

Enhanced Frequency Domain Analysis Identifies Early Autonomic Dysfunction That May Lead To Elevated Blood Pressure In Diabetics
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Background: Enhanced frequency domain (fd) analysis (EFDA) of heart rate variability (HRV) can differentiate ANS dysfunction before structural deficits present. Early ANS decline starts with the parasympathetics (PSNS) weakening, then the sympathetics (SNS). Our hypothesis is that before the SNS weakens it is strengthened by the initial PSNS weakness. This period of SNS excess might up regulate BP. Then when the SNS weakens, the ability to down regulate BP is lost.

Methods: Two or more ANS tests were performed on 389 adult diabetic patients (ages 22 to 93). From these data, the patient's EFDA (LFa and RFa) parameters and BP were measured at rest and in response to clinical challenges, including paced deep breathing (DB) and a series of short Valsalvas (V). The data are normalized to age 25.

Results: The RFa (a parasympathetic measure) declines from ages 25 to 45, whereas the LFa (a sympathetic measure) decline starts at age 35 (see Figure). Meanwhile, the BP measurements both at rest and during the Valsalva challenge both increase sharply from age 25 to 35. The resting (baseline) BP then levels off (at 130 mmHg) but the Valsalva BP decreases until about 45 before it levels off (at 110 mmHg).

Conclusions: The parasympathetics seem to be more sensitive to the effects of diabetes at first. The initially, less susceptible sympathetics start declining 10 years later, on average. This decade of relative sympathetic excess is coincident with a significant increase in BP. After the sympathetics weaken, the Valsalva BP declines and remains lower than the resting BP. A further suggestion of weakness in the sympathetics.

BACKGROUND

Enhanced frequency domain (fd) analysis (EFDA) of heart rate variability (HRV) can differentiate autonomic nervous system (ANS) dysfunction before structural deficits or autonomic neuropathy presents. This differentiation can facilitate diagnosis and therapy earlier, even before end-organ effects present. Our lab has shown that early ANS decline in the face of a chronic progressive disease such as diabetes begins with the parasympathetic nervous system (PSNS) weakening first, followed by the sympathetic nervous system (SNS) [Vinik *et al.*, 2004]. It is well known that the sympathetics (SNS) modulate the blood pressure (BP) by modulating baroreceptor reflex. It is hypothesized that the SNS, before it weakens, is strengthened by the initial PSNS weakness. Thus, this period of SNS excess might up regulate the baroreceptor reflex which in turn may elevate BP. Then when the SNS weakens and it loses its ability to down regulate the baroreceptor reflex, the BP remains elevated.

METHODS

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

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

EFDA is a means of non-invasively measuring the autonomic nervous system (ANS): both branches independently, simultaneously, and objectively [Vinik *et al.*, 2005, Fig. 1]. EFDA completes older fdHRV methodologies by including respiratory activity (RA) spectral analysis. This allows proper dissection of the ANS to further diagnostics. For example, Orthostatic Hypotension (OH) is common in Diabetics. OH is a failure of the SNS, but it could also be (partially) caused by an overdrive of the PSNS. Either way it is not an ANS structural deficit, it is a functional issue. Identifying this difference can facilitate diagnosis and therapy.

The data collected included patient's EKG (digitized at 250 Hz), respiratory activity (digitized at 60 Hz), and blood pressure. These data were collected from a clinical study that includes a resting baseline; periods of relaxed, rhythmic, deep breathing, a series of short Valsalva maneuvers, and quick stand immediately followed by quiet standing. The study challenges were separated by periods of rest to allow the patient's ANS to return to baseline.

From these data, the patient's EFDA parameters (LFa, the low frequency area representing a measure of the SNS; RFa respiratory frequency area, a measure representing the PSNS; and LFa/RFa ratio, a measure representing Sympathovagal Balance) were computed in response to clinical challenges, and at rest. Collected and presented below are the RFa responses to deep breathing (DB, a PSNS challenge), the LFa responses to Valsalva (V, a SNS challenge), the systolic and diastolic BPs (sBP and dBP, respectively) collected during the initial (resting) baseline (Bx) and Valsalva periods, and the published low end normal data for the deep breathing and Valsalva responses [Akinola, *et al.* 1999].

RESULTS

Dynamic challenge (deep breathing and Valsalva) responses provide the earliest clues to nervous system compromise. From the clinical exam presented to the patients in this study, the parasympathetic (RFa) and the sympathetic (LFa) responses to deep breathing and Valsalva challenge are the earliest indicators of autonomic decline. Assessing these responses over age provides a sensitive measure of autonomic function. Figure 1 presents the parasympathetic and the sympathetic responses to deep breathing (the upper plot) and Valsalva (the lower plot) for the cohort according to age. These data are presented together with their respective low end normal data for reference [Akinola, *et al.* 1999].

The upper plot in Figure 1 of the parasympathetic response to deep breathing challenge shows an initial decline over the first two decades represented, followed by a slight plateau for the next decade. Then the PSNS response curve drops below the curve representing the low end of the normal PSNS response to deep breathing range. Although the decline at this point slows, the PSNS response curve remains abnormally low.

The lower plot in Figure 1 of the sympathetic response to Valsalva challenge shows an initial slight decline over the first decade, followed by a more rapid decline over the second decade, then a plateau over the next two decades. While still remaining above the curve representing the low end of the normal SNS response to Valsalva range, a second period of rapid decline occurs over the last two decades presented. The SNS response curve does not drop below the SNS low end of normal curve until just before age 85 on average.

Normalizing the parasympathetic (RFa) data to the first point on the sympathetic (LFa) curve highlights this delay (see Figure 2). Also presented in Figure 2 are the baseline (resting) and Valsalva systolic and diastolic blood pressures. Notice the corresponding increase in all BP measures during the period of relative sympathetic normalcy and parasympathetic decline from age 25 to 35. Then as both autonomic measures decline together the resting (baseline) average BP (systolic and diastolic) levels off (at 130 mmHg and 79 mmHg, respectively), and remains elevated over the years. Concurrently, there is a decrease in the Valsalva BP until about 45 before it levels off (at 110 mmHg and 60 mmHg for the systolic and diastolic respectively). The lower Valsalva BP in the latter years may be a result of autonomic failure.

DISCUSSION

The plateau seen in the curves of Figure 1 starting around age 45 is due to clinical intervention. From these curves we see that autonomic function has declined by about 50% before the first intervention. Presumably this is a result of the asymptomatic nature of autonomic dysfunction. The curves also suggest that the PSNS (as represented by the RFa measure) drops below the low end normal curve around age 60 (on average), whereas the SNS (as represented by the LFa measure) does not drop below its low end normal curve until around age 85 on average. The SNS response curve staying normal may also be a result of therapy. Theoretically, by maintaining normal HR and BP the physician is helping to maintain normal SNS function. However, in the end it is the PSNS that becomes critical in helping to protect the patient's heart from sustained tachycardia due to SNS overdrive and possible sudden cardiac death.

The decline in the PSNS response curve of Figure 1, after the responses become abnormally low, is slower. This may also be due to intervention. Through the use of adrenergic blockade (Beta-blockers, angiotensin-blocking agents, and calcium channel blockers) the PSNS is clinically maintained. Thus, the PSNS decline would be slowed while any excess SNS activity is limited.

The data from Figure 2 seems to support the hypothesis that the relative PSNS weakness over the first two decades of autonomic decline temporarily maintains relative SNS strength, delaying its decline. During this period of relative SNS strength the corresponding BPs are elevated. Theoretically, this is a result of the relative excess SNS activity up-regulating the baroreceptor reflex which, in turn, drives up BP. Then, over the next decade (from age 35 to age 45), as the SNS declines, BP also declines. As mentioned above, the ensuing plateaus in the autonomic responses is correlated with clinical intervention. This plateau is associated with a period of relative stability in the BP measurements. However, the resting systolic BP remains elevated and over the last two decades the systolic BP during the Valsalva challenge increases. This may again be a result of the relative weakness in the PSNS as compared to the SNS as the PSNS drops below the SNS response curve around age 60, which is also the average age when the PSNS response drops out of the normal range as presented in Figure 1. During this time, however, the increase in BP is not as sharp as during the earlier decline, possibly due to the weakness in the ANS during this time. During the latter era neuropathies and structural deficits are known to exist, whereas during the early era only functional deficits are thought to exist.

CONCLUSIONS

The parasympathetics seem to be more sensitive to the effects of diabetes at first. The initially, less susceptible sympathetics start declining 10 years later, on average. This decade of relative sympathetic excess is coincident with a significant increase in BP. After the sympathetics weaken, the Valsalva BP declines and remains lower than the resting BP. A suggestion of later weakness in the sympathetics.

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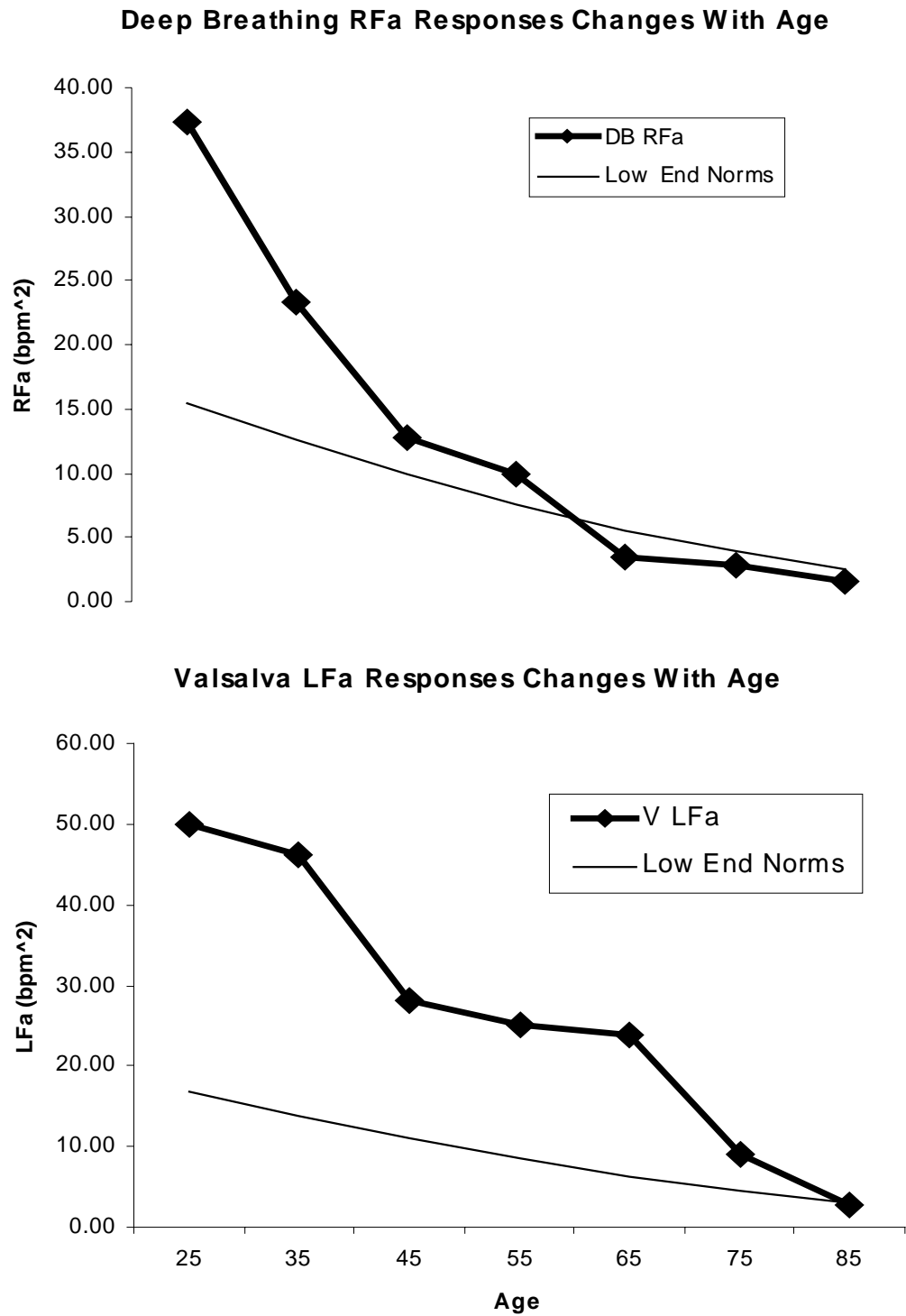


FIGURE 1: Parasympathetic (RFa) and sympathetic (LFa) responses to challenge plotted against age. The low end “norms” are from published data [Akinola, *et al.* 1999]. See text for details.

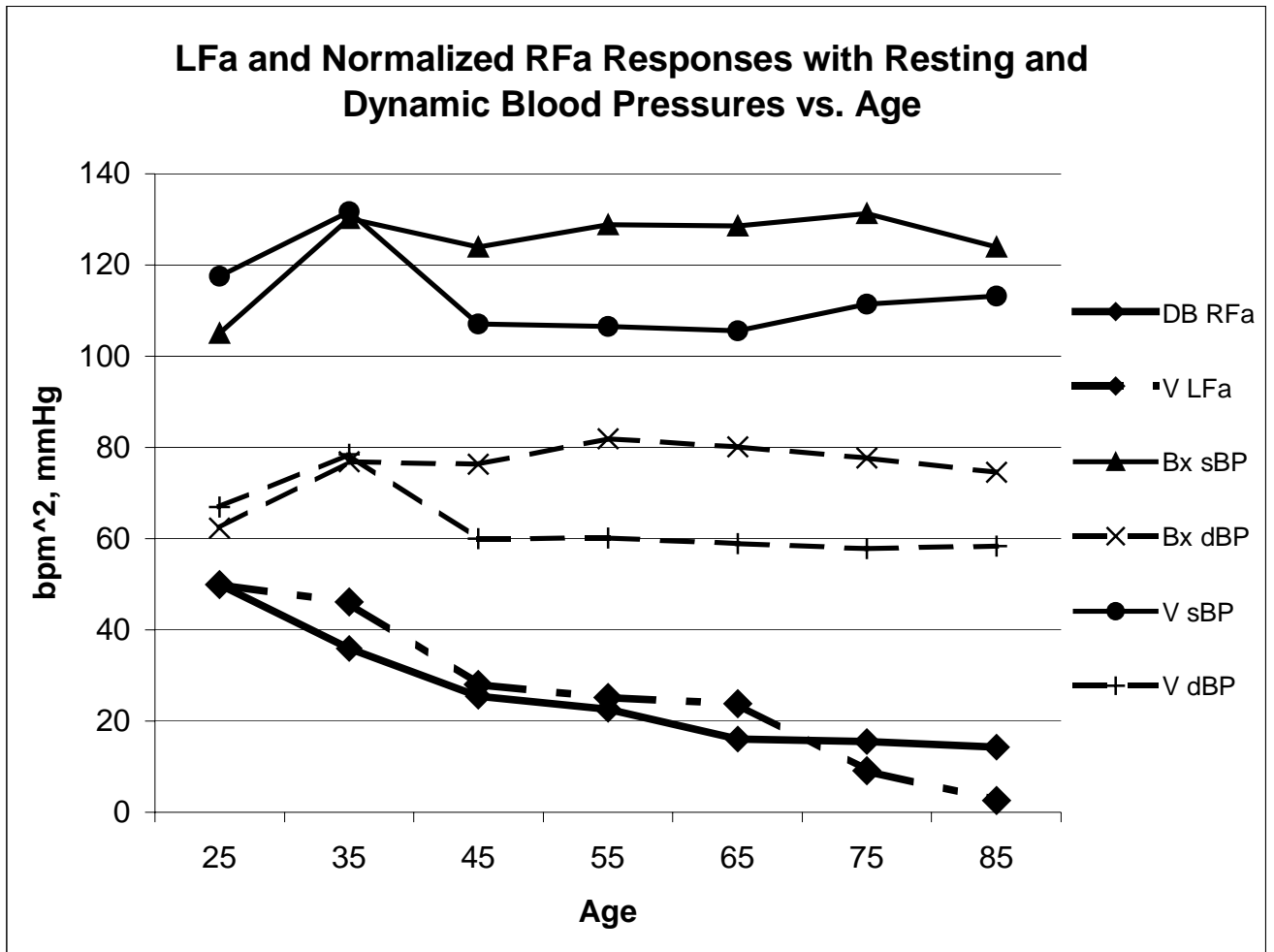


FIGURE 2: Autonomic responses (LFa and RFa) plotted with resting and Valsalva systolic and diastolic blood pressures against age. See text for details.