Does Renal Denervation Fit All Resistant Hypertension? The Role of Genetics

To the editor

Resistant hypertension (RHTN) is a clinical condition associated with high cardiovascular risk and incidence of target organ damage (TOD).[1] These patients require intensive pharmacologic and nonpharmacologic approaches to achieve blood pressure (BP) control and prevent TOD progression.[2] Despite the great number of drugs available in the clinical setting, the proportion of patients achieving adequate BP levels remains low.[3]

Recently, renal denervation (RDN) has emerged as an alternative invasive therapy for these difficult-to-treat patients. The Symplicity HTN-1 and -2 trials, which evaluated the effects of RDN on BP levels in patients with RHTN,[4,5] revealed large BP reductions; however, several methodological concerns of these studies were highlighted.[6]

On the other hand, Symplicity HTN-3, the first randomized, blinded, and sham-controlled trial was performed to overcome these methodological flaws including sham procedure as a control group. Surprisingly, no additional reduction in office or ambulatory BP were found after 6 months of RDN compared with the control group,[6] contradicting Symplicity HTN-1 and -2 findings. The reasons Symplicity HTN-3 failed to demonstrate BP reduction have been pointed out by clinicians and researchers. Some authors accurately attributed these disappointing results to the lack of experience with a procedure that has a learning curve, although the commonly attributed reason is that sympathetic activity was not increased in such patients.[7]

RHTN is a multifactorial and polygenic disease, making the decision a challenge in the physician-patient setting. It is well-known that patients fail to respond equally to treatments,[8] which may be explained by the influence of genetic and nongenetic factors.[9] Therefore, it is reasonable to infer that the therapeutic response to RDN may be affected by the presence of genetic variants in different pathophysiological pathways of BP level control, including sympathetic nervous system (SNS) genes.

For instance, some studies have demonstrated an association of polymorphisms in genes of adrenergic receptors with hypertension, which may affect SNS activity. Increased allele frequencies of some single nucleotide polymorphisms in the adrenoceptor genes were found in hypertensive patients (Arg492Cys, Asn251Lys, Gly389Arg, Arg16Gly, Gln27Glu, and Arg389).[10] Currently, approximately 4000 variants in the genes encoding adrenoceptors have been identified.[10] However, there is no consensus regarding the impact of the adrenoceptor variants on BP, as well as the therapeutic response and risk for hypertension.[10]

It is well established that RHTN implies on patients with an extreme phenotype,[11] although the prediction that genetic factors play a greater role in these patients than in the general hypertensive population is debatable. In addition, some studies have already shown the influence of polymorphisms on BP control (WNK1 AluYb8 insertion),[12] cardiovascular risk (I180V),[13] and therapy resistance[14] in RHTN patients.

Finally, similar to the majority of pharmacologic interventions, it is not surprising that RDN does not work for all RHTN patients. It is reasonable to propose the stratification of patients, taking into account the degree of SNS impairment and genetic information to identify patients prone to show greater BP reduction after RDN. To achieve this aim, efforts to identify additional genes, polymorphisms, and regulatory pathways involved in RHTN and responsiveness to antihypertensive drugs must be encouraged in order to achieve a better treatment guide and personalized intervention.

Conflict of interest: The authors declare no conflicts of interest.

Alessandra M.V. Ritter, PhD;[1] Ana Paula de Faria, PhD;[1] Vanessa Fontana PhD;[2] Rodrigo Modolo, MD, PhD;[1] Heitor Moreno, MD, PhD[1]

From the [1]Department of Pharmacology, Faculty of Medical Sciences, University of Campinas, Campinas, SP, Brazil; [2]Brazilian Biosciences National Laboratory, Brazilian Center for Research in Energy and Materials, Campinas, SP, Brazil

References

1. Acelajado MC, Pisoni R, Dudenbostel T, et al. Refractory hypertension: definition, prevalence, and patient characteristics. *J Clin Hypertens (Greenwich)*. 2012;14:7–12.
2. Cuspidi C, Macca G, Sampieri L, et al. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens*. 2001;19:2063–2070.
3. Wong ND, Lopez VA, L'Italien G, et al. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. *Arch Intern Med*. 2007;167:2431–2436.
4. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373: 1275–1281.
5. Esler MD, KrumH, Sobotka PA, Schlaich MP. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet*. 2010;376:1903–1909.
6. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370: 1393–1401.
7. Persu AJin Y, Fadl Elmula FE, et al. Renal denervation in treatment-resistant hypertension: a reappraisal. *Curr Opin Pharmacol*. 2015;21: 48–52.
8. Polimeni A, Curcio A, Indolfi C. Renal sympathetic denervation for treating resistant hypertension. *Circ J*. 2013;77:857–863.
9. van Rijn MJ, Schut AF, Aulchenko YS, et al. Heritability of blood pressure traits and the genetic contribution to blood pressure variance explained by four blood-pressure-related genes. *J Hypertens*. 2007;25:565–570.
10. Ahles A, Engelhardt S. Polymorphic variants of adrenoceptors: pharmacology, physiology, and role in disease. *Pharmacol Rev*. 2014;66:598–637.
11. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the

doi: 10.1111/jch.12642

Council for High Blood Pressure Research. *Hypertension*. 2008;51: 1403–1419.
12. Putku M, Kepp K, Org E, et al. Novel polymorphic AluYb8 insertion in the WNK1 gene is associated with blood pressure variation in Europeans. *Hum Mutat*. 2011;32:806–814.
13. Fernandes-Rosa FL, Hubert EL, Fagart J, et al. Mineralocorticoid receptor p. I180V polymorphism: association with body mass index and LDL-cholesterol levels. *J Endocrinol Invest*. 2010;33: 472–477.
14. Fontana V, de Faria AP, Barbaro NR, et al. Modulation of aldosterone levels by -344 C/T CYP11B2 polymorphism and spironolactone use in resistant hypertension. *J Am Soc Hypertens*. 2014;8:146–151.