Journal of the American Society of Hypertension 9(10) (2015) 794–801

Research Article

Spike rate of multi-unit muscle sympathetic nerve fibers after catheter-based renal nerve ablation

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Manuscript received July 3, 2015 and accepted July 23, 2015

Abstract

Patients with treatment-resistant arterial hypertension exhibited profound reductions in single sympathetic vasoconstrictor fiber firing rates after renal nerve ablation. In contrast, integrated multi-unit muscle sympathetic nerve activity (MSNA) changed little or not at all. We hypothesized that conventional MSNA analysis may have missed single fiber discharges, thus, obscuring sympathetic inhibition after renal denervation. We studied patients with difficult-to-control arterial hypertension (age 45–74 years) before, 6 (n = 11), and 12 months (n = 8) after renal nerve ablation. Electrocardiogram, respiration, brachial, and finger arterial blood pressure (BP), as well as the MSNA and raw MSNA signals were analyzed. We detected MSNA action-potential spikes using 2 stage kurtosis wavelet denoising techniques to assess mean, median, and maximum spike rates for each beat-to-beat interval. Supine heart rate and systolic BP did not change at 6 (ΔHR: -2 ± 3 bpm; ΔSBP: 2 ± 9 mm Hg) or at 12 months (ΔHR: -1 ± 3 mm Hg, ΔSBP: -1 ± 9 mm Hg) after renal nerve ablation. Mean burst frequency and mean spike frequency at baseline were 34 ± 3 bursts per minute and 8 ± 1 spikes per second. Both measurements did not change at 6 months (-1.4 ± 3.6 bursts/minute; -0.6 ± 1.4 spikes/second) or at 12 months (-2.5 ± 4.0 bursts/minute; -2.0 ± 1.6 spikes/second) after renal nerve ablation. After renal nerve ablation, BP decreased in 3 of 11 patients. BP and MSNA spike frequency changes were not correlated (slope = -0.06; $P = .369$). Spike rate analysis of multi-unit MSNA neurograms further suggests that profound sympathetic inhibition is not a consistent finding after renal nerve ablation. J Am Soc Hypertens 2015;9(10):794–801.

Keywords: Arterial hypertension; blood pressure; renal denervation; microneurography.

Introduction

Physiological studies suggest that signals generated in the kidney, conveyed through afferent renal nerves to the brain, promote arterial hypertension via sympathetic activation.[1] Local renal injury elicited by phenol injection produced sustained neurogenic hypertension in rats.[2,3] Efferent muscle sympathetic nerve activity (MSNA) recordings have been indispensable in translating these findings from animals to patients. For example, removal of the diseased native kidney-attenuated MSNA in renal transplant recipients.[4] Investigations in patients with resistant hypertension treated with catheter-based renal nerve ablation suggest that afferent renal nerves may also regulate MSNA and blood pressure (BP) in the absence of overt renal disease. In one patient treated with catheter-based renal nerve ablation, MSNA had decreased approximately 27% at week 6 and 66% at month 12 after the intervention.[5] However, subsequent studies showed no or much smaller MSNA changes after catheter-based renal nerve

Funding: The Deutsche Forschungsgemeinschaft supported J.J. and J.B. (JO 284/6-1). The German Space Agency supported J.T. and K.H. (50WB1117).

Conflict of interest: none.

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1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2015.07.012

ablation.[6–9] All these investigations recorded multiple efferent sympathetic nerve fibers analyzing the rectified and integrated nerve signal. In contrast, MSNA single fiber discharges massively decreased after catheter-based renal nerve ablation.[10] Possibly, integrated multifiber MSNA assessment obscured important information contained in MSNA raw signals, particularly discharges occurring outside regular bursts. Given that, each action potential is coupled to quantal norepinephrine release, we reasoned that changes in single-fiber activity would be of limited physiological relevance unless the total number of discharges is altered profoundly. We applied novel wavelet-based methodology[11,12] to test the hypothesis that renal nerve ablation substantially reduces the number of discharges in the MSNA raw signal in patients with drug-resistant hypertension. Because clinical trials over up to two years had suggested a delayed clinical response, we conducted measurements at about 6 and 12 months.

Methods

Patients

We studied 12 patients (11 men and 1 woman) with difficult to control arterial hypertension referred for catheter-based renal nerve ablation into an open clinical trial (NCT01355055). Patients had to have uncontrolled essential hypertension despite treatment with $\geq$3 antihypertensive medications at full doses, including a diuretic. The mean number of antihypertensive drugs was 7 ± 2. Patient characteristics were published earlier[6] together with the results of integrated MSNA analysis after 6 months after renal nerve ablation. Eight patients agreed to undergo microneurography again during follow up about 12 months after renal nerve ablation. All patients were judged to be compliant by their treating physician. In addition, we checked compliance with the antihypertensive drug regimen through phone interviews before each study visit. Medication and body mass index kept constant during the study. Participants were excluded if they had secondary hypertension. The local research internal review board ethics committees approved the study. Written informed consent was obtained.

Catheter-based Renal Nerve Ablation

The right femoral artery was punctured (Seldinger technique) after local anesthesia and a 6-French sheath was placed. Four to eight radiofrequency applications along both main renal arteries were applied (max. 8 Watts, max. 75°C for 2 min.) using the Symplicity Catheter System (Ardian, CA, USA) as described previously.[6] Operators were all well experienced in the technique and each has performed >12 such procedures in patients, according to published guidelines.

Cardiovascular Measurements

The study protocol at 12 months after renal nerve ablation was exactly the same as 6 months after renal nerve ablation.[6] During testing, patients remained in the supine position. An ECG was continuously recorded (Niccomo, Medis GmbH, Germany). Noninvasive finger BP recording was used (Finometer, Finapres Medical Systems, Netherlands) and adjusted against brachial oscillometric BP measurements (Dinamap, Critikon, USA).

Microneurography

A unipolar tungsten electrode with uninsulated tip diameter 1 to 5 μm and shaft diameter 200 μm (Frederick Haer and Co, Bowdoinham, MA, USA) was inserted into the muscle nerve fascicles of the peroneal nerve at the fibular head for multi-unit recordings. Satisfactory recordings of MSNA were defined by (1) heart pulse synchronicity; (2) facilitation during Valsalva straining and suppression during the hypertensive overshoot after release; (3) increases in response to breath holding; and (4) no change during tactile or auditory stimulation. Raw-nerve activity was amplified with a total gain of 100,000, band pass filtered from 0.7 to 2 kHz (662C-3 Nerve Traffic Analysis System, University of Iowa, Iowa City, USA) and recorded at 5000 Hz, 14-bit resolution using the WinDaq data acquisition system (DI-720, DATAQ Instruments, Akron OH, USA). The lag nerve signal of about -1.3 seconds was corrected before further processing.

Spike Detection with Kurtosis and Stationary Wavelet Transform

Action-potential spikes were detected in the raw neurogram recordings using two-stage kurtosis wavelet denoising.[11–13] This technique applies translation invariant stationary wavelet transform and mother wavelet Symlet 7, which has been shown to improve sympathetic spike detection.[11,13] The raw neurogram was decomposed into 3 bands of wavelet coefficients. Levels 2 and 3 were included for further analysis because these levels have the most dynamic response to the sympathetic activation (Figure 1A). Local Kurtosis was calculated for each level of activation (Figure 1B). A kurtosis value of around 3 indicates an ideal Gaussian distribution. Signal episodes with spike activity have usually higher kurtosis values. We extracted regions dominated by normally distributed noise identified as section with kurtosis level less than 4 (Figure 1C). Then we calculated an amplitude threshold from all coefficients with an absolute value less than 4 times the standard deviation of the identified noise regions (threshold T2 and T3 for levels 2 and 3, respectively). The thresholds were applied and values were set to zero at each wavelet decomposition level (Figure 1D). The denoised signal was reconstructed using