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# Carvedilol Reverses Standing Parasympathetic Excess in Non-Diabetics

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## INTRODUCTION

There is a segment of the patient population that presents with beta-blockers on board and with difficult to control BP, difficult to control blood sugars (as in diabetic patients), or difficult to control hormone levels (as in hypothyroid or menopause patients). These patients also present with fatigue or exercise intolerance, depression-like symptoms, sleep difficulties (requiring a long time to fall asleep, or frequent waking at night, even to go to the bathroom), GI upset (upper or lower), or frequent headache or migraine. The established need for a beta-blocker indicates a previous or continued sympathetic excess (SE). The additional symptoms are associated with parasympathetic excess (PE) [1]. The novelty is that the PE that occurs manifests during *sympathetic* challenges in a standard autonomic study (*e.g.*, Valsalva and head up postural change or stand challenges). This is a dynamic autonomic imbalance. In these patients (with a beta-blocker on board), anti-cholinergic therapy to address the additional (P) symptoms may be contra-indicated, given the need for the beta-blocker or the potential effects of the anti-cholinergic on BP.

To detect the dynamic autonomic imbalance, PE, both P&S need to be measured independently and simultaneously. Heart rate variability alone (HRV-alone) measures are mixed, dependent measures of autonomic function [2]. As a result, HRV-alone measures offer inconsistent, confounding measures that are often not clinically trended [3,4,5]. The reason for this difficulty is that HRV-alone is but a single independent measure of a system with two independent components. A second, independent, measure of the autonomic nervous system (ANS) is required. This is a fundamental principle of mathematics underlying science and engineering. A tested and convenient second measure of P & S is respiratory activity (RA) [6,7,8,9]. HRV analysis coincident with RA analysis provide independent, simultaneous measures of P & S [10,11] that are clinically trended. This approach is the P&S method.

Beta-blockers are known to restore autonomic balance, the relative responses of the parasympathetic (P) and sympathetic (S) nervous systems, specifically by decreasing S activity, including S activity to the heart [12]. Indirectly, they may also increase P activity at the heart

[13]. Increased P activity is associated with greater longevity in geriatric and heart disease patients [14,15]. Among the different beta-blockers, Propranolol and Metoprolol have been studied before for their effect on diabetic autonomic nerve dysfunction [16,17]. The problem with these agents is that they have an incomplete S blockade with only pure beta-inhibition and increased unopposed alpha-receptor activity.

The third-generation beta-blocker, Carvedilol, is a double cocktail, consisting of both a non-selective beta-adrenergic antagonist (a beta-blocker) and an alpha-1 adrenergic antagonist (alpha-blocker). The beta-blocker component affects both beta-1 and beta-2 adrenoreceptors. The alpha-blocker provides a vasodilation effect [18]. In addition Carvedilol also provides an antioxidant effect and suppresses Endothelin biosynthesis [19]. Mortality reduction with Carvedilol compared to Metoprolol appears to be relatively non specific and could be consistent with a superior effect of Carvedilol on cardiac function [20], or alternatively, differences in P and S balance.

In the past, it has been documented that nonselective β-adrenergic blockers, such as that of Carvedilol, have the ability to reduce cardiac S activity, both when given acutely and during sustained therapy [21,22]. These studies also showed that the selective β-adrenergic blocker Metoprolol had varying effects on cardiac S activity, increasing it with acute administration, while having a neutral effect during chronic therapy [21]. The mechanism of this differential effect appears to result from the ability of Carvedilol to block pre-junctional β-2-adrenergic receptors, thus inhibiting Norepinephrine release [23]. Support for the pre-junctional nature of this effect comes from extensive animal experimentation, as well as from the observation in humans, that Carvedilol reduces Norepinephrine spillover, while having no impact on peripheral S nerve firing rates [22,23,24,25] . Carvedilol was administered in place of the beta-blocker to address the additional symptoms due to PE.

This study is not funded or influenced in any way by the manufacturer of Carvedilol.

## METHODS

Serial ANS assessments were administered to 238 Patients (145 Female, 60.8%; averages: 60.1±12.0 years; 63.3±3.8 inches; 150.4±36.7 pounds) in 12 ambulatory clinics. ANS assessment was performed with the ANX-3.0 Autonomic Monitor (ANSAR Medical Technologies, Inc., Philadelphia, PA). ANS assessment included 1) five minutes of rest, 2) one-minute of paced or deep breathing, 3) a series of five short Valsalva maneuvers (15 seconds or less), and 4) a quick head-up postural change (stand) followed by five minutes of quiet standing. HR variability (HRV) analysis concurrent with respiratory activity (RA) analysis was performed to independently and simultaneously compute P&S activity [26,27]throughout the phases of the ANS study.

## RESULTS and DISCUSSION

Patients, on average, were well maintained at rest. They presented (see Table) with low normal HR, normal BP, normal S activity ($1.0 < S < 10.0$ bpm$^2$), low-normal P activity (normal resting P activity: $1.0 < S < 10.0$ bpm$^2$), and normal sympathovagal balance (SB = S/P: $0.4 < SB < 3.0$). Upon standing, patients presented with normal S responses but abnormal P responses. The expected (normal) S response to stand is an increase of between 120% and 500% from rest. The expected P response to stand is an *increase* from rest. Patients were switched from their beta-blocker to dose equivalent or lower (if their history permitted) Carvedilol (6.25mg bid on

average) and retested 4.1±1.1 months later. Their resting P and S responses remained normal, but their SB became low-normal ($0.4 < SB < 1.0$). Low-normal SB indicates extra, but not excessive, resting P activity. Excessive (relative) P activity ($SB < 0.4$) is associated with depression [1]. Extra, but not excessive, P activity (low-normal SB) is recommended in the geriatric cardiology literature [28] to minimize morbidity and mortality.

The stand responses of these patients were normalized. The stand S response was reduced, but remained normal and the stand P response (PE) was corrected. Patients' post-therapy, P responses to stand included an (expected) decrease with respect to the resting level, rather than the prior abnormal increase. Clinically, patients reported less fatigue or exercise intolerance, improvements in sleep habits (falling asleep in under 20 minutes and fewer waking episodes during the night), a reduced dependency on any prescribed anti-depressants, reduced GI upset as indicated by a reduced dependency on antacids or heart-burn medications, and fewer headache or migraine episodes.

## CONCLUSION

The two agents included in Carvedilol seem to provide additional benefits for non-diabetics requiring a beta-blocker. A questionnaire-based study is planned to substantiate the clinical findings regarding the secondary symptoms of dynamic PE, including: fatigue or exercise intolerance, depression-like symptoms, sleep difficulties, GI upset, or frequent headache or migraine. Studies considering the hemodynamic affects of Carvedilol and single agent beta-blockers have already borne out the clinical findings on the primary effects of Carvedilol [*e.g.*, 21,22,24]. Carvedilol can help to restore normal autonomic balance, both resting and in responses to challenges, in patients with both S excess and (dynamic) PE.

**Table**: Patient hemodynamic and autonomic responses, pre- and post-Carvedilol therapy.

| Measure | Pre-Carvedilol | Post-Carvedilol |
|---|---|---|
| Resting HR (bpm) | 61.5±8.5 | 60.8±8.0 |
| Resting Systolic BP (mmHg) | 137.4±26.7 | 128.5±23.4 |
| Resting Diastolic BP (mmHg) | 65.8±10.1 | 62.4±8.4 |
| Resting Sympathetics ($bpm^2$) | 1.10±0.7 | 0.63±0.2 |
| Resting Parasympathetics ($bpm^2$) | 0.77±0.3 | 0.80±0.4 |
| Resting Sympathovagal Balance | 1.72±0.2 | 0.90±0.4 |
| Stand Sympathetic Response | 4.67±2.1 | 1.19±1.0 |
| Stand Parasympathetic Response | 2.02±0.4 | -1.17±0.3 |

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