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Health related quality of life and blood pressure 12 months post renal denervation

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Abstract

Aim: To examine the effect of renal denervation (RDN) on blood pressure (BP) and health-related quality of life (QoL) in subjects with resistant hypertension, pseudo-resistant hypertension due to a white coat effect and in patients with uncontrolled masked hypertension.

Methods: Using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), Beck Depression Inventory (BDI) and Spielberger's state and trait anxiety questionnaires we examined QoL, symptoms of depression and anxiety prior to and 12 months following RDN. Blood pressure was assessed from clinic and ambulatory (ABPM) recordings.

Results: Patients with uncontrolled masked hypertension had the highest BDI and anxiety scores among all groups at baseline. Twelve months following RDN clinic and ambulatory BP were reduced only in those patients with resistant hypertension (delta systolic BP: clinic -16±3 mmHg, $ABPM_{day}$ -8±2 mmHg, $ABPM_{night}$ -8±2 mmHg, all $P<0.01$). Clinic BP was reduced in the pseudo-resistant group (-17±6 mmHg, $P<0.01$) but was elevated in the uncontrolled masked group (+13±6 mmHg, $P=0.02$). In all subjects, trait anxiety ($P<0.05$), BDI scores ($P<0.05$) and the SF-36 MCS score ($P<0.001$) were improved. The improvement in the SF-36 MCS was confined to those patients with resistant hypertension (+4.0±1.1, $P<0.01$). The change in clinic BP after RDN was related to the baseline clinic BP (systolic: $r=0.54$, $P<0.001$; diastolic $r=0.43$, $P<0.001$), the number of ablations delivered (both clinic and mean day ABPM systolic $r=0.24$, $P<0.05$) and to the change in SF-36 MCS score (systolic: $r=0.25$, $P=0.01$; diastolic $r=0.24$, $P=0.02$).

Conclusion: These results indicate that in patients with confirmed resistant hypertension RDN is associated with a reduction in BP and a sustained improvement in mental health related aspects of QoL.

Condensed Abstract

We combined measurement of clinic and ambulatory blood pressure and the assessment of health-related quality of life and symptoms of depression and anxiety in patients with hypertension prior to and 12 months following renal denervation. Clinic and ambulatory blood pressure was reduced and an improvement in mental health related quality of life was sustained out to 12 months post denervation in patients with treatment resistant hypertension.

Keywords: sympathetic nervous system; high blood pressure; depression; anxiety

Abbreviations: RDN, renal denervation; BP, blood pressure; QoL, health-related quality of life; BDI, Beck Depression Inventory; ESH, European Society of Hypertension; ESC, European Society of Cardiology

Introduction

A large body of experimental and clinical data highlights the importance of the renal sympathetic nerves in the generation and maintenance of hypertension. This evidence provided the theoretical rational and impetus for the development of a percutaneous endovascular approach to ablate the renal sympathetic nerves using radiofrequency energy in an effort to provide another avenue towards blood pressure control. The initial trials were associated with a marked reduction in clinic blood pressure in patients with treatment resistant hypertension [1, 2]. Similar falls in blood pressure have been observed 12 months post denervation in the EnligHTN I study [3], and Azizi and colleagues recently demonstrated that renal denervation added to a stepped-care antihypertensive pharmacological treatment program reduced blood pressure more than the stepped care program alone in patients with well-defined resistant hypertension [4]. Although the effectiveness of this technology has been recently questioned[5, 6], a significant reduction in clinic blood pressure has been documented out to three years post renal denervation in both SYMPLICITY HTN-1 and HTN-2 trials [7, 8] and additional benefits including the improvement in insulin sensitivity [9], cardiac structure and function [10, 11] [12] and reduction in plasma levels of N-terminal pro B-type naturetic peptide [12] have been reported. Moreover we recently demonstrated that 3 months following ablation of the renal sympathetic nerves the mental health components of health related quality of life was improved and symptoms of depression were significantly less [13]. Similarly, Lenski *et al* have shown that following renal denervation patients perform better in the tests of reactive stress tolerance 6 months post denervation [14]. In this study we report patients' subjective physical and mental health related quality of life and symptoms of depression and anxiety 12 months following renal denervation. By combining office and ambulatory blood pressure assessment we analysed the effect of renal denervation on blood pressure and subjective health related quality of life data in patients with resistant hypertension, pseudo-resistant hypertension due to a white coat effect and masked uncontrolled hypertension.

Methods

Participants

Data from 97 patients (37 females/60 males, aged 64.0±0.9 years) who were participating in our ongoing programs into the effectiveness of renal denervation in the long term control of blood pressure and who were examined prior to denervation and 12 months subsequent form the basis of this report. The relevant trials are registered at ClinicalTrials.gov (NCT01865240, NCT01865253, NCT02016573). Patients comprised primarily those with treatment resistant or uncontrolled hypertension and a small group of patients who underwent the renal denervation procedure for reasons other than resistant hypertension such as patients with significant side effects to antihypertensive therapy. All patients underwent a complete medical history and physical examination. All participants had been evaluated previously and treated at specialized clinics prior to being referred to our hypertension unit for further management. Hypertension was diagnosed based on the current European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines for the management of arterial hypertension [15]. Patients had previously been screened for secondary forms of hypertension according to current guidelines [16]. All medications were stable for at least 6 weeks prior to baseline assessment and the renal nerve denervation procedure. Medications comprised principally, in various combinations: angiotensin receptor blockers (68% of participants), angiotensin converting enzyme inhibitors (35%), calcium channel blockers (65%), thiazide or loop diuretics (65%), aldosterone antagonists (spironolactone, 32%), beta blockers (56%), centrally acting sympathoinhibitory agents (46%) and alpha blockers (29%). Statins (62%), aspirin (46%), oral hypoglycaemic agents (20%), insulin (16%), antidepressants (11%) and anxiolytics (8%) were also used. Renal nerve ablation was achieved using a radiofrequency catheter (SYMPLICITY Flex®; Medtronic Ardian Inc., Palo Alto, California, USA) that was introduced into each renal artery via femoral access. All patients underwent renal nerve ablation in one session with the

catheter positioned in the lumen of the renal artery, as described previously [7, 8]. On average, 12.7 ± 0.4 denervations were done (range 5-21). Equal numbers of denervations were delivered to the left (6.2 ± 0.2) and right (6.7 ± 0.2) renal arteries. Although there was no difference in the procedure time between the different blood pressure groups, patients with pseudo resistant hypertension received less denervations (10.4 ± 1.0) than those with either resistant (12.6 ± 0.4; P=0.04) or uncontrolled masked (14.6 ± 0.5; P=0.005) hypertension. The procedure is approved in Australia by the Therapeutic Goods and Drug Administration and the research investigation was approved by the Institutional Ethics Committee and written, informed consent was obtained from all participants.

Blood pressure assessment

Inclusion for entry into these studies applying renal denervation in patients with resistant hypertension were based exclusively on office blood pressure measurements. At each clinical visit prior to renal denervation, average sitting office blood pressure was measured in both arms after at least 5-minutes of rest, calculated as the average of three consecutive measurements within a 1-minute interval using a validated device (Omron HEM-907, Omron Healthcare Singapore Pty Ltd). The arm with higher blood pressure readings was used for the follow up visit 12 months following renal denervation. Twenty four hour ambulatory blood pressure was recorded prior to renal denervation using an oscillometric Spacelabs 90207 or 90217 monitor (Spacelabs Medical Inc, Redmond, WA, USA) with readings taken every 15 minutes in daytime and every 30 minutes during the night. Clinic blood pressure equal or greater than 140/90 mmHg and daytime average ambulatory blood pressure equal or above 135/85 mmHg were used for hypertension classification [17].

Medical quality of life assessment

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was used to assess health related quality of life [18]. The responses to the 36 items were used to determine 8 category scales: (1) physical functioning, (2) role limitations caused by physical problems, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role limitations caused by emotional problems, and (8) mental health. Scale scores range from 0 to 100, with higher scores indicating better health. The 8 category scores were aggregated into two summary scales, the physical component summary (PCS) scale and the mental component summary (MCS) scale. The summary scores were calculated as t scores based on general Australian population norms, with a mean of 50 and a standard deviation of 10 as previously described [13]. The Beck Depression Inventory (BDI-II) [19] and Spielberger's State and Trait Anxiety inventories [20] were used to assess symptoms of depression and level of anxiety, respectively. Participants completed the self-report questionnaires either at home or at the clinic prior to any laboratory investigations.

Statistics

Statistical analysis was performed using IBM SPSS Statistics Version 22. Data are reported as mean±standard error of the mean unless specified otherwise. Comparisons between groups were performed using a one way ANOVA. Post hoc testing was performed using the Holm-Sidak Test. The effects of renal denervation on SF-36 category scales and summary scores, BDI and anxiety state and trait were assessed using one way ANOVA for repeated measures. Non Gaussian data was logarithmically transformed prior to analysis. Associations between the physical and mental component summary scores and physiological variables were examined using Pearson'sproduct moment correlation coefficient and linear regression analysis. A two-tailed value of $P<0.05$ was considered significant.

Results

Baseline participant demographics and health-related quality of life

The baseline clinical characteristics of the participants are presented in Table 1. Subjects ranged in age from 27-84 years, tended to be overweight or obese with 66 subjects having a BMI >30 kg/m^2, on average had a modest impairment in renal function and were taking multiple medications (range 0-13, median 5). Daytime average ambulatory blood pressure of the entire cohort was 153±2/84±1 mmHg. There was a significant correlation between daytime average ambulatory blood pressure values and blood pressure recorded in the clinic (for systolic blood pressure: Clinic pressure = 63 + (0.6 x Ambulatory pressure), r=0.52, P<0.001; for diastolic blood pressure: Clinic pressure = -3 + (1.0 x Ambulatory pressure), r=0.61, P<0.001). Comparison of ambulatory and clinic blood pressure recordings indicated that in 69 patients blood pressure was not controlled, pseudo-resistant hypertension due to a white coat effect was present in 11 patients and 17 patients had masked uncontrolled hypertension (Figure 1). Clinic blood pressure was lower in those patients taking a greater number of medications (systolic r=-0.23, P=0.02; diastolic r=-0.31, P<0.01). Ambulatory blood pressure was negatively correlated with age (daytime: systolic r=–0.25, P=0.01; diastolic r=-0.64, P<0.001, night: systolic r=0.20, P=0.06; diastolic r=-0.57, P<0.001).

For the entire cohort the responses to the SF-36 health related quality of life assessment indicated that the participants experienced a degree of impairment, compared with the general population [18], in both the physical and mental health domains. Beck Depression Inventory scores indicated the presence of mild, moderate and severe symptoms of depression in 13, 4 and 2 subjects respectively. State and trait anxiety and BDI scores were significantly elevated in those participants with masked uncontrolled hypertension (Table 1). There occurred no discernible difference in the medication profile between the three blood pressure groups. The use of moxonidine (n=45) was associated with a higher BMI (33.0±0.7 v 29.4±0.7, P<0.001)

and less symptoms of depression (BDI score 7.0±0.8 v 10.5±1.1, P=0.02). Moxonidine was used in 46% of patients with resistant hypertension, 45% of patients with white coat hypertension and in 53% of those with masked uncontrolled hypertension.

The magnitude of the difference between clinic systolic and average daytime systolic ambulatory blood pressures was not related to age, gender or baseline SF36-MCS or PCS scores but was associated with BMI (r=0.25, P=0.02 for systolic blood pressure). In those patients with a lower BMI blood pressures recorded in the clinic tended to be higher than ambulatory recordings whereas for those patients with a higher BMI ambulatory pressures were higher than clinic readings. Patients with higher levels of anxiety and more symptoms of depression tended to have higher ambulatory readings compared with blood pressure recorded in the clinic (for systolic blood pressure: state anxiety r=0.26, P=0.01; trait anxiety r=0.23, P=0.03; BDI r=0.19, P=0.07). There was no influence of gender, age, BMI or renal function on symptoms of depression, anxiety or the SF-36 MCS score. The SF36 PCS score was lower in women (38.5±1.6 v 43.6±1.4; P=0.02) and was inversely related to age (r=-0.20, P=0.04), BDI score (r=-0.34, P<0.01) and trait anxiety (r=-0.24, P=0.02).

Twelve month follow up

Successful ABPM data was available in 86 participants 12 months following renal denervation (62 resistant hypertension, 10 pseudo hypertension due to a white coat effect and 14 masked uncontrolled hypertension). There occurred a significant reduction in both clinic and ambulatory blood pressure 12 months following renal denervation in those patients with resistant hypertension (Figure 2). In patients with pseudo resistant hypertension due to a white coat effect clinic systolic blood pressure was reduced substantially whereas average daytime and night time ambulatory systolic blood pressure remained unchanged following renal denervation. This pattern of blood pressure change differed to that seen in the masked

uncontrolled hypertension group where clinic systolic blood pressure was elevated following renal denervation. Daytime and night time average ambulatory systolic blood pressure tended to be higher following renal denervation in these patients (P=0.17 and P=0.23 respectively). Clinic and ambulatory diastolic blood pressure displayed the same trends in each patient group as those observed with systolic blood pressure (data not shown). A change in blood pressure related medication was recorded in 35% of participants (20% reduced and 15% increased either the dose or number of medications). Changes in the number of medications was not related to the change in either clinic or ambulatory blood pressure at 12 months post-denervation. There was no difference in the number of patients in whom medication was changed between the different blood pressure groups (P=0.75). Changes in medication were not related to gender, age, BMI or blood pressure prior to denervation. There occurred a significant association between the magnitude of blood pressure reduction after 12 months and the total number of denervations delivered (clinic systolic r=0.24, P=0.02; mean daytime ambulatory systolic r=0.24; P=0.03).

In the entire cohort renal denervation was without a significant detrimental effect on any elements of the patients' subjective health related quality of life (Figure 3). The SF36 MCS score had improved significantly after 12 months (Table 2), with the improvement being most evident in the resistant hypertension group (Figure 4). There was no significant change in the SF-36 MCS in either the pseudo-resistant hypertension due to a white coat effect or the uncontrolled masked hypertension groups (P=0.43 and 0.57 respectively). In all subjects combined the change in SF-36 MCS score was not significantly associated with age, gender, BMI, GFR, number of medications or the baseline level of anxiety or depression. In 46 subjects the improvement in the SF-36 MCS score was > 3, in 36 of whom the increase was more than 5. A worsening of the SF-36 MCS of more than 3 was observed in 25 participants, 19 of whom had a score reduced by more than 5. There was no significant change in the PCS

score although participants reported an improvement in general health. An increase in the SF-36 PCS score of more than 3 was observed in 29 subjects and a reduction > 3 in 38 subjects. Beck depression inventory and trait anxiety scores were improved. There was no change in the state anxiety level (Table 2). Sub group analysis indicated that the change in BDI score was confined to the patients with resistant hypertension (change in BDI -1.9±0.7, P<0.01). There was no significant change in symptoms of depression in either the pseudo-resistant hypertension (-0.3±1.5, P=0.86) or uncontrolled masked hypertension (+1.1±1.5, P=0.47) groups. The changes in SF-36 MCS, BDI or anxiety scores were not related to the change in medication.

In all subjects combined the change in office blood pressure after renal denervation was related to both the baseline blood pressure recorded in the clinic (systolic: r=0.54, P<0.001; diastolic r=0.43, P<0.001) and to the change in SF-36 MCS score (systolic: r=0.25, P=0.01; diastolic r=0.24, P=0.02). There was no relationship between the change in ABPM derived measures and any of the psychometric variables examined. Changes in clinic or ABPM were not related to age, gender, BMI or eGFR at baseline.

Discussion

In agreement with an earlier report [21], in this study we noted that percutaneous renal denervation was associated with a significant reduction in both office and ambulatory blood pressure in those patients with ABPM confirmed treatment resistant hypertension. While clinic blood pressure was reduced in those patients with pseudo resistant hypertension due to a white coat effect, renal denervation did not influence ABPM in them, or in those patients with uncontrolled masked hypertension. In line with the SYMPLICITY studies [1, 2, 5], which reported that the procedure was safe, we noted that there occurred no detrimental effect on the patients' physical or mental health related quality of life 12 months after renal

denervation. The improvement in SF-36 mental health component summary score and in symptoms of depression and level of anxiety that we have noted to occur at 3 months [13] were sustained out to one year post denervation.

By combining clinic and ABPM recordings we were able to examine the effect of renal denervation on health related quality of life and the underlying level of anxiety and depression in patients with uncontrolled hypertension, pseudo resistant hypertension due to a white coat effect and uncontrolled masked hypertension. We found that patients with uncontrolled masked hypertension experienced higher levels of depression and anxiety compared with the other blood pressure groups, with the effect being amplified particularly in comparison to those patients with pseudo resistant hypertension due to a white coat effect. This is in contrast to the observations of Ogedegbe *et al* who found no difference in trait anxiety between patients with white coat, sustained or masked hypertension but noted that situational, or state, anxiety and blood pressure were elevated in the presence of a physician only in those patients with white coat hypertension [22]. In our study patients were older, had a higher BMI and more severe hypertension despite the continued taking of medication. Whether these factors contributed to the differing results remains unknown. Previous studies have shown that the magnitude and direction of the difference between clinic and ambulatory blood pressure is age dependent [23] and is particularly influenced as to whether or not a person has been diagnosed as hypertensive [24]. Our data is perhaps consistent with longitudinal data derived from the Nord-Trøndelag Health Study where symptoms of anxiety and depression actually predicted subsequent lower clinic blood pressure [25]. For those patients with pseudo resistant hypertension due to a white coat effect the higher clinic blood pressure may be stimulus specific and not linked with markers of anxiety. The use of moxonidine, a centrally acting inhibitor of sympathetic nervous outflow, was associated with

less symptoms of depression. This latter observation may reflect a clonidine-like anxiolytic effect of moxonidine acting on I_1-imidazoline receptors [26].

The association between mood disorders and blood pressure is complicated. While Licht and colleagues noted that in a community based sample the presence of depression was associated with decreased blood pressure [27], in psychiatric outpatients the diagnosis of major depressive disorder is more common in those with high blood pressure [28]. Similarly, the presence of panic disorder is more common in patients with hypertension [29]. In a recent examination based on a community sample, Terracciano and colleagues noted that pseudo resistant hypertension due to a white coat effect was associated with higher anxiety only in those patients taking antihypertensive medications and, unlike in our cohort, patients with masked hypertension did not present with higher anxiety levels [30]. Whether observations such as these are relevant in the present context where patients attended a tertiary referral centre for the management of difficult to treat hypertension is problematic. Moreover, in our study, delineating the effect of individual medications on quality of life, anxiety, depression or blood pressure response to renal denervation is difficult given the possible permutations and combinations of medications that were used by the participants.

Over the 12 month study period the MCS score of the SF-36 increased significantly in those patients with resistant hypertension, with the score at 12 months being commensurate with that observed in the general population. The magnitude of the increase was in line with the proposed minimal important difference in SF-36 summary scores, which has been reported to be between 3-5 [31, 32], and was associated with the magnitude of the change in clinic blood pressure that occurred following renal denervation. In their recent systematic review of placebo controlled randomized trials, Frendl and Ware noted that in clinically efficacious trials there occurred a strong concordance between clinical endpoints and SF-36 physical and mental health summary scores, with the median change in the physical and mental summary

scores being 2.5 and 2.0 respectively [32].While we cannot rule out that the improvement in SF-36 MCS score at 12 months that we describe represents a placebo effect, of the nine cardiovascular related studies reported by Frendl and Ware [32] baseline or change in SF-36 MCS scores were reported in six studies. There occurred no significant change in SF-36 MCS score in the placebo treated group in five studies [33-37] while in one investigation, the examination of the effectiveness of fludrocortisone on postural hypotension in patients with chronic fatigue syndrome [38], the SF-36 MCS score was increased by approximately 3.5 in the placebo group. Interestingly, in this latter study the level of depression was quite high, with a mean BDI score of 15. Although studies have shown that depression impacts negatively on cognitive performance and quality of life in patients with orthostatic intolerance [39] and that the placebo effect on SF36-MCS scores is substantially increased in patients with depression [32], we found no significant association between baseline symptoms of depression and the change in SF-36 MCS score.

Following renal denervation a reduction in both clinic and ambulatory blood pressure was observed in those patients with resistant hypertension, as described previously [7, 8, 21]. Consistent with these earlier reports we found that the best predictor of blood pressure reduction at 12 months post denervation was the initial clinic blood pressure recording. The quantitatively smaller effect of renal denervation on blood pressure that we observed is most likely due to our inclusion of patients with milder forms of hypertension than in previous studies [7, 8, 21]. Consistent with an earlier report by Mahfoud and colleagues [21], in patients with uncontrolled hypertension due to a white coat effect, office blood pressure was reduced but there was no effect of renal denervation on ambulatory blood pressure. This pattern of treatment response in patients with white coat hypertension is strikingly similar to that observed with long term pharmacological interventions [40]. While these observations suggest that the renal sympathetic nerves are not the prime driver in the generation of

hypertension in these patients, other sympathetic neural outflows could be involved and may lead to a degree of end organ dysfunction. For instance, activation of the muscle sympathetic nervous outflow, as indicated from both single and multi-unit nerve recordings [41], and altered cardiac structure and function [42] has been described in patients with white coat hypertension. Elevated single unit muscle sympathetic nervous activity has been shown to be associated with increased cardiac norepinephrine spillover [43] which, in turn, has been linked to hypertensive left ventricular hypertrophy [44]. Importantly, a reduction in both multiunit and single unit muscle sympathetic nerve activity has been shown to occur in patients with resistant hypertension after renal denervation, both in the short [45] and in the longer term [46]. Whether renal denervation results in a reduction in muscle sympathetic activity in patients with uncontrolled hypertension due to a white coat effect remains unknown.

In those patients with masked uncontrolled hypertension blood pressure was elevated 12 months following renal denervation. This is surprising and, given that the cardiovascular risk profile of patients with masked hypertension has been shown to be similar to that of patients with sustained hypertension [47], is a noteworthy observation. Pickering and colleagues noted the influence of psychological and situational determinants of blood pressure that affect the difference between clinic and ambulatory blood pressure readings [24]. In our study, at baseline, those patients with masked uncontrolled hypertension, in whom state anxiety and symptoms of depression were high and clinic blood pressure was disproportionately low, had either an anomalous blood pressure rise with ambulatory monitoring, or an anomalous blood pressure fall in the clinic. Subjects, especially those with higher blood pressure, may find ambulatory monitoring intrusive, with the procedure being uncomfortable and disturbing sleep. Those patients with masked uncontrolled hypertension had higher levels of anxiety and more symptoms of depression. Interestingly, while thermal and electrical experimental pain

thresholds and pain tolerance are increased in patients with depression, ischaemic pain threshold and pain tolerance in response to a blood pressure cuff being inflated to 200 mmHg are reduced [48]. Whether the further elevation in ambulatory blood pressure in these patients following renal denervation occurred as a result of discomfort or an aversive effect associated with repeated blood pressure measurements is not known but merits attention. The rise in clinic blood pressure in these patients is puzzling. Blood pressure recorded in the clinic is commonly higher during the initial consultation and is lower during subsequent visits [49], with the effect being more prominent in women with higher trait anxiety [50]. Blood pressure was recorded in the same clinic and by the same members of the research team. Although state anxiety was not changed, perhaps there was a greater degree of anticipatory stress as patients awaited their 12 month blood pressure reading. Alternatively, the higher clinic blood pressure may represent regression to the mean, having measured blood pressure at a low point on the patients' first visit.

The adoption of renal denervation as a suitable option for the treatment of hypertension has been hampered by a number of factors, foremost being the absence of a sham control group, except in the SYMPLICITY HTN-3 which failed to demonstrate a beneficial effect of renal denervation on blood pressure [5], the lack of a reliable index of successful renal denervation and uncertainty with regards to which patients would potentially benefit most from the procedure. Our study shares these limitations and we therefore cannot exclude that our results reflect a placebo effect, with the sustained improvement in mental health related quality of life occurring simply as a result of the participants' involvement in a clinical trial. Although the combined use of ABPM and clinic blood pressure assessments confirmed that those patients with resistant hypertension are the best candidates for renal denervation our examination of other groups was limited as the sample size was small. Although symptoms of depression and anxiety were self-reported and there were no structured diagnostic clinical

interviews, the BDI-II has been shown to be reliable for assessing depression in a primary care, general medical setting [51] and there is a strong concordance between patient rated and clinician rated measures of depression in the clinical setting in both psychiatric [52] and medical [53] patients.

Identification of patients most likely to respond to renal denervation remains problematic. Persu and colleagues, in their analysis of patients derived from the European Network Coordinating research on Renal Denervation cohort, defined extreme responders and non-responders to renal denervation as patients belonging to the first and fifth quintile of office systolic blood pressure decrease respectively [54]. They noted that non-responders to renal denervation had lower eGFR whereas extreme responders were more likely female. We found no association between gender or eGFR and blood pressure reduction following renal denervation. The only factors related to the magnitude of clinic blood pressure reduction following renal denervation was the baseline blood pressure and the total number of denervations delivered. The recent examination of the effectiveness of central arteriovenous anastomosis for blood pressure control in patients with uncontrolled hypertension (ROX CONTROL HTN study) demonstrated a significant blood pressure reduction in those patients in whom the arteriovenous coupler was placed [55]. Interestingly in a subset of these patients renal denervation had been previously performed. Of these patients, those in the arteriovenous coupler group experienced a marked reduction in clinic and ambulatory blood pressure whereas blood pressure was unchanged in those randomised to the control group. The placement of an arteriovenous anastomosis adds a low resistance-high compliance venous segment into the arterial circulation. Whether an established impairment in arterial compliance impacts on the effectiveness of renal denervation is not known but merits further investigation.

Although there is ongoing scepticism about the effectiveness of renal denervation in the treatment of hypertension we have provided further evidence that the procedure is safe and that in those patients with ABPM confirmed resistant hypertension the intervention is associated with a reduction in blood pressure and an improvement in mental health related quality of life. The observation of an association between the magnitude of blood pressure reduction and the degree of improvement in mental health related quality of life, in the absence of physical improvement, indicates that there may be alterations in brain function in response to either blood pressure reduction or changes in renal afferent activity. This of course is speculative and our results require confirmation in an appropriately controlled study. While the SYMPLICITY HTN-3 trial [5] promised to resolve all uncertainty surrounding the procedure's place in hypertension therapy the study perhaps raised more questions than provided answers. Of particular note, only 19 patients received a full circumferential ablation in each renal artery [56]. Interestingly, in line with our observation of a relationship between the number of ablations delivered to the renal arteries and reduction in both clinic and ambulatory blood pressure 12 months post denervation, Kandzari and colleagues noted a significant reduction in blood pressure occurred in those patients in the SYMPLICITY HTN-3 trial who received full bilateral circumferential denervation in both arteries according to protocol [56]. Given the intricate distribution of afferent and efferent nerves within the renal artery wall [57, 58] it is problematic whether effective denervation was achieved. The question remains, which patients, if any, benefit most from renal denervation and are there additional effects independent of any blood pressure reduction.

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Conflict(s) of Interest/Disclosure(s)

The laboratories of Professors Lambert, Esler, Dixon and Schlaich currently or recently received research funding from Medtronic, Abbott Pharmaceuticals, Servier Australia and Allergan. Professor Lambert has acted as a consultant for Medtronic and has received honoraria or travel support for presentations from Pfizer, Wyeth Pharmaceuticals, Servier and Medtronic. Professor Esler serves on scientific advisory boards of Abbott (formerly Solvay) Pharmaceuticals and Medtronic. Professor Dixon is a consultant for Allergan Inc, Bariatric Advantage, and Scientific Intake, and is a member of the Optifast® Medical Advisory Board for Nestle Health Australia. Professor Schlaich serves on scientific advisory boards for Abbott (formerly Solvay) Pharmaceuticals, Novartis Pharmaceuticals and Medtronic and has received honoraria and travel support from Abbott, Servier, Novartis, and Medtronic.

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Figure legends

Figure 1

Office and daytime average systolic blood pressure prior to renal denervation in patients with hypertension. The dotted horizontal and vertical lines represent cut points for hypertension status in the clinic (140 mmHg) and with average daytime ABPM respectively.

Figure 2

Change in systolic blood pressure 12 months following renal denervation in patients with resistant hypertension, pseudo resistant hypertension due to a white coat effect and uncontrolled masked hypertension. *P<0.05, ** P<0.01, ***P<0.001

Figure 3

Polar plot showing the SF-36 domain scores at baseline and 12 months following renal denervation in patients with hypertension. *P<0.05, **P<0.01

Figure 4

Change in SF36 MCS score in patients with resistant hypertension, pseudo resistant hypertension due to a white coat effect and uncontrolled masked hypertension. The dotted horizontal line signifies Frendl and Ware's proposed minimal important difference[26].
***P<0.001

Table 1: Participant demographics

Parameter	Entire Cohort	Resistant	Pseudo Resistant	Masked Uncontrolled
Number (female/male)	38/59	26/43	4/7	8/9
Age (years)	64.0±0.9	63.7±1.1	64.2±2.7	65.3±3.1
BMI (kg/m^2)	31.1±0.5	31.1±0.6	30.1±2.2	31.8±2.3
Blood pressure (mmHg)				
$ABPM_{day}$ Sys	153±2	160±2	128±2**	145±3**,b
$ABPM_{day}$ Dia	84±1	87±2	74±2**	78±3*
$ABPM_{night}$ Sys	141±2	146±2	114±3**	137±4[b]
$ABPM_{night}$ Dia	74±1	76±2	65±3*	70±4
Office Sys	161±2	169±2	159±3	129±3**,b
Office Dia	82±2	86±2	82±4	67±3**, a
Heart rate (b/min)				
$ABPM_{day}$	69±1	69±2	70±4	70±3
$ABPM_{night}$	62±1	61±1	62±3	65±3
Office	64±1	64±2	63±4	67±4
Estimated GFR ($ml/min/1.73m^2$)	70±2	71±2	74±4	64±4
# Medications	5.0±0.2	4.8±0.3	4.8±1.4	5.8±1.7
SF36-Physical	40.7±1.2	40.6±1.6	43.9±3.0	37.8±3.3
SF36-Mental Health	46.7±1.0	46.9±1.2	48.4±2.4	44.7±3.5
BDI	8.9±0.7	8.6±0.8	5.4±2.0	12.4±3.2[a]
State Anxiety score	32.8±1.0	31.8±1.0	28.9±2.1	39.1±3.7*,a
Trait Anxiety score	35.1±1.0	34.1±1.1	33.4±2.3	40.8±3.6*

*P<0.05, ** P<0.01 compared with Resistant Hypertension group

[a] P<0.05, [b] P<0.01 compared with Pseudo Resistant due to a white coat effect group

Table 2: Psychometric assessment following renal denervation

Test	12 Months post renal denervation	Change from baseline (95% confidence interval)	P Value
SF-36 Domains			
Physical Function	66±3	-0.2 (-4.4 to 4.8)	0.92
Role Physical	55±5	+0.7 (-9.7 to 8.2)	0.86
Body Pain	63±3	-2.2 (-2.5 to 6.9)	0.36
General Health	57±2	+4.6 (-7.9 to -1.4)	0.006
Vitality	53±3	+5.2 (-9.2 to -1.1)	0.01
Social Function	75±3	+0.4 (-5.3 to 4.5)	0.87
Role Emotion	81±4	+6.9 (-16.4 to 2.6)	0.15
Mental Health	75±2	+4.2 (-6.9 to -1.5)	0.003
SF-36 Summary Scores			
Physical Component	41±1	-0.9 (-1.0 to 2.8)	0.34
Mental Component	50±1	+2.9 (-4.9 to -1.0)	0.003
Beck Depression Inventory	7.7±0.9	-1.2 (0.2 to 2.4)	0.047
Spielberger's Anxiety Rating			
State	32.8±1.2	-0.1 (-1.7 to 1.6)	0.99
Trait	33.7±1.1	-1.4 (0.6 to 2.7)	0.04

Figure 1

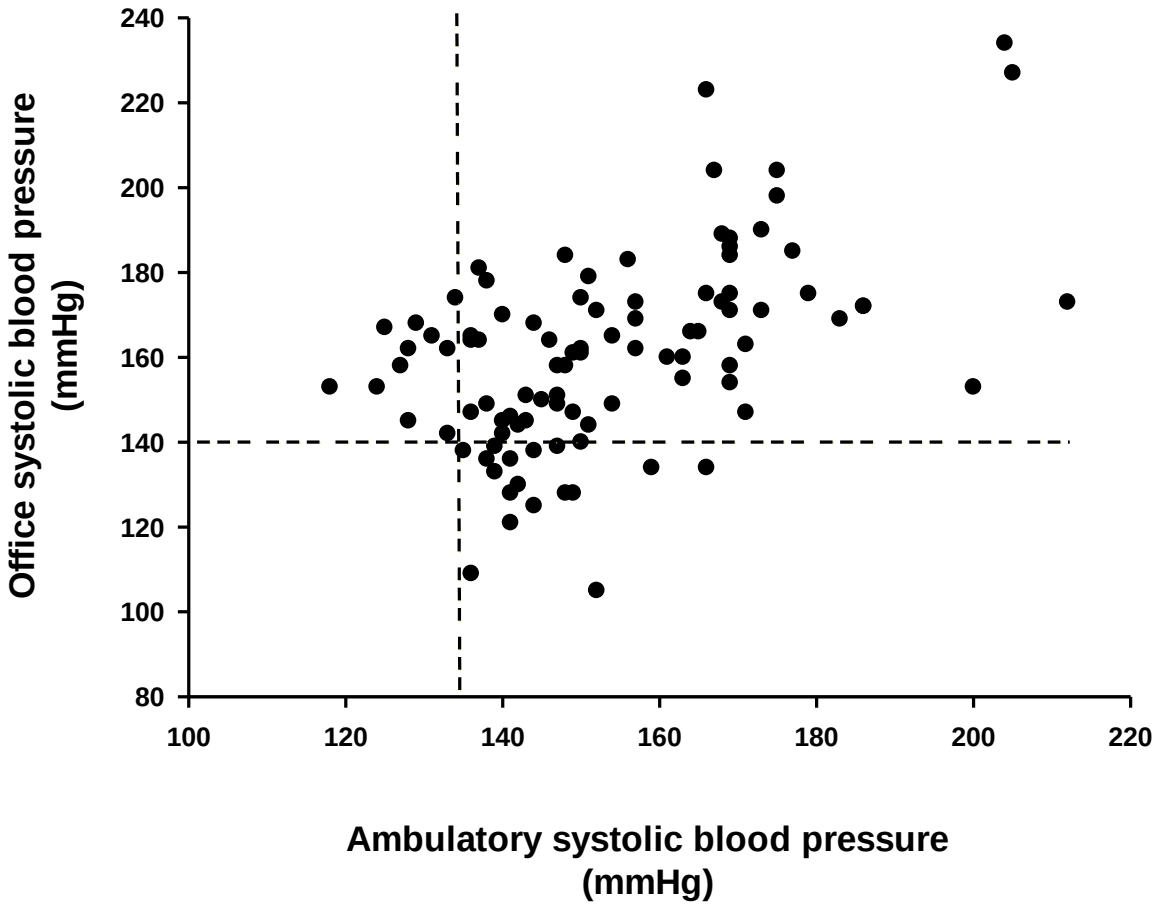
Office systolic blood pressure (mmHg)
240
220
200
180
160
140
120
100
80
100
120
140
160
180
200
220
Ambulatory systolic blood pressure (mmHg)

Figure 2

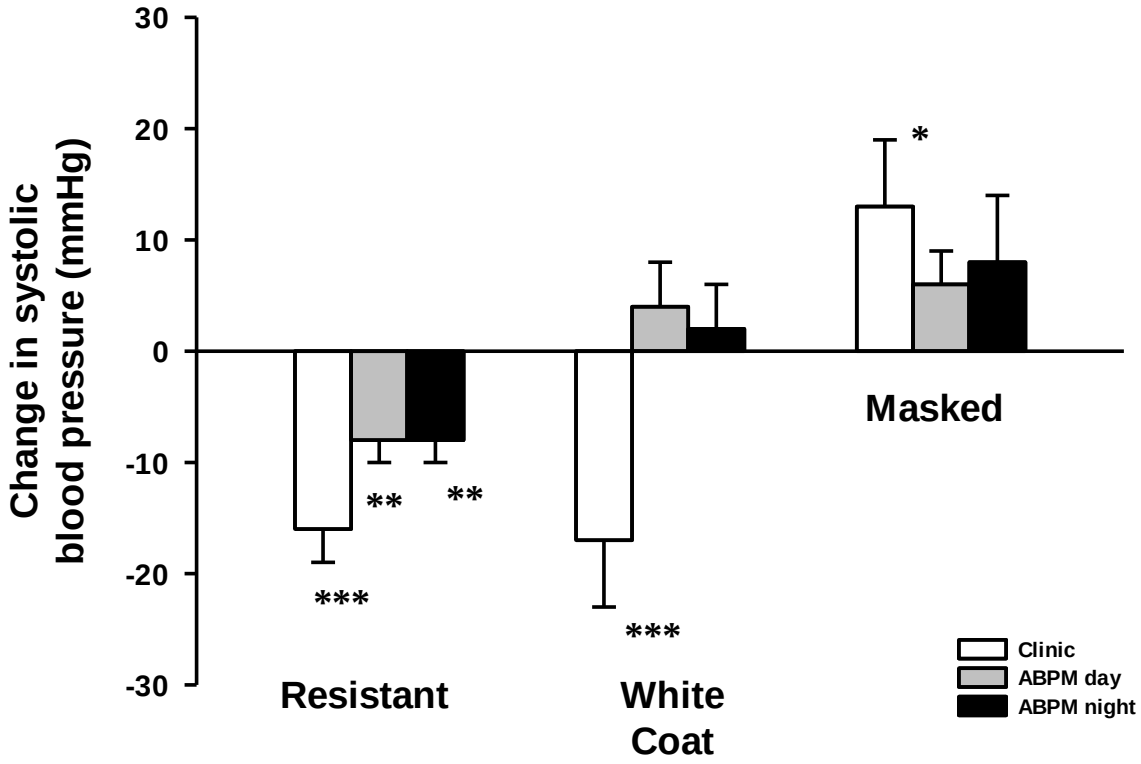
Change in systolic blood pressure (mmHg)
30
20
10
0
-10
-20
-30
***
**
**
***
*
Resistant
White Coat
Masked
Clinic
ABPM day
ABPM night

Figure 3

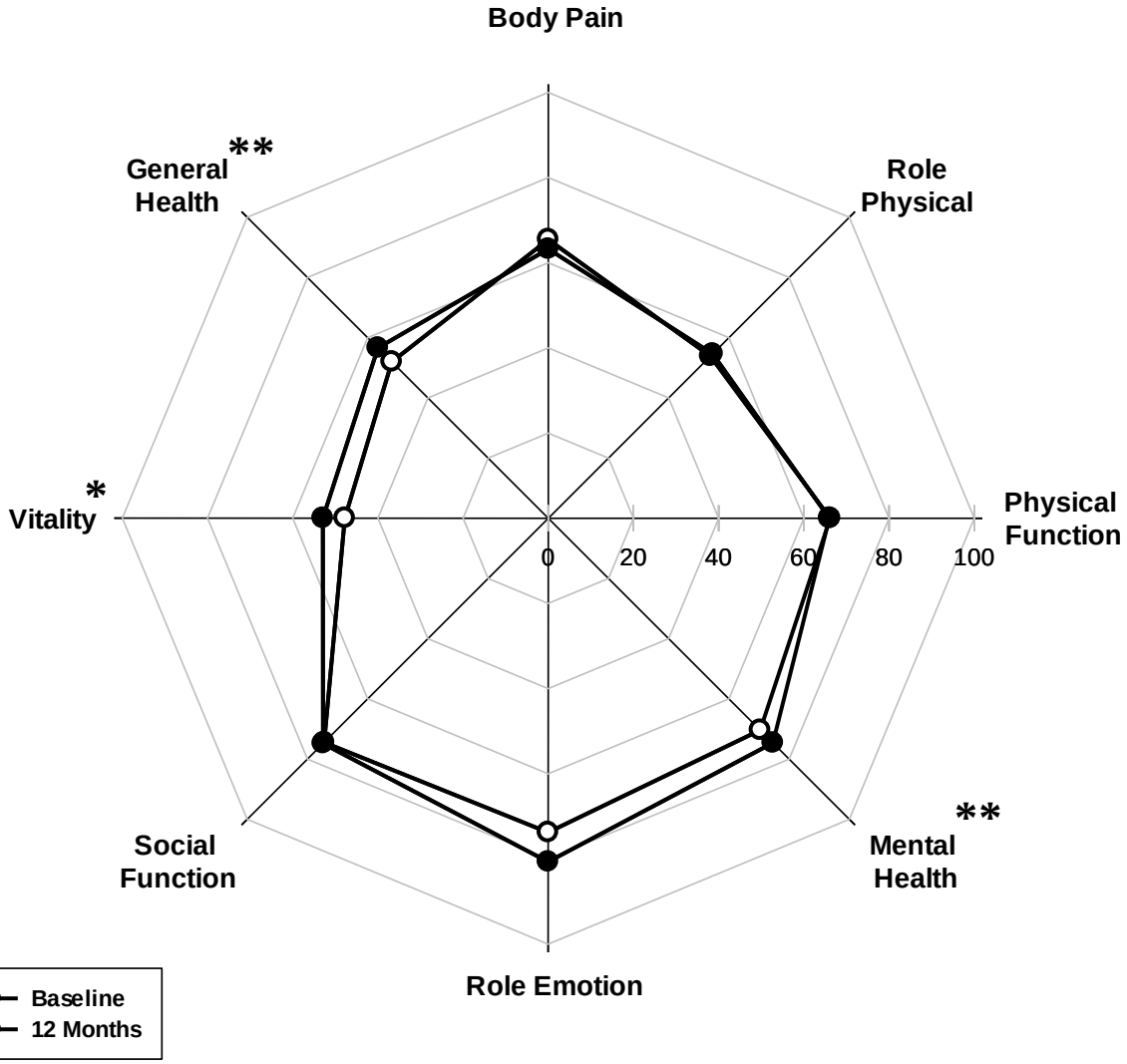
Body Pain
Role Physical
Physical Function
Mental Health
**
Role Emotion
Social Function
Vitality
*
General Health
**
0
20
40
60
80
100
Baseline
12 Months

Figure 4