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Age Matched Attenuation of Both Autonomic Branches in Chronic Disease: II. Diabetes Mellitus

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BACKGROUND

In the United States, there are an estimated 40 million patients diagnosed with diabetes, and half again more are suspected of having the disease [1]. Diabetes is well known to place patients at risk for heart disease, kidney disease, vascular disease, hypertension, and neuropathy, including autonomic neuropathy, to name a few [2,3]. Chronic disease increases the morbidity [3] and mortality risk [2], through accelerating parasympathetic and sympathetic (P and S) decline [4,5,6] and the onset of cardiovascular autonomic neuropathy (CAN) [2,7,8]. Patients with diabetes are investigated to determine if diabetes follows the same pattern as other chronic diseases [9].

Diabetes is well known to involve [10,11], and degrade [2,3,12], the ANS, shortening a patient's life expectancy through increased mortality risk, and it leads to a cascade of co-morbidities that can involve virtually every organ system [13]. The American Diabetes Association recognizes the increased risk, even in the very early stages, by stating that diabetic patients, upon first diagnosis, should have their P and S tested [12,14,15].

While diabetic neuropathy, starting with diabetic peripheral neuropathy, involves the sensory, motor and autonomic nervous systems, the P and S consequences of the disease were largely assumed to coincide with the sensory motor changes. This assumption was due to the fact that non-invasive, independent, simultaneous measures of P and S measures were not available. Assuming autonomic neuropathy progresses at the same rate as diabetic peripheral neuropathy may have been the best approximation available. It is now known to be largely in error. The cost of this assumption is measured in pain and suffering, and lives lost. It is true that sensory motor losses affect quality of life, but if the nerves that control the heart and vasculature are dysfunctional and the heart stops, what does it matter? Frequent and periodic, independent, simultaneous P&S Monitoring detects the early changes in autonomic function (P and S imbalance) that lead to involvement and degradation of the other organ systems [16]. Restoring P and S balance slows the progression of autonomic decline [2,3,9,17,18,19,20,21,22].

Autonomic decline includes (in order) Peripheral Autonomic Neuropathy (PAN), then Diabetic Autonomic Neuropathy (DAN), and finally Cardiovascular Autonomic Neuropathy (CAN).

PAN is characterized by poor peripheral circulation [12,15,23], including peripheral vascular control that can result in orthostasis. Poor peripheral circulation results in dysfunction such as poor wound healing and dry skin that facilitates wound genesis. PAN does not involve sensory and motor deficits, causing paralysis and parasthesia. In fact, if it can be felt, it is not PAN. DAN is characterized by resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure [12,15,23,24]. DAN affects many organ systems throughout the body, including the kidneys and the retina [12,15,23,24], increasing mortality risk. [2,24].

Sympathetic excess is associated with hypoglycemia [25]. One, early hypoglycemic event (typically asymptomatic) can cause (asymptomatic) SE [26], leading to secondary hypertension and the start of the cascade of secondary symptoms that characterize PAN and then DAN [26]. Establishing and maintaining normal P and S balance slows the progression of autonomic dysfunction, reducing risk of morbidity and mortality [2,3], reducing medication load, reducing hospitalizations, improving patient outcomes, and reducing healthcare costs [5].

Ultimately, CAN (the end stage) is demonstrated. CAN is measured as very low parasympathetic activity (with P&S Monitoring CAN is defined as RFa < 0.1 bpm^2). CAN indicates risk of sudden cardiac death and may be normal for the geriatric patient with diabetes, or post-MI or post-CABG patients with diabetes. However, CAN with SE (SB > 3.0) indicates high risk of sudden cardiac death. Given that autonomic dysfunction is asymptomatic until very late in the disease, independent, simultaneous P&S Monitoring is required to diagnose and differentiate parasympathetic insufficiency (CAN) with SE (CAN with SE indicates high risk of sudden death). In fact, the American Diabetes Association recommends early and frequent P&S Monitoring [12,15,23] to stay autonomic neuropathy as long as possible. The ADA specifies that P&S Monitoring is recommended as part of the standard of care for diabetes [12,15,23] . That early detection and correction of P and S imbalance (dysfunction), and maintaining normal P and S balance reduces the risk of morbidity and mortality [5].

Another reason for more accurate measures of P and S activity is that DAN and CAN places a patient at increased risk of mortality under general anesthesia. Pre-operative P and S assessment is required since DAN and CAN are often asymptomatic. If undetected or unreported, the mortality risk is exacerbated. [27,28]

See "P&S Monitoring vs. HRV-alone" subsection in the "Introduction" of "Age Matched Attenuation of Both Autonomic Branches in Chronic Disease: I. Hypertension" for a short discussion of the background to independent, simultaneous P and S assessment. With independent, simultaneous measures of P and S activity, a causal relationship between diabetes and autonomic dysfunction leading to autonomic neuropathy and eventually CAN may be possible. This study considers the relationship between the resting P and S activity and duration of the chronic disease, diabetes.

METHODS

Serial P&S Monitoring (ANX-3.0 Autonomic Monitor, ANSAR Medical Technologies, Inc., Philadelphia, PA) was performed on 511 consecutive patients diagnosed with type 2 diabetes mellitus (Females = 248; age = 63.4 ± 13.1, range 25 to 96) from four large ambulatory endocrinology clinics, one near Norfolk, VA, one near Baltimore, MD, one near Philadelphia, PA, and one near Albany, NY. Patients were assessed as they were, currently treated for

diabetes and co-morbidities, including hypertension (56.1%) and coronary artery disease (25.2%). The data are compared with preexisting data for 234 age-matched, normal controls (ages 25-90) with no history of diabetes, hypertension, cardiovascular, autonomic, or other diagnosed disorders. The controls are from a data based 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 DAN (the diabetic term for advanced autonomic dysfunction). DAN is marked on the figure by the broken horizontal line. Resting parasympathetic levels below 0.1 bpm^2 indicate CAN (see figure). 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 [7]. Patients with arrhythmia were excluded. Data were analyzed with SPSS 14.0.

RESULTS

Table 1 presents the average and standard deviations of the P and S responses, for both the diabetic patients 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 35-year-old diabetic patient to be similar to the average 70-year-old normal subject. Table 2 presents the average (resting) sympathovagal balance responses and resting BP measures. Overall, the average SB for the diabetics is higher than that for the normal subjects, and the diabetics resting BP is higher than that for the normal subjects. Within this cohort, both the diabetics' and normals' BP and SB trended. In general, higher SB responses (suggesting a higher resting, average sympathetic response), are associated with higher, resting BP responses, and vice versa (see Table 2).

Overall, resting P and S levels were found to be significantly reduced in patients with diabetes as 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 diabetics indicate that the patients with diabetes demonstrate an accelerated autonomic decline over that of the normal subject. The differences between resting P and S function are much more marked in the middle aged population (30s to 50s, see figure) and gradually decrease with age. The decrease is apparently correlated with improved patient compliance with therapy and lifestyle modification recommendations. The patients' gross differences seem to stabilize after age 65 (on average) when the P and S responses parallel the normals' resting responses, returning to the "normal" aging trend, albeit at a significantly reduced level. These trends were observed regardless of any co-morbidities or medications. The P and S values for 35-year-old patients with diabetes were similar in magnitude (or lower) than those of the 65-year-old normal controls (see Table). Both indicate an advanced state of autonomic dysfunction, also known as DAN in the diabetic patients.

DISCUSSION

In the patients with diabetes, there is a significant slowing of the decline in both P and S activity from age 45 to 64. On average, this corresponds with the period in the patients' disease course when end-organ dysfunction is demonstrated and symptoms present. As a result, therapy and

lifestyle modification recommendations are adhered to, which establish SB nearer to 1.0 (perfect balance) and slow autonomic decline. The decrease that follows nearly parallels the age-matched normal subjects and is presumed to be due to the continuing aging effect. This suggests that with the return to more normal SB, the accelerated decline si normalized to the (average) aging effect.

Another feature of these data is the difference between the P & S levels in the two groups by age 75. For the normals, P is greater than S, which has been shown to be associated with reduced morbidity and mortality [9]. For the diabetics, the opposite is the case, with the sympathetic level much higher than the parasympathetic level as compared with normals. SE is known to be associated with increased risk for morbidity and mortality [29]. In the middle years, the patients' P and S nearly overlie each other, indicating a normal balance. Normal balance is known to promote reduced mortality and morbidity [5]. The increase in morbidity and mortality for the older diabetics as compared with the normals may be due to the higher SB responses, indicating a relative, resting SE..

CONCLUSION

Between these two cohorts, both P and S activity appear to be significantly decreased in the diabetic patients as compared with age-matched normal controls. Whether these observations suggest autonomic decline is an effect of type 2 diabetes, or contributes to the cause of type 2 diabetes, remains to be established. These data suggest that autonomic assessment can guide therapy. Therapy to reduce sympathetic activity relative to parasympathetic activity reduces SB. Reducing SB in patients with diabetes (on average) helps to establish and maintain normal autonomic balance. Normalizing autonomic balance earlier can reduce morbidity and mortality in the diabetic patient, thereby reducing medication-load, hospitalizations and health care costs.

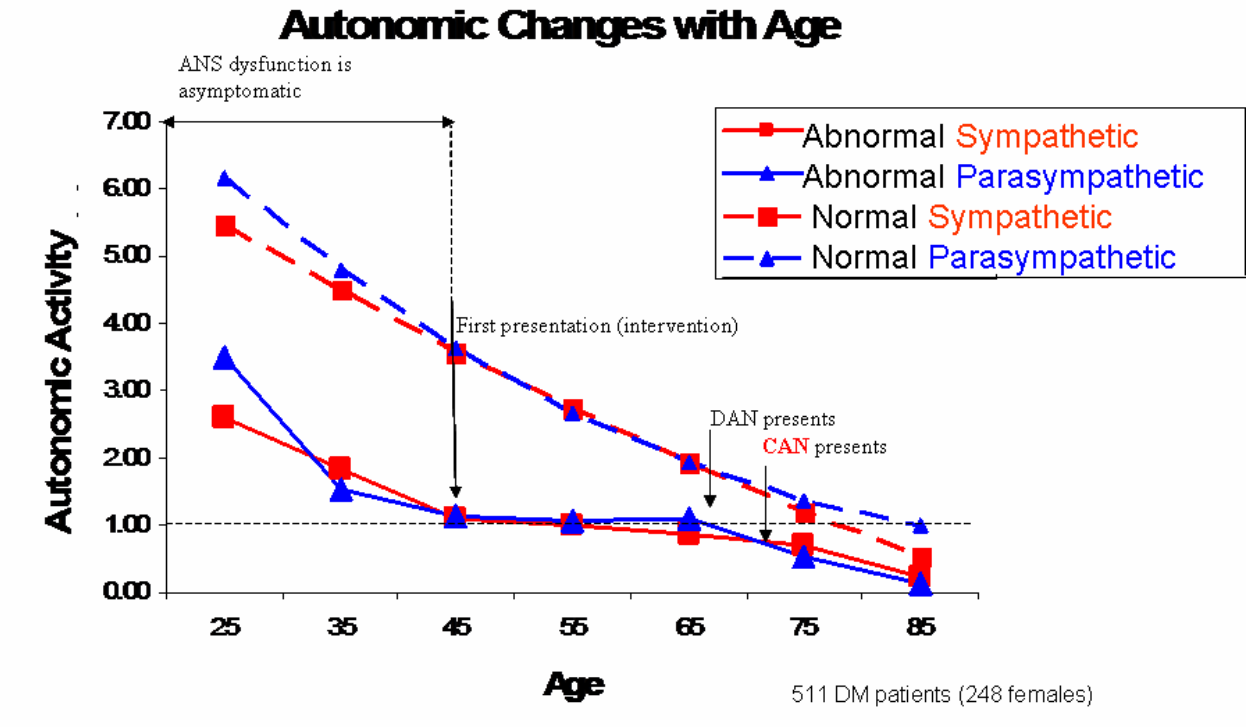

Figure: Baseline (Bx, or resting) autonomic changes with age in patients diagnosed with type 2 diabetes. The broken curves represent age matched normals. The solid lines represent the patients diagnosed with diabetes. The red lines represent average resting sympathetic activity (in bpm^2) within the cohort. The blue lines represent average resting parasympathetic activity (in bpm^2) within the cohort. The horizontal broken line indicates DAN.

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

	Diabetics			Normals		
Mean Age	S	P	N	S	P	N
26.5	2.61±1.07	3.51±1.05	17	5.46±	6.16±	39
35.9	1.84±0.75	1.55±0.55	21	4.49±	4.80±	40
43.0	1.10±0.55	1.12±0.69	59	3.58±0.24	3.64±0.52	28
54.3	1.00±0.67	1.06±0.37	116	2.73±.36	2.68±0.41	18
62.9	0.87±0.23	1.11±0.45	109	1.94±.40	1.92±0.47	15
74.2	0.69±0.36	0.54±0.16	156	1.21±.36	1.39±0.33	8
83.2	0.24±0.16	0.15±0.07	33	0.54±.35	1.00±0.14	3

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

	Diabetics		Normals	
Mean Age	SB	BP	SB	BP
26.5	0.65	123/74	0.89	120/61
35.9	2.20	133/77	0.99	124/68
43.0	0.98	121/78	1.63	129/79
54.3	1.06	130/83	0.93	123/79
62.9	0.84	129/77	0.87	127/78
74.2	1.46	130/80	0.87	128/78
83.2	1.90	131/80	0.77	114/64

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