See clinical case on page 670

Renal sympathetic denervation: a new treatment strategy in the management of refractory arterial hypertension

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Although the therapeutic management of arterial hypertension (AHT), which is a public health issue due to its importance in terms of patient health and socioeconomic impacts, has improved somewhat in Spain,[1,2] there are still substantial gaps in our ability to control this entity.

Non-compliance, therapeutic inertia, insufficient or inadequate anti-hypertensive treatment, and the characteristics inherent to each form of AHT are recognised as factors that contribute to the inadequate control of AHT, and the consequent increase in vascular morbidity and mortality rates.

One of the forms of AHT that implies the highest rates of morbidity and mortality, in addition to increased direct and indirect costs derived from diagnosis and treatment, is refractory or resistant AHT (defined as AHT in which, despite a treatment based on the application of a series of diet restrictions and lifestyle changes along with the adequate use of at least 3 anti-hypertensive drugs –one of which must be a diuretic-, blood pressure remains uncontrolled).[3,4] Although no studies have been specifically designed to measure the prevalence of AHT in hypertensive patients, the estimated prevalence is 10%-15%,[3,5] with rates 2 times higher in certain sub-groups of hypertensive subjects, such as obese patients, diabetics, chronic renal failure patients, and sleep apnoea syndrome patients.[3,4] Adequate treatment of these patients reduces significantly the percentage of cases of hypertension that are truly refractory to treatment. Even so, in spite of protocols involving detailed anamnesis and diagnostic measures, the application of a gamut of hygienic/dietetic methods for making heart-healthy changes in patient lifestyles, and the prescription of multiple combinations (5 or more) of anti-hypertensive drugs with complementary mechanisms of action at appropriate doses, approximately 2%-4% of hypertensive patients do not have their blood pressure (BP) under control, with values surpassing 140mm Hg, and a very high risk of target organ damage and/or developing vascular complications.[3,4]

In recent years, the search for cost-effective solutions for managing these patients has expanded into non-pharmacological treatment alternatives: one of these is based on radio-frequency ablation of the afferent and efferent sympathetic nerves of the renal arteries (renal sympathetic denervation [RSDN]),[6] and another one is based on parasympathetic activation of the carotid baroreceptors through electrical stimulation (Rheos® system).[7] In conjunction with anti-hypertensive medication, both techniques appear to produce positive results, reaching a significantly better control of BP in these cases of severe refractory hypertension; however, the ease of technical application makes RSDN the most commonly used technique with the greatest basis in clinical evidence.[8]

What are the rational bases for using RSDN as a treatment alternative in severe refractory hypertension patients? The fundamental basis of this treatment strategy is the central role that sympathetic hyperactivity plays in the development and maintenance of AHT, as well as in contributing to structural vascular and organ damage, along with altered carbohydrate and lipid metabolism.[9] In addition, the afferent and efferent renal sympathetic nerves contribute to the increase in sympathetic activity. Through the sympathetic nervous system, the kidneys actively participate in modulating sympathetic activity, both in the development of AHT and its

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cardiovascular complications.[10,11] Finally, the cost-effectiveness and the usefulness of RSDN as a coadjuvant therapy along with anti-hypertensive medication for refractory AHT is evidenced by the clinical benefits (better control of BP) derived from the application of this treatment to more than 5000 patients to date.[12]

Data from the clinical trials Simplicity HTN-1[13,14] and Simplicity HTN-2[15] show the short-term and long-term (up to 36 months)[16] anti-hypertensive effects and safety of this therapeutic approach.

The results from the Simplicity HTN-1, the first non-randomised clinical trial that initially included only 45 patients with refractory hypertension, showed a mean decrease in systolic and diastolic BP of -25mm Hg and -12mm Hg, respectively, after 6 months on the treatment protocol. When the sample size of this study was amplified to 153 patients,[14] the mean decreases in systolic and diastolic BP were -32mm Hg and -14mm Hg, respectively, after 2 years of follow-up, and BP control (<140/90mm HG) at 39% after 12 months, which remained unchanged 2 years later and was even accompanied by an increase in the initial number of non-responsive patients.[14] These results are accompanied by an excellent safety profile, with only 3% of treated patients developing some kind of secondary side effect in the form of one case of renal artery dissection and another case of progression of a prior renal artery stenosis.[13]

Equally significant results were obtained by the Simplicity HTN-2,[14] which was a 1:1 randomised study (test group: control group) including 106 hypertensive patients that were refractory to treatment with 5 or more anti-hypertensive drugs at high doses. As compared to the control group, which did not significantly vary in its BP values, the patients that underwent RSDN had progressive decreases in BP until reaching a mean decrease of systolic and diastolic BP of -32mm Hg and -12mm Hg, respectively, after 12 months. After only 6 months, 39% of test patients already had a systolic BP<140mm Hg, and 20% required a decrease in anti-hypertensive medication dosage.[15] However, 10% of patients received no benefit from RSDB, with the mean decrease in systolic BP lower than 10mm Hg.[15] Along this same topic, the current issue of *Nefrología* presents a clinical case of refractory AHT that was resistant to multiple anti-hypertensive drugs and that, after undergoing RSDN, an additional reduction in systolic and diastolic BP of -22mm Hg was achieved, which without a doubt contributes to the mid-term and long-term decrease in the vascular risk of the patient.

As regards the technique, the application of the endovascular procedure is not complex: a femoral approach is used to access both renal arteries, and radiofrequency ablation is applied to the sympathetic innervation of these arteries every 5mm circumferentially from the distal zone to the ostial zone. Even though the technique is quite simple, it is not without its limitations and contraindications,[8] requiring a prior evaluation of the anatomy of the main renal arteries; the procedure is contraindicated in the case of multiple renal arteries, a principal renal artery with a diameter <4mm or a length <20mm, and in cases of a previous stent or stenosis. In addition, this procedure is contraindicated in patients with type 1 diabetes, an estimated glomerular filtration rate <45ml/min/1.73m^2, unstable angina, acute myocardial infarction, or stroke within the last 3-6 months.[8]

In addition to its anti-hypertensive effects, preliminary studies show that RSDN appears to provide cardiovascular and metabolic benefits that go beyond its anti-hypertensive effects in sub-groups of hypertensive patients with sympathetic hyperactivity, such as those with altered carbohydrate metabolism, sleep apnoea syndrome, heart failure, chronic renal failure, and hepatorenal syndrome.[8,16-18] This is certainly a field open to investigation, necessitating larger randomised studies to ascertain the possible mid-term and long-term benefits of this procedure.

Apart from its limitations and contraindications, a series of criteria for patient eligibility exists, although these criteria are not completely well-defined, for administering RSDN to patients with refractory hypertension.

Without a doubt, the first criteria is to rule out the existence of pseudo-resistance, which requires a complete evaluation of the patient, including confirming the resistance to standard treatment with an ambulatory BP measurement for 24 hours, correcting exogenous factors that could maintain an elevated BP, and certifying that the possibilities for controlling BP using combinations of multiple complementary anti-hypertensive drugs at high doses have been exhausted,[8] rather than being satisfied with a systolic BP ≥160mm Hg (or ≥150mm Hg for diabetics) and the use of 3 or more anti-hypertensive drugs, as was initially proposed by certain authors.[4,8] We also believe that in candidates for RSDN, we must monitor damage indicators in affected organs that corroborate with the severity of AHT,[19] and that the cost-efficacy and cost-effectiveness of the procedure must be evaluated on an individual patient basis.

It goes without saying that the procedure must be carried out in hospitals by personnel with sufficient experience in the management of these patients and these endovascular techniques.[8]

Finally, although the RSDN technique appears to be quite promising, there are still unanswered questions referring to certain aspects such as the identification of direct predictors for treatment success, testing the effectiveness of

RSDN mid-procedure, methods for evaluating a possible process of re-innervation, evaluation of effects on target organs, and the efficacy of other procedures that might produce denervation (ultrasound, micro-wave, laser, cryotherapy, etc.).

Conflicts of interest

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REFERENCES

1. Banegas JR, Jovell A, Abarca B, Aguilar M, Aguilera L, Aranda P, et al. Hipertensión arterial y política de salud en España. Med Clin (Barc) 2009;132(6):222-9.
2. Laves CM, Vander Hoorn H, Rodgers A. Global burden of blood pressure-related disease, 2001. Lancet 2008;371:1513-8.
3. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RA. Resistant hypertension: diagnosis, evaluation and treatment: a scientific statement from the American Heart Association Professional Education Committee for the Council for High Blood Pressure Research. Circulation 2008;117:e510-e526.
4. Erdine S, Arslan E, Coca A. Resistant Hypertension. European Society Hypertension. Scientific Newsleter. Updated on Hypertension management 2011;12 (nº 15):27-8.
5. Alderman MH, Budner N, Cohen H, Lamport B, Ooi WL. Prevalence of drugs resistant hypertension. Hypertension 1988;11 (Suppl II):71-5.
6. Schaid MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension 2009;54:1195-201.
7. Mohaupt MG, Schmidli J, Luft FC. Management of uncontrolled hypertension with a carotid sinus stimulation device. Hypertension 2007;50:825-8.
8. Schmieder RE, Redon J, Grassi G, Kjeldsen S, Mancia G, Narkiewicz K, et al. ESH Position Paper: renal denervation – an interventional therapy of resistant hypertension. J Hypertens 2012;30(5):837-41.
9. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. Hypertension 2009;54:690-7.
10. Tsioufis C, Kordalis A, Lessas D, Anastosopoulos I, Tsiachiris D, Papademetriou V, et al. Pathophysiology of resistant hypertension: the role of sympathetiv nervous system. Int J Hypertens 2011;64:214-26.
11. Di Bona GF, Kopp VC. Neural control of renal function. Physiol Rev 1997;77:175-97.
12. Pietzsch JB, Geisler B, Esler M. Efficacy and Clinical and Economic effectiviness in resistant hypertensive subgroups. J Am Coll Cardiol 2012;59:E1716.
13. Krum H, Schlaid M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof-of-principle cohort study. Lancet 2009;373:1275-81.
14. Simplicity HTN-1 Investigators 2011. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 2011;57:911-7.
15. Simplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RF, et al. Renal sympathetic denervation in patients with treatment resistant hypertension (The Simplicity THN-2 trial): a randomised control trial. Lancet 2010;376:1903-9.
16. Grassi G, Seravalle G, Dell'Oro R, Turri C, Bolla GB, Mancia G. Adrenergic and reflex abnormalities in obesity-related hypertension. Hypertension 2000;36:538-542.
17. Narkiewick K, van de Borne PJH, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. Circulation 1998;98:772-6.
18. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, et al. Sympathetic nerve activity in end-stage renal disease. Circulation 2002;106:1974-9.
19. De la Sierra A, Banegas JR, Oliveras A, Gorostidi M, Segura J, de la Cruz JJ, et al. Clinical differences between resistant hypertensives and patients treated and controlled with three or less drugs. J Hypertens 2012;30:1211-6.

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