

A CURE FOR ESSENTIAL HYPERTENSION?

Ablation of the Sympathetic Nerves of the Kidney with a Radiofrequency Catheter

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ABSTRACT

The origins of the common form of high blood pressure, “essential hypertension”, have been uncertain. Diet and lifestyle factors are certainly involved, but can more be said than that? Recent evidence does indicate that a stimulant division of the autonomic (“automatic”) nervous system, the sympathetic nervous system, is activated in the majority of patients with essential hypertension. There is now good evidence that this is the prime mover in the initiation and the maintenance of the blood pressure elevation. It is the sympathetic nerves to the kidneys, activated on average 2-3 fold, which are of critical importance in the blood pressure elevation.

A newly devised treatment targets this adverse effect of activation of the renal sympathetic nerves. In a one-off procedure, the renal sympathetic nerves are silenced bilaterally by a purpose-built radiofrequency ablation catheter which is inserted with local anaesthesia in the femoral artery at the groin and advanced to lie, in turn, in both renal arteries.

The sympathetic nerves enter the kidneys in the walls of the renal arteries, within reach of the delivered energy. In a recently completed trial in 50 patients with otherwise uncontrollable hypertension (published Lancet 11 April 2009) the procedure was demonstrated to be safe, to effectively produce sympathetic denervation in the kidneys, and to be beneficial, producing an average blood pressure fall in the first 100 patients of 32/16 mm Hg at 12 month follow up.

Further research testing will now follow, in an international trial, to ascertain whether this novel therapy will become part of available medical care for patients with essential hypertension.

ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM IN ESSENTIAL HYPERTENSION

Contemporary Methods for Studying the Human Sympathetic Nervous System

Human sympathetic nervous system responses are differentiated, with activation in one regional sympathetic outflow, such as that to the kidneys which particularly concerns us here, typically being accompanied by inhibition or no change in another (1). Quantification of individual regional sympathetic nervous outflows is needed.

This need is met by recording electrically from subcutaneous sympathetic nerves, and by radiotracer derived measurements of the rates of release of the neurotransmitter, noradrenaline, from internal organs such as the heart and kidneys to plasma (1).

Microneurography: This technique involves insertion of a fine tungsten electrode through the skin, with positioning of the electrode tip in sympathetic fibres of, most commonly, the common peroneal nerve near the head of the fibula. Multifibre recordings of “bursts” of sympathetic nerve activity, synchronous with the heart beat, are generated in sympathetic efferent fibres passing to skeletal muscle blood vessels (2)

Regional Noradrenaline Spillover Measurements: The inapplicability of the neural recording methodology for clinical research on internal organs led to a continuing search for alternative techniques, especially biochemical ones. Measurement of organ-specific noradrenaline release to plasma by isotope dilution (1) became the “gold standard”. During constant rate infusion of tritiated noradrenaline, outward flux of endogenous noradrenaline from an organ (regional noradrenaline “spillover”) can be measured by isotope dilution:

Regional norepinephrine spillover = $[(C_V - C_A) + C_A E] / PF$, where C_V and C_A are the plasma concentrations of noradrenaline in regional venous and arterial plasma, E is the fractional extraction of tritiated noradrenaline in transit of blood through the organ and PF is the organ plasma flow.

Sympathetic neural pathophysiology of essential hypertension

For the past three decades, a major focus in high blood pressure research has been the renin-angiotensin system. The proven value of antihypertensive drugs which block this system has led to reduced attention to research on other blood pressure raising systems, including the sympathetic nervous system. Despite this, there is now general agreement that over-activity of the sympathetic nervous system commonly initiates and sustains the blood pressure elevation in patients with essential hypertension (3-5).

Application of the noradrenaline spillover methodology has demonstrated activation of the sympathetic nervous outflows to the kidneys and heart (3 & 4). Renal noradrenaline spillover, on average, is elevated 2-3 fold in both normal weight patients with essential hypertension and in obesity-related hypertension (3,6 & 7). Multiunit recordings from sympathetic nerve fibres directed to the skeletal muscle vasculature similarly show a doubling or trebling of sympathetic outflow (5).

The syndrome of neurogenic essential hypertension appears to account for no less than 50% of all cases of high blood pressure. This estimate is based on both the proportion of untreated patients with essential hypertension who have demonstrable sympathetic excitation, and the number in whom substantial blood pressure lowering is achieved, and the extent of this lowering, with antiadrenergic interventions. The application of sympathetic nerve recording and noradrenaline spillover methodologies, in multiple studies from different research groups (3-11), identifies activated sympathetic outflow to the skeletal muscle vasculature and kidneys

in 40 – 65% of patients.

Does this sympathetic activation initiate and maintain the blood pressure elevation, as has been suggested (4)? There is strong evidence to support this claim. Combined alpha- and beta-adrenergic blockade markedly reduces blood pressure in patients with essential hypertension, an effect particularly prominent in obese hypertensive patients (12 & 13). Ganglionic blockade lowers blood pressure nearly to normal in obesity-related hypertension (14). In patients with resistant hypertension, responding inadequately to concurrent treatment with multiple antihypertensive drug classes, including ACE inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers and diuretics, radiofrequency ablation of the renal sympathetic nerves lowers blood pressure remarkably (15).

This new, currently experimental treatment modality is described below.

ORIGINS OF SYMPATHETIC NERVOUS ACTIVATION IN ESSENTIAL HYPERTENSION

The specific causes of the increased sympathetic activity in essential hypertension remain largely unknown, although genetic influences are evident and behavioral and lifestyle factors are involved. Of prime importance, no doubt, is obesity. Obesity activates the sympathetic nervous system, including the renal sympathetic outflow (7 & 9), although through uncertain mechanisms.

Epidemiological evidence also indicates an importance for chronic mental stress, including in the workplace (16-18). A new strand of supporting evidence involves the presence of biological markers of stress exposure, in which parallels are drawn with panic disorder, which provides an explicit clinical model of recurring stress responses (19):

- (i) there is clinical co-morbidity as panic disorder prevalence is increased 3-fold in essential hypertension (20);
- (ii) plasma cortisol is elevated in both;
- (iii) in panic disorder and essential hypertension, but not in health, single sympathetic nerve fibres commonly fire repeatedly within an individual cardiac cycle; such salvos of single fiber firing have come to be seen as a “signature” of mental stress exposure;
- (iv) for both, adrenaline cotransmission is present in sympathetic nerves;
- (v) there is induction of the adrenaline synthesizing enzyme, PNMT, in sympathetic nerves (contained within a subcutaneous vein biopsy), an explicit indicator of mental stress exposure.

Physical inactivity also appears to be important. Habitual levels of exercise have progressively fallen world-wide. Changed work-life patterns now favor physical inactivity, as do replacement of walking by other transport options and the widespread adoption of labor-saving devices in

the home. The observation that aerobic exercise training in sedentary people reduces sympathetic nervous activity, and preferentially the renal sympathetic outflow, supports this concept (21).

CATHETER-BASED RENAL NERVE ABLATION AS A TREATMENT FOR RESISTANT ESSENTIAL HYPERTENSION

The sympathetic nervous system in recent years has been the “neglected pathway” in the treatment of hypertension. Despite the importance of neural pathophysiological mechanisms in pathogenesis, in the present era in which drugs antagonizing the renin-angiotensin system are the dominant therapeutic mode, therapy specifically targeting the sympathetic nervous system is currently underutilized.

However, a revolutionary treatment principle has recently been successfully tested in patients with resistant (uncontrolled) hypertension. This involves ablation of the renal sympathetic nerves with a radiofrequency emitting catheter inserted percutaneously into the femoral artery in the groin, and advanced to lie, in turn, in the lumen of both renal arteries (15). Sympathetic nerves enter the human kidneys in the walls of the renal arteries, and lie within reach of ablative energy delivery.

In some experimental models of hypertension, in laboratory animals, the sympathetic outflow to the kidneys is activated, and renal denervation typically prevents the development of the hypertension. In earlier times, prior to the availability of antihypertensive drugs, extensive surgical sympathectomy was used as a treatment for severe hypertension (22); survival benefit was demonstrated but complication rates were high, as was morbidity from the extensive denervation, which did not specifically target the kidneys.

Initiation of the new treatment strategy for hypertension was based on these observations, and the demonstration that the renal sympathetic outflow is activated in essential hypertension (1,7 & 13) . For entry into the recently published trial, patients had to meet international criteria of uncontrolled essential hypertension (clinic blood pressure in excess of 160/90 mm Hg on three drugs, including a diuretic). In participating hypertensive patients, radiofrequency energy in 90° quadrants was delivered in stepwise fashion to the full circumference of the renal artery wall.

The initial aims were to establish that the procedure does produce renal denervation in humans, that it is safe, and that blood pressure is lowered. All seem to have been confirmed (15). To establish whether the catheter ablates renal sympathetic nerves, measurements of renal noradrenaline spillover were made at baseline and at follow up; results to-date indicate that sympathetic denervation does, in fact, occur. The level of blood pressure reduction achieved in the first 50 patients studied, a mean fall of 24/10 mm Hg at 3 months and 29/16 mm Hg at 12 months ($P<0.001$)(15) was perhaps greater than anticipated, but it should be emphasized that this proof of principle trial is not a random controlled clinical trial including blinded experimental design.

At this point (with the longest follow-up now being two years), blood pressure reduction is

sustained, suggesting that renal sympathetic reinnervation, if it has occurred, is insufficient to cancel out the blood pressure benefit (Figure 1).

A CURE FOR ESSENTIAL HYPERTENSION?

It has been suggested that renal artery catheter-based renal denervation might, perhaps, provide a cure for essential hypertension in selected patients, those with milder hypertension than treated in the recent study. This speculation remains untested. For the procedure to be applied in milder forms of essential hypertension a very high level of safety would be mandatory.

It should be noted that in one of the approximately 100 patients studied to-date insertion of the catheter did cause a renal artery dissection, which was treated by stenting (15). Although no short term (up to two years) renal artery complications, other than this procedural mishap, have been detected, specifically there have been no instances of renal artery stenosis or aneurysm, undetected endothelial damage, if it occurred, might possibly contribute to delayed atherogenesis in the renal artery.

Efferent sympathetic nerve regrowth is possible, although the degree to which this would fully restore sympathetically-mediated function in the kidneys, and perhaps cancel out the observed antihypertensive effect, is unknown. With transplantation of the heart, in which the sympathetic nerves of the heart are severed, some degree of reinnervation commences 2-3 years after the surgery, but this is incomplete (23). Regeneration of renal afferent nerves is unlikely. Any blood pressure reduction attributable to renal deafferentation is likely to be permanent.

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Legend to Figure 1

The blood pressure changes subsequent to renal denervation with a radiofrequency ablation catheter. Results are plotted for all 68 participants who have been followed to a minimum of one month post-procedure, extending through to the 21 patients on whom 12-month follow up is available. Both systolic and diastolic pressures showed very material and statistically significant falls from one month onwards ($P<0.01$).

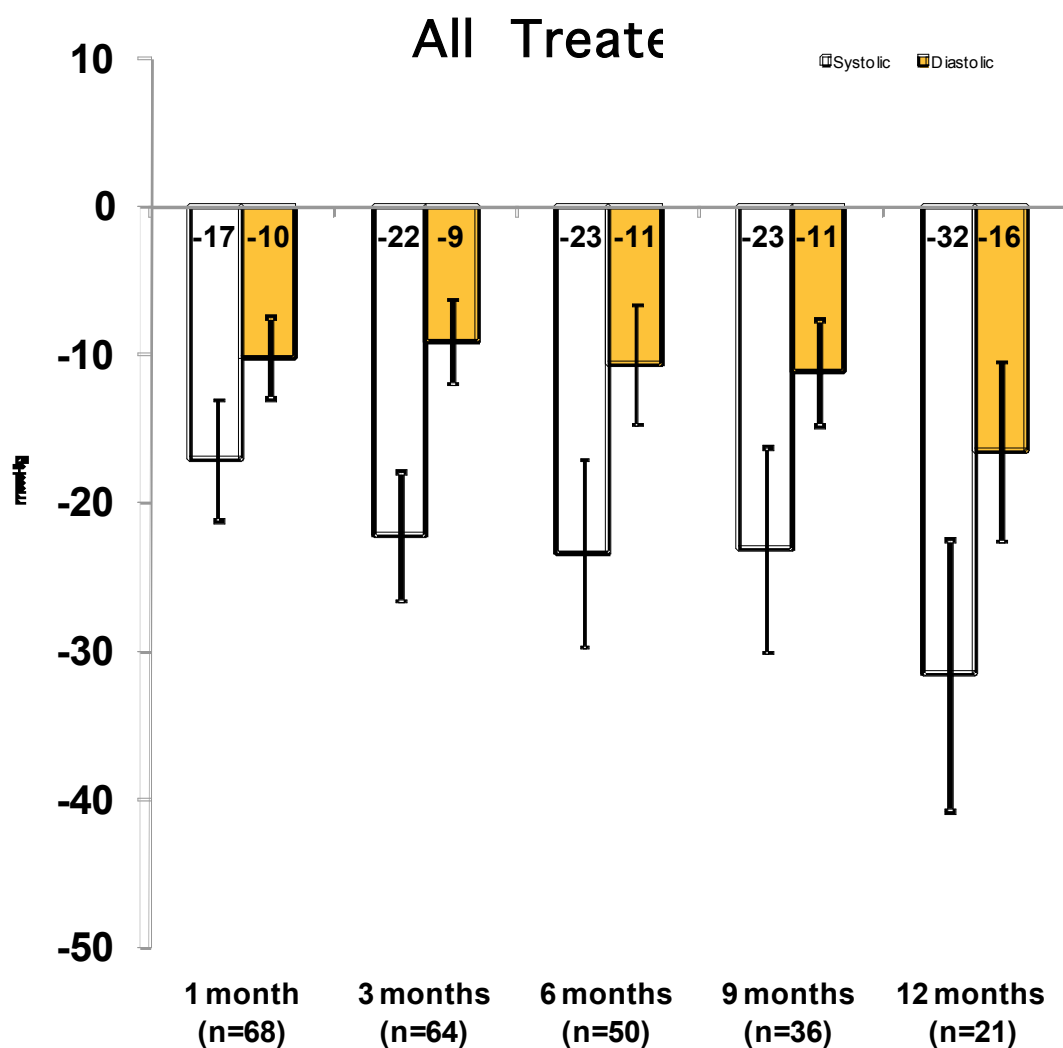


Figure 1

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