ORIGINAL ARTICLES

Renal artery nerve distribution and density in the porcine model: biologic implications for the development of radiofrequency ablation therapies

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Catheter-based renal artery denervation has demonstrated to be effective in decreasing blood pressure among patients with refractory hypertension. The anatomic distribution of renal artery nerves may influence the safety and efficacy profile of this procedure. We aimed to describe the anatomic distribution and density of periarterial renal nerves in the porcine model. Thirty arterial renal sections were included in the analysis by harvesting a tissue block containing the renal arteries and perirenal tissue from each animal. Each artery was divided into 3 segments (proximal, mid, and distal) and assessed for total number, size, and depth of the nerves according to the location. Nerve counts were greatest proximally (45.62% of the total nerves) and decreased gradually distally (mid, 24.58%; distal, 29.79%). The distribution in nerve size was similar across all 3 sections (~40% of the nerves, 50–100 μm; ~30%, 0–50 μm; ~20%, 100–200 μm; and ~10%, 200–500 μm). In the arterial segments ~45% of the nerves were located within 2 mm from the arterial wall whereas ~52% of all nerves were located within 2.5 mm from the arterial wall. Sympathetic efferent fibers outnumbered sensory afferent fibers overwhelmingly, intermixed within the nerve bundle. In the porcine model, renal artery nerves are seen more frequently in the proximal segment of the artery. Nerve size distribution appears to be homogeneous throughout the artery length. Nerve bundles progress closer to the arterial wall in the distal segments of the artery. This anatomic distribution may have implications for the future development of renal denervation therapies. (Translational Research 2013;162:381–389)

Abbreviations: BP = blood pressure; CGRP = calcitonin gene-related peptide; NBF = neutral buffered formalin; SNS = sympathetic nervous system; TH = Tyrosine hydroxylase

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AT A GLANCE COMMENTARY

Tellez A, et al.

Background

Catheter-based renal artery denervation has demonstrated to be effective in decreasing blood pressure among patients with refractory hypertension. The anatomic distribution of renal artery nerves may influence the safety and efficacy profile of this procedure.

Translational Significance

Our study used a swine model, because of its anatomic similarities to the human population, to describe the distribution, location, size, and density of sympathetic renal artery nerves. This information is paramount in translational research for making decisions with regard to target area, technology characteristics, and energy parameters of the ablation treatment (found to create lesions at a depth range of 3.0–9.5 mm).

Despite substantial advances in hypertension management therapies, resistant hypertension remains at an estimated prevalence of 12%–15% among treated patients.[1] In this subset of patients, overactivation of the sympathetic nervous system (SNS) has been demonstrated to play a significant role in the development and progression of the disease.[1,2] It has been described previously that the activation of Na/K adenosine triphosphatases, caused directly by the stimulation of efferent fibers, promotes vasoconstriction of renal arterioles, subsequently increasing blood pressure (BP).[3-5] It has been proposed that, after renal denervation, control over the functional units of the renal SNS is obtained, thus controlling the hypertensive state.

The concept of renal denervation began in 1935 with surgical sympathectomy, which involved extensive removal of sympathetic ganglia.[6] This procedure demonstrated an immediate decrease of renal sympathetic outflow and long-term BP reduction without affecting renal functions, as seen in clinical studies.[1,3,7] These results were greatly outweighed by significant side effects (ie, severe orthostatic hypotension and bowel/bladder activity impairment)[8] along with a prolonged hospital stay and recovery period.[9] Because of the undesirable side effects and development of new pharmacologic agents, the use of this procedure was discontinued in the early 1970s. However, indisputable evidence supporting the importance of the SNS in BP control was established, and the efficacy of renal sympathetic nerve inhibition for resistant hypertension was confirmed.[1] More recently, new devices have been developed to allow minimally invasive renal artery SNS denervation. A variety of ablative methods using different approaches are under development that aim to disrupt the sympathetic network, which is located in the perirenal aspects of the artery.[10,11] In humans, this approach has demonstrated substantial reduction of BP with significant clinical advantages over nonselective surgical sympathectomy.[10,12-14] Precise knowledge regarding the density and spatial distribution of this nerve network is essential for the successful development of renal denervation therapies. In the present study, we aimed to determine the anatomic distribution and density of renal artery nerves in the porcine model and discuss the potential implications for the development of renal denervation therapies.

METHODS

Experimental design. The study was approved by the Institutional Animal Care and Use Committee. All animals received standard care outlined in the study protocol and in accordance with the Animal Welfare Act[15] and Animal Welfare Regulations[16] and following the guide for the care and use of laboratory animals[17] formulated by the Institute of Laboratory Animal Resources. A total of 5 domestic Yorkshire swine (mean body weight, 46.2 ± 2.68 kg) were included in this study and were maintained on a standard chow diet. The mean age of the domestic Yorkshire swine at the time of inclusion was 4.4 ± 0.05 months. For the extraction of the area of interest, the abdominal cavity was accessed and the intestines removed to expose the retroperitoneum. A tissue block including the dorsal muscles, aorta, bilateral kidneys, and bilateral renal arteries was extracted as one block and was fixed into a surface to ensure proper tissue fixation and structural integrity. The whole tissue was immersed in 10% neutral buffered formalin (10% NBF) for at least 24 hours. The renal arteries were segmented every 3 mm. Artery lengths ranged from 15 to 27 mm. In an effort to make each artery comparable, the segments were separated into proximal, mid, and distal ranges accordingly to each artery. To evaluate accurately the nervous distribution by depth from the arterial wall, half-millimeter layers were evaluated individually moving away from the renal artery. Considering that, in preclinical research the depth of renal denervation therapies can reach beyond 9 mm, it was decided to analyze up to a threshold of 10 mm in depth.

Tissue collection and preparation for light microscopy. All animals underwent sedation via 1 intramuscular muscarinic anticholinergic dose (glycopyrrolate, 0.2 mg/mL; dosage, 0.005–0.02 mg/kg). Induction of anesthesia was achieved with a rapid-acting