

NOVEL THERAPIES

Novel Therapies for Resistant Hypertension

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KEY WORDS: *hypertension, surgery, baroreflex, carotid sinus, medical device, autonomic nervous system, renal denervation, RAAS, vaccine*

ABSTRACT

Two novel invasive therapeutic strategies for the treatment of resistant hypertension, have recently emerged, carotid baroreceptor stimulation and renal denervation. Both are effective in reducing elevated blood pressure values and display a good tolerability profile without the occurrence of any major untoward effect. A third choice, immunization against components of the renin-angiotensin-aldosterone system (RAAS) is a potential therapeutic alternative under investigation.

INTRODUCTION

Hypertension has a prevalence of 26.4% and affects nearly 72 million people in the USA, and 1 billion worldwide. Hypertension is a major cause of morbidity and mortality, responsible for 7 million deaths annually.¹ It is estimated that only 25-35% of hypertensive patients achieve a blood pressure <140/90 mmHg. Hypertension is usually defined as *resistant* or refractory to treatment when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in a full daily dosage has failed to lower systolic and diastolic blood pressure <160/90 mmHg.

ABBREVIATIONS

RAAS= rennin angiotensin aldosterone system

RSD= renal sympathetic denervation

PREVALENCE AND HEALTH BURDEN

Resistant hypertension has a reported prevalence as high as 13%. The high prevalence of hypertension in the general population renders this small percentage significant in terms of actual patient numbers. The most common *causes* of resistant hypertension is poor compliance or limitations in drug therapy (inadequate dosing, polypharmacy, and adverse drug effects) or non adherence to recommended lifestyle changes (particularly elimination of alcohol abuse). Another not infrequent cause of resistant hypertension is obstructive sleep apnea 736–739, whereas other causes include renal artery stenosis and volume overload -due to progressing renal insufficiency, excessive salt intake, hyperaldosteronism, and, most often, insufficient diuretic therapy. Finally pseudohypertension must be excluded.^{2,3} This creates the need for other therapeutic options, beyond existing antihypertensive medications, setting the basis for interventional approaches.

Recently, activation of the carotid baroreceptors using electrical stimuli (the Rheos System; CVRx, Inc., Minneapolis, Minnesota) is under investigation in phase

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Manuscript received February 8, 2010;

Accepted after revision March 22, 2010

III studies, with promising results. Another study using selective renal sympathetic denervation (RSD) marks the return of selective renal sympathectomy as a potential alternative treatment for resistant hypertension. The sympathetic innervation of the kidney is implicated in the pathogenesis of hypertension through effects on renin secretion, sodium and water reabsorption, and renal blood flow (RBF). Finally, immunization against components of the renin-angiotensin system (RAAS) have provided optimism in the development of another therapy for resistant hypertension.

CAROTID SINUS STIMULATION

The baroreflex is a series of responses to physiologic stimuli that determines the balance of sympathetic and parasympathetic activity in the heart and peripheral vessels and there be participates in long and short term control of blood pressure. Carotid baroreceptors physiologically modulate autonomic tone by inhibiting sympathetic cardiovascular drive and stimulating vagal influences on the heart. This homeostatic function is impaired in hypertension leading to vasoconstriction and tachycardia (Fig. 1). However, baroreceptor response diminishes over minutes to days, and a new threshold for activation is established (baroreceptors become less sensitive to any given change in blood pressure with chronic hypertension). Preliminary studies in experimental animals conducted to restore the baroreceptor function, showed that carotid sinus stimulation is able to lower blood pressure and reduce circulating levels of norepinephrine.⁴

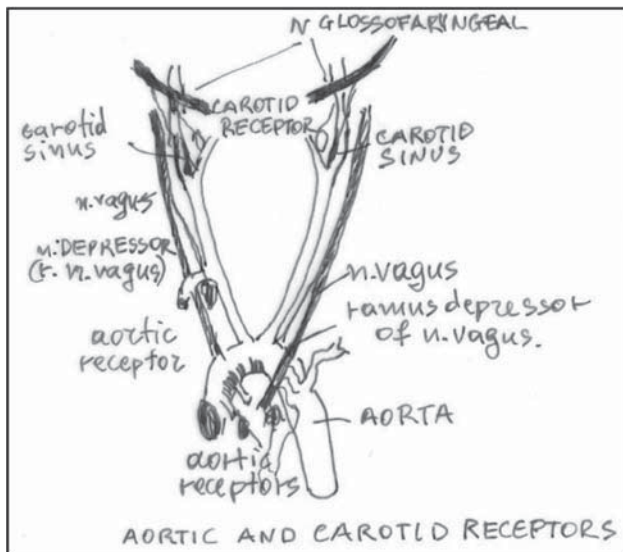


FIGURE 1. Aortic and Carotid Receptors.

DEVICE & TECHNIQUE

The *Rheos Baroreflex Hypertension Therapy System* consists of a programmable pulse generator capable of delivering between 1 and 7,5 V in a temporary variable pattern along with 2 electrodes designed to be placed at the carotid bulb. This requires surgical implantation by means of open carotid exposure, but the components are then tunneled subcutaneously, in a fashion similar to pacemaker placement (Fig. 2).¹¹

OUTCOME

The patients enrolled in the US and European Rheos Feasibility Trial, (all experiencing resistant hypertension while receiving optimal medical management) presented a systolic blood pressure (SPB) reduction of 41 mm Hg, (from 180 to 139 mmHg), (P=0.001), diastolic blood pressure (DBP) of 19 mm Hg, (P=0.005), pulse pressure from 98 to 77 mm Hg (=21 mm Hg), (P<0.005), and heart rate reduction of 9 bpm. In all cases, dose (voltage)-response curves were consistent, apparent and highly linear.^{5,6} Mean follow up was 10 months. At the end of the study the stimulation procedure caused sustained blood pressure reduction (31/14 mmHg) coupled with consistent sympatho-inhibition, without any major side effects. Two generators have had to be changed for planned battery replacement in patients requiring high voltages for blood pressure control and the total infection rate was 5.5%.⁷⁻¹⁰

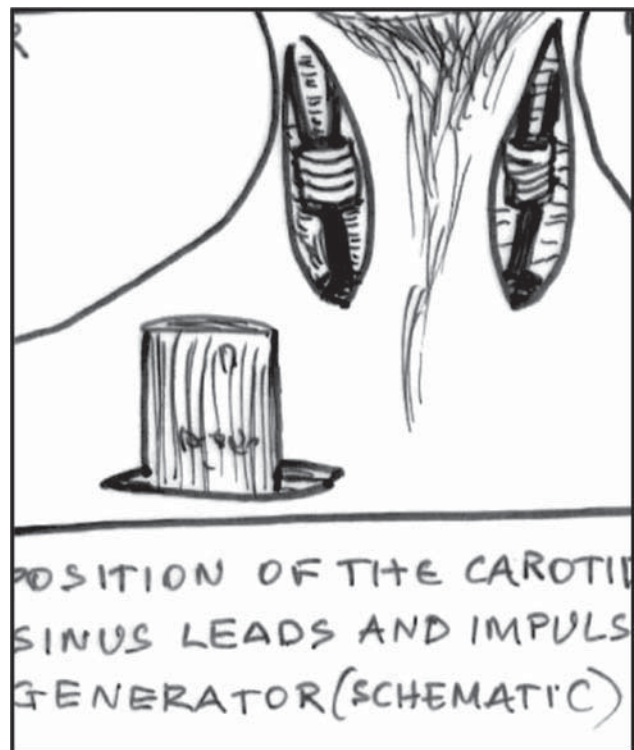


FIGURE 2. Position of the Carotid Sinus Leads and Impulse generator.

RENAL SYMPATHETIC DENERVATION (RSD)

The autonomic control of the kidney is predominantly sympathetic with postganglionic neurons. Renal sympathetic nerve activation enhances noradrenaline production or spillover (while renal denervation results in a marked decrease of noradrenaline up to 95%), renin secretion via β_1 AR when the nerve stimulation is weak, and sodium reabsorption and renal vessel vasoconstriction via α_1 AR, resulting in renal blood flow reduction (vascular smooth muscle cell contraction, more profound in preglomerular microvessels), when sympathetic nerve stimulation is stronger.

Efferent renal sympathetic nerve endings release noradrenaline directly on granular juxtaglomerular cells and increase the rate of renin release as well as indirectly by interfering with renal hemodynamics and sodium reabsorption (release of noradrenaline directly on renal epithelial cells and promotion of reabsorption of water and sodium from the tubular lumen in the proximal tubule and thick ascending limb of Henle's loop). Moreover, *afferent* renal sympathetic nerves originate mostly from the renal pelvic wall (mechanoreceptors respond to stretch and chemoreceptors detect renal ischemia) whose cell bodies lie in the ipsilateral dorsal root ganglia (T6-L4). From there ascending signals travel mainly in hypothalamic area stimulating sympathetic centers in the brain thus increasing sympathetic nervous system (SNS) activity and blood pressure levels.

HISTORICAL PERSPECTIVE OF SYMPATHETIC DENERVATION

Sympathectomy has been applied mainly in patients with severe or malignant hypertension as well as with patients of cardiovascular deterioration despite relatively good blood pressure reduction by other means. After the introduction of antihypertensive drugs, sympathectomy was reserved for patients who failed to respond to antihypertensive therapy or could not tolerate it. *Total sympathectomy* (from 8th to 12th dorsal vertebra) is impractical and poorly tolerated by humans. It was performed only in a few selected centers, in either 1 or 2 stages, and required a prolonged hospital stay (2 to 4 weeks). Adverse events were common and included orthostatic hypotension and tachycardia, palpitation, breathlessness, anhidrosis, cold hands, intestinal disturbances, loss of ejaculation, sexual dissatisfaction, thoracic duct injuries and atelectasies. However, sympathectomy was associated with higher survival rates more than doubled in patients who underwent the procedure.

TECHNIQUE

Renal artery angiography is performed to access anatomic eligibility for the procedure and to confirm the absence of

significant renal artery stenosis. The treatment catheter is then introduced into the renal artery and positioned in the distal part of the artery. The proximal end of the catheter is connected to a radiofrequency (RF) generator to apply a discrete RF ablation lasting 2 min. Up to six ablations are performed in each artery, separated both longitudinally and rotationally to achieve circumferential coverage of the renal artery. Catheter tip temperature and impedance are constantly monitored during ablation and RF energy delivery is regulated according to a predetermined algorithm (Fig. 3).¹²

CURRENT USE OF RSD

RSD presents several significant advantages over radical sympathectomy:

It is localized, minimal invasive, it has no systemic side effects and its procedural and recovery time are very short. It was achieved by radiofrequency ablation through the percutaneous insertion of modified catheter (Symplicity; Ardian Inc., Palo Alto, California). It was studied in 50 patients with resistant hypertension and resulted in impressive blood pressure reductions (27/11 mmHg) during a 12-month follow up period. Only 2 adverse events occurred (one renal artery dissection and one femoral artery pseudoaneurysm).¹³ This study demonstrated for the first time in humans that RSD can reduce blood pressure in a safe way with long acting results. However, the study lacked a proper control group (not randomized), it was

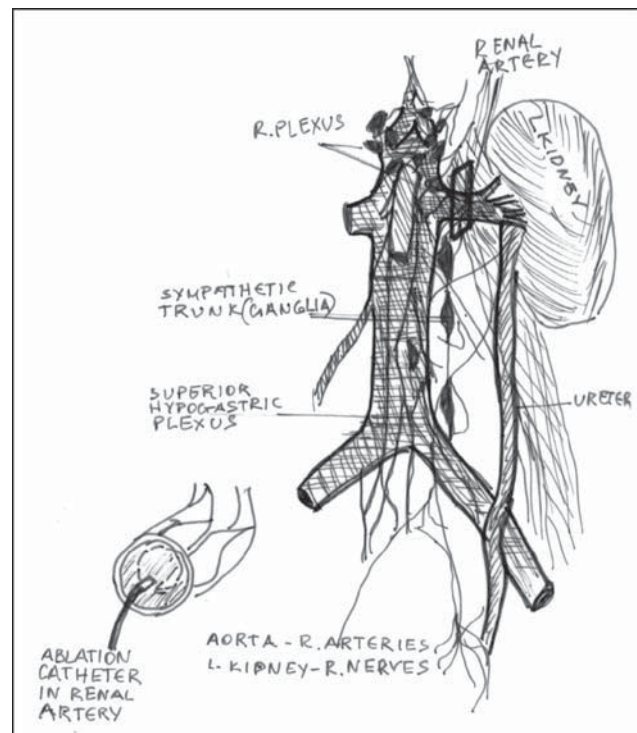


FIGURE 3. Anatomy of the kidney.

small, the group of patients recruited was not clearly defined, predictors of blood pressure response had not been identified, the potential for tissue damage (that will result in structural changes of the renal artery) was not defined. The extent of ablation induced afferent RSD is not currently known and the cost effectiveness needs to be carefully examined.^{14,15}

THE FUTURE OF RSD

RSD will be applied in other conditions such as essential hypertension, left ventricular hypertrophy (LVH), congestive heart failure (CHF), chronic kidney disease (CKD). Although attractive, RSD at the early stages of hypertension as well as in milder forms of the disease is difficult to accept at present time. Current recommendations suggest that it should be reserved for patients in whom drug therapy fails. However, in the future maybe RSD can be used as initial therapy in younger patients obtaining most of the benefit. Similar beneficial effects in heart failure has been obtained in animal experiments with the Rheos System inducing carotid baroreceptor activation and subsequently inhibiting SNS activity.

IMMUNIZATION AGAINST COMPONENTS OF THE RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS)

The RAAS commands an important role in the regulation of blood pressure and thus, at present, has been a target for clinical control by drugs affecting the entire system. Most recently, immunization against angiotensin-I with *PMD-3117* vaccine, angiotensin II with *CYT006-AngQb* vaccine and targeting angiotensin-II type 1A receptor with *ATR12181* vaccine have provided optimism in the development of a hypertension vaccine (Fig. 4).

RENIN IMMUNIZATION

Active immunization against the protein renin produced a high titre of renin antibodies, complete inhibition of endogenous plasma renin activity and decrease in blood pressure, but with presence of an auto-immune disease specific to the kidney -characterized by immunoglobulines colocalized with renin in the afferent arterioles, cellular inflammatory proliferation around the intrarenal arterial tree and interstitial nephritis.

ANGIOTENSIN-II IMMUNIZATION

Immunization against angiotensin peptides requires the covalent linkage of the peptide to a protein carrier molecule a process with increases the level of immunological background by raising antibodies against the carrier. Also, synthetic angiotensin-II was coupled to Bovine serum albumin and emulsified in Freund's adjuvant developing antibody titre 6-15 times greater, but did not alter blood pressure. A new immunization technology that conjugates antigens to the

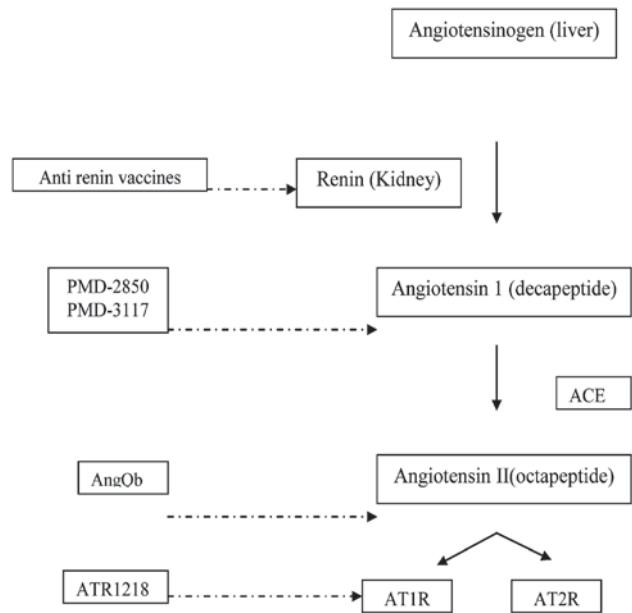


FIGURE 4. Vaccines against components of RAAS.

surface of virus like particles (VLPs) leads to strong B-cell response against self antigens was utilized. VLP conjugates with either a peptide or a hapten have been tested in clinical trials, and have been shown to be well tolerated and highly immunogenic with a 100% responder rate. This vaccine terms *CYT006-AngQb*, increase reversibly antibodies, producing a difference of 21 mm Hg of blood pressure and lasting more than 35 days after the last boost (half life of 4 months).¹⁶ In a trial (Ambuhl et al.¹⁸) using this vaccine 14 of 16 subjects showed local adverse events such erythema, edema, pain and induration at the injection site, all of mild intensity. Another study (Tissot et al.¹⁹) phase IIa trial using 72 patients receiving 100 µg or 300 µg *AngQb* responded with high IgG titres against *AngII* after only one injection and the antibody response was strongly boosted after the 2nd injection. In the 300 µg group the difference from placebo was in mean ambulatory blood pressure at 14th week was -9/-4 mm Hg. There was a significant reduction of the early-morning blood pressure surge compared with placebo in the 300 µg group, with a change at 08:00am of -25/-13 mm Hg. Change from supine to standing position did not lead to orthostatic hypotension. This trial is the first to show that vaccination against vasoactive endogenous substance can reduce blood pressure in humans. The drop in blood pressure was pronounced in the early morning, when the R A S is most active and most stroke and cardiovascular events occur.

However, concerns of *safety* issue remain as 1) repeated stimulation of the immune system by booster doses of endogenous peptide linked to a virus like particle can cause auto-immune disease. 2) whether continuous inhibition of *AngII*

for several months without the ability to quickly reverse it, is safe or does this inhibition play any detrimental role in situations of volume depletion, trauma, or shock. 3) because most of AngII is synthesized locally in tissues whether this antibody can diffuse from the circulation into the extravascular space in concentrations enough to block the local AngII. 4) or if it has organ protective effect.

ANGIOTENSIN-I IMMUNIZATION

AngI vaccine PMD3117 produced an anti-(AngI) antibody titre elevation, without influence in the BP, but with significantly blunted fall of plasma renin following withdrawal of ACEi or ARB.¹⁷

ANGIOTENSINE II-TYPE 1A (AT1A) RECEPTOR IMMUNIZATION

Virus-like particle VLP based antihypertensive vaccine *ATR 12181* which utilizes a peptide from the extracellular portion of AT1A receptor has been used in the reduction of anti-ATR 12181 antibodies. 17 mm Hg reduction of SBP was observed in slow heart rates at the 64th week with significant attenuation of LVH and reduction of LV fibrosis. Damages of glomerulus and interstitial fibrosis in kidneys were attenuated in vaccinated group and microscopic examination of different organs did not reveal any signs of auto immune disease and expression of the nuclear oncogenes c-fos and c-jun in heart and kidney were decreased in comparison to the control group. The long-term results of vaccine ATR 12181 in SHRs seemed to be encouraged in blood pressure lowering, target organ remodeling, efficacy and safety and thus, appropriate for future clinical utility.

In conclusion, if vaccination against high blood pressure proves to be safe and effective in the long run, it will increase the control rate of hypertension and thus, ease the burden of cardiovascular morbidity and mortality in our society.

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