Resistant hypertension is defined as failure to achieve goal blood pressure (BP) <140/90 mmHg (or <130/80 mmHg in patients with diabetes mellitus or chronic kidney disease) in patients with hypertension who are compliant with maximum tolerated doses of an appropriate antihypertensive drug regimen consisting of a minimum of 3 agents of different classes, including a diuretic. Patients who meet the criteria for resistant hypertension but whose BP can be controlled on maximum tolerated doses of ≥4 antihypertensive agents are classified as having controlled resistant hypertension. Although the number of failed antihypertensive drugs required for the classification of resistant hypertension is arbitrary, this diagnosis identifies patients at high risk for having a potentially curable (secondary) form of hypertension, as well as those who may benefit from specific therapeutic approaches to lower BP. The term “resistant hypertension” indicates that the patient has true resistance to otherwise effective antihypertensive treatment and not other causes including improper blood pressure measurement, an inadequately prescribed antihypertensive regimen, failure to adhere to adequately prescribed therapy, or hypertension that is elevated in the office but normal at home (white coat hypertension). The diagnosis of resistant hypertension implies that the causes of pseudoresistance (lack of BP control with treatment in a patient who does not have resistant hypertension) have been excluded with ambulatory blood pressure monitoring, assessment of adherence to a medical regimen, and other appropriate methods.

The prevalence of resistant hypertension has been a matter of debate. In randomized, controlled trials, as many as 25% to 30% of participants did not achieve goal BP despite receiving ≥3 antihypertensive agents. Patients participating in these trials were carefully assessed for medication compliance and often had ambulatory BP monitoring (ABPM), thus largely excluding pseudoresistance. Although these were forced titration studies, ensuring medication compliance, patients with resistant hypertension were excluded, and patients did not receive a diuretic in many of these studies. Therefore, the clinical trial results provide, at best, a gross estimate of the prevalence of resistant hypertension. In contrast to therapeutic trial results, observational data from the National Health and Nutrition Survey (NHANES) have predicted a relatively lower prevalence of resistant hypertension. Analyzing these data, Egan et al determined that the proportion of treated uncontrolled hypertensive patients taking ≥3 antihypertensive medications disturbedly increased from 5.5% in 1988 to 1994 to 8.5% in 1999 to 2004 to 11.8% in 2005 to 2008. Using the NHANES data accumulated from 2003 to 2008, Persell estimated that the prevalence of resistant hypertension was 8.9% of all adults with hypertension and 12.8% of adults being treated for hypertension. Roughly consistent with these estimates, a large Spanish study (68,000 patients) found that the prevalence of resistant hypertension was 14.8% of treated hypertensive subjects.

The importance of classifying patients with resistant hypertension lies, at least in part, in whether this designation conveys increased cardiovascular risk. Although it would seem logical that higher levels of BP should be related to increased risk, the specific risks related to resistant hypertension have been difficult to establish. Epidemiological studies do indicate that the relative risks of stroke, myocardial infarction, congestive heart failure, and chronic kidney disease are related linearly to the level of BP elevation. Several cross-sectional studies have indicated that resistant hypertension is associated with an increased frequency of cardiovascular events, including myocardial infarction, stroke, congestive heart failure, and chronic kidney disease. Patients with resistant hypertension have an increased prevalence of target organ damage, including carotid intima-media thickening, left ventricular hypertrophy, microalbuminuria, and retinal lesions compared with patients who have achieved goal BP. Using a rigorous definition of resistant hypertension that included screening for lack of adherence to prescribed medications in a large but nonprospective study, Daugherty et al recently found a 50% increase in cardiovascular events, particularly chronic kidney disease, and a 2-fold increased overall cardiovascular risk in patients with resistant as compared with nonresistant hypertension. Thus, the majority of currently available evidence indicates a substantially increased cardiovascular risk in patients with resistant hypertension.

One of the most vexing problems in normalizing BP in resistant hypertension is the provision of an adequately prescribed drug regimen. Inadequate dosing and inappropriate pharmacological combinations are major reasons for pseudoresistance. A recent study by Daugherty et al demonstrated that physician prescription of many classes of antihypertensive agents decreases 1 year after identification of resistant hypertension. Indeed, lack of treatment intensification and not medication adherence was significantly associated with decreased BP control in this study. Among the largest declines in medication prescriptions was a 12% reduction in the use of diuretics. Patients with resistant hypertension have

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significant extracellular fluid volume expansion, and diuretics are considered as a mainstay of therapy for this condition. Indeed, imbedded in the definition of resistant hypertension is the requirement for 1 of the 3 therapeutic agents to be a diuretic. Chlorothalidone and mineralocorticoid receptor blocker spironolactone in particular have been emphasized for their efficacy in lowering BP in resistant hypertension.

The importance of an optimal diuretic regimen to control BP in resistant hypertension was emphasized recently by Bobrie et al., who introduced the new paradigm of sequential nephron blockade applied to this condition. The rationale for low-dose sequential nephron blockade is to neutralize the effects of intrarenal compensatory increases in sodium reabsorption at unblocked sites along the nephron triggered by the use of high-dose diuretics acting at a single site. The use of low doses would also be predicted to reduce the risk of untoward drug effects. In a prospective, randomized, open, blinded end point study, these authors used sequential blockade of renal tubule sodium reabsorption by different mechanisms and in different nephron segments. Sequential nephron blockade was carried out in patients with resistant hypertension by the stepped addition of low doses of 4 different diuretics (spironolactone [connecting tubule and cortical collecting duct], furosemide [ascending limb of Henle], hydrochlorothiazide [distal tubule], and aldosterone-independent blocker amiloride [cortical collecting duct]) in patients failing to achieve BP goal with a standard triple regimen (angiotensin receptor blocker, thiazide diuretic, and calcium channel blocker). BP goal was achieved by sequential nephron blockade in a remarkable 58% of these patients. By comparison, BP goal was achieved in only 20% of patients treated with sequential renin-angiotensin system blockade. If confirmed, this approach would reduce the prevalence of uncontrolled resistant hypertension to ≈5% to 6%.

By far and away the most publicized new approach to the treatment of resistant hypertension in 2012 was catheter-based radiofrequency renal nerve ablation. Following the seminal work of DiBona defining the critical role of renal sympathetic nerve activation on sodium excretion and BP and the demonstration that interruption of renal sympathetic nerves reduces BP and organ-specific damage induced by chronic sympathetic overactivity in experimental hypertension, successful catheter-based renal denervation (RD) in humans with resistant hypertension was first reported in 2009. At present, the results of 3 prospective human RD trials have been reported and a fourth (the EnligHTN Trial) was presented at the 2012 Scientific Sessions of the American Heart Association. Simplicity-1 studied 26 patients with baseline BPs averaging 177/101 mm Hg and demonstrated a BP decrement of 22/11 mm Hg at 6 months of follow-up. Simplicity-2 studied 52 patients with control BPs of 178/96 mm Hg and demonstrated 6-month BP reductions of 33/11 mm Hg, with 39% of patients achieving their BP goals. The EnligHTN trial (multielectrode catheter instead of single-tip electrode to create a predictable lesion pattern) similarly showed a 26/10-mm Hg decrement in BP with 33% reaching goal at 6 months in 46 patients with baseline BPs of 176/96 mm Hg. None of the studies showed any significant deterioration in renal function with preservation of estimated glomerular filtration rate. In marked contrast, Brinkman et al., studying 12 patients with lower baseline BPs (157/85 mm Hg), demonstrated no change in BP or muscle sympathetic nerve activity 6 months after the denervation procedure. The reasons for discordant results in the Brinkman et al. trial, as compared with the other trials, are unknown but might be related to lower baseline BPs, lower baseline muscle sympathetic nerve activity, or technical factors in the RD procedure. The recently reported 1-year results from the Simplicity-2 trial confirmed the 6-month BP reductions in control patients who crossed over to RD, indicating the likelihood that RD will provide a sustained BP reduction in patients with resistant hypertension. Interestingly, RD resulted in a rapid and sustained reduction in the firing properties of single sympathetic vasconstrictor fibers preferentially over changes in multiunit muscle sympathetic nerve activity.

The exact changes in whole body sympathetic nerve activity in response to renal nerve ablation await further study.

The preliminary results on the efficacy and safety of catheter-based renal nerve ablation on BP control in resistant hypertension are encouraging. It is apparent, however, that the results of available clinical trials cannot simply be extrapolated to less severe or secondary forms of hypertension or other cardiovascular disorders associated with increased sympathetic nervous system activity, such as congestive heart failure. Gaps to be addressed in future studies include (1) evidence for effectiveness of RD in reducing renal and whole body sympathetic nerve activity (norepinephrine spillover) and effects of RD on the renin-angiotensin system; (2) evidence on whether renal sympathetic reinnervation occurs over the long term and, if so, whether this dampens the reduction in BP; (3) provision of a sham control group and increased ambulatory BP analysis; and (4) clinical outcomes (morbidity and mortality) data.

The year 2012 has been a banner year for the introduction of new concepts in resistant hypertension. The following articles are being highlighted as the inaugural Best Papers in Hypertension series. These are important articles published on the topic of resistant hypertension in the journal during 2012.


**Summary:** Recent studies have demonstrated the effectiveness of radiofrequency ablation of the renal sympathetic nerves in reducing BP in patients with resistant hypertension. The effect of RD on health-related quality of life has not been evaluated. Using the Medical Outcomes Study 36-Item Short-Form Health Survey and Beck Depression Inventory-II, we examined quality of life before and 3 months after RD in patients with uncontrolled BP. For baseline comparisons, matched data were extracted from the Australian Diabetes, Obesity, and Lifestyle database. Before RD, patients with resistant hypertension (n=62) scored significantly worse in 5 of the 8 36-Item Short-Form Health Survey domains and the Mental Component Summary score. Three months after denervation (n=40), clinic BP was reduced (change in systolic and diastolic BPs, −16±4 and −6±2 mm Hg, respectively; P<0.01).
The Mental Component Summary score improved (47.6±1.1 versus 52.0±1.0; P=0.001) as a result of increases in the vitality, social function, role emotion, and mental health domains. Beck Depression Inventory scores were also improved, particularly with regard to symptoms of sadness (P=0.01), tiredness (P<0.001), and libido (P<0.01). The magnitude of BP reduction or BP level achieved at 3 months bore no association to the change in quality of life. RD was without a detrimental effect on any elements of the 36-Item Short-Form Health Survey.

Conclusions: Patients with severe hypertension resistant to therapy present with a marked reduction in subjective quality of life. In this prehypothesis- and posthypothesis-generating study, several aspects of quality of life were improved after RD; however, this was not directly associated with the magnitude of BP reduction.22


Summary: Endovascular renal nerve ablation has been developed to treat resistant hypertension. In addition to lowering efferent renal sympathetic activation, the intervention may attenuate central sympathetic outflow through decreased renal afferent nerve traffic, as evidenced by a recent case report. We tested the hypothesis in 12 nonpreselected patients with difficult-to-control hypertension (aged 45–74 years) admitted for renal nerve ablation. All of the patients received antihypertensive medications at full doses, including a diuretic. ECG, respiration, brachial and finger arterial BP, and muscle sympathetic nerve activity were recorded before and 3 to 6 months after renal nerve ablation. Heart rate and BP variability were analyzed in the time and frequency domains. Pharmacological baroreflex slopes were determined using the modified Oxford bolus technique. Resting heart rate was 61±3 beats per minute before and 58±2 beats per minute after ablation (P=0.4). Supine BP was 157±7/85±4 mm Hg before and 157±6/85±4 mm Hg after ablation (P=1.0). Renal nerve ablation did not change resting muscle sympathetic nerve activity (before, 34±2 bursts per minute; after, 32±3 bursts per minute; P=0.6), heart rate variability, or BP variability. Pharmacological baroreflex control of heart rate and muscle sympathetic nerve activity did not change.

Conclusion: Reduced central sympathetic inhibition may be the exception rather than the rule after renal nerve ablation in unselected patients with difficult-to-control arterial hypertension.18


Summary: Regular physical exercise is broadly recommended by current European and American hypertension guidelines. It remains elusive, however, whether exercise leads to a reduction of BP in resistant hypertension as well. The present randomized, controlled trial examines the cardiovascular effects of aerobic exercise on resistant hypertension. Resistant hypertension was defined as a BP ≥140/90 mm Hg in spite of 3 antihypertensive agents or a BP controlled by ≥4 antihypertensive agents. Fifty subjects with resistant hypertension were randomly assigned to participate or not to participate in an 8- to 12-week treadmill exercise program (target lactate, 2.0±0.5 mmol/L). BP was assessed by 24-hour monitoring. Arterial compliance and cardiac index were measured by pulse wave analysis. The training program was well tolerated by all of the patients. Exercise significantly decreased systolic and diastolic daytime ambulatory BPs by 6±12 and 3±7 mm Hg, respectively (P=0.03 each).

Conclusions: Regular exercise reduced BP on exertion and increased physical performance as assessed by maximal oxygen uptake and lactate curves. Arterial compliance and cardiac index remained unchanged. Physical exercise is able to decrease BP even in subjects with low responsiveness to medical treatment. Regular exercise should be included in the therapeutic approach to resistant hypertension.21


Summary: Chronic electric activation of the carotid baroreflex produces sustained reductions in sympathetic activity and arterial pressure and is currently being evaluated as hypertension therapy for patients with resistant hypertension. However, the chronic changes in renal function associated with natural suppression of sympathetic activity are largely unknown. In normotensive dogs, we investigated the integrative cardiovascular effects of chronic baroreflex activation (2 weeks) alone and in combination with the calcium channel blocker amlodipine, which is commonly used in the treatment of resistant hypertension. During baroreflex activation alone, there were sustained decreases in mean arterial pressure (17±1 mm Hg) and plasma (norepinephrine; +35%), with no change in plasma renin activity. Despite low pressure, sodium balance was achieved because of decreased tubular reabsorption, because glomerular filtration rate and renal blood flow decreased 10% to 20%. After 2 weeks of amlodipine, arterial pressure was also reduced 17 mm Hg, but with substantial increases in norepinephrine and plasma renin activity and no change in glomerular filtration rate. In the presence of amlodipine, baroreflex activation greatly attenuated neurohormonal activation, and pressure decreased even further (by 11±2 mm Hg). Moreover, during amlodipine administration, the fall in glomerular filtration rate with baroreflex activation was abolished.

Conclusions: The chronic BP-lowering effects of baroreflex activation are attributed, at least in part, to sustained inhibition of renal sympathetic nerve activity and attendant decreases in sodium reabsorption before the macula densa. Tubuloglomerular feedback constriction of the afferent arterioles may account for reduced glomerular filtration rate, a response abolished by amlodipine, which dilates the preglomerular vasculature.24

Summary: Patients with resistant hypertension are at risk for poor outcomes. Medication adherence and intensiﬁcation improve BP control; however, little is known about these processes or their association with outcomes in resistant hypertension. This retrospective study included patients from 2002 to 2006 with incident hypertension from 2 health systems who developed resistant hypertension or uncontrolled BP despite adherence to ≥3 antihypertensive medications. Patterns of hypertension treatment, medication adherence (percentage of days covered), and treatment intensiﬁcation (increase in medication class or dose) were described in the year after resistant hypertension identiﬁcation. Then, the association between medication adherence and intensiﬁcation with 1-year BP control was assessed, controlling for patient characteristics. Of the 3550 patients with resistant hypertension, 49% were men, and mean age was 60 years. One year after resistance hypertension determination, fewer patients were taking diuretics (77.7% versus 92.2%; P<0.01), β-blockers (71.2% versus 79.4%; P<0.01), and angiotensinconverting enzyme inhibitor/angiotensin receptor blocker (64.8% versus 70.1%; P<0.01) compared with baseline. Rates of BP control improved over 1 year (22% versus 55%; P<0.01). Decreasing treatment intensity was associated with 1-year BP control (adjusted odds ratio, 1.18 [95% conﬁdence interval, 0.94–1.47]). Treatment was intensiﬁed in 21.6% of visits with elevated BP. Increasing treatment intensity was associated with 1-year BP control (adjusted odds ratio, 1.64 [95% conﬁdence interval, 1.58–1.71]). In this cohort of patients with resistant hypertension, treatment intensiﬁcation but not medication adherence was signiﬁcantly associated with 1-year BP control.

Conclusions: These ﬁndings highlight the need to investigate why patients with uncontrolled BP do not receive treatment intensiﬁcation.


Summary: Increased renal resistive index and urinary albumin excretion are markers of hypertensive end-organ damage and renal vasoconstriction involving increased sympathetic activity. Catheter-based sympathetic RD offers a new approach to reduce renal sympathetic activity and BP in resistant hypertension. The inﬂuence of RD on renal hemodynamics, renal function, and urinary albumin excretion has not been studied. One hundred consecutive patients with resistant hypertension were included in the study; 88 underwent interventional RD, and 12 served as controls. Systolic, diastolic, and pulse pressures, as well renal resistive index in interlobar arteries, renal function, and urinary albumin excretion, were measured before and at 3 and 6 months of follow-up. RD reduced systolic, diastolic, and pulse pressures at 3 and 6 months by 22.7±26.6, 7.7±9.7, and 15.1±17.5 mm Hg (P for all <0.001), respectively, without signiﬁcant changes in the control group. SBP reduction after 6 months correlated with SBP baseline values (r=−0.46; P<0.001). There were no renal artery stenoses, dissections, or aneurysms during 6 months of follow-up. Renal resistive index decreased from 0.691±0.010 at baseline to 0.674±0.010 and 0.670±0.010 (P=0.037/0.017) at 3- and 6-month follow-up. Mean cystatin C glomerular ﬁltration rate and urinary albumin excretion remained unchanged after RD; however, the number of patients with microalbuminuria or macroalbuminuria decreased.

Conclusions: RD reduced BP, renal resistive index, and incidence of albuminuria without adversely affecting glomerular ﬁltration rate or renal artery structure within 6 months and appears to be a safe and effective therapeutic approach to lower BP in patients with resistant hypertension.


Summary: The aim of this study was to identify the relative impact of adrenergic and cholinergic activity on atrial ﬁbrillation (AF) inducibility and BP in a model for obstructive sleep apnea. Obstructive sleep apnea is associated with sympathovagal disbalance, AF, and postapneic BP rises. RD reduces renal efferent and possibly also afferent sympathetic activity and BP in resistant hypertension. The effects of RD compared with β-blockade by atenolol on atrial electrophysiological changes, AF inducibility, and BP during obstructive events and on shortening of atrial effective refractory period (AERP) induced by high-frequency stimulation of ganglionated plexi were investigated in 20 anesthetized pigs. Tracheal occlusion with applied negative tracheal pressure (NTP; at −80 megabar) induced pronounced AERP shortening and increased AF inducibility in all of the pigs. RD but not atenolol reduced NTP-induced AF inducibility (20% versus 100% at baseline; P=0.0001) and attenuated NTP-induced AERP shortening more than atenolol (27±5 versus 43±3 ms after atenolol; P=0.0272). Administration of atropine after RD or atenolol completely inhibited NTP-induced AERP shortening. AERP 4 shortening induced by high-frequency stimulation of ganglionated plexi was not inﬂuenced by RD, suggesting that changes in sensitivity of ganglionated plexi do not play a role in the antiarrhythmic effect of RD. Postapneic BP rise was inhibited by RD and not modiﬁed by atenolol.

Conclusions: Vagally mediated NTP-induced AERP shortening is modulated by RD or atenolol, which emphasizes the importance of autonomic disbalance in obstructive sleep apnea-associated AF. RD displays antiarrhythmic effects by reducing NTP-induced AERP shortening and inhibits post-apneic BP rises associated with obstructive events.

Summary: Resistant hypertension is defined as uncontrolled office BP, despite the use of ≥3 antihypertensive drugs. ABPM is mandatory to diagnose 2 different groups, those with true and white coat–resistant hypertension. Patients are found to change categories between controlled/uncontrolled ambulatory pressures without changing their office BPs. In this way, ABPM should be periodically repeated. The aim of this study was to evaluate the most appropriate time interval to repeat ABPM to assure sustained BP control in patients with white-coat–resistant hypertension. This prospective study enrolled 198 patients (69% women; mean age 68.9±9.9 years) diagnosed as having white coat–resistant hypertension on ABPM. Patients were submitted to a second confirmatory examination 3 months later and repeated twice at 6-month intervals. Statistical analyses included Bland-Altman repeatability coefficients and multivariate logistic regression. Mean office BP was 163±20/84±17 mm Hg. White coat–resistant hypertension diagnosis presented a moderate reproducibility and was confirmed in 144 patients after 3 months. In the third and fourth ABPMs, 74% and 79% of patients sustained the diagnosis. In multivariate regression, a daytime systolic BP ≤115 mm Hg in the confirmatory ABPM tripli-cated the chance of white coat–resistant hypertension status persistence after 1 year.

Conclusions: Confirmatory ABPM is necessary after 3 months of the first white coat-resistant hypertension diagnosis, and the procedure should be repeated at 6-month intervals.27

Disclosures
None.

References