

**Resting Enhanced Frequency Domain Analysis Improves Heart Rate
Variability Sensitivity in Early and Late Diabetics**
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Background: The addition of frequency domain (FD) analysis of respiratory activity to FD of heart rate variability (HRV) is necessary to independently and simultaneously analyze both autonomic (ANS) branches non-invasively and quantitatively. This method has been presented as the enhanced FD analysis (EFDA) approach. Our clinical results have shown that EFDA improves FD heart rate variability (fdHRV) sensitivity in early and late diabetics.

Methods: Serial ANS tests were performed on 389 adult diabetic patients (ages 22 to 93). From these data, the patient's EFDA and fdHRV parameters were computed at rest. The EFDA parameters in bpm^2 are: LFa, a sympathetic measure; RFa, a parasympathetic measure; and LFa/RFa, a measure of sympathovagal balance. The fdHRV parameters in msec^2 are: LF, a measure of the sympathetics as modulated by the parasympathetics; HF, a fixed, broad spectrum measure of the parasympathetics; and LF/HF, a measure of changes in sympathetic activity. The highest value in each of the six data sets are normalized to 100 bpm^2 for the EFDA parameters and 100 msec^2 for the fdHRV parameters.

Results: The EFDA sympathetic parameter, LFa, shows a continuous decline over all ages: rapid at first, then slower, then rapid again. Clinical histories indicate that this slower decline is associated with clinical interventions. The fdHRV sympathetic parameter, LF, varies significantly over all ages. The RFa declines rapidly over the first decade and then seems to stabilize, until later in life when there is a drop and a rebound. Clinical histories indicate that this drop is coincident the onset of DAN. The rebound is due to clinical intervention. The HF varies widely with age. Neither the EFDA Ratio (LFa/RFa) or the fdHRV Ratio (LF/HF) show any consistent trending. Evidence suggests that of the Ratio data, only the resting EFDA Ratio has clinical value as an indicator of resting sympathovagal balance, including titration of therapy, indication of risk of cardiac instability and sudden cardiac death, and potential neurogenic involvement in arrhythmias.

Conclusions: As a temporal indicator of ANS decline, the sympathetic (LFa) and parasympathetic (RFa) EFDA parameters better reflect its continuous nature than their fdHRV correlates.

INTRODUCTION

It has been presented that the addition of frequency or spectral domain (FD) analysis of respiratory activity is necessary to non-invasively, independently, simultaneously, and quantitatively analyze both autonomic branches. Clinical results have shown that the Enhanced FD Analysis (EFDA) approach improves FD heart rate variability (fdHRV) sensitivity in diabetics. From the 1996 Circulation Special Report on HRV [Malik, 1996], the methodology for the fdHRV approach was standardized and the low frequency term defined as a measure of sympathetic activity as modulated by parasympathetic activity. The report leaves the correlation of the high frequency term in doubt [Malik, 1996]. However, the report also states that the only method for non-invasively measuring the autonomic nervous system (ANS) is by spectral analysis of HRV [Malik, 1996]. Therefore, the low frequency term (from fdHRV) is a measure of total ANS activity, a mixed measure [Malik, 1996]. The approach detailed in Axelrod's work (referenced in the background section of the Special Report), resolves this confusion [1981, 1985, 1987, 1988]. Axelrod, *et al.*, added a second, independent measure of the ANS, specifically the parasympathetic nervous system (PSNS) as represented by the Vagus Nerve and its influence on ventilation. By this approach there is now two independent measures of a two component system. Thereby enabling independent, simultaneous, and quantitative of both ANS branches, non-invasively. The Special Report states that spectral analysis of HRV is superior to time domain measures such as those obtained from Holter monitoring (*e.g.*, sdNN, rmsSD, and pNN50) and time domain ratio measures (*e.g.*, E/I Ratio, Valsalva Ratio, and 30:15 Ratio) in that these are only qualitative measures of parasympathetic activity.

Clinically, this provides a more pure, independent measure of systemic sympathetic nervous system (SNS) and systemic PSNS activity. These improved measures seem to have elucidated possible new, clinically relevant, autonomic disorders [Adiraju, 2004; Vinik, *et al.*, 2004], a possible cause for chronic hypertension in diabetics and other chronic progressive diseases [Vinik, *et al.*, 2005a], the possibility of detecting earlier stages of autonomic decline suggesting greater sensitivity in detecting its onset [Vinik, *et al.*, 2005b], and the ANS's acceleration effect on aging [Vinik, *et al.*, 2004; Vinik, *et al.*, 2005c], as it results from diabetes and other chronic progressive diseases.

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 (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).

Figure 1 presents a model of the computational methodology behind EFDA. Conceptually, if the faster respiratory sinus arrhythmia (RSA) signal and the slower mean heart rate changes could each be separated from the patient's cardiogram and analyzed independently, the result would yield a measure of Vagal outflow from the RSA and a measure of sympathetic activity from the changes in mean heart rate. Effectively this is what is accomplished in the frequency domain. Spectral analysis of RSA provides the indication of where in the frequency domain the Vagus is influencing the heart so that the RFa spectrum can be centered and the parasympathetic activity computed [Akselrod, 1981, 1985, 1987, 1988]. From the LFa spectrum the sympathetic activity is computed according to the spectral analysis methods defined in the 1996 Circulation Special Report on HRV [Malik, 1996]. In this way the activity levels in both ANS branches in response

to behavioral and metabolic needs are computed non-invasively, independently, simultaneously, and quantitatively.

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 clinical tests each included four autonomic challenges separated by baseline periods. The four challenges are 1) an initial resting baseline, 2) the parasympathetic challenge of paced, rhythmic, deep breathing (DB), 3) the sympathetic challenge of a series of 5 short Valsalvas (V), and 4) 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 parameters (LFa, RFa, and LFa/RFa) and the fdHRV (LF, HF, LF/HF) parameters were computed.

RESULTS

Figure 2 presents data from the initial (resting) baseline challenge. It includes the EFDA parameters for: sympathetic activity (LFa), parasympathetic activity (RFa), and sympathovagal balance (LFa/RFa). Contrasted together with the EFDA parameters, respectively, are the fdHRV parameters for: sympathetic activity as modulated by parasympathetic activity (LF); the broad spectrum high frequency (HF) term that can, in part, represent parasympathetic activity; and the LF/HF ratio which is accepted to be the fdHRV's best measure of changes in sympathetic activity. The highest data point in each set in Figure 2 is normalized to 100.

In comparing conceptually similar sets of EFDA and fdHRV data, the sympathetic EFDA measure (LFa) shows a continuous decline over all ages: rapid at first, then slower, then rapid again. Clinical histories indicate that this slower decline is associated with clinical interventions. The fdHRV sympathetic parameter, LF, varies significantly over all ages.

The parasympathetic EFDA measure (RFa) declines rapidly over the first decade and then stabilizes, until later in life when there is a drop and a rebound. Clinical histories indicate that the RFa drop between age 65 and age 75 is due to the onset of DAN. The rebound in the following decade is due to clinical intervention. The HF is widely variable over all ages.

The EFDA Ratio (LFa/RFa) nor the fdHRV Ratio (LF/HF) show any consistent trending with age. However, clinical evidence suggests that the EFDA Ratio has clinical value as an indicator of resting sympathovagal balance. This resting balance term has been found useful in the titration of therapy, indication of risk of cardiac instability and sudden cardiac death, and as an indicator of potential autonomic involvement in arrhythmias.

Since the LF/HF Ratio term is considered statistically as the better measure of changes in sympathetic activity for fdHRV [Malik, 1996], it is worth also comparing it to the EFDA sympathetic measure LFa. The fdHRV ratio shows a sharp increase over the first four decades levels off for a decade and then a sharp decline over the remaining decades. This is understood from the fact that it is a mathematical contrivance that then seemed to better explain the clinical data. Comparing the fdHRV parameters LF and HF and remembering that the ratio is just that, the sharp increase at first is due to the general decrease in HF and relatively small changes in the LF; the denominator is getting smaller faster causing the ratio to get larger. The level period and latter decline in the fdHRV ration is due to the relative slowing of the HF term and the relative increases in the LF term. However, this does not seem to correlate as well with clinical results as the EFDA sympathetic measure of LFa.

CONCLUSIONS

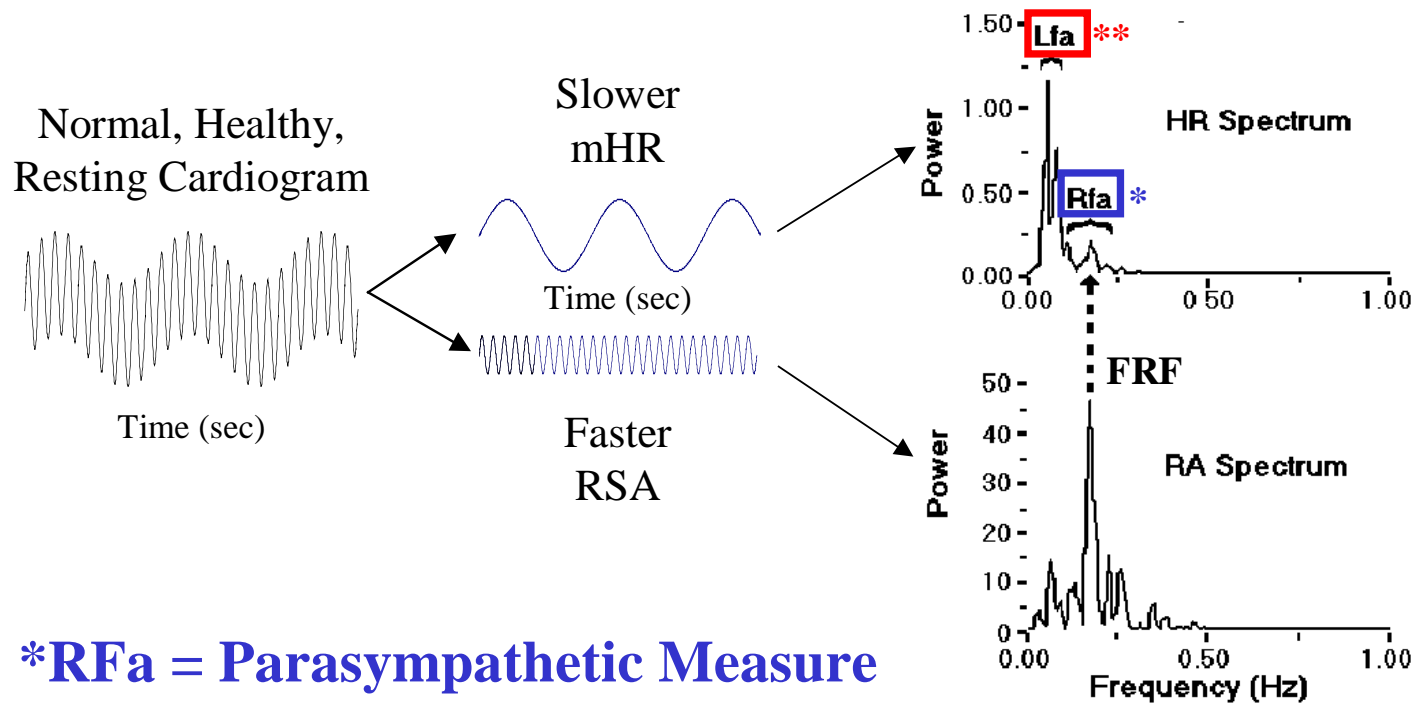
As a temporal indicator of ANS decline in the face of chronic disease, the sympathetic (LFa) and parasympathetic (RFa) EFDA parameters better reflect the disease's continuous nature and the effects of clinical intervention than their fdHRV correlates. It seems as if neither of the Ratio terms provide any consistent trending information.

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HRV & RA = ANS



***Rfa = Parasympathetic Measure**

****Lfa = Sympathetic Measure**

LFa/Rfa = Sympathovagal Balance

FIGURE 1: A conceptual model of the Enhanced Frequency Domain Analysis (EFDA) methodology. By adding spectral analysis of respiratory activity, a measure of Vagal outflow underlying respiratory sinus arrhythmia (RSA) is added to the low frequency heart rate variability measure. This now provides two measures from a two component system; physically and mathematically enabling the two branches of the autonomic to be independently, simultaneously, and qualitatively characterized; non-invasively.

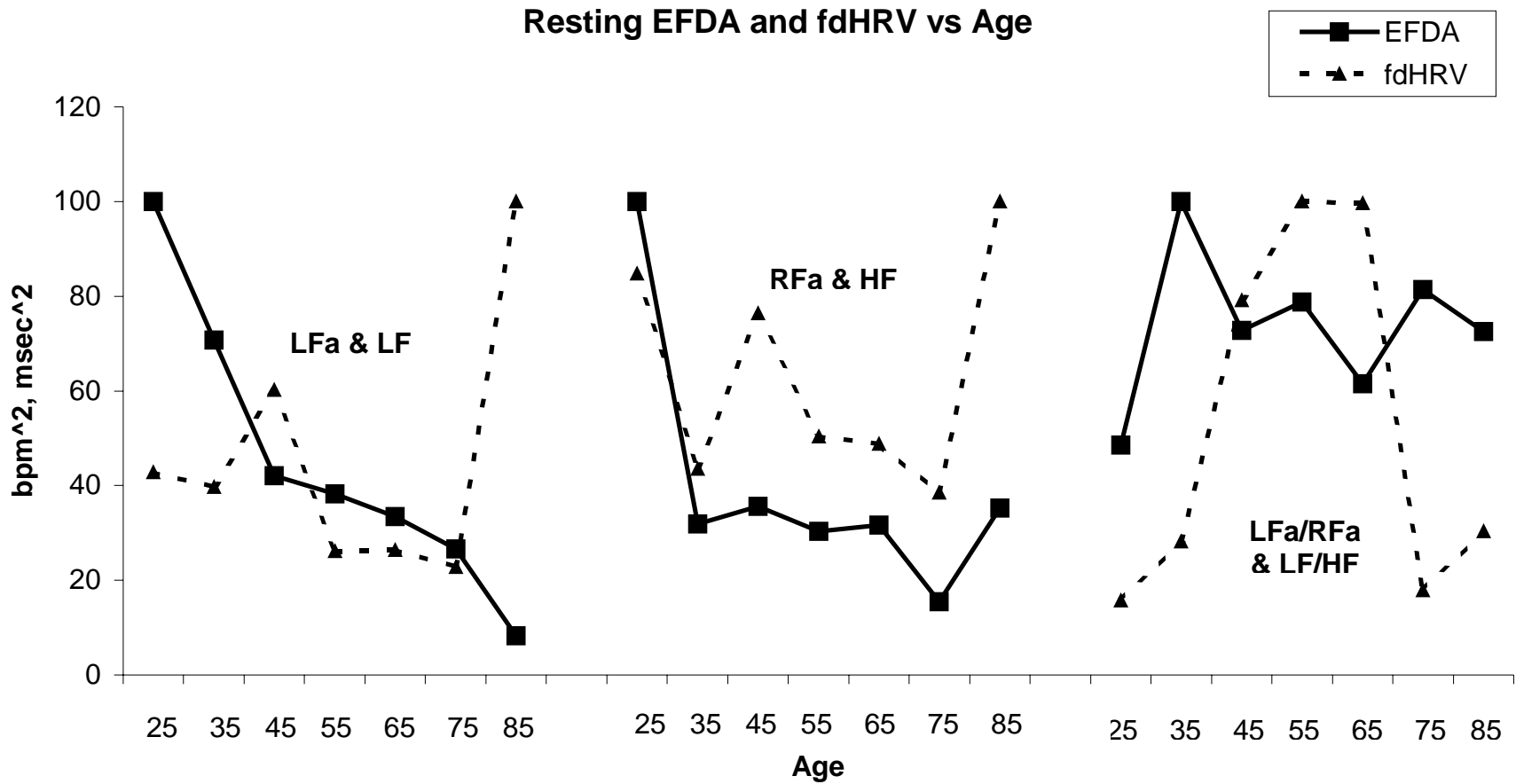


FIGURE 2: Data are presented from the initial (resting) baseline challenge. Included are the EFDA parameters for: sympathetic activity (LFa), parasympathetic activity (RFa), and sympathovagal balance (LFa/RFa). Plotted together with the EFDA parameters are the fdHRV parameters for: sympathetic activity as modulated by parasympathetic activity (LF); the broad spectrum high frequency (HF) term that can, in part, represent parasympathetic activity; and the LF/HF ratio which is accepted to be the best measure of changes in sympathetic activity. The highest data point in each set is normalized to 100. See text for details.