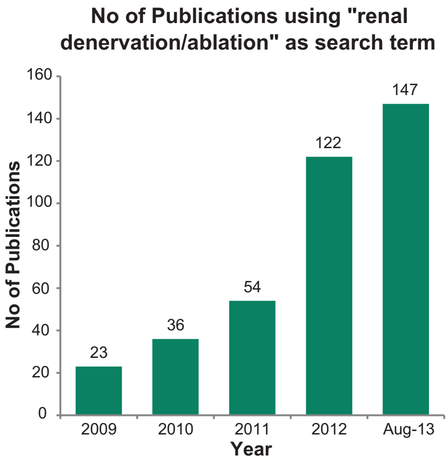
Editors' Picks

Hypertension Editors' Picks
Renal Denervation

The Editors



The following articles are being highlighted as part of *Hypertension*'s Editors' Picks series. As most of our readers would be well aware, there has been a significant increase in publications on resistant hypertension and specifically on the therapeutic renal denervation. The number of publications in PubMed has increased from 23 in 2009 to 147 in the first 7 months of 2013 (Figure). We therefore collated for our readers all full-length articles on renal denervation published in our Journal in 2012 and the first half of 2013.

Catheter-Based Renal Nerve Ablation and Centrally Generated Sympathetic Activity in Difficult-to-Control Hypertensive Patients: Prospective Case Series[1]

Abstract

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 patients received ≥3 antihypertensive medications at full doses, including a diuretic. ECG, respiration, brachial and finger arterial blood pressure, and muscle sympathetic nerve activity were recorded before and 3 to 6 months after renal nerve ablation. Heart rate and blood pressure variability were analyzed in the time and frequency domain. Pharmacological baroreflex slopes were determined using the modified Oxford bolus technique. Resting heart rate was 61±3 bpm before and 58±2 bpm after ablation (P=0.4). Supine blood pressure 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 blood pressure variability. Pharmacological baroreflex control of heart rate and muscle sympathetic nerve activity did not change. We conclude that 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

Health-Related Quality of Life After Renal Denervation in Patients With Treatment-Resistant Hypertension[2]

Abstract

Recent studies have demonstrated the effectiveness of radiofrequency ablation of the renal sympathetic nerves in reducing blood pressure (BP) in patients with resistant hypertension. The effect of renal denervation on health-related quality of life (QoL) has not been evaluated. Using the Medical Outcomes Study 36-Item Short-Form Health Survey and Beck Depression Inventory-II, we examined QoL before and 3 months after renal denervation in patients with uncontrolled BP. For baseline comparisons, matched data were extracted from the Australian Diabetes, Obesity, and Lifestyle database. Before renal denervation, patients with resistant hypertension (n=62) scored significantly worse in 5 of the eight 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 BP, −16±4 and −6±2 mm Hg, respectively; P<0.01). The Mental Component Summary score improved (47.6±1.1 versus 52±1; 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 with the change in QoL. Renal denervation was without a detrimental effect on any elements of the 36-Item Short-Form Health Survey. These results indicate that patients with severe hypertension resistant to therapy present with a marked reduction in subjective QoL. In this pre- and post-hypothesis generating study, several aspects of QoL were improved after renal denervation; however, this was not directly associated with the magnitude of BP reduction.

Renal Sympathetic Denervation Suppresses Postapneic Blood Pressure Rises and Atrial Fibrillation in a Model for Sleep Apnea[3]

Abstract

The aim of this study was to identify the relative effect of adrenergic and cholinergic activity on atrial fibrillation (AF) inducibility and blood pressure (BP) in a model for obstructive sleep apnea. Obstructive sleep apnea is associated with sympathovagal disbalance, AF, and postapneic BP rises. Renal denervation (RDN) reduces renal efferent and possibly also afferent sympathetic activity and BP in resistant hypertension. The effects of RDN 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 mbar) induced pronounced AERP shortening and increased AF inducibility in all the pigs. RDN 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 RDN or atenolol completely inhibited NTP-induced AERP shortening. AERP shortening induced by high-frequency stimulation of ganglionated plexi was not influenced by RDN, suggesting that changes in the sensitivity of ganglionated plexi do not play a role in the antiarrhythmic effect of RDN. Postapneic BP rise was inhibited by RDN and not modified by atenolol. We showed that vagally mediated NTP-induced AERP shortening is modulated by RDN or atenolol, which emphasizes the importance of autonomic disbalance in obstructive sleep apnea–associated AF. RDN displays antiarrhythmic effects by reducing NTP-induced AERP shortening and inhibits postapneic BP rises associated with obstructive events.

Systemic and Renal-Specific Sympathoinhibition in Obesity Hypertension[4]

Abstract

Chronic pressure–mediated baroreflex activation suppresses renal sympathetic nerve activity. Recent observations indicate that chronic electric activation of the carotid baroreflex produces sustained reductions in the global sympathetic activity and arterial pressure. Thus, we investigated the effects of global and renal-specific suppression of sympathetic activity in dogs with sympathetically mediated, obesity-induced hypertension by comparing the cardiovascular, renal, and neurohormonal responses with chronic baroreflex activation and bilateral surgical renal denervation. After control measurements, the diet was supplemented with beef fat, whereas sodium intake was held constant. After 4 weeks on the high-fat diet, when body weight had increased ≈50%, fat intake was reduced to a level that maintained this body weight. This weight increase was associated with an increase in mean arterial pressure from 100±2 to 117±3 mm Hg and heart rate from 86±3 to 130±4 bpm. The hypertension was associated with a marked increase in cumulative sodium balance despite an ≈35% increase in glomerular filtration rate. The importance of increased tubular reabsorption to sodium retention was further reflected by ≈35% decrease in fractional sodium excretion. Subsequently, both chronic baroreflex activation (7 days) and renal denervation decreased plasma renin activity and abolished the hypertension. However, baroreflex activation also suppressed systemic sympathetic activity and tachycardia and reduced glomerular hyperfiltration while increasing fractional sodium excretion. In contrast, the glomerular filtration rate increased further after renal denervation. Thus, by improving the autonomic control of cardiac function and diminishing glomerular hyperfiltration, suppression of global sympathetic activity by baroreflex activation may have beneficial effects on obesity beyond simply attenuating hypertension.

Renal Hemodynamics and Renal Function After Catheter-Based Renal Sympathetic Denervation in Patients With Resistant Hypertension[5]

Abstract

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 renal denervation (RD) offers a new approach to reduce renal sympathetic activity and blood pressure 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 pressure, 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 pressure at 3 and 6 months by 22.7/26.6, 7.7/9.7, and 15.1/17.5 mm Hg (P<0.001), respectively, without significant changes in the control group. Reduction in systolic blood pressure after 6 months correlated with systolic blood pressure 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±0.01 at baseline to 0.674±0.01 and 0.670±0.01 (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. RD reduced blood pressure, renal resistive index, and incidence of albuminuria without adversely affecting glomerular filtration rate or renal artery structure within 6 months and seems to be a safe and effective therapeutic approach to lower blood pressure in patients with resistant hypertension.

Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension After Witnessed Intake of Medication Before Qualifying Ambulatory Blood Pressure[6]

Abstract
It is unknown whether the decline in blood pressure (BP) after renal denervation (RDN) is caused by denervation itself or concomitantly improved drug adherence. We aimed to investigate the BP-lowering effect of RDN in true treatment-resistant hypertension by excluding patients with poor drug adherence. Patients with resistant hypertension (n=18) were referred for a thorough clinical and laboratory workup. Treatment-resistant hypertension was defined as office systolic BP >140 mm Hg, despite maximally tolerated doses of ≥3 antihypertensive drugs, including a diuretic. In addition, ambulatory daytime systolic BP >135 mm Hg was required after witnessed intake of antihypertensive drugs to qualify. RDN (n=6) was performed with the Symplicity Catheter System. The mean office and ambulatory BPs remained unchanged at 1, 3, and 6 months in the 6 patients, whereas there was no known change in antihypertensive medication. Two patients, however, had a fall in both office and ambulatory BPs. Our findings question whether BP falls in response to RDN in patients with true treatment-resistant hypertension. Additional research must aim to verify potential BP-lowering effect and identify a priori responders to RDN before this invasive method can routinely be applied to patients with drug-resistant hypertension.

Reversal of Genetic Salt-Sensitive Hypertension by Targeted Sympathetic Ablation[7]

Abstract
The sympathetic nervous system plays an important role in some forms of human hypertension and the Dahl salt–sensitive rat model of hypertension; however, the sympathetic targets involved remain unclear. To address this, we examined the role of the renal and splanchnic sympathetic nerves in Dahl hypertension by performing sham surgery (n=10) or targeted sympathetic ablation of the renal nerves (renal denervation; n=11), the splanchnic nerves (celiac ganglionectomy; n=11), or both renal and splanchnic nerves (n=11) in hypertensive Dahl rats. Mean arterial pressure increased from ≈120 mm Hg, while on a 0.1% sodium chloride diet, to ≈140 mm Hg after being fed a 4.0% sodium chloride diet for 3 weeks. At that point, rats underwent sham or targeted sympathetic ablation. Four weeks after treatment, mean arterial pressure was lower in renal-denervated (150.4±10.4) and celiac ganglionectomized (147.0±6.1) rats compared with sham rats (165.0±3.7) and even lower in rats that underwent both ablations (128.4±6.6). There were no differences in heart rate or fluid balance between sham and renal-denervated rats; however, rats that underwent either celiac ganglionectomy or both ablations exhibited marked tachycardia, as well as sodium and water retention after treatment. These data suggest that targeted sympathetic ablation is an effective treatment for established hypertension in the Dahl rat and that the kidneys and the splanchnic vascular bed are both independently important targets of the sympathetic nervous system in this model.

Translational Examination of Changes in Baroreflex Function After Renal Denervation in Hypertensive Rats and Humans[8]

Abstract
Renal denervation has shown promise in the treatment of resistant hypertension, although the mechanisms underlying the blood pressure (BP) reduction remain unclear. In a translational study of spontaneously hypertensive rats (n=7; surgical denervation) and resistant hypertensive human patients (n=8; 5 men; 33–71 years), we examined the relationship among changes in BP, sympathetic nerve activity, and cardiac and sympathetic baroreflex function after renal denervation. In humans, mean systolic BP (SBP; sphygmomanometry) and muscle sympathetic nerve activity (microneurography) were unchanged at 1 and 6 months after renal denervation ($P<0.05$). Interestingly, 4 of the 8 patients showed a 10% decrease in SBP at 6 months, but sympathetic activity did not necessarily change in parallel with SBP. In contrast, all rats showed significant and immediate decreases in telemetric SBP and lumbar sympathetic activity ($P<0.05$) 7 days after denervation. Despite no change in SBP, human cardiac and sympathetic baroreflex function (sequence and threshold techniques) showed improvements at 1 and 6 months after denervation, particularly through increased sympathetic baroreflex sensitivity to falling BP. This was mirrored in spontaneously hypertensive rats; cardiac and sympathetic baroreflex sensitivity (spontaneous sequence and the Oxford technique) improved 7 days after denervation. The more consistent results in rats may be because of a more complete (>90% reduction in renal norepinephrine content) denervation. We conclude that (1) renal denervation improves BP in some patients, but sympathetic activity does not always change in parallel, and (2) baroreflex sensitivity is consistently improved in animals and humans even when SBP has not decreased. Determining procedural success will be crucial in advancing this treatment modality.

Substantial Reduction in Single Sympathetic Nerve Firing After Renal Denervation in Patients With Resistant Hypertension[9]

Abstract

Renal denervation (RDN) has been shown to reduce blood pressure (BP) and muscle sympathetic nerve activity (MSNA) in patients with resistant hypertension. The mechanisms underlying sympathetic neural inhibition are unknown. We examined whether RDN differentially influences the sympathetic discharge pattern of vasoconstrictor neurons in patients with resistant hypertension. Standardized office BP, single-unit MSNA, and multiunit MSNA were obtained at baseline and at 3-month follow-up in 35 patients with resistant hypertension. Twenty-five patients underwent RDN, and 10 patients underwent repeated measurements without RDN (non-RDN). Baseline BP averaged 164/93 mm Hg (RDN) and 164/87 mm Hg (non-RDN) despite use of an average of 4.8±0.4 and 4.4±0.5 antihypertensive drugs, respectively. Mean office BP decreased significantly by −13/−6 mm Hg for systolic BP ($P<0.001$) and diastolic BP ($P<0.05$) in RDN but not in non-RDN at 3-month follow-up. RDN moderately decreased multiunit MSNA (79±3 versus 73±4 bursts/100 heartbeats; $P<0.05$), whereas all properties of single-unit MSNA, including firing rates of individual vasoconstrictor fibers (43±5 versus 27±3 spikes/100 heartbeats; $P<0.01$), firing probability (30±2 versus 22±2% per heartbeat; $P<0.02$), and multiple firing incidence of single units within a cardiac cycle (8±1 versus 4±1% per heartbeat; $P<0.05$), were substantially reduced at follow-up. BP, single-unit MSNA, and multiunit MSNA remained unaltered in the non-RDN cohort at follow-up. RDN results in the substantial and rapid reduction in firing properties of single sympathetic vasoconstrictor fibers, this being more pronounced than multiunit MSNA inhibition. Whether the earlier changes in single-unit firing patterns may predict long-term BP response to RDN warrants further exploration.

Renal Denervation Abolishes the Age-Dependent Increase in Blood Pressure in Female Intrauterine Growth–Restricted Rats at 12 Months of Age[10]

Abstract

Perinatal insults program sex differences in blood pressure, with males more susceptible than females. Aging may augment developmental programming of chronic disease, but the mechanisms involved are not clear. We previously reported that female growth–restricted offspring are normotensive after puberty. Therefore, we tested the hypothesis that age increases susceptibility to hypertension in female growth–restricted offspring. Blood pressure remained similar at 6 months of age; however, blood pressure was significantly elevated in female growth–restricted offspring relative to control by 12 months of age (137±3 versus 117±4 mm Hg; $P<0.01$, respectively). Body weight did not differ at 6 or 12 months of age; however, total fat mass and visceral fat were significantly increased at 12 months in female growth–restricted offspring ($P<0.05$ versus control). Glomerular filtration rate remained normal, yet renal vascular resistance was increased at 12 months of age in female growth–restricted offspring ($P<0.05$ versus control). Plasma leptin, which can increase sympathetic nerve activity, did not differ at 6 months but was increased at 12 months of age in female growth–restricted offspring ($P<0.05$ versus control). Because of the age-dependent increase in leptin, we hypothesized that the renal nerves may contribute to the age-dependent increase in blood pressure. Bilateral renal denervation abolished the elevated blood pressure in female growth–restricted offspring, normalizing it relative to denervated female control offspring. Thus, these data indicate that age induces an increase in visceral fat and circulating leptin associated with a significant increase in blood pressure in female growth–restricted offspring, with the renal nerves serving as an underlying mechanism.

Renal Sympathetic Denervation Provides Ventricular Rate Control But Does Not Prevent Atrial Electric Remodeling During Atrial Fibrillation[11]

Abstract

Renal denervation (RDN) reduces renal efferent and afferent sympathetic activity, thereby lowering blood pressure in resistant hypertension. The effect of modulation of the autonomic nervous system by RDN on atrial electrophysiology and ventricular rate control during atrial fibrillation (AF) is unknown. Here, we report a reduction of ventricular heart rate in a patient with permanent AF undergoing RDN. Subsequently, we investigated the effect of RDN on AF-induced shortening of atrial effective refractory period, AF inducibility, and ventricular rate control during AF maintained by rapid atrial pacing in 12 pigs undergoing RDN (n=7) or sham procedure (n=5). During sinus rhythm, RDN reduced heart rate (RR interval, 708±12 versus 577±19 ms; $P=0.0021$) and increased atrioventricular node conduction time (PQ interval, 112±12 versus 88±9 ms; $P=0.0001$). Atrial tachypacing for 30 minutes increased AF inducibility and decreased AF cycle length. This was not influenced by RDN. RDN reduced ventricular rate during AF episodes by ≈24% (119±9 versus 158±19 bpm; $P=0.0001$). AF episodes were shorter after RDN compared with sham (12±3 versus 34±4 seconds; $P=0.0091$), but atrial effective refractory period was not modified by RDN. RDN reduced heart rate and atrioventricular node conduction time during sinus rhythm and provided rate control during AF. AF-induced atrial electric remodeling, AF inducibility, and AF cycle length were not modified, but the duration of AF episodes was shorter after RDN. Modulation of the autonomic nervous system by RDN might provide rate control and reduce susceptibility to AF. Whether RDN may provide rate control in a larger number of patients with AF deserves further clinical studies.

Renal Denervation: Ultima Ratio or Standard in Treatment-Resistant Hypertension[12]

Abstract

Depending on studied populations and applied definitions, the prevalence of treatment-resistant hypertension varies from 10% to 15% but is higher in conditions associated with increased sympathetic drive, such as obesity, obstructive sleep apnea, diabetes mellitus, or renal dysfunction. The SYMPLICITY studies recently demonstrated that reducing sympathetic tone by intravascular renal denervation (IRD) is feasible in resistant hypertension but did not provide conclusive evidence on the size and durability of the antihypertensive, renal, and sympatholytic effects, long-term safety, quality of life, the possibility to relax antihypertensive drug treatment, cost-effectiveness, and benefit in terms of long-term hard cardiovascular-renal outcomes. At the time of writing of this report, 28 IRD trials in various indications were registered at http://www.clinicaltrials.gov, but only 7 had a randomized controlled design. In the United States, IRD remains an investigational procedure that cannot be used in clinical practice, but in Europe, CE-label certification of electric safety permits to market catheter systems to any interventional facility for regular clinical use. IRD should not be routinely applied as a substitute for the skillful management of resistant patients, which includes documentation of adherence to antihypertensive drugs, implementation of lifestyle measures, and the use of recommended combinations of antihypertensive agents at the highest tolerated daily dose. For now, IRD should, therefore, remain the ultima ratio in adherent patients with severe resistant hypertension, in whom all other efforts to reduce blood pressure have failed. IRD should only be offered within a clinical research context at highly skilled tertiary referral centers that participate in international registries constructed, independent of the manufacturers.

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