Limited destruction of renal nerves after catheter-based renal denervation: results of a human case study

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ABSTRACT

Renal denervation (RDN) is a promising novel treatment for resistant hypertension. Effectiveness of treatment is, however, highly variable and unpredictable. Incomplete denervation of the renal nerves is a plausible explanation for the variable blood pressure lowering effect of RDN. Here, we present for the first time a histopathological evaluation of the effects of RDN on perivascular nerves of the renal arteries in a human patient. Our findings potentially have important implications for future directions with RDN.

Keywords: hypertension, renal denervation, renal nerves

BACKGROUND

Catheter-based renal denervation (RDN) aims to interrupt the functional continuity of nerve bundles along the renal arteries. To this end, thermal damage is applied to the vessel wall and perivascular tissue by radiofrequency ablation (RFA).

RDN can lead to gradual decrease in blood pressure (BP), which may be sustained over years [1]. However, the BP-lowering effect of RDN is highly variable, ranging from no effect to complete normalization of BP. Theoretical explanations for this inconsistency include variability among patients in the contribution of renal nerves to the pathophysiology of hypertension. Another explanation might be that the variable response to RDN relates to variability in efficacy of the procedure itself.

CASE REPORT

A 36-year-old woman died 12 days after having undergone an uncomplicated RDN procedure. She had a 9-year history of severe hypertension with multiple intensive care unit admissions for hypertensive crises, and was referred for RDN after having been assessed several times in different hospitals, without identifying a cause of (secondary) hypertension. An extensive, well-standardized screening protocol [2] was applied, confirming the diagnosis of serious resistant hypertension with end organ damage (estimated glomerular filtration rate 49 mL/min/1.73 m², macro-albuminuria and slight left ventricular hypertrophy), using ambulatory BP monitoring (average 24-h BP: 198/129 mmHg). Possible causes of secondary hypertension were excluded. Upon admission, she used four antihypertensive medications (spironolactone 25 mg, hydrochlorothiazide 25 mg, nifedipine 600 mg, carvedilol 12.5 mg, irbesartan 300 mg), and her BP was 157/103 mmHg.

Bilateral RDN was performed without complications using the Medtronic Simplicity device. On both sides, she had a single renal artery, and the total number of ablations was 11.

She was discharged from the hospital 2 days after procedure while her BP was unchanged. Twelve days later, she experienced sudden onset severe thoracic pain and was brought to a local hospital where she died. Post-mortem examination identified a ruptured dissection of the ascending aorta as the cause of death. The abdominal aorta and renal arteries were not affected.

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Histopathology of the adventitial nerves around the renal arteries

The renal arteries were cut in the sagittal plane and alternating rings were snap frozen and embedded in paraffin, respectively. Luminal diameters were 4–2 mm (L) and 3–2 mm (R). Media thickness was 0.7–0.2 mm with intima thickness ranging from <0.01 to 0.15 mm, due to variable degrees of fibrous intima thickening with focal atheromatous and calcified plaques in association with moderate atrophy of the muscular media. Around both arteries, adventitial and peri-adventitial nerve bundles of variable calibre were noted at distances from 1 to 4 mm from the luminal surface. As for RFA damage, wedge-shaped areas of intimal to (peri-)adventitial tissue were affected, as evidenced by total absence of nuclei, and absence of staining for α-SMA (medial smooth muscle cells) and S-100 (normally marking Schwann cells in vital nerves) (Figure 1). Importantly, visual damage did not penetrate deeper than 2 mm from the luminal surface, having a relatively broad base at the luminal side of about 2 mm width, with significant tapering towards the adventitia where nerve bundles are located. Although a complete 3D reconstruction was not feasible, aggregated images indicated that RDN in this particular case could by no means have completely interrupted the continuity of all adventitial nerve bundles around the renal arteries. If this pattern occurs in other cases as well, it might explain at least in part the great variability in BP-lowering effect.

**DISCUSSION**

The present case demonstrates that RFA-induced damage to and around the vessel wall in RDN has a dome-shaped...
distribution field with limited penetration, leaving unaffected a large part of the nerves in (peri-)adventitial areas remote from the vascular lumen. This makes it unlikely that RDN would result in complete interruption of the continuity of all adventitial nerve bundles around the renal arteries. That a RDN procedure could result in an incomplete denervation was already suggested by the investigators of the HTN-I study. They showed that noradrenaline spillover technique only reduced by 47%, with a 95% confidence interval of 28–65% indicating that the degree of nerve destruction was variable after RDN [3]. Given the limited penetration of RFA (in the current case <2 mm from the luminal surface), this holds true especially for clinical cases with increased intima and/or media thickness when compared with thin-walled uncompromised renal arteries mostly addressed in preclinical studies [4, 5]. Since the patient died 12 days after the procedure, one cannot make any conclusions on the effect of RDN on BP. As suggested by others, it can take several months for the BP decrease to occur [1].

In a small human autopsy study in a non-selected population, 90.5% of the detected nerves were located within 2 mm of the lumen [6]. It is likely that, in the population treated with RDN, the distance of the nerves from the lumen is increased due to vascular hyperplasia, as illustrated by the present case study. This also stresses the need for better definition of the precise anatomy of peri-arterial nerves relevant to RDN success. Very little is known about the exact position of nerves along the renal arteries, and about possible anatomical variations among patients. Furthermore, it is also not clear where in these nerves sympathetic and parasympathetic, or afferent and efferent fibres might be located, and which of these need to be interrupted for a successful BP-lowering effect of RDN. We propose that the great variability of the BP-lowering effect of RDN might relate at least in part to incomplete coverage of critical nerves by RDN, especially with increased vascular wall thickness. Further studies are needed to define the precise (functional) anatomy of nerves around the renal arteries, and to establish a test for post-, or even intra-procedural evaluation of the efficacy of critical nerve interruptions by RDN.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part.

REFERENCES


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