

Chronic Disease Related Decline of Resting Autonomic Function Shows Gender-Based Aging Differences

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BACKGROUND

Published time domain (TD) heart rate variability (HRV) based measures of autonomic function in healthy subjects shows that resting autonomic function generally decreases over age and differs between the genders and declines with age [Umetani *et al.*, 1998]. According to the Holter data from Singer's group, older subjects have lower HRV indices than younger subjects. Females tend to have higher sympathetic output levels relative to males early in life and higher parasympathetic output levels than males later in life. The HRV indices for sympathetic output were standard deviation of the (average) normal sinus beat-to-beat (RR) heart rate intervals over five minute intervals, or sdNN or sdANN. The parasympathetic output HRV indices were root-mean-square of successive normal sinus RR interval difference (rmsSD), and the percentage of successive normal sinus RR intervals >50 ms (pNN50). The relatively higher average parasympathetic activity levels in geriatric females is associated with greater longevity in females than for males.

Since aging is known to decrease autonomic output over time, the question of how chronic disease effects the decrease remains. Some diseases, such as diabetes, have been studied and are known to decrease autonomic output with age. It is known that diabetes can lead to peripheral autonomic neuropathy, then to diabetic autonomic neuropathy, then in turn to cardiovascular autonomic neuropathy [Grundy, *et al.*, 1999; Boulton, *et al.*, 2005]. Heart failure and cardiomyopathy patients also show a decline in HRV activity over time [Lucreziotti, *et al.*, 2000].

TD-HRV indices from Holter monitoring are used as markers of autonomic function in geriatric heart failure clinics. Usually, TD HRV is derived from 24 Holter monitor recordings. Holters are often found too cumbersome to tolerate for the geriatric patient and shorter term monitoring would promote compliance [Ali, *et al.*, 2006]. Further, according to the HRV standards article [Malek, *et al.*, 1996] published in *Circulation*, the sdNN and sdANN indices are measures that include both sympathetic and parasympathetic influences, but tend to be more influenced by sympathetic activity. Similarly, rmsSD and pNN50 indices are measures that include influences from both autonomic branches, but tend to be more influenced by parasympathetic activity. All four parameters are based on averaging changes in HRV overtime, therefore preventing them from capturing dynamic activity within the ANS. As a result, the fidelity of these parameters as markers of autonomic function is a concern and a potential basis for the general lack of enthusiasm for the application of these indices.

ANS indices with higher fidelity are available with a HRV method that incorporates spectral analyses of respiration with spectral analysis of HRV [Autonomic Function Computations (AFC): Vinik, *et al.*, 2004; Aysin and Aysin, 2006, Shoemaker, *et al.*, 2006a,b]. While the indices from this method show trends that are similar to TD HRV results, the basis for the technology enables the isolation of the sympathetic and parasympathetic branches' activities in a shorter amount of time, and it can capture data that indicates dynamic autonomic responsivity to autonomic challenges. Improving the fidelity of autonomic measures can improve the care and

ultimately the outcomes in geriatric patients, including enabling physicians to better optimize a patient's quality of life and longevity.

We present resting autonomic data, as computed by AFC, of patients and healthy subjects according to age. The changes in resting autonomic output with age are highlighted and discussed relative to published Holter data results. The hypothesis is that chronic disease accelerates autonomic decline associated with aging. The gender differences noted from the Holter data are also hypothesized to present.

METHODS

Serial autonomic function testing (ANX-3.0, Ansar, Inc., Philadelphia, PA) was performed on 5752 subjects (Table 1), including 92 normal subjects (ages 7 to 88, Table 2) in 38 ambulatory clinics nationwide. The 15.5' test clinical exam included a 5' resting baseline. The average autonomic indices from the resting baseline were analyzed as markers of resting autonomic function. The indices were computed with the AFC method that incorporates SA of respiratory activity with SA of HRV. The SA method was a continuous wavelet transform with a CMORL wavelet ($Q=5$) updated every four (4) seconds. The method uses the SA of respiratory activity to isolate Vagal (parasympathetic) output from sympathetic output as presented in the time-varying HRV-spectra.

Patients with arrhythmia (more than 10 ectopic beats during the exam) were omitted, leaving 4204 patients, including 2530 females, 2310 hypertensives, 1613 diabetics, 953 patients with congestive heart failure, and 331 Parkinson patients. There were 537 patients younger than 30, 1686 patients between 30 and 55, and 2691 patients over 55, including 776 patients over 75. Patients were tested as they presented: lifestyle, disease, and medications inclusive. Statistical Analyses included second-order polynomial trend analysis of sympathetic and parasympathetic function, and sympathovagal balance.

RESULTS & DISCUSSION

The total population data for the resting sympathetics (LFa: low frequency area), parasympathetics (RFa: respiratory frequency area), and sympathovagal balance (Balance: LFa/RFa) are presented in three scatter plots against age. Added to the scatter plots are the averages for the patient data as represented by squares and the averages from the tested healthy subjects (represented by triangles). The averages data are presented in Figures 2 & 3. As expected the resting autonomic output from both branches decreases with age. The averages data show that average resting sympathetic output (Fig. 2, top) is reduced as compared to the healthy data until about age 65. The average patients' resting parasympathetic output (Fig. 2, middle) is reduced as compared to the healthy data for all ages. Healthy sympathovagal balance averages (Fig. 2, bottom) are lower than the average patient averages indicating that patients, on average, present with greater sympathetic function. In healthy subjects balance decreases from greater than 1.0 to less than 1.0 around age 65, indicating more parasympathetic activity.

AFC results by gender for resting autonomic levels (Fig. 3) show the following aging trends based on second order polynomial trend analysis. Trends are presented due to the scarcity of data for some age categories. For both patients and healthy subjects, autonomic function in both branches decreases with age from youth to about age 70 years and then increases by varying amounts thereafter.

The resting sympathetic trend for male patients (Fig. 3, top left) remains higher than that for female patients for all ages, with the difference largest at young ages up to about 55 years, smallest from about 60 to 80, then becoming progressively larger after 80. Whereas for healthy subjects (Fig. 3, top right), females begin and end with a higher resting sympathetic output than for males; similar to Holter data [Umetani *et al.*, 1998].

The resting parasympathetic trend for male patients (Fig. 3, middle left) starts lower than for females, then the differences decrease with age and the two are about the same after about age 60. Whereas the two genders in the healthy population (Fig. 3, middle right) have similar parasympathetic levels very young, the females decline at a greater rate than the males. At around age 60 the healthy female trend reverses. The healthy male trend reverses at about age 75. The trends suggest that the healthy female resting parasympathetic output increases faster than that for the healthy males, with the healthy female resting parasympathetic output becoming greater than that for the healthy males around age 75. The trends for the healthy subjects' parasympathetic output is also similar to Holter data [Umetani *et al.*, 1998].

Considering Sympathovagal Balance (SB) trends for patients and healthy subjects, all patients' SB remain above 1.0 (sympathetic dominant) over all ages, with the male trend more variable than the female trend (Fig. 3, bottom left). The healthy SB trends for both genders decline over time becoming less than 1.0 (parasympathetic dominant) by age 75 (Fig. 3, bottom right).

CONCLUSION

Disease (hypertension, diabetes, heart failure, or Parkinson's) specific effect analyses show no significant differences. Gender effects show that younger females have higher resting sympathetic function than younger males. During mid-life the differences become smaller and an inversion occurs between ages 60 and 70. Older females end up with higher resting parasympathetic function.

Resting autonomic is depressed due to all diseases. Specific disease effects are not significant. Gender effects are significant and similar to published Holter results [Umetani *et al.*, 1998]. The current data also show an upturn in AF later in patients' life, also similar to published Holter data.

REFERENCES

- Ali MA, Waheed A, Jurivich DA, Colombo J, Singer DH (2006) Short-term time domain HRV measures: Comparisons with 24-hr Holter monitoring. Geriatric Medicine Society Meeting, Chicago, IL May.
- Aysin B, Aysin E. (2006) Effect of respiration in heart rate variability (HRV) analysis. IEEE Engineering in Medicine and Biology Society Conference, New York, NY.
- Boulton AJM, Vinik AI, Arrezzo JC, Bril V, Feldman EI, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. (2005) Diabetic Neuropathies: A statement by the American Diabetes Association. *Diabetes Care*. 28(4): 956-62.
- Grundey SM, Benjamin IJ, Burke GL, Chait A. AHA Scientific Statement: Diabetes and Cardiovascular Disease, a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999; 100: 1134-46.
- Lucreziotti S, *et al.* (2000) Five-minute recording of heart rate variability in severe chronic heart failure: Correlates with right ventricular function and prognostic implications. *Am Heart J*. 139:1088-95.

- Malik, M (1996). The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability, standards of measurement, physiological interpretation, and clinical use. *Circulation.*; 93:1043-65.
- Shoemaker WC, Belzberg H, Wo CJ, Colombo J, Aysin E. (2006a) Role of autonomic activity in the hemodynamic pattern of septic shock. American College of Chest Physicians (CHEST), Salt Lake City, UT.
- Shoemaker WC, Belzberg H, Wo CJ, Colombo J, Aysin E. (2006b) Gender differences of hemodynamic and autonomic activity in septic shock. American College of Chest Physicians (CHEST), Salt Lake City, UT.
- Umetani K, Singer DH, McCraty R, and Atkinson M. (1998) Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *JACC.* 31(3), 593 – 601.
- Vinik AI, Aysin B, Colombo J. (2004) Enhanced frequency domain analysis replaces older heart rate variability methods. Fourth Annual Diabetes Technology Meeting 28-30 October.

Table 1: Patient cohort population statistics by age.

Age	<9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
Female	9	45	73	108	119	111	192	248	247	281	272	268	275	267	285	137	54	9	7
Male	14	33	48	41	47	63	83	140	132	189	225	199	195	214	140	120	17	6	1
Total	23	78	121	149	166	174	275	388	379	470	497	467	470	481	425	257	71	15	8

Table 2: Healthy cohort population statistics by age.

Age	<9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
Female	0	1	3	12	13	7	2	2	2	2	5	3	1	0	1	0	0	0	0
Male	0	1	16	4	5	6	2	3	2	1	2	1	0	1	1	0	1	0	0
Total	0	2	19	16	18	13	4	5	4	3	7	4	1	1	2	0	1	0	0

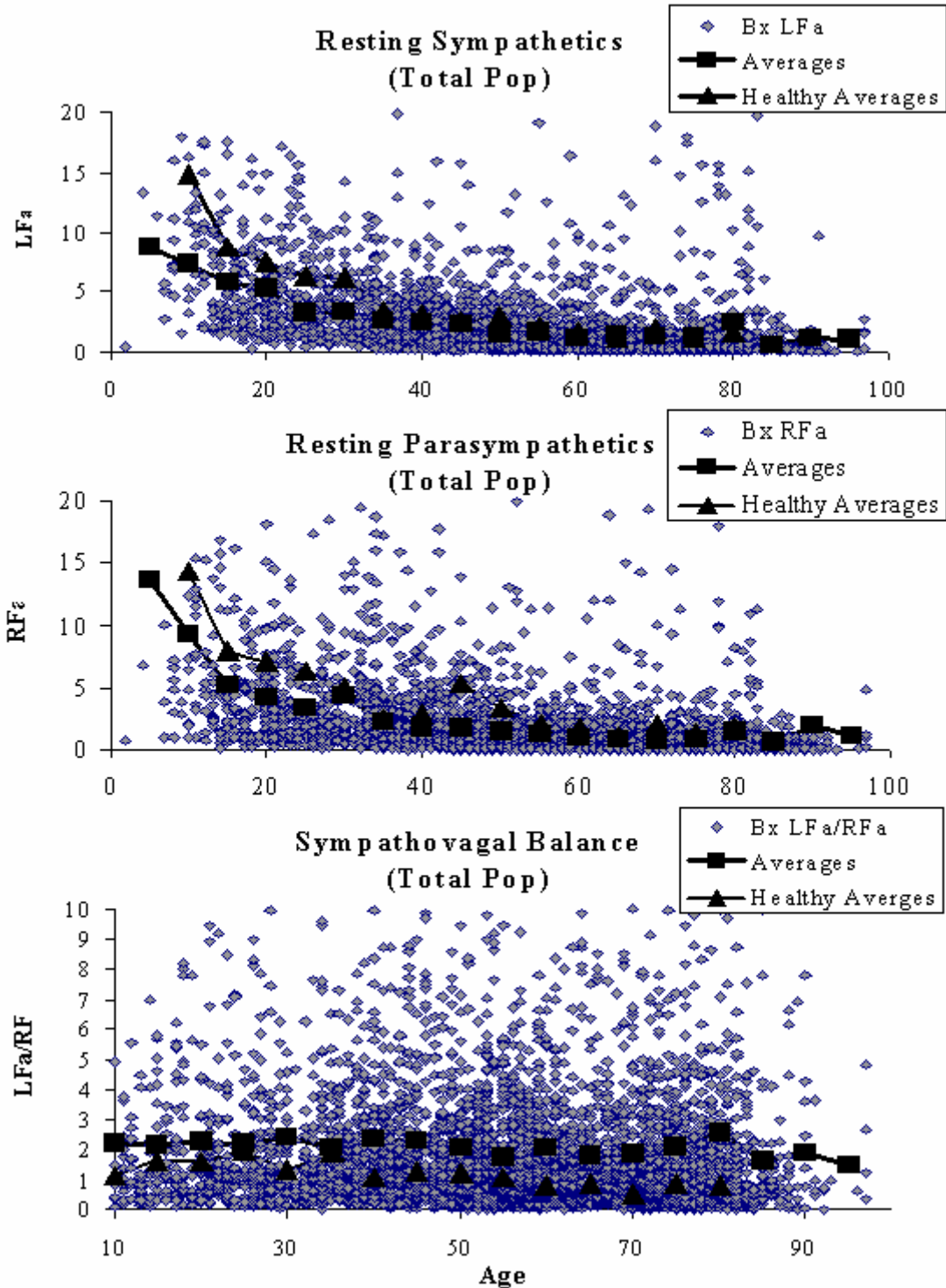


Figure 1: Resting ANS data for the entire population. The top panel presents sympathetic output (LFa). The middle panel presents the parasympathetic output (RFa). The bottom panel presents Sympathovagal Balance. The scatter points are individual patient data. Plotted against the

scatter points are the patient averages by age group. Patient averages (Averages) are represented by squares. Healthy averages are represented by triangles.

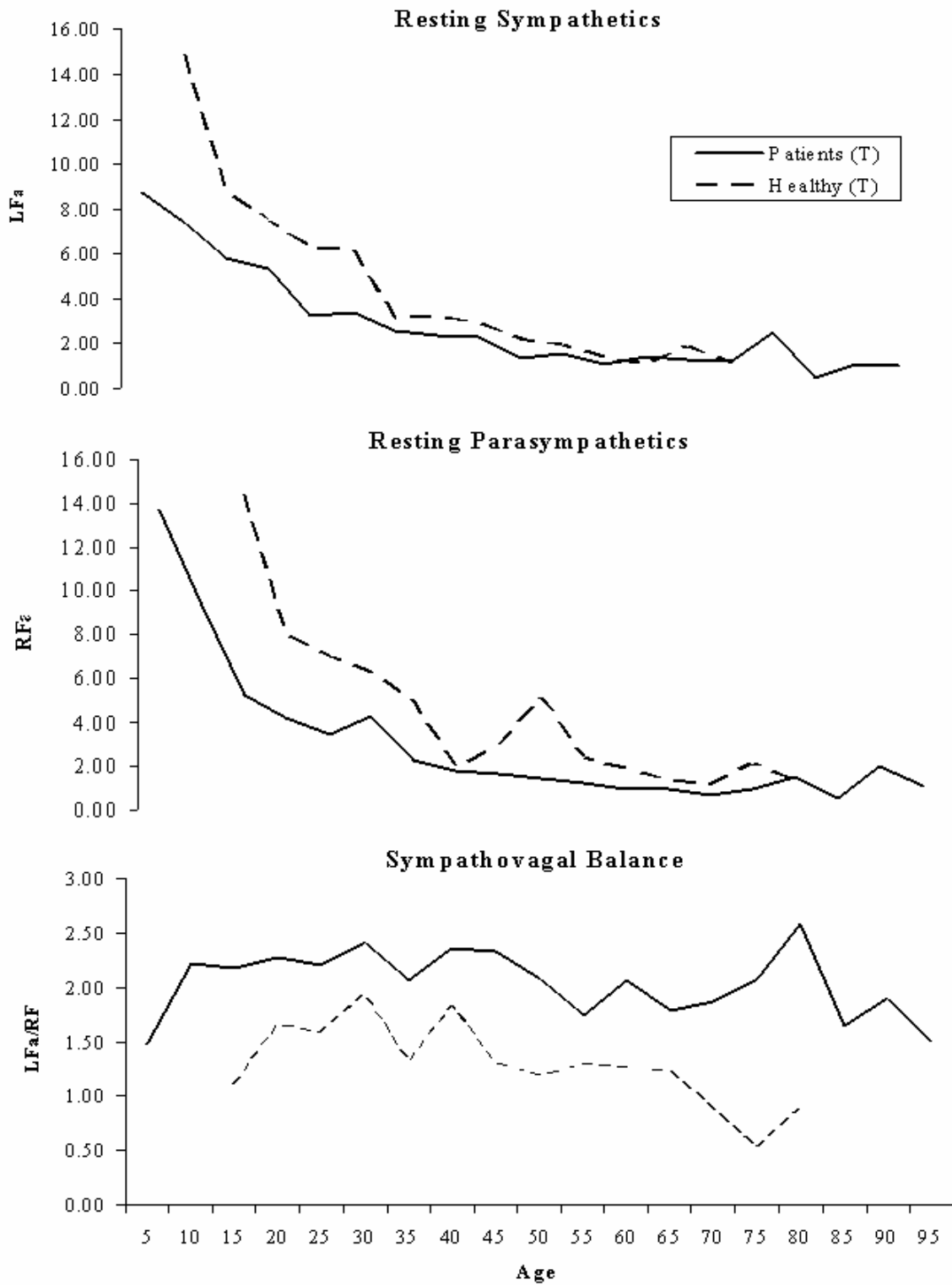


Figure 2: Average resting ANS data for the entire population taken from Fig. 1. The top panel presents sympathetic output (LFA). The middle panel presents the parasympathetic output (RFA). The bottom panel presents Sympathovagal Balance.

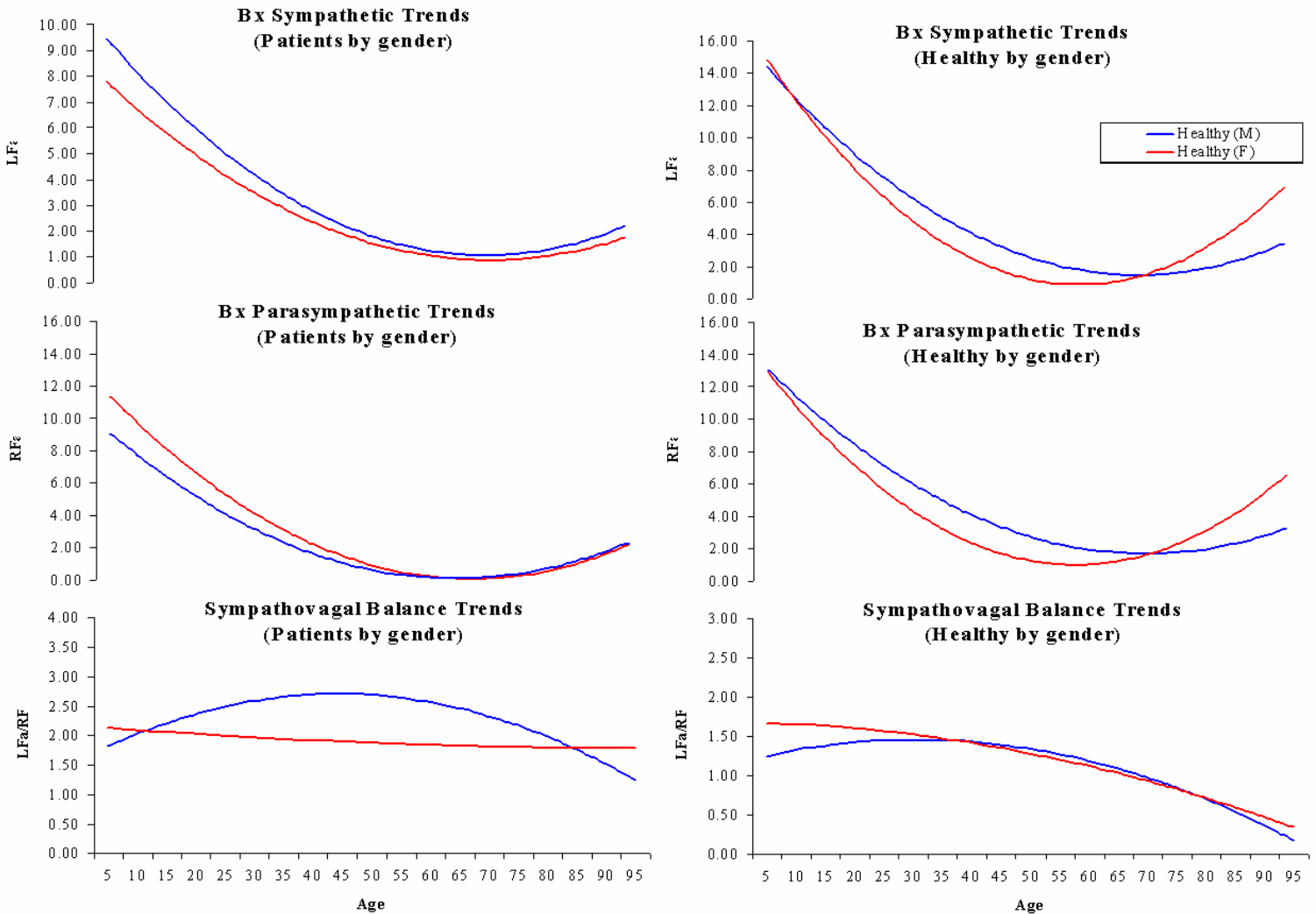


Figure 3: Resting ANS trends by gender (red for female, blue for male) separate patient (left column) from healthy (right column) for the entire population. The top row presents sympathetic output (LFA). The middle row presents the parasympathetic output (RFA). The bottom row presents Sympathovagal Balance.