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Gender Differences In Longevity and Sympathovagal Balance

Edward Pereira, MD; Scott Baker, MD; Robert Bulgarelli, DO; Gary L. Murray, MD; Rohit R. Arora, MD; Joseph Colombo, PhD

BACKGROUND

Female longevity is not yet understood. Aging is associated with progressive decline in autonomic (parasympathetic and sympathetic, or P and S) function and mortality risk. By 60 years of age, resting P and S activity may reach low levels associated with higher risk of morbidity (quality of life) and mortality (longevity). Subsequently, the decline slows and may reverse [1], implying that longevity relates to preservation of autonomic function. Gender differences in longevity could reflect gender differences in the preservation of autonomic function.

The decline in the absolute levels of P and S function seems similar for both female and males. Holter monitoring studies [1] suggest that the relative levels of P and S activity differs between the genders. Geriatric females demonstrate more parasympathetic activity relative to sympathetic activity than do age-matched males. It is known that geriatric females have reduced morbidity and mortality and greater longevity than do geriatric males [1]. Therefore, greater parasympathetic tone is associated with the greater longevity in females. This study considers the sympathovagal balance (SB) for female and male by age group to further investigate the dichotomy found in the Holter data.

Geriatric Holter data indicate [1] that elevated parasympathetic activity in elderly females (over 75 years old, including heart failure patients) is associated with longevity [2]. Elevated parasympathetic activity results in lower SB. This study investigates whether female-like SB in males is also associated with longevity.

It may be that greater parasympathetic tone enables a great degree of protection from cardiac stress through a reduction in the corresponding sympathetic tone [3]. This hypothesis is supported by the fact that the incidence of cardiac events associated with non-sustained ventricular tachyarrhythmia has greatly diminished and the life expectancy of heart failure patients has greatly increased since the advent of beta-1-adrenergic blockers.

P&S Monitoring has been shown to be a more accurate means of measuring both P and S independently, simultaneously, non-invasively, and quantitatively. P&S Monitoring also provides a true measure of SB. Short-term (15.5min) ANS assessment also suggests that elevated parasympathetic tone is associated longevity and fewer co-morbidities in geriatric females [2,4]. Elevated parasympathetic tone can present as a low-normal SB. The normal range for SB is $0.4 < SB < 3.0$. Therefore, elevated parasympathetic activity (relative to sympathetic activity) could be defined as the range of SB from 0.4 to 1.0, or low-normal SB (see right insert, blue shaded area). We hypothesize that the low normal SB sub-population will have the greatest number of patients living the longest, including males. The corollary to this hypothesis is that the more “male-like” high normal SB (indicating elevated sympathetic tone) will include females with shorter life spans. This would then suggest that low-normal SB also could be associated with reduced morbidity and mortality in the geriatric population.

The global implications of this hypothesis are improved patient outcomes and reduced healthcare costs. The first assumption is that low-normal SB (elevated parasympathetic tone), not gender, is associated with longevity. The second assumption is that adrenergic (sympathetic) blockade (*e.g.*, beta-blockers and anti-hypertensives, including ACE-Is, ARBs, CCBs, and alpha-adrenergic antagonists) induces low-normal SB. Together, it may be that the use of adrenergic blockade to establish and maintain low-normal SB (elevated parasympathetic activity) could improved patient outcomes, promoting longevity by reducing morbidity and mortality, and reducing medication-load and hospitalizations, thereby reducing healthcare costs, both for the patient and the nation.

See “P&S Monitoring vs. HRV-alone” subsection in the “Introduction” of “Age Matched Attenuation of Both Autonomic Branches in Chronic Disease: I. Hypertension” for a short discussion of the background to independent, simultaneous P and S assessment. With independent, simultaneous measures of P and S activity, a causal relationship between aging and chronic diseases, and autonomic dysfunction leading to autonomic neuropathy and eventually cardiovascular autonomic neuropathy (CAN) may be possible [5,6,7] This study considers the relationship between the resting P and S activity in the geriatric patient. This is a retrospective study.

METHODS

P&S Monitoring of 5008 consecutive geriatric cardiology patients, 65 years or older, was performed (ANX 3.0, ANSAR Medical Technologies, Inc., Philadelphia, PA). The patients were from clinics in the Chicago, IL area. All patients were assessed as they were, with all medications on board and no interruption in lifestyle. Only high density arrhythmic patients (97 total, 44 Female), with either atrial fibrillation or ventricular arrhythmia, were omitted. Of the cohort, 710 were diagnosed with diabetes; 2802 were diagnosed with heart failure; and 4016 had a history of hypertension. Most hypertensives were well managed at the time of autonomic profiling. After omitting patient records with high quality arrhythmia, 4911 patients remained (3007 females, average age = 73.6 ± 5.9).

P&S Monitoring is based on patient responses to a standard clinical study that includes a 5-min resting baseline. Figure 1 presents the (baseline) resting response plot. The abscissa represents sympathetic activity and the ordinate represents parasympathetic (Vagal) activity. Normal adult ranges for P and S are 1.0 to 10.0 bpm². SB is defined as resting sympathetic activity over resting parasympathetic activity (=S/P). “Perfect” SB is 1.0. Normal SB is between 0.4 and 3.0.

Therefore, there are at least four logical ranges for SB: 1) *high*, $SB > 3.0$; 2) *low*, $SB < 0.4$; 3) *high-normal*, $1.0 < SB < 3.0$, and 4) *low-normal*, $0.4 < SB < 1.0$. The patients were classified according to these ranges. Low SB indicates resting, parasympathetic excess (PE, see Figure 1, top left graph, blue shaded area) and is associated with complaints of fatigue, exercise intolerance, and depression. Low-normal SB indicates more parasympathetic activity (see Figure 1, top right graph, blue shaded area), and is the hypothesized range recommended for the elderly and seems associated with reduced mortality and morbidity. High-normal SB indicates more sympathetic activity (see Figure 1, bottom left graph, red shaded area), and is thought to be the range appropriate for (physiologically) younger patients. High SB indicates resting, sympathetic excess (SE, see Figure 1, bottom right graph, red shaded area) and is associated with increased morbidity and mortality, including increased risk of cardiovascular events and sudden cardiac death. Data were analyzed with SPSS 14.0.

RESULTS AND DISCUSSION

The results are presented in Figure 2. Patients from the four categories of SB are plotted separately, by age and by gender, in the four bar graphs of Figure 2. Age is indicated on the abscissa of each graph, grouped by half decades from age 65. Gender is indicated by color: pink for females and blue for males. The ordinates indicate percent of population on a logarithmic scale. Therefore, each bar indicates the percent of the total population whose age and gender are indicated in that bar (bin) at the time of autonomic assessment. Longevity is indicated by the numbers of people in that group that have lived longer than in other groups.

- With SE (as indicated by $SB > 3.0$, and presented in the lower right graph of Figure 2) no patient lived beyond 85, with more women reaching their 7th and 8th decade than men. This is the subpopulation with the highest mortality risk. It is also the subpopulation that is reported to have the highest morbidity risk with the greatest medication-load and number of hospitalizations [8]. SE is associated with poor outcomes [3]. Many of these patients demonstrate CAN. CAN, together with SE, indicates high risk of mortality [9].
- With PE (as indicated by $SB < 0.4$, and presented in the upper left graph of Figure 2), no male lived beyond 85 years of age, with some females living into their upper 80s. PE can be associated with depression, fatigue, exercise intolerance, and sleep difficulties. CAN compromises cardiac and vascular control leading to cardiovascular disease. Depression is known to increase mortality risk in patients with cardiovascular disease [10]. This may be the reason for the association of low SB with the second highest mortality risk reported.
- With high-normal SB (indicating sympathetic dominance: $1.0 < SB < 3.0$), women lived into the first half of their 9th decade. No males lived past 85 years of age, and more females lived into their late 70s and early 80s. High-normal SB indicates more sympathetic activity, and seems to be associated with physiologically younger adults. Perhaps high-normal SB is a physiologic condition of child-rearing. It has been observed that younger adult patients with low-normal SB (indicating more parasympathetic activity, see next paragraph) tend to report symptoms of depression, fatigue, exercise intolerance, and sleep difficulties. It may be that low-normal SB is too low for these younger patients. With therapy to establish and maintain high-normal SB (*e.g.*, anti-cholinergic therapy in the form of low-dose, short-term, anti-depressants), these patients report a reduction in symptoms and a return to normal function.
- With low-normal SB (indicating parasympathetic dominance: $0.4 < SB < 1.0$), women lived into the second half of their 9th decade, and the males in this sub-population lived into the

first half of their 9th decade. This is the only condition under which males survived past 85 years of age. Again, more females than males lived into their late 70s and early 80s. Low-normal SB is associated with the “more parasympathetic activity” indicated by Umetani, *et al.* [1]. Therapy may be titrated against establishing and maintaining low-normal SB. Therapy includes: 1) sympathetic blockade, in the form of beta-blockers or anti-hypertensives, if baseline SB indicates SE; or 2) anti-cholinergic therapy if baseline SB indicates PE. Low-normal SB may also be established by titrating lower the on-board sympathetic blockade (history dependent). This is a possible therapy recommendation, history dependent, in cases where patients demonstrate CAN [9]. Establishing and maintaining low-normal SB minimizes morbidity and mortality risk [8] in all CAN patients, including geriatric patients, post-MI and post-CABG patients, and advanced chronic disease patients, such as Parkinson’s disease, Diabetes, and Heart disease patients.

These results suggest that from a simple and accurate measure of autonomic balance (SB), a patient’s longevity may be optimized through objectively titrating common therapies to lower sympathetic tone or raise parasympathetic tone such that a patient’s SB is low-normal. The evidence suggests that lower SB is similar to the more resting parasympathetic activity associated with longevity documented in the geriatric cardiology literature [1], and that low-normal SB in males can be associated with a longer life expectancy as seen in females. An empirical corollary to this finding is that high-normal SB is associated with health in (physiologically) younger subjects.

In all four SB categories, females survived longer than males, except in the high SB cases where there were no significant gender differences. The data suggest that patients (female and male) with low-normal SB tend to live longer. Low-normal SB (parasympathetic dominance) is associated with a 10-year longevity advantage in males, and up to a 15-year longevity advantage in females. The only males to survive beyond their 85th year had low-normal SB. The only females to survive beyond their 95th year had low-normal SB. Low-normal SB is associated with longevity independent of gender or disease.

Males, with female-like SB (*e.g.*, with low-normal SB indicating resting parasympathetic dominance) live longer than males without. Females, with male-like SB (*e.g.*, with high-normal SB indicating resting sympathetic dominance) have a shorter-life expectancy than females without. This is additional evidence that low normal SB is associated with optimal longevity for a given patient.

It is known that resting SE is associated with cardiac and vascular stress, including conditions leading to sudden cardiac death. SE is associated with abnormally high SB. Resting SE can be treated either by titrating higher (on-board) sympathetic blockade (history dependent), or titrating lower (on-board) anti-cholinergics (history dependent). Resting PE (abnormally low SB) is associated with depression, which is also associated with greater mortality risk in geriatric heart patients. Resting PE can be treated either by titrating lower (on-board) sympathetic blockade (history dependent), or titrating higher (on-board) anti-cholinergics (history dependent).

Geriatric patients may present with chronic conditions causing (or caused by) SE, before CAN is demonstrated. In these cases, establishing and maintaining low-normal SB still reduces morbidity and mortality. Again, this can be established and maintained by titrating sympathetic blockade. Geriatric patients may present with chronic conditions causing (or caused by) PE, before CAN is demonstrated. In these cases, establishing and maintaining low-normal SB still

reduces morbidity and mortality. Again, this can be established and maintained by titrating parasympathetic blockade (*i.e.*, anti-cholinergics). Establishing and maintaining low normal SB reduces the severity or number of co-morbidities (*e.g.*, upper or lower GI-upset, sleep difficulties, urogenital dysfunction, secondary hypertension, or dizziness or lightheadedness) and can reduce hospitalizations [8]; thereby, low-normal SB also promotes reduced healthcare costs.

CONCLUSION

Holter data does indeed indicate that geriatric females demonstrate more parasympathetic activity relative to sympathetic activity than do age-matched males. However, Holter data cannot differentiate normal levels of parasympathetic activity from PE. Low and high SB are associated with poor outcomes. Low-normal SB appears to be correlated ($p < 0.001$) with greater longevity, and as shown elsewhere, reduced morbidity and mortality [8], leading to reduced medication-load and hospitalization, and thereby reduced healthcare costs. Gender differences in longevity are associated with autonomic function.

Gender Differences

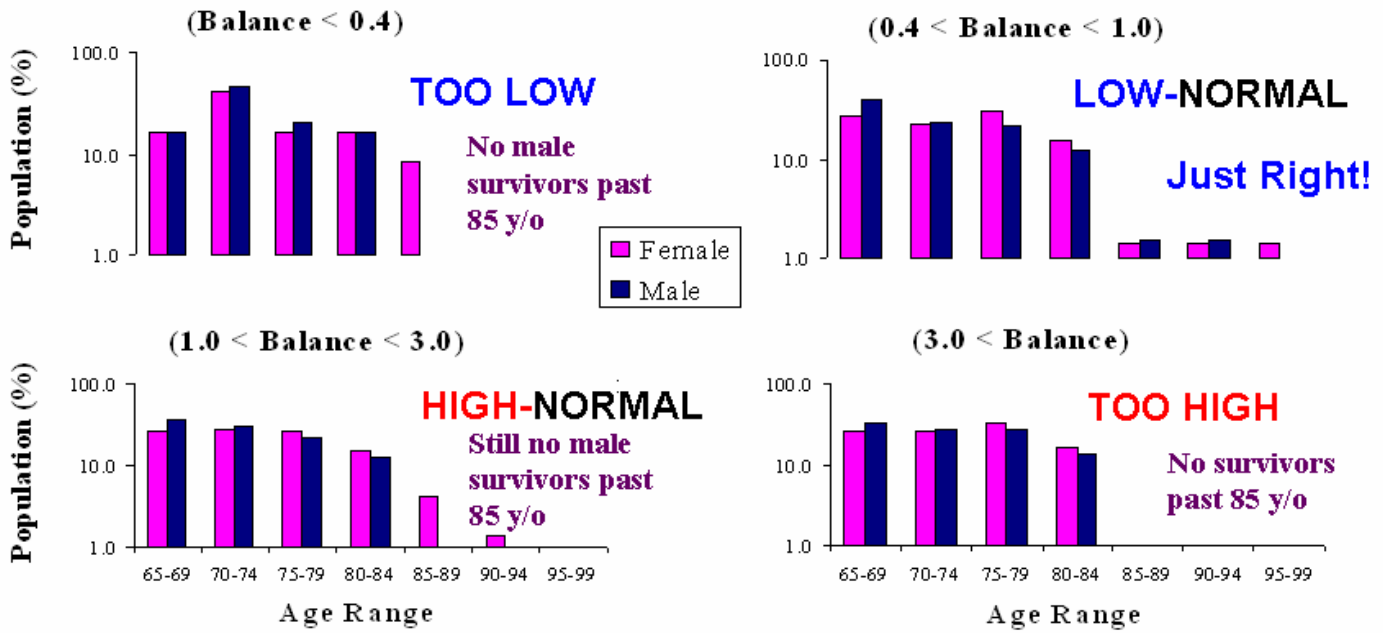


Figure 2: Patients from the four categories of SB are classified and plotted separately, by age and by gender, in the four bar graphs. The four categories of SB are: 1) *high*, $SB > 3.0$; 2) *low*, $SB < 0.4$; 3) *high-normal*, $1.0 < SB < 3.0$, and 4) *low-normal*, $0.4 < SB < 1.0$. See text for details.

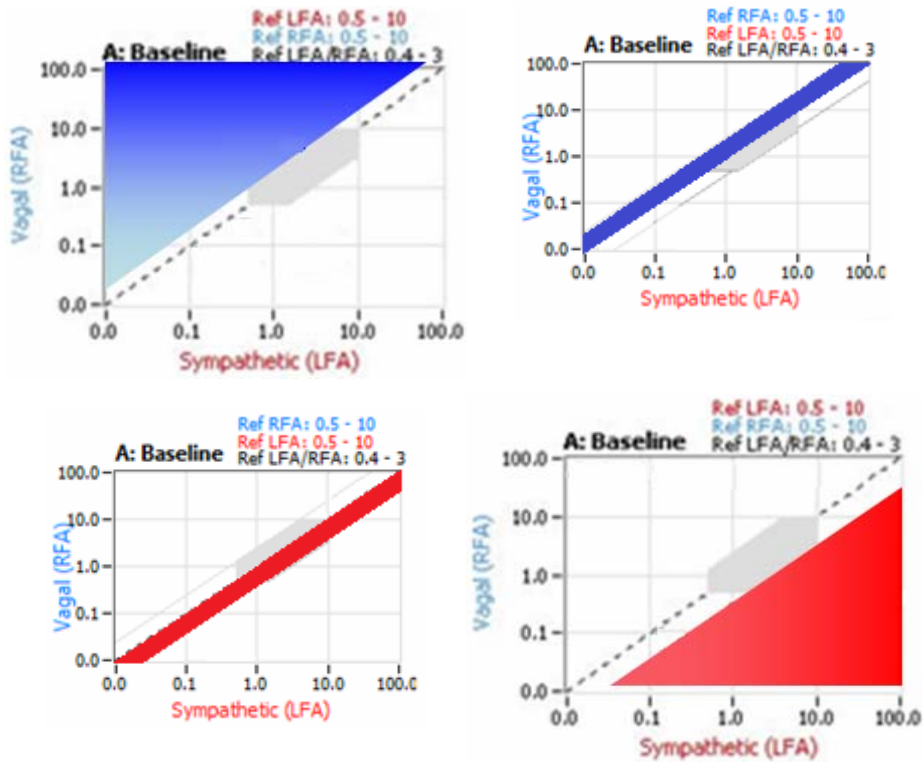


Figure 1: SB can be classified in four categories. The shaded areas in the baseline (resting) response plots depict the four categories: 1) *high*, $SB > 3.0$; 2) *low*, $SB < 0.4$; 3) *high-normal*, $1.0 < SB < 3.0$, and 4) *low-normal*, $0.4 < SB < 1.0$. See text for details.

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