

# Renal Denervation for Severe Hypertension: Past, Present and Future

## *Desnervación renal en la hipertensión arterial grave: pasado, presente y futuro*

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### ABSTRACT

The seventh anniversary of the first catheter-based renal denervation procedure for resistant hypertension is near. At the “end of the beginning”, it is timely to reflect on the next phase in the development and clinical application of renal denervation in hypertension treatment. Unresolved procedural and technical questions are central: To what extent is renal denervation optimal? Is unilateral denervation, now commonly used, beneficial? Will renal denervation show a “class effect”, with the different energy forms now used for renal nerve ablation producing equivalent blood pressure lowering? The Achilles heel in catheter-based studies of renal denervation for severe hypertension is the almost universal failure to apply a confirmatory test for renal denervation. When I assessed renal denervation efficacy, using measurements of the spillover of norepinephrine from the renal sympathetic nerves to plasma, the only test validated to this point, denervation was found to be incomplete and non-uniform between patients. It is probable that the degree of denervation has typically been sub-optimal in renal denervation trials. This criticism applies with special force to the Symplicity HTN-3 trial, where the proceduralists, although expert interventional cardiologists, had no prior experience with the renal denervation technique. Their learning curve fell during the trial, a shortcoming accentuated by the fact that one third of operators performed one procedure only. Recently presented results from the Symplicity HTN-3 trialists confirm that renal denervation was not effectively or consistently achieved in the trial.

**Key words:** Kidney / Innervation - Hypertension - Sympathectomy

### RESUMEN

Se acerca el séptimo aniversario del primer procedimiento de desnervación renal vía catéter en la hipertensión arterial resistente. Al “final del principio” es oportuno reflexionar sobre la próxima fase en el desarrollo y la aplicación clínica de la desnervación renal en el tratamiento de la hipertensión arterial. Los problemas técnicos y de procedimiento no resueltos son cruciales: ¿Cuán óptima es la desnervación renal? ¿La desnervación unilateral, comúnmente utilizada en la actualidad, es beneficiosa? ¿La desnervación renal mostrará un “efecto de clase”, con un descenso de la presión arterial equivalente al observado con las distintas formas de energía utilizadas actualmente para la ablación nerviosa renal? El talón de Aquiles en los estudios de desnervación renal vía catéter para la hipertensión arterial grave es el fracaso casi universal en la aplicación de una prueba confirmatoria de la desnervación. Al evaluar la eficacia del procedimiento, utilizando mediciones de difusión del excedente de noradrenalina (spillover) desde los nervios simpáticos renales al plasma, la única prueba validada hasta el momento, se halló desnervación incompleta y no uniforme entre pacientes. Es probable que el grado de desnervación haya sido en general subóptimo en los estudios de desnervación renal. Esta crítica también se aplica especialmente al ensayo Symplicity HTN-3, en el cual los especialistas a cargo de realizar el procedimiento, a pesar de ser cardiólogos intervencionistas expertos, no tenían experiencia previa en la técnica de desnervación renal. Su curva de aprendizaje cayó durante el ensayo, una deficiencia acentuada por el hecho de que un tercio de los cirujanos realizaron solo un procedimiento. Los resultados del Symplicity HTN-3 recientemente presentados confirman que la desnervación renal no se logró efectiva y consistentemente en el ensayo.

**Palabras clave:** Riñón / Inervación - Hipertensión - Simpatectomía

### A SHORT HISTORY OF THE “PRESSOR NERVES”

Stimulation of the sympathetic nerves, by Claude Bernard and Charles Brown-Sequard demonstrated them to be vasoconstrictor, and to elevate blood pressure, leading to their categorisation as the “pressor nerves” (1), and to the subsequent idea that high blood pressure was caused by the nervous system. In the early

years of the twentieth century no treatment of hypertension was available until the introduction of surgical sympathectomy (2), which surgically severed sections of the sympathetic chain, and all sympathetic nerves of the thorax and abdomen within reach, cutting as many “pressor nerves” as possible to remove their systemic vasoconstrictor influence. Selective re-

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nal sympathectomy was not performed, as there was no theory suggesting the importance of the kidney sympathetic nerves in the pathogenesis of hypertension. Surgical sympathectomy, which was applied in the years 1935-1960 for the treatment of hypertension, was demonstrably of value in prolonging life in patients with severe and malignant hypertension, but at the cost of disabling side effects, most notably postural hypotension and syncope.

Ganglionic blocking drugs, developed by Paton and colleagues (3), ended the period of surgical sympathectomy for hypertension, and ushered in an era of antiadrenergic drugs. Neurone-blocking drugs such as guanethidine, centrally-acting sympathetic nervous inhibitors including methyldopa and clonidine, beta-adrenergic receptor blocking drugs such as propranolol, and alpha-adrenergic receptor blockers followed in quick succession (4). Antiadrenergic drugs, coupled with diuretics and direct-acting vasodilators were the preferred antihypertensive therapy from 1960-1990 (4).

#### **DRUG-RESISTANT ESSENTIAL HYPERTENSION: FAILURE TO TARGET THE NEURAL PATHOPHYSIOLOGY?**

In the modern era, drugs antagonizing the renin-angiotensin system have become the dominant antihypertensive therapy. ACE-inhibitor drugs and angiotensin receptor blocking drugs gradually replaced antiadrenergic drugs as the preferred antihypertensive agents because they were at least equally efficacious, and substantially better tolerated. Subsequently joined by dihydropyridine calcium channel blocking drugs, the anti-renin drugs, calcium channel blockers and diuretics came to occupy the preferred position, at the top of international cardiovascular society hypertension guidelines "league tables" (5), with antiadrenergic antihypertensive drugs edging towards the bottom of the lists. The sympathetic nervous system lost its earlier prominence in discussions of essential hypertension pathogenesis and treatment, and became to be considered as passé, and of only marginal relevance in hypertension care.

But there was a problem. Despite the widespread availability and prescribing of ACE-inhibitors, angiotensin receptor blockers, diuretics and calcium channel blockers, in a substantial minority of patients with essential hypertension, perhaps 10% (6,7), goal blood pressure was not achieved. In these drug-resistant hypertensives a new strategy was needed, and in fact, devised. This was the development of device-based therapies targeting the sympathetic nervous system, the surgically implanted barostimulator device (8) and catheter-based renal denervation (9,10), the latter being the subject of this review.

#### **RATIONALE FOR ENDOVASCULAR RENAL DENERVATION**

Central to the development of radiofrequency renal denervation was knowledge of the physiology of the renal sympathetic nerves, and their pathophysiology

in experimental and human hypertension. In untreated essential hypertensive patients, the application of regional noradrenaline isotope dilution methodology (11), to measure the outward flux of the transmitter from renal sympathetic nerves to plasma ("renal nor-epinephrine spillover"), demonstrated that a high level of activation of the renal sympathetic outflow was present (12,13). This renal sympathetic activation is central to hypertension pathogenesis (14,15).

In experimental animals the renal nerves have been demonstrated to stimulate secretion of renin from the juxtaglomerular apparatus, to promote renal tubular reabsorption of sodium, and to cause renal vasoconstriction, all potentially blood pressure elevating responses (14,15). The renal tubules receive a dense sympathetic innervation, at all tubular levels. A specific and important relation of the renal sympathetic nerves to renal tubular sodium reabsorption, key to hypertension pathogenesis, concerns pressure natriuresis, the normal capacity of the kidneys to excrete sodium at higher arterial perfusion pressures (16). Impairment of pressure natriuresis is believed to be a central element in the development of hypertension (15,16). Renal sympathetic denervation shifts the renal pressure-natriuresis curve to the left, promoting urinary sodium excretion and lowering of blood pressure (15,16).

These facts, and a third, knowledge of the anatomy of the postganglionic renal sympathetic nerves in their passage to the kidneys, provided the intellectual framework for the development of catheter-based renal denervation for treatment of essential hypertension. In humans, the renal sympathetic nerves pass from the sympathetic chain and ganglia to the kidneys via the outer wall of the renal arteries, or just outside in perirenal adipose tissue and connective tissue, within reach of radiofrequency energy delivered by a catheter in the artery lumen (17).

The California start-up company, Ardian, commenced a developmental program to design a radiofrequency ablation catheter suitable for human use, testing this purpose-designed catheter for safety and renal denervation capacity in pigs (18). The first-in-man studies were conducted in Melbourne. The patient class of resistant hypertension was selected for initial investigation because of the very evident clinical need, and because the potential benefit-risk balance made the study defensible ethically. This first trial, which commenced in June 2007, became known as Symplicity HTN-1 (9). It has subsequently been demonstrated that patients with drug-resistant hypertension actually do have very pronounced activation of the renal sympathetic outflow (19), providing a retrospective justification based on the existing pathophysiology.

#### **ENDOASCULAR RENAL DENERVATION TRIALS: THE END OF THE BEGINNING**

Renal denervation for hypertension has a long pedi-

gree. As described, in the 1940s surgical sympathectomy was performed as the first effective treatment for severe hypertension. At this time no theory identified the sympathetic nerves of the kidneys as pivotal in the pathogenesis of hypertension, but the procedures performed no doubt often sectioned postganglionic sympathetic fibres directed to the kidneys.

The Symplicity trials in endovascular renal nerve ablation, HTN-1 (9) and HTN-2 (10) have opened a door to a new future in the treatment of drug-resistant hypertension. More than six years after the first patient was treated with the Symplicity radiofrequency catheter system, these initial trials, their continuation to later specified endpoints (20,21), accompanying resistant hypertension renal denervation registry files (22), and trials with other, newly engineered renal denervation devices (23,24) have established important therapeutic principles:

1. Efferent sympathetic renal denervation can be achieved with luminal delivery of radiofrequency and ultrasonic energy.
2. The mean BP reduction across the trials shows consistency, office systolic BP falling on average by 20-30 mm Hg at the primary endpoints. Renal function is preserved. The BP reduction is durable, demonstrably persisting for 3 years and beyond.
3. New renal artery stenoses in the field of RF energy delivery are very uncommon.
4. Treatment failure does occur (estimated at 15-50% in the trials); this cannot be predicted from patient clinical characteristics. No doubt it is sometimes and perhaps usually (Figure 1), due to technical failure to achieve denervation.

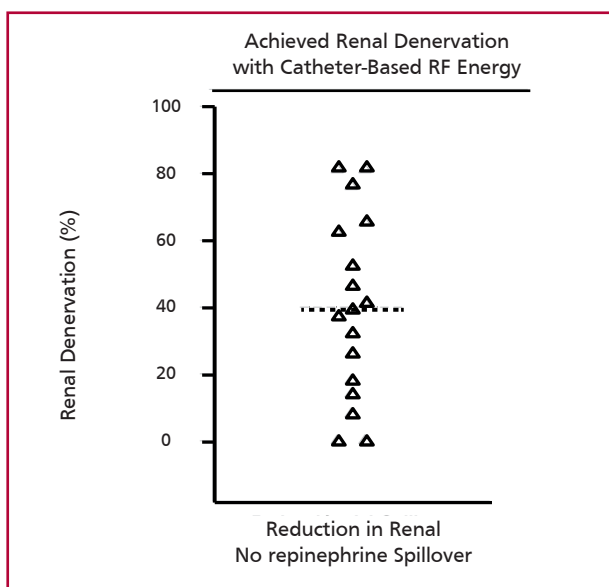
The new therapy of endovascular renal denervation has now been applied world-wide in approximately 10,000 patients with severe drug-resistant essential hypertension. In my own tertiary care hypertension clinical practice, many of my previously most challenging severely hypertensive patients now have normal blood pressure subsequent to renal denervation, although usually still also requiring multi-drug anti-hypertensive therapy.

**Renal denervation for resistant hypertension: "The end of the beginning"**

The first catheter-based renal denervation procedure for drug-resistant hypertension was performed on 6 June 2007. As I wrote in a review (19) just prior to the 9 January 2014 Medtronic press release for the US Pivotal renal denervation trial, more than six years later there remained many unanswered questions. To paraphrase the memorable wartime quote of Winston Churchill (November 1942), out of context, "this is, perhaps, the end of the beginning"? Then came Armageddon !

**RENAL DENERVATION "ARMAGEDDON"? THE SYMPPLICITY HTN-3 PIVOTAL US TRIAL**

A challenge to the percutaneous renal denervation



**Table 1.** The effectiveness of catheter-based radiofrequency renal nerve ablation assessed with renal norepinephrine spillover measurements made before, and 30 days after the procedure. The denervation was incomplete, sometimes markedly so, and with pronounced non-uniformity between individual patients. These results contradict the idea that achieving sympathetic denervation is technically "easy". The results suggest that blood pressure non-response to renal denervation must commonly be due to very imperfect denervation, and not only to the absence of sympathetic nervous activation, which is often invoked as the cause. From unpublished results of the author, Markus Schlaich, Gavin Lambert and Dagmara Hering.

treatment of resistant hypertension came with the 9 January 2014 press release concerning the Symplicity HTN-3 trial in drug-resistant hypertension, the pivotal study for US FDA licensure, and in the subsequent New England Journal of Medicine publication on 29 March (25), indicating that the primary efficacy endpoint had not been reached in the trial. This is a comprehensive, rigorously designed study, but there is an Achilles heel as with most clinical trials of renal denervation for hypertension, including this one. Whether renal denervation was actually achieved in individual patients was not evaluated in Symplicity HTN-3. For such an otherwise meticulously designed trial this is a noteworthy deficiency, especially as unlike in Australian and European renal denervation trials, the majority of participating interventionists, although experienced in other procedures, had never before performed a percutaneous renal denervation; their learning curve fell within the trial.

As has been documented (in the Symplicity HTN-1 study, with renal noradrenaline spillover measurements), the degree of renal denervation achieved with catheter-based renal sympathetic ablation (mean 47%, range 0-85%) is substantially less than with experimental surgical denervation (90-95%)(14,15). Circumferential RF energy deployment with a unipolar

catheter to achieve denervation is difficult and dependent on the skills of the operator. The Symplicity Flex catheter, a unipolar RF catheter, was exclusively used in the Symplicity HTN-3 study (25). It is inevitable that the usually less than complete denervation in the hands of experienced proceduralists evident in Symplicity HTN-1 (10) was materially compromised in Symplicity HTN-3 by operator inexperience and lack of training and skill (26).

In this context it is pertinent to ask whether current catheter designs and, in particular energy level administered are optimal. Should we be aiming for more complete renal denervation, given the high level of safety of the procedure? Are some sympathetic nerves in humans, perhaps, more distant from the lumen of the renal arteries than is generally believed (17,27), so that deeper penetration of ablating energy is needed? There is evidence that renal sympathetic nerves in humans are closer to the renal arteries in the more distal part of the arteries, nearer to the kidneys, where they should be preferentially targeted in nerve ablation procedures (17,27), an anatomical fact neglected in Symplicity HTN-3, where energy was inexplicably delivered primarily to the proximal renal artery (25,26).

It should be noted that the field of renal denervation for experimental hypertension is active, in fact energized by the clinical studies. Experimental surgical and catheter-based denervation for hypertension still works! This was recently well exemplified with catheter-based renal denervation abolishing hypertension in an obese dog model (28). Why should experimental renal denervation, in four mammalian species (rats, dogs, rabbits and pigs) invariably be antihypertensive (14,15), but not in the human mammal, in Symplicity HTN-3? For the Pivotal US study, a failure to achieve renal denervation comes first to mind (26).

#### **SCIENTIFIC POLITICAL CORRECTNESS IN EVALUATING THE US PIVOTAL RENAL DENERVATION STUDY: LAUDING OF THE SHAM PROCEDURE BUT NEGLECT OF TRIAL NEUROSCIENCE FAILINGS**

A lot was expected of the Symplicity HTN-3 study. Five times larger than the first two Symplicity renal denervation trials, and incorporating a blinded sham design, this trial was expected to provide the definitive statement on the value of renal denervation in the treatment of patients with severe hypertension. To many it did – “renal denervation does not work!” (29). The sham design was lauded; purist trial ideology was unrestrained (29). This trial exemplar had comprehensively exposed the fallacy of imagined renal denervation benefits!

Much of this hyperbole was reminiscent of “knowledge-free management” theory and practice, where the proscribed process (in this case the sham procedure) outranks and overrides the specific and essential knowledge base (in this case neuroscience knowledge of the renal nerves and their denervation). The power

of FDA branding in a pivotal trial added to the allure.

But much was amiss with Symplicity HTN-3. At eighty-eight too many centers were recruited for the trial, and at 111 too many proceduralists (25). No hands-on experience in renal denervation prior to the trial was permissible in US (unlike in the earlier Symplicity trials, where it was mandatory). Experts in their field of interventional cardiology, all participants were novices in the renal denervation procedure. Proctoring (on-site mentoring) was done primarily by company staffers, rather than experienced physicians or renal denervation engineers, in contrast to the earlier trials. Energy delivery was not preferentially to the distal renal artery, where it should have been, but inexplicably more to the proximal renal artery; the renal nerves are, in fact, closer to the distal artery (17,27). It is now a matter of record that the denervation procedure fared badly in Symplicity HTN-3 (30). Retrospective analysis of stored angiographic records of all RF energy applications demonstrated that in 74% of patients not even one fully circumferential renal artery application of energy was achieved, when it was a mandatory protocol requirement that this be achieved bilaterally, making effective nerve ablation impossible (30).

How could this happen? Presumably because renal denervation was thought and said to be procedurally easy, to the point of being “boring”, a commonly used descriptor. Physical aspects of the catheter procedure perhaps looked easy, but achieving denervation was not (Symplicity HTN-1).

#### **WAYS OF KNOWING IN MEDICINE**

I would wish the reader to be mindful of methods of decision-making in medical science and clinical medicine. In the past, medical knowledge derived from many sources. The historical starting point was often astute observation and description by doctors of the illness of their individual patients. This was elaborated on with autopsies (in the regrettable instances of medical failure), community-wide observations to detect patterns of the identified illness and its causes (epidemiology in its various forms), clinical investigation to better understand the biological mechanisms of disease (the “pathophysiology”), animal experimentation to confirm and extend these ideas, prevention and treatment strategies based on a logic deriving from all of the above, and observations in patients of the benefits, or lack of, when the logically-based treatments were applied. Some elements of this evidence path are strongly evident in the renal denervation saga.

Some emphases in “evidence-based medicine”, those which are too rigid and codified, have short-changed these ways of knowing, especially in relation to medical therapies. The final, and usually only, arbiter is the randomized double-blinded clinical trial, the other forms of medical knowledge not qualifying as real, or certainly not valuable evidence. My departing

point is that although in therapeutics well designed clinical trials are of critical relevance, there are many ways of “knowing” in medicine. A single well-designed clinical trial can be fallible, remembering that the Symplicity HTN-3 trial is a deeply flawed study (30), and should not stand alone as an absolute arbiter. The animal experimentation, the neural hypertension pathophysiology, and earlier clinical trials should not be discounted.

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