*

[46] *Papademetriou Dec.*, ¶¶ 21-36; *Webster Dec.*, ¶¶ 24-41; *Haemmerich Dec.*, ¶¶ 39-52.

[47] *Id.*

[48] *Id.*

pathways to treat WPW.[49] Several years later, Swartz published radiograph images of a similar technique in which an ablative catheter (labeled ABL in the figure below) was intravascularly advanced into the heart.[50]



These minimally invasive intravascular procedures proved effective and gradually replaced the more invasive surgical techniques.[51]

AV nodal reentrant tachycardia (AVNRT) is a type of tachycardia (fast rhythm) of the heart.[52] AVRNT was previously treated surgically in an open-heart procedure.[53] In the early 1990s various authors proposed intravascular ablative catheter approaches for the treatment of AVNRT.[54] Here again, the intravascular catheter procedures proved to be effective and substantially safer than invasive surgical approaches.[55]

AF is a cardiac arrhythmia caused by irregular electrical impulses in the heart.[56] AF was previously treated by an open heart cardiac procedure, called the Cox Maze procedure, in which scars were made in the heart to block abnormal electrical signals.[57] Starting in 1994 the surgical techniques for treatment of AF by the Cox Maze procedure began to transition to minimally invasive intravascular approaches to make the necessary lesions.[58] Throughout the middle and late 1990s various groups

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[49] *Id.*

[50] *Id.*

[51] *Id.*

[52] *Id.*

[53] *Id.*

[54] *Id.*

[55] *Id.*

[56] *Id.*

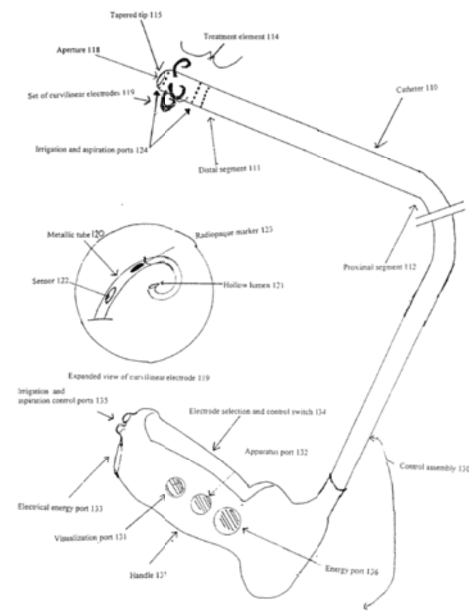
[57] *Id.*

[58] *Id.*

developed and publicized intravascular ablative catheter techniques to treat AF.[59] These techniques likewise proved successful and effectively displaced the more invasive surgical techniques.[60]

By the year 2000 many medical publications, such as Huang, S. K. S., et al. "*Radiofrequency catheter ablation of cardiac arrhythmias: Basic concepts and clinical applications*." 2nd ed. Armonk, NY: Futura Publishing Co., 3-7 (2000), taught that chemical destruction, radiofrequency heating, direct current heating, cryogenics, focused ultrasound, microwave heating, laser heating, induction heating, and mechanical methods were all well recognized and alternative methods and energy sources for tissue ablation.[61]

In addition, it was understood prior to the earliest priority date of the '948 patent that cardiovascular ablative catheters were applicable for treatments in other areas of the body besides the heart.[62] A patent application originally filed by Edwards in 1999, and published on April 5, 2001, was directed to the application of ablative catheter techniques to various urinary tract disorders (see Fig. 1 therefrom).[63] Edwards noted that techniques for ablating cardiac tissues (e.g. by RF or cryothermy) were well known.[64] Indeed, Edwards himself had previously developed RF cardiovascular ablation catheters.[65] In the '897 PCT publication Edwards proposed an alternative application for this technology – a universal catheter that could "treat[] disorders of the genito-urinary tract" by "ablation."[66] Edwards taught that the device was useful to perform procedures in "[a]ny biological conduit or tube."[67]



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[59] *Id.*

[60] *Id.*

[61] *Huang (2000)*, 4.

[62] *Edwards*, S. D., "Treatment of tissue by application of energy and drugs." *PCT Publication No. WO 01/22897*, filed in 2000; *Papademetriou Dec.*, ¶ 53; *Webster Dec.*, ¶ 50; *Haemmerich Dec.*, ¶ 65.

[63] *Edwards '897*; *Haemmerich Dec.*, ¶ 65.

[64] *Edwards '897*, 2:9-11 ("The use of a catheter to apply radio frequency (RF) and other types of energy to ablate tissue in the body (such as heart muscle tissue) is known in the art of cardiac treatment.").

[65] *Edwards*, S. D., et al. "Electrode and associated systems using thermally insulated temperature sensing elements." *U.S. Patent No. 5,688,266*, filed October 1995 (App. P).

[66] *Edwards '897*, 4:16-18.

[67] *Id.* at 7:7-17.

C. Prior Art Intravascular Catheters Were Used to Ablate Nerves Which Run Along the Outside of a Vessel

Not only were ablative catheters utilized to create lesions and scarring in tissue walls, ablative catheters were used to ablate nerves that run along the outside of a vessel. For instance, Schauerte, P., et al. "Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation." *Circulation*, 102:2774-2780 (2000) (App. K) taught a technique for the destruction of nerves on the outside of the pulmonary artery.[68] As can be seen in Schauerte's Figure 1, below, a catheter bearing a basket-style electrode is used to "stimulat[e] or ablat[e]" nerves borne by the pulmonary artery.[69]

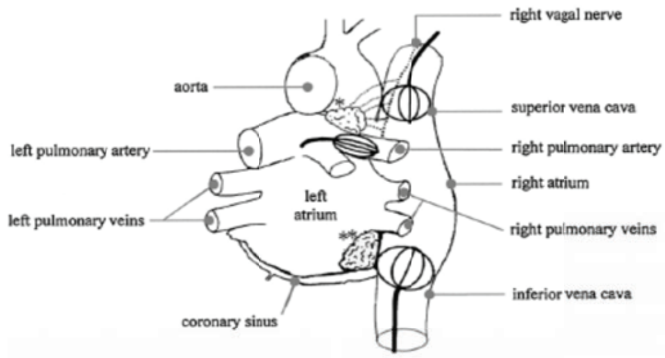

Figure 1. Illustration of parasympathetic innervation of atria. Dorsal view of atria and great vessels is shown. Course of nerves depicted is functional course rather than anatomically correct description of parasympathetic atrial innervation. Most of right and left vagal fibers that innervate atria and sinus or AV node converge to fat pad between RPA, base of aorta, and SVC (RPA fat pad [*]). Some vagal fibers that innervate atria are located in fat pad between IVC, left atrium, and ostium of coronary sinus (**) and along SVC. Stimulation and ablation of parasympathetic nerves was performed with expandable electrode catheter, which was introduced into upper RPA (n=7), SVC (n=1), or IVC (n=2).

Schauerte concluded that "intravascular RFCA [radiofrequency catheter ablation] of these parasympathetic nerves can be achieved."[70]

Webster '695 proposed a similar device to alternatively stimulate or ablate sympathetic or parasympathetic nerves.[71] According to the Webster technique a "denaturing or ablating stimulus (e.g., radiofrequency or cryoablation) is applied across the vessel wall to the sympathetic fibers at any desired

[68] *Haemmerich Dec.*, ¶ 53.

[69] *Schauerte*, 2775.

[70] *Id.* at 2777.

[71] *Webster '695*, 2:49-52; *Haemmerich Dec.*, ¶ 56; *Papademetriou Dec.*, ¶ 93.

location."[72] Webster further explained that this technique could be used in any blood vessel which bears the nerve fibers of interest:

> the superior vena cava. Sympathetic bundles may be stimulated from discrete sites, for example, transvascularly from the aorta or the main pulmonary artery to the sympathetic fibers that run alongside. As will be apparent to one of skill in the art, the invention is not limited to sites directly adjacent to the heart, but can be practiced at any of the variety of sites (primarily thoracic) where blood vessels suitable for catheter access run parallel to or otherwise intersect with autonomic fibers serving the heart. Target fibers can thus be accessed from different sites on the patient, for example from near the subclavian, jugular, or azygous veins. [73]

The examples taught in Webster '695 were mainly focused on stimulation applied "transvascularly, to a sympathetic or parasympathetic nerve that innervates the heart at a strength sufficient to depolarize the nerve and effect control of the heart."[74] However, Webster '695 specifically teaches that the techniques were applicable to ablate nerves across any suitable vascular structure.[75]

In another prior art reference, Mest, R. A. "Method and system for treatment of tachycardia and fibrillation." *U.S. Patent No. 6,564,096*, filed in 2001, similar devices and methods for treating fibrillation were disclosed.[76] Like Webster '695, Mest teaches that intravascular catheters can be used to ablate neural fibers transvascularly.

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[72] *Webster '695*, 12:21-24.

[73] *Id.* at 10:56-67.

[74] *Id.* at Abstract.

[75] *Papademetriou Dec.*, ¶ 79.

[76] *Haemmerich Dec.*, ¶ 54.

> Selective sympathetic denervation, performed by transvascular ablation using the method of the invention, can reduce these patients' risk of sudden death from acute arrhythmias. Selective parasympathetic denervation may be indicated in patients with atrial tachycardia or fibrillation induced or maintained by excessive vagal nerve stimulation. A denaturing or ablating stimulus (e.g., radio frequency or cryoablation) is applied across the vessel wall to the sympathetic fibers at any desired location. Preferably sites are selected where a purely or nearly pure sympathetic or parasympathetic branch runs very close to the vessel and where there are few other nerves or other sensitive tissues. Ablating stimulation is applied until conduction in the fiber is impaired or ceases altogether. This can be monitored by any means, including recording from the heart to observe a change in heart rate. [77]

Mest is also focused on transvascular ablation of sympathetic or parasympathetic nerves in the heart but the devices and methods disclosed there may be used achieve transvascular denervation at any location.[78]

The '948 patent itself concedes that catheters for transvascularly ablating nerves (i.e., performing a transvascular sympathectomy) were known as of the earliest claimed priority date. As noted above, the '948 says nothing specific about catheter dimensions, electrode size, steerability requirements, electrical parameters, materials, etc.[79] Rather, the applicants merely stated that previously known cardiovascular ablation catheters were suitable for the described renal denervation technique:

> U.S. Pat. No. 6,292,695 describes in detail a method and apparatus for transvascular treatment of tachycardia and fibrillation with nerve stimulation and ablation. Similar catheter based apparatus can be used to ablate the renal nerve with an intent to treat CRF [cardiorenal failure].[80]

The parent applications incorporated by reference into the '948 patent further highlight that denervation by thermal ablation was quite well known. For instance, the parent application which matured into U.S. Patent No. 7,162,303 includes various figures depicting catheters but no mention of wattages, temperature ranges, or catheter sizes. Here again, the specification simply references the Webster '695 patent and indicates that it discloses a suitable apparatus.[81]

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[77] *Mest*, 12:47-62.

[78] *Mest,* 11:22-45.

[79] *Papademetriou Dec.*, ¶ 82.

[80] *Levin*, H. R., et al. "Renal nerve stimulation method and apparatus for treatment of patients." *U.S. Patent No.* 7,162,303, 10:35-39 (App. F).

[81] *Id.*

D. Intravascular Catheters Were Readily Adaptable to a Wide Variety of Different Applications

Catheters were modified as appropriate to obtain access to the desired location and in order to accommodate different vessel sizes.[82] The electrodes on the catheters likewise could be modified to accommodate the desired lesion size given the nature of the tissue involved.[83] Professors Papademetriou, Webster and Haemmerich explain in their declarations that modification of ablative catheters, electrodes, and the adjustment of power levels was accomplished by consultation of well-known and widely published interrelationships between electrode configuration and lesion size.[84] For example, Petersen, H. H., et al. "Lesion dimensions during temperature controlled radiofrequency catheter ablation of left ventricular porcine myocardium: Impact of ablation site, electrode size, and convective cooling." *Circulation*, 99:319-325 (1999), is an exemplary reference that tabulates then-well-known relationship between catheter electrode tip dimensions, power, temperature and lesion size.[85]

TABLE 1. In Vitro Data

	4-mm Tip			8-mm Tip			12-mm Tip		
	0-m/s Flow	0.1-m/s Flow	0.2-m/s Flow	0-m/s Flow	0.1-m/s Flow	0.2-m/s Flow	0-m/s Flow	0.1-m/s Flow	0.2-m/s Flow
n	12	12	15	15	14	13	13	15	13
Temperature,* °C	76±1	75±1	73±2	72±1	68±3	65±5	67±2	53±4	47±4
Power, W	19±5	28±7	33±9	38±5	54±9	61±7	57±7	68±1	69±1
Lesion depth, mm	5±0	7±1	7±1	5±1	7±1	8±1	5±1	6±2	5±1
Lesion width, mm	8±1	10±1	11±1	10±2	11±2	13±2	9±1	10±2	9±3
Lesion volume, mm^3	120±28	272±84	404±119	306±80	466±124	768±174	347±101	433±225	317±180

Values are mean±SD.
*Average reached tip temperature.

Mehdirad, A., et al. "Temperature controlled RF ablation in canine ventricle and coronary sinus using 7 Fr or 5 Fr ablation electrodes." *PACE*, 21:310-321 (1998), is another reference that is representative of the state of the art with respect to the ways in which electrode geometries and power levels were selected for various applications.[86] As a further example, Nakagawa, H., et al. "Inverse relationship between electrode size and lesion size during radiofrequency ablation with active electrode cooling." *Circulation*, 98:458-465 (1998), tabulates in detail the interrelationships among electrode dimensions, voltage, current, power, electrode temperature, tissue temperature, and impedance.[87] Means to control operative side

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[82] *Papademetriou Dec.*, ¶¶ 82-83; *Haemmerich Dec.*, ¶¶ 59, 79.

[83] *Papademetriou Dec.*, ¶ 85.

[84] *Webster Dec.*, ¶¶ 52-56; *Papademetriou Dec.*, ¶ 85; *Haemmerich Dec.*, ¶¶ 69-79.

[85] *Petersen*, 321.

[86] *Haemmerich Dec.*, ¶ 76.

[87] *Nakagawa* 1998, 460; *Webster Dec.*, ¶ 54; *Papademetriou Dec.*, ¶ 96; *Haemmerich Dec.*, ¶ 78.

effects of RF ablation were likewise well known.[88] By referencing this knowledge base, miniaturization or enlargement of catheters was routinely accomplished in the field of surgical instrument design as of the year 2000.[89]

E. Various Techniques Were Used Successfully to Manage the Risk of Complications, Especially in Arterial Tissues

As of the early 2000s complications such as stenosis (abnormal narrowing or occlusion of a vessel) in connection with ablative intravascular catheter procedures had become rare. For example, in 1998, the North American Society of Pacing and Electrophysiology registry reported only one coronary occlusion in 3357 ablation procedures.[90]

Various techniques were used to manage the risk of such complications, including maintaining proper electrode-tissue contact, using lower temperature and power, using tissue temperature feedback, monitoring impedance, and using irrigation to cool the tissue.[91] By the year 2000 it had been widely reported that stenosis and thrombosis could be avoided if the temperature of ablation was maintained within a certain range.[92]

Moreover, arteries were known to be substantially more resistant to stenosis than veins.[93] Although stenosis had been reported as an issue in the pulmonary vein, stenosis had not been reported as a significant issue in the coronary sinus.[94] Moreover, in 2002 it was believed that stenosis of the pulmonary vein (PV) could be avoided by using lower temperature and power settings.[95] Reports of stenosis were largely due to the fact that the wall of the PV is relatively frail and that oftentimes there was poor electrode-tissue contact in the PV ostium.[96] The PV comprises collapsible, flexible material that is easily perforated.[97] In contrast, the artery walls consist of stiffer and stronger tissue that is substantially

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[88] *Webster Dec.*, ¶ 52; *Haemmerich Dec.*, ¶ 69.

[89] *Id*.

[90] *Papademetriou Dec.*, ¶ 43.

[91] *Id.* at ¶ 48.

[92] *Id.* at ¶¶ 48-49.

[93] *Id.* at ¶¶ 37-39, 49.

[94] *Id.* at ¶¶ 43-47.

[95] *Id.* at ¶¶ 48-49.

[96] *Id.* at ¶¶ 40-42, 48, 49.

[97] *Id.*

more resistant to stenosis.[98] In addition, the anatomy of the renal artery would have been expected to permit good tissue-electrode contact which further reduces the risk of stenosis.[99]

F. Summary

In summary, the state of the art at the time of the earliest effective priority date included a general understanding that ablation of the renal arterial nerves (sometimes called renal denervation or renal sympathectomy) was an effective treatment for hypertension and that conventional intravascular electrophysiology catheters would have been appropriate instruments with which to ablate nerves that run along the outside of such vessels. The state of the art further included an understanding that controlling power levels, monitoring tissue temperature and the use of irrigation were generally successful in preventing complications such as stenosis in patients undergoing intravascular ablation, particularly in arteries.

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[98] *Id.*

[99] *Id.*

IV. THE PROSECUTION HISTORY OF THE '948 PATENT

In U.S. patent application serial no. 11/840,142 the Applicants presented a single new independent claim:[100]

> 31. (New) A method for treating a patient from within a body lumen of the patient, the method comprising:
>
> positioning a thermal apparatus within the body lumen; and
>
> thermally altering tissue adjacent to the body lumen with the thermal apparatus and reducing neural activity across or proximate to the thermally altered tissue adjacent to the body lumen.

Examiner Helling rejected the pending claims as obvious in view of Sluijter, U.S. Patent No. 6,161,048.[101] Examiner Helling made the following findings:

> Regarding claim 31, Sluijter teaches a method and system for neural tissue modification (title) from within a body lumen (Figs. 1 and 10-14), the method comprising positioning a thermal apparatus (Col. 1, lines 23-26 teach that heating of neural tissues via RF power is well known and common in the art) within the body (Col. 4, lines 34-38) and thermally altering tissue adjacent to the body tissue being treated (Col. 4, lines 34-54) and reducing neural activity across or proximate to the thermally altered tissue (Col. 2, line 49-Col. 3, line 12). However, Sluijter does not explicitly teach the thermal apparatus being positioned within a body lumen. However, the examiner asserts that positioning of a thermal apparatus of the present invention, i.e. a catheter, within a body lumen to alter adjacent body tissue is well known in the art, and therefore would have been obvious to one having ordinary skill in the art at the time of the invention. [102]

The Applicants then interviewed with the Examiner, during which it was discussed that the claims would be amended to specifically recite renal neuromodulation. The relevant portion of the interview summary is reproduced below:

> Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant had an overview presentation of the invention. Applicant proposed a claim amendment to more specifically inclue renal neuromodulation which would appear to overcome the prior art rejection and put the claims in condition for allowance. Applicant will submit new claims in a response to the Office Action reflecting the proposed amended material.* [103]

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[100] *U.S. Patent Application No.* 11/840,142 File History, August 16, 2007 Preliminary Amendment, 3 (App. Q).

[101] *Id.* at April 3, 2009, Non-final Office Action, 3-4.

[102] *Id.* at 4.

In their response to the pending office action the Applicants cancelled the pending claims and replaced them with new claims 64-90.[104] New claim 64 read as follows:

> 64. A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising:
>
> delivering a device to a vicinity of a neural fiber associated with renal function; and
>
> thermally inhibiting neural communication along the neural fiber with the device.
>
> [105]

The Applicants argued that the pending claims were allowable for substantially the same reason as the claims of the '117 parent application (i.e. a recitation of thermally induced renal modulation in the vicinity of nerves that contributed to renal function).[106]

After an interview during which the Examiner and Applicants discussed printed matter issues in connection with potential "kit claims," Examiner Helling issued a notice of allowance which included a statement of reasons for allowance:

> ***Reasons for Allowance***
>
> 3. Claims 64-89 are allowed.
>
> 4. The following is an examiner's statement of reasons for allowance:
>
> 5. none of the prior art of record discloses or suggests a method of treating a medical condition and specifically a cardio-renal condition through thermal inhibition of the nerve signals across the neural pathway that carries nerve signal to and from the kidney of a patient.
>
> [107]

The '142 application issued as U.S. Patent No. 7,717,948 (App. A), the subject of the instant Request.

Thus, the prosecution history taken as a whole indicates that the '948 patent was allowed primarily because the Examiner believed that the prior art failed to teach treatment of a cardio-renal condition through thermal inhibition of nerve signals across the neural pathway that carries nerve signals to and from the kidney.

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[103] *Id.* at August 28, 2009, Interview Summary.

[104] *Id.* at August 31, 2009, Amendment, 2-5.

[105] *Id.* at 2.

[106] *Id.* at 8.

[107] *Id.* at February 23, 2010, Notice of Allowance.

V. BROADEST REASONABLE CONSTRUCTION OF THE TERM "THERMALLY INHIBITING NEURAL COMMUNICATION"

All independent claims in the '948 patent (App. A) use the term "thermally inhibiting," which appears to have been used for the first time in the application that matured into the '948 patent. The specification of the '948 patent explains that the "invention" involves renal neuromodulation via heating and/or cooling. According to the Overview section, "[t]he present invention provides methods and apparatus for renal neuromodulation via thermal heating and/or thermal cooling mechanisms, e.g., to achieve a reduction in renal sympathetic nerve activity."[108] The Overview goes on to state that thermal heating mechanisms include ablative and non-ablative techniques.

> As used herein, thermal heating mechanisms for neuromodulation include both thermal ablation and non-ablative thermal injury or damage (e.g., via sustained heating or resistive heating). Thermal heating mechanisms may include raising the temperature of target neural fibers above a desired threshold, for example, above a body temperature of about 37° C. e.g., to achieve non-ablative thermal injury, or above a temperature of about 45° C. (e.g., above about 60° C.) to achieve ablative thermal injury. [109]

Thermal cooling mechanisms are similarly described as including freezing injury, non-freezing injury, and non-freezing thermal slowing.

> As used herein, thermal cooling mechanisms for neuromodulation include non-freezing thermal slowing of nerve conduction and/or non-freezing thermal nerve injury, as well as freezing thermal nerve injury. Thermal cooling mechanisms may include reducing the temperature of target neural fibers below a desired threshold, for example, below the body temperature of about 37° C. (e.g., below about 20° C.) to achieve non-freezing thermal injury. Thermal cooling mechanisms also may include reducing the temperature of the target neural fibers below about 0° C., e.g., to achieve freezing thermal injury. [110]

Accordingly, the term "thermally inhibiting neural communication" covers, under the broadest reasonable construction,[111] the following five sub-categories of thermal heating and cooling: i) ablative

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[108] *'948 patent*, 3:55-58.

[109] *Id.* at 4:6-14.

[110] *Id.* at 4:15-25.

heating, ii) non-ablative heating, iii) non-freezing thermal slowing, iv) non-freezing thermal nerve injury, and v) freezing thermal nerve injury.

The dependent claims in the '948 patent and its parent patents further demonstrate that the broadest reasonable interpretation of the term "thermally inhibiting" includes both ablative and non-ablative techniques that involve delivery of both heat and cold. For instance, claim 7 of the '948 patent specifically recites that "thermally inhibiting" comprises "at least partially ablating the neural fiber."[112] The '765 great-grandparent application (now U.S. Patent No. 7,653,438), which is incorporated by reference into the '948 patent, similarly includes dependent claims which indicate that the term "modulating" the renal nerve comprises "ablating the renal nerve."[113] The '665 great-grandparent application (now U.S. Patent No. 7,162,303), also incorporated by reference, includes dependent claims which indicate that "blocking" the renal nerve "is accomplished by ablation."[114]

There may be other aspects of the term "thermally inhibiting," but a basic understanding that thermal inhibition expressly includes[115] the following five sub-categories of techniques suffices for the purposes of the instant Request: i) ablative heating, ii) non-ablative heating, iii) non-freezing thermal slowing, iv) non-freezing thermal nerve injury, and v) freezing thermal nerve injury.

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[111] This Request is based upon the broadest reasonable interpretation of the claim language. Requester's position regarding the scope of the claims under their broadest reasonable interpretation is not to be taken as stating any position regarding the appropriate scope to be given the claims in court or other adjudicative body in infringement litigation under the different interpretation standard that courts must apply in such proceedings.

[112] *'948 patent*, 16:28-31.

[113] Deem, M., et al. "Methods and apparatus for renal neuromodulation." *U.S. Patent No.* 7,653,438, claims 23-30 (App. BB).

[114] Levin, H. R., et al. "Renal nerve stimulation method and apparatus for treatment of patients." *U.S. Patent No.* 7,162,303, claim 14 (App. F).

[115] Under the broadest reasonable construction. (Rule 42.100)

VI. REPRESENTATIVE PROPOSED REJECTIONS AND SHOWING THAT REQUESTER IS LIKELY TO PREVAIL

Requester submits that it is likely to prevail on each of the proposed rejections set forth below. These proposed rejections are premised on, among other things, numerous references and evidence that were not before the Examiner: the Weinstock, Kompanowska, Stella, Han and Curtis references and the declarations of three skilled artisans, namely, Professors Webster, Haemmerich and Papademetriou.

First presented are proposed rejections based on the Weinstock reference's teaching that renal denervation was expected to treat hypertension by lowering blood pressure in humans. This teaching renders the claimed subject matter obvious when taken in combination with the expectation of skilled artisans that then-conventional intravascular electrophysiology catheters could be used without substantial modification to destroy, or ablate, the nerves that run along the outside of the renal artery.

The next group of proposed rejections is premised on Kompanowska's teaching of a method for thermally destroying renal arterial nerves to alter sodium excretion. Kompanowska cites various articles which explain in greater detail the impact of sodium excretion on cardiovascular function and hypertension.

The third group of proposed rejections is based on the Stella reference, which discloses a technique for cooling the renal arterial nerves to lower blood pressure. In the years following the publication of Stella and leading up to the claimed priority date, various intravascular cryothermal catheters had been developed and skilled artisans would have known that the Stella technique could advantageously be performed with conventional and minimally invasive intravascular cyrothermal catheters.

The fourth group of proposed rejections is premised upon prior art that was cited (but not applied by the Examiner) in light of new evidence that clearly links the relevant teachings. More particularly, the declarations of Professors Webster, Haemmerich and Papademetriou explain that skilled artisans would have understood, on the one hand, that the cited prior art clearly established that ablating the renal nerves in humans was likely to be an effective treatment for various cardiovascular conditions and, on the other hand, that conventional electrophysiology catheters could be used essentially "off the shelf" to perform such a procedure in a minimally invasive way.

The fifth group of proposed rejections involves references which are directed to ancillary procedures like kidney removal (nephrectomy) or kidney destruction (embolization). Because the claims are not limited to renal denervation procedures, the Curtis and Han references anticipate or render obvious the claimed subject matter.

Group 1: Proposed Rejections based on the Weinstock Reference

Weinstock (App. E) qualifies as prior art under 35 U.S.C. §102(b) because it was published more than a year before the earliest claimed priority date. Weinstock was not before the Examiner.

Weinstock specifically teaches that destruction of the renal arterial nerves was expected to decrease high blood pressure (hypertension) in humans.[116] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure:

> **1. Rabbits with a genetic impairment in baroreflex control of heart rate become hypertensive on a high salt diet. The present study determined the effect of bilateral renal denervation on blood pressure and sodium balance after salt loading (four times normal intake; 28–36 mEq NaCl/day) in normotensive rabbits with high (Group I) and low (Group II) baroreflex sensitivity, respectively.** [117]

Weinstock's results show that mean arterial pressure (MAP) fell substantially after renal denervation, as reflected by the black triangle data points in the upper portion of Weinstock's Figure 1, which is reproduced below.[118]

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[116] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[117] *Weinstock*, Abstract.

[118] *Id.* at 289.

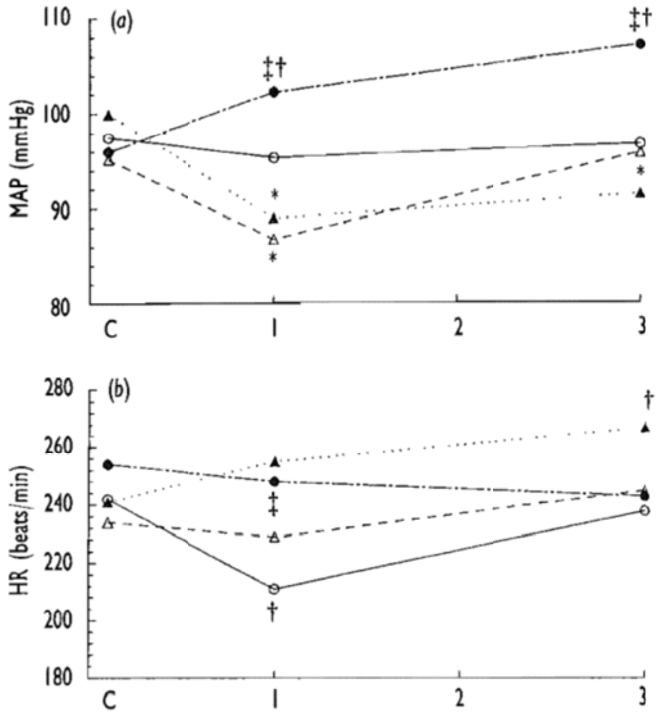

Fig. 1. Effect of a high salt diet on MAP (*a*) and HR (*b*) in renal-denervated and sham-denervated rabbits. C, control period before denervation. ○, Group I SDN; ●, Group II SDN; △, Group I RDN; ▲, Group II RDN. * Significantly different from SDN, $P < 0.05$; † significantly different from control diet, $P < 0.05$; ‡ significantly different from Group I SDN.

As summarized in the abstract, Weinstock concludes that the observed behavior was an appropriate predictor of human biological responses:

> **6. Since they display several of the characteristics of salt-sensitive hypertensive humans, i.e. salt retention, normal plasma renin activity, but abnormal regulation of plasma renin activity and blood flow in response to salt loading, Group II are an appropriate model of human salt-induced hypertension.** [119]

Accordingly, Weinstock discloses that renal denervation was expected to treat hypertension by lowering blood pressure in humans.[120]

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[119] *Id.* at Abstract.

[120] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

1-A Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Swartz

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[121] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[122]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[123]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[124] One method that would have immediately commanded itself to the attention of the skilled artisan was the technique used for the ablation of cardiovascular tissue to treat Wolff-Parkinson-White syndrome.[125]

As discussed above in the Technical Background section, Wolff-Parkinson-White (WPW) syndrome was the first of three prolific cardiovascular surgeries to transition to minimally invasive intravascular catheter procedures.[126] In the 1980s, with advances in mechanical catheter technology, surgical techniques to treat WPW had evolved into an intravascular procedure in which an electrode-tipped catheter was used to ablate electrically conductive tissue transvascularly, or through the cardiac wall tissue.[127]

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[121] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[122] *Weinstock*, Abstract.

[123] *Id.* at 288.

[124] *Papademetriou Dec.*, ¶ 77; *Webster Dec.*, ¶¶ 72-75; *Haemmerich Dec.*, ¶¶ 89-91.

[125] *Id.* at ¶¶ 78, 112-113; *Id.* at ¶¶ 72-75; *Id.* at ¶¶ 89-91.

[126] *Id.* at ¶¶ 21, 25; *Id.* at ¶¶ 29-30; *Id.* at ¶¶ 43-45.

[127] *Id.*

Another reference that was not before the Examiner, Swartz (App. O), teaches that "high rates of success using radiofrequency ablation energy have rapidly transformed catheter ablation from an investigational procedure to the nonpharmacological therapy of choice of symptomatic Wolff-Parkinson-White syndrome."[128] Swartz studied the safety and efficacy of accessory pathway ablation using radiofrequency energy delivered solely to accessory atrioventricular pathway atrial insertion sites.[129] Specifically, Swartz describes the accessory pathway localization and ablation procedures as follows:

> [e]ndocardial mapping was accomplished using a steerable 7F 3-4 mm tip electrode catheter with 2-mm electrode spacing . . . Bipolar . . . and distal electrode unipolar electrograms were continuously recorded from the localization/ablation catheter . . . After atrial insertion localization and characterization, endocardial ablation catheter contact and stability were assessed.
>
> Radiofrequency ablating energy used . . . was unmodulated 500-KHz alternative current derived from a standard electrosurgical unit . . . Ablation catheter position was fluoroscopically monitored throughout each energy application to ensure stable catheter position and appropriate delivery of energy to the targeted tissue. When necessary, repeat mapping and ablation attempts were pursued until accessory pathway block was achieved.
>
> Monopolar delivery of radiofrequency alternative current between the endocardial ablation catheter tip electrode and large surface area skin electrode eliminated accessory pathway conduction in 116 of 122 accessory pathways (95%) . . . As with other measures of ablation procedure efficiency, the number of radiofrequency applications required for successful ablation declined as knowledge and experience accumulated.[130]

The ablative catheter used by Swartz is depicted in Figure 1, reproduced below (see catheter labeled ABL):

[128] *Swartz*, Abstract.

[129] *Id.*

[130] *Id.* at 488, 489, 491-493.

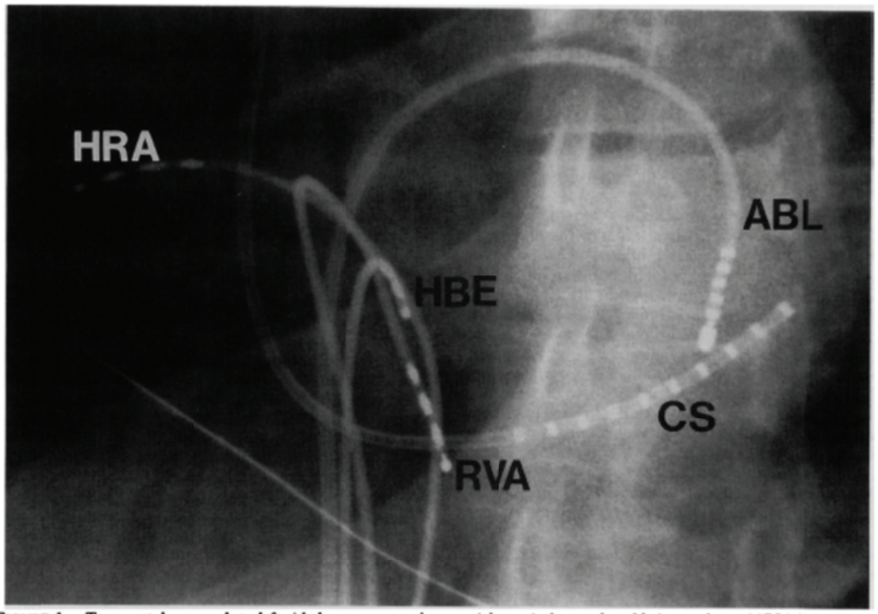

FIGURE 1. *Transseptal approach to left-sided accessory pathways. A large-tip hexapolar ablation catheter (ABL) is positioned on the mitral annulus midway between the third and fourth coronary sinus (CS) catheter electrodes. In this 45° left anterior oblique view, the ablation catheter ascends from the inferior vena cava, crosses the interatrial septum, and curves around the endocardial aspect of the mitral annulus from anterior to posterior. HBE, His bundle; HRA, high right atrium; RVA, right ventricular apex.* [131]

The skilled artisan would have understood that using the Swartz catheter to execute renal denervation would have provided substantially the same benefits that were observed in the transition from open heart to intravascular procedures.[132] Most significantly, the intravascular techniques are minimally invasive, which reduces recovery time and the risk of complications.[133] Moreover, RF ablative catheters had proven both highly reliable and clinically effective.[134] It was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[135] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[136] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[137]

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[131] *Id.* at 489.

[132] *Papademetriou Dec.*, ¶ 112; *Webster Dec.*, ¶¶ 67, 75; *Haemmerich Dec.*, ¶¶ 39, 91.

[133] *Id.*

[134] *Id.*

[135] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[136] *Id.*

[137] *Id.*

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Swartz.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Swartz catheter is introduced to the ablation site intravascularly.[138] In the combined method of Weinstock and Swartz, the catheter is likewise introduced to the renal artery intravascularly.[139]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

Swartz describes a tissue ablation procedure. "Monopolar delivery of radiofrequency alternative current between the endocardial ablation catheter tip electrode and large surface area skin electrode eliminated accessory pathway conduction in 116 of 122 accessory pathways (95%) . . . As with other measures of ablation procedure efficiency, the number of radiofrequency applications required for successful ablation declined as knowledge and experience accumulated."[140]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

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[138] *Swartz*, 488.

[139] *Papademetriou Dec.*, ¶ 98; *Webster Dec.*, ¶¶ 73-75; *Haemmerich Dec.*, ¶ 91.

[140] *Swartz*, 491-493.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[141] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[142]

For the reasons set forth above, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Swartz.

[141] *Weinstock*, 292.

[142] *Haemmerich Dec.*, ¶ 37.

1-B Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Webster '695

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[143] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[144]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[145]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[146] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for transvascular sympathectomies in the cardiovascular context.[147] Representative devices and methods for transvascular sympathectomies are disclosed in Webster '695 (App. J).

The Webster '695 reference teaches an intravascular electrode-tipped catheter that can be used to ablate sympathetic nerve tissue where indications require a sympathectomy.[148] Webster '695 states that:

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[143] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[144] *Weinstock*, Abstract.

[145] *Id.* at 288.

[146] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

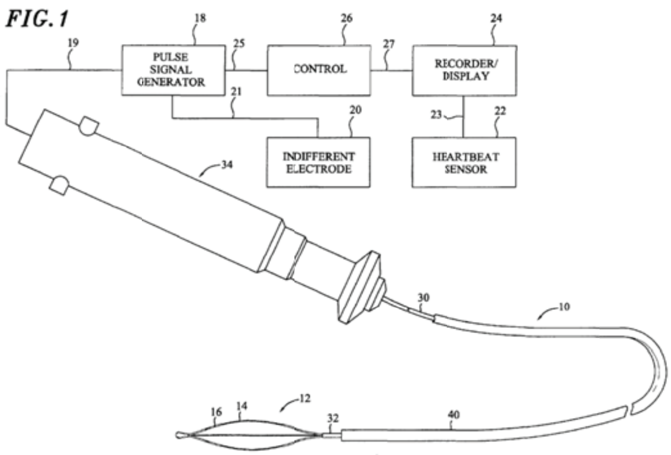
[147] *Id.*

[148] *Webster '695*, Abstract, 12:13-29.

> The system and methods of the invention can be used to ablate sympathetic and parasympathetic nerves if necessary. Sympathectomy is indicated in certain patients, for example those with contraindications to β-blockers. Selective sympathetic denervation, performed by transvascular ablation using the method of the invention, can reduce these patients' risk of sudden death from acute arrhythmias. Selective parasympathetic denervation may be indicated in patients with atrial tachycardia or fibrillation induced or maintained by excessive vagal nerve stimulation. A denaturing or ablating stimulus (e.g., radiofrequency or cryoablation) is applied across the vessel wall to the sympathetic fibers at any desired location. Preferably, sites are selected where a purely or nearly pure sympathetic or parasympathetic branch runs very close to the vessel, and where there are few other nerves or other sensitive tissues. Ablating stimulation is applied until conduction in the fiber is impaired or ceases altogether. [149]

As illustrated in Webster '695's FIG. 1, reproduced below, the device is connected to a signal generator 18 and includes basket electrode 12 at its distal end.[150]

FIG. 1



In use, the "catheter is inserted into a blood vessel and directed to a location wherein the electrode through which a stimulus is delivered is adjacent to one or more predetermined cardiac parasympathetic or sympathetic nerves."[151]

The Webster '695 catheter is well suited to the renal denervation procedure suggested by Weinstock and others.[152]

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[149] *Id.* at 12:13-29.

[150] *Id.* at 16:50-60.

[151] *Id.* at 2:56-60.

[152] *Papademetriou Dec.*, ¶¶ 79-81; *Haemmerich Dec.*, ¶¶ 89-92.

Significantly, the basket catheter taught by Webster '695 is quite similar to a preferred embodiment of the '948 patent (shown below) (App. A) in which the electrode is positioned within the vessel with a positioning element 304 that can take the form of a "balloon, an expandable wire basket, [or] other mechanical expander[]."[153] Accordingly, it is apparent that Webster '695's basket catheter could be adapted for use within renal vessels.[154]

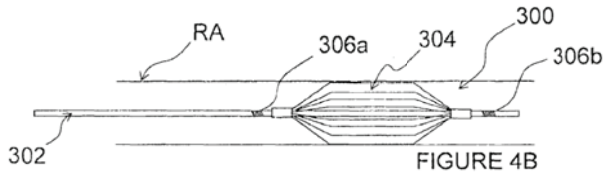

FIGURE 4B

The Webster '695 catheter could be used in a renal artery with little or no modification. Webster '695 discloses that: "[t]he outer diameter of the catheter body 30 is not critical but is preferably no more than about 8 French and more preferably no more than about 7 French."[155] Although the '948 patent does not discuss the sizes of the catheters or electrodes depicted therein, renal catheters generally range in size from about 6 to 9 French (or about 2-3 mm).[156] A skilled artisan might desire to modify the dimensions of the basket electrode or to make the catheter more highly maneuverable. However, such modifications were routine in the industry long before the earliest effective priority date, as demonstrated by the '948 patent's failure to provide any disclosure concerning the engineering aspects of the catheter design.[157]

The fact that a skilled artisan would have known how to adapt the Webster '695 catheter to renal applications is further demonstrated by the '948 patent's lack of any teaching or explanation as to the technical specifications for the catheter or how it would be constructed.[158] The '948 patent discloses no specific dimensions, frequencies, power levels, steerability metrics, or component material properties for the catheter.[159]

The skilled artisan would have seen various apparent and compelling motivations to use the Webster '695 catheter for the renal denervation procedure described by Weinstock.[160] First, as discussed

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[153] *'948 patent*, 7:13-14, Fig. 4B; *See also Papademetriou Dec.*, ¶ 80.

[154] *Papademetriou Dec.*, ¶ 80.

[155] *Webster '695*, 7:27-29.

[156] *Papademetriou Dec.*, ¶ 82.

[157] *Id.* at ¶¶ 82-83.

[158] *Id.* at ¶ 82.

[159] *Id.* at ¶ 82.

[160] *Papademetriou Dec.*, ¶¶ 77-81; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

in the Technical Background section, by the year 2000 it was well known that in the related field of cardiovascular sympathectomies (denervations) surgical techniques had evolved into intravascular procedures in which an electrode-tipped catheter was used to ablate electrically conductive tissue transvascularly, or through the wall of the vessel.[161] Second, the Webster '695 device is specifically described as being useful for sympathectomies.[162] Third, as Webster '695 explains, "the expandable or basket catheter of the invention allows . . . stable placement of the electrode for accurate, repeatable stimulation at the desired location."[163] Fourth, the RF pulse technique taught in Webster '695 is described as reducing the risk of undesired stimulation of surrounding tissues.[164] Fifth, Webster '695's intravascular technique is minimally invasive, which reduces recovery time, risk of complications and associated health care costs.[165]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[166] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[167] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[168]

As noted above in the Technical Background section, a skilled artisan further would have understood that the stenosis (abnormal narrowing of the vessel) which occurred in some prior cardiovascular ablative procedures (notably certain early intravascular pulmonary vein ablation techniques) was less likely to pose a problem with the renal artery.[169] The renal arterial tissue is significantly stronger than that that of the pulmonary vein.[170] The body of the renal artery is relatively straight and thus poor tissue-electrode contact would not have been expected to be an issue.[171] It would

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[161] *Papademetriou Dec.*, ¶ 86.

[162] *Webster '695*, 4:20-27; *Papademetriou Dec.*, ¶ 86.

[163] *Id.* at 4:33-37; *Id.*

[164] *Id.* at 4:37-38; *Id.*

[165] *Papademetriou Dec.*, ¶ 86.

[166] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[167] *Id.*

[168] *Id.*

[169] *Papademetriou Dec.*, ¶¶ 37-39, 48-50.

[170] *Id.* at ¶¶ 40, 41.

[171] *Id.* at ¶¶ 48, 49, 101.

have been expected that the renal arterial tissue would be substantially less prone to stenosis.[172] The availability of ablative catheters with cooled catheter tips (which would serve to keep the inside of the renal artery cool) would also have given a skilled artisan a high degree of confidence that any stenosis issue could be surmounted.[173]

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Webster ‘695.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

Webster ‘695’s Summary section similarly teaches that the catheter is to be used intravascularly: “[t]he method involves the intravascular stimulation and/or ablation of cardiac parasympathetic and sympathetic nerves sufficient to regulate or slow the heart rate or prevent the occurrence of these arrhythmias.”[174] In the combined method of Weinstock and Webster ’695, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[175]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

The Webster ‘695 catheter is used to ablate sympathetic nerve tissue where indications require a sympathectomy.[176] Webster ‘695 states that:

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[172] *Id.* at ¶¶ 48-50.

[173] *Papademetriou Dec.*, ¶¶ 48-49; *Haemmerich Dec.*, ¶¶ 69-79.

[174] *Webster ‘695*, 2:48-52.

[175] *Papademetriou Dec.*, ¶¶ 98, 115; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[176] *Webster ‘695*, Abstract and 12:13-28.

> The system and methods of the invention can be used to ablate sympathetic and parasympathetic nerves if necessary. Sympathectomy is indicated in certain patients, for example those with contraindications to β-blockers. Selective sympathetic denervation, performed by transvascular ablation using the method of the invention, can reduce these patients' risk of sudden death from acute arrhythmias. Selective parasympathetic denervation may be indicated in patients with atrial tachycardia or fibrillation induced or maintained by excessive vagal nerve stimulation. A denaturing or ablating stimulus (e.g., radiofrequency or cryoablation) is applied across the vessel wall to the sympathetic fibers at any desired location. Preferably, sites are selected where a purely or nearly pure sympathetic or parasympathetic branch runs very close to the vessel, and where there are few other nerves or other sensitive tissues. Ablating stimulation is applied until conduction in the fiber is impaired or ceases altogether. [177]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*

> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt

[177] *Id.* at 4:20-27.

intake."[178] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[179]

For the reasons set forth above, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Webster '695.

[178] *Weinstock*, 292.

[179] *Haemmerich Dec.*, ¶ 37.

1-C Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Schauerte

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[180] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[181]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[182]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[183] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for transvascular sympathectomies in the cardiovascular context.[184] Representative devices and methods for transvascular sympathectomies are disclosed in Schauerte (App. C).

The Schauerte reference teaches an intravascular catheter and associated procedure for either stimulating or ablating nerves locating on the exterior of the vasculature.[185] As shown in Schauerte's Figure 1, reproduced below, a basket catheter is used to ablate vagal nerves associated with cardiac vessels (e.g., the right pulmonary artery).[186]

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[180] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[181] *Weinstock*, Abstract.

[182] *Id.* at 288.

[183] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[184] *Id.*

[185] *Schauerte*, Abstract.

[186] *Id.* at 2775.

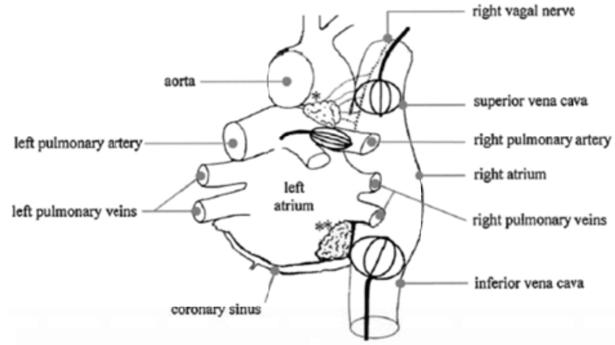

Figure 1. Illustration of parasympathetic innervation of atria. Dorsal view of atria and great vessels is shown. Course of nerves depicted is functional course rather than anatomically correct description of parasympathetic atrial innervation. Most of right and left vagal fibers that innervate atria and sinus or AV node converge to fat pad between RPA, base of aorta, and SVC (RPA fat pad [*]). Some vagal fibers that innervate atria are located in fat pad between IVC, left atrium, and ostium of coronary sinus (**) and along SVC. Stimulation and ablation of parasympathetic nerves was performed with expandable electrode catheter, which was introduced into upper RPA (n=7), SVC (n=1), or IVC (n=2).

Figure 7 of Schauerte further shows that the vagal nerves surround the right pulmonary artery, just as the renal nerves surround the renal artery.[187]

Schauerte concluded that radiofrequency current catheter ablation (RFCA) was a promising technique for transvascular ablation of sympathetic nerves:

> Transvascular atrial parasympathetic nerve system modification by RFCA abolishes vagally mediated AF. This antifibrillatory procedure may provide a foundation for investigating the usefulness of neural ablation in chronic animal models of AF and eventually in patients with AF and high vagal tone.[188]

Schauerte thus teaches that the expandable catheter and techniques disclosed therein would be useful for transvascular sympathectomies.[189] One skilled in the art would have readily concluded that the transvascular ablative catheter of Schauerte was useful for the renal denervations recommended by Weinstock.[190]

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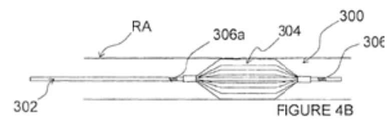
[187] *Id.* at 2778.

[188] *Id.* at Abstract.

[189] *Papademetriou Dec.*, ¶¶ 92-93.

[190] *Id.* at ¶¶ 91-93.

The Schauerte catheter is described as being useful for ablation of neural tissue on the exterior of arteries and veins.[191] Schauerte also teaches that the expandable catheter was effective at transvascularly ablating the neural tissue and thus a skilled artisan would be motivated to, at the very least, attempt to use a Schauerte-type catheter for the denervation treatment taught by Weinstock and others.[192] Further, the fact that the expandable basket catheter of Schauerte is adapted for renal procedures is evidenced by the similarity between the Schauerte catheter (below left) and the ‘948 patent’s preferred embodiment shown in Figure 4B:[193]



The size of the Schauerte catheter is largely irrelevant, as the claims of the ‘948 patent are not limited to any particular size of human.[194]

In any event, as explained by the declarations of Professors Papademetriou, Webster and Haemmerich, a skilled artisan would understand the Schauerte ablative catheter, which is identified as having a 7 French shaft, would be suitable for use in renal applications without modification.[195] Although the ‘948 patent does not discuss the sizes of the catheters or electrodes depicted therein, renal catheters generally range in size from about 6 to 9 French (or about 2-3 mm).[196] The Schauerte catheter was delivered in the right pulmonary artery, which requires substantially more maneuverability than delivering the same catheter to the renal artery.[197]

Moreover, it was known that RF ablation had “emerged as the most successful and effective energy source for clinical applications in many specialties.”[198] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in

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[191] *Schauerte*, Abstract, 2775 (Figure 1).

[192] *Id.* at 2777-2778; *Papademetriou Dec.*, ¶ 93.

[193] *Papademetriou Dec.*, ¶ 93.

[194] *Id.* at ¶ 96.

[195] *Schauerte*, 2775; *Papademetriou Dec.*, ¶¶ 96, 103; *Haemmerich Dec.*, ¶¶ 82, 84.

[196] *Papademetriou Dec.*, ¶ 96.

[197] *Papademetriou Dec.*, ¶¶ 99-103.

[198] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58*.

neurosurgery, urology, dermatology, oncology, and cardiology.[199] The professors conclude that those skilled in the art understood that "[t]he lasting advantages and control of the RF lesion suggest that it is indeed the superior methodology in many areas of clinical practice, especially in the nervous system . . ."[200]

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Schauerte.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Schauerte catheter is designed for intravascular use, as shown in Schauerte's Figure 1.[201] In the combined method of Weinstock and Schauerte, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[202]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

Further to the discussion above in connection with claim 1, Schauerte teaches a method for radiofrequency current catheter ablation (RFCA) and methods for non-ablative stimulation.[203]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

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[199] *Id.*

[200] *Id.* at 7.

[201] *Schauerte*, 2775.

[202] *Papademetriou Dec.*, ¶¶ 98, 115; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[203] *Schauerte*, 2775.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[204] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[205]

For the foregoing reasons, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Schauerte.

[204] *Weinstock*, 292.

[205] *Haemmerich Dec.*, ¶ 37.

1-D Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Webster '885

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[206] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[207]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[208]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[209] One method that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue or nerve ablation in the cardiovascular context.[210] One such method is shown in Webster, W. W., Jr. "Multi-electrode ablation catheter." *U.S. Patent No.* 5,893,885, filed Nov. 1996 ("Webster '885") (App. R).

Webster's '885 patent discloses a multi-electrode RF ablation catheter useful for treating arrhythmias in the heart.[211] Each electrode is electrically connected to a switching unit by leads comprising paired copper and constantan wires.[212] The switching unit enables an operator to switch between a first mode for monitoring ECG and a second mode for delivering RF energy for tissue ablation to a selected electrode and monitoring the temperature of that electrode.[213]

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[206] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[207] *Weinstock*, Abstract.

[208] *Id.* at 288.

[209] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[210] *Id.*

[211] *Webster '885*, Abstract, 1:4-5.

[212] *Id.* at Abstract; *Papademetriou Dec.*, ¶ 107.

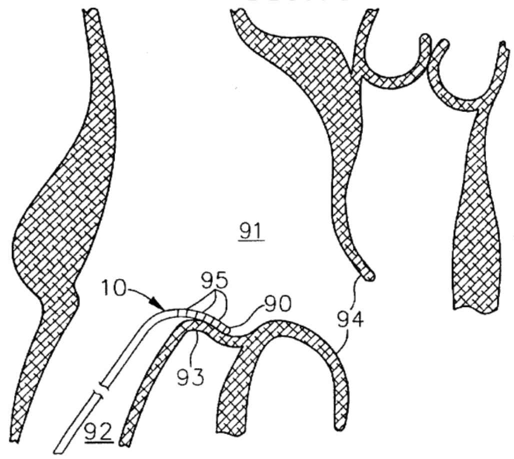
[213] *Webster '885*, Abstract.

The paired copper and constantan lead wires reduce the need for more lead wires and/or larger diameter lead wires.[214] This in turn allows for a smaller diameter catheter than would be otherwise necessary for the number of electrodes carried by the catheter.[215]

The diameter of the catheter tip section 12 is preferably the same as or slightly smaller than the catheter body.[216] In a preferred embodiment the diameter of the catheter body is about 0.08 inches.[217] The length of the catheter tip section can vary as desired, but is preferably about three inches long.[218]

Figure 13 below shows that the deflectable ablation catheter 10 can deflect from a larger inferior vena cava vessel 92 around the corner to perform ablation at the vessel wall isthmus 93.[219]

FIG. 13



One skilled in the art would have readily concluded that steerable intravascular catheters, like Webster '885, were available to accomplish thermal ablation by using radiofrequency electric power to heat the tissue and therefore could perform the renal denervation procedures described by Weinstock.[220]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[221] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in

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[214] *Id.* at 8:10-12.

[215] *Id.* at 8:12-14.

[216] *Id.* at 3:37-38.

[217] *Id.* at 3:38-40.

[218] *Id.* at 3:36-42.

[219] *Id.* at Fig. 13.

[220] *Papademetriou Dec.*, ¶¶ 107, 110; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[221] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

neurosurgery, urology, dermatology, oncology, and cardiology.[222] The professors conclude that those skilled in the art understood that "[t]he lasting advantages and control of the RF lesion suggest that it is indeed the superior methodology in many areas of clinical practice, especially in the nervous system . . ."[223]

Further, it was generally known in the early 2000s that as an alternative to contacting the tissue and transmitting a stimulating energy into the tissue itself, one could equally apply an ablative stimulus across a vessel wall from inside the renal artery, for example, rather than from the outside of the artery.[224] Accordingly, one skilled in the art would know that using this approach would have been desirable for ablating the renal nerves located on the outside wall of the renal arteries because less invasive surgery is required when the ablation is conducted from inside the artery.[225]

Regarding the general maneuverability of steerable catheters within the renal artery, Professors Webster, Haemmerich and Papademetriou explain in their declarations that there is ample room for a 6-7F (2 mm - 2.3 mm) steerable catheter, for example, to advance up the aorta and turn into the renal artery.[226] The renal artery is about 5 mm in diameter branching from the aorta, which is about 15 mm in diameter.[227] Given the known geometrical dimensions of the catheters and the vessels discussed above, one of ordinary skill in the art would understand that the Webster '885 catheter would be maneuverable through the renal vasculature and is well-suited to the renal denervation suggested by Weinstock, as the Webster '885 catheter, which is 0.08 inch (or 2.03 mm or about 6F), can easily pass from the 15 mm aorta into the 5 mm diameter renal artery.[228]

Additionally, to the extent that a given catheter such as that taught by Webster '885 was judged too stiff or insufficiently steerable for a given vessel, one of ordinary skill in the art would understand that making it more maneuverable would have been considered routine engineering around the year 2000.[229] As of the year 2000, making the catheters more highly steerable was primarily a cost consideration.[230] The basic design principles would not change, although it would have been generally more expensive to

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[222] *Id.*

[223] *Id.*

[224] *Papademetriou Dec.*, ¶ 107; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[225] *Id.*

[226] *Uflacker*, R., "Atlas of vascular anatomy: An angiographic approach." Baltimore: Williams & Wilkins, 424 (1997); *Papademetriou Dec.*, ¶ 100; *Webster Dec.*, ¶ 69; *Haemmerich Dec.*, ¶ 84.

[227] *Id.* at 424; *Id.* at ¶ 99; *Id.* at ¶ 68; *Id.*

[228] *Id.*; *Id.* at ¶ 100; *Id* at ¶ 69; *Id.*

[229] *Papademetriou Dec.*, ¶ 102; *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[230] *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

fabricate smaller parts because they would be fashioned from materials with higher strength and toughness.[231]

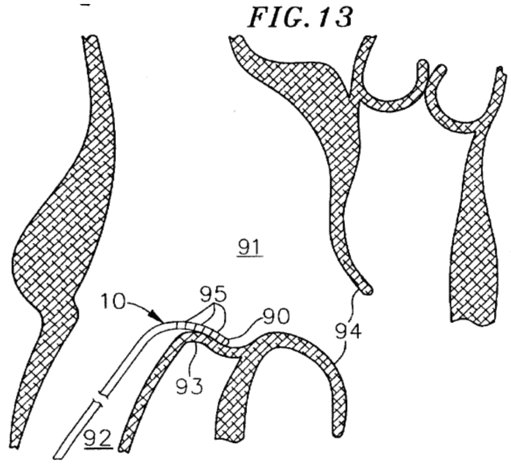
In use, the Webster '885 catheter would, for instance, be introduced through the femoral artery with a guide sheath configured to position the catheter at the ostium, or entrance, to the renal artery. The catheter would then be advanced, with or without the assistance of a guide sheath, to the treatment site in the renal artery.

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Webster '885.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Webster '885 catheter is designed for intravascular use.[232] Figure 13 below shows that the deflectable ablation catheter 10 can deflect from a larger inferior vena cava vessel 92 around the corner to perform ablation at the vessel wall isthmus 93.[233]

FIG. 13



In the combined method of Weinstock and Webster '885, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[234]

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[231] *Webster Dec.*, ¶ 70.

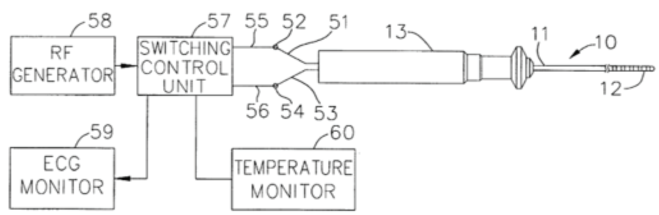
[232] *Webster '885*, 8:7-17.

[233] *Id.* at 7:61-64, Fig. 13.

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

Webster '885 discloses a multi-electrode RF ablation catheter useful for treating arrhythmias in the heart.[235] Each electrode is electrically connected to a switching unit by leads comprising paired copper and constantan wires.[236] The switching unit enables an operator to switch between a first mode for monitoring ECG and a second mode for delivering RF energy for tissue ablation to a selected electrode and monitoring the temperature of that electrode.[237] FIG. 11 below illustrates the switching unit being electrically connected to an RF generator, a temperature monitor and an ECG monitor.[238]

FIG. 11



11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

See discussion above in connection with claim 7.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

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[234] *Papademetriou Dec.*, ¶ 115; *Webster Dec.*, ¶¶ 74-76; *Haemmerich Dec.*, ¶¶ 89-92.

[235] *Webster '885*, Abstract, 1:4-5.

[236] *Id.* at Abstract.

[237] *Id.*

[238] *Id.* at Fig. 11.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[239] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[240]

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Webster '885.

[239] *Weinstock*, 292.

[240] *Haemmerich Dec.*, ¶ 37.

1-E Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Edwards

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[241] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[242]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[243]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[244] One method that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue ablation in the cardiovascular context.[245] One such method is shown in Edwards, S. D., et al. "Electrode and associated systems using thermally insulated temperature sensing elements." *U.S. Patent No.* 5,688,266, filed Oct. 1995 (App. P).

FIG. 1 of Edwards teaches a steerable catheter for ablation therapy carrying a radiofrequency emitting tip electrode with a temperature sensing element for measuring the temperature of the tissue being ablated.

> [A] physician steers the catheter 14 through a main vein or artery (typically the femoral artery) into the interior region of the heart that is to be treated. The physician then further manipulates the catheter 14 to place the tip electrode 16 into contact with the tissue within the heart that is targeted for ablation. The user directs radiofrequency energy from the

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[241] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[242] *Weinstock*, Abstract.

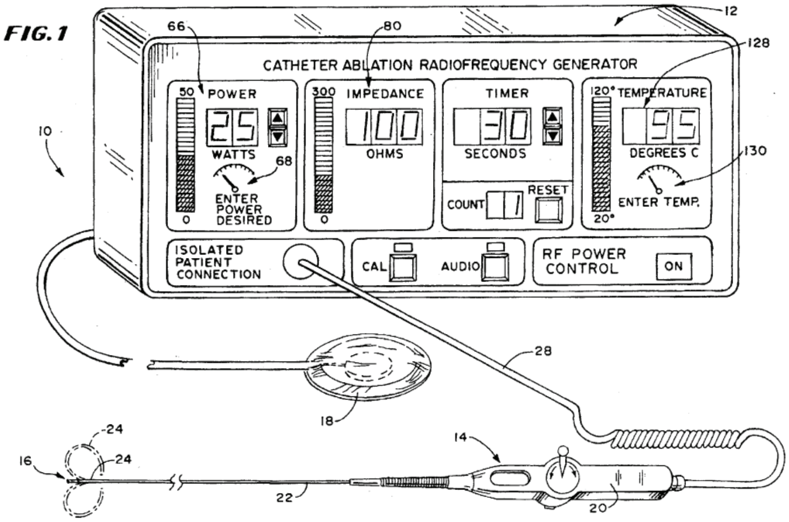
[243] *Id.* at 288.

[244] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[245] *Id.*

generator 12 into the tip electrode 16 to form a lesion on the contacted tissue.[246]

FIG. 1



One skilled in the art would have readily concluded that steerable intravascular catheters, like Edwards, were available to accomplish thermal ablation by using radiofrequency electric power to heat the tissue and therefore could perform the renal denervation procedure described by Weinstock and others.[247] Moreover, it was generally known in the early 2000s that as an alternative to contacting the tissue and transmitting a stimulating energy into the tissue itself, one could equally apply an ablative stimulus across a vessel wall from inside the renal artery, for example, rather than from the outside of the artery.[248] Accordingly, one skilled in the art would know that using this approach would have been desirable for ablating the renal nerves located on the outside wall of the renal arteries because less invasive surgery is required when the ablation is conducted from inside the artery.[249]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[250] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in

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[246] *Edwards '266*, 2:53-60.

[247] *Papademetriou Dec.*, ¶¶ 105, 110; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[248] *Id.* at ¶ 107; *Id.* at ¶¶ 72-76; *Id.* at ¶¶ 89-92.

[249] *Id.*

[250] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

neurosurgery, urology, dermatology, oncology, and cardiology.[251] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[252]

Additionally, to the extent that a given catheter such as that taught by Edwards was judged too stiff or insufficiently steerable for a given vessel, one of ordinary skill in the art would understand that making it more maneuverable would have been considered routine engineering around the year 2000.[253] As of the year 2000 making the catheters more highly steerable was primarily a cost consideration.[254] The basic design principles would not change, although it would have been generally more expensive to fabricate smaller parts because they would be fashioned from higher strength and "toughness" materials.[255]

Regarding the general maneuverability of steerable catheters within the renal artery, the renal artery is about 5 mm in diameter branching from the aorta, which is about 15 mm in diameter.[256] Thus, there is ample room for a 6-7F steerable catheter, for example, to advance up the aorta and turn into the renal artery.[257] As further evidenced by Dr. Papademetriou's declaration, the anatomy of the renal arteries reveals that the renal arteries are relatively more straight than tortuous, which would allow a steerable catheter to more easily navigate and maneuver through the renal vasculature.[258]

In use, the Edwards catheter would, for instance, be introduced through the femoral vein with a guide sheath configured to position the catheter at the ostium, or entrance, to the renal artery.[259] The catheter would then be advanced, with or without the assistance of a guide sheath, to the treatment site in the renal artery.[260]

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Edwards.

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[251] *Id.*

[252] *Id.*

[253] *Papademetriou Dec.*, ¶ 102; *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[254] *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[255] *Webster Dec.*, ¶ 70.

[256] *Uflacker*, R., "Atlas of vascular anatomy: An angiographic approach." Baltimore: Williams & Wilkins, 424 (1997); *Papademetriou Dec.*, ¶ 99; *Webster Dec.*, ¶ 68; *Haemmerich Dec.*, ¶ 84.

[257] *Id.* at 424; *Id.* at ¶ 100; *Id.* at ¶ 69; *Id.*

[258] *Papademetriou Dec.*, ¶ 101.

[259] *Edwards '266*, 2:54.

[260] *Id.* at 3:3-11.

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Edwards steerable catheter is designed for intravascular use:

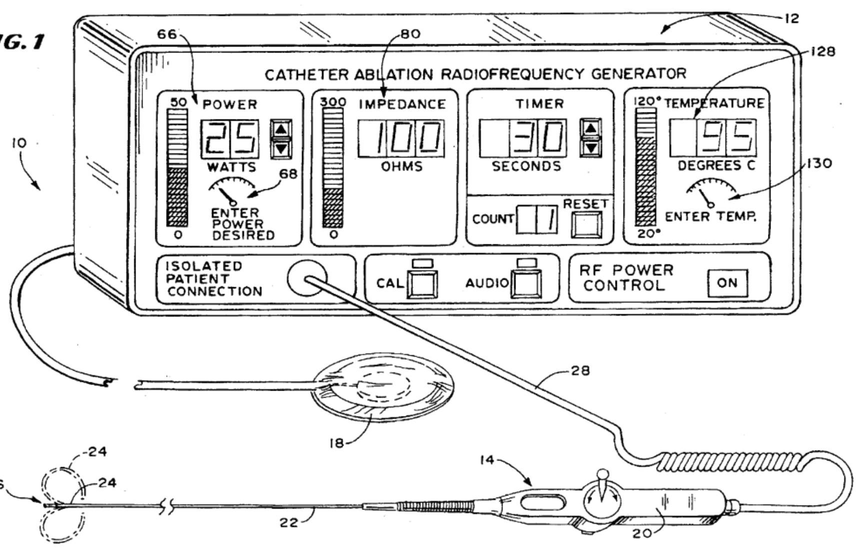
> [A] physician steers the catheter 14 through a main vein or artery (typically the femoral artery) into the interior region of the heart that is to be treated. The physician then further manipulates the catheter 14 to place the tip electrode 16 into contact with the tissue within the heart that is targeted for ablation. The user directs radiofrequency energy from the generator 12 into the tip electrode 16 to form a lesion on the contacted tissue.[261]

In the combined method of Weinstock and Edwards, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[262]

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

FIG. 1 of Edwards teaches a steerable catheter for ablation therapy carrying a radiofrequency emitting tip electrode with a temperature sensing element for measuring the temperature of the tissue being ablated.

FIG. 1



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[261] *Id.* at 2:53-60.

[262] *Papademetriou Dec.*, ¶¶ 105, 110; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

See discussion above in connection with claim 7.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[264] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[265]

For the foregoing reasons, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Edwards.

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[263] *Edwards '266*, 2:56-60.

[264] *Weinstock*, 292.

[265] *Haemmerich Dec.*, ¶ 37.

1-F Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Uchida

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[266] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[267]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[268]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[269] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue or nerve ablation in the cardiovascular context.[270] Representative devices and methods for transvascular sympathectomies are disclosed in Uchida, F., et al. "Effect of radiofrequency catheter ablation on parasympathetic denervation: A comparison of three different ablation sites." *PACE*, 21:2517-2521 (1998) (App. S).

According to Uchida, "[r]adiofrequency (RF) catheter ablation has become a treatment of choice for patients with symptomatic atrioventricular reentrant tachycardia (AVRT) or atrioventricular nodal reentrant tachycardia (AVNRT)."[271] Uchida's procedure was as follows:

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[266] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[267] *Weinstock*, Abstract.

[268] *Id.* at 288.

[269] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-82.

[270] *Id.*

[271] *Uchida*, 2517.

> Three 5 Fr quadripolar electrode catheters were introduced percutaneously into the femoral and subclavian veins and positioned at the high right atrium, His-bundle region, right ventricular apex, and coronary sinus for recording and stimulation. Meticulous mapping and ablation were performed using a steerable 7 Fr quadripolar catheter with a 4-mm tip and 2-mm interelectrode spacing. RF current was supplied by a 500 KHz generator (NL 50-I, Central Industry, Japan) at a constant preset electrical power (20 to 35 W) between the tip electrode of the ablation catheter and a large skin electrode positioned in the left subscapular region.
>
> The ablation catheter was positioned below the mitral valve for left free-wall and posteroseptal APs, above the tricuspid valve for right free-wall and posteroseptal APs, and near the ostium of the coronary sinus for slow pathways of AVNRT, respectively.
>
> Once a target was chosen, RF energy was applied for 5 seconds. If ablation was unsuccessful during this time, the current was turned off immediately and the ablation catheter was repositioned. If AP conduction disappeared or junctional rhythm (in slow pathway ablation) appeared, the current was delivered for a total of 60 seconds. [272]

Uchida's results demonstrate that "[r]adiofrequency (RF) catheter ablation of supraventricular tachycardias (SVT) has been shown to result in local parasympathetic denervation."[273] Uchida also demonstrated that effectiveness of parasympathetic denervation was a function of the cumulative RF energy delivered through the electrode.[274]

A skilled artisan would be motivated to use the Uchida catheter to perform the renal denervation taught by Weinstock and others.[275] The Uchida device would have been understood to be substantially

[272] *Id.* at 2518.

[273] *Id.* at Abstract.

[274] *Id.* at 2517, 2519.

[275] *Papademetriou Dec.*, ¶¶ 89-90; *Webster Dec.*, ¶¶ 80-81; *Haemmerich Dec.*, ¶ 91-93.

less invasive than the surgical nerve resection described in Weinstock.[276] Use of the Uchida ablative catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[277]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[278] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[279] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[280] Accordingly, a skilled artisan would have seen a strong motivation to use the Uchida RF catheter to achieve the renal denervation prescribed by Weinstock.[281]

It should also be noted that, as discussed in the Technical Background section above, in parallel with the aforementioned developments in the renal sympathectomy (denervation) field, related surgical procedures had been evolving in the field of cardiovascular tissue and nerve ablation.[282] For instance, AVNRT was traditionally treated with a surgical method performed with a scalpel.[283] With advances in mechanical catheter technology in the 1990s, AVNRT surgery evolved into an intravascular procedure in which a catheter is inserted into the heart and ablative energy was applied through the wall of the heart in order to achieve the same result.[284] In order to accommodate different vessel sizes catheters were modified as appropriate to obtain the appropriate lesion size given the nature of the tissue involved.[285] By referencing the existing knowledge base which interrelated design parameters and lesion size, miniaturization or enlargement of catheters was routinely accomplished in the field of surgical instrument design as of the year 2000.[286]

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Uchida.

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[276] *Id.* at ¶ 115; *Id.* at ¶ 67; *Id.* at ¶¶ 91-93.

[277] *Id.*

[278] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[279] *Id.*

[280] *Id.*

[281] *Papademetriou Dec.*, ¶¶ 89-90; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶ 89-92.

[282] *Id.* at ¶ 21; *Id.* at ¶ 24; *Id.* at ¶ 39.

[283] *Id.* at ¶ 24; *Id.* at ¶ 26; *Id.* at ¶ 41.

[284] *Id.* at ¶¶ 25, 30, 31; *Id.* at ¶¶ 31, 32; *Id.* at ¶ 46.

[285] *Papademetriou Dec.*, ¶¶ 85, 102; *Haemmerich Dec.*, ¶¶ 69-79.

[286] *Webster Dec.*, ¶¶ 52-55; *Haemmerich Dec.*, ¶¶ 69-79.

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Uchida catheter is designed for intraluminal deployment such as in coronary sinus (a cardiac vein) and related pathways.[287] When used to perform the Weinstock denervation, the Uchida catheter would be inserted into the renal artery.[288]

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

See discussion above in connection with claim 1. The Uchida catheter ablates tissue through the application of RF energy.[289]

11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

See discussion above in connection with claim 7.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

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[287] *Uchida*, Abstract; *Papademetriou Dec.*, ¶ 31; *Webster Dec.*, ¶ 32; *Haemmerich Dec.*, ¶ 55.

[288] *Papademetriou Dec.*, ¶¶ 89-90; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶ 89-92.

[289] *Uchida*, 2517.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[290] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[291]

For the foregoing reasons, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Uchida.

[290] *Weinstock*, 292.

[291] *Haemmerich Dec.*, ¶ 37.

1-G Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by Weinstock Taken in Combination with Benito

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Weinstock (App. E) specifically teaches that destruction of the renal arterial nerves was expected to decrease blood pressure (hypertension) in humans.[292] Weinstock's abstract explains that the purpose of the study was to determine the effect of renal denervation (or destruction) on blood pressure.[293]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Weinstock method, the denervation was accomplished by surgically severing the renal nerves: "After a mid-line incision and laparotomy, the renal nerves were carefully dissected on both sides and the surrounding tissue was covered with 10% phenol in alcohol for 1 min."[294]

A skilled artisan having the Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[295] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue ablation in the cardiovascular context.[296] Representative devices and methods for transvascular sympathectomies are disclosed in Benito, F., et al. "Radiofrequency catheter ablation of accessory pathways in infants." *Heart*, 78:160-162 (1997) (App. T).

Benito explains that "[r]adiofrequency catheter ablation has been established as a highly effective and safe technique for eliminating accessory atrioventricular (AV) connections in adults and children."[297] An AV accessory connection is an electrical conduction pathway, akin to neural tissue.[298] Benito discloses a 5 French (1.67 mm) electrical ablative catheter for use in a pediatric cardiovascular neural

[292] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[293] *Id.* at Abstract.

[294] *Id.* at 288.

[295] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-81.

[296] *Id.*

[297] *Benito*, 160.

[298] *Papademetriou Dec.*, ¶ 23.

ablation procedure, for example in the coronary sinus (cardiac vein).[299] "Ablation was done for medically refractory tachyarrhythmia associated with aborted sudden death in two patients, left ventricular dysfunction in one, failure of antiarrhythmic drugs in one, and planned cardiovascular surgery in one."[300] Benito concluded that the RF catheter technique could in fact be used effectively to ablate cardiovascular nerves associated with refractory tachyarrhythmia, among other conditions:

> ***Conclusions*—Radiofrequency catheter ablation can be performed successfully in infants. Temperature monitoring in 5F ablation catheters would be desirable to prevent the development of coagulum. Echocardiography must be performed after the ablation procedure to investigate pericardial effusion.**

[301]

The Benito RF ablative catheter is well suited to renal arterial procedures.[302] As explained above in connection with the discussion of the Schauerte reference, a 5 French a catheter would be appropriately sized for use in a renal arterial application.[303] Moreover, the figures in the Benito reference reveal that the catheter has ample flexibility and maneuverability to navigate the renal vessels:

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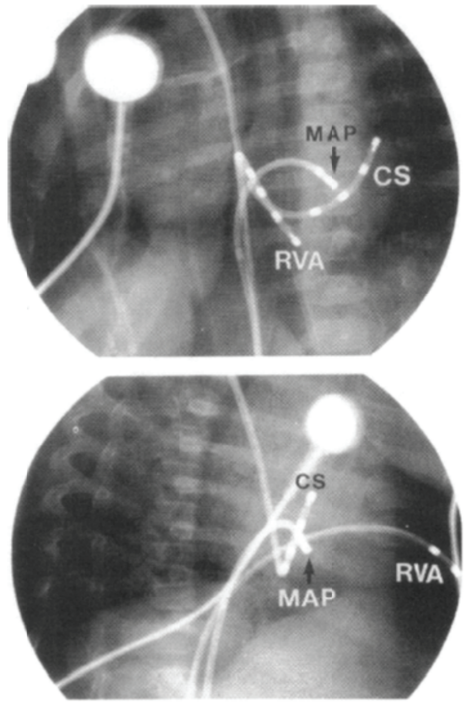
299 *Benito*, Abstract; *Papademetriou Dec.*, ¶¶ 45, 100; *Webster Dec.*, ¶¶ 45, 69; *Haemmerich Dec.*, ¶¶ 63, 84.

300 *Benito*, Abstract.

301 *Id.*

302 *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 84, 92.

303 *Id.*



Chest radiographs of catheter electrode position during ablation of a left posterior pathway in patient 5. The ablating catheter is positioned by transseptal approach at the mitral annulus, in close proximity to the third electrode of the coronary sinus catheter. Left anterior oblique projection is shown in top panel and right anterior oblique is shown in bottom panel. CS, coronary sinus catheter; MAP, ablation/mapping catheter; RVA, right ventricular apex catheter. [304]

Using well-documented interrelationships between catheter configuration and ablative lesion size, a skilled artisan would be able to readily and without undue effort adapt the Benito catheter to a renal application.[305]

A skilled artisan would be motivated to use the Benito catheter to perform the renal denervation taught by Weinstock.[306] The Benito device would have been understood to be substantially less invasive than the surgical nerve resection described in Weinstock.[307] Use of the Benito ablative catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[308]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[309] The declarations of Professors Webster,

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[304] *Benito*, 161.

[305] *Id.*

[306] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-81.

[307] *Papademetriou Dec.*, ¶ 106; *Webster Dec.*, ¶¶ 75-76; *Haemmerich Dec.*, ¶¶ 91-92.

[308] *Id.*

[309] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58*.

Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[310] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[311] Accordingly, a skilled artisan would have seen a strong motivation to use the Benito RF catheter to achieve the renal denervation prescribed by Weinstock.[312]

Accordingly, the subject matter of claim 1 is rendered obvious by Weinstock when viewed in light of Benito.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Benito catheter is designed for intraluminal deployment such as in a coronary sinus (cardiac vein) and related pathways.[313] When used to perform the Weinstock denervation, the Benito catheter would be inserted into the renal artery.[314]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

See discussion above in connection with claim 1. The Benito catheter ablates tissue through the application of RF energy.[315]

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[310] *Id.*

[311] *Id.*

[312] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-81.

[313] *Benito*, Abstract, 160.

[314] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 84, 92.

[315] *Benito*, 160-161.

11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

See discussion above in connection with claim 7.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[316] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[317]

For the foregoing reasons, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Weinstock taken in combination with Benito.

[316] *Weinstock*, 292.

[317] *Haemmerich Dec.*, ¶ 37.

Group 2: Proposed Rejections based on the Kompanowska Reference

Kompanowska (App. B) qualifies as prior art under 35 U.S.C. § 102(b) because it was published in the March 1, 2001 edition of the *Journal of Physiology*, more than a year prior to the earliest possible priority date of the '948 patent, April 8, 2002. Kompanowska was not before the Examiner.

The Kompanowska reference teaches thermal ablative renal denervation (RD) for treatment of hypertension.[318] More particularly, Kompanowska discloses an electrocautery technique for renal denervation and explains that renal denervation inhibits secretion of renin (a hormone responsible for increases in blood pressure), enhances renal natriuresis (sodium excretion through the kidneys) and enhances renal blood flow.[319] Each of these was known to treat hypertension by lowering blood pressure.[320]

Kompanowska teaches an alternative technique for renal denervation in view of the disadvantages of traditional approaches wherein nerves are surgically removed with a scalpel.[321] The alternative technique involves ablation by electrocautery.[322]

> of intrarenal or systemic haemodynamics. The tissue within the loop, including renal nerve fibres, was electro-coagulated: a 5 MHz current generated by a neurosurgical cautery device (Famed, Warsaw, Poland) was applied for 5–10 s until the tissue was cut completely and the loop could be removed.

Kompanowska concludes that the electrocautery approach is an improved and effective mechanism to achieve renal natriuresis.

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318 *Kompanowska*, 527.

319 *Id.*

320 *Papademetriou Dec.*, ¶ 67; *Webster Dec.*, ¶¶ 62-63; *Haemmerich Dec.*, ¶¶ 35, 80.

321 *Kompanowska*, 527.

322 *Id.* at 528.

> In summary, we have developed a novel approach for a rapid renal denervation in the rat, which is less invasive but as effective as the classical approach, as demonstrated by the marked reduction in tissue noradrenaline level. Owing to the reduced invasiveness of our procedure, measurements of renal haemodynamics and renal excretion were not interrupted at the moment of denervation and protocols could be designed whereby an experimental intervention and measurement (including suitable controls) could be made before and then after denervation, within the same experiment in one animal. It was found that the responses of the cortical and medullary circulation were dissociated: CBF increased almost immediately after denervation whilst MBF did not. In addition, we demonstrated that a natriuresis developed within about 0·5 h after denervation, without changes in GFR.[323]

The articles cited in the Kompanowska publication demonstrate that it was well known that renal denervation treats hypertension by impacting sodium excretion and renal blood flow.[324] As of the effective filing date, it was known that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[325]

[323] *Id.* at 534.

[324] *Id.* at 533 (citing generally to *DiBona 1997* (App. M)).

[325] *Papademetriou Dec.*, ¶¶ 54-62; *Haemmerich Dec.*, ¶¶ 28-36.

2-A Claims 1, 7, 12, 20 and 21 are Rendered Obvious by Kompanowska Taken in Combination with the DiBona 1997 Paper Cited Therein

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Kompanowska (App. B) discloses an electrocautery technique for renal denervation and explains that renal denervation can be used to decrease secretion of renin (the hormone responsible for increases in hypertension) and effect renal natriuresis (sodium excretion through the kidneys) and blood flow.[326]

The articles cited in the Kompanowska reference demonstrate that it was well known that renal denervation affected hypertension and congestive heart failure by impacting natriuresis, i.e., sodium excretion, which caused a reduction in water retention that, in turn, reduced blood pressure. For instance, Kompanowska cites the DiBona 1997 article (App. M). The DiBona 1997 reference devotes fourteen pages to a discussion of the interaction between renal nerve activity, including denervation, and cardiovascular conditions such as hypertension and congestive heart failure.[327] The reference explains that renal denervation lowers blood pressure in subjects having over-stimulated renal nerves by reducing sympathetic nerve activity.[328] DiBona 1997's hypertension findings are summarized in a table listing various hypertension models that are treatable with renal denervation:

326 *Kompanowska*, 527.

327 *DiBona 1997*, 142-155.

328 *Id.*

TABLE 9. *Models of experimental hypertension in which renal denervation prevents or delays the development of hypertension*

Models	Reference No.
Spontaneously hypertensive rat (SHR)	832, 946, 1150, 1383, 1540, 1674
Borderline hypertensive rat	932
SHR stroke prone	1112
New Zealand SHR	373
Goldblatt 1K, 1C (rat)	798, 1149
Goldblatt 2K, 1C (rat)	798
Aortic coarctation (dog)	1663
Aortic nerve transection (rat)	834, 1354
DOCA-NaCl (rat)	796, 1150, 1539
DOCA (pig)	1168
Grollman renal wrap (rat)	464, 831
Low sodium, 1K hypertension (rat)	1622
Angiotensin II hypertension (rat)	1623
Obesity hypertension (dog)	791
NaCl (baroreflex-impaired rabbit)	1658

1K, 1C, one kidney, one clip; 2K, 1C, two kidney, one clip; DOCA, deoxycorticosterone acetate. [329]

In DiBona 1997 the findings concerning the impact of denervation are summarized as follows:

> It is evident that the uniform effect of complete renal denervation on the development of hypertension in such a diverse group of experimental forms of hypertension strongly suggests a universally important role for the renal sympathetic nerves in hypertension. However, it should be noted that not all experimental forms of hypertension are ameliorated by renal denervation; renal denervation does not affect the development of hypertension in the Dahl NaCl-sensitive rat (1692) or in canine hypertension induced by chronic NOS inhibition (581). [330]

The articles cited in Kompanowska (such as DiBona 1997) thus demonstrate that as of Kompanowska's publication date it was well known that renal denervation treats hypertension by altering sodium excretion and water retention and reducing stimulation of the renal nerves.[331]

With regard to the recitation in the preamble that the treatment is performed on a human patient, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation a skilled

[329] *Id.* at 144.

[330] *Id.* at 152.

[331] *Kompanowska*, 533 (citing generally to *DiBona 1997* (App. M), 155-156).

artisan would have appreciated that Kompanowska's study was performed in rats as a proxy for humans.[332]

> *delivering a device to a vicinity of a neural fiber associated with renal function; and*
> *thermally inhibiting neural communication along the neural fiber with the device.*

In the Kompanowska method, the denervation was accomplished by using an electrocautery loop to server the nerve fibers entering the renal hilus, including the renal nerves.[333]

Electrocautery was by definition a form of thermal ablation as of the priority date. The Miller-Keane Encyclopedia and Dictionary of Medicine (2003) defines ablation as "removal, especially by cutting with a laser or electrocautery."[334] Accordingly, Kompanowska's teaching of renal denervation by electrocautery would have been understood by those skilled in the art to be a form of thermal ablation. [335]

Accordingly, the subject matter of claim 1 is rendered obvious by Kompanowska taken in combination with DiBona 1997.

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

See discussion above in connection with claim 1. The Kompanowska electrocautery loop cuts the renal nerve fibers entering the renal hilus through the application of heat.[336]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

A 5 MHz signal was applied to the electrocautery loop:

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[332] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[333] *Kompanowska*, 528.

[334] *Papademetriou Dec.*, ¶ 69.

[335] *Id.*

[336] *Kompanowska*, 528.

> was injected through the tubing, twice at 20 s intervals. This was done in order to minimize the potential trauma due to subsequent cutting of the nerves. The trauma could include a momentary efferent and afferent renal nerve stimulation leading to disturbances of intrarenal or systemic haemodynamics. The tissue within the loop, including renal nerve fibres, was electro-coagulated: a 5 MHz current generated by a neurosurgical cautery device (Famed, Warsaw, Poland) was applied for 5–10 s until the tissue was cut completely and the loop could be removed. [337]

5 MHz is within the radiofrequency range.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

As explained above, the state of the art as of the filing date included a general understanding, evidenced by the DiBona 1997 article among others, that renal denervation had renal and cardiovascular implications including as a treatment for hypertension and congestive heart failure.[338]

For the foregoing reasons claims 1, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Kompanowska taken in combination with the DiBona 1997 reference cited therein.

[337] *Id.*

[338] *DiBona 1997*, 142-155.

2-B Claims 1, 7, 12, 20 and 21 are Rendered Obvious by Kompanowska Taken in Combination with Weinstock

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

Kompanowska (App. B) discloses an electrocautery technique for renal denervation and explains that renal denervation can be used to decrease secretion of renin (the hormone responsible for increases in hypertension) and effect renal natriuresis (sodium excretion through the kidneys) and blood flow.[339]

The articles cited in the Kompanowska reference demonstrate that it was well known that renal denervation affected hypertension and congestive heart failure by impacting natriuresis, i.e., sodium excretion, which caused a reduction in water retention that in turn reduced blood pressure.[340]

The Weinstock reference (App. E) is discussed above in connection with Group 1 of the proposed rejections, which discussion is incorporated herein by reference. Weinstock teaches that renal denervation was expected to treat hypertension by lowering blood pressure in humans.[341]

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

In the Kompanowska method, the denervation was accomplished by using an electrocautery loop to server the nerve fibers entering the renal hilus.[342]

Electrocautery was by definition a form of thermal ablation as of the priority date. The Miller-Keane Encyclopedia and Dictionary of Medicine (2003) defines ablation as "removal, especially by cutting with a laser or electrocautery."[343] Accordingly, Kompanowska's teaching of renal denervation by electrocautery would have been understood by those skilled in the art to be a form of thermal ablation.[344]

Accordingly, the subject matter of claim 1 is rendered obvious by Kompanowska taken in combination with Weinstock.

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[339] *Kompanowska*, 527.

[340] *Id.* at 533 (citing generally to *DiBona 1997* (App. M), 155-156).

[341] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[342] *Kompanowska*, 528.

[343] *Papademetriou Dec.*, ¶ 69.

[344] *Id.*

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

See discussion above in connection with claim 1. The Kompanowska electrocautery loop cuts the separated nerve fibers entering the renal hilus through the application of heat.[345]

11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

A 5 MHz signal was applied to the electrocautery loop:

> was injected through the tubing, twice at 20 s intervals. This was done in order to minimize the potential trauma due to subsequent cutting of the nerves. The trauma could include a momentary efferent and afferent renal nerve stimulation leading to disturbances of intrarenal or systemic haemodynamics. The tissue within the loop, including renal nerve fibres, was electro-coagulated: a 5 MHz current generated by a neurosurgical cautery device (Famed, Warsaw, Poland) was applied for 5–10 s until the tissue was cut completely and the loop could be removed. [346]

This is within the radiofrequency range.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

[345] *Kompanowska*, 528.

[346] *Id.*

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

Weinstock concludes that "the current study showed that renal denervation prevents the development of Na + retention and hypertension in salt-sensitive rabbits given a moderately high salt diet. . . . The rabbits react in a similar manner to human salt-sensitive subjects to a moderate increase in salt intake."[347] As noted in the Technical Background section, above, sodium (Na+) retention causes an increase in blood volume and thus an increase in blood pressure.[348]

For the foregoing reasons, claims 1, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Kompanowska taken in combination with Weinstock.

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[347] *Weinstock*, 292.

[348] *Haemmerich Dec.*, ¶ 37.

2-C Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Swartz

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Swartz reference (App. O) is discussed in Proposed Rejection 1-A, which discussion is incorporated herein by reference. The Swartz catheter is introduced to the ablation site intravascularly.[349]

In the combined method of Kompanowska (App. B) and Swartz, the catheter is likewise introduced to the renal artery intravascularly.[350]

The skilled artisan would have understood that using the Swartz catheter to execute renal denervation would have provided substantially the same benefits that were observed in the transition from open heart to intravascular procedures.[351] Most significantly, the intravascular techniques are minimally invasive, which reduces recovery time and the risk of complications.[352] Moreover, RF ablative catheters had proven both highly reliable and clinically effective.[353]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[354] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[355] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[356]

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[349] *Swartz*, 488.

[350] *Papademetriou Dec.*, ¶¶ 77-78, 98, 111; *Webster Dec.*, ¶¶ 64-67; *Haemmerich Dec.*, ¶¶ 81-83.

[351] *Papademetriou Dec.*, ¶ 112; *Webster Dec.*, ¶¶ 67, 75; *Haemmerich Dec.*, ¶¶ 39, 91.

[352] *Id.*

[353] *Id.*

[354] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[355] *Id.*

[356] *Id.*

Claim 5 is thus rendered obvious by Kompanowska taken in combination with Weinstock and Swartz.

2-D Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Webster '695

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Webster '695 reference (App. J) is discussed in Proposed Rejection 1-B, which discussion is incorporated herein by reference.

The Webster '695 catheter is introduced to the ablation site intravascularly.[357] In the combined method of Kompanowska (App. B) and Webster '695, the catheter is likewise introduced to the renal artery intravascularly.[358]

The skilled artisan would have seen various apparent and compelling motivations to use the Webster '695 catheter for the renal denervation procedure described by Weinstock.[359] First, as discussed in the Technical Background section, by the year 2000 it was well known that in the related field of cardiovascular sympathectomies (denervations) surgical techniques had evolved into intravascular procedures in which an electrode-tipped catheter was used to ablate electrically conductive tissue transvascularly, or through the wall of the vessel.[360] Second, the Webster '695 device is specifically described as being useful for sympathectomies.[361] Third, as Webster '695 explains, "the expandable or basket catheter of the invention allows . . . stable placement of the electrode for accurate, repeatable stimulation at the desired location."[362] Fourth, the RF pulse technique taught in Webster '695 is described as reducing the risk of undesired stimulation of surrounding tissues.[363] Fifth, Webster '695's intravascular technique is minimally invasive, which reduces recovery time, risk of complications and associated health care costs.[364]

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[357] *Webster '695*, Abstract.

[358] *Papademetriou Dec.*, ¶¶ 80, 82, 117; *Webster Dec.*, ¶¶ 64, 65, 67; *Haemmerich Dec.*, ¶¶ 81, 83.

[359] *Papademetriou Dec.*, ¶¶ 77-81; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[360] *Papademetriou Dec.*, ¶ 86.

[361] *Webster '695*, 4:20-27; *Papademetriou Dec.*, ¶ 86.

[362] *Id.* at 4:33-37; *Id.*

[363] *Id.* at 4:37-38; *Id.*

[364] *Papademetriou Dec.*, ¶ 86.

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[365] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[366] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[367]

Claim 5 is accordingly rendered obvious by Kompanowska taken in combination with Weinstock and Webster '695.

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[365] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[366] *Id.*

[367] *Id.*

2-E Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Schauerte

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Schauerte reference (App. K) is discussed in Proposed Rejection 1-C, which discussion is incorporated herein by reference.

The Schauerte catheter is introduced to the ablation site intravascularly.[368] In the combined method of Kompanowska (App. B) and Schauerte, the catheter is likewise introduced to the renal artery intravascularly.[369]

As supported by the declarations of Professors Papademetriou, Webster and Haemmerich, a skilled artisan would understand the Schauerte ablative catheter, which is identified as having a 7 French shaft, would be suitable for use in renal applications without modification. Although the '948 patent does not discuss the sizes of the catheters or electrodes depicted therein, renal catheters generally range in size from about 6 to 9 French (or about 2-3 mm).[370] The Schauerte catheter was delivered in the right pulmonary artery, which requires substantially more maneuverability than delivering the same catheter to the renal artery.[371]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[372] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[373] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[374]

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[368] *Schauerte*, 2775 (Figure 1).

[369] *Papademetriou Dec.*, ¶ 117; *Webster Dec.*, ¶¶ 64-66; *Haemmerich Dec.*, ¶ 82-84.

[370] *Papademetriou Dec.*, ¶ 96.

[371] *Id.* at ¶¶ 99-103.

[372] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[373] *Id.*

[374] *Id.*

Thus claim 5 is rendered obvious by Kompanowska taken in combination with Weinstock and Schauerte.

2-F Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Webster '885

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Webster '885 reference (App. R) is discussed in Proposed Rejection 1-D, which discussion is incorporated herein by reference.

The Webster '885 catheter is introduced to the ablation site intravascularly.[375] In the combined method of Kompanowska (App. B) and Webster '885, the catheter is likewise introduced to the renal artery intravascularly.[376]

One skilled in the art would have readily concluded that steerable intravascular catheters, like Webster '885, were available to accomplish thermal ablation by using radiofrequency electric power to heat the tissue and therefore could perform the renal denervation procedures described by Weinstock and Kompanowska.[377]

Moreover, it was generally known in the early 2000s that as an alternative to contacting the tissue and transmitting a stimulating energy into the tissue itself, one could equally apply an ablative stimulus across a vessel wall from inside the renal artery, for example, rather than from the outside of the artery.[378] Accordingly, one skilled in the art would know that using this approach would have been desirable for ablating the renal nerves located on the outside wall of the renal arteries because less invasive surgery is required when the ablation is conducted from inside the artery.[379]

It also was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[380] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of

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[375] *Webster '885*, 8:7-17.

[376] *Papademetriou Dec.*, ¶ 117; *Webster Dec.*, ¶¶ 64-66; *Haemmerich Dec.*, ¶¶ 81, 84.

[377] *Haemmerich Dec.*, ¶ 93.

[378] *Papademetriou Dec.*, ¶ 107; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[379] *Id.*

[380] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[381] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[382]

Claim 5 is thus rendered obvious by Kompanowska taken in combination with Weinstock and Webster '885.

[381] *Id.*

[382] *Id.*

2-G Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Edwards

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Edwards reference (App. P) is discussed in Proposed Rejection 1-E, which discussion is incorporated herein by reference.

The Edwards catheter is introduced to the ablation site intravascularly.[383] In the combined method of Kompanowska (App. B) and Edwards, the catheter is likewise introduced to the renal artery intravascularly.[384]

One skilled in the art would have readily concluded that steerable intravascular catheters, like Edwards, were available to accomplish thermal ablation by using radiofrequency electric power to heat the tissue and therefore could perform the renal denervation procedure described by Weinstock and others.[385] Moreover, it was generally known in the early 2000s that as an alternative to contacting the tissue and transmitting a stimulating energy into the tissue itself, one could equally apply an ablative stimulus across a vessel wall from inside the renal artery, for example, rather than from the outside of the artery.[386] Accordingly, one skilled in the art would know that using this approach would have been desirable for ablating the renal nerves located on the outside wall of the renal arteries because less invasive surgery is required when the ablation is conducted from inside the artery.[387]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[388] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in

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[383] *Edwards '266*, 2:53-60.

[384] *Papademetriou Dec.*, ¶ 77-78; *Webster Dec.*, ¶¶ 64-66; *Haemmerich Dec.*, ¶ 81.

[385] *Id.* at ¶¶ 105, 110; *Id.* at ¶¶ 72-76; *Id.* at ¶¶ 89-92.

[386] *Id.* at ¶ 107; *Id.* at ¶¶ 72-76; *Id.* at ¶¶ 89-92.

[387] *Id.*

[388] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

neurosurgery, urology, dermatology, oncology, and cardiology.[389] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[390]

Additionally, to the extent that a given catheter such as that taught by Edwards was judged too stiff or insufficiently steerable for a given vessel, one of ordinary skill in the art would understand that making it more maneuverable would have been considered routine engineering around the year 2000.[391] As of the year 2000, making the catheters more highly steerable was primarily a cost consideration.[392] The basic design principles would not change, although it would have been generally more expensive to fabricate smaller parts because they would be fashioned from higher strength and "toughness" materials.[393]

Thus claim 5 is rendered obvious by Kompanowska taken in combination with Weinstock and Edwards.

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[389] *Id.*

[390] *Id.*

[391] *Papademetriou Dec.*, ¶ 102; *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[392] *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[393] *Webster Dec.*, ¶ 70.

2-H Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Uchida

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Weinstock (App. E) and Uchida (App. S) references are discussed in Proposed Rejection 1-F, which discussion is incorporated herein by reference.

The Uchida catheter is introduced to the ablation site intravascularly (for example, through a cardiac vein).[394] In the combined method of Kompanowska and Uchida, the catheter is likewise introduced to the renal artery intravascularly.[395]

A skilled artisan would be motivated to use the Uchida catheter to perform the renal denervation taught by Weinstock and Kompanowska.[396] The Uchida device would have been understood to be substantially less invasive than the surgical nerve resection described in Kompanowska and Weinstock.[397] Use of the Uchida ablative catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[398]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[399] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[400] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[401]

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394 *Uchida*, 2518.

395 *Papademetriou Dec.*, ¶¶ 82-83; *Webster Dec.*, ¶¶ 64-67; *Haemmerich Dec.*, ¶ 83.

396 *Id.* at ¶¶ 82-83; *Id.* at ¶ 64-66; *Id.* at ¶¶ 81-83.

397 *Id.* at ¶¶ 89-90; *Id.* at ¶¶ 75-76; *Id.* at ¶¶ 91-92.

398 *Id.*

399 *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

400 *Id.*

401 *Id.*

Accordingly, claim 5 is rendered obvious by Kompanowska taken in combination with Weinstock and Uchida.

2-I Claim 5 is Rendered Obvious by Kompanowska Taken in Combination with Weinstock and Benito

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Weinstock (App. E) and Benito (App. T) references are discussed in Proposed Rejection 1-G, which discussion is incorporated herein by reference.

The Benito catheter is introduced to the ablation site intravascularly.[402] In the combined method of Kompanowska and Benito, the catheter is likewise introduced to the renal artery intravascularly.[403]

A skilled artisan would be motivated to use the Benito catheter to perform the renal denervation taught by Weinstock and Kompanowska.[404] The Benito device would have been understood to be substantially less invasive than the surgical nerve resection described in Kompanowska and Weinstock.[405] Use of the Benito ablative catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[406]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[407] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[408] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[409]

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[402] *Benito*, Abstract, 160.

[403] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80, 81, 83, 84.

[404] *Id.*

[405] *Id.*

[406] *Id.*

[407] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[408] *Id.*

[409] *Id.*

Claim 5 is thus rendered obvious by Kompanowska taken in combination with Weinstock and Benito.

Group 3: Proposed Rejections based on the Stella Reference

Stella (App. C) was not before the Examiner. Stella qualifies as prior art at least under 35 U.S.C. § 102(b) because it was published more than a year prior to the earliest claimed priority date.

Stella teaches that cooling of the renal nerves provides a form a reversible denervation that has substantially the same effect on natriuresis and renin release as surgical denervation.[410] That, in turn, was well understood to reduce blood pressure in hypertensive patients.[411]

Stella's operative technique, illustrated in Fig. 1 below, involves placing cooled brass elements into contact with the renal nerves.[412]

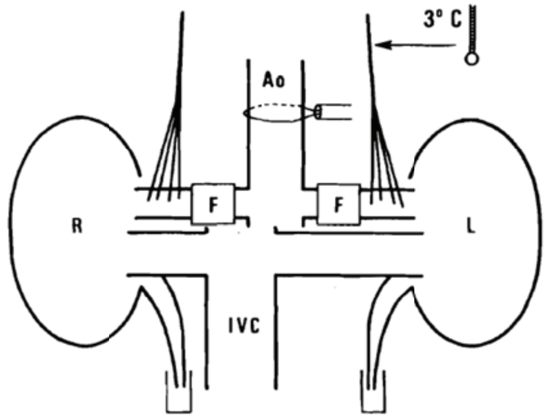

Fig. 1. Diagram of experimental procedures. The transient block of renal nerve conduction of the left kidney (L) is obtained by cooling (3°C). The right kidney (R) is innervated. Electromagnetic flow probes (F) are placed on both renal arteries. Snare around the aorta (Ao) and urine collection from both ureters are indicated. IVC, inferior vena cava.

Stella described the surgical technique as follows:

> Renal nerves on both sides were identified and carefully isolated from surrounding tissues using a dissecting microscope (Zeiss, Stereo Microscope). The left renal nerves were placed on a small thermode, consisting of a hooked brass (outside diameter 2.4 mm, inner diameter 1.4 mm), which could be suitably cooled by connecting its two extremities to a refrigerating circuit. This circuit consisted of a reservoir and a copper coil through which absolute alcohol was made to flow by the motion of a peristaltic pump (Holter RE 161). Reservoir and coil were enclosed in a

[410] *Stella*, 182.

[411] *Papademetriou Dec.*, ¶ 121; *Haemmerich Dec.*, ¶¶ 29, 35.

[412] *Stella*, 182.

> metal cylinder into which controlled expansion of Freon 22 refrigerated the alcohol to a pre-determined temperature. The magnitude of nerve refrigeration was controlled by measuring the temperature of the alcohol up- and downstream from the thermode. The transient block of renal nerve activity was obtained in a few seconds by lowering the temperature to 3 °C for 16 min, and then the denervation was reversed by stopping the pump and rewarming the renal nerves by washing with warm saline (40°C). In the same animal, the cold block of left renal nerves was repeated after surgically cutting the right renal nerves (contra-lateral kidney).[413]

Stella studied the effect of renal denervation (by cooling or surgical resection) on renal hemodynamics and renal excretory functions:

> In anaesthetized cats reversible denervation of one kidney was performed by cooling of the left renal nerves to 3°C for 16 min. The response of the left (ipsilateral) kidney was compared with the response of the right (contralateral) kidney twice in the same animal: (1) when the right kidney was still innervated, and (2) after it had been surgically denervated. Left renal nerve cooling did not cause any changes in arterial pressure. In the left kidney, blood flow, vascular conductance, sodium and water excretions increased, and renin release decreased. Simultaneously in the contralateral kidney, no haemodynamic changes were observed, glomerular filtration was only transiently decreased, whereas sodium and water excretion significantly decreased and renin release increased. When left renal nerve cooling was repeated after surgical denervation of the right kidney, similar changes were observed in the left (ipsilateral) kidney, whereas all contralateral effects were abolished. These experiments suggest that tonically active afferent fibres from one kidney exert a reflex inhibitory action on sympathetic activity directed to the contralateral kidney controlling tubular sodium reabsorption and renin release.

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Table 2 shows the effects of the left renal nerve cooling on hemodynamics of both kidneys after contralateral denervation (i.e., denervation of the kidney on the opposite side of the body).

Table 2. Effects of left renal nerve cooling on haemodynamics of both kidneys after contralateral denervation.

		Control	Cooling		Recovery
			1-8 min	9-16 min	
Mean arterial pressure (mmHg)		130.6 ± 3.4	127.9 ± 2.8	123.7 ± 3.2	124.6 ± 3.5
Renal blood flow (ml/min)	L.K.	26.2 ± 2.5	31.7 ± 2.9†	32.7 ± 3.0†	28.5 ± 2.6
	R.K.	29.6 ± 3.0	30.0 ± 3.1	30.5 ± 3.2	30.3 ± 3.3
	P	<0.01	NS	NS	NS
Renal vascular conductance (ml/mn per mmHg)	L.K.	0.20 ± 0.02	0.25 ± 0.02†	0.26 ± 0.02†	0.23 ± 0.02
	R.K.	0.23 ± 0.03	0.23 ± 0.02	0.25 ± 0.02	0.24 ± 0.03
	P	<0.05	NS	NS	NS
Glomerular filtration rate (ml/min)	L.K.	6.6 ± 0.7	7.7 ± 0.5	7.1 ± 0.7	6.0 ± 0.8
	R.K.	7.4 ± 0.5	7.2 ± 0.4	8.0 ± 0.4	6.8 ± 0.9
	P	<0.05	<0.05	NS	NS

Values are means ± s.e.m of seven trials in seven cats. *P*-values refer to significance of differences between the ipsilateral (left) kidney (L.K.) and the contralateral denervated (right) kidney (R.K.). Significance of differences between measurements made during cooling or recovery and control measurements: †$P < 0.01$. NS, not significant.

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413 *Id.*

414 *Id.* at Abstract.

415 *Id.* at 184.

The table shows that blood pressure immediately drops from 130.6 mmHg to 124.6 mmHg, which is accompanied by an increase in renal blood flow of the ipsilateral kidney. Thus, this data suggests that cooling and surgical resection may have similar effects on renal hemodynamics including renal blood flow as a function of blood pressure.[416]

Table 3 shows that sodium excretion (natriuresis) increases after surgical denervation or cooling of the renal nerves.

Table 3. Effects of left renal nerve cooling on excretory functions of both kidneys before contralateral denervation.

		Control	Cooling		Recovery
			1-8 min	9-16 min	
Water excretion	L.K.	135.3 ± 23.8	200.6 ± 16.9*	222.1 ± 18.0*	109.1 ± 16.8
(μl/min)	R.K.	122.1 ± 21.6	90.7 ± 17.5*	89.7 ± 16.3*	103.7 ± 18.0
	P	NS	<0.001	<0.001	NS
Sodium excretion	L.K.	33.8 ± 6.6	46.3 ± 5.5*	52.6 ± 5.9†	27.8 ± 4.6
(μmol/min)	R.K.	30.4 ± 5.9	22.3 ± 4.7*	23.2 ± 4.7*	27.1 ± 4.9
	P	NS	<0.001	<0.01	NS
Fractional free water tubular reabsorption	L.K.	2.41 ± 0.28	3.21 ± 0.12*	3.34 ± 0.46*	2.41 ± 0.30
	R.K.	2.41 ± 0.33	2.38 ± 0.26	2.38 ± 0.27	2.45 ± 0.26
(×100)	P	NS	<0.05	<0.05	NS
Fractional sodium	L.K.	3.1 ± 0.6	4.4 ± 0.6*	5.4 ± 1.1	2.9 ± 0.5
excretion (×100)	R.K.	3.1 ± 0.7	2.5 ± 0.6	2.4 ± 0.5*	2.7 ± 0.5
	P	NS	<0.01	<0.05	NS

Values are means ± s.e.m. of seven studies in seven cats. *P*-values refer to significance of differences between the ipsilateral (left) kidney (L.K.) and the contralateral innervated (right) kidney (R.K.). Significance of differences between measurements made during cooling or recovery and control measurements: **P* < 0.05; †*P* < 0.01; ‡*P* < 0.001., NS, not significant.

[417]

Stella found that both reversible denervation by cooling and surgical denervation inhibited renal release of renin, the hormone produced by the kidney responsible for increase in renal blood flow.[418] Stella <u>thus teaches that cooling of the renal nerves provides a form a reversible denervation that has substantially the same effect on natriuresis, renin release and renal blood flow as surgical denervation</u>.[419]

At the time of the earliest claimed priority date it was well known that natriuresis (sodium excretion) and inhibition of renin release triggered by renal denervation caused a reduction in water retention that in turn reduced blood pressure.[420]

As supported by the declaration of Dr. Papademetriou, although more invasive than other intravascular approaches, the Stella procedure is suitable for use in humans in appropriate circumstances.[421] The anatomy of cats and humans is similar, which is the precise reason why researchers like Stella conducted their experiments on cats.[422]

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[416] *Id.*

[417] *Id.* at 185.

[418] *Id.* at 187.

[419] *Id.* at 185.

[420] *Papademetriou Dec.*, ¶¶ 121-122.

[421] *Papademetriou Dec.*, ¶ 123.

[422] *Id.*

3-A Claims 1, 20 and 21 are Rendered Obvious by Stella Taken Alone

Stella (App. C) expressly teaches all recitations of claims 1, 20 and 21 except the recitation in the preamble that the method is used to treat a human patient.

> *Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising*

Stella teaches that cooling of the renal nerves provides a form a reversible denervation that has substantially the same effect on natriuresis and renin release as surgical denervation.[423] That, in turn, was well understood to reduce blood pressure in hypertensive patients.[424]

Even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that Stella's study was performed on cats as a proxy for humans.[425]

> *delivering a device to a vicinity of a neural fiber associated with renal function; and*

Stella's operative technique, illustrated in Fig. 1, above, involves placing cooled brass elements into contact with the renal nerves.[426]

> *thermally inhibiting neural communication along the neural fiber with the device.*

Stella teaches that cooling of the renal nerves provides a form a reversible denervation that has substantially the same effect on natriuresis and renin release as surgical denervation.[427] Cooling the renal nerves inhibited neural communication along the fibers.[428]

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[423] *Stella*, 182.

[424] *Papademetriou Dec.*, ¶ 121; *Haemmerich Dec.*, ¶¶ 29, 35.

[425] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[426] *Stella*, 182.

[427] *Id.*

[428] *Id.*

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

Stella teaches that cooling of the renal nerves provides a form a reversible denervation that has substantially the same effect on natriuresis and renin release as surgical denervation.[429] That, in turn, was well understood to reduce blood pressure in hypertensive patients.[430]

For the reasons set forth above, claims 1, 20 and 21 are rendered obvious under 35 U.S.C. §103 by Stella.

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[429] *Id.*

[430] *Papademetriou Dec.*, ¶ 121; *Haemmerich Dec.*, ¶¶ 29, 35.

3-B Claims 5 and 7 are Rendered Obvious by Lustgarten Taken in Combination with Stella

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

An additional article which was not before the Examiner, Lustgarten, D. L., et al. "Cryothermal ablation: Mechanism of tissue injury and current experience in the treatment of tachyarrhythmias." *Progr Cardiovasc Dis*, 41, 6:481-498 (1999) (App. U), shows that it was likewise well known that intravenous cryothermal catheters were well suited for treatment of neural tissue.[431]

The Lustgarten catheter is designed for intravascular use.[432] Lustgarten teaches that:

> [t]he technology has been applied to numerous clinical conditions, initially in open surgical procedures and, subsequently, in percutaneous approaches using intravascular cryocatheters. The results of these studies and the technologies as they have evolved are the subject of the remainder of this review.[433]

In the combined method of Lustgarten and Stella, the cryocatheter is introduced into the renal artery and advanced to the treatment site.[434]

The rational explained above with respect to the use of intravascular electrophysiology catheters to execute denervations applies with equal force to the use of cryothermal catheters to perform Stella's neural cooling procedure.[435] The Lustgarten device would have been understood to be substantially less invasive than the surgical nerve resection described in Stella.[436] Use of the Stella cryothermal catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[437]

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[431] *Lustgarten*, 485.

[432] *Id.*

[433] *Id.*

[434] *Papademetriou Dec.*, ¶¶ 127, 129; *Webster Dec.*, ¶¶ 90-91; *Haemmerich Dec.*, ¶¶ 97-99.

[435] *Id.* at ¶¶ 127, 129, 130; *Id.* at ¶¶ 92, 94, 95; *Id.* at ¶¶ 97-99.

[436] *Id.* at ¶ 127; *Id.* at ¶ 90; *Id.* at ¶ 99.

[437] *Id.*

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

As noted above, Stella teaches that cooling and denervation achieve similar results in terms of blood pressure control.[438] Lustgarten teaches intravascular cryoablation of tissue.[439]

Accordingly, skilled artisans would have understood that, in the combined method of Stella and Lustgarten the cryothermal catheter could optionally be used to cool or ablate the renal nerve tissue.[440]

Claims 5 and 7 are thus rendered obvious by Lustgarten taken in combination with Stella.

[438] *Stella*, 185.

[439] *Lustgarten*, 485.

[440] *Papademetriou Dec.*, ¶ 130; *Webster Dec.*, ¶ 93; *Haemmerich Dec.*, ¶ 98.

3-C Claims 5 and 7 Are Rendered Obvious by Dubuc Taken in Combination with Stella

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

Dubuc, M., et al. “Feasibility of cardiac cryoablation using a transvenous steerable electrode catheter.” *J Interv Cardiac Electrophysiol*, 2:285–292 (1998) (App. V) teaches that it was likewise well known that intravenous cryoablation catheters were well suited to treatment of neural tissue.[441]

Dubuc’s abstract explains that cyroablative catheters were successfully used to map and ablate neural tissue:

> ***Abstract.*** **We investigated the feasibility of using cryogenic technology in an electrode catheter for percutaneous ablation of cardiac tissue. Despite its high success rate, radiofrequency catheter ablation has important limitations especially with regards to the treatment of ventricular arrhythmias associated with a chronic scar. Arrhythmia surgery experience has shown that freezing with a hand held probe can permanently ablate the arrhythmogenic substrate of ventricular tachycardia associated with an old scar. Moreover, cryosurgery also allows for reversible “ice mapping,” in which the area likely responsible for the arrhythmia can be evaluated by suppressing its electrophysiologic properties prior to the creation of an irreversible state. A new steerable cryoablation catheter using Halocarbon 502 as a refrigerant was utilized in six dogs. Serial cryoapplications were performed in the right and left ventricles. In two dogs, we attempted reversible ice mapping of the AV node. Pathological evaluation of the lesions was done acutely in all the animals. Forty-two cryoapplications were delivered at a mean temperature of −45 ± 9.8°C. No lesion was found at pathological evaluation for 16 cryoapplications which did not achieve a temperature of less (colder) than −30°C. The remaining applications resulted in 26 lesions which were hemorrhagic and sharply demarcated from normal myocardium. Histological evaluation revealed contraction band necrosis. Reversible ice mapping of the AV node was successfully achieved in two animals. Cryoablation is feasible using an electrode catheter with multiple electrodes. This technology has the potential to allow for reversible ice mapping to confirm a successful ablation target before definitive ablation.** [442]

[441] *Dubuc*, Abstract.

Dubuc's procedure involved introducing the catheter through the femoral artery, advancing the electrode tip proximate the cardiovascular neural tissue to be ablated, and cooling the tissue for a maximum of 4 minutes.[443] Dubuc, like other references presented herein, provides a tabulation showing the interrelationship between procedure parameters and lesion size:

Table 1. *Cryoablation in the ventricles.*

		Temperature attained Number of applications				Average dimensions of lesions			
Animal	Total number of applications	>−30°C	−30 to −50°C	< −50°C		Length (mm^3 ± SD)	Width (mm^3 ± SD)	Depth (mm^3 ± SD)	Volume of lesions* average (mm^3 ± S D)
1	5	4	1	0		4	3	3	18.85
2	6	3	3	0		5.5 ± 2.7	2.9 ± 2.3	2.4 ± 1.1	23.5 ± 29.1
3	10	3	4	3		4.9 ± 2.6	4.3 ± 1.8	3.7 ± 2.9	75.6 ± 115.9
4	8	2	6	0		4.7 ± 2	2.8 ± 0.8	3.1 ± 1.9	26.5 ± 20.3
5	6	1	2	3		4.8 ± 1.1	3.2 ± 0.8	4.2 ± 1.5	37.2 ± 18.6
6	7	3	2	2		5.5 ± 0.6	4.8 ± 0.5	4.0 ± 0	55.0 ± 10.0
Total	42	16	18	8		5 ± 1.9	3.6 ± 1.5	3.5 ± 1.9	45.4 ± 62.6
					Range:	(2–10)	(0.6–7)	(1–9)	(1.57–329.8)

*Volume of lesions was estimated from the formula of 1/2 volume of prolate ellipsoid. Volume = 2π/3(L/2×W/2×D); L = length; W = width; D = depth.

[444]

Dubuc concludes that the cyroablative catheter "technology has the potential to allow for greater catheter stability during energy application, as well as reversible ice mapping to confirm a successful ablation target before definitive ablation."[445]

One skilled in the art having read the Stella reference would have understood from Dubuc that the Stella procedure could be advantageously performed with a cryoablative intravascular catheter, which procedure would be optimal for human patients.[446] Dubuc's steerable catheter had a 9 French (2.7 mm) diameter and a 4mm tip, which is suitable for use in renal arteries.[447]

The rational explained above with respect to the use of intravascular electrophysiology catheters to execute denervations applies with equal force to the use of cryothermal catheters to perform Stella's neural cooling procedure.[448] The Dubuc device would have been understood to be substantially less

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[442] *Id.*

[443] *Id.* at 286.

[444] *Id.* at 287.

[445] *Id.* at 292.

[446] *Papademetriou Dec.*, ¶¶ 127-129; *Webster Dec.* ¶¶ 90-91; *Haemmerich Dec.*, ¶¶ 97, 99.

[447] *Dubuc*, 285; *Papademetriou Dec.*, ¶ 129.

[448] *Papademetriou Dec.*, ¶¶ 128-130; *Haemmerich Dec.*, ¶ 99.

invasive than the surgical nerve resection described in Stella.[449] Use of the Dubuc cryothermal catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[450]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

See discussion above. Dubuc's cyroablative catheters were successfully used to map and ablate neural tissue.[451]

For these reasons, claims 5 and 7 are rendered obvious under 35 U.S.C. §103 by Dubuc taken in combination with Stella.

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[449] *Papademetriou Dec.*, ¶¶ 127-128; *Webster Dec.*, ¶¶ 90, 94; *Haemmerich Dec.*, ¶ 99.

[450] *Id.*

[451] *Dubuc*, Abstract.

Group 4: Proposed Rejections based on Evidence Linking the Renal Denervation Prior Art with Electrophysiology Catheter Prior Art

As discussed above in the Technical Background section, in the 1990s cardiovascular treatments for Wolff-Parkinson-White, AVNRT and atrial fibrillation evolved from open heart surgeries to much less invasive intravascular catheter procedures.[452] The rationale underlying this transition to intravascular ablation applied with equal force to the renal denervation procedure suggested by DiBona 1997 and DiBona 2002. Such intravascular approaches had substantial and well-understood advantages and were, at an absolute minimum, obvious to try.

Skilled artisans such as Professors Webster, Haemmerich and Papademetriou fully expected that intravascular ablative cardiovascular catheters could be used without substantial modification to destroy the nerves that run along the outside of the renal artery.[453] As detailed in the declarations of Professors Webster, Haemmerich and Papademetriou, a wide variety of related cardiovascular and urinary tract procedures had recently evolved from surgical techniques into minimally invasive procedures in which ablative catheters were advanced to the treatment site through a vessel such as the femoral artery or vein.[454] Professors Webster, Haemmerich and Papademetriou explain that there would have been a definite expectation that renal denervation could be accomplished with a similar device and a similar procedure.[455]

The fact that cardiovascular catheters could be used essentially "off the shelf" for renal denervation is highlighted by the '948 patent's failure to provide any specific teaching concerning the physical properties of the catheter itself.[456] The '948 patent says nothing specific about catheter dimensions, steerability requirements, electrical parameters, materials, etc.[457] Rather, the applicants merely stated that previously known cardiovascular ablation catheters were suitable for the described renal denervation technique: "[s]imilar catheter based apparatus can be used to ablate the renal nerve with an intent to treat CRF [chronic renal failure]."[458]

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[452] *Haemmerich Dec.*, ¶¶ 39-52; *Papademetriou Dec.*, ¶¶ 21-51; *Webster Dec.*, ¶¶ 24-41.

[453] *Haemmerich Dec.*, ¶¶ 39-52, 84, 87, 93; *Papademetriou Dec.*, ¶¶ 21-51; *Webster Dec.*, ¶¶ 24-41.

[454] *Id*.

[455] *Id.*

[456] Papademetriou Dec., ¶¶ 82, 96.

[457] *Id.*

[458] *Gelfand*, M., et al. "Treatment of renal failure and hypertension." *U.S. Patent Application No. 60/442,970*, 13:13-14 (App. L).

4-A Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Swartz

DiBona 1997 (App. M) qualifies as prior art under 35 U.S.C. § 102(b). The DiBona 1997 article was disclosed in an information disclosure statement but never discussed by either an examiner or the Patent Owner during prosecution of the application that matured into the '948 patent or any of the priority applications.[459] The DiBona 1997 reference is over 120 pages long and the portions relied upon herein are embedded in the middle of the reference. Accordingly, the record provides no reason to believe any of the *ex parte* examiners considered these portions of the DiBona 1997 reference even standing alone.[460]

> *Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising*

DiBona 1997 is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[461] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[462] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

> *delivering a device to a vicinity of a neural fiber associated with renal function; and*
> *thermally inhibiting neural communication along the neural fiber with the device.*

A skilled artisan having the DiBona 1997 and Weinstock references in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[463] One method that would have immediately commanded itself to the attention of the skilled artisan was the technique used for the ablation of cardiovascular tissue to treat Wolff-Parkinson-White syndrome.[464]

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[459] *U.S. Patent Application No.* 11/840,142 File History, September 1, 2009 IDS (App. Q).

[460] *U.S. Patent Application No.* 11/840,142 File History.

[461] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[462] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

[463] *Papademetriou Dec.* ¶¶ 77-78; *Webster Dec.*, ¶¶ 72-75; *Haemmerich Dec.*, ¶¶ 89-91.

[464] *Id.*

As discussed above, Wolff-Parkinson-White (WPW) syndrome was traditionally treated surgically.[465] By the year 2000, with advances in mechanical catheter technology, surgical techniques to treat WPW had evolved into an intravascular procedure in which an electrode-tipped catheter was used to ablate electrically conductive tissue transvascularly, or through the cardiac wall tissue.[466]

Swartz (App. O), for example, teaches that high rates of success using radiofrequency ablation energy have rapidly transformed catheter ablation from an investigational procedure to the nonpharmacological therapy of choice of symptomatic Wolff-Parkinson-White syndrome.[467] Swartz studied the safety and efficacy of accessory pathway ablation using radiofrequency energy delivered solely to accessory atrioventricular pathway atrial insertion sites. Specifically, Swartz describes the accessory pathway localization and ablation procedures as follows:

> [e]ndocardial mapping was accomplished using a steerable 7F 3-4 mm tip electrode catheter with 2-mm electrode spacing . . . Bipolar . . . and distal electrode unipolar electrograms were continuously recorded from the localization/ablation catheter . . . After atrial insertion localization and characterization, endocardial ablation catheter contact and stability were assessed.
>
> Radiofrequency ablating energy used . . . was unmodulated 500-KHz alternative current derived from a standard electrosurgical unit . . . Ablation catheter position was fluoroscopically monitored throughout each energy application to ensure stable catheter position and appropriate delivery of energy to the targeted tissue. When necessary, repeat mapping and ablation attempts were pursued until accessory pathway block was achieved.
>
> Monopolar delivery of radiofrequency alternative current between the endocardial ablation catheter tip electrode and large surface area skin electrode eliminated accessory pathway conduction in 116 of 122 accessory pathways (95%) . . . As with other measures of ablation procedure efficiency, the number of radiofrequency applications required for successful ablation declined as knowledge and experience accumulated.[468]

The ablative catheter used by Swartz is depicted in Figure 1, reproduced below (see catheter labeled ABL):

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[465] *Id.* at ¶¶ 21, 25; *Id.* at ¶¶ 29-30; *Id.* at ¶¶ 43-45.

[466] *Id.*

[467] *Swartz*, Abstract.

[468] *Id.* at 488, 489, 491-493.

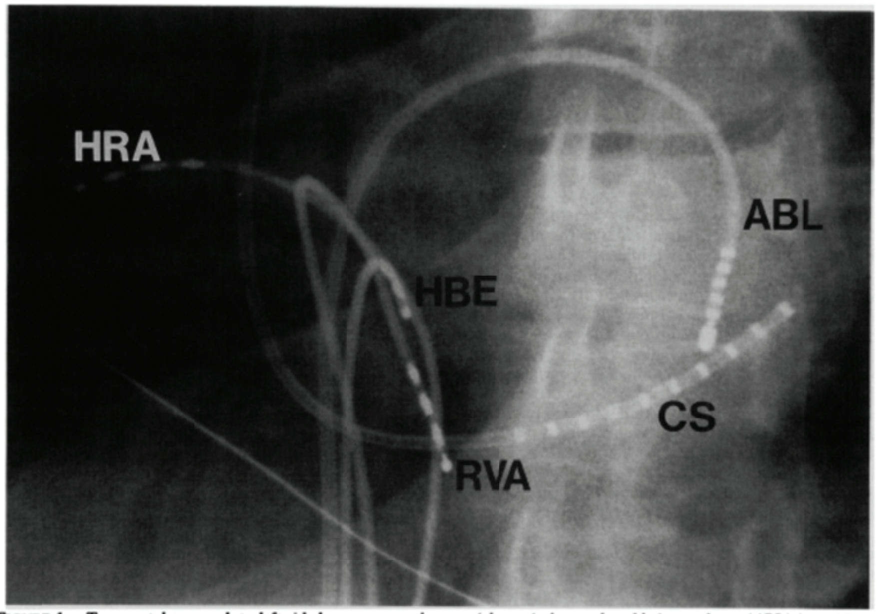

FIGURE 1. *Transseptal approach to left-sided accessory pathways. A large-tip hexapolar ablation catheter (ABL) is positioned on the mitral annulus midway between the third and fourth coronary sinus (CS) catheter electrodes. In this 45° left anterior oblique view, the ablation catheter ascends from the inferior vena cava, crosses the interatrial septum, and curves around the endocardial aspect of the mitral annulus from anterior to posterior. HBE, His bundle; HRA, high right atrium; RVA, right ventricular apex.* [469]

The skilled artisan would have understood that using the Swartz catheter to execute renal denervation would have provided substantially the same benefits that were observed in the transition from open heart to intravascular procedures.[470] Most significantly, the intravascular techniques are minimally invasive, which reduces recovery time and the risk of complications.[471] Moreover, RF ablative catheters had proven both highly reliable and clinically effective.[472]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[473] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[474] The professors conclude that those

[469] *Id.* at 489.

[470] *Papademetriou Dec.* ¶ 112; *Webster Dec.*, ¶¶ 67, 75; *Haemmerich Dec.*, ¶¶ 39, 91.

[471] *Id.*

[472] *Id.*

[473] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[474] *Id.*

skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[475]

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Swartz.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Swartz catheter is introduced to the ablation site intravascularly.[476] In the combined method of DiBona 1997, Weinstock and Swartz, the catheter is likewise introduced to the renal artery intravascularly.[477]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

Swartz describes a tissue ablation procedure. "Monopolar delivery of radiofrequency alternative current between the endocardial ablation catheter tip electrode and large surface area skin electrode eliminated accessory pathway conduction in 116 of 122 accessory pathways (95%) . . . As with other measures of ablation procedure efficiency, the number of radiofrequency applications required for successful ablation declined as knowledge and experience accumulated."[478]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

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[475] *Id.*

[476] *Swartz*, 488.

[477] *Papademetriou Dec.* ¶ 98; *Webster Dec.*, ¶¶ 72-75; *Haemmerich Dec.*, ¶¶ 89-91.

[478] *Swartz*, 491-493.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

DiBona 1997 is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[479] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[480] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Swartz.

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[479] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[480] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-B Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Webster '695

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[481] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[482] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

A skilled artisan having the DiBona 1997 and Weinstock references in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[483] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for transvascular sympathectomies in the cardiovascular context.[484] Representative devices and methods for transvascular sympathectomies are disclosed in Webster '695 (App. J).

The Webster '695 reference teaches an intravascular electrode-tipped catheter that can be used to ablate sympathetic nerve tissue where indications require a sympathectomy.[485] Webster '695 states that:

[481] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[482] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

[483] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

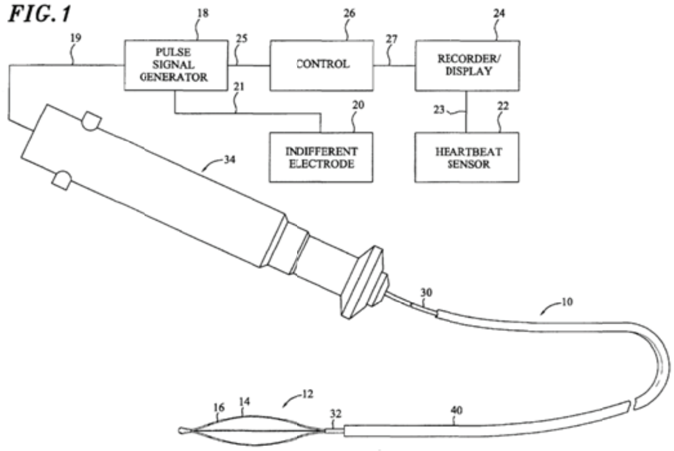
[484] *Id.*

[485] *Webster '695*, Abstract, 12:13-29.

> The system and methods of the invention can be used to ablate sympathetic and parasympathetic nerves if necessary. Sympathectomy is indicated in certain patients, for example those with contraindications to β-blockers. Selective sympathetic denervation, performed by transvascular ablation using the method of the invention, can reduce these patients' risk of sudden death from acute arrhythmias. Selective parasympathetic denervation may be indicated in patients with atrial tachycardia or fibrillation induced or maintained by excessive vagal nerve stimulation. A denaturing or ablating stimulus (e.g., radiofrequency or cryoablation) is applied across the vessel wall to the sympathetic fibers at any desired location. Preferably, sites are selected where a purely or nearly pure sympathetic or parasympathetic branch runs very close to the vessel, and where there are few other nerves or other sensitive tissues. Ablating stimulation is applied until conduction in the fiber is impaired or ceases altogether. [486]

As illustrated in Webster '695's FIG. 1, reproduced below, the device is connected to a signal generator 18 and includes basket electrode 12 at its distal end.[487]

FIG. 1



In use, the "catheter is inserted into a blood vessel and directed to a location wherein the electrode through which a stimulus is delivered is adjacent to one or more predetermined cardiac parasympathetic or sympathetic nerves."[488]

The Webster '695 catheter is well suited to the renal denervation procedure suggested by Kompanowska and others.[489] Significantly, the basket catheter taught by Webster '695 is quite similar to

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[486] *Id.* at 12:13-29.

[487] *Id.* at 16:50-60.

[488] *Id.* at 2:56-60.

the preferred embodiment of the '948 patent (shown below) in which the electrode is positioned within the vessel with a positioning element 304 that can take the form of a "balloon, an expandable wire basket, [or] other mechanical expander[]."[490] Accordingly, it is apparent that Webster '695's basket catheter could be adapted for use within renal vessels.[491]

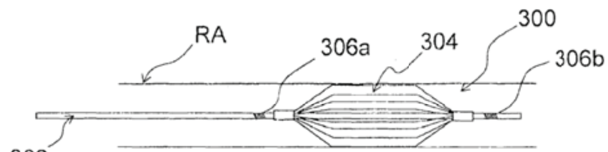

FIGURE 4B

The Webster catheter could be used in a renal artery with little or no modification. Webster '695 discloses that: "[t]he outer diameter of the catheter body 30 is not critical but is preferably no more than about 8 French and more preferably no more than about 7 French."[492] Although the '948 patent does not discuss the sizes of the catheters or electrodes depicted therein, renal catheters generally range in size from about 6 to 9 French (or about 2-3 mm).[493] A skilled artisan might desire to modify the dimensions of the basket electrode or to make the catheter more highly maneuverable. However, such modifications were routine in the industry long before the earliest effective priority date, as demonstrated by the '948 patent's failure to provide any disclosure concerning the engineering aspects of the catheter design.[494] The fact that a skilled artisan would have known how to adapt the Webster '695 catheter to renal applications is further demonstrated by the '948 patent's lack of any teaching or explanation as to the technical specifications for the catheter or how it would be constructed.[495] The '948 patent discloses no specific dimensions, frequencies, power levels, steerability metrics, or component material properties for the catheter.[496]

The skilled artisan would have seen various apparent and compelling motivations to use the Webster '695 catheter for the renal denervation procedure described by DiBona 1997 and Weinstock.[497]

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[489] *Papademetriou Dec.*, ¶¶ 79-81; *Haemmerich Dec.*, ¶¶ 89-92.

[490] *'948 patent*, 7:13-14, Fig. 4B; *Papademetriou Dec.*, ¶ 80.

[491] *Papademetriou Dec.*, ¶ 80.

[492] *Webster '695*, 7:27-29.

[493] *Papademetriou Dec.*, ¶ 82.

[494] *Id.* at ¶¶ 82-83.

[495] *Id.* at ¶ 82.

[496] *Id.*

[497] *Papademetriou Dec.*, ¶¶ 77-81; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

First, as discussed in the Technical Background section, by the year 2000 it was well known that in the related field of cardiovascular sympathectomies (denervations) surgical techniques had evolved into intravascular procedures in which an electrode-tipped catheter was used to ablate electrically conductive tissue transvascularly, or through the wall of the vessel.[498] Second, the Webster '695 device is specifically described as being useful for sympathectomies.[499] Third, as Webster '695 explains, "the expandable or basket catheter of the invention allows . . . stable placement of the electrode for accurate, repeatable stimulation at the desired location."[500] Fourth, the RF pulse technique taught in Webster '695 is described as reducing the risk of undesired stimulation of surrounding tissues.[501] Fifth, Webster '695's intravascular technique is minimally invasive, which reduces recovery time, risk of complications and associated health care costs.[502]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[503] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[504] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[505]

A skilled artisan further would have understood that the stenosis (abnormal narrowing of the vessel) which occurred in some prior cardiovascular ablative procedures (notably certain early intravascular pulmonary vein ablation techniques) was less likely to pose a problem with the renal artery.[506] The renal arterial tissue is significantly stronger than that that of the pulmonary vein.[507] It would have been expected that the renal arterial tissue would be substantially less prone to stenosis.[508] The availability of ablative catheters with cooled catheter tips (which would serve to keep the inside of

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[498] *Papademetriou Dec.*, ¶ 86.

[499] *Webster '695*, 4:20-27; *Papademetriou Dec.*, ¶ 86.

[500] *Id.* at 4:33-37; *Id.*

[501] *Id.* at 4:37-38; *Id.*

[502] *Papademetriou Dec.*, ¶ 86.

[503] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[504] *Id.*

[505] *Id.*

[506] *Papademetriou Dec.*, ¶¶ 37-39, 48-50.

[507] *Id.* at ¶¶ 40, 41.

[508] *Id.* at ¶¶ 48-50.

the renal artery cool) would also have given a skilled artisan a high degree of confidence that any stenosis issue could be surmounted.[509]

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Webster '695.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

Webster '695's Summary section similarly teaches that the catheter is to be used intravascularly: "[t]he method involves the intravascular stimulation and/or ablation of cardiac parasympathetic and sympathetic nerves sufficient to regulate or slow the heart rate or prevent the occurrence of these arrhythmias."[510] In the combined method of DiBona 1997, Weinstock and Webster '695, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[511]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

The Webster '695 catheter is used to ablate sympathetic nerve tissue where indications require a sympathectomy.[512] Webster '695 states that:

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[509] *Papademetriou Dec.*, ¶¶ 48-49; *Haemmerich Dec.*, ¶¶ 69-79.

[510] *Webster '695*, 2:48-52.

[511] *Papademetriou Dec.*, ¶¶ 98, 115; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[512] *Webster '625*, Abstract, 12:13-28.

> The system and methods of the invention can be used to ablate sympathetic and parasympathetic nerves if necessary. Sympathectomy is indicated in certain patients, for example those with contraindications to β-blockers. Selective sympathetic denervation, performed by transvascular ablation using the method of the invention, can reduce these patients' risk of sudden death from acute arrhythmias. Selective parasympathetic denervation may be indicated in patients with atrial tachycardia or fibrillation induced or maintained by excessive vagal nerve stimulation. A denaturing or ablating stimulus (e.g., radiofrequency or cryoablation) is applied across the vessel wall to the sympathetic fibers at any desired location. Preferably, sites are selected where a purely or nearly pure sympathetic or parasympathetic branch runs very close to the vessel, and where there are few other nerves or other sensitive tissues. Ablating stimulation is applied until conduction in the fiber is impaired or ceases altogether. [513]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[514] The teachings of DiBona 1997 are discussed at length in

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[513] *Id.* at 4:20-27.

[514] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[515] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

For the foregoing reasons, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Webster '695.

[515] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-C Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Schauerte

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[516] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[517] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

A skilled artisan having the DiBona 1997 and Weinstock references in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[518] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for transvascular sympathectomies in the cardiovascular context.[519] Representative devices and methods for transvascular sympathectomies are disclosed in Schauerte (App. K).

The Schauerte reference teaches an intravascular catheter and associated procedure for either stimulating or ablating nerves located on the exterior of the vasculature.[520] As shown in Schauerte's Figure 1, reproduced below, a basket catheter is used to ablate vagal nerves associated with cardiac vessels (e.g., the right pulmonary artery).[521]

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[516] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[517] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

[518] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[519] *Id.*

[520] *Schauerte*, Abstract.

[521] *Id.* at 2775.

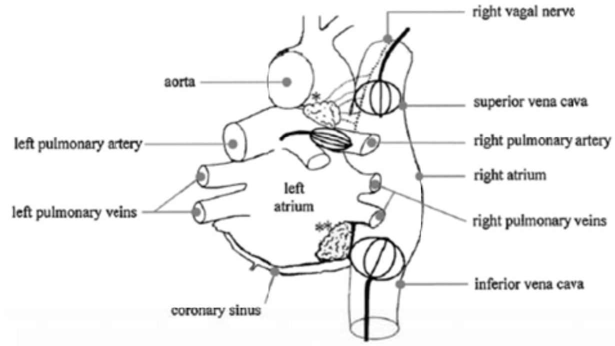

Figure 1. Illustration of parasympathetic innervation of atria. Dorsal view of atria and great vessels is shown. Course of nerves depicted is functional course rather than anatomically correct description of parasympathetic atrial innervation. Most of right and left vagal fibers that innervate atria and sinus or AV node converge to fat pad between RPA, base of aorta, and SVC (RPA fat pad [*]). Some vagal fibers that innervate atria are located in fat pad between IVC, left atrium, and ostium of coronary sinus (**) and along SVC. Stimulation and ablation of parasympathetic nerves was performed with expandable electrode catheter, which was introduced into upper RPA (n=7), SVC (n=1), or IVC (n=2).

Figure 7 of Schauerte further shows that the vagal nerves surround the right pulmonary artery, just as the renal nerves surround the renal artery.[522]

Schauerte concluded that radiofrequency current catheter ablation (RFCA) was a promising technique for transvascular ablation of sympathetic nerves:

> Transvascular atrial parasympathetic nerve system modification by RFCA abolishes vagally mediated AF. This antifibrillatory procedure may provide a foundation for investigating the usefulness of neural ablation in chronic animal models of AF and eventually in patients with AF and high vagal tone.[523]

Schauerte thus teaches that the expandable catheter and techniques disclosed therein would be useful for transvascular sympathectomies.[524] One skilled in the art would have readily concluded that the transvascular ablative catheter of Schauerte was useful for the renal denervations recommended by DiBona 1997 and Weinstock.[525]

The Schauerte catheter is described as being useful for ablation of neural tissue on the exterior of arteries and veins.[526] Schauerte also teaches that the expandable catheter was effective at transvascularly

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[522] *Id.* at 2778.

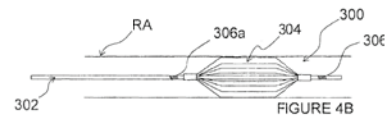
[523] *Id.* at Abstract.

[524] *Papademetriou Dec.*, ¶¶ 92-93.

[525] *Id.* at ¶¶ 91-93.

[526] *Schauerte*, Abstract, 2775 (Figure 1).

ablating the neural tissue and thus a skilled artisan would be motivated to, at the very least, attempt to use a Schauerte-type catheter for the denervation treatment taught by DiBona 1997, Weinstock, DiBona 2002 and others.[527] Further, the fact that the expandable balloon catheter of Schauerte is adapted for renal procedures is evidenced by the similarity between the Schauerte catheter (below left) and the '948 patent's preferred embodiment shown in Figure 4B:[528]



The size of the Schauerte catheter is largely irrelevant, as the claims of the '948 patent are not limited to any particular size of human.[529]

In any event, as supported by the declarations of Professors Papademetriou, Webster and Haemmerich, a skilled artisan would understand the Schauerte ablative catheter, which is identified as having a 7 French shaft, would be suitable for use in renal applications without modification.[530] Although the '948 patent does not discuss the sizes of the catheters or electrodes depicted therein, renal catheters generally range in size from about 6 to 9 French (or about 2-3 mm).[531] The Schauerte catheter was delivered in the right pulmonary artery, which requires substantially more maneuverability than delivering the same catheter to the renal artery.[532]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[533] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[534] The professors conclude that those

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[527] *Id.* at 2777-2778; *Papademetriou Dec.*, ¶ 93.

[528] *Papademetriou Dec.*, ¶ 93.

[529] *Id.* at ¶ 96.

[530] *Schauerte*, 2775; *Papademetriou Dec.*, ¶¶ 96, 103; *Haemmerich Dec.*, ¶¶ 82, 84.

[531] *Papademetriou Dec.*, ¶ 96.

[532] *Papademetriou Dec.*, ¶¶ 99-103.

[533] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[534] *Id.*

skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[535]

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Schauerte.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Schauerte catheter is designed for intravascular use, as shown in Schauerte's Figure 1.[536] In the combined method of DiBona 1997, Weinstock and Schauerte, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[537]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

Further to the discussion above in connection with claim 1, Schauerte teaches a method for radiofrequency current catheter ablation (RFCA) and methods for non-ablative stimulation.[538]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

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[535] *Id.*

[536] *Schauerte*, 2775.

[537] *Papademetriou Dec.*, ¶¶ 98, 115; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[538] *Schauerte*, 2775.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[539] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[540] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Accordingly, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Schauerte.

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[539] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[540] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-D Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Webster '885

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[541] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[542] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

A skilled artisan having the DiBona 1997 and Weinstock reference in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[543] One method that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue ablation in the cardiovascular context.[544] One such method is shown in Webster '885 (App. R).

Webster's '885 patent discloses a multi-electrode RF ablation catheter useful for treating arrhythmias in the heart.[545] Each electrode is electrically connected to a switching unit by leads comprising paired copper and constantan wires.[546] The switching unit enables an operator to switch between a first mode for monitoring ECG and a second mode for delivering RF energy for tissue ablation to a selected electrode and monitoring the temperature of that electrode.[547]

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[541] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[542] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

[543] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[544] *Id.*

[545] *Webster '885*, Abstract, 1:4-5.

[546] *Id.* at Abstract; *Papademetriou Dec.*, ¶ 107.

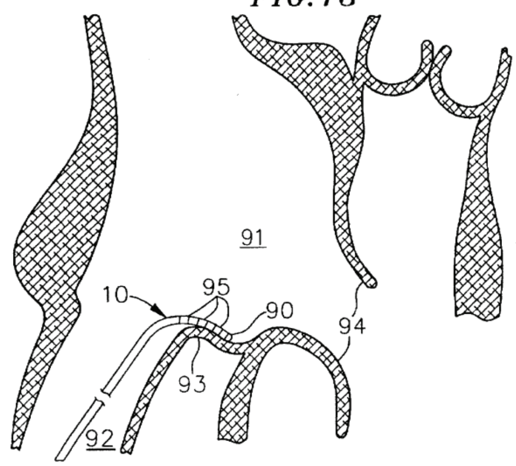
[547] *Webster '885*, Abstract.

The paired copper and constantan lead wires reduce the need for more lead wires and/or larger diameter lead wires.[548] This in turn allows for a smaller diameter catheter than would be otherwise necessary for the number of electrodes carried by the catheter.[549]

The diameter of the catheter tip section 12 is preferably the same as or slightly smaller than the catheter body.[550] In a preferred embodiment the diameter of the catheter body is about 0.08 inches (2.03 mm).[551] The length of the catheter tip section can vary as desired, but is preferably about three inches long.[552]

Figure 13 below shows that the deflectable ablation catheter 10 can deflect from a larger inferior vena cava vessel 92 around the corner to perform ablation at the vessel wall isthmus 93.[553]

FIG. 13



One skilled in the art would have readily concluded that steerable intravascular catheters, like Webster ‘885, were available to accomplish thermal ablation by using radiofrequency electric power to heat the tissue and therefore could perform the renal denervation procedures described by DiBona 1997 and Weinstock.[554]

Moreover, it was generally known in the early 2000s that as an alternative to contacting the tissue and transmitting a stimulating energy into the tissue itself, one could equally apply an ablative stimulus across a vessel wall from inside the renal artery, for example, rather than from the outside of the artery.[555]

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548 *Id.* at 8:10-12.

549 *Id.* at 8:12-14.

550 *Id.* at 3:37-38.

551 *Id.* at 3:38-40.

552 *Id.* at 3:36-42.

553 *Id.* at Fig. 13.

554 *Papademetriou Dec.*, ¶¶ 107, 110; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

555 *Papademetriou Dec.*, ¶ 107; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

Accordingly, one skilled in the art would know that using this approach would have been desirable for ablating the renal nerves located on the outside wall of the renal arteries because less invasive surgery is required when the ablation is conducted from inside the artery.[556]

It also was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[557] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[558] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[559]

Regarding the general maneuverability of steerable catheters within the renal artery, Professors Webster, Haemmerich and Papademetriou explain in their declarations that there is ample room for a 6-7F steerable catheter, for example, to advance up the aorta and turn into the renal artery.[560] The renal artery is about 5 mm in diameter branching from the aorta, which is about 15 mm in diameter.[561] Given the known geometrical dimensions of the catheters and the vessels discussed above, one of ordinary skill in the art would understand that the Webster '885 catheter would be maneuverable through the renal vasculature and is well-suited to the renal denervation procedure suggested by DiBona 1997, as the Webster '885 catheter, which is 0.08 inch (or 2.03 mm or about 6F), can easily pass from the 15 mm diameter aorta into the 5 mm diameter renal artery.[562]

Additionally, to the extent that a given catheter such as that taught by Webster '885 was judged too stiff or insufficiently steerable for a given vessel, one of ordinary skill in the art would understand that miniaturizing it to make it more maneuverable would have been considered routine engineering around the year 2000.[563] As of the year 2000, making the catheters more highly steerable was primarily a cost consideration.[564] The basic design principles would not change, although it would have been generally

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[556] *Id.*

[557] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[558] *Id*.

[559] *Id.*

[560] *Uflacker*, R., "Atlas of vascular anatomy: An angiographic approach." Baltimore: Williams & Wilkins, 424 (1997); *Papademetriou Dec.*, ¶ 100; *Webster Dec.*, ¶ 69; *Haemmerich Dec.*, ¶ 84.

[561] *Id.* at 424; *Id.* at ¶ 99; *Id.* at ¶ 68; *Id.*

[562] *Id.*; *Id.* at ¶ 100; *Id* at ¶ 69; *Id.*

[563] *Papademetriou Dec.*, ¶ 102; *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[564] *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

more expensive to fabricate smaller parts because they would be fashioned from materials with higher strength and toughness.[565]

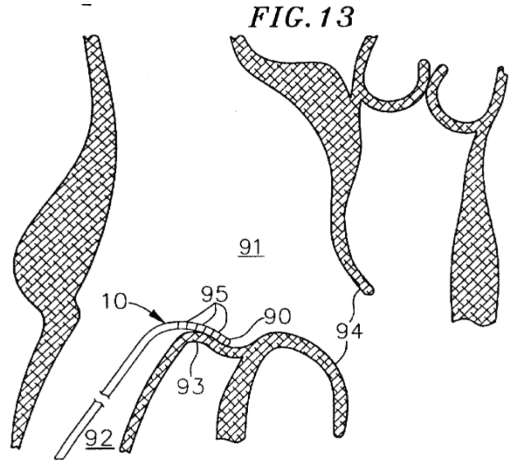
In use, the Webster '885 catheter would, for instance, be introduced through the femoral artery with a guide sheath configured to position the catheter at the ostium, or entrance, to the renal artery. The catheter would then be advanced, with or without the assistance of a guide sheath, to the treatment site in the renal artery.

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Webster '885.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Webster '885 catheter is designed for intravascular use.[566] Figure 13 below shows that the deflectable ablation catheter 10 can deflect from a larger inferior vena cava vessel 92 around the corner to perform ablation at the vessel wall isthmus 93.[567]

FIG. 13



In the combined method of DiBona 1997, Weinstock and Webster '885, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[568]

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[565] *Webster Dec.*, ¶ 70.

[566] *Webster '885*, 8:7-17.

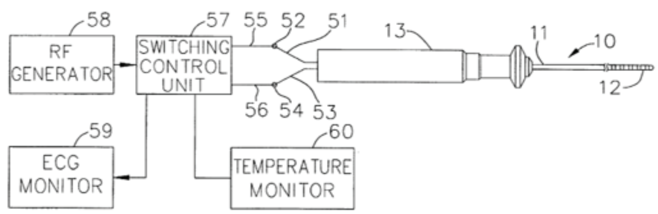
[567] *Id.* at 7:61-64, Fig. 13.

[568] *Papademetriou Dec.*, ¶ 115; *Webster Dec.*, ¶¶ 74-76; *Haemmerich Dec.*, ¶¶ 89-92.

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

Webster '885 discloses a multi-electrode RF ablation catheter useful for treating arrhythmias in the heart.[569] Each electrode is electrically connected to a switching unit by leads comprising paired copper and constantan wires.[570] The switching unit enables an operator to switch between a first mode for monitoring ECG and a second mode for delivering RF energy for tissue ablation to a selected electrode and monitoring the temperature of that electrode.[571] FIG. 11 below illustrates the switching unit being electrically connected to an RF generator, a temperature monitor and an ECG monitor.[572]

FIG. 11



11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

See discussion above in connection with claim 7.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

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[569] *Webster '885*, Abstract, 1:4-5.

[570] *Id.* at Abstract.

[571] *Id.*

[572] *Id.* at Fig. 11.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[573] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[574] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Webster '885.

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[573] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[574] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-E Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Edwards

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[575] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[576] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

A skilled artisan having the DiBona 1997 and Weinstock references in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[577] One method that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue or nerve ablation in the cardiac context.[578] One such method is shown in Edwards (App. P).

FIG. 1 of Edwards teaches a steerable catheter for ablation therapy carrying a radiofrequency emitting tip electrode with a temperature sensing element for measuring the temperature of the tissue being ablated.

> [A] physician steers the catheter 14 through a main vein or artery (typically the femoral artery) into the interior region of the heart that is to be treated. The physician then further manipulates the catheter 14 to place the tip electrode 16 into contact with the tissue within the heart that is targeted for ablation. The user directs radiofrequency energy from the

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[575] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

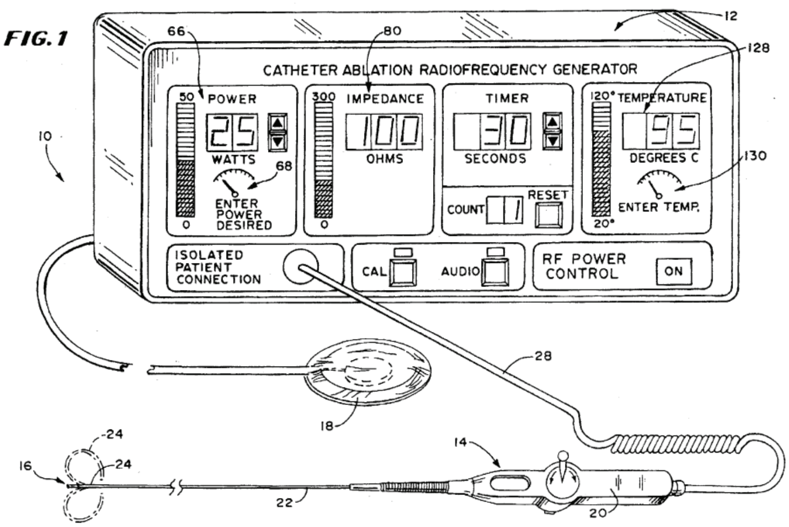
[576] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

[577] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[578] *Id.*

generator 12 into the tip electrode 16 to form a lesion on the contacted tissue.[579]

FIG. 1



One skilled in the art would have readily concluded that steerable intravascular catheters, like Edwards, were available to accomplish thermal ablation by using radiofrequency electric power to heat the tissue and therefore could perform the renal denervation procedure described by DiBona 1997, Weinstock and others.[580] Moreover, it was generally known in the early 2000s that as an alternative to contacting the tissue and transmitting a stimulating energy into the tissue itself, one could equally apply an ablative stimulus across a vessel wall from inside the renal artery, for example, rather than from the outside of the artery.[581] Accordingly, one skilled in the art would know that using this approach would have been desirable for ablating the renal nerves located on the outside wall of the renal arteries because less invasive surgery is required when the ablation is conducted from inside the artery.[582]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[583] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in

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[579] *Edwards '266*, 2:53-60.

[580] *Papademetriou Dec.*, ¶¶ 105, 110; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

[581] *Id.* at ¶ 107; *Id.* at ¶¶ 72-76; *Id.* at ¶¶ 89-92.

[582] *Id.*

[583] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

neurosurgery, urology, dermatology, oncology, and cardiology.[584] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[585]

Additionally, to the extent that a given catheter such as that taught by Edwards was judged too stiff or insufficiently steerable for a given vessel, one of ordinary skill in the art would understand that miniaturizing it to make it more maneuverable would have been considered routine engineering around the year 2000.[586] As of the year 2000, making the catheters more highly steerable was primarily a cost consideration.[587] The basic design principles would not change, although it would have been generally more expensive to fabricate smaller parts because they would be fashioned from higher strength and "toughness" materials.[588]

Regarding the general maneuverability of steerable catheters within the renal artery, the renal artery is about 5 mm in diameter branching from the aorta, which is about 15 mm in diameter.[589] Thus, there is ample room for a 6-7F steerable catheter, for example, to advance up the aorta and turn into the renal artery.[590] As further evidenced by Dr. Papademetriou's declaration, the anatomy of the renal arteries reveals that the renal arteries are relatively more straight than tortuous, which would allow a steerable catheter to more easily navigate and maneuver through the renal vasculature.[591]

In use, the Edwards catheter would, for instance, be introduced through the femoral vein with a guide sheath configured to position the catheter at the ostium, or entrance, to the renal artery.[592] The catheter would then be advanced, with or without the assistance of a guide sheath, to the treatment site in the renal artery.[593]

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Edwards.

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[584] *Id.*

[585] *Id.*

[586] *Papademetriou Dec.*, ¶ 102; *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[587] *Webster Dec.*, ¶ 70; *Haemmerich Dec.*, ¶ 87.

[588] *Webster Dec.*, ¶ 70.

[589] *Uflacker*, R., "Atlas of vascular anatomy: An angiographic approach." Baltimore: Williams & Wilkins, 424 (1997); *Papademetriou Dec.*, ¶ 99; *Webster Dec.*, ¶ 68; *Haemmerich Dec.*, ¶ 84.

[590] *Id.* at 424; *Id.* at ¶ 100; *Id.* at ¶ 69; *Id.*

[591] *Papademetriou Dec.*, ¶ 101.

[592] *Edwards '266*, 2:54.

[593] *Id.* at 3:3-11.

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Edwards steerable catheter is designed for intravascular use:

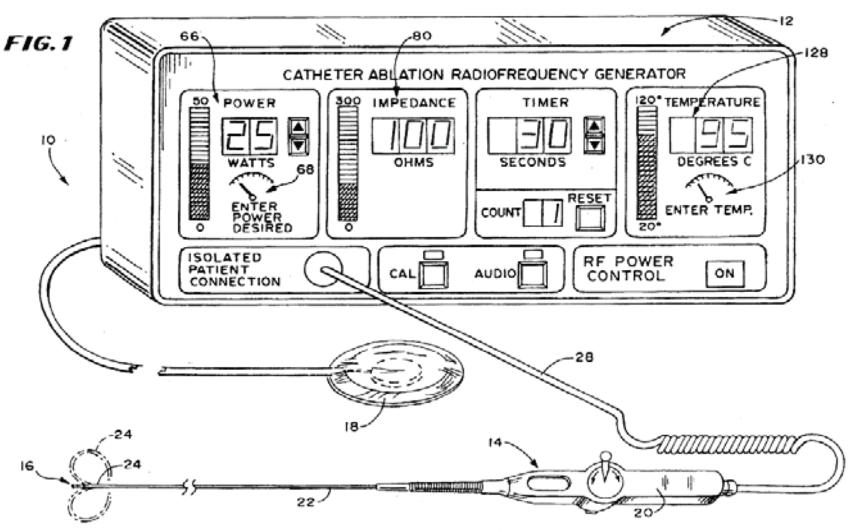
> [A] physician steers the catheter 14 through a main vein or artery (typically the femoral artery) into the interior region of the heart that is to be treated. The physician then further manipulates the catheter 14 to place the tip electrode 16 into contact with the tissue within the heart that is targeted for ablation. The user directs radiofrequency energy from the generator 12 into the tip electrode 16 to form a lesion on the contacted tissue.[594]

In the combined method of DiBona 1997, Weinstock and Edwards, the catheter is introduced into the renal artery and used to execute a renal denervation procedure.[595]

7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.

FIG. 1 of Edwards teaches a steerable catheter for ablation therapy carrying a radiofrequency emitting tip electrode with a temperature sensing element for measuring the temperature of the tissue being ablated.

FIG. 1



[596]

[594] *Id.* at 2:53-60.

[595] *Papademetriou Dec.*, ¶¶ 105, 110; *Webster Dec.*, ¶¶ 72-76; *Haemmerich Dec.*, ¶¶ 89-92.

11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.

12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.

See discussion above in connection with claim 7.

20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[597] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[598] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Edwards.

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[596] *Edwards '266*, 2:56-60.

[597] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[598] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-F Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Uchida

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[599] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[600] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

A skilled artisan having the DiBona 1997 and Weinstock references in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[601] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue or nerve ablation in the cardiovascular context.[602] Representative devices and methods for transvascular sympathectomies are disclosed in Uchida (App. S).

According to Uchida, "[r]adiofrequency (RF) catheter ablation has become a treatment of choice for patients with symptomatic atrioventricular reentrant tachycardia (AVRT) or atrioventricular nodal reentrant tachycardia (AVNRT)."[603] Uchida's procedure was as follows:

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[599] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[600] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

[601] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-82.

[602] *Id.*

[603] *Uchida*, 2517.

> Three 5 Fr quadripolar electrode catheters were introduced percutaneously into the femoral and subclavian veins and positioned at the high right atrium, His-bundle region, right ventricular apex, and coronary sinus for recording and stimulation. Meticulous mapping and ablation were performed using a steerable 7 Fr quadripolar catheter with a 4-mm tip and 2-mm interelectrode spacing. RF current was supplied by a 500 KHz generator (NL 50-I, Central Industry, Japan) at a constant preset electrical power (20 to 35 W) between the tip electrode of the ablation catheter and a large skin electrode positioned in the left subscapular region.
>
> The ablation catheter was positioned below the mitral valve for left free-wall and posteroseptal APs, above the tricuspid valve for right free-wall and posteroseptal APs, and near the ostium of the coronary sinus for slow pathways of AVNRT, respectively.
>
> Once a target was chosen, RF energy was applied for 5 seconds. If ablation was unsuccessful during this time, the current was turned off immediately and the ablation catheter was repositioned. If AP conduction disappeared or junctional rhythm (in slow pathway ablation) appeared, the current was delivered for a total of 60 seconds. [604]

Uchida's results demonstrate that "[r]adiofrequency (RF) catheter ablation of supraventricular tachycardias (SVT) has been shown to result in local parasympathetic denervation."[605] Uchida also demonstrated that effectiveness of parasympathetic denervation was a function of the cumulative RF energy delivered through the electrode.[606]

A skilled artisan would be motivated to use the Uchida catheter to perform the renal denervation taught by DiBona 1997 and Weinstock.[607] The Uchida device would have been understood to be substantially less invasive than the surgical nerve resection described in these references.[608] Use of the

[604] *Id.* at 2518.

[605] *Id.* at Abstract.

[606] *Id.* at 2517, 2519.

[607] *Papademetriou Dec.*, ¶¶ 89-90; *Webster Dec.*, ¶¶ 80-81; *Haemmerich Dec.*, ¶ 91-93.

[608] *Id.* at ¶ 115; *Id.* at ¶ 67; *Id.* at ¶¶ 91-93.

Uchida ablative catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[609]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[610] The declarations of Professors Webster, Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[611] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[612] Accordingly, a skilled artisan would have seen a strong motivation to use the Uchida RF catheter to achieve the renal denervation prescribed by DiBona 1997 and Weinstock.[613]

It should also be noted that, as discussed in the Technical Background section above, in parallel with the aforementioned developments in the renal sympathectomy (denervation) field, related surgical procedures had been evolving in the field of cardiovascular tissue and nerve ablation.[614] For instance, AVNRT was traditionally treated with a surgical method performed with a scalpel.[615] With advances in mechanical catheter technology in the 1990s, AVNRT surgery evolved into an intravascular procedure in which a catheter is inserted into the heart and ablative energy was applied through the wall of the heart in order to achieve the same result.[616] In order to accommodate different vessel sizes catheters were modified as appropriate to obtain the appropriate lesion size given the nature of the tissue involved.[617] By referencing the existing knowledge base which interrelated design parameters and lesion size, miniaturization or enlargement of catheters was routinely accomplished in the field of surgical instrument design as of the year 2000.[618]

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Uchida.

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[609] *Id.*

[610] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

[611] *Id.*

[612] *Id.*

[613] *Papademetriou Dec.*, ¶¶ 89-90; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 89-92.

[614] *Id.* at ¶ 21; *Id.* at ¶ 24; *Id.* at ¶ 39.

[615] *Id.* at ¶ 24; *Id.* at ¶ 26; *Id.* at ¶ 41.

[616] *Id.* at ¶¶ 25, 30, 31; *Id.* at ¶¶ 31, 32; *Id.* at ¶ 46.

[617] *Papademetriou Dec.*, ¶¶ 85, 102; *Haemmerich Dec.*, ¶¶ 69-79.

[618] *Webster Dec.*, ¶¶ 52-55; *Haemmerich Dec.*, ¶¶ 69-79.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Uchida catheter is designed for intraluminal deployment such as in coronary sinus and related pathways.[619] When used to perform the DiBona 1997/Weinstock denervation, the Uchida catheter would be inserted into the renal artery.[620]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

See discussion above in connection with claim 1. The Uchida catheter ablates tissue through the application of RF energy.[621]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

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[619] *Uchida*, Abstract; *Papademetriou Dec.*, ¶ 31; *Webster Dec.*, ¶ 32; *Haemmerich Dec.*, ¶ 55.

[620] *Papademetriou Dec.*, ¶¶ 89-90; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶ 89-92.

[621] *Uchida*, 2517.

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[622] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[623] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Uchida.

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[622] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[623] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-G Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 1997 and Weinstock Taken in Combination with Benito

Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[624] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[625] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

delivering a device to a vicinity of a neural fiber associated with renal function; and
thermally inhibiting neural communication along the neural fiber with the device.

A skilled artisan having the DiBona 1997 and Weinstock references in hand would consider the ways in which a renal sympathectomy (or denervation) could be effectuated.[626] One operative approach that would have immediately commanded itself to the attention of the skilled artisan was the technique used for tissue or nerve ablation in the cardiovascular context.[627] Representative devices and methods for transvascular sympathectomies are disclosed in Benito (App. T).

Benito explains that "[r]adiofrequency catheter ablation has been established as a highly effective and safe technique for eliminating accessory atrioventricular (AV) connections in adults and children."[628] An AV accessory connection is an electrical conduction pathway, akin to neural tissue.[629] Benito discloses a 5 French (1.67 mm) electrical ablative catheter for use in a pediatric cardiovascular neural

[624] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[625] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 64, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 80, 89.

[626] *Papademetriou Dec.*, ¶¶ 77-78; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-81.

[627] *Id.*

[628] *Benito*, 160.

[629] *Papademetriou Dec.*, ¶ 23.

ablation procedure.[630] "Ablation was done for medically refractory tachyarrhythmia associated with aborted sudden death in two patients, left ventricular dysfunction in one, failure of antiarrhythmic drugs in one, and planned cardiac surgery in one."[631] Benito concluded that the RF catheter technique could in fact be used effectively to ablate cardiovascular nerves associated with refractory tachyarrhythmia, among other conditions:

> ***Conclusions*—Radiofrequency catheter ablation can be performed successfully in infants. Temperature monitoring in 5F ablation catheters would be desirable to prevent the development of coagulum. Echocardiography must be performed after the ablation procedure to investigate pericardial effusion.**
>
> [632]

The Benito RF ablative catheter is well adapted to renal arterial procedures.[633] As explained above in connection with the discussion of the Schauerte reference, for example, a 5 French a catheter would be appropriately sized for use in a renal arterial application.[634] Moreover, the figures in the Benito reference reveal that the catheter has ample flexibility and maneuverability to navigate the renal vessels:[635]

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[630] *Benito*, Abstract; *Papademetriou Dec.*, ¶¶ 45, 100; *Webster Dec.*, ¶¶ 45, 69; *Haemmerich Dec.*, ¶¶ 63, 84.

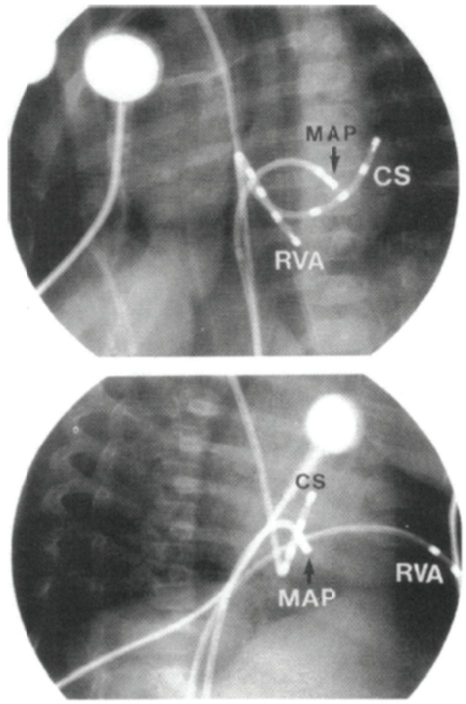
[631] *Benito*, Abstract.

[632] *Id.*

[633] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 84, 92.

[634] *Id.*

[635] *Benito*, 161.



Chest radiographs of catheter electrode position during ablation of a left posterior pathway in patient 5. The ablating catheter is positioned by transseptal approach at the mitral annulus, in close proximity to the third electrode of the coronary sinus catheter. Left anterior oblique projection is shown in top panel and right anterior oblique is shown in bottom panel. CS, coronary sinus catheter; MAP, ablation/mapping catheter; RVA, right ventricular apex catheter.

Using well-documented interrelationships between catheter configuration and ablative lesion size, a skilled artisan would be able to readily and without undue effort adapt the Benito catheter to a renal application.[636]

A skilled artisan would be motivated to use the Benito catheter to perform the renal denervation taught by DiBona 1997 and Weinstock.[637] The Benito device would have been understood to be substantially less invasive than the surgical nerve resection described in DiBona 1997 and Weinstock.[638] Use of the Benito ablative catheter would thus minimize patient discomfort and surgical complications and shorten hospital stays.[639]

Moreover, it was known that RF ablation had "emerged as the most successful and effective energy source for clinical applications in many specialties."[640] The declarations of Professors Webster,

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[636] *Id.*

[637] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-81.

[638] *Papademetriou Dec.*, ¶ 106; *Webster Dec.*, ¶¶ 75-76; *Haemmerich Dec.*, ¶¶ 91-92.

[639] *Id.*

[640] *Papademetriou Dec., ¶¶ 65, 104; Webster Dec., ¶ 33; Haemmerich Dec., ¶ 58.*

Papademetriou and Haemmerich explain that from the 1960s through the 1990s the applications of radiofrequency lesion generators had been growing, in conjunction with advances in technologies, in neurosurgery, urology, dermatology, oncology, and cardiology.[641] The professors conclude that those skilled in the art understood that RF ablation was considered the superior technique in many areas of clinical practice, including neural applications.[642] Accordingly, a skilled artisan would have seen a strong motivation to use the Benito RF catheter to achieve the renal denervation prescribed by DiBona 1997 and Weinstock.[643]

Accordingly, the subject matter of claim 1 is rendered obvious by DiBona 1997 and Weinstock when viewed in light of Benito.

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

The Benito catheter is designed for intraluminal deployment such as in coronary sinus and related pathways.[644] When used to perform the DiBona 1997/Weinstock denervation, the Benito catheter would be inserted into the renal artery.[645]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

See discussion above in connection with claim 1. The Benito catheter ablates tissue through the application of RF energy.[646]

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[641] *Id.*

[642] *Id.*

[643] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 80-81.

[644] *Benito*, Abstract, 160.

[645] *Papademetriou Dec.*, ¶¶ 100, 106; *Webster Dec.*, ¶¶ 77-81; *Haemmerich Dec.*, ¶¶ 84, 92.

[646] *Benito*, 160-161.

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
>
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

See discussion above in connection with claim 7.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure. [647] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Weinstock (App. E) similarly teaches that destruction of the renal arterial nerves was expected to alleviate high blood pressure (hypertension) in humans.[648] The teachings of Weinstock are discussed at length in connection with Group 1 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 1997 and Weinstock taken in combination with Benito.

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[647] *DiBona 1997*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

[648] *Weinstock*, 287; *Papademetriou Dec.*, ¶¶ 56, 113; *Webster Dec.*, ¶¶ 17, 63, 72, 78; *Haemmerich Dec.*, ¶¶ 32, 89.

4-H Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Swartz

DiBona 2002 (App. N) is prior art under 35 U.S.C. §102(a) because it was published before the earliest claimed priority date. DiBona 2002 reviews the findings of the DiBona 1997 paper (App. M) (presented above in Proposed Rejections 4A-4G) and summarizes the relevant state of the art as follows:

> There is growing evidence that an important cause of the defect in renal excretory function in hypertension is an increase in renal sympathetic nerve activity (RSNA). First, increased RSNA is found in animal models of hypertension and hypertensive humans. Second, renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[649]

Accordingly, DiBona 2002 provides teachings similar to DiBona 1997 but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[650]

The analysis set forth above in connection with Proposed Rejection 4-A applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[651]

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Swartz (App. O) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[652] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-A.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Swartz.

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[649] *DiBona 2002*, Abstract (Emphasis added).

[650] *Id.*

[651] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[652] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 82-84; *Papademetriou Dec.*, ¶ 112.

4-I Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Webster '695

As explained above, DiBona 2002 (App. N) provides teachings similar to DiBona 1997 (App. M) but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[653]

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[654]

The analysis set forth above in connection with Proposed Rejection 4-B applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Webster '695 (App. J) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[655] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-B.

For the foregoing reasons, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Webster '695.

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[653] *DiBona 2002*, Abstract.

[654] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[655] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 77-80; *Papademetriou Dec.*, ¶¶ 84-86.

4-J Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Schauerte

As explained above, DiBona 2002 (App. N) provides teachings similar to DiBona 1997 (App. M) but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[656]

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[657]

The analysis set forth above in connection with Proposed Rejection 4-C applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Schauerte (App. K) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[658] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-C.

Accordingly, claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Schauerte.

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[656] *DiBona 2002*, Abstract.

[657] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[658] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 77-81; *Papademetriou Dec.*, ¶ 91-96.

4-K Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Webster '885

As explained above, DiBona 2002 (App. N) provides teachings similar to DiBona 1997 (App. M) but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[659]

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[660]

The analysis set forth above in connection with Proposed Rejection 4-D applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Webster '885 (App. R) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[661] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-D.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Webster '885.

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[659] *DiBona 2002*, Abstract.

[660] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[661] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 77-81; *Papademetriou Dec.*, ¶¶ 107, 110.

4-L Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Edwards

As explained above, DiBona 2002 (App. N) provides teachings similar to DiBona 1997 (App. M) but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[662]

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[663]

The analysis set forth above in connection with Proposed Rejection 4-E applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Edwards (App. P) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[664] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-E.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Edwards.

[662] *DiBona 2002*, Abstract.

[663] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[664] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 77-81; *Papademetriou Dec.*, ¶¶ 105, 110.

4-M Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Uchida

As explained above, DiBona 2002 (App. N) provides teachings similar to DiBona 1997 (App. M) but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[665]

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[666]

The analysis set forth above in connection with Proposed Rejection 4-F applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Uchida (App. S) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[667] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-F.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Uchida.

[665] *DiBona 2002*, Abstract.

[666] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[667] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 77-81; *Papademetriou Dec.*, ¶¶ 89-90.

4-N Claims 1, 5, 7, 12, 20 and 21 are Rendered Obvious by DiBona 2002 Taken in Combination with Benito

As explained above, DiBona 2002 (App. N) provides teachings similar to DiBona 1997 (App. M) but more plainly states that renal denervation prevents or alleviates hypertension in virtually all animal models of hypertension.[668]

With respect to the preamble of the independent claims, even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that the animal studies described by DiBona 2002 were performed as proxies for experimentation in humans.[669]

The analysis set forth above in connection with Proposed Rejection 4-G applies with equal force to DiBona 2002. For efficiency's sake Requester will not repeat that analysis. Rather, that analysis is incorporated herein by reference.

In view of the advantages and motivations set forth above, it follows that one of ordinary skill in the art looking to implement the renal denervation procedure taught by DiBona 2002 in an effective non-invasive manner would recognize the suitability of the Benito (App. T) catheter for delivering a device to a vicinity of a neural fiber associated with renal function and thermally inhibiting neural communications along the neural fiber with the device.[670] By analogy, the combination suggests the subject matter recited in the dependent claims in the same manner described above in proposed rejection 4-G.

For the foregoing reasons claims 1, 5, 7, 12, 20 and 21 are rendered obvious under 35 U.S.C. §103 by DiBona 2002 taken in combination with Benito.

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[668] *DiBona 2002*, Abstract.

[669] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[670] *Haemmerich Dec.*, ¶ 93; *Webster Dec.*, ¶¶ 77-81; *Papademetriou Dec.*, ¶ 106.

Group 5: Proposed Rejections based on Prior Art Disclosing Other Renal Surgical Procedures

Han et al., *Renal Artery Embolization with Diluted Hot Contrast Medium: An Experimental Study*, Journal of Vascular and Interventional Radiology, July 2001 (App. D) qualifies as prior art under 35 U.S.C. § 102(a). Han was not before the Examiner.

Han teaches that diluted hot contrast medium delivered via a balloon catheter is an effective means to achieve renal ablation to treat a variety of renal conditions.[671] Han begins by noting that "percutaneous transcatheter renal arterial embolization has been found beneficial for the treatment of renal trauma, symptomatic renal angiomyolipoma, and preoperative and palliative treatment of renal cell carcinoma."[672] Han indicates that the purpose of the study is to "investigate the safety and efficacy of the injection of diluted hot contrast medium for the safe ablation of the kidney."[673] The experimental method was to introduce an "angioplasty balloon catheter (5-7-mm; Boston Scientific/Medi-tech Watertown, MA)" at the "ostium of the renal artery over an exchange guide wire."[674] "The balloon was inflated with 1:1 ratio of contrast medium and saline solution and the diluted hot contrast medium was injected into the renal artery under fluoroscopic guidance."[675] The balloon catheter size "was selected according to renal artery diameter, which was measured by cine angiogram in each animal."[676] The balloon was inflated by hand by injection of the hot contrast medium.[677] Han concluded that "diluted hot contrast medium may be a safe embolic agent in effectively ablating renal arteries."[678]

The Han procedure destroys the renal artery adventitia[679] and thus inherently ablates the renal nerves.[680] Adventitia is the outermost connective tissue covering of an organ or vessel and, in the case of the kidney, the adventitia encases the renal nerves.[681] Accordingly, the Han procedure ablates the renal nerves by virtue of causing necrosis of the surrounding adventitia.

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[671] *Han*, 868.

[672] *Id.* at 862.

[673] *Id.* at 863.

[674] *Id.*

[675] *Id.*

[676] *Id.*

[677] *Id.*

[678] *Id.* at 868.

[679] *Id.* at 864-865.

[680] *Papademetriou Dec.*, ¶¶ 135-136; *Webster Dec.*, ¶ 96.

[681] *Papademetriou Dec.*, ¶ 10.

Accordingly, Han teaches that hot contrast medium injected via a balloon catheter may be an effective treatment for renal conditions such as renal trauma, symptomatic renal angiomyolipoma, and preoperative and palliative treatment of renal cell carcinoma.[682] This maps closely to the feature identified by the Examiner in the Statement of Reasons for Allowance: treatment of a cardio-renal condition through thermal inhibition of nerve signals across the neural pathway that carries nerve signals to and from the kidney.[683] The '948 patent characterizes both renal and cardiac conditions as "cardio-renal conditions"[684] and thus Han et al.'s teaching concerning the treatment of various renal conditions meets the claim recitation referenced in the Notice of Allowance.

Moreover, thermally inhibiting the nerve signals by delivering a hot fluid is one of the preferred embodiments of the '948 patent.[685]

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[682] *Han*, 862.

[683] *U.S. Patent Application No.* 11/840,142 file history, February 23, 2010 Notice of Allowance/Allowability, 3 (App. Q).

[684] *'948 patent*, 16:51-53 ("CHF, hypertension, renal disease, myocardial infarction, atrial fibrillation, contrast nephropathy and/or other cardio-renal diseases…").

[685] See, e.g., *Id.* at Fig. 9; 13:10-13 ("A thermal fluid [fluid] may be delivered through the needles to the target neural fibers. The thermal fluid may be heated in order to raise the temperature of the target neural fibers above a desired threshold.").

5-A Claims 1, 5, 7 and 20 are Rendered Obvious by Han Taken Alone

Han (App. D) expressly teaches all recitations of claims 1, 5, 7 and 20 except the recitation in the preamble that the method is used to treat a human patient.

> *Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising*

Han teaches that diluted hot contrast medium delivered via a balloon catheter is an effective means to achieve renal ablation to treat a variety of renal conditions.[686]

Even if one assumes that the preamble is a limitation under the broadest reasonable interpretation, a skilled artisan would have appreciated that Han's study was performed in canines as a proxy for humans.[687]

> *delivering a device to a vicinity of a neural fiber associated with renal function; and*
> *thermally inhibiting neural communication along the neural fiber with the device.*

The Han procedure destroys the renal artery adventitia[688] and thus inherently ablates the renal nerves which lie in the adventitia.[689]

Further, thermally inhibiting the nerve signals by delivering a hot fluid is one of the preferred embodiments of the '948 patent.[690]

> *4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.*
>
> *5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.*

Han's method was to introduce an "angioplasty balloon catheter (5-7-mm; Boston Scientific/Medi-tech Watertown, MA)" at the "ostium of the renal artery over an exchange guide wire."[691]

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[686] *Han*, 868.

[687] *Webster Dec.*, ¶ 23; *Papademetriou Dec.*, ¶¶ 54-64.

[688] *Han*, 864-865.

[689] *Papademetriou Dec.*, ¶¶ 135-136; *Webster Dec.*, ¶ 96.

[690] *'948 patent*, 13:5-13.

"The balloon was inflated with 1:1 ratio of contrast medium and saline solution and the diluted hot contrast medium was injected into the renal artery under fluoroscopic guidance."[692]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

Han concluded that "diluted hot contrast medium may be a safe embolic agent in effectively ablating renal arteries."[693]

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

For the foregoing reasons claims 1, 5, 7 and 20 are rendered obvious under 35 U.S.C. §103 by Han.

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[691] *Han*, 863.

[692] *Id.*

[693] *Id.* at 868.

5-B Claim 21 is Rendered Obvious by Han Taken in Combination with DiBona 1997

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[694] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Claim 21 is thus rendered obvious by Han taken in combination with DiBona 1997.

[694] *DiBona (1997)*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

5-C Claims 1, 7, 12 and 20 are Rendered Obvious by Valente Taken in Combination with Rosar or Lee

In related Patent Application Serial No. 11/368,577 ("the '577 application") (App. W), now U.S. Patent No. 8,145,317, Examiner Bockelman found that it would have been obvious to use the ablative electrocautery device disclosed in Rosar, G., et al. "Electrosurgical apparatus." *U.S. Patent No. 5,300,068* (App. Y) to carry out the renal denervation procedure discussed in Valente, J., et al. "Laproscopic renal denervation for intractable ADPKD-related pain." *Nephrol Dial Transport,* 16:160 (2001) (App. X).[695] More particularly, at page 2 of the April 14, 2011 office action, Examiner Bockelman issued the following rejection:

> Claims 21-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valente et al. "Laproscopic renal denervation for intractable ADPKD-related pain" in view of Rosar et al USPN 5,300,068 or Baker et al. USPN 6,149,620 and "USRDS United States Renal Data System 2003 Annual Data Report" as cited by Applicant. Valente et al. teach a method where renal nerves are exposed and severed by a harmonic scalpel so as to treat kidney pain due to polycystic kidney disease. While the details of the scalpel are not available, it would have been obvious to one of ordinary skill in the art to have used a scalpel such as that of Rosar which uses a monopolar electrode 15 with a dispersive electrode 14 to be attached to the patient including skin. Such scalpels are well known for severing nerve tissue (see column 1 lines 63-65) and for ablating. Alternatively Baker et al. teach a similar device for ablating tissue which may be operated in a monopolar configuration. (Column 13 lines 18-35). The device may ablate tissue, but may also cut in a non-thermal manner. Column 9 line 43. Both devices uses pulses and at least ablate. Cutting the tissue will inherently reduce communication in the nerves. Valente's method is post ganglionic. Both devices use

[695] *'577 application*, April 14, 2011 office action, 2-3.

> feedback for energy transmission, Rosar uses impedance, however such is a secondary indicator of temperature.
>
> As noted in the USRDS publication in numerous instances and as by example page vii column 1, Polycystic Kidney disease has been documented as one of the causes of ESRD. To have treated a patient with ESRD and polycystic Kidney disease by the Valente et al. method thereby treating a patient with ESRD would have been obvious.

The Examiner thus found that it would have been obvious to execute a renal denervation (as taught by Valente) with an ablative electrode (as taught by Rosar) in order to treat polycystic kidney disease, which was known to be linked to end stage renal failure (as taught by the USRDS report), which is one of the cardio-renal conditions identified in the '948 patent.[696]

The claims of the '577 application were amended to distinguish the combination of Valente and Rosar. More particularly, the independent claims were amended to recite "wherein reducing neural communication to and from the kidney results in improved cardio-renal function of the patient" or "wherein at least partially ablating the neural fibers results in a therapeutically beneficial reduction in central sympathetic overactivity of the patient."[697] Those limitations do not appear in the claims of the '948 patent.[698]

> *Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising*

Valente discloses a procedure for executing a renal denervation to treat kidney pain due to polycystic kidney disease.[699]

> *delivering a device to a vicinity of a neural fiber associated with renal function; and*
> *thermally inhibiting neural communication along the neural fiber with the device.*

The Examiner correctly found that it would have been obvious to execute a renal denervation (as taught by Valente) with an ablative electrode (as taught by Rosar) in order to treat polycystic kidney

[696] *Id.* at 3.

[697] *Id.* at September 28, 2011 Amendment, 2, 4.

[698] *'948 patent*, 16:2-3.

[699] *Valente*, 160.

disease, which was known to be linked to end stage renal failure (as taught by the USRDS report), which is one of the cardio-renal conditions identified in the '948 patent.[700]

Professors Webster and Papademetriou explain in their declarations that Examiner Bockelman need not have relied upon the Rosar reference, as the Valente harmonic scalpel was known to work via a thermal mechanism.[701] As explained in Lee, S.-J., et al. "Ultrasonic Energy in Endoscopic Surgery." *Yonsei Med J*, 40:545-549 (1999) (App. Z) harmonic scalpels cut tissue by operation of mechanical energy and heat.

> The Harmonic Scalpel denatures protein by the transfer of mechanical energy to the tissue, which is sufficient to break tertiary hydrogen bonds and by the generation of heat from internal cellular friction which results from the high frequency vibration of the tissue.[702]

The Valente harmonic scalpel would have been understood by a skilled artisan as operating according to a thermal mechanism.[703]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

See discussion above in connection with claim 1. As explained there, the harmonic scalpels of Valente, Rosar and Lee work according to thermal and vibratory mechanisms.

The Miller-Keane Encyclopedia and Dictionary of Medicine (2003) defines ablation as "removal, especially by cutting with a laser or electrocautery."[704] Accordingly, the harmonic scalpels of Valente, Rosar and Lee achieve thermal ablation.

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

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[700] '577 application, April 14, 2011 office action, 2-3.

[701] *Webster Dec.*, ¶ 98; *Papademetriou Dec.*, ¶ 137.

[702] *Lee*, 546.

[703] *Webster Dec.*, ¶ 98; *Papademetriou Dec.*, ¶ 137.

[704] *Papademetriou Dec.*, ¶ 69.

As explained by Lee, the harmonic scalpel delivers energy at 55.5 kHz to the neural fiber:[705]

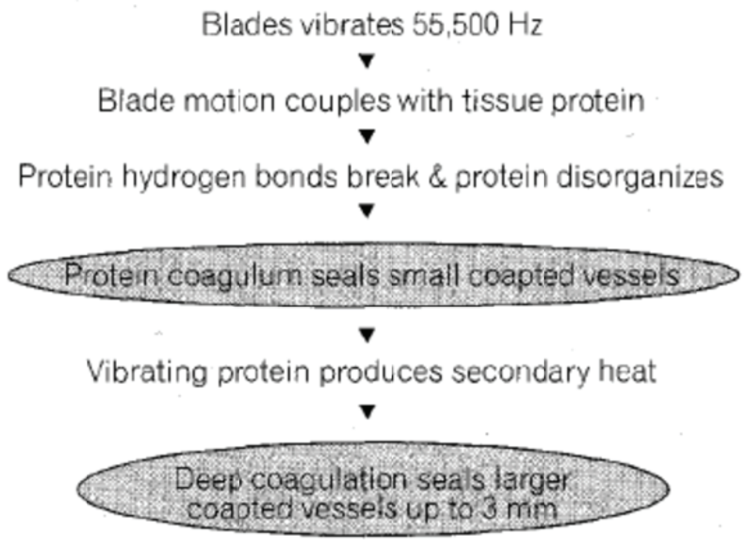

Fig. 4. Coagulation using ultracision technology.

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

For the foregoing reasons, claims 1, 7, 12 and 20 are rendered obvious under 35 U.S.C. §103 by Valente taken in combination with Rosar or Lee.

[705] *Lee*, 545, 547.

5-D Claim 5 is Rendered Obvious by Valente Taken in Combination with Swartz

4. The method of claim 1 wherein delivering a device to a vicinity of a neural fiber associated with renal function comprises delivering the device via a blood vessel to a position proximate to the neural fiber.

5. The method of claim 4 wherein delivering the device via a blood vessel to a position proximate to the neural fiber comprises delivering the device via a renal blood vessel to a position proximate to the neural fiber.

The Swartz (App. O) catheter is introduced to the ablation site intravascularly.[706] In the combined method of Valente (App. X) and Swartz, the catheter is likewise introduced to the renal artery intravascularly.[707] The rationale for combining Weinstock (App. E) and Swartz discussed above in connection with Proposed Rejection 1-A applies with equal force here and that discussion is incorporated herein by reference.

Thus claim 5 is rendered obvious by Valente taken in combination with Swartz.

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[706] *Swartz*, Abstract; *Papademetriou Dec.*, ¶ 28; *Webster Dec.*, ¶ 30; *Haemmerich Dec.*, ¶ 44.

[707] *Papademetriou Dec.*, ¶ 138; *Webster Dec.*, ¶ 99.

5-E Claim 21 is Rendered Obvious by Valente Taken in Combination with DiBona 1997

21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[708] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Claim 21 is accordingly rendered obvious by Valente taken in combination with DiBona 1997.

[708] *DiBona (1997)*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

5-F Claims 1, 7, 12 and 20 are Rendered Obvious by Curtis Taken in Combination with Rosar

Curtis, J. J., et al., "Surgical Therapy for Persistent Hypertension after Renal Transplantation." *Transplantation*, 31:125-128 (1981) (App. AA) qualifies as prior art under 35 U.S.C. §102(b) and was not before the Examiner. In the related '577 application (App. W), Examiner Bockelman found that it would have been obvious to use the ablative electrocautery device disclosed in Rosar (App. Y) to carry out the nephrectomy (kidney removal) procedure discussed in Curtis.[709] Examiner Bockelman found that it would have been obvious to use an ablative scalpel to execute the nephrectomy procedure, which inherently severs the renal nerves:[710]

> Curtis et al teaches a method of reducing hypertension by performing a bilateral nephrectomy on native kidneys to lower blood pressure. While he does not teach ablating the renal arteries for removal, the procedure involves severing the renal arteries. To have done so with a ablation scalpel device so as to help cauterize the tissue would have been obvious over Rosar or Baker.

With respect to Rosar, Examiner Bockelman held that

> it would have been obvious to one of ordinary skill in the art to have used a scalpel such as that of Rosar which uses a monopolar electrode 15 with a dispersive electrode 14 to be attached to the patient including skin. Such scalpels are well known for severing nerve tissue (see column 1 lines 63-65) and for ablating.[711]

The declarations submitted herewith explain that Examiner Bockelman's reasoning in this regard is sound.[712] An electrocautery scalpel is an intuitive and natural choice for an instrument with which to conduct a nephrectomy or rhizotomy (renal nerve resection).[713]

The claims of the '577 application were amended to distinguish the combination of Curtis and Rosar. One independent claim was amended to recite "wherein the kidney continues to secrete renin in the patient after reducing neural communication with the nerve modulation device" and the other independent claim was amended to recite "wherein at least partially ablating the renal nerve results in a

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[709] *'577 application*, April 14, 2011 office action, 3.

[710] *Id.*

[711] *Id.* at 2.

[712] *Webster Dec.*, ¶¶ 101-102; *Papademetriou Dec.*, ¶ 132; *Haemmerich Dec.*, ¶ 102.

[713] *Id.*

therapeutically beneficial reduction in blood pressure of the patient."[714] Neither limitation exists in the claims of the '948 patent.[715]

> *Claim 1: A method of treating a human patient diagnosed with a cardio-renal disease or disorder, the method comprising*

As noted above, Curtis discloses a nephrectomy procedure to treat persistent hypertension.[716]

> *delivering a device to a vicinity of a neural fiber associated with renal function; and*
> *thermally inhibiting neural communication along the neural fiber with the device.*

As discussed above, an electrocautery scalpel is an intuitive and natural choice for an instrument with which to conduct a nephrectomy (kidney removal) or rhizotomy (renal nerve resection).[717]

> *7. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises at least partially ablating the neural fiber with the device.*

Electrocautery was by definition a form of thermal ablation as of the priority date. The Miller-Keane Encyclopedia and Dictionary of Medicine (2003) defines ablation as "removal, especially by cutting with a laser or electrocautery."[718] Accordingly, Curtis's teaching of renal denervation by electrocautery would have been understood by those skilled in the art to be a form of thermal ablation.[719]

> *11. The method of claim 1 wherein thermally inhibiting neural communication along the neural fiber with the device comprises delivering an energy field to the neural fiber via the device.*
> *12. The method of claim 11 wherein delivering an energy field to the neural fiber via the device comprises delivering radiofrequency energy via the device.*

According to Rosar's abstract, the "electrosurgical apparatus for cutting tissue and for ablating occlusions includes a pulse generator for selectively generating a train of pulses of electrical energy for

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[714] *'577 application*, September 28, 2011 Amendment, 2, 4.

[715] *'948 patent*, 16:2-3.

[716] *Curtis*, 126.

[717] *Webster Dec.*, ¶¶ 101-102; *Papademetriou Dec.*, ¶ 132; *Haemmerich Dec.*, ¶ 102.

[718] *Papademetriou Dec.*, ¶ 69.

[719] *Papademetriou Dec.*, ¶ 131-134; *Webster Dec.*, ¶¶ 100-102; *Haemmerich Dec.*, ¶¶ 101-102.

application to a wire having an attached electrode, the generator having a variable output impedance, the wire and the electrode being at least part of a load impedance."[720]

> *20. A method of treating a human patient diagnosed with a medical condition, the method comprising: positioning a device in proximity to a neural pathway that carries nerve signals to and from a kidney of the patient; and thermally inhibiting the nerve signals across the neural pathway with the device.*

This claim is similar in scope to claim 1. Claim 20, however, is not expressly limited to treatment of "a cardio-renal disease or disorder." Claim 20 is thus broader than claim 1. *See* discussion above in connection with claim 1.

For the foregoing reasons, claims 1, 7, 12 and 20 are rendered obvious under 35 U.S.C. §103 by Curtis taken in combination with Rosar.

[720] *Rosar*, Abstract.

5-G Claim 21 is Rendered Obvious by Curtis Taken in Combination with DiBona 1997

> *21. The method of claim 20 wherein treating a human patient diagnosed with a medical condition comprises treating a human patient diagnosed with hypertension.*

DiBona 1997 (App. M) is representative of a body of literature which teaches that denervation inhibits the onset of hypertension and alleviates hypertension by affecting renin release and salt retention which in turn affects blood pressure.[721] The teachings of DiBona 1997 are discussed at length in connection with Group 2 of the Proposed Rejections, above, and that discussion is incorporated herein by reference.

Claim 21 is thus rendered obvious by Curtis taken in combination with DiBona 1997.

[721] *DiBona (1997)*, 142-144; *Papademetriou Dec.*, ¶ 111; *Webster Dec.*, ¶¶ 63, 77; *Haemmerich Dec.*, ¶ 30.

VII. CONCLUSION

Substantial, new and noncumulative technical teachings have been presented for each of claims 1, 5, 7, 12, 20 and 21 of the ’948 patent, which claims are rendered obvious under 35 U.S.C. §103 for the reasons set forth in the foregoing sections. There is a reasonable likelihood that Requester will prevail as to each of the claims. Reexamination of claims 1, 5, 7, 12, 20 and 21 is accordingly requested.

Respectfully submitted,
OBLON SPIVAK

Dated: August 29, 2012

/Greg H. Gardella/
Greg H. Gardella
Reg. No. 46,045

Customer Number
22850
Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 02/10)