Original Article

Changes in renal artery dimensions are associated with clinical response to radiofrequency renal denervation: a series of studies using quantitative angiography and intravascular ultrasound

Thomas Weber[a], Jörg Kellermair[b], Karen T. Witberg[c], Jurgen Ligthart[c], Robert J. Melder[d], Thomas Forstner[e], and Bernd Eber[a]

Objective: Renal denervation (RDN) can cause focal (notches) and global (spasms) changes in renal artery dimensions. We quantified these changes and related them to renal norepinephrine tissue content in animals and to blood pressure (BP) changes in patients.

Methods: We measured renal artery dimensions pre-RDN and post-RDN, utilizing quantitative renal angiography (QRA) in a porcine model and in a retrospective patient cohort, and intravascular ultrasound (IVUS) in a prospective patient cohort. Focal and global measurements were minimum and mean diameter/area/volume with QRA, minimum lumen/vessel/wall area and volume with IVUS. BP was assessed with 24-h ambulatory monitoring, norepinephrine content with liquid chromatography.

Results: In 36 pigs treated unilaterally with RDN, norepinephrine content of the treated right kidney was 48.2% of the untreated left kidney. QRA measurements following RDN were associated with norepinephrine content only of the (treated) right kidney. In the human QRA study ($n = 43$ patients), mean 24-h BP fell by 8/4 and 12/6 mmHg at 1 and 12 months, respectively. More pronounced changes in QRA measurements were associated with a more pronounced BP drop. In multiple regression models, the change in minimum diameter was independently associated with BP changes at 12 months. In the prospective IVUS study ($n = 17$ patients), a larger decrease in minimum lumen/vessel area and larger increase of wall area/volume were associated with a larger BP drop.

Conclusion: Focal and global changes in renal arteries following RDN can be quantified, using QRA or IVUS, and may serve as markers of a successful procedure.

Keywords: quantitative renal angiography, renal artery, renal denervation, renal nerves, sympathetic nervous system

Abbreviations: ABPM, ambulatory blood pressure monitoring; AUC, area under the curve; BP, blood pressure; DICOM, digital imaging and communications in medicine; ICC, intraclass correlation coefficient; IVUS, intravascular ultrasound; LA, lumen area; LV, lumen volume; NE, norepinephrine; OCT, optical coherence tomography; QRA, quantitative renal angiography; RA, renal artery; RDN, renal denervation; RF, radiofrequency; ROC, receiver operating characteristics; VA, vessel area; VV, vessel volume; WA, wall area; WV, wall volume

INTRODUCTION

Renal sympathetic denervation (RDN) using radiofrequency energy is an emerging technique to treat patients with resistant hypertension [1–3]. A recent single-blind, randomized, sham-controlled trial, however, failed to show a significant blood pressure (BP) reduction in RDN patients, as compared with the sham group [4]. The possible explanations have been widely discussed [5], and it was pointed out that the success of RDN cannot be predicted during the procedure [6]. In a recent consensus document, it was stated that 'The lack of reliable markers of procedural success to immediately establish on time whether denervation has been completely achieved in a specific patient remains the major unmet need' [7].

The pathophysiological mechanism of RDN is believed to be the disruption of renal sympathetic nerves that are distributed around the circumference of the renal arteries [8]. In animal studies, consecutive axonal degeneration of these nerves in addition to early and late vessel wall changes induced by RDN has been confirmed [9,10]. In patients, constant monitoring of temperature and impedance during the ablation ensures stable vessel wall contact of the catheter, but the biological effect of the

Journal of Hypertension 2017, 35:2069–2076

[a]Cardiology Department, Klinikum Wels-Grieskirchen, Wels, [b]Cardiology Department, Kepler University Clinic, Linz, Austria, [c]Thoraxcentre Erasmus MC, Rotterdam, The Netherlands, [d]Medtronic Cardiovascular, Santa Rosa, California, USA and [e]Department of Applied Systems Research and Statistics, Johannes Kepler University, Linz, Austria

Correspondence to Thomas Weber, MD, Cardiology Department, Klinikum Wels-Grieskirchen, Grieskirchnerstrasse 42, 4600 Wels, Austria. Tel: +43 7242 415 2215; e-mail: thomas.weber3@liwest.at

Received 4 December 2016 **Revised** 11 March 2017 **Accepted** 11 April 2017

DOI:10.1097/HJH.0000000000001409

radiofrequency energy has not been quantified during the procedure so far.

In preclinical experiments [9] and in clinical studies [1,2,4], acute discrete narrowings in the angiographic image of the renal artery corresponding to the region of energy application (known as notches) and global spasm of the renal artery following radiofrequency energy delivery were noted in some, but not all, patients [4]. So far, these lesions have been viewed primarily as a possible safety issue. A study using optical coherence tomography (OCT) [11] and various energy delivery systems for RDN reported vasospasm in 42% of the patients and endothelial–intima edema of varying degree in most patients, some of them invisible on angiography.

We hypothesized that more pronounced physical vessel wall changes, which can be seen as a marker of the biological effect of radiofrequency energy on the renal artery, might be associated with more pronounced sympathetic nerve injury. This in turn might influence renal norepinephrin content and BP changes following RDN. We tested this hypothesis in an animal model and in patients undergoing RDN, using quantitative renal angiography (QRA) and intravascular ultrasound (IVUS).

METHODS

Animal study

Data from 36 male (castrated) or female (nulliparous) Yorkshire domestic farm swine, weighing between 54 and 68 kg, were analyzed. This post-hoc analysis of a previously performed study, investigating the impact of lesion placement on efficacy and safety of RDN, was designed to examine the changes in QRA measurement of renal artery dimensions induced by RDN acutely and at days 7–8 and the possible impact of renal artery dimensions post-RDN on norepinephrin concentrations in the cortex of the kidney. To control for potential variations in norepinephrin concentration between swine, RDN was performed only in the right renal arteries. Thus, the untreated left renal artery and kidney served as the control within the test system. Angiograms were performed, using a GE OEC 9800 C-Arm and transferred to a GE AI 1000 CRS with GE OEC medical systems software version 4.2.2.2 (GE Healthcare, Chalfont St Giles, Buckinghamshire, UK) for review and file transfer. Once angiography was performed, a single-electrode RDN catheter (Symplicity Flex; Medtronic Cardiovascular, Santa Rosa, California, USA) was advanced into the main right renal artery, and treatment ablations were performed with six 120-s ablations delivered in a helical pattern, employing a proximal movement of the catheter toward the aortic ostium following each treatment. Seven to eight days after the radiofrequency ablation, treatments were performed; all test animals underwent follow-up angiography to check for vessel patency, and tissues were collected from all animals following termination for bioanalytical analysis. Renal cortical norepinephrin content was measured as previously described [12], using frozen tissue samples and HPLC. All animal experiments were performed at Surpass Silicon Valley (Mountain View, California, USA) and adhered to the Guide for the Care and Use of Laboratory Animals of the National Research Council, Eighth Edition, 2011, under an approved Institutional Animal Care and Use Committee protocol, in compliance with the Animal Welfare Act and the US Food and Drug Administration regulations and their amendments. Animal care and analytical procedures were similar to a follow-up study, in which treatment was advanced into more distal parts of the renal artery [12]. We obtained ethics committee permission for this post-hoc analysis (Ethics committee of Upper Austria, K-81-15).

Patients for quantitative renal angiography study

RDN was performed in all patients due to resistant hypertension. With respect to patient selection and diagnostic procedures, we followed the principles outlined in our national recommendations [13]. In this retrospective analysis, we included all patients ($n=51$) who underwent RDN from January 2011 to December 2013 at our institution, a tertiary care Cardiology Department and Center of Excellence (European Society of Hypertension). We excluded patients due to simultaneous renal artery stenting ($n=4$), failure to obtain similar angiographic projections pre-RDN and post-RDN ($n=2$), and missing 24-h ambulatory BP monitoring at follow-up ($n=2$), leaving 43 patients for this analysis. Ethics committee approval has been obtained (Ethics committee of Upper Austria, K-35-13).

Patients for intravascular ultrasound study

We prospectively investigated renal arteries of 17 patients undergoing RDN at our institution from August 2013 to June 2015. Ethics committee approval has been obtained (Ethics committee of Upper Austria, D-19-13), and all patients gave written informed consent.

Intervention

RDN was performed in (and in most patients confined to) the main renal artery, using a single-electrode RDN catheter (Symplicity Flex) in all study patients of the QRA study, and in nine patients of the IVUS study, and a multielectrode catheter (Spyral; Medtronic Cardiovascular, Santa Rosa, California, USA), in eight patients of the IVUS study. With the Flex catheter, multiple radiofrequency ablations of 8 W or less for up to 2 min each were applied, aiming for at least five ablations per renal artery, at least 5 mm apart, and circumferentially rotated as previously described [1]. With the Spyral catheter, in which four radiofrequency electrodes are mounted approximately 5 mm apart and at 90° of separation from each other in a helical pattern, we aimed to achieve at least one automated four-quadrant ablation treatment for 1 min in each renal artery. Prior to RDN, 200 μg nitroglycerine was administered in each renal artery.

Quantitative renal angiography

In patients, renal angiography and RDN were performed on a monoplane or biplane digitized coronary angiography equipment (Cathcor; Siemens, Erlangen, Germany). Anonymized copies of the angiograms were stored on DVD and sent to the blinded analysts (J.L. and K.W.). From the angiograms, pre-RDN and post-RDN from each renal artery in identical projections, a frame at the same moment in the ECG was selected for QRA and imported in the analysis system (CAAS 5.11.2; Pie Medical, Maastricht, The Netherlands). Angiographic images were calibrated using the 6-F-guiding catheter.

The region of interest was determined by the most distal location that the RDN catheter had reached, documented on the angiograms. The region borders were set between the first side branch distal from the most distal location of the RDN catheter and the ostium of the renal artery. Vessel dimensions were determined via automated contour detection, in case of error corrected semiautomatically (J.L.). For analysis, the region of interest was divided into segments of 5 mm. All results and contours were documented in a visible digital imaging and communications in medicine file and in a numeric Excel file. Resulting parameters from the analysis included analyzed length, mean diameter/area, minimum diameter/area, volume, as well as corresponding changes in these parameters following RDN.

To determine reproducibility, 40 renal arteries from 20 patients were randomly selected by a second independent reviewer and reanalyzed.

All QRA analyses were performed independently by two experienced technicians (J.L. and K.W.), who were fully blinded to all clinical and procedural characteristics.

Intravascular ultrasound

IVUS was performed pre-RDN and post-RDN, using Atlantis pro system (iLab; Boston Scientific, Marlborough, Massachusetts, USA) with automated pullback set at 0.5 mm/s. IVUS images were analyzed with QCU-CMS research software (LUMC, Leiden, The Netherlands) yielding global measures of renal artery size (vessel volume, lumen volume, and wall volume) and measures of most pronounced focal changes (minimum vessel area, lumen area, and wall area). All IVUS analyses were performed by one experienced technician (J.L.), who was fully blinded to all clinical and procedural characteristics.

Twenty-four-hour ambulatory blood pressure monitoring

Automated ambulatory blood pressure monitoring (ABPM) was performed according to European Society of Hypertension guidelines [14], using validated Spacelabs (Spacelabs Healthcare, Snoqualmie, Washington, USA) or Mobilograph (i.e., m., Stolberg, Germany) ABPM monitors. For this study, we defined 'BP responder' to RDN as a patient who experienced a minimum decrease in mean 24-h SBP or DBP of at least 5 mmHg.

Statistics

The QRA studies were designed as monocentric hypothesis-generating studies without type-I error correction. The IVUS study was a prospective observational study without type-I error correction. In these studies, continuous measurements are presented using arithmetic mean (SD). In patients, minimum renal artery diameter/area was calculated as the mean value of left and right renal artery, renal artery areas and volumes were calculated as the sum of right and left renal artery. Changes in renal artery dimensions following RDN were calculated as post minus pre, giving a negative value to the deltas (Δ) in case of a decrease in the measurement (i.e. smaller diameter post-RDN, etc.).

In the QRA studies, agreement between both raters was assessed with the intraclass correlation coefficient (ICC). Norepinephrin content of the right kidney was expressed as a percentage from norepinephrin content of the left kidney. QRA parameters (pre-RDN and post-RDN, at 7-day follow-up; right versus left kidney) were compared using paired t tests (normal distribution assumed) or exact Wilcoxon tests (no normal distribution assumed). For the verification of normal distribution, the Kolmogorov–Smirnov test with Lilliefors correction was used. The relationship between QRA/IVUS parameters and BP/norepinephrin content was calculated with Bravais–Pearson correlation coefficient (normal distribution assumed) or Spearman rank correlation coefficient (no normal distribution assumed).

Receiver operating characteristic curve (ROC) analysis was used, yielding areas under the curve (AUC) for assessing the predictive value of QRA parameters on BP changes during follow-up. Multiple regression models were calculated to assess the independent contribution of changes in renal artery dimensions for BP changes.

A P value of less than 0.05 was considered to indicate a statistically relevant trend.

The GraphPad Prism statistical package version 6.0b (GraphPad Inc, La Jolla, California, USA), Statistica 6.0 (StatSoft Inc, Tulsa, Oklahoma, USA), as well as MedCalc 9.5.1 (Med-Calc Software, Mariakerke, Belgium) were used.

RESULTS

Quantitative renal angiography animal study

The ICC for minimum diameter, mean diameter, minimum area, and mean area were 0.863, 0.904, 0.858, and 0.897, respectively, indicating substantial or almost perfect agreement. Therefore, mean values of both raters were used for analysis.

Mean norepinephrin contents of left and right kidney were 247.3 (SD 52.9) and 119.2 (SD 92.8) pg/mg, respectively. The difference was highly statistically relevant ($P < 0.001$).

At baseline, the right renal artery had slightly smaller diameters and areas than left renal artery. Following RDN, right renal artery dimensions decreased globally (mean diameter and area) and focally (minimum diameter and area), leading to a 13.8, 40.0, 22.6, and 62.3% reduction of mean diameter, minimum diameter, mean area, and minimum area, respectively. At 7-day follow-up, right renal artery dimensions increased again, both globally and focally, and did not differ from the dimensions pre-RDN. The left renal artery, which did not undergo RDN, did not change its dimensions at 7-day follow-up (Figs. 1 and 2, Table S1, http://links.lww.com/HJH/A784).

When measured post-RDN and at 7-day follow-up immediately, we observed a weak direct relationship between mean renal artery diameter/area and norepinephrin content of the right kidney ($r = 0.33$–0.41, $P = 0.013$–0.48) (Table S2, http://links.lww.com/HJH/A784). These relationships may indicate that more pronounced changes in right renal artery dimensions were associated with a lower norepinephrin content of the right kidney. In contrast, no QRA parameter of the left renal artery was associated with norepinephrin content of the left kidney. Finally, the relationship between QRA measures and norepinephrin

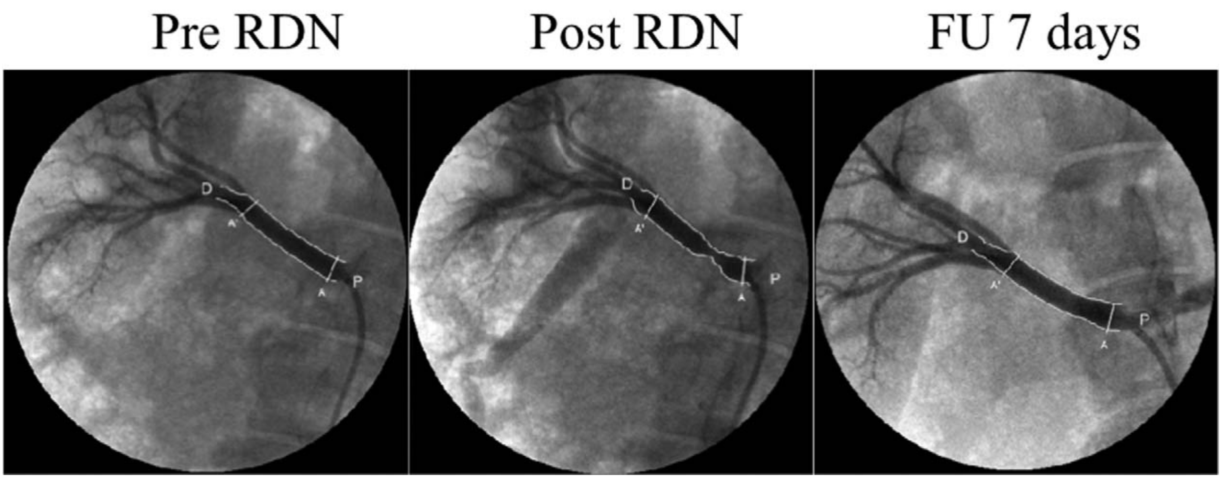

FIGURE 1 Focal narrowing of a renal artery immediately post renal denervation, which is no longer visible at day 7 (animal quantitative renal angiography study).

content was statistically different between the right and the left kidney for all QRA parameters ($P = 0.001-0.015$) (Table S3, http://links.lww.com/HJH/A784).

Quantitative renal angiography human study

Baseline characteristics are given in Table S4, http://links.lww.com/HJH/A784. A total of 29 patients (67.4%) were men, 23 (53.3%) were people with diabetes , and 19 (44.2%) had coronary artery disease. Mean age was 61.1 years, mean office BP 172 (21)/96 (13) mmHg, and mean 24-h BP 150 (13)/96 (13) mmHg. Patients took 4.7 (1.1) antihypertensive drugs at baseline and 4.7 (1.3) at 1 year. In 39.5% of the patients, no changes occurred; in 46.4%, one drug was added or reduced; in 14% of the patients, more than one drug was changed. About 9.8 (2.0) ablation points were set successfully (i.e. over 2 min) with RDN per patient.

Reproducibility of the measurements was tested in 40 randomly selected renal arteries: coefficient of variation was 2.3% for mean diameter, 4.5% for mean area, and 6.0% for renal artery volume, respectively. According to the method of Bland–Altman, mean differences and SDs were 0.02 (0.17) mm for mean diameter, 0.1 (1.4) mm^2 for mean area, and 3.5 (97.8) μl for renal artery volume, respectively. There was no trend toward increasing differences with higher or lower values for all parameters. The correlation coefficients for changes pre-RDN and post-RDN in the 20 patients with duplicate analysis were 0.81 ($P < 0.001$) for mean diameter, 0.71 ($P < 0.001$) for mean area, and 0.84 ($P < 0.001$) for renal artery volume, respectively.

Following RDN, mean diameter, area, and volume decreased by 1.97 (4.5), 3.95 (9.1), and 3.59 (9.38)%, respectively, whereas minimum diameter and area decreased by 10.25 (9.56) and 17.47 (17.1)%, respectively (Table S5, http://links.lww.com/HJH/A784).

At 1 and 12 months, mean 24-h BP decreased by 8/4 and 12/6 mmHg, respectively. According to the definition of ‘BP responder’, 60.5 and 65.1% of the patients were responders at 1 and 12 months, respectively. ‘BP responders’ had more pronounced changes in QRA measurements of renal artery size, as compared with ‘Nonresponders’ (Table S6, http://links.lww.com/HJH/A784).

Responder status to RDN could be predicted using focal and global QRA measures (Table 1). ROC curve analysis yielded significant AUC between 0.670 and 0.779, the latter for prediction of 12-month responder status with change in minimum renal artery area.

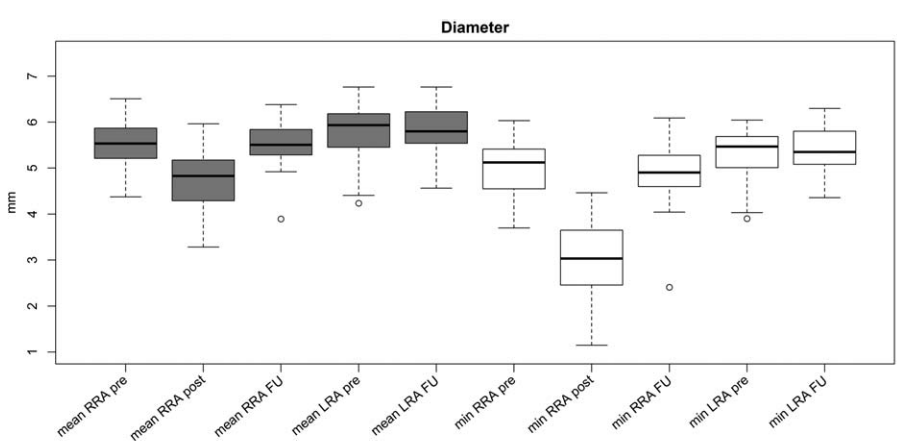

FIGURE 2 Boxplots for the time course of changes in quantitative renal angiography parameters induced by renal denervation (animal quantitative renal angiography study). Quantitative renal angiography parameters of right renal artery post renal denervation were significantly ($P < 0.001$) different from pre renal denervation and from FU. FU, at 7-day follow-up; LRA, left renal artery; min, minimum; post, post renal denervation; pre, pre renal denervation; RRA, right renal artery.

TABLE 1. Focal and global quantitative renal angiography measures to predict 24-h blood pressure-based responder status to renal denervation

	Responder 1 month	*P* value	Responder 12 months	*P* value
Minimum diameter post-RDN	0.679 (0.512–0.817)	0.033		
Mean diameter post-RDN	0.728 (0.564–0.856)	0.005		
Δ Minimum diameter			0.744 (0.579–0.870)	0.002
Δ Minimum diameter (%)	0.681 (0.515–0.819)	0.039	0.711 (0.544–0.845)	0.015
Δ Mean diameter	0.673 (0.507–0.813)	0.047	0.679 (0.510–0.819)	0.069
Δ Mean diameter (%)	0.670 (0.504–0.810)	0.049	0.675 (0.507–0.816)	0.077
Minimum area post-RDN	0.679 (0.512–0.817)	0.033		
Mean area post-RDN	0.723 (0.558–0.852)	0.007		
Δ Minimum area			0.779 (0.618–0.896)	<0.001
Δ Minimum area (%)	0.681 (0.515–0.819)	0.040	0.744 (0.579–0.870)	0.003
Volume post-RDN	0.709 (0.544–0.841)	0.018		

Values are areas under the curve (95% confidence intervals) from receiver operating characteristics analysis. RDN, renal denervation.

Global and focal measures of renal artery size were relevantly and directly related to BP changes at 1 month following RDN, meaning that a smaller renal artery size post-RDN was associated with a larger BP drop. Moreover, more pronounced changes in global and focal QRA measures were associated with a more pronounced BP decrease following RDN at 1 month and at 1 year (Table S7, http://links.lww.com/HJH/A784).

In a multiple regression model with change in 24-h DBP at 12 months as outcome (coefficient of determination $R^2 = 0.65$), a higher 24-h DBP at baseline, older age, female sex, an increase in antihypertensive drugs, and a more pronounced change of minimum diameter were relevantly associated with a larger drop in 24-h DBP (Table 2). In a similar model, the change in minimum diameter was an independent predictor of the change in 24-h SBP at 12 months (Table 3).

Intravascular ultrasound study

Baseline characteristics are given in Table S8, http://links.lww.com/HJH/A784. A total of 58.8% of the patients were men, mean age was 61.9 (12.4) years, mean office BP 168 (18)/96 (15) mmHg, mean 24-h BP 152 (12)/88 (11) mmHg, patients took 5.5 (1.1) antihypertensive drugs at baseline, and 5.2 (1.6) at 1 year. About 11.8 (3.8) ablation points were set successfully with RDN per patient. IVUS prolonged the procedure time by 8 min. Mean 24-h BP decreased by 11/6 mmHg at 1 and by 18/9 mmHg at 12 months.

RDN induced a nonrelevant decrease in renal artery vessel volume of 5.6 (9.4)%, a relevant decrease of renal artery lumen volume of 8.9 (10.4)%, and a nonrelevant increase of renal artery wall volume of 6.9 (11.0)%. Minimum lumen area decreased relevantly by 10.5 (13.9)%, as did minimum vessel area by 6.8 (12.2)%. Maximum wall area increased relevantly by 14.1 (SD 21.1)%, minimum wall area tended to increase by 5.3 (10.6)% (Table 4).

Twenty-four-hour BP changes at 1 and 12 months were relevantly and directly related to focal changes in minimum lumen area and minimum vessel area ($r = 0.65–0.72$, P values 0.003 to <0.05) (Table 5, Fig. 3). Therefore, a more pronounced decrease in focal renal artery size was associated with a more pronounced decrease in BP. The change in wall volume and the change in minimum wall area was relevantly and inversely related to the change BP ($r = -0.47$ and -0.72, respectively, $P = 0.006$ to <0.05). Therefore, more pronounced renal artery wall thickening was associated with a more pronounced decrease in BP (typical individual examples are shown in Fig. 4). The changes in global measures of renal artery size showed only a trend toward an association with BP changes.

In multiple regression models with change in 24-h SBP or 24-h DBP at 1 month as outcome, only a more pronounced change in minimum lumen area was relevantly associated with a larger drop in 24-h BP (Tables S9 and S10, http://links.lww.com/HJH/A784). Baseline 24-h BPs and catheter type did not reach statistical relevance in the model.

Comparison between the two renal denervation systems in the intravascular ultrasound study

Baseline characteristics and BP response did not differ between the Flex and the Spyral groups (Table S11,

TABLE 2. Multiple regression model to predict the change in 24-h DBP at 12 months (coefficient of determination $R^2 = 0.65$; $P < 0.001$)

Independent variables	Coefficient	Std. error	$r_{Partial}$	*P* value
Δ Minimum diameter (mm)	4.23	2.05	0.35	0.047
Baseline 24-h DBP (mmHg)	−0.61	0.12	−0.66	<0.0001
Age (years)	−0.20	0.10	−0.35	0.049
Sex; male = 1, female = 2	−6.31	2.27	−0.45	0.009
Δ Number antihypertensive drugs	1.36	0.65	0.35	0.04

The number of ablation points and the presence of accessory renal arteries did not reach statistical relevance.

TABLE 3. Multiple regression model to predict the change in 24-h SBP at 12 months (coefficient of determination $R^2 = 0.44$; $P < 0.001$)

Independent variables	Coefficient	Std. error	$r_{Partial}$	*P* value
Δ Minimum diameter (mm)	9.37	4.34	0.35	0.038
Baseline 24-h SBP (mmHg)	−0.63	0.17	−0.54	0.0007
Accessory renal arteries; yes = 1, no = 0	13.11	4.46	0.45	0.006
Δ Number of antihypertensive drugs	3.78	1.52	0.39	0.018

Age, sex, the number of renal arteries treated, and the sum of ablation points did not reach statistical relevance.

TABLE 4. Changes in intravascular ultrasound parameters following renal denervation

Parameter	Pre-RDN	Post-RDN	Δ	Δ %	*P* value
Lumen volume (mm^3)	791.3 (280.2)	719.0 (252.7)	−72.3 (110.4)	−8.9 (10.4)	0.016
Vessel volume (mm^3)	1020.7 (342.8)	961.6 (318.3)	−59.0 (130.4)	−5.6 (9.4)	0.08
Wall volume (mm^3)	229.4 (75.5)	242.7 (75.1)	13.3 (28.9)	6.9 (11.0)	0.076
Minimum lumen area (mm^2)	23.5 (5.4)	20.8 (4.9)	−2.7 (3.5)	−10.5 (13.9)	0.006
Minimum vessel area (mm^2)	31.4 (5.7)	29.1 (6.0)	−2.3 (3.9)	−6.8 (12.2)	0.032
Minimum wall area (mm^2)	5.7 (1.1)	5.9 (0.9)	0.2 (0.7)	5.3 (10.6)	0.17
Maximum wall area (mm^2)	12.6 (3.0)	14.1 (3.1)	1.5 (2.7)	14.1 (21.1)	0.04

RDN, renal denervation.

TABLE 5. Individual correlations between changes in intravascular ultrasound parameters and 24-h blood pressure changes

IVUS parameter	Δ SBP 1 month	Δ DBP 1 month	Δ SBP 12 months	Δ DBP 12 months
Δ Wall volume (mm^3)			−0.58*	
Δ Wall volume (%)			−0.63*	
Δ Minimum lumen area (mm^2)	0.65**	0.70***		0.66*
Δ Minimum lumen area (%)	0.66**	0.68***		0.72**
Δ Minimum vessel area (mm^2)	0.65**	0.71***		0.63*
Δ Minimum vessel area (%)	0.66**	0.70***		0.68**
Δ Minimum wall area (mm^2)	−0.46		−0.71**	−0.47
Δ Minimum wall area (%)	−0.54*		−0.72**	−0.55*

Only significant correlations are shown. IVUS, intravascular ultrasound.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.005$.

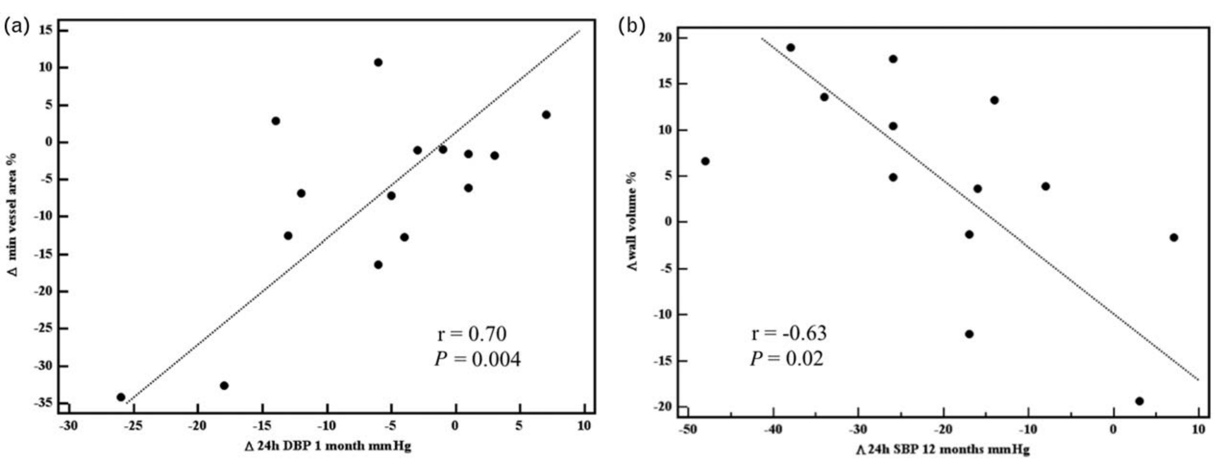

FIGURE 3 Intravascular ultrasound study. (a) Relationship between decrease of focal renal artery size (minimum vessel area) and decrease of 24-h DBP at 1 month. (b) Relationship between increase in renal artery wall thickening (wall volume) and 24-h SBP decrease at 12 months.

http://links.lww.com/HJH/A784). As expected, more ablations were performed with the Spyral system (15 versus 9, $P < 0.001$). IVUS parameters pre-RDN did not differ between the Flex and the Spyral groups (Table S12, http://links.lww.com/HJH/A784). Post-RDN, global (lumen volume and vessel volume) and focal (minimum lumen area and vessel area) changes were more pronounced with the Flex catheter (Table S13, http://links.lww.com/HJH/A784).

DISCUSSION

In this series of studies, we aimed to investigate whether changes in renal artery dimensions could serve as procedural markers of successful RDN. We observed that radiofrequency-based RDN induces a reversible global and focal decrease in renal artery size, which is accompanied by an increase in renal artery wall thickness. These changes can be quantified, using QRA or IVUS, and are related to the effects of RDN on renal norepinephrine content and on BP. In particular, BP response to RDN can be predicted from renal artery changes, and renal artery changes are independently associated with BP changes at follow-up.

A decrease of renal artery size due to radiofrequency-based RDN has been well described previously. In the initial report on RDN [1], 'focal renal artery irregularities' immediately after radiofrequency energy delivery have been identified, which were no longer evident on angiography at 14–30 days and on MRI at 6 months. In systematic animal

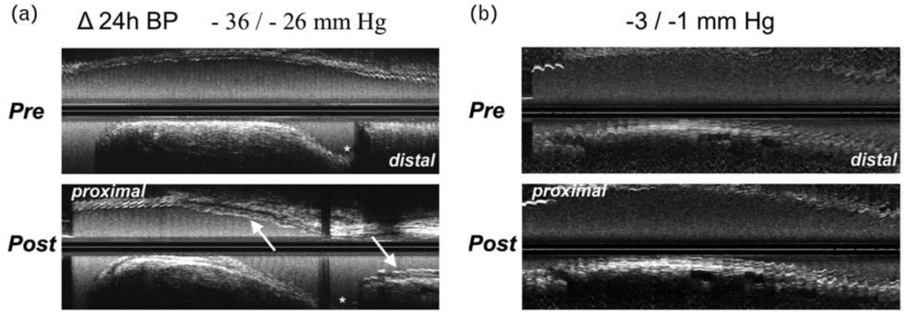

FIGURE 4 Two typical examples of renal artery changes (longitudinal reconstruction from intravascular ultrasound images) post renal denervation and their relationship with blood pressure changes. (a) Renal artery size decreased (lumen volume −29.5%) and wall volume increased (+13.7%) (arrows) post renal denervation. After 1 month, 24-h blood pressure change was significant (−36/−26 mmHg). (b) Renal artery size remained virtually unchanged following renal denervation (lumen volume −2.8%), as did renal artery wall volume (+3.7%). After 1 month, 24-h blood pressure was also virtually unchanged (−3/−1 mmHg).

studies [9], RDN led to focal notches and a decrease in minimum lumen diameter by roughly 12%. In a human study using OCT [15], 32 renal arteries of patients were investigated following radiofrequency-based RDN. Mean renal artery diameter decreased by 9.7% in the entire cohort, by 10.2% in patients treated with the EnligHTN catheter (St Jude Medical, St Paul, Minnesota, USA), and by 9.3% in patients treated with the Symplicity catheter. In addition, focal renal artery wall thickening (endothelial–intimal edema) was observed in all patients treated with the Simplicity catheter, which was confirmed by case reports from other centers [16]. In our studies, following RDN, mean and minimum diameter decreased by 13.8 and 40.0% (treated right renal artery in the animal study) and 1.97 and 10.25% (human QRA study). Mean and minimum area decreased by 22.6 and 62.3% (treated right renal artery in the animal study) and 3.95 and 17.47% (human QRA study), whereas minimum lumen area and lumen volume decreased by 10.5 and 8.9% (IVUS study), respectively. The differences in the extent of the effect of RDN on changes in renal artery size may arise from differences between animal and human studies and between different imaging modalities. As IVUS and OCT offer much higher resolution, as compared with QRA, changes as measured with the latter two facilities seem to be more pronounced. In addition, with OCT, as with IVUS, a shorter segment is imaged because of the fact that the catheter cannot be always positioned deep enough, whereas QRA can analyze any vessel length. A longer length may 'dilute' the result due to averaging. Finally, IVUS (as well as OCT) can measure the full three-dimensional effects of RDN on renal artery size, which is not possible with single-plane QRA. However, irrespectively of the absolute amount of RDN-induced changes, in all three studies we performed, a consistent relationship between changes in renal artery size due to RDN and clinical effects was evident.

Currently, the main predictor of successful RDN is a high BP at baseline [17–19], which is completely in line with Wilder's principle [20] (pretreatment values determine post-treatment response). In contrast, no easily applicable procedural measurement can be used to predict the response to radiofrequency-based RDN [21]. High-frequency renal nerve stimulation, which is far more complex than QRA or IVUS, has been tested in animals [22] and in a feasibility study [23] in humans, but no outcome data have been provided so far. In some [24], but not all [19], studies, the number of ablation points was related to BP response. In our human QRA study, the relationship between the number of ablation points and 24-h DBP change was of borderline significance. Only when we analyzed the effect (i.e. the changes in renal artery dimensions), not the simple number of radiofrequency ablations of renal arteries, we found a consistent relationship with outcome.

We observed that the tools we used for determination of changes in renal artery size, QRA and IVUS, are highly reproducible. They are either already available in a typical cardiac cathlab or can be implemented easily. Analysis can be performed offline, but immediately following radiofrequency delivery. Results could be available within minutes, which would allow the operator to repeat ablations if results are unfavorable, that is, if the renal arteries do not show changes associated with a BP drop in the long term. Before such a strategy could be implemented into daily practice, our results need to be confirmed in larger, randomized trials. In particular, efficacy and safety of this approach need to be established, as well as cutoff values (what is the degree of reduction in minimum diameter needed to ensure a sufficient BP drop, etc.).

The main limitation of our studies is the small sample size. Confirmation in larger databases, ideally from existing studies, is mandatory. Next, most of our results were obtained with one specific catheter type (Symplicity Flex) and may not be generalizable to other systems. In fact, renal artery changes following RDN with the Spyral catheter seem to be less pronounced. Finally, as our treatment was confined mainly to the main renal artery, we could not assess the impact of RDN performed more distally in the renal artery. Recent animal data [12] suggest that more distal ablations may be superior, a principle that is further investigated in ongoing clinical studies [25]. Taken together with our data, it may well be that effective ablation (as determined by QRA or IVUS) at effective locations (i.e. more distally) may result in optimal BP reduction.

The main strength obviously is the fact that we observed similar results in three different settings, using animal and clinical data, using two different methods for renal artery size determination. Moreover, we had fully blinded QRA and IVUS analysis by two experienced technicians, and we used 24-h ambulatory BP monitoring to assess BP changes during follow-up.

In conclusion, changes in renal artery size after RDN can be quantified, using QRA or IVUS, and may be associated with BP response following the procedure. If our results are confirmed in larger databases, the next step should be a randomized study of standard care versus immediately repeated renal denervation, if no 'spasm' or 'notches' can be identified following the procedure.

ACKNOWLEDGEMENTS

QRA analysis was supported by an unrestricted grant from Medtronic. Preliminary results of the studies have been presented at the 24th and 26th meetings of the European Society of Hypertension in Athens and Paris, respectively.

Conflicts of interest

T.W. received honoraria for lectures and travel support from Medtronic. J.L. is the founder, owner, and only employee of LIMIC Medical, a company dedicated to vessel imaging. R.J.M. is an employee of Medtronic PLC. The other authors have no conflicts of interest.

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