Point:Counterpoint: The dominant contributor to systemic hypertension: chronic activation of the sympathetic nervous system vs. activation of the intrarenal renin-angiotensin system

POINT: CHRONIC ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM IS THE DOMINANT CONTRIBUTOR TO SYSTEMIC HYPERTENSION

For the past three decades, the renin-angiotensin system has been the major focus in high blood pressure research. The proven value of antihypertensive drugs that block this system has deflected research from other blood pressure-raising systems, including the sympathetic nervous system. Despite this, undeniable evidence exists for the importance of chronic activation of the sympathetic nervous system in the pathogenesis of both experimental and human hypertension.

Experimental hypertension. The case appears strongest in the Okamoto-Kyoto hypertensive rat and experimental overfeeding models of obesity-hypertension. Sympathetic nervous system abnormalities catalogued in the spontaneously hypertensive rat importantly include increased efferent sympathetic nerve traffic in younger animals, particularly to the kidneys, with normal nerve firing in older animals (17, 29). Overfeeding in rats, dogs, and rabbits consistently increases body weight, sympathetic nervous activity, and blood pressure, the activation of the renal sympathetic outflow being particularly prominent (11).

Human hypertension. Application of sympathetic nerve recording and norepinephrine spillover methodology has demonstrated activation of sympathetic nervous outflows to the kidneys, heart, and skeletal muscle vasculature, typically a doubling or trebling overall, in patients with essential hypertension (7, 8, 13, 14, 16, 20, 24). 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 patients with essential hypertension who have demonstrable sympathetic excitation and the number in whom substantial blood pressure lowering is achieved with antiadrenergic drugs or devices (19, 22). Multiple studies from different research groups (1, 7–10, 13, 14, 16, 20, 24, 25, 30), identify activated sympathetic outflow to the skeletal muscle vasculature, heart, and kidneys in 40–65% of patients (notably, the cardiac sympathetic outflow is spared in obesity-hypertension), with the caveat that in those aged more than 60 yr, although MSNA is increased, cardiac and renal norepinephrine spillover is typically normal. Single fiber sympathetic recording demonstrates increased firing frequencies (16, 20) and multiple firings within a cardiac cycle (firing salvos), not seen in health (20). Sympathetic nervous activation also characterizes human renal hypertension. In end-stage renal disease, sympathetic nervous activation is at a high level, equal to or exceeding that seen in cardiac failure (4,15).

Fig. 1. Fall in blood pressure after an endovascular bilateral renal sympathetic denervation procedure in patients with hypertension resistant to treatment with multiple antihypertensive drugs, including a diuretic. Notably, all patients were under treatment with an ACE inhibitor or angiotensin receptor blocker (or both). The patients shown represent the initial treatment cohort (19), with subsequent ongoing surveillance of these patients and additional recruitment. Histogram depicts the changes in clinic systolic and diastolic pressures at differing follow up time points (M = months postprocedure). Number of patients at each time point is indicated in brackets.
Does this sympathetic activation cause the blood pressure elevation? Once it was thought that the sympathetic nervous system exerts minute by minute circulatory control only and was not of importance in the pathogenesis of hypertension. The regulatory effects of the renal sympathetic nerves on renin release, glomerular filtration rate, and renal tubular reabsorption of sodium are, however, now seen to provide a range of potential hypertension-producing mechanisms. Experimental studies establish the important concept that subvasoconstrictor levels of renal sympathetic activity can increase renin secretion and renal sodium retention, without changing renal hemodynamics (5). Of relevance, younger patients with mild essential hypertension very commonly have “high renin essential hypertension,” where renal sympathetic activity is sufficiently elevated to increase renal secretion of renin, but not to reduce renal blood flow (8, 9, 24). Renin-angiotensin inhibitors work well in these patients, in part because they are counteracting neurally mediated RAS activation.

Human hypertension. Does this sympathetic activation initiate and maintain the blood pressure elevation in patients with essential hypertension? There is strong evidence to support this claim, both historical and contemporary. In earlier times, prior to the availability of antihypertensive drugs, extensive surgical sympathectomy was effectively used as a treatment of severe hypertension (28). Of the antihypertensive drugs subsequently developed from the mid-20th century, many were antianadrenergic. The recent case made against β-adrenergic blocker prescribing in hypertension is based on the adverse metabolic side effects of this drug class, and certainly not a lack of blood pressure lowering efficacy.

In end-stage renal disease, renal transplantation restores renal function but does not abolish the hypertension. Ne- phrectomy does through normalizing sympathetic tone (4, 15) via removal of the sympathetic excitatory influence of renal afferents from the failed kidneys (3). The hypertension of renal failure is explicitly a neurogenic hypertension (4, 15, 27).

Experimental renal denervation. In multiple forms (5) of experimental hypertension renal denervation completely prevents, delays the onset of, or ameliorates the magnitude of the hypertension. Where examined, the beneficial effect of renal denervation on the hypertension was associated with a concur- rent decrease in renal sodium retention (5).

The “bottom line”: the antihypertensive effect of renal sympathetic denervation in resistant essential hypertension. The sympathetic nervous system is the “forgotten pathway” in hypertension treatment. This may soon change, with the recent testing of device-based therapies, including the surgically implantable arterial barostimulator, in patients with hypertension (22). Another revolutionary treatment principle recently success- fully tested in patients with drug-resistant essential hyper- tension (19, 26) involves bilateral ablation of the renal sympa- thetic nerves with a purpose-developed radiofrequency emitting catheter (the Symplicity catheter, Ardan Corporation, Palo Alto, CA). The catheter is inserted percutaneously via the femoral artery to lie in the renal artery lumen, and radiofre- quency energy is delivered in 90° quadrants in stepwise fash- ion to the full circumference of both renal arteries (19). Sympathetic nerves enter the human kidneys in the renal artery walls, within reach of ablative energy delivery.

The study established that the procedure does produce renal denervation, that it is safe, and that blood pressure is lowered (19, 26). Blood pressure fell markedly, with a mean fall of 24/10 mmHg at 3 mo and 27/13 mmHg at 12 mo (P < 0.001; Ref. 19). At this point (with the longest follow-up in partici- pants being 2 yr), blood pressure reduction is sustained, sug- gesting that if renal sympathetic reinnervation occurs it is insufficient to cancel out the blood pressure benefit (Fig. 1).

The renin-angiotensin system in hypertension: science and metaphysics? Given that antihypertensive drugs antagonizing the renin-angiotensin system are the dominant therapy, how can a case for pre-eminence of sympathetic neural origins of human hyperten- sion be sustained? Drug prescribing practices in hypertension, how- ever, manifestly do not prove pathogenesis. In any era, the drug class used most widely for an illness commonly dictates which research stream is followed for the illness (especially if the drug patents have not expired!), determining the prevailing notions of pathophysiology. But there is a logical flaw in attempting to ascertain the biology of a disease from the presumed mode of action of an efficacious drug, very evident with psychotropic drugs (12), and applying also in essential hypertension.

Despite the current dominance in therapy of drugs antago- nizing the renin-angiotensin system, plasma renin levels in essential hypertension are often low (2), when plasma renin activity is high this typically has a neural mechanism, high sympathetic outflow to the kidneys stimulating renin release (8, 9), the clinical case made for specific therapeutic benefit with renin-angiotensin inhibitors has been claimed by eminent educ- ators to have, in fact, been overstated (18, 21), and the importance of a cellular, extrarenal renin-angiotensin system, often invoked since plasma renin values are unremarkable in hypertension, is disputed (23). Well known to clinicians and experimenters alike is the diagram, now iconic (6) and gener- ously used in pharmaceutical marketing, of the “Renin-Angiotensin Based Cardiovascular Continuum,” where the path from cardiac risk factors, through to myocardial infarction, cardiac arrhythmias, heart failure, and death has angiotensin as the noxious prime mover at every step (6). This construction, although true in parts, is as much metaphysics as science, and leaves little place for the sympathetic nervous system to claim its birthright!

REFERENCES
Point: Counterpoint

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COUNTERPOINT: ACTIVATION OF THE INTRARENAL RENIN-ANGIOTENSIN SYSTEM IS THE DOMINANT CONTRIBUTOR TO SYSTEMIC HYPERTENSION

Our discussion regarding the dominant mechanism responsible for hypertension calls to mind the famous poem, “The Blind Men and the Elephant,” by John Godfrey Saxe based on an ancient fable from India. In essence, the blind men described the elephant based on their specific encounter, thus concluding that the elephant was a wall, a spear, a snake, a tree, a fan, or a rope. The lesson is that our interpretations regarding a specific experience are very much dependent on how it presented itself. Because of my predoctoral and postdoctoral training experiences with Arthur Guyton (10) and the fact that my research has been highly focused on the cardinal role of the kidneys in the pathophysiology of hypertension, I support the concept that alterations in kidney function in hypertension are predominantly due to an inappropriately increased activity of the intrarenal renin-angiotensin system (RAS; Refs. 12, 17, 19, 21). While the nervous system is important (4, 5), I contend that chronic activation of the sympathetic nervous system is not the dominant contributor to hypertension, but may also contribute to the activation of the intrarenal RAS that is characteristic of many forms of hypertension (3, 19, 22).

Hypertension is characterized by increased peripheral vascular resistance due to increased vascular smooth muscle contractile activity and endothelial dysfunction (15, 29), but it is more likely that the vasculature is the victim rather than the culprit of the injurious processes that occur in hypertension (27). The nervous system regulates blood pressure by integrating signals coming from all parts of the body and sending neural signals to various organ systems. However, there is limited evidence that chronic increases in sympathetic activity serve as the dominant contributor to most forms of hypertension. Because the neurocentric view is being addressed by Esler, Lambert, and Schlaich (6), I will defer further consideration of this issue to them. Nevertheless, it is important to point out that the successful treatment of resistant hypertension using catheter-based renal sympathetic denervation was restricted to selected patients that were resistant to standard therapy (14).

Through its multiple actions, the kidneys exert a predominant role to regulate arterial pressure (10, 12, 19, 24). Importantly, transplantation studies have demonstrated that the hypertension follows the kidneys (9). There are many models of experimental hypertension but most of them involve procedures or genetic manipulations that activate the RAS (8, 11, 13, 22, 23). While enhanced activity of renal sympathetic nerves contributes to the magnitude of the hypertension, the hypertensive response is only attenuated and the increases in intra-