International Journal of Cardiology 202 (2016) 388–393

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Renal artery anatomy affects the blood pressure response to renal denervation in patients with resistant hypertension☆

Dagmara Hering [a,b], Petra Marusic [a,b], Antony S. Walton [c], Jacqueline Duval [a], Rebecca Lee [a], Yusuke Sata [a], Henry Krum [c,d], Elisabeth Lambert [a], Karlheinz Peter [c,e], Geoff Head [f], Gavin Lambert [a], Murray D. Esler [a,c], Markus P. Schlaich [a,b,d,g,]*

[a] Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia
[b] School of Medicine and Pharmacology — Royal Perth Hospital Unit, University of WA, Perth, Australia
[c] Heart Centre Alfred Hospital, Melbourne, Australia
[d] Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia
[e] Atherosclerosis & Vascular Biology Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia
[f] Neuropharmacology Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia
[g] Faculty of Medicine, Nursing and Health Sciences and Department of Physiology, Monash University, Melbourne, Australia

ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form 20 June 2015
Accepted 15 September 2015
Available online 21 September 2015

Keywords:
Resistant hypertension
Renal denervation
Renal artery anatomy

ABSTRACT

Background: Renal denervation (RDN) has been shown to reduce blood pressure (BP), muscle sympathetic nerve activity (MSNA) and target organ damage in patients with resistant hypertension (RH) and bilateral single renal arteries. The safety and efficacy of RDN in patients with multiple renal arteries remains unclear.
Methods: We measured office and 24-hour BP at baseline, 3 and 6 months following RDN in 91 patients with RH, including 65 patients with single renal arteries bilaterally (group 1), 16 patients with dual renal arteries on either one or both sides (group 2) and 10 patients with other anatomical constellations or structural abnormalities (group 3). Thirty nine out of 91 patients completed MSNA at baseline and follow-up.
Results: RDN significantly reduced office and daytime SBP in group 1 at both 3 and 6 months follow-up ($P < 0.001$) but not in groups 2 and 3. Similarly, a significant reduction in resting baseline MSNA was only observed in group 1 ($P < 0.05$). There was no deterioration in kidney function in any group.
Conclusion: While RDN can be performed safely irrespective of the underlying renal anatomy, the presence of single renal arteries with or without structural abnormalities is associated with a more pronounced BP and MSNA lowering effect than the presence of dual renal arteries in patients with RH. However, when patients with dual renal arteries received renal nerve ablation in all arteries there was trend towards a greater BP reduction. Insufficient renal sympathetic nerve ablation may account for these differences.

1. Introduction

The presence of multiple renal arteries is not uncommon ranging from 10% to 60% depending on the population studied [1–3]. Multiple or accessory renal arteries occur more frequently in hypertensive patients and increase the risk of developing hypertension [4–7]. Although a causal relationship between multiple/accessory renal arteries and the development of hypertension has been suggested, magnetic resonance angiography studies failed to support this hypothesis [8]. Increased activity of sympathetic nerves surrounding renal arteries is a typical feature in most forms of hypertension (EH) [9] and is a prime mover of the BP elevation [10]. Similarly, augmented muscle sympathetic nerve activity (MSNA) is clearly evident in patients with high-normal BP [11], EH [12], renovascular hypertension [13] and specifically in patients with RH [14,15]. Catheter-based renal denervation (RDN) is a treatment option that directly targets sympathetic overactivity [16,17] and has been shown to improve BP control and attenuate end organ damage [18–20] in RH [21–24]. While the recent Symplicity HTN-3 study could not confirm a BP lowering effect above that of a sham control [25], it has been questioned whether RDN was actually achieved in this study [26].

The initial clinical studies applying RDN mandated bilateral single renal arteries with an artery length of ≥20 mm, a diameter of ≥4 mm and absence of structural abnormalities. Consequently, the procedure was typically not offered to patients with multiple renal arteries or renovascular abnormalities [27]. However, in the absence of other therapeutic options RDN was offered to patients with accessory renal

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: School of Medicine and Pharmacology — Royal Perth Hospital Unit, Faculty of Medicine, Dentistry & Health Sciences, University of Western Australia, Level 3, MRF Building, Rear 50 Murray St, Perth WA 6000, Australia.
E-mail address: markus.schlaich@uwa.edu.au (M.P. Schlaich).

http://dx.doi.org/10.1016/j.ijcard.2015.09.015
0167-5273/

arteries [28] and renovascular hypertension [29]. To better understand the potential impact of various renal anatomies on BP and sympathetic responses to RDN we investigated the safety and efficacy of RDN in RH patients who presented with various anatomical renal artery constellations.

2. Methods

2.1. Subjects

The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all patients. In this prospective study a total of 91 patients (57 males, 34 females) with successful 24-hour BP monitoring (ABPM) at baseline, 3 and 6 months after RDN were included. Nine out of 91 patients were current smokers. All patients underwent a comprehensive medical history, physical examination and review of medication. Patients were interviewed whether they had taken their complete medication at defined doses at each visit. Treating physicians and patients were instructed not to change medications except when medically required. EH and RH were diagnosed as per European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines [30] and the current statement of the American Heart Association [31]. Twenty eight patients previously diagnosed with OSA who remained hypertensive despite adequate treatment efforts including continuous positive airway pressure (CPAP) treatment (n = 13) were included in this study. Patients with history of CKD with creatinine-based estimated glomerular filtration rate (eGFR) > 30 and < 60 ml/min/1.73 m^2 or previous stroke ≥ 6 months (n = 2) were also included.

2.2. Study protocol

Subjects were comprehensively examined in a quiet room and in a comfortable position and were asked to refrain from smoking and alcoholic beverages for at least 24 and 48 h respectively, prior to the study. All measurements were obtained at baseline (before RDN), 3 and 6 months post procedure. On the first visit, BP was measured as described below followed by fasting blood sampling for biochemistry assessment. All patients underwent 24-hour ABPM measurements. On the second visit, microneurography was performed in a subset of patients in the supine position.

2.3. Serum biochemistry

Routine blood tests and estimated glomerular filtration rate (eGFR) were performed in all patients at each time visit as described previously [14].

2.4. Office-seated and ambulatory blood pressure

Office seated BP was measured after 5 min of rest on both arms and was calculated as the average of three consecutive measurements within a 2-minute interval at baseline and during each visit at follow-up using a validated device (Omron HEM-907, Omron Healthcare Singapore PTE Ltd). The arm with higher BP readings was used for subsequent measures.

To confirm resistant hypertension, 24-hour ABPM was performed using a validated device (Spacelabs 90207 or 90217 recorder; Spacelabs Healthcare, Washington, USA) in all patients (n = 91) at baseline, 3 and 6 months follow-up as described previously [14].

2.5. Muscle sympathetic nerve activity (Microneurography)

After 15 min of rest, resting multi-unit MSNA was recorded from postganglionic sympathetic nerves using microneurography over a period of 15 min (662C-3 Nerve Traffic Analysis System, Bioengineering of Iowa University, USA) as described previously [14]. Patients with atrial fibrillation and those presenting with frequent extra systoles during MSNA recording at baseline (n = 6) were excluded from the final analysis. Multi-unit MSNA was analysed over a period of 5 min. MSNA bursts were identified and sympathetic activity was calculated as burst frequency (bursts/min) and as burst incidence (bursts/100 heartbeats) as described previously [14].

2.6. Catheter-based renal denervation (RDN)

Bilateral RDN was performed using a radiofrequency ablation catheter (Symplicity™; Medtronic Ardian Inc., Palo Alto, California, USA) as described previously [14].

2.7. Peri-and post-procedural medications

Baseline medication was kept unchanged for at least 6 weeks prior to RDN and was maintained in the majority of the patients at follow-up. Antihypertensive medication was either reduced or stopped in a subset of patients at 3 and 6 month follow-up due to achieved BP control. Five out of 91 patients required an increase in dose of antihypertensive drugs from baseline to follow-up. Changes in medication are described in the results section and Fig. 1. Female subjects were post-menopausal and were not receiving hormone replacement therapy.

2.8. Statistical analysis

Data in the text and tables are presented as mean ± SD. Statistical analysis was performed using SigmaStat Version 3.5 (Systat Software, Point Richmond, CA). The comparisons between visits in BP and MSNA from baseline to 3 and 6 month follow-up were analysed using One Way ANOVA for repeated measurements. A p-value of <0.05 was considered significant.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the study cohort and prescribed medication are summarized in Table 1.

3.2. Renal anatomy characteristics

Group 1 (n = 65) had single renal arteries bilaterally. In group 2 (n = 16) 8 patients had dual renal arteries on the left side and single renal arteries on the right side; 5 patients had dual renal arteries on the right side and single renal arteries on the left side. Three patients had dual renal arteries bilaterally.

Renal anatomy characteristics and RDN treatment characteristics of group 3 (n = 10) are summarized in Table 2.

3.3. Procedural aspects

Renal angiograms were performed prior to RDN and anatomy of renal arteries was confirmed in all patients. An average of 13.4 ± 2.9 (group 1), 14.1 ± 4.3 (group 2) and 10.5 ± 4.3 (group 3) ablation treatments were delivered in each patient without any peri-or post-procedural complications. There were no intra- or peri-procedural RDN complications.

3.4. Effects of renal denervation

In group 1, RDN significantly reduced average office SBP from 156 ± 24 to 143 ± 18 mm Hg ($P < 0.001$) at 3 months and to 144 ± 18 mm Hg at 6 months ($P < 0.001$), and DBP from 79 ± 20 to 75 ± 17 mm Hg ($P = 0.003$) at 3 months and to 75 ± 17 mm Hg ($P < 0.001$) at 6 months