

Differentiation Of Autonomic Dysfunction By Enhanced Frequency Domain Analysis Reveals Additional Stages In The Progression Of Autonomic Decline In Diabetics

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Background: The three clinical stages of autonomic dysfunction are: 1) Peripheral Autonomic Neuropathy (PAN), 2) Quality of Life Compromise (QOL; including Orthostasis), and 3) Diabetic AN (DAN) or Cardiac AN (CAN). Autonomic dysfunction before PAN is asymptomatic. EFDA reveals three additional stages.

Methods: Serial ANS tests were performed on 389 diabetics (ages 22 to 93) while performing EFDA (LFa is a measure sympathetic nervous system activity, RFa is a measure of parasympathetic activity). ANS tests include: a resting baseline (Bx) period, a paced, rhythmic, deep breathing (DB) period, a Valsalva (V) challenge, and a rapid postural change (PC) to and followed by a period of quiet upright posture. Sympathetic Withdrawal (SW) is defined as a decrease in sympathetic activity from a seated or supine resting posture to an upright posture. SW indicates Orthostasis ($SW = (PC\ LFa) - (Bx\ LFa)$). A sympathetic change from resting to upright that is greater than 0.0 bpm^2 indicates a sympathetic surge and is normal. Except the SW results (for clarity), the data are normalized to age 25. DAN is defined as the patient state for which the parasympathetic measure, RFa, is less than 0.5 bpm^2 but greater than 0.1 bpm^2 ($0.5\text{ bpm}^2 > RFa > 0.1\text{ bpm}^2$). CAN is defined as the patient state for which the parasympathetic measure, RFa, is less than 0.1 bpm^2 ($RFa < 0.1\text{ bpm}^2$).

Results: The resting parasympathetic (Bx RFa) response declines rapidly and stabilizes by age 35. Another decline occurs around 65 when the average Bx RFa becomes less than 0.1 bpm^2 , indicating cardiac instability and DAN. The resting sympathetic (Bx LFa) response declines gradually until age 45. The decline slows until age 75, then increases sharply. The sharp increase indicates poor cardiac control and CAN. The parasympathetic response to deep breathing (DB RFa) declines until age 45 then changes to a shallower slope. The sympathetic response to Valsalva challenge (V LFa) is relatively level until age 35. The V LFa decline accelerates from age 35 to age 45, it becomes almost zero between ages 45 and 65, and then increases sharply from age 65 to age 85. Although positive (greater than zero), the expected sympathetic surge from resting to upright posture decreases rapidly between ages 25 and 35, then stabilizes until age 55. The sympathetic surge becomes negative (defining a SW) between ages 55 and 75; coincident with the onset of Orthostasis and QOL degradation. The subsequent recovery and stabilization in the sympathetic surge (the change in sympathetic activity above 0.0 bpm^2) seems to be due to clinical intervention. The DAN and CAN periods are coincident with cardiac arrhythmias.

Conclusions: Different rates of ANS decline seem to differentiate six phases of autonomic dysfunction: 1) an initial parasympathetic decline, 2) a resulting sympathetic release, 3) an eventual sympathetic decline, 4) the onset of SW which seems to be coincident with QOL compromise, 5) the onset of DAN, and 6) the onset of CAN.

INTRODUCTION

We have reported that enhanced frequency domain (fd) analysis (EFDA) of heart rate variability (HRV) can differentiate ANS dysfunction before structural deficits or autonomic neuropathy presents. Clinically, there are presently identified three stages of autonomic disorder: 1) Peripheral Autonomic Neuropathy (PAN), 2) Quality of Life Compromise, and 3) Diabetic Autonomic Neuropathy (DAN) or Cardiac Autonomic Neuropathy (CAN). Typically, the first stage and any autonomic dysfunction prior to onset of peripheral autonomic neuropathy is difficult to diagnose due to its asymptomatic nature. The differentiation afforded by EFDA seems to reveal additional stages that occur prior to PAN.

METHODS

Two or more ANS tests were performed on 389 adult diabetic patients (ages 22 to 93). The average age of the cohort is 63.2 (the range is from 25 to 96), with 161 females (see Table 1). The cohort includes 354 NIDDM patients with an average age of 63.5 years and 35 IDDM patients with an average age of 61.1 years.

Table 1: Population Age Data

Age Range	Numbers	Average Age	Females
< 31	2	26.5	1
31 to 40	15	35.9	7
41 to 50	43	45.6	21
51 to 60	84	56.0	30
61 to 70	79	66.3	35
71 to 80	113	75.0	53
> 81	24	83.4	13

The tests each included four autonomic challenges separated by baseline periods. The four challenges were 1) an initial resting baseline (Bx), 2) a parasympathetic challenge of paced, rhythmic, deep breathing (DB), 3) a sympathetic challenge of a series of 5 short Valsalva maneuvers (V), and 4) a system challenge of a quick postural change from seated or supine rest to upright posture followed by quiet period of up right posture (stand, S). Throughout the test heart rate (HR) and blood pressures (BP) were collected and the EFDA parameters (LFa, RFa, and LFa/RFa) representing measures of sympathetic activity, parasympathetic activity, and sympathovagal balance, respectively, were computed from the EKG and the respiratory activity [see Vinik, *et al.*, 2005a, Figure 1 for computational methodology]. From these data, the patient's autonomic parameters were read at rest and in response to the clinical challenges.

RESULTS

Figure 1 presents data from: 1) the parasympathetic response to deep breathing (DB RFa); 2) the sympathetic response to Valsalva (V LFa); 3) the sympathetic and parasympathetic responses to resting (initial) baseline (Bx LFa and Bx RFa, respectively); and 4) the net sympathetic response to upright posture (S). Except the stand (S) results, the data are normalized to 50 bpm² at age 25 years.

The lowest curve is comprised of points that are computed by taking the average LFa during the upright posture period and subtracting the average LFa during the initial resting baseline (the sympathetic activity during quiet standing, S, less the resting baseline sympathetic activity, Bx LFa, is represented by the symbol 'S-Bx LFa'). The result indicates the magnitude of the sympathetic change during standing. This is expected to be greater than 0.0 bpm². Anything less than 0.0 bpm² is considered abnormal, and is labeled sympathetic withdrawal (SW).

The data show that in this population from ages 25 to 45, the resting baseline (Bx) RFa (the parasympathetic measure) declines more rapidly and reaches its lows by age 35, whereas the Bx LFa (the resting sympathetic measure) decline is more gradual until 45 and then becomes even more gradual until about 75 years of age. In the last decade presented, both Bx values increase sharply. The DB RFa declines steadily from ages 25 through 85 with a change to a more shallow slope around age 45. The V LFa, however, is approximately level until about age 35 and then declines rapidly until age 45. The slope of the V LFa curve becomes almost flat again from age 45 through age 65, and then becomes steep again from age 65 through age 85. The measure of sympathetic withdrawal (SW) is the stand LFa (S LFa) minus the resting baseline LFa (Bx LFa), as presented on the right-hand axis of the plot in Figure 1. As long as the value is greater than 0.0 bpm², the patient's sympathetics are being stimulated to counter Orthostasis. Although the magnitude of the sympathetic surge upon standing decreases rapidly over the first decade presented, it seems to stabilize for a time. Then between ages 55 and 75 years the measure of sympathetic surge becomes negative, suggesting that the majority of the population experiences SW. The data then show that the population recovers and stabilizes with the sympathetic surge becoming positive again; above 0.0 bpm².

DISCUSSION

In the face of disease, all response measures of ANS activity presented show a significant decline over the first one to two decades. At the beginning of the third decade all of the ANS parameters have begun or are beginning to level off, at least for the first time. Clinically, this seems to be related to the first time the patients report symptoms (*e.g.*, elevated or high BP or HR, overweight, exercise intolerance) and clinical interventions are prescribed [see Vinik, 2005b,c]. Although these symptoms are potentially of ANS origin, typically they are not correlated with the ANS by healthcare providers or patients at this time due to the belief in the asymptomatic nature of early ANS dysfunction. After about two decades of relative stability, the ANS parameters take another down turn. The up-turn during the last decade in a couple of the ANS parameters (specifically the resting parameters) seems to be clinically correlated with the occurrence of cardiac arrhythmias.

The different rates of decline within and between the four ANS parameters presented seem to help define multiple stages of ANS decline as seen clinically. First there is the initial parasympathetic decline as seen on both the dynamic (DB RFa) and static (resting baseline; Bx RFa) responses. Second there is the (resulting) sympathetic over-drive suggested by the relative normalcy in the dynamic sympathetic measure (V LFa) as compared to the declining parasympathetic measures from age 25 to 45. This differential may possibly result in elevated blood pressures due to the stronger sympathetics up modulating the baroreceptor reflex, especially before the sympathetics begin to decline around age 35 [see also Vinik, *et al.*, 2005b].

Third, there is the onset of SW between the ages of 55 and 65 years, on average, as the net sympathetic response to stand drops below 0.0 bpm². SW is an indicator of Orthostasis or pre-

Orthostasis [Stoupakis *et al.*, 2002]. As expected, SW characterized by patient reports of becoming dizzy more often than not upon standing. If left untreated SW eventually results in Orthostasis (including Orthostatic Hypotension, Orthostatic Intolerance, Orthostatic Hypertension, Postural Orthostatic Tachycardia Syndrome, or any of the pre-clinical forms of these disorders). SW also coincides with the onset of QOL compromises (gastro-intestinal upset, and bladder or sexual dysfunction). The data show a correction in SW after age 65. This correction is correlated with the initiation of therapy for Orthostasis or pre-Orthostasis.

Fourth, between the ages of 65 to 75 there is another decline in the ANS parameters. Clinically this is correlated with the onset of neuropathy: diabetic autonomic neuropathy (DAN) or cardiac autonomic neuropathy (CAN). In diabetics, DAN precedes CAN. This is also the case in this cohort. Finally, there is a sharp increase in resting ANS values. Clinically, the sharp increase is correlated with an increase in the cases of cardiac arrhythmias, suggesting the increases are indicative of cardiac instability which can cause cardiac arrhythmias. If the arrhythmic patients are omitted the average resting baseline parasympathetic (Bx RFa) tone is 0.22 bpm^2 with 58% of them presenting with Bx RFa's less than 0.1 bpm^2 . Bx RFa is considered critically low. It indicates a lack of parasympathetic protection for the heart, which if a sustained tachycardic situation should occur, the parasympathetics may not be able to slow the HR. This is regarded as equivalent to the Framingham Heart Study threshold for sudden cardiac death and it has been found in chronic patients to continue to indicate high risk as long as the chronic patient's Bx RFa remains below 0.1 bpm^2 (acute patients follow the five year time course as indicated by the Framingham Heart Study [Tsuji, 1994]) [Adiraju, 2005]. The sub population with Bx RFa's between 0.5 bpm^2 and 0.1 bpm^2 are correlated with DAN patients and those with RFa's less than 0.1 bpm^2 are correlated with CAN patients.

CONCLUSIONS

ANS monitoring seems to differentiate six phases of autonomic decline in diabetics: 1) early parasympathetic weakness, 2) excess sympathetic activity, 3) sympathetic weakness, 4) quality of life compromise, 5) DAN, and 6) CAN. Table 2 proposes a comparison of these six phases to the currently accepted three clinical phases of autonomic neuropathy,.

TABLE 2: A hypothetical correlation between the six physiologic phases of autonomic decline and the currently accepted three phases of clinical autonomic neuropathy. See text for details

Physiologic Phase	Clinical Phase
1) Early parasympathetic weakness	1) Peripheral autonomic Neuropathy
2) Excess sympathetic activity	
3) Sympathetic weakness	
4) Quality of life compromise	2) DAN
5) DAN	
6) CAN	3) CAN

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Resting and Dynamic LFa and Normalized RFa & VLF Responses with Resting and Valsalva Blood Pressures vs. Age

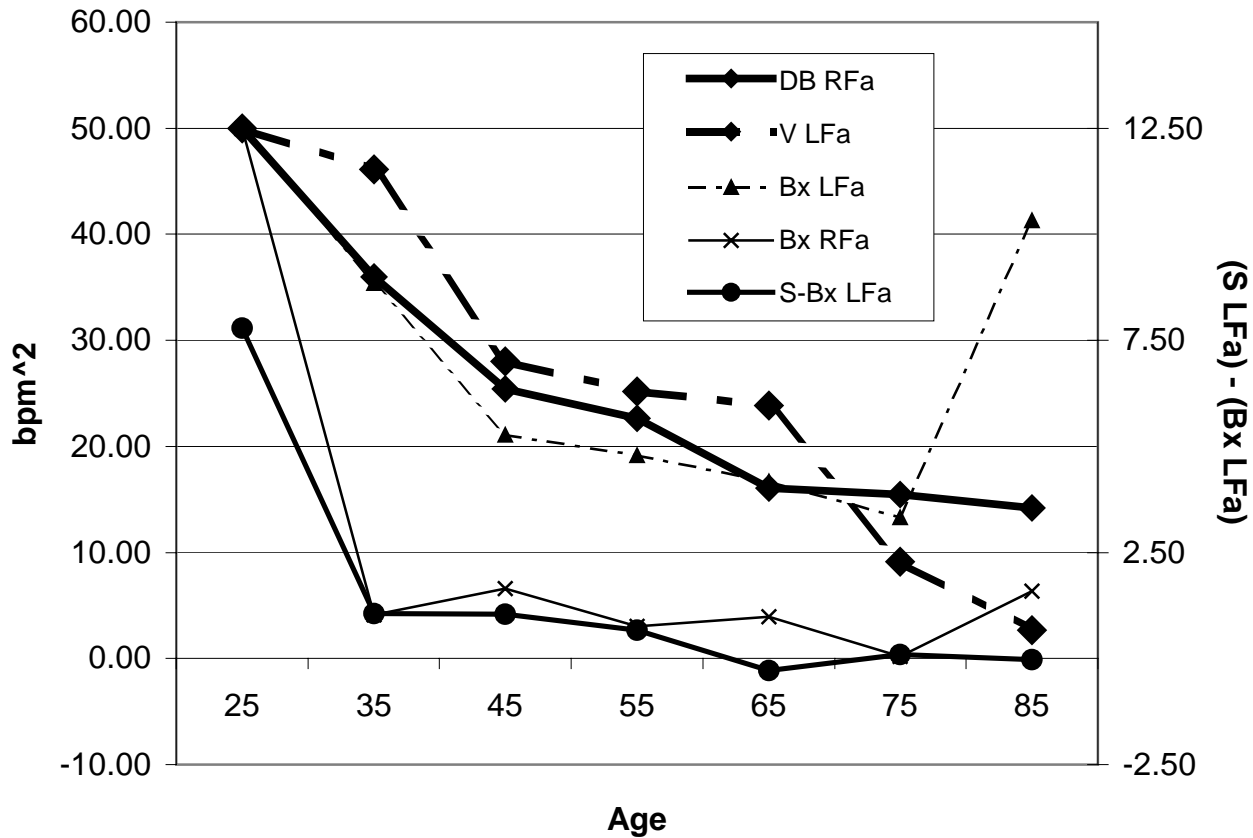


FIGURE 1: The lowest curve represents the magnitude of the sympathetic change during standing (see the text for details). Except the stand results, the data are normalized to 50.