

Diabetes Technology Society Meeting, San Francisco, CA
5th Annual Diabetes Technology Meeting, November 10 – November 12, 2005
ACCEPTED (#VINI5137)

Dynamic Enhanced Frequency Domain Analysis Indicates A Significant Decline In Autonomic Function Before Age 50
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Background: As we age, our nervous system activity slows and becomes less sensitive. Disease, injury, exposure, major surgery, and adverse lifestyles have been shown to accelerate this decline. Here, we assessed the autonomic nervous system's (ANS) decline in diabetics. It is known that in diabetics the ANS decline is accelerated. However, the magnitude of this acceleration is not well documented. We studied the age related changes in the two ANS branches (the sympathetic and the parasympathetic nervous systems) in diabetics using enhanced frequency domain (FD) analysis (EFDA) and FD heart rate variability (fdHRV) analysis.

Method: ECG and respiratory data of 357 diabetics (ages 22 to 93) were acquired in patients performing paced, rhythmic, deep breathing (DB) and short Valsalva maneuvers (V). The sympathetic and parasympathetic EFDA and fdHRV parameters (LFa, RFa in bpm^2 ; and LF, HF in msec^2 ; respectively) were computed according to published methodologies. We assume that both the LFa and LF are sympathetic measures and that both the RFa and HF are parasympathetic measures. The curve indicating the expected or normal aging effect on the ANS (in bpm^2) is from the HRV literature. The data are normalized to age 25.

Result: The EFDA method shows a continuous decrease in the sympathetic (V LFa) and parasympathetic (DB RFa) measures with age with the largest decrease occurring before age 45. These decreases exceeded the expected (normal) decreases due to aging by 250.5% and 467.9%, respectively. After age 45, the decreases continue but are slower, more in concert with the expected aging processes until later in life (after 65). The fdHRV analysis shows the sympathetic V LF and parasympathetic DB HF activity measures with age have no specific trend.

Conclusion: In this study, as indicated by EFDA, diabetics show an accelerated decrease in ANS function as compared with expected (normal) aging.

INTRODUCTION

As we age, our nervous system activity slows and becomes less sensitive. Disease, injury, surgery, exposure, and adverse lifestyles have been shown to accelerate this decline. Eventually, ANS decline due to chronic clinical conditions or age results in autonomic neuropathy. Once autonomic neuropathy symptoms present, relatively few clinical intervention options remain. However, autonomic dysfunction is known to be asymptomatic. Thus, autonomic function testing can be critical in the early evaluation of autonomic decline to enable earlier intervention that can slow or stay the progression of autonomic decline and delay the onset of autonomic neuropathy (*e.g.*, diabetic or cardiac autonomic neuropathy, DAN or CAN).

Autonomic Nervous System (ANS) activity of people with diabetes usually worsens by age faster than people without diabetes. It is known that in diabetics ANS decline is accelerated [Vinik *et al.*, 2004, 2005a] eventually resulting in DAN and then CAN. The magnitude of the acceleration in autonomic decline due to diabetes is not well documented. Here, we assess the autonomic decline in diabetics by investigating the changes in the two ANS branches, the sympathetic and parasympathetic branches, in diabetic people over all ages. We studied these age related changes using enhanced frequency domain (FD) analysis (EFDA) and FD heart rate variability (fdHRV) analysis.

METHODS

ECG and respiratory data of 389 diabetics (ages 22 to 93) were acquired in patients performing paced, rhythmic, deep breathing (DB) and short Valsalva maneuvers (V). The sympathetic and parasympathetic EFDA and fdHRV parameters (LFa, RFa in bpm^2 ; and LF, HF in msec^2 ; respectively) were computed according to published methodologies [Akselrod *et al.*, 1981, 1985, 1987, 1988; Malik *et al.*, 1996; Vinik *et al.*, 2005b]. An online data analysis is performed while acquiring data. The EFDA analysis is based on ECG and respiration signals which were sampled at 250 Hz and 50 Hz, respectively. Beat-to-beat (RR) time series are obtained from the ECG. Ectopic beats are eliminated while the RR time series was obtained and interpolation is used to connect the discontinuities caused by eliminating ectopic beats. LFa (the EFDA sympathetic measure) and RFa (the EFDA parasympathetic measure) are obtained by continuous wavelet transform (CWT) on instantaneous HR (IHR) and respiratory activity (RA) signals [Akselrod, *et al.*, 1981, 1985, 1987, 1988]. LF (the fdHRV sympathetic measure) and HF (the fdHRV parasympathetic measure) are obtained by short-time fast Fourier transform on the heart beat interval (HBI) signal [Malik, 1996]. For purposes of comparing the EFDA and the fdHRV methodologies, the LF is assumed to be a sympathetic measure and the HF is assumed to be a parasympathetic measure. The curve indicating the expected aging effect on the ANS (in bpm^2) is from the HRV literature [Akinola, 1999]. The data are normalized to age 25 and plotted on a logarithmic scale.

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

The tests each included four autonomic challenges separates by baseline periods. The four challenges were an initial resting baseline, the parasympathetic challenge of paced,

rhythmic, deep breathing (DB), the sympathetic challenge of a series of 5 short Valsalva maneuvers (V), and the system challenge of a quick postural change followed by quiet up right posture (stand, S). Throughout the test, heart rate (HR) and blood pressures (BP) were collected and the EFDA and FDHRV parameters were computed. From these data, the patient's autonomic parameters were read at rest and in response to the clinical challenges.

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

RESULTS

From Figure 1, the EFDA method shows a continuous decrease in the EFDA sympathetic (V LFa) and EFDA parasympathetic (DB RFa) responses with age with the largest decrease occurring before age 45. These decreases exceeded the expected (normal) decreases due to aging by 250.5% and 467.9%, respectively. After age 45, the decreases continues but are slower, more in concert with the expected aging processes until late in life (after 65). The fdHRV analysis shows the fdHRV sympathetic (V LF) and fdHRV parasympathetic (DB HF) activity responses with age have no specific trend.

DISCUSSION

As we age, our nervous system activity slows and becomes less sensitive. In a comparison of EFDA and fdHRV analysis methods the EFDA method was found to be more sensitive earlier in the disease process. EFDA suggests that the biggest decrease in ANS activity is during the first three decades of the disease (between the ages of 25 and 45). After that the decrease slows. EFDA was able to better elucidate clinically relevant, asymptomatic changes in ANS activity over age. Early detection of autonomic dysfunction before neuropathy enables earlier clinical interventions. These interventions can be implemented to prevent or slow the acceleration of ANS decline before age 45. Thereby potentially preventing further damage and health problems and helping to preserve quality of life and possibly maintain normal longevity.

CONCLUSIONS

The EFDA method when applied to diabetics shows significant decrease in ANS function prior to age 50 (on average). This decrease is accelerated as compared with the expected

(normal) aging effect. This acceleration diminishes and is more like that due to normal aging later in life.

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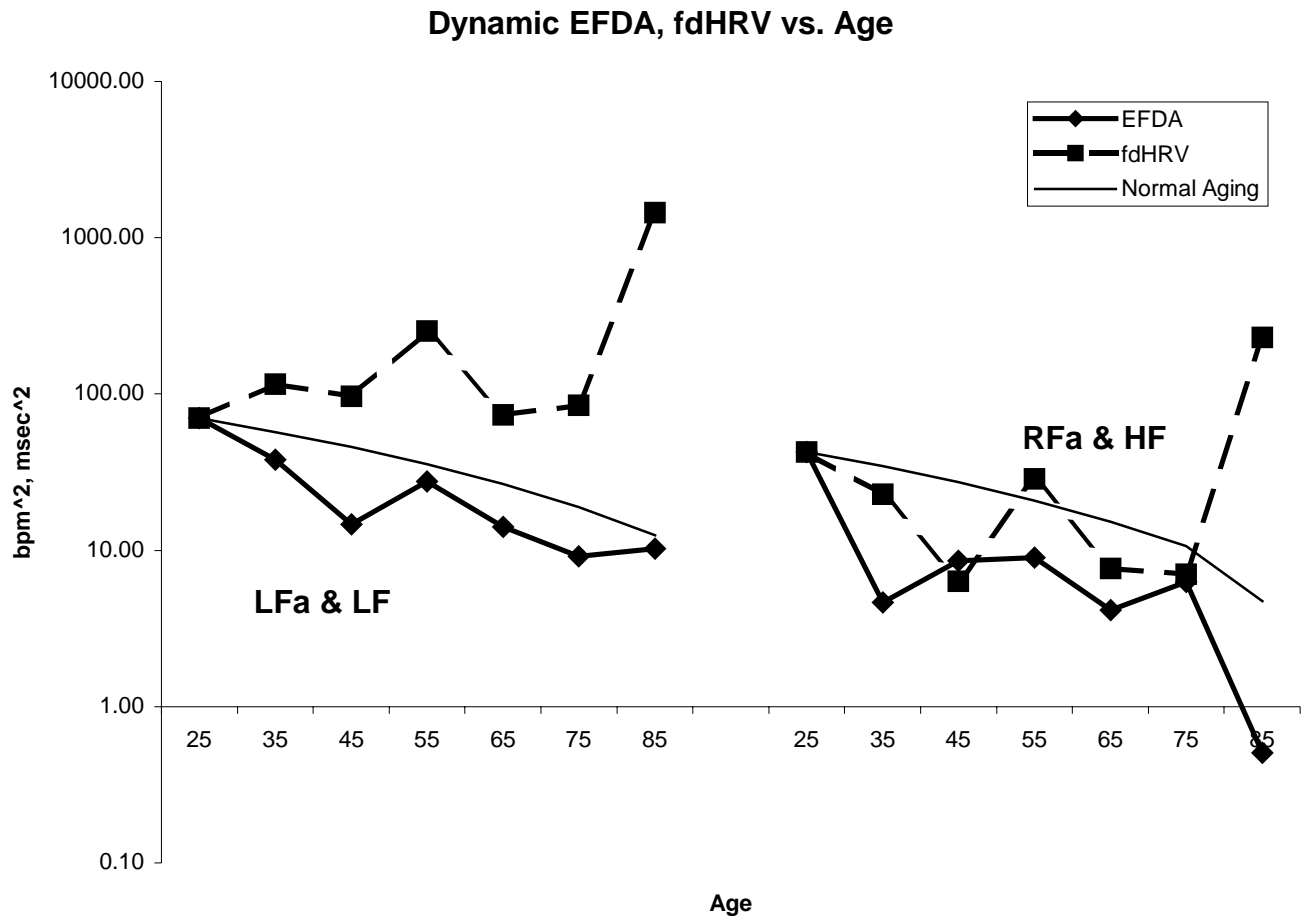


FIGURE 1: EFDA and fdHRV sympathetic (LFa and LF, respectively) and parasympathetic (RFa and HF, respectively) each plotted with the expected normal aging curve against age. The EFDA data are plotted as bpm² and the fdHRV data are plotted as msec² on a logarithmic scale.