

## Impact of local vascular lesions assessed with optical coherence tomography and ablation points on blood pressure reduction after renal denervation

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### Summary

Local vascular injury is detectable with optical coherence tomography (OCT) after catheter-based renal denervation (RDN). However, it is unclear whether the number and type of vascular lesions or the number of ablation points could affect blood pressure (BP) reduction.

The aim of the study was to assess the impact of vascular injury induced by RDN detected with OCT and the number of ablation points on BP response after 1, 3 and 6 months. **METHODS:** RDN was either performed with a Simplicity<sup>®</sup> catheter or an EnligHTN<sup>™</sup> multielectrode basket followed by OCT. BP was recorded prospectively as office measurement and 24-hour ambulatory blood pressure monitoring (24-h ABPM) at each time point. Correlations between type and number of vascular lesions, as well as ablation points, on BP reduction were performed.

**RESULTS:** Out of 16 patients, two were lost to BP follow-up. We documented a BP reduction at 1, 3 and 6 months in both office and 24-h ABPM. The  $\Delta$ mean office systolic BP (SBP) reduction was  $-18.75 \pm 24.55$  mm Hg,  $-20.58 \pm 16.92$  mm Hg and  $-18.75 \pm 29.39$  mm Hg, respectively, and the  $\Delta$ mean 24h-ABPM SBP reduction was  $-6.50 \pm 23.45$  mm Hg,  $-16.88 \pm 26.64$  mm Hg and  $-13.89 \pm 21.20$  mm Hg, respectively. The number of vascular lesions did not correlate with office and 24h-SBP and diastolic BP reduction. However, there was a correlation between ablation points and office  $\Delta$ mean SBP reduction at 6 months ( $p < 0.02$ ).

**CONCLUSIONS:** Our study demonstrates for the first time that the number and type of vascular lesions as assessed with OCT did not predict the success of BP reduction after RDN. However, we observed a substantial decrease in office SBP in relation to the number of ablation points at 6 months.

**Key words:** catheter-based renal nerve ablation; optical coherence tomography; office blood pressure; 24-hour ambulatory blood pressure measurement

### Introduction

Renal sympathetic denervation (RDN) is a catheter-based procedure which has been established after first randomised trials as a treatment option for patients with resistant hypertension [1]. Different percutaneous RDN systems are currently available using different ablation techniques [2]. Given the conflicting results from previous studies and SYMPPLICITY HTN-3 trial the predicted response and success after RDN with respect to blood pressure (BP) reduction is still unknown [3–5].

In this context, there are no data as to whether the number or type of vascular lesions, irrespective of ablation points, could potentially affect the results for BP reduction. Furthermore, it is unclear if the amount of ablation points could affect BP reduction. The Simplicity HTN-2 and HTN-3 study, which assessed the effectiveness and safety of RDN with the Simplicity<sup>®</sup> catheter, did not show any vascular abnormalities at any sites of radiofrequency delivery on angiography [1]. However, we have recently shown with optical coherence tomography (OCT) that renal vascular injury is present after RDN with either the Simplicity<sup>®</sup> catheter or the EnligHTN<sup>™</sup> multielectrode basket [6, 7]. These vascular tissue lesions specifically include vessel wall oedema, thrombus formation and dissections, which are not visible with classic coronary angiography. OCT offers a technique with the immense advantage of creating high-resolution images allowing accurate tissue characterisation, and the spatial resolution is approximately 10-fold higher than intravascular ultrasound (IVUS) [8]. Vascular damage such as vessel wall oedema, a common side effect of RDN, may reflect the effectiveness of renal

denervation in successfully reducing BP [6]. Furthermore, extensive tissue damage including all detectable vascular lesions could lead to a more pronounced decrease in BP. Therefore, the aim of the present study was to evaluate the BP response in relation to vascular tissue damage and number of ablation points after RDN.

## Methods

### Patient population and catheter-based renal denervation

This was a sub-analysis of a prospective comparative RDN OCT study at two cardiology sites in patients with resistant hypertension [6]. Patient recruitment and inclusion criteria

have been already published elsewhere [6]. Briefly, patients were included with resistant hypertension, which was defined as primary or idiopathic with systolic blood pressure (SBP) values >160 mm Hg values and ineffective BP treatment. Patients were excluded if they had a glomerular filtration rate <45 ml/min or allergies to contrast medium. BP was sequentially recorded at 1, 3 and 6 months after RDN. RDN was either performed with the Simplicity<sup>®</sup> catheter (Medtronic-Adrian) or the EnligHTN<sup>™</sup> multielectrode (St. Jude Medical).

Postdischarge information was obtained as part of our hospital quality assurance using a standardised clinical questionnaire.

### Optical coherence tomography

In all patients OCT was performed using the C7–XR imaging system (Light-Lab Imaging, Inc., Westford, USA) before and after renal denervation, as previously reported [6].

### Vascular lesion characterisation

Oedema was characterized as a significant endothelial-intimal notch identified on OCT at the luminal wall surface. Furthermore, vasospasm and vessel dissections, as well as thrombus formation (protruding mass with a diameter of  $\geq 5$  mm in cross sections), were noted if present [6].

### Clinical examination of arterial blood pressure

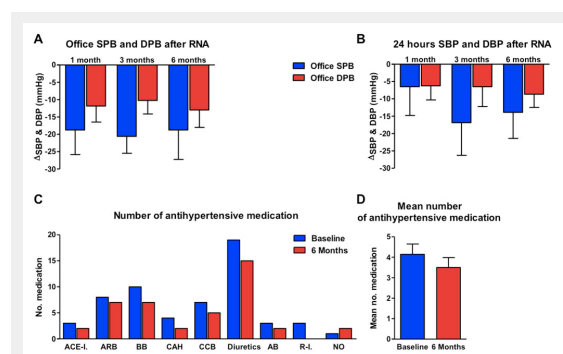
Blood pressure and heart frequency monitoring was performed in an ambulant setting using an inflatable digital electrical sphygmomanometer (Microlife<sup>®</sup> or Omron<sup>®</sup> devices) in accordance with the current guidelines. At intervals of 1, 3, and 6 months after RDN, BP was recorded and compared with baseline data. All patients also underwent digital 24-hour ambulatory blood pressure monitoring (24-h ABPM) (Spacelab<sup>®</sup> devices) to analyse daily and nocturnal variations of the BP profile. In this regard, participants were requested not to change daily habits and not to move their arm during measurements. Furthermore, every patient was requested to document bed and waking time for adequate interpretation of the protocol.

### Statistical analysis

Continuous variables are given as mean  $\pm$  standard error of the mean (SEM) or standard deviation (SD) if appropriate. Differences between groups were tested using two-sided t-tests for continuous endpoints when normally distributed (Shapiro-Wilk test) or Wilcoxon rank-sum test for non-normally distributed continuous endpoints. Correlation analysis was used to determine the association between ablation points as well as lesions and BP reduction. SPSS software (Chicago, Illinois; Version 20.0) and Graph pad (Version 5.0) were applied for statistical analysis. A p-value <0.05 was considered as statistical significant.

## Results

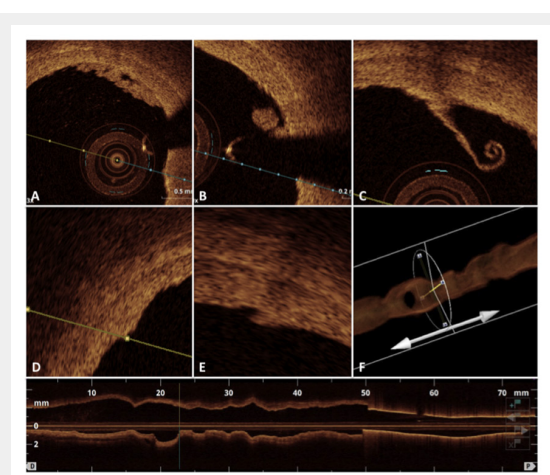
Sixteen patients were enrolled in the study and two patients were lost to blood pressure follow-up. Baseline characteristics are shown in table 1. The mean baseline office systolic BP was  $168.50 \pm 18.29$  mm Hg and 24-h ABPM was  $159.29 \pm 16.37$  mm Hg. During repeat BP measurement at



**Figure 1**

Blood pressure changes from baseline at 1 month, 3 months and 6 months as determined by office measurement (A) and 24-hour ambulatory blood pressure measurements (B). Mean antihypertensive medication intake at baseline and at 6 months of follow-up (C and D).

AB = alpha-blocker; ACE-I = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CAH = centrally acting antihypertensive; CCB = calcium channel blocker; DBP = diastolic blood pressure; NO = nitrovasodilator; R-I = renin inhibitor; RNA = renal nerve ablation; SBP = systolic blood pressure



**Figure 2**

Intraluminal local morphological defects in the acute phase just after the procedure of renal denervation including intraluminal thrombus formations (A and B), endothelial detachment (C), vessel wall oedema (D), dissection (E) and massive vascular vasospasm as detected by the 3D optical coherence tomography reconstruction.

1, 3 and 6 months the mean office systolic BP was  $150.83 \pm 19.14$  mm Hg,  $146.50 \pm 15.58$  mm Hg and  $147.42 \pm 18.42$  mm Hg, respectively. The mean systolic 24-h ABPM was  $155.25 \pm 16.15$  mm Hg,  $138.25 \pm 13.33$  mm Hg and  $141.00 \pm 15.91$  mm Hg, respectively. We documented an essential  $\Delta$ mean BP reduction at all time-points in both office and 24-h ABPM (fig. 1A and B, table 2). At 1, 3 and 6 months, the office  $\Delta$ mean systolic BP (SBP) reduction was  $-18.75 \pm 24.55$  mm Hg,  $-20.58 \pm 16.92$  mm Hg and  $-18.75 \pm 29.39$  mm Hg, respectively, and the  $\Delta$ mean 24-h ABPM SBP reduction was  $-6.50 \pm 23.45$  mm Hg,  $16.88 \pm 26.64$  mm Hg and  $13.89 \pm 21.20$  mm Hg, respectively.

By 6 months, patients were able to reduce antihypertensive therapy from  $4.14 \pm 1.88$  drugs at baseline to  $3.00 \pm 2.00$  at follow-up (fig. 1C and D).

During renal denervation procedures, 197 ablation points were performed in 28 renal arteries. Patients received an average of  $7.0 \pm 1.3$  ablations per renal artery (range 4 to 11). There were no major clinical complications related to the RDN procedure as previously reported.

The OCT pullbacks performed before and after each procedure documented in total 141 different local acute morphological vascular changes. In detail, 60 areas of prominent oedema, 57 intraluminal thrombi, 21 vessel vasospasms and 3 wall dissections were observed (fig. 2). The total amount of all vascular lesions including the combination of

oedema, thrombus formation, dissections and spasms did not reveal any correlation to BP reduction at 1, 3 and 6 months follow-up (office BP and 24-h ABPM) (fig. 3). Furthermore, no correlation between oedema and BP reduction was documented at any time of follow-up (fig. 4).

Interestingly, at 6 months of follow-up there was a correlation between the total number of ablation points and systolic BP reduction, although no correlation was observed at earlier follow-up time-points (1 and 3 months) ( $r = -0.66$ ,  $p < 0.02$ ) (fig. 5). Complete correlation analysis is given in table 2.

## Discussion

Although previously the effectiveness of RDN in reducing blood pressure in patients with resistant hypertension has been documented by different investigations and randomised trials [1, 3, 9–11], the SYMPPLICITY HTN-3 trial failed to confirm these results [5].

Conflicting data on RDN efficacy in resistant hypertension could be caused by many factors including different study design, lack of statistical power, effectiveness of the RDN procedure, mixed medication therapy, and different patient populations [12].

To date, no harmful long-term effects of RDN have been observed and the safety profile [13] has been studied by re-

**Table 2:** Correlations between optical coherence tomography findings and blood pressure (BP) in follow up (n = 14).

	Office BP						24-hour ambulatory BP monitoring					
	Systolic BP			Diastolic BP			Systolic BP			Diastolic BP		
Follow up	1 month	3 months	6 months	1 month	3 months	6 months	1 month	3 months	6 months	1 month	3 months	6 months
$\Delta$ mean	-18.750	-20.580	-18.750	-11.830	-10.250	-13.000	-6.500	-16.880	-13.890	-6.250	-6.500	-8.667
SD	24.550	16.920	29.390	16.080	13.420	17.320	23.450	26.640	21.200	11.510	16.170	10.750
<b>Ablation points</b>												
p-value	0.113	0.063	<b>0.019</b>	0.060	0.499	0.221	0.100	0.589	0.489	0.114	0.266	0.301
r	-0.482	-0.551	0.664	-0.558	-0.217	-0.382	-0.622	-0.227	-0.266	-0.602	-0.448	-0.389
<b>Lesions (overall)</b>												
p-value	0.792	0.581	0.262	0.819	0.246	0.610	0.458	0.735	0.463	0.760	0.877	0.957
r	-0.085	-0.178	-0.352	-0.074	-0.363	-0.164	0.308	0.144	0.282	0.130	0.066	0.021
<b>Oedemas</b>												
p-value	0.948	0.351	0.958	0.924	0.041	0.143	0.443	0.709	0.572	0.893	0.716	0.712
r	-0.021	0.295	-0.017	0.031	0.596	0.450	0.318	0.158	0.219	-0.057	-0.154	-0.144

peated renal angiograms and magnetic resonance imaging (MRI) [9]. Recently, we have shown that, despite the above mentioned safety issues, local tissue damage at the ablation sites such as oedema, dissection and thrombus formation can occur after RDN, and that OCT has the ability to visualise vascular lesions, which are primarily not apparent on angiography [6]. The present study explored the impact of endothelial damage after RDN on blood pressure reduction in order to identify a potential marker in terms of morphological tissue damage that may predict the response to RDN; this would be of major interest also potentially to explain non-responsiveness, which is estimated to affect between 8–16% of patients [9, 14]. Although it is speculated that non-responsiveness might be attributed to a different mechanism of hypertension, which is not caused by sympathetic hyperactivity, non-responsiveness may also be

caused by technical aspects, i.e. in patients with dual renal arteries and/or accessory arteries not accessible for RDN and advanced vascular remodelling [15].

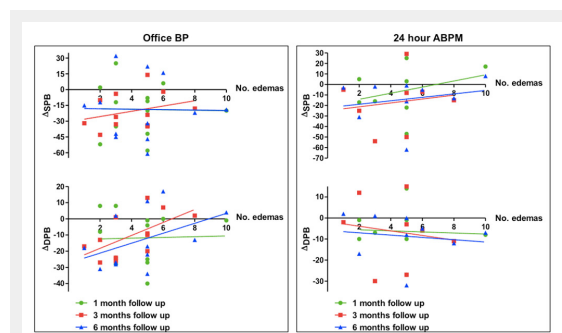
In line with previously published trials [3, 9, 10, 14, 16–21], we documented a reduction in systolic and diastolic BP as assessed by office and 24-h ABPM at 1, 3 and 6 months of follow up.

Furthermore, we also show that the total amount of local vascular lesions could not predict the success of blood pressure reduction in patients with resistant hypertension. Specifically, vessel wall oedema which is well defined by OCT and histologically corresponds to cellular swelling and connective tissue coagulation within the medial and adventitial layers [22] failed to show an effect on blood pressure reduction. Although preclinical studies have demonstrated that 17% of the artery wall circumference is affected by a transmural injury after RDN affecting particularly the media and adventitia [22], it is conceivable that most observed vascular wall oedema represents only a surface response to RDN, and that most of the sympathetic nerve fibres in the adventitial layer are impacted by OCT, with invisible damage caused by the applied high-frequency energy. In this respect, OCT has a very high spatial resolution, but the penetration depth is limited, particularly in large vessels, such as renal arteries. This is in line with the fact that not all ap-

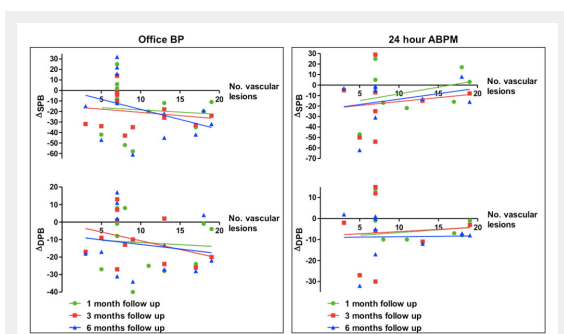
**Table 1: Baseline Characteristics (n = 14).**

Age, years	57.8 ± 9.9
Gender, male	8 (57)
<b>Cardiovascular history</b>	
Known CAD or stroke	4 (29)
<b>Cardiovascular risk factors</b>	
Hypertension	14 (100)
Hyperlipidaemia	9 (64)
Smoking, current	6 (43)
Obesity	7 (50)
Diabetes mellitus	3 (21)
<b>Medication on admission</b>	
Aspirin	4 (29)
Clopidogrel	1 (7)
Statin	7 (50)
Beta-blocker	10 (71)
ACEI/AT-II	11 (79)
Diuretics	11 (79)
CCB	7 (50)

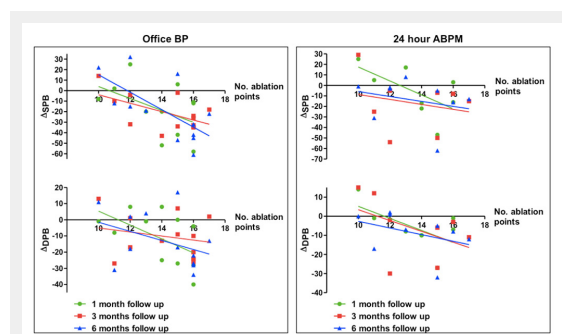
Depicted are counts, n, incidence (%) or mean ± SD  
 ACEI = angiotensin converting-enzyme inhibitors; AT-II = angiotensin-receptor blocking agents; CAD = coronary artery disease; CCB = calcium-channel blocker



**Figure 4**  
 Correlation between blood pressure (BP) reduction ( $\Delta$ mean office and 24-hour ambulant blood pressure monitoring [ABPM]) and oedema.  
 DBP = diastolic blood pressure; SBP = systolic blood pressure monitoring



**Figure 3**  
 Correlation between blood pressure (BP) reduction ( $\Delta$ mean office and 24-hour ambulant blood pressure monitoring [ABPM]) and vascular lesions.  
 DBP = diastolic blood pressure; SBP = systolic blood pressure monitoring



**Figure 5**  
 Correlation between blood pressure reduction (BP) ( $\Delta$ mean office and 24-hour ambulant blood pressure monitoring [ABPM]) and ablation points.  
 DBP = diastolic blood pressure; SBP = systolic blood pressure monitoring

plied ablation points correspond to vessel wall oedema. In this regard, it has been shown that newer-generation RDN devices such as the One Shot balloon from Covidien did not result in any vascular lesion [23], although the clinical response on BP reduction has been shown in previous studies [20]. Therefore, it seems that local vascular lesions induced at the vascular surface are not able to predict the success of RDN in terms of BP reduction. It is more likely that deeper damage in the vessel wall (e.g. in the adventitial layer) is responsible for the success of RDN; however, these lesions are undetectable with OCT.

Recently, Vogel et al. demonstrated no impact of applied ablation points on BP reduction [24]. In contrast to these results, in the present study we demonstrated a correlation between ablation points and systolic BP reduction at 6 months follow up. However, future studies are needed to confirm this preliminary observation in a larger patient population.

### Study limitations

The number of patients studied is still small to draw final conclusions, but this is the first study that demonstrated with OCT that vascular lesions apparently do not influence the blood pressure outcome. Larger studies are warranted to assess carefully patients who will benefit from RDN and to define solid predictors for the success of RDN. Since OCT has a limited penetration depth, renal nerves localised in the adventitial layer of the arterial wall cannot be directly visualised [25]. Vascular lesions are contact points between ablation electrode and arterial wall. However, these points should be related to the nerve ablation points localized in adventitia.

### Conclusions

This study for the first time indicates that the magnitude and type of vascular lesions induced by RDN as assessed by OCT could not predict the success of blood pressure reduction in patients with resistant hypertension. In addition, we observed a significant correlation between the number of applied ablation points and SBP reduction after 6 months of follow up. Therefore, not the vascular lesions but the ablation points could serve as an important predictor for the success of blood pressure reduction.

**Funding / potential competing interests:** JRG was supported by a grant "research time" from the University of Zurich. The institution of the authors has received educational and research grants from Medtronic, Tollachenaz, Switzerland and St. Jude Medical, Brussels, Europe. TFL has received consultant honoraria from both companies.

**Authors' contribution:** JRG, MJ and RG contributed equally

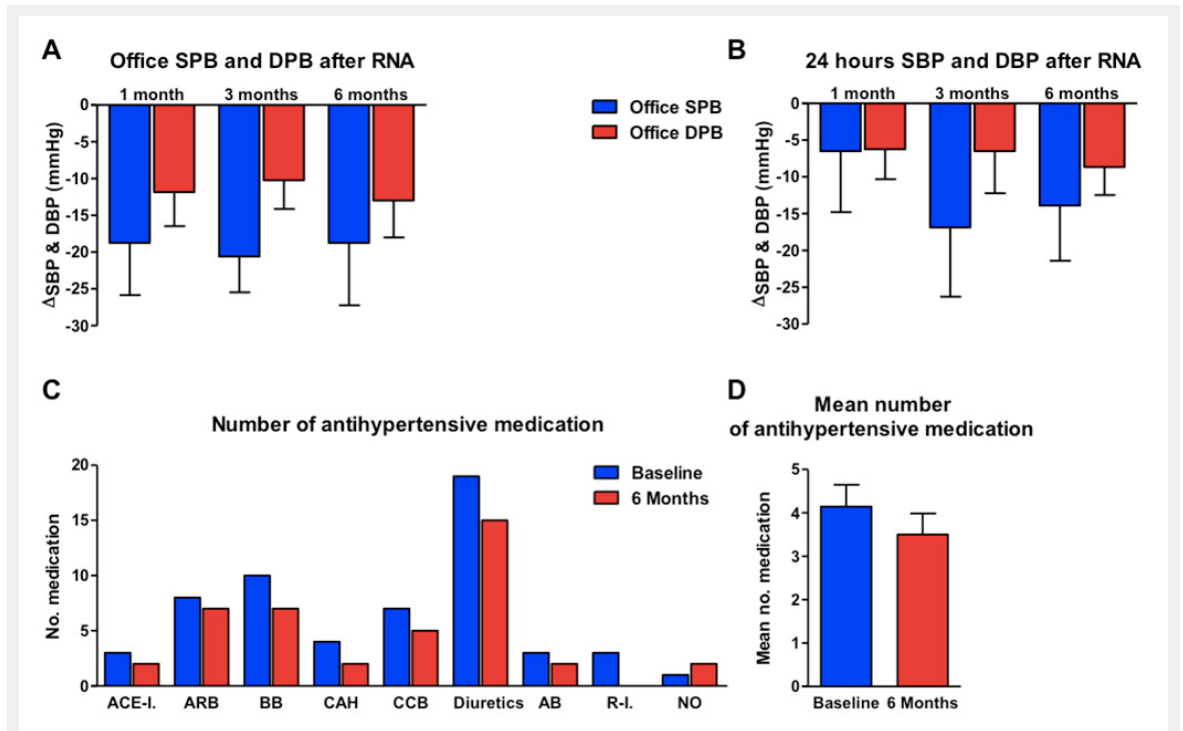
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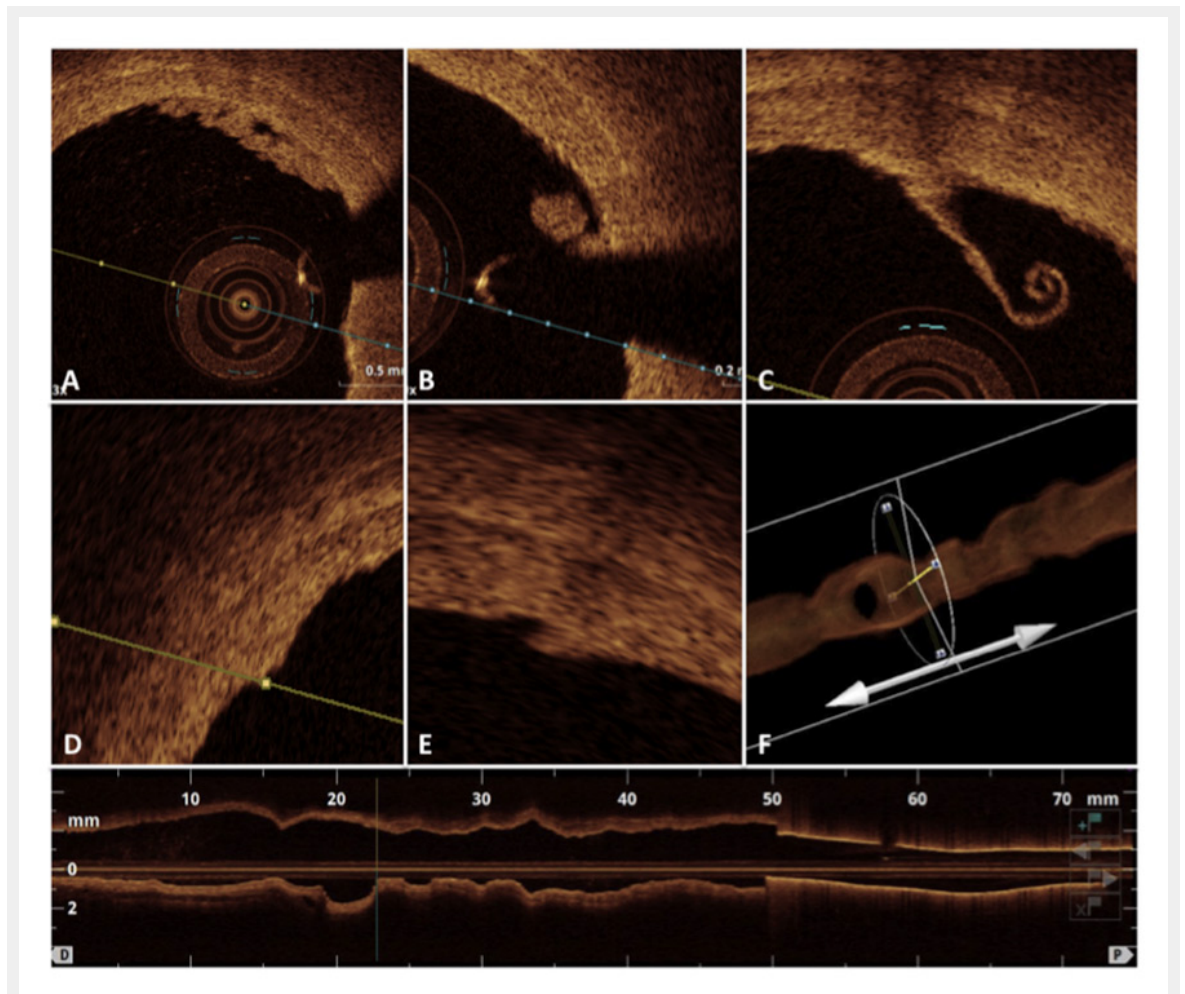
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Figures (large format)



**Figure 1**

Blood pressure changes from baseline at 1 month, 3 months and 6 months as determined by office measurement (A) and 24-hour ambulatory blood pressure measurements (B). Mean antihypertensive medication intake at baseline and at 6 months of follow-up (C and D).  
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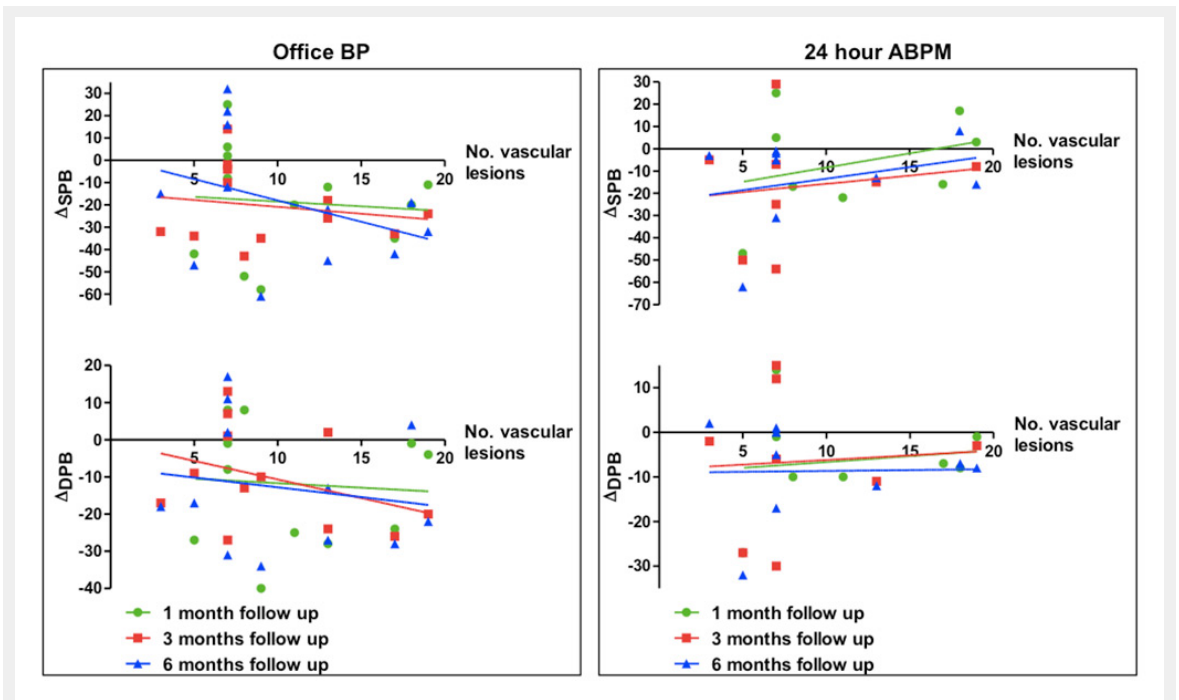


Figure 3

Correlation between blood pressure (BP) reduction ( $\Delta$ mean office and 24-hour ambulant blood pressure monitoring [ABPM]) and vascular lesions.

DBP = diastolic blood pressure; SBP = systolic blood pressure monitoring

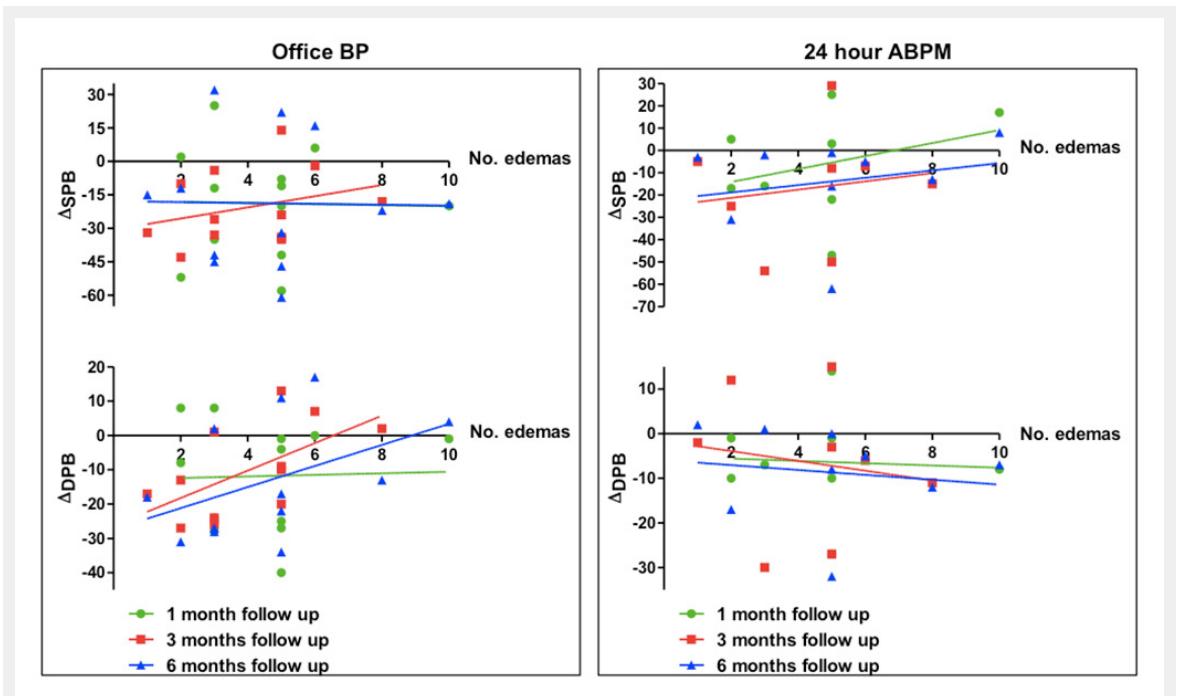
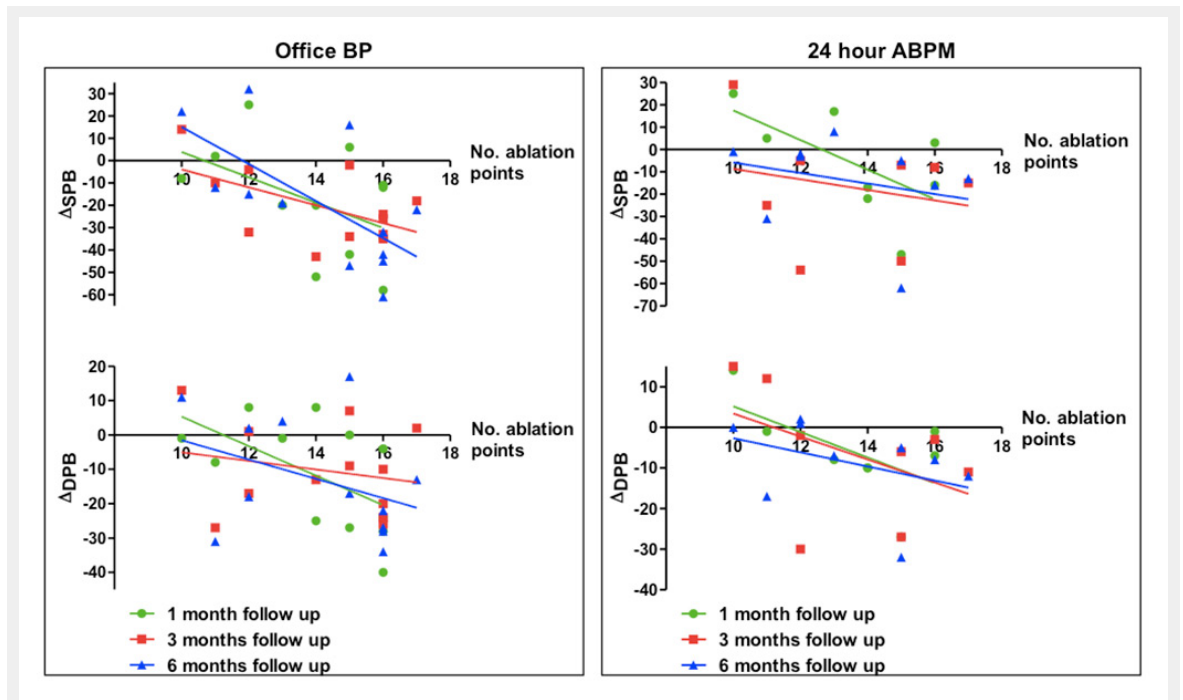


Figure 4

Correlation between blood pressure (BP) reduction ( $\Delta$ mean office and 24-hour ambulant blood pressure monitoring [ABPM]) and oedema.

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**Figure 5**

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