

Chronic Disease Accelerates Decline of Autonomic Responsivity

Arora RR, Iffrig K, Aysin E, Aysin B, Colombo J

BACKGROUND

Aging alone is known to cause a decline in autonomic function (AF). Resting AF changes with age have been well documented [Arora, 2006a; Umetani, 1998]. Dynamic AF changes (changes in autonomic response to challenge (*e.g.*, deep breathing, Valsalva, and upright posture) are less documented. In general, chronic diseases are known to cause a decline in autonomic function [Arora, 2006a, Vinik, *et al.*, 2004]. It has also been found that autonomic responsivity to challenge decreases earlier and faster than resting AF, possibly providing a means for earlier detection of disease effects on the autonomic nervous system (ANS).

Current non-invasive autonomic measures compute ANS indices that tend to be mixed measures of both ANS branches with inherent averaging over relatively long periods of time (*i.e.*, 32 seconds) making it difficult to assess changes in individual ANS branch function independently and simultaneously during challenge periods. ANS indices with higher fidelity are available with a heart rate variability (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]. Where the spectral analyses are performed with continuous wavelet transforms. This technology enables the isolation of the sympathetic and parasympathetic branches' activities in a shorter amount of time (*i.e.*, 4 seconds), so that 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. This investigation considered the differences in the aging effects on autonomic responsivity, as computed by AFC, between healthy individuals and patients, and within patients between genders and disease states.

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 deep breathing, short Valsalva, and upright posture challenges; all preceded by periods of rest. The parasympathetic responses to deep breathing and sympathetic responses to the short Valsalva series are measures of autonomic responsivity. The autonomic 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 fourth-order polynomial trend analysis of sympathetic and parasympathetic function, and sympathovagal balance.

RESULTS & DISCUSSION

The total population data are presented in scatter plots against age (Fig. 1). Added to the scatter plots are the trend lines for the patient data, the age grouped patient averages (squares), the published average normals (triangles, only available for deep breathing and Valsalva [Akinola, *et al.*, 1999]), and the age grouped averages for the healthy subjects (gray line). Trends are presented due to the scarcity of data for some age categories. For Valsalva (Fig. 1 middle) healthy data (gray line) show greater responsivity than the patient data (squares) for all ages. For the parasympathetic response to deep breathing and sympathetic response to stand, the healthy data show more responsivity than the patient data for the young and middle age years then the reverse is the case. This reversal may be a result of therapy. With the advent of beta-1-adrenergic antagonists (β -blockers), it is known that the mortality rate due to ventricular tachyarrhythmias has decreased and the life expectancy of heart failure patients has increased. β -blockers suppress sympathetic responsivity and can increase parasympathetic responsivity as a result. The increase in parasympathetic responsivity in the older patients seems to be a reflection of this result.

The patient regression curves (DB and V Response Trend lines, black) show that the parasympathetic responses decline before the sympathetic responses. This has been reported previously (Vinik, *et al.*, 2004) and may be a source of chronic hypertension in patients (Vinik, *et al.*, 2005). The tested healthy subjects' regression curves (Healthy DB & V Trend lines, grey) do not indicate a delay in sympathetic decline. For healthy subjects the initial decline in the sympathetic response to Valsalva is greater than that for the parasympathetic response to deep breathing. Later, the sympathetic responsivity decline slows, while the parasympathetic responsivity reaches a nadir and then increases. The functions of the parasympathetics include restoration. The increase in parasympathetic responsivity in healthy subjects may reflect this function. This function would also be included in the patient results, and the fact that the patient parasympathetic responsivity increases more than that for the healthy subjects may be due to the addition of the β -blocker therapy (see above).

Comparing the published normal data (Fig. 2 triangles) to the healthy trends (Fig. 2 gray lines) shows that the healthy parasympathetic response to deep breathing (Fig. 2, top) is considerably different than the published normal data. This is not unexpected. The methods used to compute the ANS indices are different, especially for the parasympathetic (or high frequency) indices. The published data are computed by spectral analysis of HRV alone and the healthy data are computed with AFC which include an analysis of respiratory activity to isolate and better specify parasympathetic influence on HRV. The differences in the data are a reflection of the differences in methodology [Aysin and Aysin, 2006]. The AFC results include the increase in parasympathetic responsivity later in life as reported from Holter data [Umetani, *et al.*, 1998], the published data do not. The published normal (triangles) and healthy (gray) sympathetic Valsalva response data (Fig. 2, middle) are similar. Again, this is not unexpected since the low frequency computations in both methodologies are similar [Aysin and Aysin, 2006, Arora, *et al.*, 2006b].

Analysis of autonomic responsivity specific for gender are presented in Fig. 3. Comparing patient and healthy gender differences for parasympathetic responses to deep breathing challenge (Fig. 3, top row, left and right respectively) shows that the females are more responsive early, declining more rapidly than males becoming less responsive than males during the mid-life years. The female patients then become more responsive than males again later in life. The healthy female data does not show this late life reversal. The increase in females'

parasympathetic responsivity later in life seems to be associated with their greater longevity as compared to males [Arora, *et al.*, 2006c] and is in keeping with the resting parasympathetic increase observed from Holter data [Umetani, *et al.*, 1998].

The sympathetic responses to Valsalva shows that the female patients (Fig. 3. middle row left) are more responsive early and become less responsive later in life as compared to male patients. The opposite is true for the healthy patients' sympathetic responses to Valsalva (Fig. 3. middle row right). The lower sympathetic responsivity in older females is also in keeping with the resting parasympathetic increase observed from Holter data [Umetani, *et al.*, 1998].

The sympathetic response to upright posture (standing) trends are presented in the bottom row of Fig. 3. A negative change in sympathetic response to upright posture is referred to as sympathetic withdrawal (SW) [Vinik, *et al.*, 2006] and is associated with the forms of orthostasis. Sympathetic responsivity to upright postural change declined with age for all subjects. Male patients declined more rapidly and presented with SW later in life whereas the females tended not to present with SW later in life. In the healthy population, both genders present with SW later in life and it is the females that decline more rapidly than the males.

CONCLUSION

Autonomic function declines with aging, even in healthy individuals. Autonomic decline is associated with aging. Disease accelerates autonomic decline. The apparent acceleration of autonomic responsivity decline seems to be independent of gender and a function of chronic disease.

REFERENCES

- Akinola A, Bleasdale-Barr K, Everall L, Mathias CJ (1999) Investigation of Autonomic Disorders: Appendix I. In: *Autonomic Failure : A Textbook of Clinical Disorders of the Autonomic Nervous System*. Oxford Medical Publications, London, England. Mathias CJ and Bannister R (eds.), pp 194-5.
- Arora RR, Colombo J, Iffrig K. (2006a) Chronic disease related decline of resting autonomic function shows gender-based aging differences. American Autonomic Society Symposium, Rio Grande, PR.
- Arora RR, Shoemaker WC, Colombo J, Iffrig K. (2006b) Spectral analysis of respiratory activity provides a second autonomic measure associated with spectral analysis of heart rate variability. American Autonomic Society Symposium, Rio Grande, PR.
- Arora RR, Colombo J, Iffrig K. (2006) Geriatric female longevity associated with elevated parasympathetic tone. Can the same be affected in geriatric males? American Autonomic Society Symposium, Rio Grande, PR.
- 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.
- Shoemaker WC, Belzberg H, Wo CJ, Colombo J, Aysin E. (2006a) From the Department of Surgery, Division of Trauma/Critical Care, U Southern California, LA. 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) From the Department of Surgery, Division of Trauma/Critical Care, U Southern California, LA. 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. Diabetes Technology Conference, Philadelphia, PA.
- Vinik AI, Iffrig K, Aysin B, Aysin E, Colombo J. (2006) Diabetes may accelerate the onset of orthostasis. Diabetes Technology Society Meeting, Atlanta, GA.

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

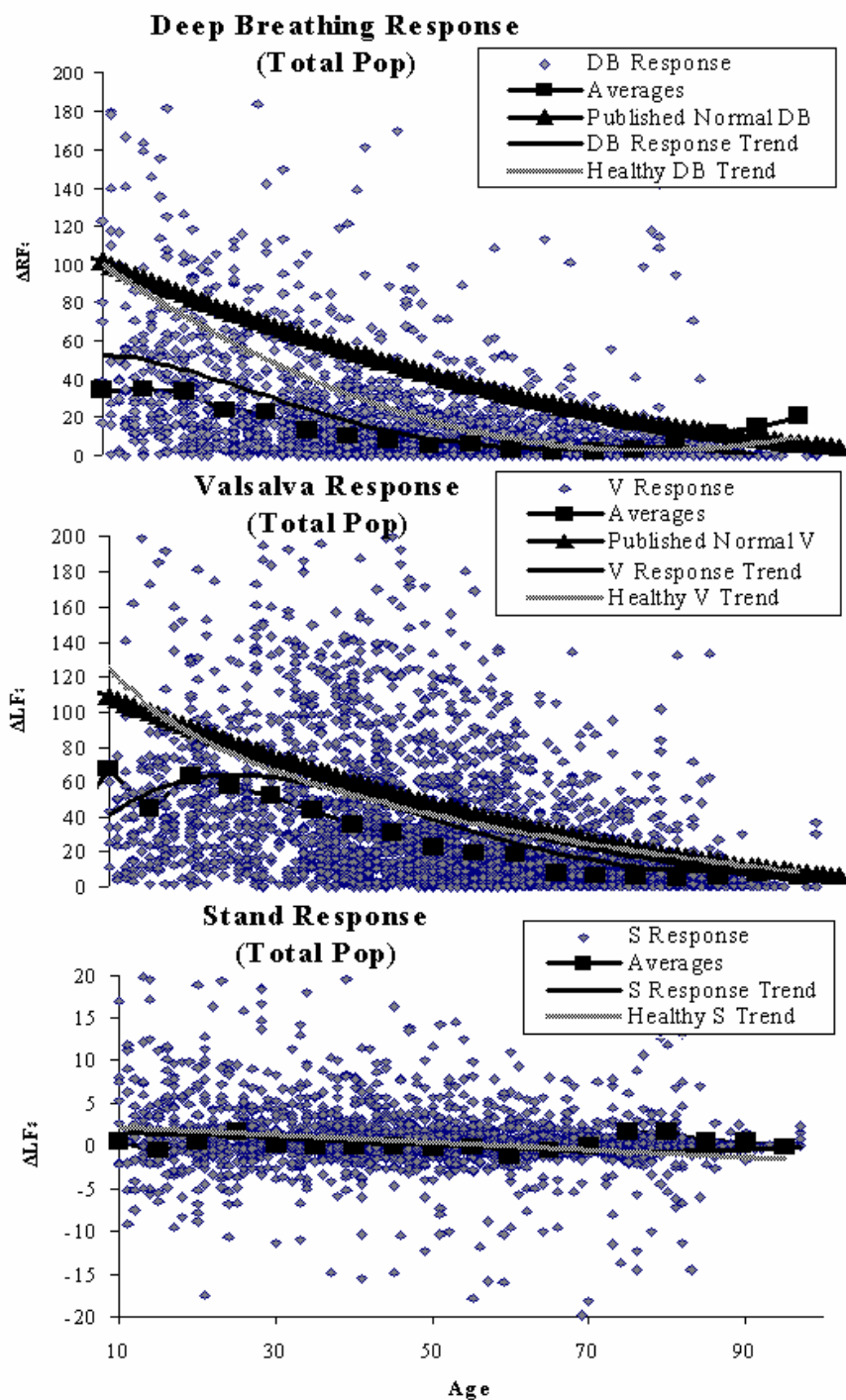


Figure 1: Dynamic ANS data for the entire population. The top panel presents parasympathetic response (ΔRFa) to paced deep breathing. The middle panel presents the sympathetic response (ΔLFa) to a series of short Valsalva maneuvers. The bottom panel presents the sympathetic response (ΔLFa) to upright posture. 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.

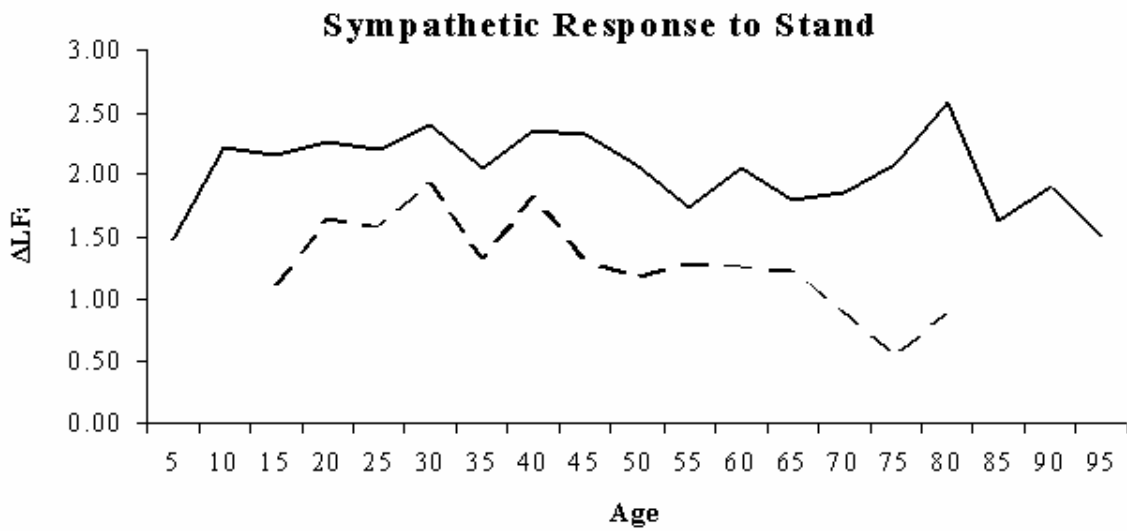
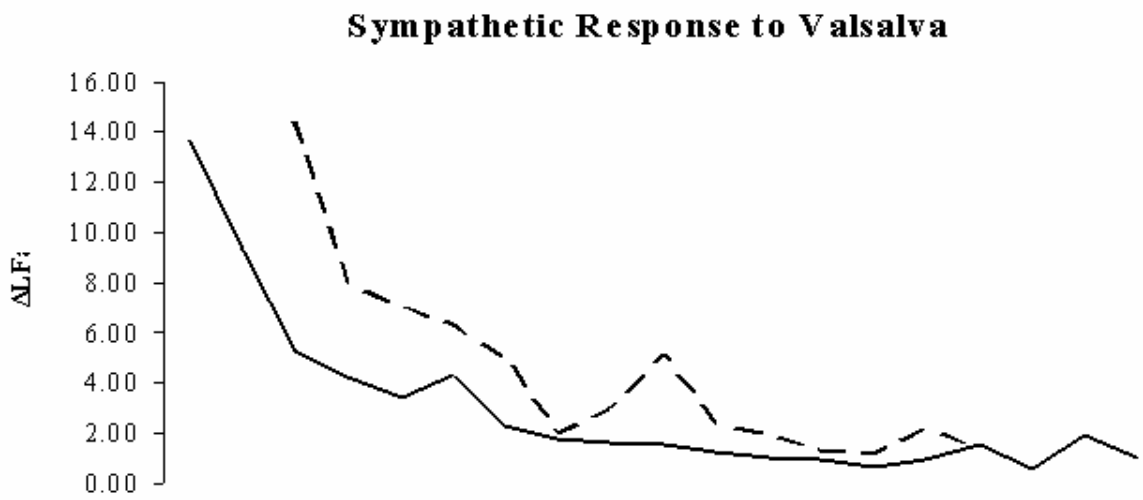
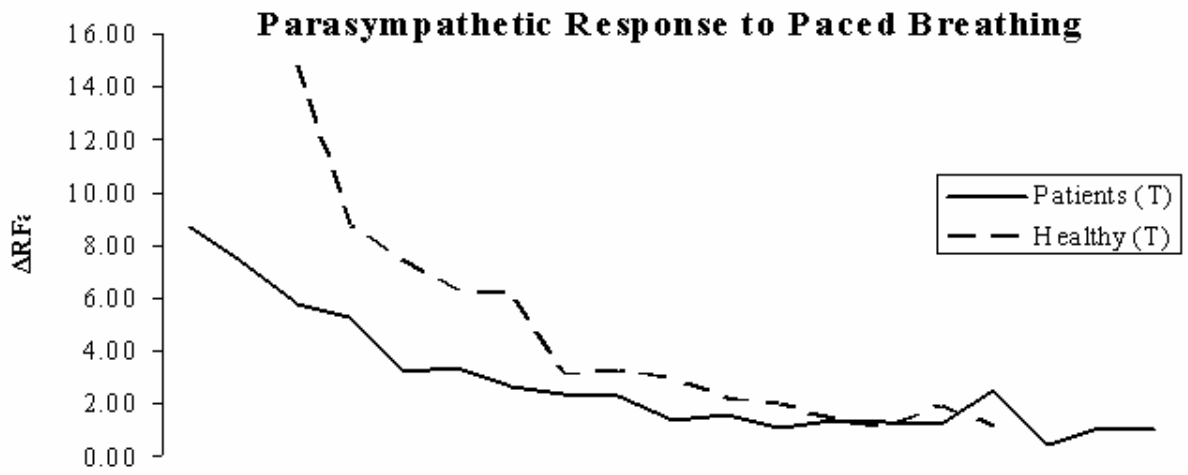


Figure 2: Average dynamic ANS data for the entire population taken from Fig. 1. The top panel presents parasympathetic response (ΔRFa) to paced deep breathing. The middle panel presents the sympathetic response (ΔLFa) to a series of short Valsalva maneuvers. The bottom panel presents the sympathetic response (ΔLFa) to upright posture.

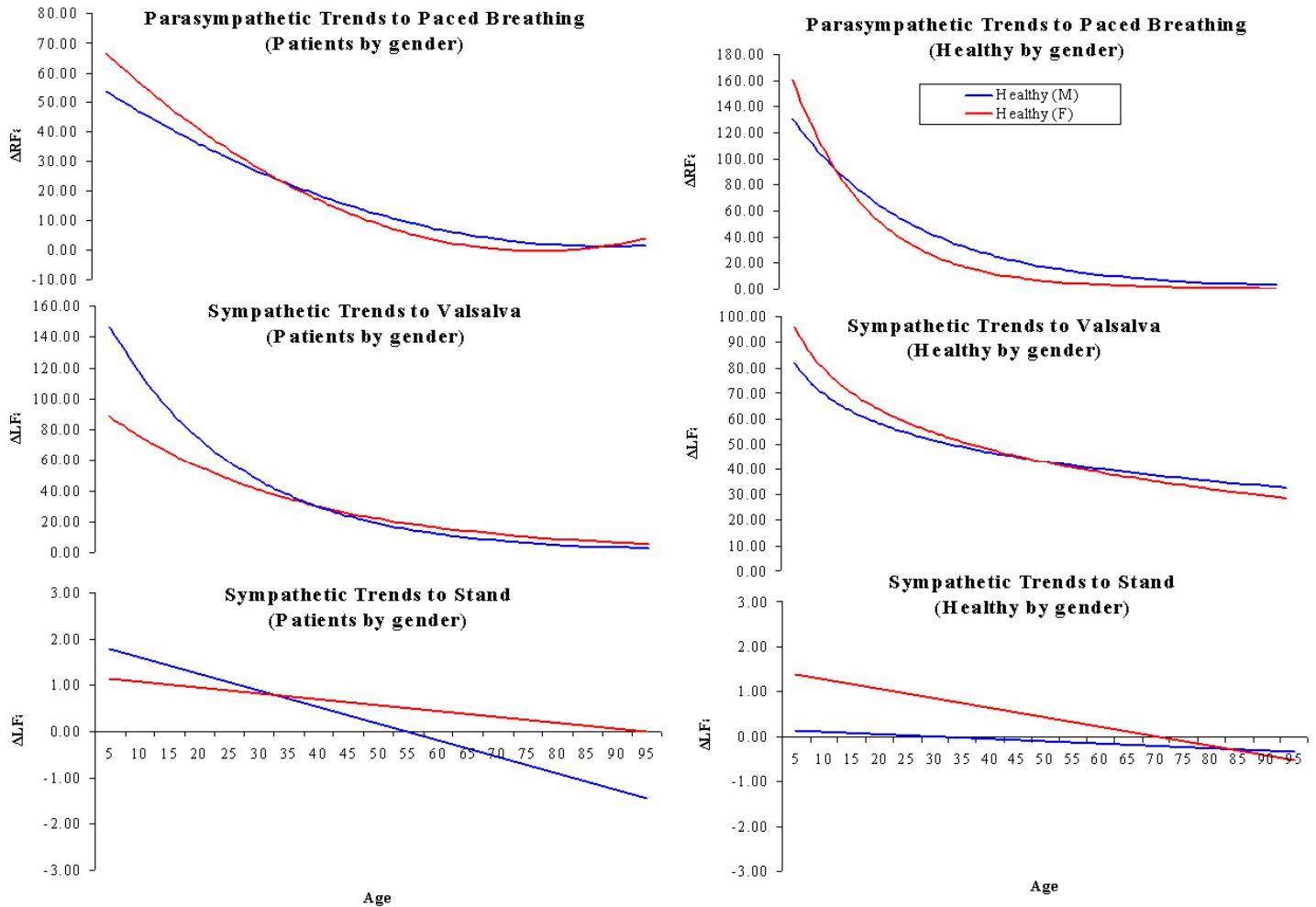


Figure 3: Resting ANS trends by gender (red for female, blue for male) separate patient (left column) from healthy (right column) for the entire population. The top row presents sympathetic output (ΔLFa). The middle row presents the parasympathetic output (ΔRFa). The bottom row presents Sympathovagal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