Effect of Arteriovenous Anastomosis on Blood Pressure Reduction in Patients With Isolated Systolic Hypertension Compared With Combined Hypertension

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Background—Options for interventional therapy to lower blood pressure (BP) in patients with treatment-resistant hypertension include renal denervation and the creation of an arteriovenous anastomosis using the ROX coupler. It has been shown that BP response after renal denervation is greater in patients with combined hypertension (CH) than in patients with isolated systolic hypertension (ISH). We analyzed the effect of ROX coupler implantation in patients with CH as compared with ISH.

Methods and Results—The randomized, controlled, prospective ROX Control Hypertension Study included patients with true treatment-resistant hypertension (office systolic BP ≥140 mm Hg, average daytime ambulatory BP ≥135/85 mm Hg, and treatment with ≥3 antihypertensive drugs including a diuretic). In a post hoc analysis, we stratified patients with CH (n=31) and ISH (n=11). Baseline office systolic BP (177±18 mm Hg versus 169±17 mm Hg, P=0.163) and 24-hour ambulatory systolic BP (159±16 mm Hg versus 154±11 mm Hg, P=0.463) did not differ between patients with CH and those with ISH. ROX coupler implementation resulted in a significant reduction in office systolic BP (CH: −29±21 mm Hg versus ISH: −22±31 mm Hg, P=0.445) and 24-hour ambulatory systolic BP (CH: −14±20 mm Hg versus ISH: −13±15 mm Hg, P=0.672), without significant differences between the two groups. The responder rate (office systolic BP reduction ≥10 mm Hg) after 6 months was not different (CH: 81% versus ISH: 82%, P=0.932).

Conclusions—Our data suggest that creation of an arteriovenous anastomosis using the ROX coupler system leads to a similar reduction of office and 24-hour ambulatory systolic BP in patients with combined and isolated systolic hypertension.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01642498. (Am Heart Assoc. 2016;5:e004234 doi: 10.1161/JAHA.116.004234)

Key Words: arteriovenous anastomosis • combined hypertension • isolated systolic hypertension • treatment resistant hypertension
A terial hypertension is the most prevalent and major modifiable risk factor for cardiovascular morbidity and mortality worldwide. Although several effective and safe antihypertensive drug classes are available, the prevalence rate of treatment-resistant hypertension (TRH) remains ≈8% to 15%. Moreover, it has been reported that within a median of 1.5 years after initiation of antihypertensive treatment, 1 of 50 patients develops TRH. This is of crucial importance, since the diagnosis of TRH carries significantly greater cardiovascular risk compared with patients without TRH. Therefore, innovative therapeutic strategies are needed to achieve blood pressure (BP) control and reduction of cardiovascular mortality in this population.

Several interventional approaches for lowering BP in patients with TRH have recently been introduced. Most depend on modulation of sympathetic activity, for example through renal denervation (RDN) or baroreflex activation. However, the BP response to RDN is markedly heterogeneous and it is not fully known whether this is due to technical failure or a diminished role of renal sympathetic signaling in nonresponders. It has been suggested that the effect of reduced sympathetic activity (due to RDN), and hence the potential to decrease BP in the short term may be limited in patients with advanced vascular remodeling. Furthermore, in patients with isolated systolic hypertension (ISH) (office BP ≥140 mm Hg systolic and <90 mm Hg diastolic), indicative of arterial stiffness, BP reduction due to RDN was attenuated compared with patients with combined hypertension (CH) (office BP ≥140/≥90 mm Hg). This was confirmed in a post hoc analysis of pooled data from the Symplicity HTN-3 trial and the Global SYMPLICITY Registry. Even though patients with ISH had a reduction in systolic BP (SBP) 6 months after RDN, the magnitude of SBP reduction was less pronounced than that seen in patients with CH.

An alternative approach to nonpharmacological BP reduction targeting mechanical aspects of the circulation is the percutaneous creation of a therapeutic arteriovenous anastomosis using the ROX coupler system, thereby increasing arterial compliance and reducing total peripheral resistance. In the randomized controlled ROX Control Hypertension Study (NCT01642498), a central iliac arteriovenous anastomosis resulted in significant reductions in both office and 24-hour ambulatory BP (ABP) compared with medically managed patients.

The aim of the current post hoc analysis was to assess the effects of ROX coupler implantation on office and 24-hour ABP in patients with CH compared with patients with ISH using data from the ROX Control Hypertension Study.

Methods

Study Design and Cohort

The ROX Control Hypertension Study was conducted between October 2012 and April 2014, and its design has been published elsewhere. In brief, the study was a European, open-label, multicenter, prospective, randomized, controlled trial assessing the safety and efficacy of an arteriovenous anastomosis for BP-lowering purposes in patients with TRH. Inclusion criteria were age between 18 and 80 years and presence of TRH (office SBP ≥140 mm Hg and average daytime ABP ≥135/85 mm Hg despite treatment with at least 3 antihypertensive drugs including a diuretic) on a stable drug regimen (without change in dose or medication) for at least 2 weeks. Exclusion criteria were secondary hypertension other than sleep apnea, RDN within the previous 6 months, an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m² and type 1 diabetes, current diagnosis of unstable cardiac disease requiring intervention, history of heart failure, recent myocardial infarction, unstable angina, coronary angioplasty or bypass surgery within last 6 months, current severe cerebrovascular disease or stroke within the previous year, and significant peripheral arterial or venous disease. Furthermore, patients in the intervention group with pulmonary arterial hypertension (mean pulmonary artery pressure >25 mm Hg) and/or elevated pulmonary capillary wedge pressure (>15 mm Hg) were excluded.

Patients were randomly (stratified by study site and previous treatment with RDN) assigned to intervention (percutaneous creation of an arteriovenous anastomosis) plus continuation of antihypertensive medication alone in a 1:1 fashion. However, for this post hoc analysis, only patients who were randomized to ROX coupler implementation and were not lost to follow-up were included.

The study was approved by the ethics committees of the participating centers and was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before study entry. The study was registered at www.clinicaltrials.gov (ID: NCT01642498).

Creation of an Arteriovenous Anastomosis

The procedure for creation of an arteriovenous anastomosis is described in detail elsewhere. In brief, the placement of the ROX coupler creates a fixed caliber 4-mm arteriovenous anastomosis between the distal external iliac artery and vein in a standard cardiovascular catheterization laboratory setting under fluoroscopic guidance. The self-expanding nitinol device permits a controlled shunt volume of 800 to 1000 mL/min. Use of anticoagulation was determined on an individual basis by the interventionalist.

Office and 24-Hour ABP Monitoring

Office BP was measured according to standard recommendations in the nondominant arm, and the average of 3
measurements was taken. If BP values were more than 15 mm Hg apart, measurements were repeated and the means of the last 3 consecutive consistent readings were taken. ABP measurements were performed with validated automatic portable devices. Readings were taken every 30 minutes during daytime and every 60 minutes during nighttime. Measurements were deemed acceptable if there were at least 70% successful readings over 24 hours or if 14 successful readings during daytime and 7 during nighttime were recorded. Patients were graded according to their dipping pattern into dippers (nighttime BP fall ≥10%) and nondippers (nighttime BP fall <10%).

A responder was defined as a patient with office SBP reduction ≥10 mm Hg 6 months after intervention.

Statistical Analysis
All analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Following our hypothesis, patients were categorized into CH or ISH groups according to their baseline office BP. Data were compared by paired and unpaired Student t tests, Wilcoxon and McNemar tests, and Fisher exact test as appropriate, and were presented as mean±SD in the text and mean±SEM in the figures, respectively. A general linear model was used to assess interaction and adjust for possible influencing factors between the two groups. A 2-sided P value of <0.05 was considered statistically significant.

Results
Baseline characteristics of patients stratified according to type of hypertension (CH [n=31] versus ISH [n=11]) are given in Table 1. Office SBP and 24-hour systolic ABP were higher in patients with CH compared with those with ISH, but the difference did not reach statistical significance. Per definition, office diastolic BP (DBP) and 24-hour diastolic ABP were higher in patients with CH compared with those with ISH. There was no difference in the number of patients with prior RDN between the two groups (P=0.372).

Office BP
There was a significant reduction of office SBP and DBP after 6 months by −29±21/−24±13 mm Hg (both P<0.001) in the CH group and by −22±31/−10±13 mm Hg (both P<0.05) in the ISH group. Most importantly, the change in office SBP did not significantly differ between the two groups (P=0.445) (Figure 1). The general linear model did not reveal an interaction between baseline office SBP and type of hypertension (P=0.226). After adjusting for baseline office

Table 1. Clinical Characteristics of Patients Stratified According to Subtype of Hypertension Into CH and ISH

|                      | CH (n=31) | ISH (n=11) | P Value |
|----------------------|-----------|------------|---------|
| Age, y               | 58.4±10   | 63.1±6     | 0.110   |
| Male/female          | 22/9      | 10/1       | 0.182   |
| Body mass index, kg/m² | 30.0±3.4  | 31.0±4.8   | 0.571   |
| Office blood pressure|           |            |         |
| Systolic, mm Hg      | 177±18    | 169±17     | 0.163   |
| Diastolic, mm Hg     | 106±12    | 87±2       | <0.001  |
| Pulse pressure, mm Hg| 72±15     | 82±17      | 0.092   |
| Ambulatory blood pressure|        |            |         |
| Systolic, mm Hg      | 159±16    | 154±11     | 0.463   |
| Diastolic, mm Hg     | 95±12     | 86±7       | 0.019   |
| Pulse pressure, mm Hg| 63±11     | 68±11      | 0.172   |
| eGFR, mL/min per 1.73 m² | 79.1±20 | 67.8±19    | 0.163   |

CH indicates combined hypertension; eGFR, estimated glomerular filtration rate; ISH, isolated systolic hypertension.

SBP, there was no difference in office SBP reduction 6 months after ROX coupler implementation between the two groups (P=0.991). Even after full adjustment (sex, age, and office SBP and DBP), no difference in office SBP reduction was detected (P=0.669).

Responder Rate
A total of 25 patients in the CH group (81%) and 9 patients in the ISH group (82%) had an office SBP reduction ≥10 mm Hg (usually defined as a BP responder after an intervention strategy of BP lowering), which was not significantly different (P=0.932).

Figure 1. Change in office systolic and diastolic blood pressure (BP) 6 months after ROX coupler implementation in the combined hypertension group (black columns) vs in the isolated systolic hypertension group (white columns).
24-Hour ABP Measurements

ROX coupler implementation resulted in a significant reduction of 24-hour ABP in the CH group by $-14\pm20/\text{-}14\pm10$ mm Hg (both $P<0.005$) and in the ISH group by $-13\pm15/\text{-}11\pm9$ mm Hg (both $P<0.05$), respectively. In both groups, average daytime (CH: $-14\pm21/\text{-}16\pm10$ mm Hg; ISH: $-13\pm16/\text{-}11\pm9$ mm Hg [all $P<0.05$]) and nighttime ABP (CH: $-11\pm19/\text{-}10\pm10$ mm Hg; ISH: $-12\pm14/\text{-}11\pm8$ mm Hg [all $P<0.05$]) were significantly reduced 6 months after ROX coupler implementation. There was no difference in the reduction of 24-hour systolic ABP ($P=0.765$, and full adjustment [sex, age, and nighttime systolic ABP]: $P=0.695$) as well as after full adjustment (sex, age, and nighttime systolic and diastolic ABP): $P=0.940$) and nighttime systolic ABP reduction (adjustment for baseline nighttime systolic ABP: $P=0.649$, and full adjustment [sex, age, and nighttime systolic and diastolic ABP]: $P=0.786$).

In addition, there was no change in SBP/DBP dipping (baseline: $P=0.501/0.286$; 6 months: $P=0.540/0.665$) as well as dipping status between baseline and 6 months in both subgroups (CH: $P=0.705$; ISH: $P=0.317$).

Antihypertensive Medication

There was no difference in number and type of antihypertensive medication between the two groups at baseline (Table 2).

![Image of 24-Hour ABP Measurements](Image)

**Figure 2.** Change in systolic 24-hour, daytime, and nighttime ambulatory blood pressure (BP) 6 months after ROX coupler implementation in the combined hypertension group (black columns) vs in the isolated systolic hypertension group (white columns).

Antihypertensive medication (net effect of change) was decreased/increased in 8/2 patients in the CH subgroup and in 2/2 patients in the ISH group, respectively, while antihypertensive medication remained unchanged in 28 of 42 patients during follow-up. Overall, there was no significant difference in (net effect of change) antihypertensive medication between the subgroups ($P=0.499$).

Renal Function

There was no change in eGFR between baseline and 6-month follow-up in the two groups. eGFR changed from 79.1 $\pm$ 20 to 77.6 $\pm$ 21 mL/min per 1.73 $m^2$ ($P=0.420$) in patients with CH and from 67.8 $\pm$ 19 to 65.2 $\pm$ 16 mL/min per 1.73 $m^2$ ($P=0.234$) in patients with ISH. Accordingly, no significant mean change in eGFR from baseline was documented between the groups (CH: $-1.5\pm10$ versus ISH: $-2.6\pm6$ mL/min per 1.73 $m^2$ [$P=0.906$]).

**Table 2.** Baseline Antihypertensive Medications of Patients Stratified According to Subtype of Hypertension Into CH and ISH

|                      | CH (n=31) | ISH (n=11) | $P$ Value |
|----------------------|-----------|------------|-----------|
| No. of antihypertensive medications, mean±SD | 4.7±1.6  | 4.4±1.4    | 0.652     |
| Patients taking ≥5 medications | 16 (52%) | 5 (45%)    | 1.0000    |
| Diuretics | 28 (90%) | 11 (100%)  | 0.5544    |
| Thiazide | 19 (61%) | 6 (55%)    | 0.7327    |
| Loop | 7 (23%) | 5 (45%)    | 0.2432    |
| Aldosterone antagonist | 13 (42%) | 3 (27%)    | 0.4854    |
| Potassium-sparing | 0 (0%)  | 0 (0%)     | 1.0000    |
| ACE inhibitors | 13 (42%) | 5 (45%)    | 1.0000    |
| Angiotensin receptor blockers | 18 (58%) | 5 (45%)    | 0.5038    |
| Direct renin inhibitors | 3 (10%)  | 0 (0%)     | 0.5544    |
| β-Blockers | 23 (74%) | 7 (64%)    | 0.6992    |
| Calcium channel blockers | 24 (77%) | 7 (64%)    | 0.4369    |
| Dihydropyridine | 20 (65%) | 7 (64%)    | 1.0000    |
| Nondihydropyridine | 4 (13%)  | 0 (0%)     | 0.5583    |
| α-Blockers | 8 (26%)  | 6 (55%)    | 0.1358    |
| Centrally acting sympatholytics | 5 (16%)  | 0 (0%)     | 0.3025    |
| α-Adrenergic agonist | 4 (13%)  | 2 (18%)    | 0.6437    |
| Vasodilators | 1 (3%)   | 0 (0%)     | 1.0000    |
| Nitroglycerin or nitrates | 4 (13%)  | 0 (0%)     | 0.5583    |

Data are expressed as number (percentage) unless otherwise indicated. ACE indicates angiotensin-converting enzyme; CH, combined hypertension; ISH, isolated systolic hypertension.
Discussion

The main finding of our current analysis is that percutaneous creation of a central iliac arteriovenous anastomosis reduced office and ABP to a similar extent in patients with CH and ISH. The magnitude of the BP-lowering effects in patients with CH is similar to results achieved with other interventional techniques such as RDN. However, it was observed that in TRH patients similar to results achieved with other interventional techniques such as RDN. However, it was observed that in TRH patients with ISH, BP reduction of both office BP and 24-hour ABP after RDN was clearly reduced in contrast to our observation following creation of an arteriovenous anastomosis.11,12 This discrepancy may be due to the fact that the underlying treatment mechanism targets different pathophysiologic concepts. In fact, recent expert consensus statements on RDN noted that the failure of RDN to lower BP in some individuals could be the consequence of arterial stiffness with subsequent inability to dilate and decrease vascular resistance, rather than due to technical failure of the procedure itself.16,17

From a biophysical standpoint, creating a fixed-caliber central iliac arteriovenous anastomosis adds a low-resistance, high-compliance venous segment to the central arterial tree, resulting in a reduction of systemic vascular resistance.18 Activation of the Frank-Starling mechanism due to increased venous return increases cardiac output, but not commensurate with the reduction of systemic vascular resistance. Most important, the addition of a highly compliant venous parallel compartment, compared with the chronically hypertrophied and maximally filled arterial tree, reduces the effective arterial blood volume. This small reduction of effective arterial blood volume restores arterial compliance to some extent by modulating the stress-strain curve of the aorta, which shifts to the left with aging and in ISH.19 Improvement of structural alterations may change the stress-strain relationship back towards the right, resulting in increased arterial compliance for any given BP, thereby restoring the Windkessel effect.

It is worth noting that reduction in effective arterial blood volume is achieved without depleting the intracellular, interstitial, and venous capacitance spaces, and hence without activation of the neurohormonal system. As early as 1937, Hallock and Benson20 analyzed the relationship between vascular stiffness, aging, and volume expansion and were able to demonstrate that with aging and stiffening of the arteries, a small increase in arterial blood volume is associated with an exaggerated increase in BP. In contrast, diuretics reduce intracellular, interstitial, and venous capacitance volumes before reducing effective arterial blood volume and this is accompanied by activation of the sympathetic nervous system and the renin-angiotensin system.21,22 In a crossover study comprising patients with TRH, low- versus high-salt diet resulted in a marked decrease in both office and 24-hour ABP, as well as a tendency toward decreased vascular stiffness. Notably, the magnitude of BP reduction induced by sodium restriction is substantially greater in patients with TRH than in normotensive or (stage 1 or 2) hypertensive patients.23 These findings support the hypothesis that in patients with TRH, increased sodium retention (and hence intravascular volume expansion) is a major contributor to resistance to antihypertensive therapy, particularly when associated with increased arterial stiffness.

Additional analyses strengthened the concept of comparable BP reductions in patients with and without stiffened arteries following ROX coupler implementation. Pulse pressure (PP) is a valid and widely applicable proxy for arterial stiffness.24 An office PP ≥60 mm Hg in the elderly is an acknowledged marker of target organ damage that influences prognosis and is used for stratification of total cardiovascular risk.25 Dichotomization (and full adjustment) of our cohort for PP below versus above this threshold revealed a similar BP reduction in both subgroups (data not shown). Moreover, even after stratifying (and full adjustment) the cohort according to presence of marked ISH (defined as 24-hour ambulatory PP ≥63 mm Hg),26,27 comparable office BP and 24-hour ABP reduction was evident (data not shown). Notably, only one patient had neither an office PP ≥60 mm Hg nor 24-hour ambulatory PP ≥63 mm Hg, indicating that all patients were at high cardiovascular risk.

We observed that the responder rate to coupler therapy did not significantly differ between patients with CH and ISH. Our findings are also not influenced by changes in antihypertensive medication. Notably, the responder rates were also similar whether patients were stratified according to office PP ≥60 mm Hg or 24-hour ambulatory PP ≥63 mm Hg (data not shown).

From a clinical perspective, ISH is difficult to treat with no formal evidence-based guidance, but it is nonetheless responsible for a substantially increased risk of cardiovascular morbidity and mortality.28–30 The effectiveness of antihypertensive medication may also be limited by vascular aging and arterial stiffness, both known to contribute to treatment resistance.31 Indeed, studies have consistently shown lower rates of SBP than DBP control in patients with ISH.32,33 A central iliac arteriovenous anastomosis may therefore offer a new therapeutic option to treat ISH and may result in an improvement in renal and cardiovascular outcomes.34–36

Study Limitations

Several limitations should be discussed. Our findings are based on post hoc analyses with a small sample size, and thus further corroborration by additional studies is required. The ROX Control Hypertension Study was not sham-controlled, but immediate BP reduction after arteriovenous coupler implantation and the resulting palpable thrill in the ipsilateral
Conclusions

Our analyses suggest that percutaneous creation of a fixed-caliber arteriovenous anastomosis using the ROX coupler, and therefore modifying the mechanical properties of the arterial vascular tree, reduces office SBP and ambulatory SBP to the same extent in patients with CH and ISH. These data contrast with the results of diminished BP reduction in patients with ISH after RDN. Given the primacy of effective arterial volume as a determinant of BP, this is perhaps not surprising and the >90% response rate to coupler therapy observed in the ROX Control Hypertension Study attests to this. Ongoing studies are examining hemodynamic effects of the coupler in greater detail and future studies should address whether patients with TRH due to ISH would benefit from treatment targeting mechanical properties of the circulation (arteriovenous anastomosis formation) as a first choice rather than RDN.

Appendix

Investigators of the ROX Control Hypertension Study were: Christian Ott, Michael Schmid, Stephan Achenbach, and Roland E. Schmieder, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; Ajay Jain, Charles Knight, Melvin D. Lobo, Anthony Mathur, and Manish Saxena, Barts NIHR Cardiovascular Biomedical Research Institute, Queen Mary University of London, London, UK; Peter Balmforth, Sandra F. Luitjens, and Paul A. Sobotka, ROX Medical Inc, San Clemente, CA, USA; and Gerard Smits, Santa Barbara, CA, USA; Felix Mahfoud, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; Alice Stanton, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland; John R. Cockcroft, Wales Heart Research Institute, Cardiff, UK; Neil Sulke, Eastbourne District General Hospital, East Sussex, UK; Eamon Dolan, Connolly Hospital, Dublin, Ireland; Markus van der Giet, Universitätsmedizin Berlin, Berlin, Germany; Joachim Hoyer, Universitätsklinikum Gießen und Marburg GmbH, Marburg, Germany; Stephen S. Furniss, East Sussex Healthcare NHS Trust, East Sussex, UK; John P. Foran and Dhanraj Mungur, Royal Brompton Hospital, London, UK, and St Heller Hospital, Surrey, UK; Adam Witkowski, Andrzej Januszewicz, Aleksander Prebjisz, Jaciek Kadziela, and Elzbieta Florczak, Institute of Cardiology, Warsaw, Poland; Joseph Galvin, Mater Private Hospital, Dublin, Ireland; Danny Schoors, Universitair Ziekenhuis Brussel, Brussels, Belgium; Kyriakos Dimitriadis and Konstantinos Tsioufis, Hippokration General Hospital of Athens, Athens, Greece; Benno J. Rensing, St Antonius Ziekenhuis, Nieuwegein, Netherlands; Benjamin Scott, ZNA Cardio Middelheim, Antwerp, Belgium; André Ng, University of Leicester Glenfield Hospital/NIHR Leicester Cardiovascular Biomedical Research, Leicester, UK.

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References

1. Kearney PM, Whelton, M, Reynolds K, Muntner P, Whelton PK. He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365:217–223.

2. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Riuolpe LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57:898–902.

3. Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014;28:463–468.

4. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, Lee KL, Ohman M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2149–2157.

5. Persu A, Jin Y, Azizi M, Baelen M, Volz S, Elvan A, Severino F, Rosa J, Adiyaman M, Hoyer J, Sweep FC, Diedrich A, Jordan J, Tank J. Catheter-based renal denervation in patients with isolated systolic hypertension: a prospective case series. J Hum Hypertens. 2012;26:110–116.

6. Kim J, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. European Network for Non-invasive Investigation of Large Artery, Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2008;29:2255–2266.

7. Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Sobotka PA, Bakris GL, Blankestijn PJ, Bohm M, Campese VM, Schmieder RE, Bakris G, Blankestijn PJ, Bohm M, Renal sympathetic denervation in patients with resistant hypertension (the Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376:1903–1909.

8. Brinkmann J, Heusser K, Schmidt BM, Menne J, Klein G, Bauersachs J, Haller SW, Friedcich D, Andero J, Jordan J, Tank J. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertension: patients’ prospective case series. Hypertension. 2012;60:1489–1490.

9. Persu A, Jin Y, Azizi M, Baelen M, Volz S, Elvan A, Severino F, Rosa J, Adiyaman M, Hoyer J, Sweep FC, Diedrich A, Jordan J, Tank J. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertension: patients’ prospective case series. Hypertension. 2012;60:1489–1490.

10. Ott C, Schmid A, Toennis FW, Dittrich T, Veelken R, Uder M, Schmieder RE. Central pulse pressure predicts BP reduction after renal denervation in patients with resistant hypertension. EuroIntervention. 2015;11:110–116.

11. Ewen S, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, Wagenpfel S, Schroeder RE, Bohm M, Mahfoud F. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. Hypertension. 2015;65:193–199.

12. Maurhold T, Renkijn J, Rieman M, de Vries J, van der Ploeg I, van Dijk J, van der Graaf Y, Kahan T. Symplicity HTN-3 Investigators. Effect of central pulse wave velocity on response to renal denervation: the Symplicity HTN-3 Randomized Controlled Trial. J Hypertens. 2014;32:150–156.

13. Burchell AE, Lobo MD, Sulke N, Sobotka PA, Paton JF. Arteriovenous Anatomos in CH Compared With ISH. Ott et al.
individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63:636–646.

31. Mancia G, Giannattasio C. Diagnostic and therapeutic problems of isolated systolic hypertension. J Hypertens. 2015;33:33–43.

32. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Prevalence of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension. 2001;37:869–874.

33. Mancia G, Bombelli M, Lanzarotti A, Grassi G, Cesana G, Zanchetti A, Sega R. Systolic vs diastolic blood pressure control in the hypertensive patients of the PAMELA population. Pressioni Aterosclerotiche Monitorate e Loro Associazioni. Arch Intern Med. 2002;162:582–586.

34. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991;265:3255–3264.

35. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bul Witt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Foretta F, Leonetti G, Nachev C, O’Brien ET, Rosenfield J, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350:757–764.

36. Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic hypertension in China (Syst-China) Collaborative Group. J Hypertens. 1998;16:1823–1829.

37. Sobotka P, Munnery M, Davies L, Gale NS, Cockcroft JR. Creation of a fixed central arterial-venous anastomosis on arterial stiffness and central haemodynamics: a treatment for hypertension targeting the physical properties of the arterial vasculature. Artery Res. 2014;8:176.

38. Saxena M, Sobotka PA, Hamshire SM, Jain A, Mathur A, Knight C, Collier DJ, Lobo MD. Antihypertensive effects of a central arteriovenous anastomosis are mediated through profound reduction in systemic vascular resistance. Circ Cardiovasc Interv. 2016;9:e004012 doi: 10.1161/CIRCINTERVENTIONS.116.004012.

39. MacRae JM, Pandeya S, Humen DP, Krivitski N, Lindsay RM. Arteriovenous fistula-associated high-output cardiac failure: a review of mechanisms. Am J Kidney Dis. 2004;43:E17–E22.

40. Basile C, Lomonte C, Vernaglione L, Casucci F, Antonelli M, Losurdo N. The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. Nephrol Dial Transplant. 2008;23:282–287.

41. Omboni S, Parati G, Palatini P, Vanasia A, Muesan ML, Cuspidi C, Mancia G. Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation. J Hypertens. 1998;16:733–738.

42. Fedecostante M, Barbatelli P, Guerra F, Espinosa E, Dessi-Fulgheri P, Sarzani R. Summer does not always mean lower: seasonality of 24 h, daytime, and night-time blood pressure. J Hypertens. 2012;30:1392–1398.
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