

Pulse Wave Velocity Predicts Response to Renal Denervation in Isolated Systolic Hypertension

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Background—Renal sympathetic denervation seems to be less effective as a treatment for hypertension in patients with isolated systolic hypertension, a condition associated with elevated central arterial stiffness. Because isolated systolic hypertension can also be caused by wave reflection or increased cardiac output, a more differentiated approach might improve patient preselection for renal sympathetic denervation. We sought to evaluate the additional predictive value of invasive pulse wave velocity for response to renal sympathetic denervation in patients with combined versus isolated systolic hypertension.

Methods and Results—Patients scheduled for renal sympathetic denervation underwent additional invasive measurement of pulse wave velocity and pulse pressure before denervation. Blood pressure was assessed via ambulatory measurement at baseline and after 3 months. In total 109 patients (40 patients with isolated systolic hypertension) were included in our analysis. After 3 months, blood pressure reduction was more pronounced among patients with combined hypertension compared with patients with isolated systolic hypertension (systolic 24-hour average 9.3 ± 10.5 versus 5.0 ± 11.5 mm Hg, $P=0.046$). However, when stratifying patients with isolated systolic hypertension by invasive pulse wave velocity, patients in the lowest tertile of pulse wave velocity had comparable blood pressure reduction (12.1 ± 12.6 mm Hg, $P=0.006$) despite lower baseline blood pressure than patients with combined hypertension (systolic 24-hour average 154.8 ± 12.5 mm Hg in combined hypertension versus 141.2 ± 8.1 , 148.4 ± 10.9 , and 150.5 ± 12.7 mm Hg, respectively, by tertiles of pulse wave velocity, $P=0.002$).

Conclusions—Extended assessment of arterial stiffness can help improve patient preselection for renal sympathetic denervation and identify a subgroup of isolated systolic hypertension patients who benefit from sympathetic modulation. (*J Am Heart Assoc*. 2017;6:e005879. DOI: 10.1161/JAHA.117.005879.)

Key Words: arterial stiffness • isolated systolic hypertension • pulse wave velocity • pulse wave velocity • renal nerves • renal sympathetic denervation • resistant hypertension • sympathetic nervous system • vascular calcification

Isolated systolic hypertension (ISH) was identified recently as a predictor of less pronounced response to renal sympathetic denervation (RDN) in therapy-resistant hypertension.^{1,2} ISH is believed to be a consequence of central arterial

stiffness, which is caused by chronic vascular remodeling³ and thus less modifiable by RDN. Consequently, ISH has been proposed as an exclusion criterion for RDN.^{4,5}

ISH can also be the consequence of pulse pressure amplification secondary to wave reflection from the peripheral vasculature, especially among younger patients,⁶ where it is representative of an elevated peripheral vascular tone, and it may be caused by increased cardiac output.⁷ Both parameters are suggestive of elevated sympathetic activity among these patients, hypothetically making them good candidates for RDN.

Selecting those patients with ISH but less vascular stiffness, thereby assuming that elevated peripheral vascular tone is an important contributor to ISH, could result in adequate blood pressure (BP) reduction despite the presence of ISH. We were recently able to demonstrate invasive pulse wave velocity (iPWV), the reference marker for vascular stiffness estimation,⁸ as an excellent predictor of response to RDN.⁹

In this study, we evaluated the ability of iPWV to differentiate between responders and nonresponders with ISH in a prospective cohort of patients with therapy-resistant hypertension.

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Methods

Patients undergoing RDN at the University of Leipzig Heart Center underwent invasive assessment of central arterial stiffness before RDN. Patients were eligible if treated for resistant hypertension, defined as mean daytime systolic BP ≥ 135 mm Hg or diastolic BP ≥ 90 mm Hg in 24-hour ambulatory BP measurement (ABPM) despite intake of at least 3 antihypertensive agents, including 1 diuretic unless intolerant of diuretics. Antihypertensive medication had to be unchanged during the 4 weeks before RDN and was intended to remain stable for a follow-up period of 3 months. Only patients with stable antihypertensive medication after 3 months were included in the analysis. Patients with renal anatomy unsuitable for denervation were excluded. The study was performed according to the 1975 Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Ambulatory BP Measurement

ABPMs were acquired with a cuff-based oscillometric device (Spacelabs model 90207; Spacelabs Healthcare GmbH). Cuff size was adapted to the patient's arm circumference by specially trained study nurses. BP recordings were performed every 15 minutes during the day (7 AM to 10 PM) and every 30 minutes at night (10 PM to 7 AM). BP recordings were analyzed with a dedicated software (CardioNavigator version 2.4.13; Del Mar Reynolds Medical).

Invasive Measurement of Arterial Stiffness

iPWV was determined immediately before renal denervation. A 6-French sheath was placed in the right femoral artery and a 4-French pigtail catheter (Cordis) in the ascending aorta. The foot-to-foot method was used to determine iPWV. iPWV was calculated using the following equation: $v = \text{pigtail-length} / (\text{foot-to-foot distance [m]} / \text{recording speed [m/s]})$.

Invasive pulse pressure (iPP) was measured from the foot of the pressure wave in the ascending aorta to the top of the wave or directly from continuous invasive recordings. The average of 3 measurements was used to calculate iPWV and iPP.

Renal Sympathetic Denervation

RDN was performed according to a standardized protocol, as described previously.^{10,11} In brief, repeated ablation runs were delivered to each renal artery. The ablation points were placed circumferentially to the renal artery wall from distal to proximal. All patients received intravenous remifentanyl to control visceral pain. Overall, 83 patients underwent ablation

with a Symplicity Flex catheter, 21 patients were treated with Spyral catheters (both from Medtronic), and 27 patients underwent ablation with an ultrasound-based denervation system (Paradise; ReCor Medical).

Definitions

ISH was defined as 24-hour average diastolic BP < 80 mm Hg on ABPM, as recommended in the latest practice guidelines for ABPM by the European Society of Hypertension.¹² BP response was defined as a drop ≥ 5 mm Hg of daytime systolic BP on ABPM after 3 months, as recommended in a recent consensus paper by the European Society of Cardiology.⁵ Responder rate was defined as the percentage of patients fulfilling this criterion in the analyzed group.

Statistics

Categorical variables are expressed as number and percentage of patients. Continuous data are reported as mean and standard deviation or standard error of mean, as appropriate.

Within-group change was assessed using a paired Student *t* test. Between-group differences were compared using a 2-tailed independent samples *t* test for continuous data or univariate ANOVA with post hoc-testing, as appropriate. The χ^2 test was used for categorical variables. Because the tertiles of iPWV were not perfectly balanced, an additional age-adjusted regression model was calculated for the average drop in daytime BP at 3 months. In addition, a stepwise-forward logistic regression analysis for BP response at 3 months was calculated using previously described predictors for a successful RDN (office pulse pressure, presence of ISH, use of vasodilators and aldosterone antagonists as well as iPWV).^{1,9} All statistics were calculated using SPSS 19.0.0.2 (IBM Corp).

Results

In total, 131 consecutive patients underwent RDN and invasive measurement of iPWV and iPP at our center. Of these, 109 patients were on stable medication at 3-month follow-up and were included in analyses. Patients with ISH were split into 3 groups according to iPWV tertiles.

Baseline Characteristics

At baseline, patients with combined hypertension (CH) were younger than patients with ISH (Table 1) and had higher systolic and diastolic BP on ABPM average (Table 2). Comorbidities were balanced between the groups, with no significant differences in prevalence of diabetes mellitus or

Table 1. Clinical Baseline Characteristics

	CH (n=69)	ISH (n=40)	P Value (CH vs ISH)	Tertile 1 (n=13)	ISH Tertile 2 (n=14)	Tertile 3 (n=13)	P Value (Tertile vs CH)
Age, y	60.4±9.0	66.5±9.8	0.002	60.8±13.4	70.1±5.3	68.3±6.8	0.001
Female, %	14 (20)	10 (25)	0.57	3 (23)	5 (36)	2 (15)	0.57
Smoker	32 (46)	19 (48)	0.91	6 (46)	5 (36)	8 (62)	0.61
Diabetes mellitus	32 (46)	24 (60)	0.17	8 (62)	7 (50)	9 (69)	0.41
Peripheral arterial disease	6 (9)	7 (18)	0.17	2 (15)	3 (21)	2 (15)	0.54
Coronary artery disease	28 (40)	22 (55)	0.15	8 (62)	7 (50)	7 (54)	0.48
Stroke	3 (4)	3 (8)	0.49	1 (8)	1 (7)	1 (8)	0.92
Acute myocardial infarction	7 (10)	7 (18)	0.27	3 (23)	2 (14)	2 (15)	0.62
Atrial fibrillation	10 (14)	7 (18)	0.68	1 (8)	4 (28)	2 (15)	0.48
Oral anticoagulation	11 (16)	9 (23)	0.39	2 (15)	4 (28)	3 (23)	0.68
Dyslipidemia	45 (65)	30 (75)	0.29	9 (69)	10 (71)	11 (85)	0.58
Serum creatinine, μmol/L	87.0±17.7	88.5±26.6	0.74	86.9±19.6	79.2±10.8	99.9±39.3	0.08
eGFR, mL/min	80.5±18.0	78.9±19.5	0.66	80.5±18.4	80.7±18.4	75.5±25.6	0.84

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

cardiovascular diseases. The mean number of prescribed antihypertensive drug classes was not different between the groups (CH versus ISH 5.0 ± 1.6 versus 4.8 ± 1.3), and drug classes did not differ significantly between the groups apart from renin antagonists, which were prescribed more frequently among patients with CH with small absolute numbers (Table 3).

Invasive Measurements

iPWV was lower in patients with CH compared with patients with ISH (15.2 ± 3.7 versus 17.8 ± 5.6 m/s, $P=0.014$) but was lowest in the lower tertile of patients with ISH (Figure 1A). iPP was lowest in patients with CH and increased among the iPWV

tertiles in patients with ISH (87.6 ± 21.6 in CH versus 107 ± 22.1 mm Hg in ISH, $P<0.001$) (Figure 1B).

BP Reduction

After 3 months, ABPM 24-hour systolic BP decreased by 9.3 ± 10.5 mm Hg in the CH group and by 5.0 ± 11.5 mm Hg in the ISH group, ABPM 24-hour diastolic BP decreased by 6.4 ± 7.5 mm Hg in the CH group and by 1.9 ± 4.7 mm Hg in the ISH group ($P=0.046$ and $P<0.001$, respectively, for between-group comparison, for systolic change within groups $P<0.001$ and $P<0.001$ and for diastolic change $P=0.010$ and 0.013 , respectively). Using the median of our previously published study on iPWV,⁹ patients with iPWV <14.4 m/s had

Table 2. Baseline Ambulatory Blood Pressure

	CH (n=69)	ISH (n=40)	P Value (CH vs ISH)	Tertile 1 (n=13)	ISH Tertile 2 (n=14)	Tertile 3 (n=13)	P Value (Tertile vs CH)
24-h average							
Systolic	154.8±12.5	146.8±11.2	0.001	141.2±8.1	148.4±10.9	150.5±12.7	0.002
Diastolic	90.6±10.3	72.3±5.1	<0.001	71.7±5.4	72.6±5.6	72.6±4.7	<0.001
Daytime							
Systolic	158.6±12.4	150.0±11.9	0.001	144.5±8.9	151.6±11.4	153.5±13.9	0.001
Diastolic	93.7±11.2	74.7±5.5	<0.001	74.3±5.4	75.0±5.8	74.8±5.6	<0.001
Nighttime							
Systolic	143.9±18.2	137.3±15.2	0.057	131.8±11.6	138.0±12.6	142.0±19.6	0.12
Diastolic	81.4±11.6	65.3±6.7	<0.001	64.6±6.8	64.6±6.2	66.7±7.3	<0.001

All values are in mm Hg. CH indicates combined hypertension; ISH, isolated systolic hypertension.

Table 3. Baseline Medication

	CH (n=69)	ISH (n=40)	P Value CH vs ISH	Tertile 1 (n=13)	ISH Tertile 2 (n=14)	Tertile 3 (n=13)	P Value (Tertile vs CH)
Number of drug classes	5.0±1.6	4.8±1.3	0.56	4.6±1.5	4.6±1.1	5.3±1.4	0.51
≥5 drug classes	37 (54)	21 (53)	0.91	6 (46)	5 (36)	10 (77)	0.18
Angiotensin-converting enzyme inhibitors	33 (48)	22 (55)	0.47	8 (62)	8 (57)	6 (46)	0.76
Angiotensin receptor antagonists	42 (61)	21 (53)	0.39	5 (38)	7 (50)	9 (69)	0.35
Renin antagonists	8 (12)	0 (0)	0.025	0 (0)	0 (0)	0 (0)	0.17
Beta blockers	63 (91)	37 (93)	0.83	12 (86)	14 (100)	11 (85)	0.54
Calcium channel blockers	44 (64)	29 (73)	0.35	8 (62)	11 (79)	10 (77)	0.59
Diuretics	67 (97)	38 (95)	0.57	13 (93)	14 (100)	11 (85)	0.10
Second diuretic	16 (23)	5 (13)	0.17	2 (15)	0 (0)	3 (23)	0.23
Aldosterone antagonists	12 (17)	5 (13)	0.50	3 (23)	2 (14)	0 (0)	0.37
Vasodilators	9 (13)	6 (15)	0.78	1 (8)	1 (7)	4 (31)	0.25
Alpha blockers	14 (20)	10 (25)	0.57	2 (15)	3 (21)	5 (38)	0.48
Centrally acting sympatholytics	34 (49)	18 (45)	0.67	6 (46)	4 (28)	8 (62)	0.37

CH indicates combined hypertension; ISH, isolated systolic hypertension.

a significantly better daytime BP response than patients above of this value (11.7±12.7 versus 7.2±10.4 mm Hg, P=0.047) (Figure 2). When stratifying patients with ISH by

iPWV tertiles, patients in the lower tertile and patients with CH had the most pronounced reductions in daytime BP compared with the middle and upper tertiles (Figure 2). This

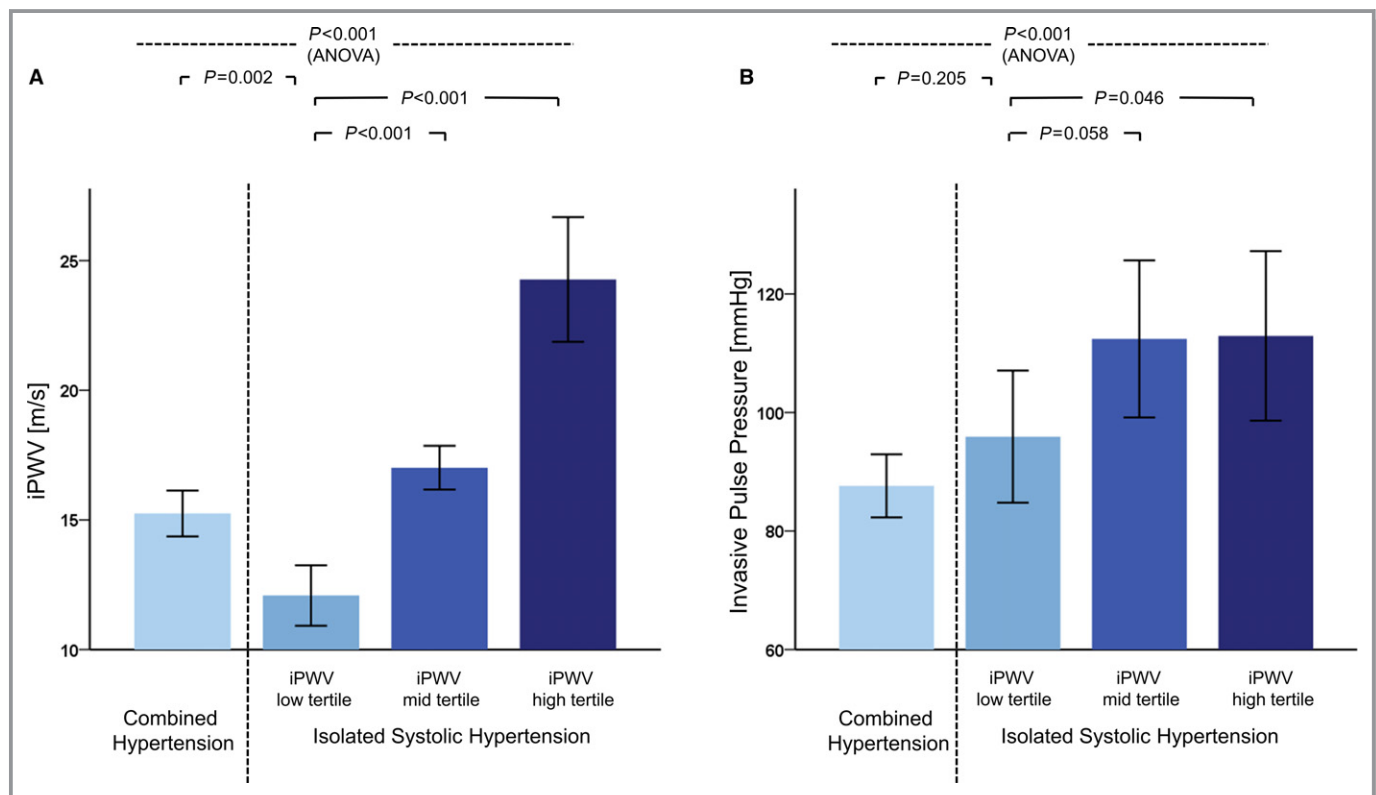


Figure 1. Baseline invasive pulse wave velocity (iPWV) (A) and pulse pressure (B) among patients with isolated systolic and combined hypertension stratified by iPWV.

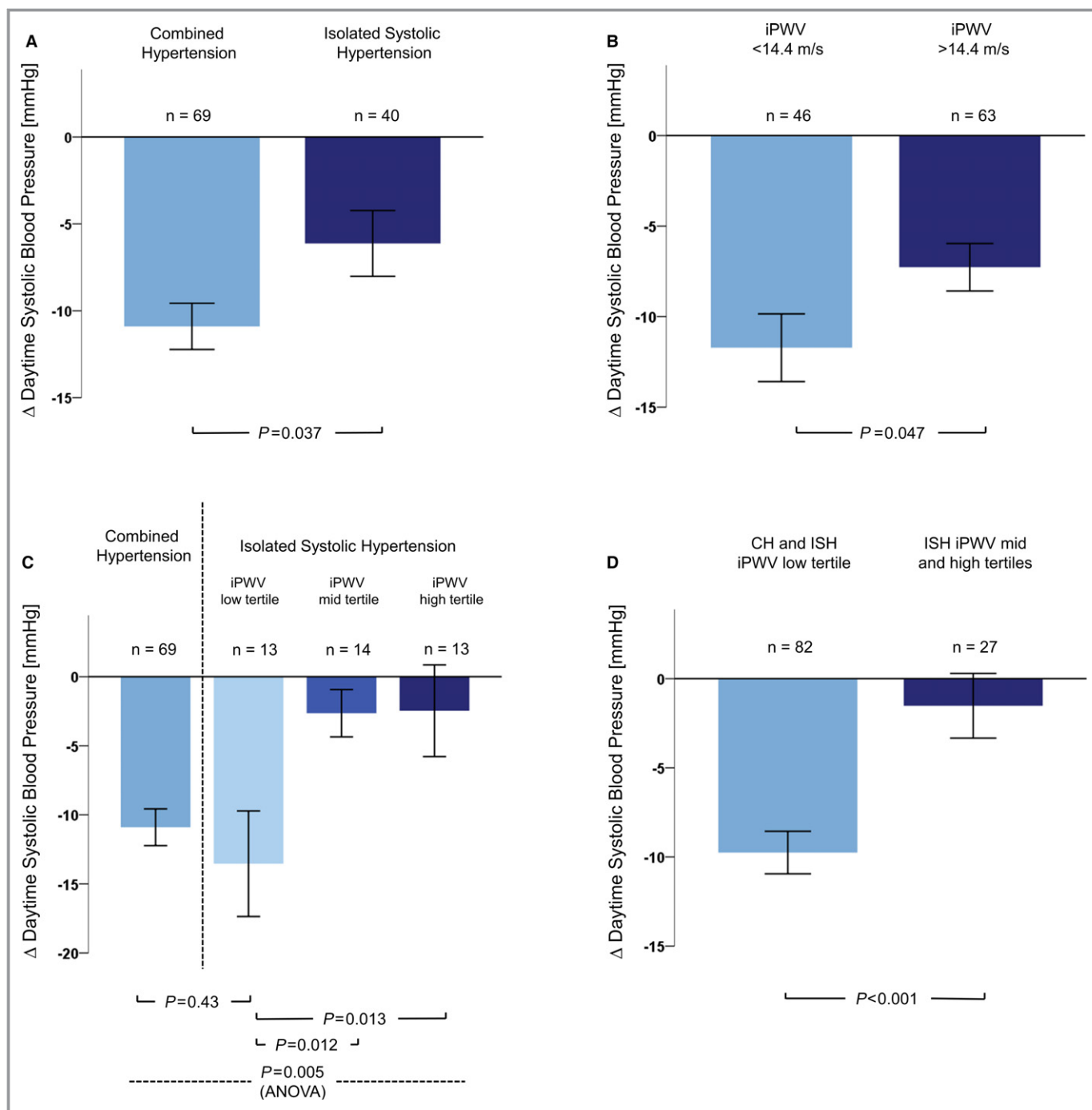


Figure 2. Mean change in daytime systolic blood pressure 3 months after renal sympathetic denervation in patients with combined hypertension (CH) and isolated systolic hypertension (ISH) (A), patients with invasive pulse wave velocity (iPWV) >14.4 m/s and <14.4 m/s (B), patients with CH vs ISH stratified among the tertiles of iPWV (C), and patients with CH and patients in the lower tertile of iPWV vs patients in the middle and upper tertiles of iPWV (D).

difference persisted after adjusting for age ($P=0.032$). In contrast, stratification of patients with CH among iPWV tertiles did not reveal any significant difference (Figure S1).

Responder rates were 75% for patients with CH and 50% for patients with ISH ($P=0.007$). Among lower, middle, and upper iPWV tertiles, rates were 77%, 50%, and 23%,

respectively ($P=0.001$). No difference was observed among the 3 applied ablation devices ($P=0.21$ and $P=0.27$ for 24-hour and daytime values, respectively). Because most patients in this trial were treated with the Symplicity Flex device, a subanalysis of these patients was performed. A strong trend toward better results in patients with lower

iPWV was found without reaching statistical significance ($P=0.07$) (Figure S2).

A multivariate logistic regression analysis for BP response after 3 months revealed iPWV as the only significant predictor ($P=0.037$; odds ratio 0.91 per 1 m/s, 95% CI 0.83–0.99).

Discussion

Recent results of RDN trials underscore the importance of defining optimal candidates for this procedure. Ideally, the level of sympathetic activation before RDN should differentiate between responders and nonresponders, since RDN can be effective only if sympathetic overdrive is the key contributor to therapy-resistant hypertension. Unfortunately, techniques to assess sympathetic activity in a robust and safe manner are still lacking. Alternatively, ISH has been suggested as a surrogate for advanced and at least partly irreversible central arterial stiffness, which would be unaffected by RDN. Consequently, ISH is considered an exclusion criterion in the latest RDN hypertension trials.⁴

Our results, however, indicate that patients with ISH show a heterogeneous response to RDN rather than uniform nonresponse.

Apparently, among patients in whom elevated pulse pressure (and resulting ISH) was predominantly mediated by factors other than central stiffness, RDN was effective. The most pronounced BP reduction in the low iPWV tertile is intriguing, given the lowest baseline systolic BP in this cohort; higher baseline BP is usually associated with more pronounced BP reduction.^{1,13}

Several different pathologies can contribute to an elevated pulse pressure, resulting in the clinical phenomenon of ISH: (1) increased stroke volume,⁷ (2) increased central arterial stiffness and impedance,^{7,14,15} and (3) pulse pressure amplification caused by wave reflection from the periphery.^{6,15} Discrimination among these components is of relevance because, unlike central stiffness caused by structural remodeling, peripheral vasoconstriction and stroke volume are believed to be directly or indirectly influenced by sympathetic overdrive. This is in line with the results from a recent study that found a reduction in systemic resistance to be the key effector of RDN.¹⁶ Our data support the hypotheses that ISH can also be caused by increased sympathetic activity and that this subgroup represents a patient population that could benefit from RDN.

Our findings might also explain why the use of iPP and noninvasive central pulse pressure as predictors of nonresponse might be inferior to iPWV^{1,9,17}: iPP indicates central pressure amplification, leading to ISH, but unlike iPWV, iPP is not specific to central arterial stiffness.

Importantly, iPWV and iPP are sex¹⁸ and age¹⁹ dependent. Among healthy persons, pulse pressure amplification

measured by aortic augmentation index increases asymptotically over the first 5 to 6 decades and reaches a plateau thereafter. In contrast, aortic pulse wave velocity follows a flattened exponential course that inclines mostly after the fifth decade.¹⁹ The 2 subgroups with the most BP improvement after RDN in our analysis were younger and had lower pulse wave velocity than the other patients, in whom RDN seemed to be ineffective. Simplified, age is a broad marker of arterial stiffness. However, because age has not been found to be an independent predictor of response in larger cohort studies,^{1,13} we believe that assessing arterial stiffness and estimating the potential to reverse those pathologies that contribute to arterial hypertension represent a better approach than relying on patient age.

Limitations

The value of our findings is limited in 2 major respects. First, our cohort consists of patients with severe therapy-resistant hypertension and severely altered vasculature, as indicated by highly pathological overall iPWV values; therefore, these results cannot be transferred to a general hypertensive population. Second, our cohort lacks thorough assessment of other hemodynamic parameters, such as cardiac output, stroke volume, and a more detailed analysis of the wave reflection and augmentation, as well as noninvasive assessment of pulse wave velocity, leaving a detailed investigation of these interesting factors as a task for future trials. Moreover, direct measurement of sympathetic nervous activity would improve interpretation of our results; however, this is known to be a challenging task in human trials. In addition, because it is more reliable than office BP, we used an ABPM-based definition for ISH in our analysis. The fact that previous publications mostly used the office BP-based definition should be considered when comparing results of individual studies. Finally, because patients were on combined drug treatment, we cannot exclude the possibility that some of the patients now diagnosed with ISH would not fulfill this criterion if they were drug naïve.

Conclusions

Among patients with ISH, low iPWV—and thus a lower degree of arterial stiffening—indicates a subgroup that might benefit from RDN. Consequently, ISH might not generally be considered an exclusion criterion for interventional treatment of arterial hypertension using RDN. For future trials, systematic assessment of the factors leading to BP elevation might be a superior approach to preselect patients who are likely to benefit the most from RDN.

Disclosures

Philipp Lurz is consultant to ReCor Medical (Palo Alto, CA, USA) and Medtronic (Minneapolis, MN, USA). The remaining authors have no disclosures to report.

References

- Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M, Kandzari D, Kario K, Mancia G, Weber M, Bohm M. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from simplicity htn-3 and the global simplicity registry. *Eur Heart J*. 2017;38:93–100.
- Ewen S, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, Wagenpfeil S, Schmieder 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.
- Wallace SM, McEniery CM, Maki-Petaja KM, Booth AD, Cockcroft JR, Wilkinson IB. Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. *Hypertension*. 2007;50:228–233.
- Kandzari DE, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S, Townsend R, Weber MA, Bohm M. The spyrat htn global clinical trial program: rationale and design for studies of renal denervation in the absence (spyrat htn off-med) and presence (spyrat htn on-med) of antihypertensive medications. *Am Heart J*. 2016;171:82–91.
- Mahfoud F, Bohm M, Azizi M, Pathak A, Durand Zaleski I, Ewen S, Tsioufis K, Andersson B, Blankestijn PJ, Burnier M, Chatellier G, Gafoor S, Grassi G, Joner M, Kjeldsen SE, Luscher TF, Lobo MD, Lotan C, Parati G, Redon J, Ruilope L, Sudano I, Ukena C, van Leeuwen E, Volpe M, Windecker S, Witkowski A, Wijns W, Zeller T, Schmieder RE. Proceedings from the european clinical consensus conference for renal denervation: considerations on future clinical trial design. *Eur Heart J* 2015;36:2219–2227.
- Hulsen HT, Nijdam ME, Bos WJ, Uiterwaal CS, Oren A, Grobbee DE, Bots M. Spurious systolic hypertension in young adults; prevalence of high brachial systolic blood pressure and low central pressure and its determinants. *J Hypertens*. 2006;24:1027–1032.
- McEniery CM, Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, Retallick C, Franklin SS, Brown MJ, Lloyd RC, Cockcroft JR, Wilkinson IB; Investigators ES. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension*. 2005;46:221–226.
- Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large A. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605.
- Okon T, Rohnert K, Stiermaier T, Rommel KP, Muller U, Fengler K, Schuler G, Desch S, Lurz P. Invasive aortic pulse wave velocity as a marker for arterial stiffness predicts outcome of renal sympathetic denervation. *EuroIntervention*. 2016;12:e684–e692.
- Desch S, Okon T, Heinemann D, Kulle K, Rohnert K, Sonnabend M, Petzold M, Muller U, Schuler G, Eitel I, Thiele H, Lurz P. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension*. 2015;65:1202–1208.
- Stiermaier T, Okon T, Fengler K, Mueller U, Hoellriegel R, Schuler G, Desch S, Lurz P. Endovascular ultrasound for renal sympathetic denervation in patients with therapy-resistant hypertension not responding to radiofrequency renal sympathetic denervation. *EuroIntervention*. 2016;12:e282–e289.
- Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, van Montfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure M, Cardiovascular V. European society of hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens*. 2014;32:1359–1366.
- Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL. Predictors of blood pressure response in the simplicity htn-3 trial. *Eur Heart J*. 2015;36:219–227.
- Mitchell GF, Lacourciere Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, Block AJ, Pfeffer MA. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation*. 2003;108:1592–1598.
- O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. *Hypertension*. 2005;45:652–658.
- Ewen S, Cremers B, Meyer MR, Donazzan L, Kindermann I, Ukena C, Helfer AG, Maurer HH, Laufs U, Grassi G, Bohm M, Mahfoud F. Blood pressure changes after catheter-based renal denervation are related to reductions in total peripheral resistance. *J Hypertens*. 2015;33:2519–2525.
- Ott C, Schmid A, Toennes SW, Ditting T, Veelken R, Uder M, Schmieder RE. Central pulse pressure predicts bp reduction after renal denervation in patients with treatment-resistant hypertension. *EuroIntervention*. 2015;11:110–116.
- Casey DP, Curry TB, Joyner MJ, Charkoudian N, Hart EC. Relationship between muscle sympathetic nerve activity and aortic wave reflection characteristics in young men and women. *Hypertension*. 2011;57:421–427.
- McEniery CM, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR; Investigators A. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005;46:1753–1760.

SUPPLEMENTAL MATERIAL

Figure S1. Mean change in 24 h systolic blood pressure after three months among patients with combined hypertension, stratified among the tertiles of invasive pulse wave velocity (iPWV, n = 69).

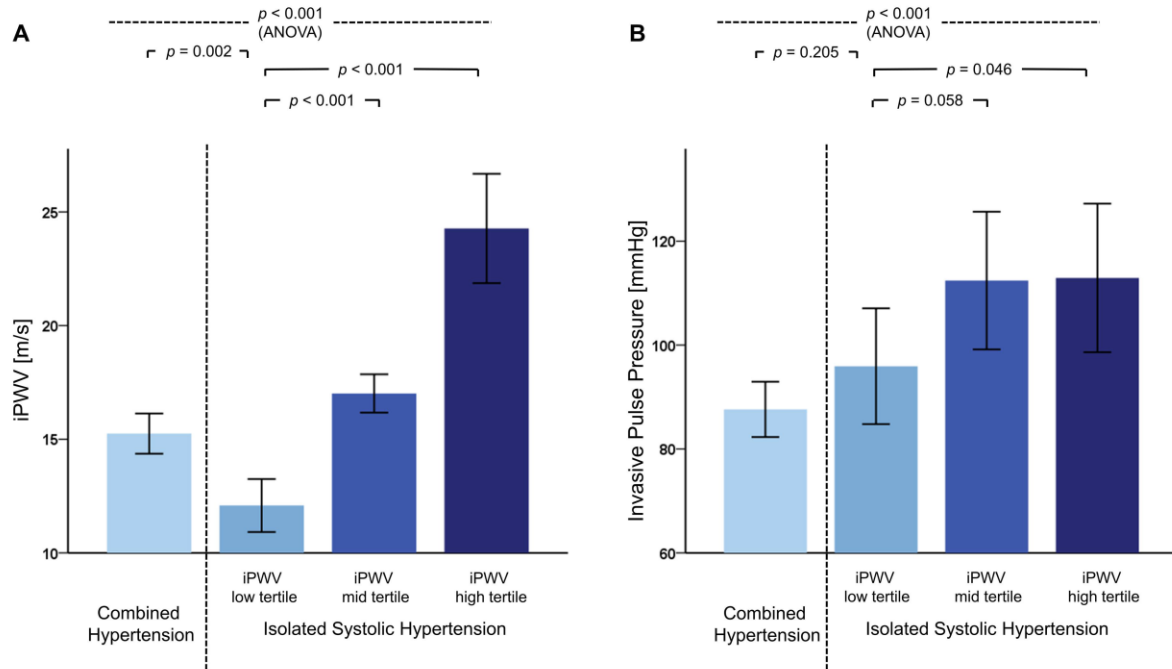


Figure S2. Mean change in 24 h systolic blood pressure after three months among patients with combined hypertension and isolated systolic hypertension, stratified among the tertiles of invasive pulse wave velocity (iPWV) in patients treated with the Symplicity Flex device (n = 65).

