Hypertension

ORIGINAL ARTICLE

Twenty-Four-Hour Pulsatile Hemodynamics Predict Brachial Blood Pressure Response to Renal Denervation in the SPYRAL HTN-OFF MED Trial

Thomas Weber, Siegfried Wassertheurer, Christopher C. Mayer, Bernhard Hametner, Kathrin Danninger, Raymond R. Townsend, Felix Mahfoud, Kazuomi Kario, Martin Fahy, Vanessa DeBruin, Nicole Peterson, Manuela Negoita, Michael A. Weber, David E. Kandzari, Roland E. Schmieder, Konstantinos P. Tsioufis, Ronald K. Binder, Michael Böhm

BACKGROUND: Renal denervation (RDN) lowers blood pressure (BP), but BP response is variable in individual patients. We investigated whether measures of pulsatile hemodynamics, obtained during 24-hour ambulatory BP monitoring, predict BP drop following RDN.

METHODS: From the randomized, sham-controlled SPYRAL HTN-OFF MED Pivotal trial, we performed a post hoc analysis of BP waveforms from 111 RDN patients and 111 sham controls, obtained with a brachial cuff-based sphygmomanometer. Waveforms were acquired during ambulatory BP monitoring at diastolic BP level and processed with validated ARCSolver algorithms to derive hemodynamic parameters (augmentation index; augmentation pressure; backward and forward wave amplitude; estimated aortic pulse wave velocity). We investigated the relationship between averaged 24-hour values at baseline and the change in 24-hour BP at 3 months in RDN patients, corrected for observed trends in the sham group.

RESULTS: There was a consistent inverse relationship between baseline augmentation index/augmentation pressure/backward wave amplitude/forward wave amplitude/estimated aortic pulse wave velocity and BP response to RDN: the decrease in 24-hour systolic BP/diastolic BP was 7.8/5.9 (augmentation index), 8.0/6.3 (augmentation pressure), 6.7/5.4 (backward wave amplitude), 5.7/4.7 (forward wave amplitude), and 7.8/5.2 (estimated aortic pulse wave velocity) mm Hg greater for patients below versus above the respective median value ($P<0.001$ for all comparisons, respectively). Taking augmentation index/augmentation pressure/backward wave amplitude/forward wave amplitude/estimated aortic pulse wave velocity into account, a favorable BP response following RDN, defined as a drop in 24-hour systolic blood pressure of ≥5 mm Hg, could be predicted with an area under the curve of 0.70/0.74/0.70/0.65/0.62 ($P<0.001$ for all, respectively).

CONCLUSIONS: These results suggest that pulsatile hemodynamics, obtained during 24-hour ambulatory BP monitoring, may predict BP response to RDN. **(*Hypertension*. 2022;79:1518–1526. DOI: 10.1161/HYPERTENSIONAHA.121.18641.)**

• **Supplemental Material**

Key Words: area under the curve ■ blood pressure ■ denervation ■ heart rate ■ sphygmomanometer

A series of well-conducted, randomized, sham-controlled clinical trials has established the blood pressure (BP) lowering effect of catheter-based renal denervation (RDN).[1–3] However, mirroring the situation with antihypertensive drugs,[4] the magnitude of the individual BP drop following RDN is highly variable.[1–3] A

Correspondence to: Thomas Weber, Cardiology Department, Klinikum Wels-Grieskirchen, Grieskirchnerstrasse 42, 4600 Wels, Austria. Email thomas.weber3@liwest.at
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NOVELTY AND RELEVANCE

What Is New?

Measures of pulsatile hemodynamics are associated with blood pressure response after RF-based renal denervation. Specifically, 24-hour systolic blood pressure drop at 3 months following renal denervation was up to 8 mm Hg greater with baseline augmentation index/pressure augmentation/backward wave amplitude/forward wave amplitude/estimated aortic pulse wave velocity below the median, as compared with above the median.

What Is Relevant?

These measures can be derived from automated analysis of 24-hour blood pressure waveforms with commercially available 24-hour blood pressure monitors and predict a favourable blood pressure response to renal denervation with area under the curves in the range of 0.70 to 0.74 (for measures of wave reflections).

Clinical/Pathophysiological Implications

Automated measurement of pulsatile hemodynamics, particularly wave reflections, obtained during the routine workup before renal denervation may help selecting patients with a favourable blood pressure response to renal denervation. Additional studies are needed to confirm the findings and to expand the results to patients treated with antihypertensive drugs.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
AIx	augmentation index
AIx75	heart-rate corrected augmentation index
AP	pressure augmentation
AUC	area under the curve
BP	blood pressure
DBP	diastolic blood pressure
ePWV	estimated aortic pulse wave velocity
HR	heart rate
Pb	backward wave amplitude
Pf	forward wave amplitude
PWV	pulse wave velocity
RDN	renal denervation
SBP	systolic blood pressure

number of factors may influence the short- and long-term treatment effect, for example, the variable contribution of the sympathetic nervous system to BP elevation, genetic background, comorbidities, or accompanying antihypertensive treatments. Therefore, a simple, noninvasive predictor of BP response to RDN remains a major unmet need. Multiple indices of increased sympathetic nervous system activity or reduced arterial stiffness have been proposed, although the only consistent finding has been the association between a higher baseline BP and a larger BP drop following the intervention, which is rather nonspecific for both device and pharmaceutical therapies.

Nighttime systolic BP measured by 24-hour ambulatory BP monitoring (ABPM) and its variability have been shown to predict BP response following ultrasound-based RDN, albeit with low sensitivity.[5] Beyond BP measured at the brachial artery, other hemodynamic measures may play a role in identifying appropriate candidates for RDN. Often summarized as pulsatile hemodynamics, arterial stiffness (pulse wave velocity [PWV]), wave reflections, and central (aortic) hemodynamics can be quantified noninvasively, easily, and reproducibly.[6,7] Arterial wave reflections predict cardiovascular events,[8–11] independent of brachial BP, and may be more sensitive than brachial BP to detect antihypertensive drug-induced hemodynamic changes.[12,13] Recently, assessment of pulsatile hemodynamics with dedicated brachial cuffs, suitable for 24-hour ABPM, became commercially available.[14,15] We hypothesized that hemodynamic measures, particularly wave reflections, obtained during regular 24-hour ABPM in the workup before RDN, may predict BP response to RDN.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Medtronic at sandeep.brar@medtronic.com.

Study Design and Randomization

SPYRAL HTN-OFF MED Pivotal[16] was a multicenter, single-blind, randomized, sham-controlled trial conducted at 44 sites in Australia, Austria, Canada, Germany, Greece, Ireland, Japan, the United Kingdom, and the United States. Adult patients (age 20–80 years) with office systolic BP (SBP) ≥150 mm Hg and <180 mm Hg, office diastolic BP (DBP) ≥90 mm Hg, and an average 24-hour ambulatory SBP ≥140 mm Hg and <170 mm Hg were enrolled in the trial. Twenty-four-hour ABPM was considered valid if at least 21 day-time readings and 12 night-time readings had been recorded and was performed at baseline and at 3 months. The trials complied with the Declaration of Helsinki, all local ethics committees approved the research protocols, and all patients provided written informed consent. T. Weber, B. Hametner, C.M. Mayer, and S. Wassertheurer had full

access to all the data in the study and take responsibility for its integrity and the data analysis.

Full details of the randomization strategy have been described previously.[16] Briefly, patients were randomized 1:1 to RDN or sham procedure. Before randomization, patients were required to be off all antihypertensive medications. Tandem high performance liquid chromatography and mass spectroscopy of urine and plasma by an independent laboratory were used to evaluate and confirm absence of antihypertensive medications.[17] Office BP measurements were obtained via automatic BP monitor (Omron, Omron Healthcare, Inc, Lake Forest, IL).

Procedures

Ablation treatment with the Symplicity Spyral multielectrode catheter (Medtronic, Galway, Ireland) and the Symplicity G3 (Medtronic, Minneapolis, MN) generator was performed using a standardized approach of targeting all accessible renal arterial vessels, including branch vessels and accessory arteries with a diameter >3 mm to <8 mm.[1,16] The sham procedure consisted of a renal angiogram only. Patients remained off antihypertensive medications until the primary end point at 3 months, unless there were safety concerns related to uncontrolled hypertension.

Measurement of Pulsatile Hemodynamics

Twenty-four-hour ABPM, providing brachial SBP and DBP, as well as heart rate (HR), was performed in all study participants with an identical automated brachial cuff-based oscillometric device (Mobil-O-Graph PWA, IEM, Stolberg, Germany), following published recommendations.[18] The device has been validated in adults for 24-hour HR,[19] for brachial BP measurement according to recommendations of the British Hypertension Society[20] and the European Society of Hypertension,[21] for 24-hour brachial ABPM[22] against a widely used device, and has received clearance from the US Food and Drug Administration and bears the Conformité Européenne mark.

The ARCSolver algorithm for assessment of aortic SBP with the device has been published and validated invasively against high-fidelity pressure measurements[15] and fluid-filled catheter-based measurements.[23] Briefly, immediately after the conventional brachial oscillometric BP measurement, pulse waves are recorded, using the brachial cuff, at DBP level for ≈10 seconds, using a high-fidelity pressure sensor (MPX5050, Freescale Inc., Tempe, AZ). The sensor is connected to a 12-bit A/D converter by means of an active analogue band bass filter. After digitalization, a 3-step quality-control algorithm is applied.[15] The recorded brachial pulse wave is calibrated with measured brachial BP. Thereafter, an aortic pulse waveform is generated by means of a generalized transfer function. Modulus and phase characteristics of the transfer function have been published.[24] Parameters associated with wave reflection, derived by mathematical analysis directly from pressure curves (pulse waveform analysis), are augmented pressure (the increase in BP following the inflection point of the BP curve) and augmentation index (AIx; the ratio pressure augmentation [AP]/cPP). As AIx is inversely related to HR, a normalization for HR 75/min can be used (AIx75). A complimentary method to quantify wave reflections is Wave Separation Analysis,[25] a method using simultaneous calculation of pressure and flow waves, yielding estimates of the amplitudes of antegrade and reflected (forward: Pf; backward: Pb) waves—Figure 1. Finally, an estimate of aortic PWV (ePWV), based on age, SBP and waveform characteristics, is determined.[26] A more detailed description is given in the Supplemental Material. Both sets of parameters, measured with the Mobil-O-Graph PWA device, have been validated against accepted gold standards.[10,24] The reproducibility and the feasibility of ambulatory hemodynamic measurements with the device have also been confirmed.[27] To allow a standardized procedure, all analyses were performed centralized using ARCSolver version DLL 1.7.2.

Statistical Analysis

All valid ambulatory BP measurements were included in the analysis based on the snapshot dated January 2020. Only study participants with available full pressure waveform data from 24-hour ABPM could be included.

Enrollment in the SPYRAL trial was not stratified per baseline pulsatile hemodynamics. Baseline continuous variables were summarized as mean±SD and compared using *t* tests or Welch test, as appropriate. Categorical variables were summarized as counts and percentages and compared between groups using χ^2 or Fisher exact tests for categorical variables. For all parameters, 24-hour averages per patient were calculated. Average 24-hour BP changes from baseline to 3 months in each RDN and sham patient were compared, using paired *t* tests (within the group) and unpaired *t* tests (RDN versus sham).

The aim of this post hoc analysis of the SPYRAL HTN-OFF MED Pivotal trial was to investigate, whether pulsatile hemodynamics, in particular measures of wave reflections (AIx, AIx75, AP, Pb), can predict changes in 24-hour BP from baseline to 3 months after RDN. Due to the sham-controlled design of the studies, the BP changes due to the sham effect could be taken into account, which gave us the opportunity to investigate true effects of the intervention.

Linear regression was used to investigate the relationship between a baseline parameter and BP changes at 3 months in the sham group. When the baseline parameter values are replaced by the residuals from the regression line and the mean value of the parameter is added, the trends in the sham group can be removed (Figure S1). To account for this effect obtained from the sham group and the RDN group, the same procedure, that is, with the beta coefficient obtained from the Sham group, was applied to the data from the RDN group. By this, the linear trends between BP change and baseline parameters, as obtained in the sham group, were removed from the RDN group. This correction was performed for each parameter of interest separately. This approach was taken to allow the following analysis of prediction for corrected parameter values for multivariable models (combination of parameters as predictors, eg, AIx and HR).

Receiver-operating characteristics curve analysis was performed to assess the predictive value of the parameters of interest for a clinically relevant BP response at 3 months, defined by a reduction of average 24-hour SBP of at least 5 mm Hg.[28] To investigate the additive/independent value of measures of pulsatile hemodynamics for BP responder status, logistic regression models (enter method) were constructed, including age, SBP, body height, and HR (with the exception

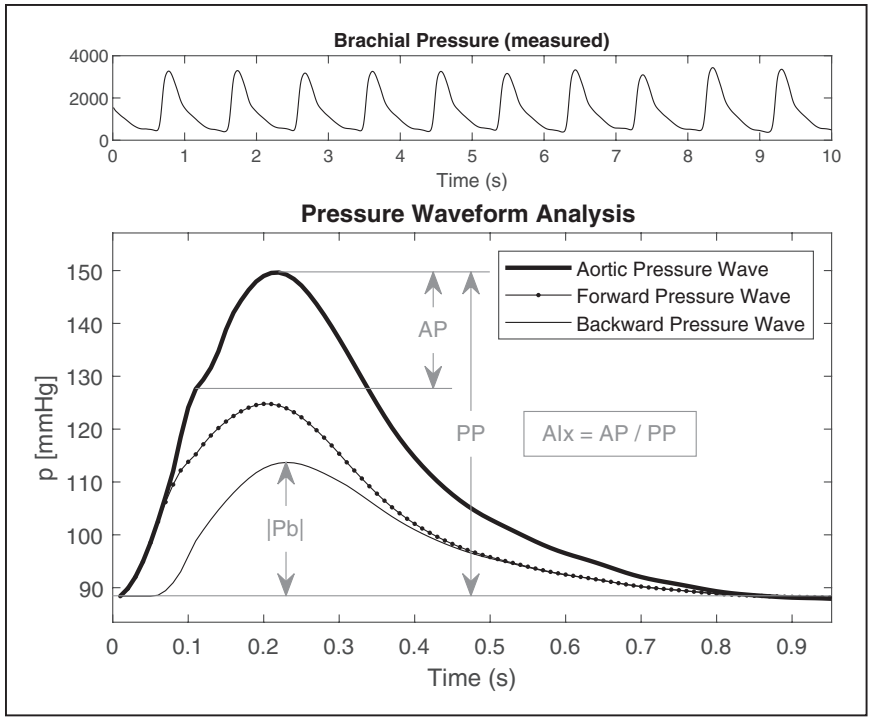

Figure 1. Quantification of wave reflections from brachial cuff-based waveforms.
Upper: Example of high-quality pressure waveforms, obtained with a brachial cuff. **Lower**: Using pulse waveform analysis, an inflection point is identified, and pressure augmentation (AP) is determined; augmentation index (AIx) is calculated as AP/central pulse pressure (PP). Using combined analysis of pressure and flow signals (derived from validated flow models), wave separation is performed, yielding amplitudes of forward (Pf) and backward (Pb) waves.

of the model including AIx75) and one pulsatile hemodynamics parameter.

Statistical significance was assumed at a 5% level. Statistical analyses were performed using Matlab R2019b (The MathWorks, Inc, Natick, MA) and MedCalc Statistical Software 19.2 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

The final study sample consisted of 222 SPYRAL HTN-OFF MED pivotal patients (111 RDN, 111 sham), out of 166 RDN and 165 sham patients in the original publication.[16] There were a few slight differences in baseline characteristics between patients included and not included (as full data were not available) in the current analysis, but importantly no differences between baseline SBP and DBP (Table S1).

Baseline characteristics were well balanced between RDN and sham patients (Table 1), as in the original publication.[16] Average 24-hour SBP/DBP at baseline was 151 (SD 7.9)/98 (SD) mm Hg in RDN patients and 151 (SD 7.8)/99 (SD) mm Hg in sham controls, exactly matching these values in the original publication.[16] Likewise, changes in average 24-hour SBP/DBP at 3 months were − 4.5 (SD 10.6)/−3.6 (SD 6.6) mm Hg (RDN patients) and −0.6 (SD 9.0)/−0.7 (SD 5.4) mm Hg (sham controls) in our sample, and −4.7 (SD 10.4)/−3.7 (SD 6.6) mm Hg (RDN patients) and −0.6 (SD 8.6)/−0.8 (SD 5.3) mm Hg (sham controls) in the original publication.[16]

Average 24-hour measures of pulsatile hemodynamics (AIx, AIx75, AP, Pb, Pf, ePWV) at baseline were not different between RDN and sham controls groups (Table 2). AIx75 decreased significantly from baseline to 3 months in both groups. There were no significant differences in changes of measures of antegrade and reflected waves from baseline to 3 months between RDN and sham controls, only ePWV decreased slightly more in RDN patients (Table 2).

Predictors of BP Response

Without adjustments, average 24-hour SBP at baseline was directly related to BP changes at 3 months (Figure S2) in the RDN and sham group, illustrating the law of the initial value in RDN patients and regression to the mean in sham controls. Of note, contrasting effects were seen for baseline HR and AIx in the RDN and sham group: higher baseline HR was associated with a greater BP response at 3 months in the RDN group, but not in the sham group (Figure S2). In addition, a lower AIx was associated with a greater change in average 24-hour SBP at 3 months in the RDN group, with an opposite trend in the sham group. Results for the remainder measures of wave reflections and antegrade wave as well as ePWV (AIx75, AP, Pb, Pf, ePWV) were consistent (Figure S2).

After corrections for the sham group (illustrated in Figure S1), baseline average 24-hour SBP in the RDN group was no longer associated with BP changes at 3 months (Figure S3). In contrast, sham group corrected average 24-hour HR at baseline was directly associated with BP changes following RDN, with SBP/DBP drop following RDN being 6.5/5.0 mm Hg greater in the group with baseline HR above as compared with below the median, respectively. All measures of wave

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Table 1. Baseline Data of the Study Population

Characteristic Mean±SD or No. (%)	RDN (N=111)	Sham control (N=111)
Age, y	53.0±11.0	51.6±11.0
Male	72.1% (80/111)	69.4% (77/111)
BMI, kg/m²	31.3±6.3	30.6±5.5
Race		
White	31.5% (35/111)	31.5% (35/111)
Black	18.0% (20/111)	14.4% (16/111)
Asian	4.5% (5/111)	3.6% (4/111)
Other	0.9% (1/111)	0.9% (1/111)
Not reportable per local laws	45.0% (50/111)	49.5% (55/111)
Diabetes (all type 2)	1.8% (2/111)	3.6% (4/111)
Current smoker	18.0% (20/111)	17.1% (19/111)
Obstructive sleep apnea	9.0% (10/111)	7.2% (8/111)
Peripheral artery disease	0.0% (0/111)	0.0% (0/111)
Coronary artery disease*	0.0% (0/111)	4.5% (5/111)
Average 24-hour SBP baseline, mm Hg	151.0±7.9	151.1±7.8
Average 24-hour DBP baseline, mm Hg	97.8±7.4	99.1±7.4
Average 24-hour heart rate, bpm	73.8±10.3	74.4±10.3

BMI indicates body mass index; DBP, diastolic blood pressure; RDN, renal denervation; and SBP, systolic blood pressure.

*Coronary events occurred >3 mo before randomization.

reflections showed a similar association with RDN-related BP changes at 3 months: after correction for the BP changes in the sham group, average 24-hour SBP/DBP reduction in RDN patients was 7.8/5.9, 4.2/2.3, 8.0/6.3, and 6.7/5.4 mm Hg greater for the respective baseline values of AIx, AIx75, AP, and Pb below the median, as compared with above the median (Figure 2A through 2D, Table S2). Likewise, after correction for the BP changes in the sham group, average 24-hour SBP/DBP reduction at 3 months in RDN patients was 5.7/4.7 and 7.8/5.2 mm Hg greater for the respective baseline values of Pf (a measure of forward wave) and ePWV below the median, as compared with above the median (Figure 2E and 2F, Table S2).

Analysis stratified by age and sex showed similar trends in men and women, and young (<54 years) and older (≥54 years) participants (Figures S4 and S5).

Additional analysis, excluding the small number of patients in whom antihypertensive medications were detected at baseline (n=10 for RDN; n=9 for Sham), were consistent with the main findings (data not shown).

In receiver-operating characteristics analysis, sham-group corrected baseline average 24-hour HR, AIx, AIx75, AP, Pb, Pf, and ePWV were all significant predictors of a clinically relevant BP change following RDN (Table 3). The largest area under the curve (AUC) was obtained for AP (0.74 [CI, 0.64–0.84], $P<0.0001$), with AUCs in the same range for AIx75, AP and Pb, but also Pf and ePWV, respectively. In contrast, AUC for HR was 0.62 (CI, 0.52–0.71; $P=0.02$). The difference between AUCs for SBP and HR were statistically not different, whereas the AUCs for all wave reflection parameters were statistically different (larger) than the AUCs for HR (Table S3). The combination of HR with one of the parameters related to wave reflection led to minor improvements of AUCs (Table S4).

In logistic regression models, including HR, age, body height, and baseline SBP, all measures of pulsatile hemodynamics were inversely and independently associated with BP responder status at 3 months (Table S5).

DISCUSSION

Accurate noninvasive, reproducible, easy-to-obtain predictors of future BP reduction following RDN have not yet been identified. Against the background of a randomized, single-blinded, sham controlled clinical trial,

Table 2. Average 24-Hour Measures of Wave Reflection at Baseline and Change at 3 mo Follow Up, Stratified by Treatment Group

Measurement	Baseline			Change from baseline to 3 mo		
	RDN (N=111)	Sham control (N=111)	*P* value*: RDN vs sham control	RDN	Sham Control	*P* value†: RDN vs sham control
AIx	26.1 (SD 7.3)	26.1 (SD 7.4)	1.00	−0.7 (SD 4.2)	−1.3 (SD 5.3)‡	0.30
AIx75	24.8 (SD 7.6)	25.2 (SD 7.2)	0.63	−0.9 (SD 3.8)‡	−1.0 (SD 4.4)‡	0.93
AP mm Hg	11.2 (SD 3.9)	11.2 (SD 4.6)	1.00	−0.3 (SD 2.5)	−0.5 (SD 3.5)	0.69
Pb mm Hg	16.4 (SD 2.5)	16.3 (SD 3.0)	0.68	−0.1 (SD 1.9)	0.1 (SD 2.3)	0.49
Pf mm Hg	25.5 (SD 3.3)	25.2 (SD 3.6)	0.49	−0.3 (SD 2.6)	0.03 (SD 2.8)	0.36
ePWV m/s	8.5 (SD 1.3)	8.4 (SD 1.3)	0.37	−0.12 (SD 0.3)	−0.01 (SD 0.3)	0.009
HR bpm	73.8 (SD 10.3)	74.4 (SD 10.3)	0.64	−0.5 (SD 6.1)	0.7 (SD 5.6)	0.14
SBP mm Hg	151.0 (SD 7.9)	151.1 (SD 7.8)	0.92	−4.5 (SD 10.6)‡	−0.6 (SD 9.0)	0.003

AIx indicates augmentation index; AIx75, augmentation index normalized for heart rate 75/min; AP, pressure augmentation; ePWV, estimated aortic pulse wave velocity; HR, heart rate; Pb, backward wave amplitude; Pf, forward wave amplitude; RDN, renal denervation; and SBP, systolic blood pressure.

**P* values comparing RDN and sham controls at baseline (unpaired *t* test).

†*P* values comparing changes from baseline to 3 mo between RDN and sham controls (unpaired *t* test).

‡$P<0.05$ comparing baseline and 3 mo values for RDN and Sham, respectively (paired *t* test).

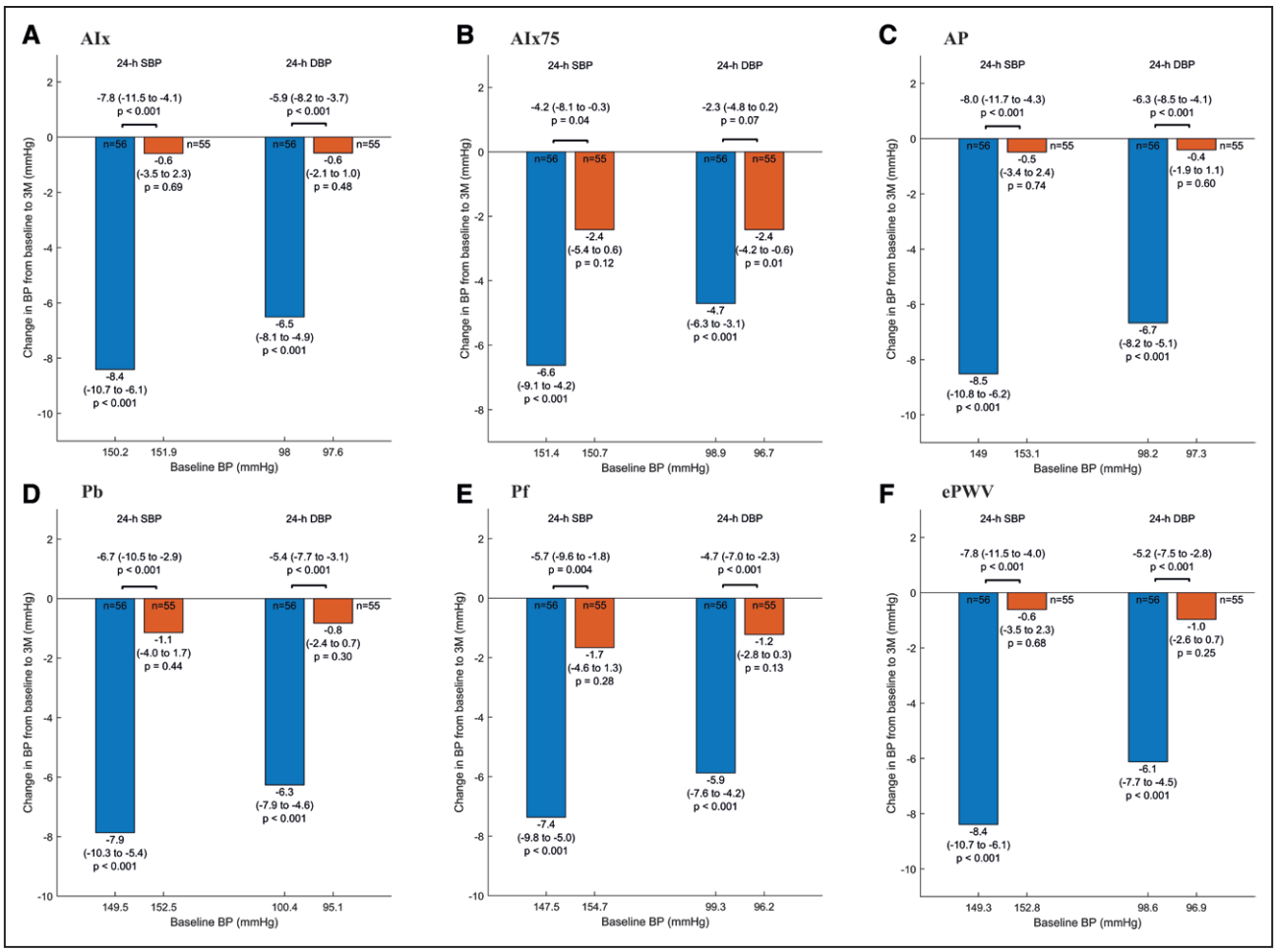

Figure 2. Changes in 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3 mo in renal denervation (RDN) patients, corrected for changes in the sham group.
Changes of average 24-hour SBP and DBP from baseline to 3 mo, stratified by baseline average 24-hour values (below and equal the respective median value–blue columns–vs above the respective median value–orange columns) in RDN patients, corrected for changes in the sham group. *P* values below the bars are from a pairwise comparison between baseline and 3 mo; *P* values above the bars comparing changes from baseline to 3 mo for ≤ median vs > median of corrected baseline value (unpaired *t* test); data in parentheses are 95% CIs. **Upper**: Augmentation Index (Aix; **A**), heart-rate 75 adjusted AIx (AIx75; **B**), pressure augmentation (AP; **C**). **Lower**: Backward wave amplitude (Pb; **D**), forward wave amplitude (Pf; **E**), estimated pulse wave velocity (ePWV; **F**).

we observed that measures of pulsatile hemodynamics, mainly pressure wave reflections, obtained during regular 24-hour ABPM, were associated with greater BP response 3 months after RDN in patients with uncontrolled hypertension in the absence of antihypertensive drug therapy.[29]

Wave reflections are thought to arise at sites of impedance change or mismatch along the arterial tree, such as points of branching, change in lumen diameter (taper) and structural properties.[6] Multiple small reflections, originating from distributed reflection sites, are transmitted back toward the heart and merge and summate into a single net reflected wave.[6] Wave reflections cannot be detected from conventional (auscultatory or oscillometric) BP measurement, but may be quantified from pressure waveforms alone, yielding AIx, AIx75 and AP, or through combined analysis with flow waveforms, yielding Pb. As a more sensitive measure of BP, wave reflections provide closer insights into hypertension-associated organ damage,[10] cardiac function[30] and the risk of cardiovascular events,[8–10] as compared with brachial BP. Compared with brachial BP, measures of wave reflections are more sensitive to monitor antihypertensive drug-induced hemodynamic changes,[31] as well as changes of hypertension-mediated organ damage.[12,13] RDN has previously been shown to attenuate wave reflections in patients with resistant hypertension.[32,33] Changes in AIx75 following RDN, however, were not related to changes in muscle sympathetic nerve activity.[32]

Analyses of increased RDN response have focused primarily on indices of increased sympathetic nervous system activity (or in association with an increased activity of the renin-angiotensin-system[34]) or lower arterial stiffness at baseline. The hypothesis that patients with a stiffer arterial system might not respond as well to RDN was initially based on observational trials showing

Table 3. Receiver-Operating Curve Analysis Investigating the Predictive Value for Waveform Parameters and Heart Rate to Predict a Clinically Meaningful Blood Pressure Response to Renal Denervation, Defined as a Reduction in Average 24-Hour Systolic Blood Pressure From Baseline to 3 mo of at Least 5 mm Hg

Measurement	AUC	95% CI	*P* value
AIx	0.70	0.61–0.79	<0.0001
AIx75	0.62	0.52–0.71	0.02
AP	0.74	0.64–0.82	<0.0001
Pb	0.70	0.61–0.79	<0.0001
Pf	0.65	0.55–0.74	0.004
ePWV	0.62	0.53–0.71	0.03
HR	0.62	0.52–0.71	0.02
SBP	0.54	0.44–0.63	0.48

Blood pressure response was adjusted for changes in the sham group. AIx indicates augmentation index, AIx75, augmentation index normalized for heart rate 75/min; AP, augmentation pressure; AUC, area under the curve; ePWV, estimated aortic pulse wave velocity; HR, heart rate; Pb, backward wave amplitude; Pf, forward wave amplitude; and SBP, systolic blood pressure.

apparently worse treatment response in patients with isolated systolic hypertension (defined as office DBP<90 mm Hg), a condition characterized by increased arterial stiffness.[35] These findings were supported by observational results, suggesting that increased arterial stiffness, measured invasively as aortic PWV, may be associated with less BP lowering following RDN.[36] Thus, patients with office DBP <90 mm Hg were excluded from the SPYRAL HTN-OFF MED Pilot[1] and Pivotal[16] trials. Wave reflections, in particular, when quantified with pulse waveform analysis, are related to arterial stiffness through the timing of the arrival of the reflected wave. Our results therefore confirm and extend these previous findings.

However, pulse waveform analysis-derived measures of wave reflections also depend on age, sex, body height, HR and left ventricular function.[6,37–40] A previous analysis of the association between HR and BP response to RDN in the SPYRAL HTN OFF MED pilot trial[41] demonstrated that RDN reduces 24-hour ambulatory HR (plus HR in numerous time windows) and that higher baseline 24-hour HR, likely a sign of higher sympathetic nervous system activity, predicted greater BP reductions following RDN.[42] Taking the inverse relationship between HR and measures of wave reflections[43] into consideration, our results are again consistent. Furthermore, receiver-operating characteristics analysis showed that the predictive value for RDN-induced BP response provided by measures of wave reflections outperformed HR alone, and is indeed additive when the less HR-dependent WSA-based measure Pb is used. The other determinants of a lower AIx/AP, that is, younger age and male sex, appear to play only a minor role, as evidenced by our stratified analysis. Also, severely impaired systolic function, another determinant of a low AIx/AP,[37,38] was not present in the patients studied.

We would like to stress one methodological aspect of our study: previously, potential predictors of BP response to RDN have been addressed often in treatment cohorts[36,44] only, that is, without a control group. Even if such analysis provides important insights, including the much-needed real-world evidence from large registries,[45] interpretation of the results can be challenging. Statistical phenomena such as regression to the mean can occur, nicely depicted in the sham group of our study (Figure S1). The only consistent predictor of a greater BP response following RDN so far was a higher baseline BP.[46] This finding is evident in the RDN group of our study as well. However, due to the study design, we were able to correct our results for BP changes in the sham group. This led to complete disappearance of the law of the initial value in RDN patients. In other words, sham-corrected baseline BP was no longer predictive of BP changes following RDN. In contrast, the predictive value of measures of wave reflections and, to a lesser degree, measures/estimates of forward wave and aortic stiffness, was strengthened, suggesting that the latter is a true biological mechanism.

Study Limitations

The current study is a post hoc analysis from a prospective, randomized sham-controlled clinical trial, including the majority, but not all of the original study participants. Next, as patient inclusion in the trial was not stratified by measures of pulsatile hemodynamics, causality cannot be inferred. However, assessment of wave reflections, forward wave and arterial stiffness was blinded, and independent from the treatment assigned. Moreover, taking advantage of the study design, the results in RDN patients could be compared with and adjusted for the sham-group results. Next, no adjustment for multiple statistical testing was performed due to the explorative design of the study. Finally, the predictive value of pulsatile hemodynamics for RDN-induced BP reduction in patients treated with antihypertensive drugs and in patients with ISH needs to be tested in the future.

Perspectives

Measures of pulsatile hemodynamics (wave reflections—AIx, AIx75, AP, Pb; forward wave—Pf; aortic stiffness—ePWV) obtained from routine 24-hour ABPM were associated with BP response to radiofrequency RDN at 3 months. More accurate identification of patients most likely to respond to RDN therapy may require a combination of 2 or more measurements, for instance pulsatile hemodynamics and neurohormonal indices.[34]

ARTICLE INFORMATION

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Affiliations

Cardiology Department, Klinikum Wels-Grieskirchen, Austria (T.W., K.D., R.K.B.). AIT - Austrian Institute of Technology, Vienna, Austria (S.W., C.C.M., B.H.). Perelman School of Medicine, University of Pennsylvania, Philadelphia (R.R.T.). Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany (F.M., M.B.). Jichi Medical University School of Medicine, Tochigi, Japan (K.K.). Medtronic PLC, Santa Rosa, CA (M.F., V.D., N.P., M.N.). SUNY Downstate College of Medicine, Brooklyn, NY (M.A.W.). Piedmont Heart Institute, Atlanta, GA (D.E.K.). Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich Alexander University Erlangen Nürnberg, Germany (R.E.S.). 1st Cardiology Clinic, National and Kapodistrian University of Athens, Hippokration Hospital, Greece (K.P.T.).

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