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Renal denervation reloaded: where to go from here?

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Almost half a century after the first placebo-controlled trials showed that reducing blood pressure (BP) was associated with a reduced risk for major cardiovascular complications, and despite the availability of effective and safe antihypertensive drugs, a substantial proportion of hypertensive subjects remain inadequately controlled[1]. New strategies which promise to help reduce BP in uncontrolled patients are urgently needed. Catheter-based renal denervation has been developed to target renal sympathetic nerves surrounding the renal arteries using radiofrequency energy or ultrasound, thereby reducing sympathetic efferent signalling to the kidneys and other organ systems, including the heart[2-4]. The underlying pathophysiological concept is sound. Evidence suggests that hypertension and its comorbidities, such as left ventricular hypertrophy and diastolic dysfunction, atrial fibrillation, chronic kidney disease, and metabolic syndrome, are initiated and sustained by sympathetic nervous system overactivity[5,6]. Further, historical observations have shown that surgical sympathectomy can lead to significant reductions in BP and cardiovascular morbidity and mortality[7]. In line with this, several first-in-man and open-label registries[8-11] and one randomised trial[12] have suggested that catheter-based renal denervation is able to reduce office and ambulatory BP significantly in patients with resistant hypertension. However, with the publication of the first sham-controlled SYMPLICITY HTN-3 study[13] in March 2014 doubts arose concerning the effectiveness of the procedure, as the trial met the primary safety endpoint but failed to meet the primary efficacy endpoint. The findings challenged the medical community and, soon after the publication of the results, potential factors contributing to the disparate results began to be discussed[14-16]. In the meantime, our knowledge about the procedure of catheter-based renal denervation, in preclinical[17-20] and clinical investigations[21,22], has evolved significantly.

What we have recently learned

SYMPLICITY HTN-3: PREDICTORS OF BLOOD PRESSURE RESPONSE

Kandzari et al[21] recently shared some interesting insights and hypotheses. They critically examined the results of the SYMPLICITY HTN-3 trial in the context of existing renal denervation data and clinical trial design and found that:

1. Although stable antihypertensive medication was required, 22% of all patients had medication changes two to six weeks prior to screening. Between baseline and the six-month endpoint assessment, medication changes were documented in another 39%.
2. Baseline office systolic blood pressure ≥180 mmHg, aldosterone antagonist use, and non-use of vasodilators were predictors of office systolic blood pressure change at six-month follow-up in patients undergoing renal denervation.
3. The average number of radiofrequency ablation attempts was 11.2±2.8, of which only 9.2±2.0 (84%) were complete ablations of 120 s duration, which is considerably lower compared with previous studies.
4. Only 6% of all patients received two four-quadrant ablations (both sides), 20% received one four-quadrant ablation (either right or left), and 74% received no four-quadrant ablation.
5. The number of ablation attempts and energy delivery in all four quadrants (anterior, inferior, posterior, and anterior) were associated with greater reductions in office and ambulatory blood pressure change.
6. Non-African Americans receiving renal denervation had a significantly greater change in office blood pressure compared with those receiving sham.

PRAGUE-15

The prospective, randomised, open-label multicentre PRAGUE-15 trial by Rosa et al[22] investigated the efficacy and safety of catheter-based renal denervation (using Medtronic's Symplicity device; Medtronic, Minneapolis, MN, USA) versus intensified pharmacological treatment including spironolactone in patients with mild to moderate resistant hypertension (office BP at baseline >140 mmHg, 24-hour BP at baseline >130 mmHg). Patient's adherence was confirmed by plasma toxicological analyses at the beginning (but unfortunately not after six months) and secondary causes of hypertension were systematically excluded. The study provided interesting insights[23]:

1. Renal denervation and intensified drug treatment significantly lowered 24-hour and office blood pressure at six-month follow-up, which was comparable between the groups.
2. Patients in the intensified drug treatment group received significantly more drugs after six months.
3. Aside from BP changes, after RDN patients experienced a significant reduction in heart rate with no significant between-group differences.
4. Overall, 39% in the pharmacological group experienced adverse events, such as hyperkalaemia (11%), anti-androgen effects (13%), and one patient with persistent worsening of renal function, compared with 23% in the renal denervation group, experiencing events such as spasm/oedema after application of radiofrequency

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energy (8%), post-puncture pseudoaneurysms (4%), and one dissection of the renal artery requiring stent implantation.

5. In the pharmacological group, serum creatinine increased and in parallel creatinine clearance decreased significantly. Between-group differences were borderline significant in favouring renal denervation.
6. In seven patients (14%) undergoing renal denervation the recommended number of complete radiofrequency ablations (at least four per side) was not achieved, of which two had only unilateral ablations. Patients with ≥4 ablations per side appeared to experience more pronounced BP changes compared to patients with <4 ablations per side (office systolic: –4.7 vs. –14.0 mmHg, office diastolic: –0.9 vs. –9.2 mmHg, 24-hour systolic: –5.0 vs. –9.2 mmHg, heart rate: +1.2 vs. –4.4 bpm).

REDUCE-HTN AND RAPID

In this issue of EuroIntervention several interesting papers dealing with renal denervation are published. The open-label, single-arm, first-in-man and post-marketing REDUCE-HTN[24] study evaluated

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the safety and efficacy of renal denervation using a bipolar, occlusive balloon-based catheter in 146 patients with resistant hypertension. Significant reductions in office and ambulatory blood pressure were documented at six-month follow-up, comparable to previously published studies, and office blood pressure changes were much more pronounced compared with ambulatory blood pressure changes. Treatment was delivered safely in the majority of patients (overall 6% of patients had serious procedure-related adverse events); however, duplex ultrasound and consecutive CT imaging revealed development/progression of pre-existing renal artery stenosis in four of 123 patients. The investigators also tried to identify predictors of response to renal denervation. Unfortunately, neither procedure-related parameters nor specific baseline characteristics, besides height of baseline blood pressure, which might be at least in part explained by the statistical phenomenon of "regression to the mean", were associated with greater odds of a six-month reduction in ambulatory blood pressure. The identification of reliable predictors of response to treatment remains one of the most important targets for future studies[25]. Boston Scientific is currently conducting a randomised, sham-controlled trial in the USA to investigate renal denervation in hypertensive patients.

The RAPID trial[26] was a prospective, multicentre, single-arm study, which enrolled 50 patients with resistant hypertension at 11 clinical

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sites in Europe and New Zealand. Renal denervation was performed using an irrigated RF balloon catheter delivering energy in a circumferential manner to achieve denervation of renal arteries using a single two-minute ablation to each renal artery. After the procedure, significant reductions in office and ambulatory blood pressure were noted, again in line with previously published studies. In total, five serious adverse events were reported, including one renal artery stenosis. Although the device used in the trial is no longer commercially available, these data are consistent with other studies, suggesting that effective ablation of renal sympathetic nerves lowers office and ambulatory blood pressure in patients with uncontrolled hypertension.

Where to go from here?

Current available evidence strongly suggests that renal denervation lowers blood pressure in hypertensive patients; however, the hitherto published clinical trials are susceptible to potential placebo response, the Hawthorne effect, regression to the mean, unknown co-interventions and other bias. With this controversy in mind, a multidisciplinary European expert group was convened on December 9th, 2014, to assess the current gaps in our knowledge about renal denervation, unmet needs and where clinical trials may be best focused in the future. Specific procedural aspects, the appropriate patient populations and the design of future clinical trials were extensively discussed, and the proceedings of the meeting will be published soon. Once the methodological and device-related issues have been resolved and it has been confirmed that renal denervation undoubtedly and safely decreases sympathetic activity, its application might be particularly beneficial in other conditions with high sympathetic tone, such as left ventricular hypertrophy, heart failure with impaired or preserved left ventricular ejection fraction, arrhythmias, metabolic syndrome and chronic kidney disease.

Irrespective of the potential benefits of renal denervation, for patients with target end-organ damage at high risk, a systematic holistic approach, including lifestyle counselling, antihypertensive medication adjustments and device-based therapies remains crucial. This year's Resistant Hypertension Course – TRENDS 2015 – will be held on 27-28 February in Berlin as a joint initiative of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Society of Hypertension (ESH), the PCR Organisation and CSI/TRENDS. The interactive course aims to provide a forum for practical exchanges for the medical community managing hypertensive patients, to share scientific data and experience, and ultimately to improve patient care and stimulate further research and innovation in device technology. The main thrusts of the RHC/TRENDS concept are to help practitioners answer the fundamental question that impacts on their daily practice, namely "What is the best management and strategy for each individual patient presenting with difficult-to-control blood pressure?", and to ensure a successful integration of promising new technologies into the therapeutic armamentarium.

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