THE MULTIDISCIPLINARY APPROACH TO RENAL DENERVATION: CURRENT EVIDENCES AND OPEN QUESTIONS

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ABSTRACT

Renal denervation (RD) is a new clinical procedure which aims to treat resistant hypertensive patients. As with every new technology introduced into the clinical setting, many aspects were not explored sufficiently in order to be implemented into routine clinical practice. Advances in clinical technology require different steps of development, which start from preliminary *in vitro* experiments and finally arrive in the market, available for physicians when they have been proven to produce benefits for patients. Each stage usually takes many years before acquiring consensus from specialists involved in specific fields. In our opinion, this is a long and blind way and is a disadvantage to patients who need rapid, specific, and effective treatments. Otherwise, a multidisciplinary approach can provide the right evaluation of RD position and its potential for clinical application and research development. Therefore, we decided to draw a well-structured literature review from different specialists' points of view in order to cover the subject in a translational manner. We reported animal models and experimental trials, in chronological order, and their evidences which have created the basis for human research. Technologies and devices were compared to underlined advantages and disadvantages. An update of clinical data was considered to define clinical needs in order to build focused trials. Furthermore, we evaluate the feasibility of routine RD clinical use by means of an economic analysis. Finally, we tried to settle the main unresolved questions and then assessed future RD perspectives, including non-hypertension indications.

Keywords: Resistant hypertension, sympathetic hyperactivity, catheter, radiofrequency, heart failure, incremental cost effectiveness ratio.

INTRODUCTION

Renal denervation (RD) is a newcomer in the field of antihypertensive therapies. Since its arrival a lot of trials and reviews have been published, dividing the scientific community between those for and those against this procedure. In the last few months, several published reviews have focused on epidemiology of resistant hypertension and clinical aspects of RD. Arterial hypertension is a diffuse and complex disease which involves severe complications in different organs and apparatuses, so as a result hypertensive patients are referred to general practitioners as well as to different specialists (cardiologists, nephrologists, internists). In this setting, RD could be defined as a 'translational procedure' which involves different medical specialists but also different professionals, such as engineers and biologists. Nowadays, hypertension treatment has a heavy economic impact on the healthcare system compared to the past, due to technological improvements.

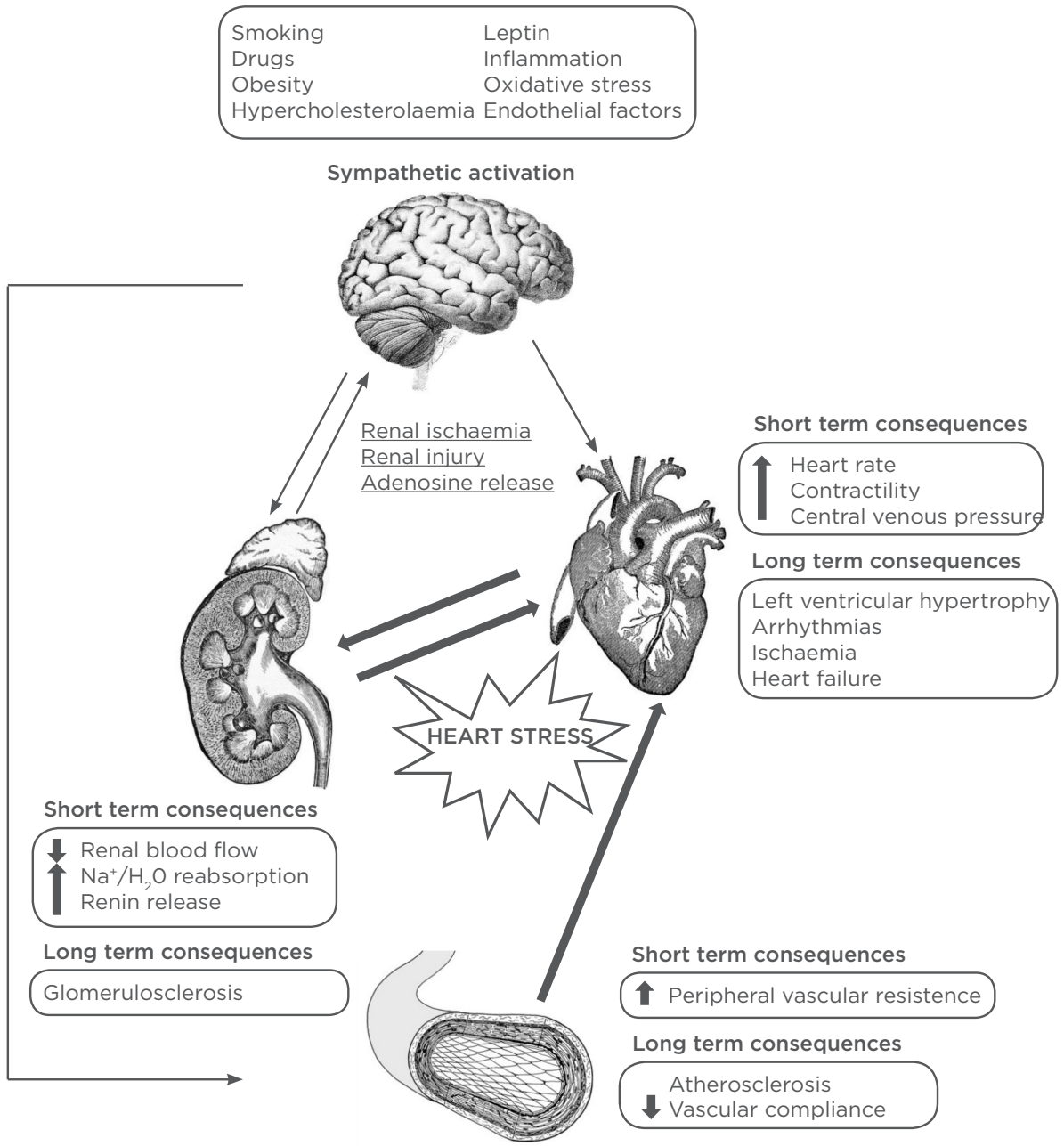

Figure 1: Short and long-term consequences associated with sympathetic activation.

The long-term control of BP has been attributed to the kidney by the mechanisms of pressure natriuresis and diuresis, in which it couples the regulation of blood volume to the maintenance of sodium and water balance. The activation of renal afferent fibres by decreased renal blood flow and by variation of ultrafiltrate composition increases the sympathetic tone. An increased sympathetic tone to the heart increases contractility, heart rate, and central venous pressure; to the peripheral vessels it increases vascular resistance; and to the kidneys it either decreases renal blood flow (effect mediated by α-adrenergic receptors), increases renin release out of the granular cells in the walls of afferent arterioles (effect mediated by β-adrenergic receptors), or increases proximal tubular sodium reabsorption (by means of Na-H antiporters and Na-K pumps). Angiotensin II increases peripheral vascular resistance and, to the kidneys, it increases proximal tubular sodium reabsorption, GFR, prostaglandin, and aldosterone release. Aldosterone increases distal tubular sodium reabsorption (by means of epithelial sodium channel). An increased sympathetic tone is also involved in several pathological conditions such as left ventricular hypertrophy, cardiac arrhythmias, and heart failure, as well as in obstructive sleep apnoea syndrome, hyperinsulinaemia, and chronic kidney disease (thin arrows). In hypertensive patients the increased sympathetic tone, which has been displayed to the kidney and other organs, leads to increased peripheral vascular resistance and hydrosaline retention, which both definitively cause heart stress (thick arrows).

Therefore, it is fundamental to assess the economic sustainability of these new, relatively expensive, procedures through economic analysis. Literature partially covers these issues, so the aim of this paper is to provide a multifaceted review about interdisciplinary techniques for the treatment of a systemic disease.

RD

Kidney and Sympathetic Hyperactivity: the Background for RD

The role of the sympathetic nervous system (SNS) and the involvement of kidneys in the development of sympathetic hyperactivity supporting hypertension has been known since the 1930s, leading to the early practice of surgical sympathectomy.[1,2] Related complications guided the development of a chemical sympathectomy, later displaced by the introduction of new antihypertensive drugs. Progressively, the therapeutic RD has been explored by preclinical experiments that included multiple animal species and different primary diseases.[3] These studies contributed to revealing the role of renal sympathetic efferent and sensory afferent nerves to renal and systemic organ function in normal and pathological conditions (hypertension,[4] heart failure [HF],[5-8] or chronic kidney disease [CKD]),[9] as well as to investigate the potential therapeutic implications of RD.[10] Marked effects of RD on blood pressure (BP) were demonstrated in multiple animal models of hypertension, including salt-sensitive swines[11] and genetically hypertensive rats:[12] two-kidney one-clip Goldblatt hypertension[13] and one-kidney renal hypertension.[14]

In healthy humans, there is a fine physiological balance aimed at maintaining homeostasis between parasympathetic and sympathetic activity.[15] In a pathological condition, the increased sympathetic tone increases sodium reabsorption, acting directly on renal tubules proportionally to the density of the innervation. The association of hydrosaline retention with high peripheral vascular resistance definitively causes hypertension and heart stress (Figure 1). As a proof of this, an increase of renal sympathetic nerve activity (RSNA) is found both in animal models of hypertension and in hypertensive humans.[16] The sympathetic overactivity is the hallmark of CKD and renal failure. Campese[17] found that afferent impulses from the kidney to central integrative structures in the brain are supposed to be responsible for the rise in BP in CKD, in 5/6 nephrectomised rats. This discovery might justify the uncommon practice of bilateral nephrectomy in patients with end-stage renal disease and uncontrollable hypertension. The ligation of renal nerves has been shown to improve the responsiveness to atrial natriuretic peptide in rats with cirrhosis and HF,[5] and to reduce the ventricular filling pressure, improving ventricular function in dogs with high-output HF compared with nondenervated controls.[7]

Resistant Hypertension

The BP reduction through pharmacological intervention is one of the most powerful and successful ways to reduce complications and improve outcomes.[18,19] Although several appropriate and integrated pharmacological strategies are available, BP control still remains largely unsatisfactory;[20] indeed >40% of patients with hypertension are not controlled.[21] In 2007, the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines discriminated among the hypertensive population and those patients with other comorbidities (e.g. diabetes, nephropathies). In December 2013, the ESH/ESC guidelines were revised. Resistant hypertension is now defined as a condition where: "Therapeutic strategy includes appropriate lifestyle measures plus a diuretic, and two other antihypertensive drugs belonging to different classes at adequate doses fail to lower systolic BP and diastolic BP values to <140 and 90 mmHg, respectively."[22] The ESH/ESC guidelines do not discern patients on the basis of BP values: the definition of resistant hypertension includes indistinctly both patients with extreme BP levels and patients with BP levels just above the threshold. For this reason, it is difficult to identify those patients affected by resistant hypertension who may benefit from RD procedure. Furthermore, trials published to date have not adequately divided the hypertensive population into groups defined by BP levels. In the clinical practice, resistant hypertension has to be distinguished from arterial secondary hypertension due to treatable diseases (renal artery stenosis, pheochromocytoma, aldosterone-secreting adrenal adenoma) and pseudo-resistant hypertension caused by inaccurate measurement technique. Furthermore, it is necessary to differentiate between resistant and uncontrolled hypertension related to drug interactions, inadequate therapy,

and/or poor compliance. In this setting the prevalence of resistant hypertension is not well established. However, literature data suggest a widespread value from 5-30% of the overall hypertensive population, indicating that resistant hypertension is relatively common.[23-27]

Technical Aspects of RD

In the case where the patient presents with resistant hypertension, if the anatomy of the renal artery appears suitable for the procedure (artery length >20 mm; artery diameter >4 mm), RD might

Table 1: Specifications for renal denervation on-the-market devices.

	Symplicity™ Renal Denervation System	St. Jude Medical's EnligHTN™ System	Vessix's V2™ Renal Denervation System	Covidien's OneShot™ System	Terumo's Iberis™ System	Recor's Paradise™ System
						
Power source	RF	RF	RF	RF	RF	US
Catheter size	6F	8F	8F	7-8F	4F	6F
Catheter length	90 cm	115 cm	90 cm	74 cm	155 cm	100 cm
Type of power source	Single tip electrode	4 electrodes at a nitinol basket-like	Array of bipolar electrodes	Balloon with continuous spiral electrode	Single tip electrode	One US transducer inside an inflatable low-pressure over-the-wire balloon
Max temperature	75 °C	75 °C	68 °C	60 °C	70 °C	68 °C
Max power	5-8 Watt	6 Watt	1 Watt	25 Watt	8 Watt	12 Watt
Time	2 min/ ablation	90 sec/ ablation	30 sec/ ablation	2 min/ ablation	2 min/ ablation	30 sec/ ablation
Number of recommended ablations	4 APA	8 APA	½ APA	1 APA	4-6 APA	2 APA
Access	Femoral	Femoral	Femoral	Femoral	Radial	Femoral
CE mark	February, 2008	December, 2011	February, 2012	April, 2012	April, 2013	2012
Studies	Symplicity HTN1 Symplicity HTN1 Registry Symplicity HTN2 Symplicity HTN3	EnligHTN I EnligHTN II EnligHTN III EnligHT-Nment	Reduce HTN	RHAS RAPID	IBERIS-HTN	REDUCE REALISE ACHIEVE

RF: radio frequency; APA: ablation(s) per artery; US: ultrasound.

represent a novel solution. Catheter-based RD is a minimally invasive procedure, involving the delivery of radiofrequency (RF) energy along 1-2 cm in the main renal arteries, to ablate the renal nerves located in the adventitia. The procedure is generally performed exploiting a standard femoral vascular access. A contrast angiography can be performed to localise and evaluate the accessibility of the renal arteries. The catheter is advanced near the bifurcation of the renal artery under fluoroscopic guidance, and the electrodes at the distal tip are brought into contact with the endothelium. When the impedance is stable, a RF-wave generator locally provides a signal of controlled energy. The applied frequencies range between 1 MHz and 10 GHz. When the produced current reaches the electrodes, heat is locally generated because biological tissues act like resistors, enhancing the temperature to around 65-70 °C and causing thermal ablation of the renal nerves. Since the relationship between the RF generator output and the tip temperature depends on parameters that widely vary, then impedance, temperature, power, and time intervals are continuously monitored. In the case in which one of these quantities differs from the desired/predicted values, the treatment is automatically stopped by the embedded/control algorithm.

At present, RF ablation is the main technology applied for RD; on the other hand, the first promising results of RD have led to the development of other techniques. Devices exploiting ultrasound (US) waves seem to be a promising alternative; sound waves with a frequency higher than 1 MHz, passing through fluids, generate frictional heating in soft tissues, without direct contact with the intimate endothelium, causing thermal ablation. A very interesting implementation of this technique seems to be the use of externally focused US and low intensity US (frequency=800 kHz and irradiance=2 mW/cm^2),[28] with the potential benefit of a reduced invasive clinical procedure. Moreover, other technologies are under development: cryoablation (at present with reports in animal models only), β-radiations (experimental studies in swine only), and injection of neurotoxins (guanethidine,[29] ethanol,[29] Botox B or vincristine[30]). On-the-market devices and some of their major characteristics are summarised in Table 1.

Current Evidences from Clinical Trials

Since the first proof-to-concept trial performed with the Symplicity RF catheter,[31] several trials performed with different devices have been designed in order to evaluate the efficacy and safety of RD, as summarised in Table 2. Symplicity HTN-1 investigators have recently published the positive results of a 36-month follow-up.[32] While the 6-month follow-up Symplicity HTN-3 data have confirmed a BP reduction from baseline, investigators have found no significant differences between treated and control groups.[33] Symplicity HTN-3 trial remains the only single-blinded randomised controlled trial (RCT), with a sham-control group, designed to evaluate the safety and effectiveness of RD. The study design might explain the different results obtained in the previous clinical trials. Indeed, the presence of a sham procedure can delete the placebo effect, but it does not remove bias due to the Hawthorne effect. Even if Symplicity HTN-3 does not achieve the efficacy primary outcome, it will be followed up for 5 years in order to evaluate potential long-term RD benefits.[33]

At the same time, the perspectives of RD in the treatment of some other diseases associated with sympathetic hyperactivity are still under investigation. The first small clinical trials suggest promising effects of RD in improving glucose metabolism and insulin sensitivity,[34] decreasing sleep apnoea severity,[35] and reducing left ventricular mass,[36] thus, providing protection in patients at high cardiovascular risk. At present, two studies - DIASTOLE[37] and Symplicity HF trial - are ongoing to assess the effectiveness and safety of RD in the treatment of normal and impaired left ventricular ejection fraction HF, respectively. Presently, according to evaluated RCTs, RD does not significantly affect renal functioning as measured by estimated glomerular filtration rate or Cystatin C.[38,39] Moreover, RD needs future RCTs to evaluate renal function for a longer period of follow-up as well as its effectiveness and safety in moderate-to-severe CKD.

Economic Analysis

An economic analysis, through comparisons among technology costs and all relevant long-term benefits, allows us to understand whether RD might replace the current standard of care (SoC).[40] Geisler et al.[41] have made an economic evaluation of RD, which shows that it can be cost-effective when compared to well-accepted medical treatments. Exploiting a Markov state-transition model, they simulated the RD treatment on a cohort of patients to assess its cost-effectiveness and long-term clinical benefits (cardiovascular

Table 2: RD clinical trials in resistant hypertension.

Clinical trial	Trial status	Study design	N° pts	Follow-up	Results
Symplicity HTN1[31]	Concluded	Multicentre proof-on-concept	45	12 months	Office BP reduction (-27/-17 mmHg)* acute procedural and long-term safety (2 adverse events)
Symplicity HTN1 Registry[32]	Active	Multicentre prospective	153		36-month follow-up: office BP reduction (-32/-14 mmHg)**, acute procedural, and long-term safety (8 adverse events)
Symplicity HTN2[46]	Concluded	Multicentre randomised	106	6 months	Office BP reduction in RD group (-32/-12 mmHg, p<0.0001) compared with control group (+7/+1 mmHg)
Symplicity HTN2 with cross-over group[39]	Concluded	Multicentre randomised	106	12 months	Office BP reduction in initial RD group (-28/-10 mmHg, p=0.16) and in cross-over group (-24/-8 mmHg, p<0.001)
Symplicity HTN3[47]	Active, not recruiting	Multicentre single-blinded RCT	535	5 years	6-month follow-up: not significantly office BP reduction, safety through 6 months
EnligHTN I[48]	Active, not recruiting	Multicentre prospective	46	24 months	18-months follow-up: office BP reduction (-24/-10 mmHg, p<0.0001), acute procedural safety, and long-term safety (4 adverse events)
EnligHTN II	Recruiting	Multicentre prospective	500	5 years	N.A.
EnligHTN III	Active, not recruiting	Multicentre prospective	50	24 months	N.A.
EnligHTNment	Recruiting	Multicentre RCT	4,000	5 years	N.A.
Reduce HTN	Active, not recruiting	Multicentre prospective	146	12 months	Office BP reduction (-28/-11 mmHg)*** acute procedural and long-term safety (adverse events in 5.5% of patients)
RHAS[49]	Concluded	First-in-man prospective	8	6 months	Office SBP reduction (30.6±22.0)**** acute procedural and long-term safety (minor adverse events)
RAPID	Recruiting	Multicentre prospective	50	6 months	N.A.
REDUCE	Active, not recruiting	First-in-Man prospective	15	6 months	60-days follow-up: office SBP reduction (31 mmHg)
REALISE	Recruiting	Prospective	20	12 months	N.A.
ACHIEVE	Recruiting	Multicentre prospective	50	24 months	N.A.

RD: renal denervation; BP: blood pressure; SBP: systolic blood pressure.
*At all time points after procedure (1, 3, 6, 9, and 12 months), both systolic and diastolic BP were significantly (p<0.01) lower than baseline BP, with the exception of the 12-month diastolic BP (p=0.02).
**At all time points after procedure (1, 6, 12, 24, and 36 months), both systolic and diastolic BP were significantly (p<0.01) lower than baseline BP. 88 patients had complete data at 36 months.
***At all time points after procedure (1, 3, 6, and 12 months), both systolic and diastolic BP were significantly (p<0.0001) lower than baseline BP. 41 patients had complete data at 12 months.
****At all time points after procedure (1, 3, 6, and 12 months) SBP was significantly lower than baseline.

consequences in hypertension) with respect to SoC. They exploited the systolic blood pressure (SBP) reduction values observed in the Symplicity HTN-2 trial, and estimated the state transition probabilities to the clinical endpoints considered in the model (cardiovascular consequences and mortality) from previous cohort studies.

Assuming a discount rate of 3% per year, they found that the discounted incremental direct medical cost divided by the incremental years of life adjusted for a life quality coefficient (Incremental Cost Effectiveness Ratio [ICER]) is $3,071 per quality-adjusted life-year (QALY). Results are robust even taking into account variations in the model structure; indeed, even in the hypothesis of no persistence of BP reduction, the ICER increases only to $13,300. The 95% ICER confidence interval obtained with a probabilistic analysis ranges from a negative cost (i.e. cost-saving) to $31,460, with a 99.6% probability of being below the commonly accepted threshold of $50,000 per QALY (21% cost-saving).[41] The lack of available data limits the possibility to deepen the analysis. However, even though at the present time there is no conclusive evidence in the scientific literature, further benefits resulting from this therapy could be taken into account in the model, increasing the possibility of offsetting the additional costs borne at the time of treatment.

OPEN QUESTIONS

The results obtained with RD should be balanced against some potentially harmful or still undefined effects of the procedure. A recent study using optical coherence tomography (OCT) analysed 32 renal arteries, before and after RD, using Symplicity or EnligHTN catheters. It showed the occurrence of diffuse renal artery vasospasm and local tissue damage at the ablation site with oedema and thrombus formation, suggesting the beneficial use of dual antiplatelet therapy during RD.[42] These vascular injuries have not been reported after RD using the OneShot system, probably because of the vessel wall's saline irrigation during ablation. Otherwise the possibility of endothelial disruption underlines the importance of catheter measure and operator skills.[43] The development of new devices and technologies might avoid these complications in the future.

Regarding the efficacy of RD, the risk of not reaching the target fibres by RF energy is a technical problem that presently cannot be carried out by non-invasive examinations. Experience in kidney transplantation has shown that sympathetic efferent fibres can regrow after being injured. Nevertheless, it is supposed that clinical consequences of RD are mainly related to afferent fibres' destruction.[44] The possibility of regrowing fibres and the clinical consequences of the damage-repair processes are unknown at present.

Regarding the feasibility of RD, the presence of double and triple or multiple renal arteries, respectively, in 20% and 4% of the population, represents a procedure limit.[45] Finally, the lack of specific inclusion criteria based on BP levels in the prescription of RD, as mentioned above, may represent a gap in clinical practice as well as in the analysis of the results of previous trials. In conclusion, safety and effectiveness combined with long-term effects of RD procedure remain the main objectives on the research agenda. The lack of criteria for RD suggests the need to focus on creating the consensus statement through the translational work-group.

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