

REVIEW

Review of the evidence for renal sympathetic denervation

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Abstract: Resistant hypertension is characterized by persistently high blood pressure levels in spite of multiple anti-hypertensive medications, given at maximum doses, including a diuretic, after lack of adherence to treatment has been eliminated. Renal sympathetic denervation is a procedure consisting of destroying renal nerves with a radiofrequency catheter, being a possible therapeutic alternative to treat this condition. Current data are inconclusive to support this procedure to improve blood pressure control in patients with resistant hypertension as well as cardiac or renal patient condition. Future studies focusing hard-endpoints outcomes, with longer duration and higher population are needed, to identify whether individuals can benefit from renal sympathetic denervation.

Keywords: interventional treatment, resistant arterial hypertension, sympathetic nervous system, renal sympathetic denervation, radiofrequency denervation

Rezumat: Hipertensiunea rezistentă este caracterizată de valori persistent crescute ale tensiunii arteriale în ciuda tratamentului antihipertensiv administrat în doze maxime, incluzând un diuretic, și după excluderea lipsei de aderență la tratament. Denervarea renală este o procedură ce constă în intreruperea filetelor nervoase simpatice cu un cateter de radiofrecvență, fiind o alternativă terapeutică posibilă pentru a trata această afecțiune. Datele actuale sunt neconcludente pentru a susține această procedură pentru îmbunătățirea controlului presiunii arteriale la pacienții cu hipertensiune arterială rezistentă, precum și la starea pacientului cardiac sau renal. Sunt necesare studii viitoare care întărescă rezultatele, cu o durată mai lungă și pe o populație mai mare, pentru a identifica dacă indivizii pot beneficia de denervare simpatică renală.

Cuvinte cheie: tratament intervențional, hipertensiune arterială rezistentă, sistem nervos simpatic, denervare simpatică renală, denervare prin radiofrecvență

INTRODUCTION

Resistant arterial hypertension (RAH) is defined as persistent high values of systolic / diastolic pressure despite the concomitant use of at least 3 anti-hypertensive drugs (4 drugs according to other authors) at optimal doses, from different therapeutic classes, including a diuretic, after lack of adherence to treatment has been eliminated. RAH affects approximately 10 to 30% of hypertensive patients. Its prevalence is significantly higher (up to 50%), in conditions characterized by increased sympathetic activity, e.g. chronic kidney disease and obstructive sleep apnea¹. The high cardiovascular risk that arterial hypertension (HTN) entails and the significant impact it has on cardiovas-

cular mortality have been the reason for seeking alternative, non-pharmacological, strategies for the control of blood pressure values in patients unresponsive to conventional therapies for HTN.

This review concentrates on just one of the, now classic, three non-pharmacological strategies used in the approach of RAH – that is, renal sympathetic denervation (RDN), the other two being baroreflex activation therapy (BAT) and continuous positive airway pressure (CPAP) therapy. Each of these therapies acts at different levels of the pathophysiological pathways but have the same goal: reduction of sympathetic activity.

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RENAL SYMPATHETIC DENERVATION

The role that the sympathetic nervous system plays in the etiopathogenesis of HTN, both by its efferent and afferent renal fibers, has been convincingly demonstrated in preclinical and human trials. Afferent sympathetic activity has an important role in renin release, sodium retention and renal blood flow reduction that contribute to the rise and persistence of high blood pressure values^{3,4}. Surgical renal denervation has proven to be an efficient means of reducing renal sympathetic stimulation, increasing natriuresis and diuresis while, in the meantime, decreasing renin release without negatively impacting the glomerular filtration rate or renal blood flow. In a similar fashion, by removing the afferent nervous fibers there is a decrease in central sympathetic stimulation that modulates the general sympathetic status. Being a central modulator of sympathetic activity, renal denervation selectively diminishes sympathetic activity without interfering with the activity of other peripheral chemo- and mechano-receptors, including cardiac, pulmonary and baroreceptors. The classical surgical approach was rude and brutal, frequently-occurring complications being orthostatic hypotension, impotence and incontinence. A minimally invasive, percutaneous approach, to the renal sympathetic system has developed in recent years, yielding a success rate similar to that of the classical surgical approach meanwhile eliminating the complications and adverse reactions^{5,6,7}.

Radiofrequency catheter ablation is the most widely-used method of renal denervation⁸. There are also other techniques, some of which are innovative. Devices that use ultrasound, nanoparticles, radiation and controlled drug release have been developed. An overview of these devices is given below.

RADIOFREQUENCY DENERVATION

Medtronic Symplicity

The device created by Medtronic (Mountain View, Ca, USA) and branded Symplicity (initially Ardian) was the first developed and the most thoroughly researched of the kind. The procedure requires an arterial approach (6 Fr), femoral in most cases, a catheter that is placed at the ostium of the renal artery and a radiofrequency ablation device. The ablation device is placed in the distal renal artery where radiofrequency is applied to the vascular wall thus generating thermic energy that destroys the adventitial nerve structures on a small radius. The first-generation device allowed for contact with the vascular wall in only one point; the new mo-

del allows multiple contact points thus enhancing the efficiency of the method. The device is connected to a radiofrequency generator that gives off thermal energy in the wall of the artery through the contact points. With the first-generation the procedure was repeated up to 4-6 times in the same artery, with a duration of about 2 minutes per application followed by the same procedure in the contralateral artery. With the second-generation device thermal energy is applied only once for each renal artery. The devices developed by Medtronic remain the best-known, most widely utilized and researched (the Symplicity HTN-1, Symplicity HTN-2, Symplicity HTN-3 trials)^{9,10,11}.

St. Jude EnlighHTN

The device developed by St. Jude Medical (Little Canada, MN, USA) branded EnlighHTN uses an 8 Fr catheter and a radiofrequency generator. The distal tip of the device is bendable in order to minimize vascular trauma and contains four electrodes that apply thermal energy to the lumen of the renal artery. The special shape of the device offers a firmer endoluminal contact that gives an uniform distribution of energy that is reproducible in time. The time needed for ablation is 90 seconds per artery, with eight points of application for each artery. There are two catheter sizes currently available for renal arteries of all sizes. Trials that support the efficiency of this device are the EnlighHTN I and II^{12,13}.

Covidien OneShot

The device created by Covidien (Dublin, Republic of Ireland) and branded OneShot contains a modified balloon that has a spiral-shaped electrode on its surface through which radiofrequency is applied for two minutes and a saline-irrigation system that has proven to help expand the denervation area. RHAS and RAPID 1 are two trials that support this device¹⁴.

Boston Vessix Vascular V2

The device developed by Boston Scientific (Natick, MA, USA) branded Vessix Vascular V2 also contains a modified balloon with multiple electrodes on its surface (four or six). Once inflated, the balloon stops the blood flow in the renal artery which in turn diminishes energy loss due to blood flow and reduces exposure time to about 30 seconds. Two inflations are required for each renal artery. The REDUCE-HTN trials have proven the efficiency of this device^{15,16}.

None of these devices remain in the vessel. At the end of the procedure they are taken out.

ULTRASOUND DENERVATION

Apart from radiofrequency denervation there is also a method that uses ultrasound for endovascular denervation. High frequency sound waves pass through fluids and generate heat in the soft tissues and do not require direct contact. The energy is delivered by volumes to a specific target to restrict excessive heating of adjacent tissues and allowing for the ultrasound energy to be applied endovascularly from a distance, without direct contact with the vessel wall. Therefore, there is no risk for endo-intimal damage as the blood absorbs only a small part of the ultrasound energy and acting as an endo-vascular cooling agent¹⁷. Sounds Intervention (Stony Brook, NY, USA) has presented this method as safe and functional after bench-testing on porcine subjects. The Sound-ITV trial is the first one testing this device on human subjects¹⁸.

A new model of ultrasound device uses a method from outside the patient's body. A transducer that is placed on the exterior of the body generates ultrasound energy that is directed toward the renal artery, enveloping it and damaging the peri-vascular nerves. By generating an energy field that is concentrated on the exterior of the artery, this device may yield a more efficient ablation therapy totally noninvasive thus eliminating the risk of any vascular complication. Kona Medical (Bellevue, WA, USA) has presented the SurroundSound™ System. The company presents two models of this device: one that requires the placement of an electrode in the renal artery, its sole purpose being to guide the exterior transducer and a second one which is completely non-invasive. Data from the WAVE I trial support the efficiency and safety of this device¹⁹.

PHARMACOLOGICAL DENERVATION

In the 1950's guanetidine was introduced as an anti-hypertensive agent acting as a powerful systemic sympatholytic but with adverse effects matching its potency. Starting from this, ingenious methods of delivering these substances locally at the vascular wall have been developed thus eliminating the risks of systemic adverse effects and subsequently increasing the efficiency of sympathetic denervation. Mercator MedSystems (San Leandro, CA, USA) have presented the devices branded Cricket™ and Bullfrog® Micro-Infusion Catheters through which guanetidine is delivered at the vascular wall. Other innovative solutions have been presented by Ablative Solutions Inc. (Kalamazoo, MI, USA) that imply the delivery of ethanol through a mi-

cro-needle as a perivascular neurolytic agent; other proposed methods imply the delivery of neurotoxin-filled (Botox B) nanoparticles through magnetic guidance at the vascular wall; vincristine is another drug proposed as a pharmacological agent for sympathetic denervation²⁰⁻²³.

There are countless areas of research and new devices being developed. There is probably less momentum than in the 2010-2014 period after the publication of data from Symplicity HTN-3, which was prematurely stopped after the publication of preliminary data – as we will be discussing ahead – but the intention is to identify the particularities and characteristics of patients with truly resistant arterial hypertension, who would benefit the most from these innovative methods²⁴.

CASE SELECTION AND INITIAL RESULTS

The cases initially selected for renal denervation were those with RAH to medical treatment. The goal of these interventional procedures for selected patients was the assessment of efficacy and safety⁸. Considerable effort was put into ensure adequate patient selection and correct assessment of relevant adverse events. Patients with blood pressure values between 160 and 180 mmHg (despite the use of more than 3 anti-hypertensive drugs of which one was a diuretic) were included in these trials. Renal artery angiogram was performed to exclude atherosclerosis and other anatomical anomalies. Patients with significant chronic kidney disease were also excluded from the procedure. As the first such study that was published in the Lancet it showed a substantial and progressive fall of blood pressure beginning with the first month and continued in the 12 months of follow-up⁸. An extensive cohort of patients (n=153) was subjected to an 18-months follow-up period and data obtained up to that moment were encouraging as blood pressure levels were kept in the low range throughout the whole interval²⁵. Patient follow-up was complex. In addition to blood pressure values measured in the doctor's office, a careful ambulatory monitoring was carried on. This increased the efficiency of the method; a decrease in sympathetic activity was also noticed by well-defined dosing of circulatory epinephrine levels. In addition, a decrease of afferent sympathetic activity at muscular level showed a decrease in central sympathetic activity²⁶.

MONITORING AND SAFETY

Monitoring of possible periprocedural complications has been carefully carried out. The procedure itself is more or less painful as pain levels are subject to personal bias. The pain was described as being located in the lumbar area during applications with the radiofrequency catheter thus confirming the presence of type C afferent somatic fibers and the effects of the ablative procedure at this level. The patients were under mild sedation but conscious throughout the entire procedure. In the first trials that were carried out no cases of renal artery thrombosis or embolization were reported. Patients were carefully followed-up in the post-procedural period either by a repeat-angiography done after 1 to 2 weeks or evaluation through angio-CT or angio-MRI done at 6 months. Renal artery dissection induced by catheter manipulation was an extremely rare occurrence and was resolved by stent implantation without any long-term complications^{25,27,28}.

In contrast to the efferent sympathetic fibers which have the capacity to regenerate after surgical mechanical ligature, the afferent fibers have a very low or no regenerative capacity²⁹. By eliminating the sympathetic nervous impulses travelling from the kidney to the brain, the contribution to the central sympathetic tonus is diminished so that the anti-hypertensive effect of the procedure seems to be long-lasting. Long term blood pressure monitoring in patients who underwent this procedure supports this idea.

Renal function, estimated through serum creatinine and glomerular filtration rate (GFR) remained unchanged throughout the follow-up period. This was better than expected. By comparison with the GFR calculated at the time of the procedure, expectations were that a 12 ml/min per year drop would occur, but, only a 2 ml/min drop was noticed after one-year follow-up. Although blood pressure has protective effects by itself, further study is required into the protective effects of reduced efferent renal sympathetic activity³⁰.

Similarly, albumin urinary loss was also on a constant downward trend. Although it might be simply the effect of blood pressure drop undoubtedly it can also be attributed to the protection of the target organ (kidney) in these patients with RAH. It is also worth mentioning the fact that renal denervation was followed by a decrease of 50% in renin secretion and baroreflex cardiac sensibility was also significantly improved (from 7.8 to 11.7 ms/mmHg). Furthermore, MRI imaging revealed a substantial decrease in LV

mass from 184 to 169 g (from 78.8 to 73.1 g/m²) after 12 months of follow-up^{26,30}.

EVIDENCE-BASED AND WITHHOLDINGS

A critical assessment of current studies such as Sym-licity is needed before a definitive direction is dictated. The study HTN 1 with primary objective concerning the efficiency of the method was not randomized and had a limited number of subjects for 24 months of follow-up (n=105)^{25,27}. The study HTN- 2 tried to improve the methodology having a control group, however to improve the results a simulation of renal denervation was needed²⁸. Almost all the results of the studies regarding the denervation procedure focused on the measurement of arterial blood pressure in a private practice. However, there is a significant difference when measuring the blood pressure ambulatory. Ambulatory measurements are less inflected by the procedure. They represent an important form in the final assessment of blood pressure. The reasons in differences between measurements in an ambulatory service and an office are unclear. The study HTN-3 brought more data regarding the ambulatory measurements proving an important reduction of the blood pressure in the private practice in comparison to the expected value and the ambulatory value²⁴. Histological human studies on ablation of renal arteries were not performed. Current histological data are based on studies performed on animals (pigs) which did not show significant differences on interventional renal arteries; observations made 6 months post ablation³¹. However, the authors indicated that the histological studies showed a slightly altered media layer of the arteries, secondary to radio-frequency energy applied. The study HTN -2 reported a significant stenosis (>60%). Consequently, the number of patients with stenosis less than 60% is unknown²⁸. Moreover, there was a single reported case of a significant post-procedural stenosis of renal artery³², which took place approximately 6 months after radio frequency procedure.

The study HTN-1 demonstrated that 13% (n=6) of subjects enrolled had a reduction with less the 10 mmHg of the blood pressure at the private practice^{25,27}. The rate of non-responders proved to be higher (up to 39%) when using the ambulatory measurement of blood pressure in comparison to the measurement of blood pressure in a private practice^{33,34}. The reason behind the non-responders is unknown, but it may be

due to failure or inclusion of the patients with secondary cause of hypertension. Current devices do not permit a good evaluation of successful ablation during the procedure.

The study that changed the view regarding RAH and the procedure of renal denervation was Symplicity HTN-3²⁴, stopped before completion. The key message of Symplicity HTN-3 is simple and we should accept it as it is: the true advantage of the procedure of denervation on the systolic blood pressure is modest, <3 mmHg, with no evidence on significant impact on morbidity and mortality in the present. A few theories criticized the way the study was performed, or they addressed questions regarding the obtained results. The following theories are listed above.

- The reduction of the blood pressure assessed in a private practice was 3 times higher than the reduction of the ambulatory blood pressure, because the white robe effect was treated efficiently by renal denervation. This fact sounded interesting, however the white robe is not constant, and it is not treated definitively by renal denervation. It would be the first case of a biological complex phenomenon which would be mediated totally by one single pair of nerves in the organism.
- The theory that the study has low statistical strength because most of the studies with medication are frequently larger. This is not an adequate explanation, because the Symplicity study HTN-3 was much larger than other non-randomized, positive studies which were considered of value. The authors of the Symplicity HTN-3 study published the statistic strength of the study before the beginning of the study, in opposition to other positive studies considered important.
- The theory that the operators of the United States of America in Symplicity HTN-3 did not perform the procedure as well as the others from previous studies from other countries outside United States of America. The problem is that there is no evidence that the American interventionists are less skilled and none of the previous studies did not report the necessity of intensive training or a period of training well elaborated that would raise the effectiveness of the procedure ten times.
- The theory that the patients on placebo in Symplicity HTN-3 maybe increased their dosage of medication. The Symplicity HTN-3 was a blinded study so this fact could occur in both groups.

- The theory that the final measurements were assessed too early; though it were requested repeated measurements and long term follow up different than those planned before in the study. This is an inadequate explanation because in the non-randomized studies the evaluation is done at some point. Moreover, when Symplicity HTN-3 was completed, the demonstration of the primary objective became evident in both groups. What is the utility of a therapy if the therapy is efficient only when it is assessed in a study of this form?

The results of other three recent randomized and control clinical studies with a rigorous concept, Oslo RDN, Dener-HTN46 and PRAGA-1547 which included a small number of operators but very well trained are in concordance with the Symplicity HTN-3 and confirm the lack of superiority of denervation procedure in front of the medical treatment, downsizing the theory that the final results of Symplicity-HTN 3 were due to inclusion of high percentage of Afro-Americans or that the insufficient ablation of renal nerve. In same direction comes a fourth study randomized and controlled with placebo performed on mild RAH (systolic blood pressure during the day between 135 and 149 mmHg and/or diastolic blood pressure between 90 and 94 mmHg in patients in treatment with more than 3 classes of drugs, including a diuretic, Symplicity Flex 48 which failed to prove the advantage of procedure of renal denervation in comparison to medical treatment^{35,36}.

Is the failure of Symplicity HTN-3 meaning the end of the procedure of renal denervation? Not really. As previous mentioned, RDN is based on a solid background with more than 50 years of meticulous research on nervous sympathetic system and the implication on physiopathology of HTN³⁷⁻⁴¹. Moreover, in cohorts studies recruited from the 3rd decade to the 5th decade of the last century it was shown that abdominal sympathectomy associated to splanchnicectomy is efficient in severe arterial hypertension treatment. Most centers reported major improvements of RDN in a minority of patients. There is a practice in optimization and adapting the technique and technology to the category of patients who would benefit the most. We are not discussing a drug which could be easily administered to every patient. We discuss a procedure which is performed by trained physicians in this field. Another issue would be if all the hypertensive patients despite the phenotype respond to renal denervation in the same manner. There are few studies quit inte-

resting, under development, some of them with results in short time released, which outline one of the unsolved matter⁴²⁻⁴⁴.

PRESENT & FUTURE FOR RDN AND RAH

Thus, the research should continue to discover the minority of patients that are true responders to RDN and the predictive factors of RDN efficiency. A network called ENCOReD⁴¹ was developed to include hundreds of patients in randomized protocols, observational studies and independent registers. Some early results⁴³⁻⁴⁶ were already published. They suggested that it would be of use the search of potential predictors to RDN response.

Following the failure of the trial Symplicity HTN-3, results of an interim analysis of an ongoing trials are available starting with August 2017, trials that provide "proof of principle" that renal denervation works. Spyral-HTN-OFF-Med⁴⁷ is testing the effect of RDN in hypertensive patients after withdrawal of antihypertensive therapy. It is one of two ongoing initial trials with the device. The second trial, Spyral-HTN-ON-Med 48, has a similar design but it is testing the device in patients treated with antihypertensive drug therapy. In both trials patients will be followed for three years, but they will be unblinded after a year.

SPYRAL HTN-OFF MED is a multicenter, single-blind, randomized trial with a sham-control designed as a proof-of-concept of RDN. Participants were non-medicated in order to remove the confounding basis of medication adherence. Absence of antihypertensive medication was evaluated by plasma and urine testing at baseline and 3 months with an overall compliance rate of over 85%. A new four-electrode ablation system was used by experienced operators leading to a four-fold increase in the average number of ablations compared with SYMPPLICITY HTN-3 (both the main arteries and smaller branches were ablated). They found that both systolic and diastolic ambulatory BP measurements (mmHg) were significantly reduced at baseline and 3 months in the RDN group (-5.5; $p=0.0031$ and - 4.8; $p<0.0001$) but not in the sham procedure arm (-0.5; $p=0.7644$ and -0.4; $p=0.6448$). The study has a small sample size and was not prospectively powered for statistical significance.

The extent of ablation in this trial was reported to be higher than previous studies²⁴. This suggests that perhaps we still do not have the optimum technique to ensure complete renal denervation. Another important observation is that despite RDN, the majority

of patients in this trial remained above recommended BP levels. Whether it can play a role in those with „resistant hypertension“ may be answered by the currently recruiting SPYRAL HTN-ON MED trial⁴⁸.

Global modest benefits and high costs of RDN should be equilibrated with potential risks of them. More than 20 cases of new stenosis of renal artery were reported after RDN, most of them after the announcement that Symplicity HTN-3 did not accomplish the primary objective. RDN deserves supplementary evaluations; RDN is not ready at this moment for extensive clinical practice, its utilization should be limited to research protocols⁴⁹. In Germany the assurance companies were the first in Europe to refund the money for this procedure, however now they announced that they suspend the refund. Even the most ardent supporters of RDN technique admit that it should be reconsidered and, why not, returned to academic field before new clinical utility⁵⁰.

In a big percentage of the patients, RAH could reflect their reluctance in taking medication, and not the resistance to medication⁵¹. In this perspective, monitoring the medication therapy could prove to be an effective strategy not only for detection the low adherence to therapy but also to boost blood pressure control. When non-adherent patients are discovered with low plasmatic or undetected levels of medication and offered additional counseling to surmount the adherence barriers, the control of blood pressure improved considerably without intensifying the therapy⁵². A recent analysis exposed the adherence monitoring to treatment is a cost-efficient attitude for public health which can be applied to the patients with resistant hypertension. This ascertainment is valid for a wide range of patients, despite their age and gender⁵³. Even the patients with true resistance to therapy hypertension who prove the adherence to medication, the control of blood pressure could be fulfilled in a substantial part by agile adjustment of medication therapy^{42,44}. While RDN deserves further research, in this current state of knowledge, the initiative for the adherence diagnosis and improvement could be more profitable, individually but also for the public health⁵⁴.

Before any form of non-medication intervention for hypertension, certain aspects should be clarified, which could resolve multiple situations, otherwise very difficult to elucidate.

- RAH definition should be corrected done.
- All secondary causes of HTN should be removed, including different medications intake or alcohol, which maintain high levels of blood pressure.

- Should be solved the problem of medication adherence or inadequate dosage of medication for HTN control.
- A correct definition of the blood pressure monitoring in doctor's office, ambulatory or at home should be done.
- If there are no contraindications, aldosterone antagonist diuretic therapy should not miss from the therapeutic scheme of the patients with RAH. Spironolactone proved accurate efficiency for these patients in the studies Pathway-2 and above-mentioned Symplicity HTN- 3⁵⁵.

Once clarified those aspects, invasive procedure previously described and others like positive end expiratory pressure ventilation could be taken into consideration in very selected cases^{56,57}. Two major trials were simultaneously published in Lancet this year followed by oral communication at Euro PCR Congress held in Paris in May 2018, where renal denervation was one of the hot topics: RADIANCE-HTN SOLO and SPYRAL HTN-ON MED

Compared with a sham procedure, endovascular ultrasound renal denervation in RADIANCE-HTN SOLO trial reduced ambulatory blood pressure at 2 months in patients with combined systolic–diastolic hypertension in the absence of medications

The 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial gave us the conclusions that renal denervation in the main renal arteries and branches reduced significantly the blood pressure compared with sham control, with no major safety events. Incomplete medication adherence is common. Blood pressure reductions following renal denervation were present throughout the day and night; Authors conclude that there is an “always on” effect; No major safety events despite a more complete denervation procedure that extended into renal artery branch vessels were noticed^{58,59}.

With this new context, our final conclusion for such procedure is: exciting times for renal denervation, with much more to come!

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