In silico trial of baroreflex activation therapy for the treatment of resistant hypertension

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Introduction: Approximately 10% of US patients have resistant hypertension (HTN), or uncontrolled blood pressure (systolic blood pressure, SBP > 140 mmHg) even with the use of ≥3 drugs, estimated to cost >$10 billion. Clinical trials evaluating the efficacy of chronic electrical stimulation of the carotid baroreflex in the treatment of resistant HTN are ongoing. However, the mechanisms that account for its sustained cardiovascular effects are still unclear. This lack of knowledge adds to the uncertainty as to which patients are most likely to benefit from this therapy.

Materials and Methods: We used an established, integrative mathematical model of human physiology, HumMod, that is comprised of over 8000 variables and previously used to validate cardiovascular responses after baroreflex activation therapy (BAT)\(^1\). First, we generated 3000 unique models (virtual patients) and subjected them to a 3 drug protocol for 1 month (thiazide, ACE inhibition, and calcium channel inhibition). We conditioned the nonresponding virtual patients on individual level data from African American males with resistant HTN. The resulting population induced a distribution on HumMod’s parameters that was sampled to generate a new virtual population who were then subjected to BAT for 1 month.

Results and Discussion: At baseline, 664 virtual patients had HTN despite the 3 pharmacological therapies (144 ± 1 mmHg SBP). As compared to non-responders (<15 mmHg fall in SBP), responders to BAT (>30 mmHg fall in SBP) had greater reductions in renal sympathetic nerve activity (RSNA) and angiotensin II and potentiated increases in atrial natriuretic peptide, all of which improved renal hemodynamic responses and significantly decreased renal vascular resistance (Figure 1). These data suggests in a population model of resistant HTN, important factors that play a role in the response to BAT may be related to RSNA suppression and the ability to renal vasodilate during decreases in blood pressure.

![Figure 1](image1)

**Figure 1.** Virtual responses to 1 month BAT, groups stratified by the fall in SBP: <15, 15-20, 20-30, and >30 mmHg. Variables include the changes in systolic blood pressure (SBP), renal sympathetic nerve activity (RSNA), angiotensin II (ANG II), atrial natriuretic peptide (ANP), renal blood flow (RBF), and afferent arteriolar (Aff) resistance; *p<0.05 vs. <15.

Translational Impact: While the response to BAT in clinical trials has shown promise, the mechanisms of nonresponse to this device are unknown. Physiological factors that may play an important role include the inability to maintain renal hemodynamics through neural and hormonal mechanisms.

No Disclosures.