Baroreceptor activation therapy for treating resistant hypertension: a status report

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For decades, elevated sympathetic nervous system (SNS) activation has been known as an important pathophysiologic maladaptation associated with the initiation of cardiovascular disease (CVD). Increased SNS activity is associated with a variety of pathophysiologic changes, all of which may contribute to elevated blood pressure (BP), increased vascular tone and resistance, compromised central and peripheral hemodynamics, renal vasoconstriction, oxidative stress, metabolic abnormalities, and adverse remodeling of cardiac and vascular smooth muscle. If not treated properly, chronic hypertension is a strong predictor of risk for stroke, myocardial infarction (MI), and congestive heart failure. Early pharmacologic attempts to treat hypertension focused on the blockade of SNS activity and the renin-angiotensin-aldosterone system (RAAS). Ironically, many traditional pharmacologic agents used to treat hypertension may result in a reflex activation of the SNS. Menon et al. (2009) recently reported observations of increased SNS activation and concurrent insulin resistance with a thiazide-type diuretic (chlorthalidone), a commonly used first-line therapy for hypertension [1]. Dihydropyridine calcium channel blockers have historically been associated with a reflex tachycardia likely due to activation of sympathetic activity [2]. An elegant report by Fu and colleagues (2005) highlighted the enhanced SNS activity in patients after treatment with losartan-hydrochlorothiazide, which was identified as one possible mechanism to explain persistent morbidity in hypertension despite adequate blood pressure control [3]. Thus, despite many years of research, clinicians are currently left with few therapeutic options that fully address the underlying pathophysiology of this disorder. If patients are resistant to treatment or develop side effects to medications, the clinician may have to choose therapies that lower blood pressure but which may aggravate the pathology of SNS hyperactivation.

Fortunately, a novel therapeutic option is becoming available that allows appropriate physiologic adaptation to elevated SNS activation and reduced parasympathetic activation (and thus elevated BP) by electrically stimulating the carotid baroreflex. The Rheos® System (CVRx Inc., Minneapolis, MN), which provides Baroreflex Activation Therapy (BAT®), is an implantable device with a generator and lead technology (very similar to cardiac pacemakers) which activates the baroreceptors located in the carotid sinus; activation thus provides a signal to medullary brain centers that BP is elevated, thereby triggering a specific and coordinated alteration of physiologic systems to offset the perceived elevated BP. Indeed, a recent study indicated that BAT reduces sympathetic activation and promotes parasympathetic activation in resistant hypertension [4]. This novel therapy holds the promise of providing clinicians with the first practical device-based therapeutic option to induce sympathoinhibition in hypertension.

Electrically modulating the baroreflex for therapeutic effects is not an entirely new concept. In the 1960's and 1970's, carotid sinus nerve stimulation therapy was shown to reduce BP and alleviate angina pectoris [5,6]. However, shortcomings in the technology prevented widespread adoption of carotid sinus nerve stimulation as a clinically acceptable therapy. The Rheos system, developed after many years of research in generator and lead technology, is a new market-approved in Europe and is currently being evaluated in a U.S. Pivotal trial for safety, efficacy, and clinical utility in the treatment of resistant hypertension (defined as patients with BP greater than 160/80 mmHg and being treated with 3 or more anti-hypertensive medications, one of which being a diuretic). Interestingly, published pre-clinical and clinical data suggest the device could be considered a viable treatment for hypertension management in those patients who are not at goal and who are unable to take additional medications due to side effects, poor compliance, etc. Pre-clinical studies with the Rheos System demonstrate that chronic baroreflex activation ameliorates hypertension [7-10] and heart failure [11] in animal models. Zucker and colleagues found that baroreflex activation enhanced survival in the canine pacing-induced heart failure model [12]. Importantly, a key observation was that angiotensin II levels were much lower in the canines receiving baroreflex stimulation.

To date, sixteen patients of over 350 patients treated worldwide to date, have completed follow-up through 3 years of Rheos Therapy [13]. Baseline SBP, diastolic pressure (DBP), and heart rate (HR) are provided in Table 1. Significant reductions in office cuff SBP and DBP were noted at all time points (all p < 0.005) (Table 1). Similarly, HR was significantly reduced by approximately 10 bpm (p < 0.001 at 1 year, p < 0.01 at 2 years) and by 6
Table 1: Change in Blood Pressure and Heart Rate in Patients Receiving Rheos Therapy with 3 Year Follow-Up Data.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N=16)</th>
<th>1 Year (N=16)</th>
<th>2 Year (N=16)</th>
<th>3 Year (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>190 ± 30</td>
<td>152 ± 22</td>
<td>123 ± 21</td>
<td>101 ± 19</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>111 ± 22</td>
<td>64 ± 12</td>
<td>50 ± 10</td>
<td>41 ± 9</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>79 ± 9</td>
<td>73 ± 9</td>
<td>71 ± 7</td>
<td>69 ± 6</td>
</tr>
</tbody>
</table>

Note. Data are presented as mean ± SE. *p ≤ 0.01; †p ≤ 0.005. SBP = systolic blood pressure, DBP = diastolic blood pressure.

Fig. 1: Left ventricular mass index categorized according to American Society of Echocardiography standards. At baseline, 49% of patients have severely abnormal mass. After 12 months of Rheos Therapy, 71% of patients have normal or mildly abnormal mass.

Despite emphasizing “individualized” therapy for patients with CVD, clinicians lack the tools to truly tailor therapy for patients with significant hypertension or heart failure. In resistant hypertension and overt heart failure, there are multiple lines of therapy which are commonly used, but the interactions of drugs which exploit these pathways are poorly understood. Early investigations with the Rheos device have shown benefit on the background of aggressive pharmacologic therapy. Importantly, acute evaluation of the proper “dose” of Rheos therapy can be easily performed due to its short-term hemodynamic effects which allows for rapid individualized titration. Thus, the ease by which the Rheos device can be modified for an individual patient may provide an incremental benefit to its use above pharmacologic agents.

Given the growth in our aging population and the manifestations of CVD (which maybe mediated by increased SNS activation), the question is who should be considered for this novel therapeutic approach. The final results of the ongoing pivotal trials investigating the safety and efficacy of the device in hypertension and heart failure are eagerly anticipated to provide a more conclusive answer to this question. Consequently, it appears that the time is close at hand for clinicians to apply novel device-based therapy, such as Baroreflex Activation Therapy, in addition to drug therapy or possibly, at some point, exclusive of drug therapy for patients with increased arterial stiffness and diastolic dysfunction. There was a substantial reduction of LVMI toward the reference range (Figure 1). Not surprisingly, the rate pressure product (a surrogate for myocardial oxygen demand) was also significantly reduced following 12 months of therapy (17288 ± 571 to 10577 ± 590, p < 0.001). Furthermore, a sub-analysis of 24 patients with chronic kidney disease (CKD; Stage 2: n=11, Stage 3: n=13) indicated that estimated glomerular filtration rate (eGFR) remained unchanged in Stage 2 CKD (78.3±5.8 to 74.9±10.3 mL/min/1.73m², p = 0.20) and 3 CKD (54.2±4.9 to 57.4±11.3 mL/min/1.73m², p=0.34); LVMI was reduced after 1 year of Bx indicating that Rheos Therapy may have favorable renal and cardiovascular effects [16]. Given the appropriate

sympathoinhibition, enhanced parasympathetic activation (as indicated by decreased HR), reduced cardiac workload, and improved arterial compliance, these data taken together provide the basis by which one might suggest that patients already in the CVD continuum (i.e., heart failure with preserved ejection fraction, chronic kidney disease, etc.) may also benefit from this potential therapy. Indeed, a feasibility study of the Rheos System in patients with congestive heart failure patients is currently underway enrolling patients in Europe and the U.S.-based heart failure pivotal trial has begun enrollment. Of course, application of the Rheos System to these other patient populations must await ongoing clinical trial evaluations.
with resistant hypertension and possibly other cardiovascular disorders.

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REFERENCES


