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Is successful renal denervation a function of adherence to antihypertensive medication?

Some 10–15% of all patients attending primary health care with a recorded diagnosis of hypertension and treated with three or more antihypertensive drug classes have uncontrolled hypertension with 140/90 mm Hg or above (often described as *treatment resistant* or refractory hypertension), despite being adherent to prescribed antihypertensive medication [1]. Some of these patients may have unrecognized secondary causes of hypertension. However, with the recent introduction of catheter based sympathetic renal nerve denervation as a possible alternative method for the treatment of resistant hypertension it has become clear that many patients with *apparent resistant* hypertension are poorly adherent to antihypertensive drug therapy [2]. Thus, medication adherence may be an important contributor to the reported highly variable response to renal denervation therapy.

Recently, de Jager and associates reported on the SYMPATHY trial and on the impact of medication adherence on the effect of renal denervation in apparently resistant hypertension [3]. This multicentre study in the Netherlands randomized patients with resistant hypertension, defined as an average daytime systolic ambulatory blood pressure of 135 mm Hg or above despite three or more blood pressure lowering agents (or with documented intolerance to two or more agents), by 2:1 to renal denervation in addition to usual care, or usual care only, stratified for site and estimated glomerular function. Blood samples were collected on the same day as blood pressure was assessed. Primary outcome was change in average daytime systolic ambulatory blood pressure at six months.

There were 95 patients randomized to renal denervation and 44 to usual care; however four declined renal denervation and eight (five in the intervention group) withdrew their participation. Mean age was 61 years, about one third were male, average daytime ambulatory blood pressure was 160/93 mm Hg, and the participants were on an average of 3.4 antihypertensive drug classes. Mean average daytime ambulatory blood pressure was reduced by six months. However, in confirmation of other randomised controlled studies on renal denervation [4], the difference (mean values and 95% confidence values) between the study groups in average daytime systolic and diastolic ambulatory blood pressures were small, +2 (–6 to +10) and +1 (–7 to +9) mm Hg, respectively.

For the assessment of medication adherence, liquid chromatography combined with tandem mass spectrometry was used to screen for antihypertensive drugs in blood samples collected on the same day as blood pressure was assessed. Patients were characterized into adherent, poorly adherent, and non-adherent, corresponding to more than 80%, 20–80%, or 0% of the prescribed drugs present in the samples, respectively. Data for 78 patients at both baseline and follow up were available. On both occasions 80% were poorly adherent or completely non-adherent, and one third of the participants changed from one adherence category to another during the course of the study. The highest blood pressure values were observed in patients completely non-adherent. In patients within the same adherence category at baseline and at follow up, daytime and 24 h systolic ambulatory blood pressure, and office systolic blood pressures were lower (–3, –5, and – 14 mm Hg, respectively) in the intervention group, as compared to usual care.

While SYMPATHY [3] confirms previous observations of small effects by renal denervation on ambulatory blood pressure by renal denervation [4], it extends our knowledge on renal denervation in resistant hypertension and medication adherence. First, poor medication adherence is common in resistant hypertension, is associated with higher blood pressure values, and may contribute to apparent treatment resistant hypertension. Second, patients with better medication adherence appear

to respond to renal denervation with a greater reduction in blood pressure. This emphasizes the importance of improving medication adherence in patients with hypertension.

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Hot Off the Press

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From RAG to Riches And Back Again: always keep an eye on our mice models

Kathryn Sandberg and her team very recently conducted a study[1], to be published in the June 2017 issue of Hypertension, focusing on the loss of resistance to angiotensin II–induced hypertension in Recombination-Activating Gene 1 knockout mice (Rag1-/-) on the C57BL/6J background (Jackson Laboratory). This mouse model is deficient in functional T and B cells due to the lack of the V-D-J recombination enzyme, and has been used by several groups in the past decade to explore the involvement of the adaptive immune arm in hypertension.

In 2007, Guzik et al.[2] were the first to demonstrate a role for T cells, and not B cells, in angiotensin II- and DOCA-salt-induced blood pressure elevation and vascular remodeling. In Rag1-/- mice, they showed that repletion via tail-vein injection with T cells, but not B cells, from a wild-type source rescued the otherwise blunted hypertensive response to angiotensin II and DOCA-salt. This study prompted the extensive use of this model to further explore the role of various T cell subsets in hypertension.

However, since 2015, Rag1-/- mice seem to have lost protection against angiotensin II-induced blood pressure increase. This observation was reported by different independent laboratories previously, and addressed in detail in the present study. The authors showed that glomerular angiotensin type 1-receptor binding was higher in recently purchased Rag1-/- mice, suggesting that blood pressure protection as a result of the lack of T cells is lost due to an increase in renal angiotensin type 1-receptor activity. They stressed that spontaneous genetic drift due to mutations lead to phenotypic change in all animals, including inbred mouse strains, because of the universal drive to increase genetic variation.

The gradual loss in blood pressure protection in Rag1-/-