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Age Matched Attenuation of Both Autonomic Branches in Chronic Disease: I. Hypertension

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BACKGROUND

In the United States, more people have or have had high BP than any other disease. It is estimated that more than 60 million patients are diagnosed with hypertension [1]. Hypertension is well known to place patients at risk for heart disease, kidney disease, vascular disease, retinal disorders, stroke, and aneurysm, to name a few [2]. Chronic disease increases the morbidity and mortality risk through accelerating parasympathetic and sympathetic (P and S) decline [3,4,5] and the onset of cardiovascular autonomic neuropathy (CAN) [2,6,7,8]. Hypertensives are investigated to determine if hypertension follows the same pattern as other chronic diseases [9].

It is well known that from the autonomic nervous system only the sympathetic nervous system (SNS) innervates the vasculature, thereby controlling peripheral resistance. Both the P and S nervous systems innervate the heart and control HR (chronotropic activity) and strength of compression (inotropic activity). The SNS mediates baroreceptor reflex, which in turn mediates BP. The angiotensin-renin system controls fluid levels in the body, including blood volume. The angiotensin component is part of the SNS [1,2,3]. Therefore, conditions or activities that result in persistent or chronic increases in sympathetic activity (sympathetic excess or SE), including emotional and psychological, as well as physiological, stress can lead to chronic increases in BP and ultimately hypertension [2]. Conversely, prior to organ damage (*e.g.*, heart or vasculature), conditions or activities that reduce sympathetic activity, including stress management programs, as well as beta-blockers and anti-hypertensives, decrease sympathetic activity, and thereby can decrease BP and relieve hypertension [2].

P&S Monitoring vs. HRV-alone

Autonomic dysfunction as evidenced by reduced low frequency (LF) and high frequency (HF) power of baseline heart rate variability (HRV) has been implicated in chronic hypertension. However, thus far there is very little consensus on the validity of the correlation between LF power and hypertension. Moreover, LF power from traditional HRV analysis (HRV-alone) has been shown to be an inaccurate indicator of sympathetic activity [10,11]. From the HRV standards report, published in *Circulation* [12] and the *European Heart Journal* [13], LF is

sympathetic activity as modulated by parasympathetic (Vagal N.) activity. HRV-alone measures are mixed measures, requiring assumption or approximation to assess P and S activity [14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29].

P and S Nervous System profiling, using HRV and respiratory activity (RA) analyses simultaneously, yields accurate, independent, simultaneous measures of sympathetic activity (LF Area or LFa), parasympathetic activity (Respiratory Frequency Area or RFa), and sympathovagal balance (SB = resting LFa/RFa ratio) [10,30]. By adding the second independent measure, RA, to the independent measure, HRV, P&S profiling completes the analyses required by fundamental mathematics for fully characterizing a system with two independent components [31,32,33,34].

With independent, simultaneous measures of P and S activity, a causal relationship between hypertension and sympathetic activity may be possible. Furthermore, a potential relationship between parasympathetic activity and hypertension may also be possible. This study considers the relationship between the resting sympathetic activity (relative to parasympathetic activity) and the chronic disease, hypertension [2].

METHODS

Serial P&S Monitoring (ANX-3.0 Autonomic Monitor, ANSAR Medical Technologies, Inc., Philadelphia, PA) was performed on 79 consecutive hypertensive patients (Females = 5; Age = 66.6 ± 12.2) from two large ambulatory cardiology clinics, one near Chicago, IL and the other near New York, NY. Patients were assessed as they were, with anti-hypertension medication on board and with or without co-morbidities (Diabetes = 45; Coronary Artery Disease = 46). The data were compared with preexisting data for 112 age-matched, normal controls (Ages 40-90) with no history of diabetes, or cardiovascular and autonomic disorders. The controls are from a database that has been collected over the past decade. P&S Monitoring is based on patient responses to a standard clinical study that includes a 5-min resting baseline. Normal adult ranges for P and S are 1.0 to 10.0 bpm^2. Resting P or S levels below 1.0 bpm^2 indicate advanced autonomic dysfunction (see the broken horizontal line in the figure). Resting parasympathetic levels below 0.1 bpm^2 indicate cardiovascular autonomic neuropathy (CAN). CAN indicates risk of sudden cardiac death, and may be normal for geriatric patients, or post-MI and post-CABG patients. Normal SB is between 0.4 and 3.0. As Umetani, *et al*. indicate, more resting parasympathetic activity is beneficial for geriatric patients to reduce morbidity and mortality. This translates to low-normal SB as the recommended normal for geriatric patients ($0.4 < SB < 1.0$). CAN with high SB indicates high risk for sudden cardiac death. Low-normal SB minimizes morbidity and morality risk [6]. Patients with arrhythmia were excluded. Data were analyzed with SPSS 14.0.

RESULTS

A student T-test was performed given the low number of females in this cohort. The T-test finds that the females' results are statistically similar to the males ($p=0.016$). Table 1 presents the average P and S responses, along with the respective standard deviations, for both the hypertensives and the normal subjects. These data are plotted in the figure: red is the respective average, resting sympathetic responses and blue are the parasympathetic responses. The acceleration in sympathetic decline causes the average 60-year-old hypertensive to be similar to the average 80-year-old normal subject. Table 2 presents the average (resting) sympathovagal balance responses and resting BP measures. Overall, the average SB for the hypertensives is

more than double that for the normal subjects, and the (medicated) hypertensives' resting BP is higher than that for the normal subjects.

On average, resting P and S levels were found to be significantly reduced in chronic hypertension patients compared to age-matched, normal controls (see Figure and Table 1). The normal subjects' resting responses revealed that the P and S activity normally decreases with age. The differences between normal controls and hypertensives indicate that the hypertensive patient demonstrates an accelerated decline over that of the normal subject. The differences between resting P and S function are much more marked in the younger population and gradually decrease with age. These trends were observed regardless of any co-morbidities or medications. The P and S values for 45-year-old hypertension patients were similar in magnitude (or lower) than those of 85-year-old normal controls (see Table).

DISCUSSION

Excess S activity relative to parasympathetic activity at rest (high sympathovagal balance [SB=S/P]) is associated with high BP and hypertension [8]. Even with anti-hypertension medication on aboard, and their BPs controlled (average BP for the cohort was 133/84), the hypertensives presented at ages 45 and 55 with average SB nearly double that of the normals (see Table 2).

In the hypertensive patients, there is an average increase in P and S levels from age 45 to 55, before they decrease again by age 65. This increase may be due to the greater presence of anti-hypertension therapy in the patients in their fifth decade as compared to their fourth, helping to relieve some (functional) autonomic dysfunction. Although the average BP is lower, the average SB is higher in the 50-year-olds as compared to the 40-year-olds, suggesting that some patients may benefit from additional anti-hypertensive therapy to maintain a lower SB. The decrease that follows is nearly parallel to the age-matched normal subjects for about two decades and is presumed to be due to the continuing aging effect.

Another feature of these data is the difference between the P & S levels in the two groups by age 85. For the normals, P is greater than S, which has been shown to be associated with reduced morbidity and mortality [9]. For the hypertensives, the opposite is the case, with the sympathetic level much higher than the parasympathetic level, as compared with normals. SE is known to be a cause of hypertension and the patients' increased morbidity and mortality. In the earlier years, the normal subject's P and S nearly overlie each other, indicating a normal balance. Normal balance is known to promote reduced mortality and morbidity [4]. Only after therapy is prescribed and complied with (by age 65) do the resting P and S responses for the patients overlie each other, until late in life as discussed above.

CONCLUSION

Early resting SE (relative to resting parasympathetic levels, or high SB) is the autonomic condition associated with hypertensive patients. Between these two cohorts, both P and S activity appear to be significantly decreased in chronic hypertensives compared with age-matched normal controls. Whether these observations suggest autonomic decline as the effect of hypertension, or as the cause of hypertension, still remains to be established. These data suggest that autonomic assessment can guide therapy. Anti-hypertensive therapy reduces sympathetic activity relative to parasympathetic activity, thereby reducing SB. Reducing SB in hypertensive patients (on average) helps to establish and maintain normal autonomic balance. Normalizing

autonomic balance earlier can reduce morbidity and mortality in the hypertensive patient, thereby reducing hospitalizations and health care costs.

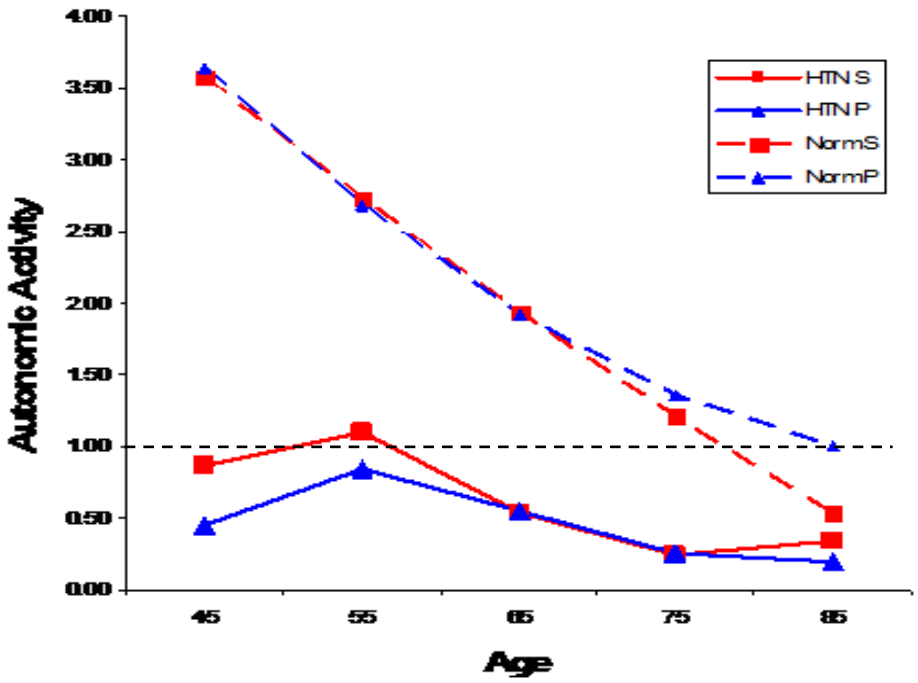

Figure: Baseline (Bx, or resting) autonomic changes with age in Hypertensives. The broken curves represent age matched Normals. The solid lines represent the hypertensive patients. The red lines represent average resting sympathetic activity (in bpm^2) within the cohort. The blue lines represent average resting parasympathetic activity (in bpm^2) within the cohort. The horizontal broken line indicates advanced autonomic dysfunction.

Table 1: Baseline (Bx, or resting) autonomic changes with age in (medicated) Hypertensives and in Normals.

	Hypertensives			Normals		
Mean Age	S	P	N	S	P	N
43.0	0.87±0.12	0.45±0.14	8	3.58±0.24	3.64±0.52	28
54.3	1.11±0.59	0.84±0.53	18	2.73±.36	2.68±0.41	18
62.9	0.54±0.22	0.55±0.40	24	1.94±.40	1.92±0.47	15
74.2	0.25±0.10	0.25±0.07	14	1.21±.36	1.39±0.33	8
83.2	0.34±0.11	0.19±0.05	15	0.54±.35	1.00±0.14	3

Table 2: Average resting BP changes with age in (medicated) Hypertensives and in Normals.

	Hypertensives		Normals	
Mean Age	SB	BP	SB	BP
43.0	2.55	130/84	1.63	129/79
54.3	2.97	127/76	0.93	123/79
62.9	2.75	128/72	0.87	127/78
74.2	2.00	133/68	0.87	128/78
83.2	2.94	123/59	0.77	114/64

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