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Original Article

Effects of renal sympathetic denervation on blood pressure, sleep apnoea severity and metabolic indices: a prospective cohort study

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ABSTRACT

Background: Catheter-based renal sympathetic denervation (RSD) significantly reduces blood pressure in patients with resistant hypertension, who commonly have obstructive sleep apnoea (OSA). These patients are considered particularly responsive to the antihypertensive effects of RSD, but additional benefits of metabolic control on sleep apnoea severity have not been thoroughly investigated.
Methods: The effect of RSD was evaluated prospectively in a cohort of patients with OSA (apnoea −hypopnea index (AHI) ≥15 events per hour and an Epworth Sleepiness Scale (ESS) score ≤9) and treatment resistant hypertension. Changes in blood pressure, polysomnographic parameters and metabolic indices were evaluated at baseline and six months post procedure.
Results: At baseline, mean office blood pressure was 166.3/92.8 (14.5/11.7) mmHg and mean ambulatory blood pressure was 154.0/87.3 (11.9/8.5) mmHg. At six months post RSD, mean office blood pressure reduced by 6.6/6.5 (1.9/2.0) mmHg ($p < 0.05$) and mean ambulatory blood pressure reduced by 8.3/6.2 (2.3/2.0) ($p < 0.05$). The mean AHI at baseline was 21.3 events/h and 20.5 events/h at six months post RSD, with a mean reduction of 0.9 events/h (95% CI −0.7−1.6, $p = 0.39$). Glucose at two hours/2 h following tolerance testing reduced by 1.14 mmol/L (95% CI 0.22−2.06, $p = 0.03$) but changes in other metabolic indices were not statistically significant.
Conclusion: In patients with resistant hypertension and OSA, RSD resulted in modest improvements in blood pressure control, but no significant changes in sleep apnoea severity. Our study showed small increments in glucose tolerance but no significant changes in other markers of carbohydrate or lipid metabolism.

1. Introduction

Persistent activation of the sympathetic nervous system represents an important pathogenic mechanism in multiple disease states including hypertension, obstructive sleep apnoea (OSA) and disorders of carbohydrate and lipid metabolism [1]. Interruption of renal sympathetic signalling by percutaneous renal sympathetic denervation (RSD) is a treatment strategy for resistant hypertension, used in more than 80 countries including North America, Europe and Australia [2]. In both proof-of-concept [3] and randomised trials [4] this technique proved to be safe and resulted in persistent reductions in blood pressure.

However, a blinded, sham-controlled trial calls renal denervation as a blood pressure lowering strategy into question [5]. Numerous factors explaining the procedure's perceived inadequacy have emerged [6], including failure to select patients with a significant sympathoadrenal component to their resistant hypertensive state. One subset of patients with resistant hypertension and highly active sympathetic drives are those with OSA [7], where the upper airway collapse and leads to cyclical intermittent hypoxia and hypercapnia, as well as chemoreflex actions that increases sympathetic nerve activity. Accordingly, these patients may be particularly responsive to the antihypertensive effect of RSD [8].

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In addition to the association between OSA and hypertension [9], there is a focus on the role of sleep apnoea in the aggravation of metabolic dysfunction and subsequent contribution to cardiovascular risk [10]. RSD has been proposed to not only alleviate hypertension in patients with OSA, but also improve sleep apnoea severity and glucose metabolism, with potential for cardiovascular risk reduction. Studies in this area have been inadequate and the results are largely heterogeneous [11,12].

In this prospective study of patients with OSA and treatment resistant hypertension, we evaluated the efficacy of RSD as an antihypertensive strategy. The additional benefits of improved metabolic control and reduced sleep apnoea severity were also assessed.

2. Methods

2.1. Study design and participants

Patients (≥18 years) were prospectively recruited from a multidisciplinary, hospital-based resistant hypertension clinic. Inclusion criteria included resistant hypertension defined by repeat office systolic blood pressures (SBP) ≥160 mmHg despite ≥3 antihypertensive medications at maximal dosage, including a diuretic [13]. Exclusion criteria included pregnancy, excess salt (>6 g/day) or alcohol (>14 units/week) intake, medications known to cause treatment resistance, psuedoresistant hypertension (suspected poor patient adherence, previous documentation of white-coat effect, inadequate antihypertensive doses or inappropriate combinations), hypertension due to secondary causes, estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2 and insulin-treated type 2 diabetes mellitus.

Patients meeting these eligibility criteria underwent preliminary sleep testing and OSA was defined by an AHI ≥15 events per hour. Of these newly diagnosed sleep apnoea patients, we included only those not already being treated with continuous positive airway pressure (CPAP) with an Epworth Sleepiness Scale [14] (ESS) ≤ 9. Patients underwent computed tomography renal angiography to assess suitability for RSD. Those with unfavourable descending aorta or renal artery anatomy were excluded.

Baseline blood pressure measurement, assessment of metabolic indices and overnight polysomnography were performed before and at six months after RSD. Recruitment, follow-up and denervation were carried out at a single centre in the Republic of Ireland from October 2014 to June 2015. The study was approved by the participating institution and local ethics committee. Each patient provided written informed consent.

2.2. Blood pressure measurement

Over a two-week period, patients had multiple assessments of blood pressure (BP). Home BP was measured twice daily (morning and evening) using a brachial artery oscillometric device (Omron M3 Comfort), and recorded in a diary. Office blood pressure was measured (Omron HEM-907) in the sitting position after at least five minutes rest and calculated as the average of three consecutive measurements taken at one minute intervals. If the discrepancy between any two systolic readings was greater than 10 mmHg, the readings were repeated until consistent. Ambulatory blood pressure monitoring was performed for a 24-h period where the patient conducted normal daily activities. Monitors (Spacelabs 90207) were programmed to record blood pressure every 20 min during the daytime period and every 30 min during the night-time period. Participants were classified as dippers or non-dippers (defined as a <10% drop in average night-time systolic blood pressure (SBP) compared to average daytime SBP).

2.3. Polysomnography

Overnight attended polysomnography was performed at an accredited sleep laboratory with monitoring of electroencephalography, submental electromyography, electrooculography, thoracoabdominal motion, oronasal air flow, finger pulse oximetry and body position. Sleep-wake state, arousals and periodic limb movements were scored according to standard criteria [15]. Mean SaO_2, minimum SaO_2, number of desaturations <90% and AHI were recorded with an apnoea defined as complete cessation of airflow for ≥10 s at the mouth and nose, and hypopnoea as a decrease in respiratory effort accompanied by drop in saturation ≥4%.

2.4. Assessment of metabolic indices

Physical measurements including waist-to-hip ratio, body mass index (BMI) and neck circumference were measured using standardised methodology. Following a 10–12 h overnight fast, blood samples were collected for total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), fasting glucose and glycosylated haemoglobin A (HbA_{1c}). The Modification of Diet in Renal Disease formula was used to calculate estimated Glomerular Filtration Rate (eGFR) [16]. An oral glucose tolerance test was performed with a 75-g glucose load and glucose measurements at 120 min. New diagnoses of type 2 diabetes mellitus were made based on an oral glucose tolerance test (OGTT) 2 h value ≥ 11.1 mmol/L or HbA_{1c} ≥ 48 mmol/mol (6.5%) [17]. Insulin sensitivity (%S) and β-cell function (%β) were calculated from fasting plasma glucose and insulin values using the online Homeostasis Model Assessment-Insulin Resistance (HOMA) modelling calculator [18].

2.5. Renal denervation procedure

Renal sympathetic denervation was achieved through an endovascular catheter-based technique that delivered discrete low level radiofrequency (RF) energy across the wall of the renal artery. The femoral artery was catheterised using a 6F guide and the catheter tip placed in the vasculature adjacent to the target neural site under fluoroscopic guidance. To provide circumferential disruption of adventitial sympathetic nerves, four to six applications of radiofrequency energy were delivered in a helical pattern within each renal artery. Two catheters were used (Symplicity Spyral and Symplicity Flex), and both were powered by the Symplicity G3 generator that delivered RF energy through an operator-independent algorithm. The procedure was carried out under conscious sedation with additional narcotic analgesia when required.

2.6. Other interventions

Antihypertensive agents were not altered during follow-up, and physicians were asked to refrain from dose modifications. Oral hypoglycaemic agents were adjusted at the discretion of the patients' physicians. Patients did not receive any form of positive airway pressure during follow-up.

2.7. Statistical analysis

Descriptive statistics are used to describe the cohort and differences in blood pressure control, polysomnographic parameters and metabolic profile at baseline (pre-RSD) and at six months post-RSD. Continuous variables are reported using mean (standard deviation) or median (range), as appropriate. Change in continuous parameters is reported as mean with 95% confidence intervals. Categorical variables are reported as % (n). Paired *t*-test was used to