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Renal Sympathetic Denervation and Daily Life Blood Pressure in Resistant Hypertension: Simplicity or Complexity?

Running title: *Parati et al.; 24h blood pressure and renal denervation*

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Drug resistant hypertension is a clinically relevant problem, which has attracted increasing attention over the past few years. This is certainly due to a growing awareness of the importance of blood pressure (BP) control in reducing hypertension-related cardiovascular risk. It is also due, however, to a recent major technological breakthrough in the management of resistant hypertension, because of the introduction of two novel invasive therapeutic approaches: carotid baroreceptor stimulation and catheter based renal sympathetic denervation (RDN) [1, 2]. For a number of reasons the latter method seems to be taking the upper hand, and is used with growing enthusiasm all over the world, even if the strength of the evidence in its support is not currently overwhelming.

The concept of RDN derives from a known pressor effect of sympathetic stimuli, arriving to the kidney via efferent fibers located in the adventitia of renal arteries, in the frame of a complex regulation of sympathetic activity also including reflex modulation by renal afferent neural influences [3, 4, 5.] Hence the hypothesis was made that destruction of these fibers, by bilaterally applying radiofrequency electrical current through an ablation catheter positioned inside renal artery, might reduce sympathetic activity in general. It was also hypothesized that, in particular, renal sympathetic fibers ablation might interfere with sympathetic renal modulation, leading to increased sodium and water excretion and to vasodilation, thereby effectively lowering elevated BP levels. This hypothesis has been first tested in animal studies [3, 4] and, subsequently explored in two major studies in humans: Symplicity HTN-1 [6] and Symplicity HTN-2 [7] followed by a growing number of reports from registries.

While the results of Symplicity studies clearly supported the efficacy of RDN in lowering office BP, their design left several major questions unanswered. One of the key issues was related to the fact that, strangely enough, resistant hypertension status was only defined based on

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conventional BP measurements and pseudoresistance due to a white coat effect had not been excluded by means of out-of-office measurements. Focus on conventional office BP only was a common approach in most available RDN studies, an approach which is somehow surprising, on the background of the growing awareness of the limitations of office BP measurements and of the acknowledged need to combine them with out-of-office BP monitoring through home self BP measurements or, even better, through 24 h ambulatory BP monitoring (ABPM). [8, 9]

Basing available RDN studies on office BP measurements only, and thus failing to exclude patients whose office BP elevation was largely due to a "white coat effect",[10] also raises some ethical concerns, since the contribution of white coat effect to cardiovascular risk is modest [11] and prognostic benefits (if any) derived from improving office BP control in subjects with controlled out-of-office BP may not outweigh the risks of an invasive procedure such as RDN. Indeed, ABPM was only performed in a small subset of Symplicity participants and principal assessment of efficacy was based on office BP. Apart from the issue of a white coat phenomenon, an office BP-based approach to assessing the efficacy of antihypertensive intervention has been extensively criticized in the past for several reasons [12]: 1) the selection of patients only based on elevated office BP in a clinical study frequently leads to a bias due to imperfect standardization of the procedure (usually with overestimation of true BP) and to an observer bias. Although the investigators of the Symplicity HTN-2 [7] trial tried to at least partly overcome this problem, by employing automated BP measuring devices with data printout, this approach might have prevented only the observer bias but not the alarm reaction induced by the medical visit. Moreover, not all studies have properly reported the type of device employed for office BP measurement as in the case of Symplicity HTN-1 [6]; 2) office BP is highly variable and thus affected by a regression to the mean phenomenon (a patient may be recruited based on a

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high BP value even if his or her usual BP levels may be lower, thus leading to an artificial BP "lowering" during subsequent follow-up measurements). In fact, these problems led European Medical Agency to recommend that BP lowering efficacy by treatment should be assessed by means of ABPM in registration studies of antihypertensive drugs.[13] The above issues might be largely resolved when Symplicity HTN-3 trial results are available: this trial is in fact designed as a randomized study with a control group undergoing sham procedure, a blinded outcome assessment and with 24 h BP as a secondary outcome, and will exclude patients with controlled or mildly elevated 24 h BP [14]. At present, however, only non-randomized observations on the 24h ABP effects of RDN are available. Several such reports have been published until now, but the number of subjects included has been invariably small. [6, 15, 16] The paper by Mahfoud et al. published in the current issue of Circulation, offers for the first time data on ambulatory BP changes after RDN in a relatively large sample (N= 346) of subjects who underwent RDN following the Symplicity protocol, and were followed over up to 12 months.[17] The principal result of the analysis carried out on such dataset is the demonstration that in true resistant hypertensives (i.e. patients with office SBP ≥160 mmHg, or ≥150 mmHg for diabetic patients, combined with 24 h SBP >130 mmHg in subjects treated with ≥3 antihypertensive drugs including a diuretic) clinically and statistically significant reductions occurred in ambulatory SBP and DBP (8-10 mmHg and 4-7 mmHg, respectively, at different follow-up times). Much larger reductions in office SBP and DBP also occurred (21-27 and 9-12 mmHg, respectively), which were however slightly less pronounced than in Symplicity studies. Ambulatory BP reductions were similar during daytime and night-time. Among possible predictors of response to RDN, only baseline BP resulted to be significantly related to BP reduction.

These results need to be placed in the context of previous studies comparing the effect of

various antihypertensive therapies on office and ambulatory BP. In a vast majority of these papers the reductions in office BP with treatment exceeded those in ambulatory BP. As shown in a meta-analysis of a large number of such drug studies, [18] the reductions in ABP on average corresponded to 70% of the reductions in office BP. In the paper by Mahfoud et al. [17] the corresponding figures are much lower: at 3 months 24 h ABP reduction corresponded to 39% (systolic) and 47% (diastolic) of reduction in office systolic or diastolic BP, respectively, [17] these figures being higher than those reported in some of the previous studies. This data is shown in Figure 1, which compares reductions in office and in 24h ambulatory BP reported in drug studies with the corresponding reductions described in the available RDN studies in which both methods of BP measurements were implemented (Figure 1). [6, 7, 15, 16 , 17.]

This greater discrepancy between office and ambulatory BP reduction might be due to a less controlled office BP measurement setting in the study by Mahfoud et al (i.e. to a larger bias in office BP assessment), compared with clinical trials on antihypertensive drugs, and/or to true attenuation of a white coat effect by RDN, as suggested by the Authors [17]. Whichever the case, these results, while confirming the antihypertensive efficacy of RDN, indicate that the degree of ambulatory BP reduction is not as impressive as that of office BP.

Another interesting finding of the study by Mahfoud *et al.* [17] is that the reduction in night-time BP was similar to that in daytime BP and, consequently, no improvement occurred in altered (nondipper or reverse dipper) circadian BP profiles [17]. While an additional benefit in this regard would be welcome, the finding that night-time BP is effectively reduced by RDN is nevertheless reassuring, on the background of the results of several studies and of a large meta-analysis which indicated that nocturnal BP may be more closely related to outcome compared with daytime BP levels [14].

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Importantly, 43 of subjects included in the study by Mahfoud *et al*. [17] had pseudo-resistant hypertension (i.e. 24 h SBP <130 mmHg at recruitment). While performing RDN in these subjects may be questioned on ethical grounds, it provides some answers (but probably also raises more questions) on the effects of RDN in these particular cases. In these patients significant reduction occurred in office BP while ABP, already within normal range, remained unaffected. This is an important finding in terms of subjects' safety since, apparently, no clinically relevant hypotension occurred in these subjects, in spite of having normal 24h ABP at the time of RDN. Given the uncontrolled design of the study, however, it is impossible to conclude on to what extent the intrinsic limitations of office BP measurement contributed to such an effect. We cannot exclude, however, that RDN, by attenuating sympathetic activity, reduced excessive BP responsiveness to external stimuli (related to white coat effect) in otherwise controlled subjects. This hypothesis is supported by previous findings of reduction in BP variability after RDN, findings which need to be confirmed by additional evidence, however. [19] The question remains open whether office BP lowering provides any benefit in these patients and, consequently, whether "pseudo-resistant" hypertensive patients should be considered eligible for this interventional approach.

The above issue needs to be considered in the context of an even more important problem related to RDN efficacy: not only no "hard" outcome studies are available to support the value of this approach, but only two studies reported on its effects in terms of organ damage markers, one on left ventricular mass [20] and one on pulse wave velocity.[21] This is surprising, as these markers are routinely obtained in resistant hypertensive patients and have proved useful in assessing the efficacy of pharmacological therapies in hypertension, even over relatively short follow-up periods.

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Apart from a nonrandomized and uncontrolled design, the study by Mahfoud *et al.* [17] has another important limitation, that is a high rate of subjects lost to follow-up. In fact, follow-up ABPM data at 3 months are available only in 245 out of 346 patients who entered the study. The figure is similar at 6 months (236) and data at 12 months are available in only 90 subjects. This inevitably raises questions on possible biases due to the exclusion of a large subgroup of patients from the analyses. There may be also some doubts regarding the quality of ABPM recordings since as many as 47 patients failed to record night-time BP at baseline.

Despite these limitations, while waiting for the Symplicity-3 results, the study by Mahfoud *et al.*[17] provides interesting novel insights into the efficacy of RDN, supporting use of this approach in patients with true resistant hypertension. At the same time, the results of this study emphasize the importance of combining out-of-office BP, and in particular 24h ABPM, to properly assess the effects of RDN on hypertension control in daily life.

Conflict of Interest Disclosures: None

References:

1. Grassi G, Bombelli M, Seravalle G, Brambilla G, Dell'oro R, Mancia G. Role of ambulatory blood pressure monitoring in resistant hypertension. *Curr Hypertens Rep*. 2013;15:232-237.

2. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A. 2007 esh-esc practice guidelines for the management of arterial hypertension: ESH-ESC task force on the management of arterial hypertension. *J hypertens*. 2007;25:1751-1762.

3. Salman IM, Ameer OZ, Sattar MA, Abdullah NA, Yam MF, Najim HS, Abdulkarim MF, Abdullah GZ, Kaur G, Khan MA, Johns EJ. Characterization of renal hemodynamic and structural alterations in rat models of renal impairment: Role of renal sympathoexcitation. *J Nephrol.* 2011;24:68-77.

4. Stella A, Zanchetti A. Interactions between the sympathetic nervous system and the kidney:

Experimental observations. *J Hypertens Suppl*. 1985;3:S19-25.

5. Parati G, Esler M. The human sympathetic nervous system: Its relevance in hypertension and heart failure. *Eur Heart J.* 2012;33:1058-1066.

6. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: A multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275-1281.

7. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the symplicity htn-2 trial): A randomised controlled trial. *Lancet*. 2010;376:1903-1909.

8. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, Kario K, Lurbe E, Manolis A, Mengden T, O'Brien E, Ohkubo T, Padfield P, Palatini P, Pickering T, Redon J, Revera M, Ruilope LM, Shennan A, Staessen JA, Tisler A, Waeber B, Zanchetti A, Mancia G. European society of hypertension guidelines for blood pressure monitoring at home: A summary report of the second international consensus conference on home blood pressure monitoring. *J hypertens*. 2008;26:1505-1526.

9. Parati G, Bilo G. Should 24-h ambulatory blood pressure monitoring be done in every patient with diabetes? *Diabetes care*. 2009;32 Suppl 2:S298-304.

10. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, Gregorini L, Zanchetti A. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet*. 1983;2:695-698.

11. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: A meta-analysis. *J Hypertens*. 2007;25:2193-2198.

12. Parati G, Bilo G, Mancia G. Blood pressure measurement in research and in clinical practice: Recent evidence. *Curr Opin Nephrol Hypertens.* 2004;13:343-357.

13. European Medical Agency CfMPfHU. Guideline on clinical investigation of medicinal products in the treatment of hypertension. London, 18 november 2010 ema⁄238⁄1995⁄rev. 3. Http://www.Ema.Europa.Eu/docs/en_gb/document_library/scientific_guideline/2010/12/wc500100191.Pdf.

14. Kandzari DE, Bhatt DL, Sobotka PA, O'Neill WW, Esler M, Flack JM, Katzen BT, Leon MB, Massaro JM, Negoita M, Oparil S, Rocha-Singh K, Straley C, Townsend RR, Bakris G. Catheter-based renal denervation for resistant hypertension: Rationale and design of the symplicity htn-3 trial. *Clin Cardiol*. 2012;35:528-535.

15. Witkowski A, Prejbisz A, Florczak E, Kadziela J, Sliwinski P, Bielen P, Michalowska I,

Kabat M, Warchol E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension*. 2011;58:559-565.

16. Papademetriou V. Enlightn I: Safety and efficacy of a novel multi-electrode renal denervation catheter in patients with resistant hypertension: A first-in-human multicenter study. *AHA Scientific Sessions. 2012 Presented at AHA 2012 Congress, Los Angeles, USA, November 3-7, 2012.* 2012.

17. Mahfoud F, Ukena C, Schmieder R, Cremers B, Rump L, Vonend O, Weil J, Schmidt M, Hoppe U, Zeller T, Bauer A, Ott C, Blessing E, Sobotka P, Krum H, Schlaich M, Esler M, Bohm M. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation*. 2013;XX:XX-XXX.

18. Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: A meta-analysis. *J Hypertens.* 2004;22:435-445.

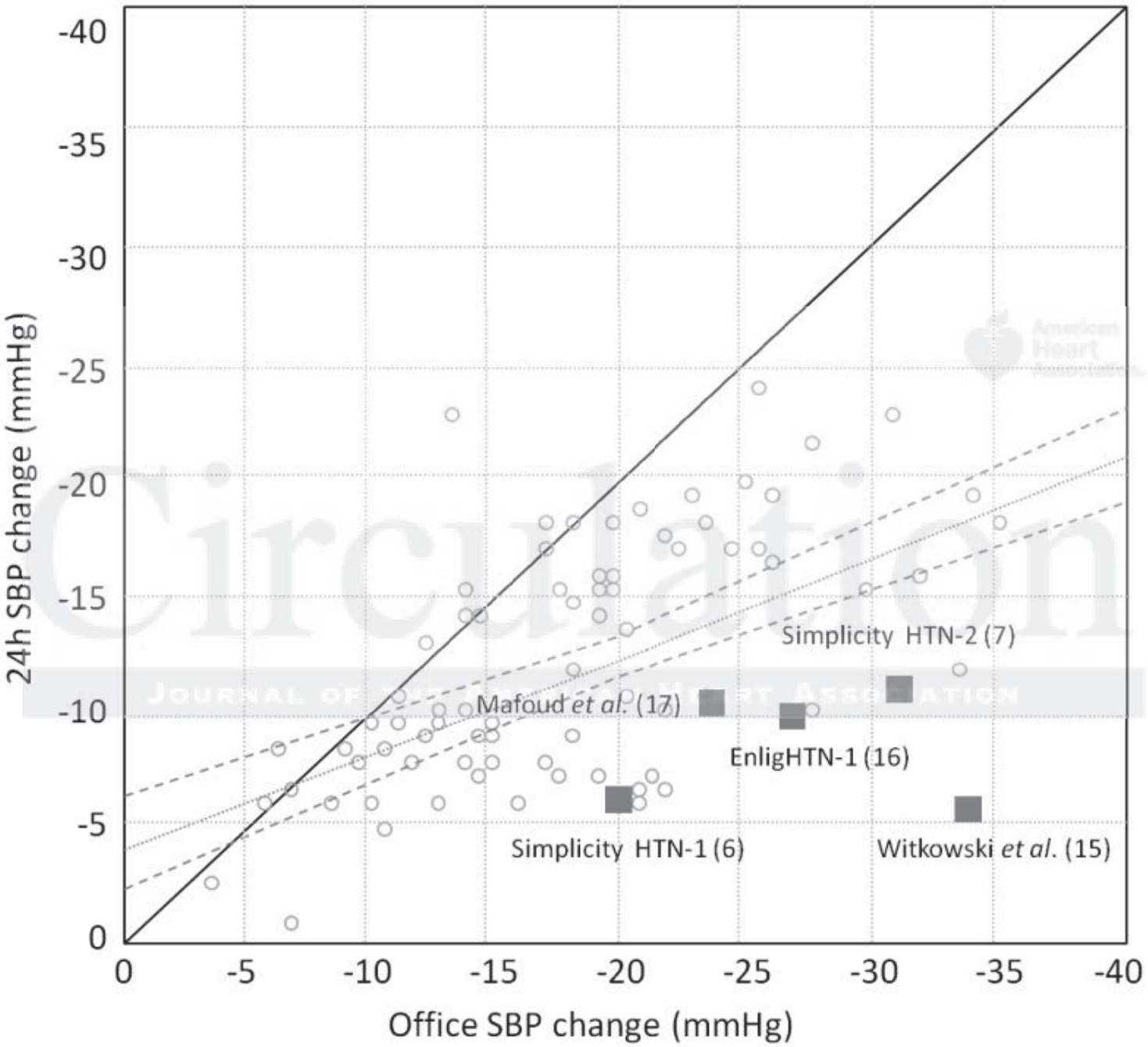
19. Zuern CS, Rizas KD, Eick C, Stoleriu C, Bunk L, Barthel P, Balletshofer B, Gawaz M, Bauer A. Effects of renal sympathetic denervation on 24-hour blood pressure variability. *Front Physiol.* 2012;3:134.

20. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Engl J Med.* 2009;361:932-934.

21. Mortensen K, Franzen K, Himmel F, Bode F, Schunkert H, Weil J, Reppel M. Catheter-based renal sympathetic denervation improves central hemodynamics and arterial stiffness: A pilot study. *J Clin Hypertens (Greenwich)*. 2012;14:861-870.

Figure Legend:

Figure. Discrepant effects of antihypertensive pharmacological treatment (light circles) and renal sympathetic denervation (dark squares) on office and ambulatory BP levels. Regression line with 95% confidence intervals refers to the relationship between office and ambulatory BP reductions in pharmacological studies. From [18,] modified.



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