Vagal modulation and aging

2 authors, including:

Phyllis K Stein
Washington University in St. Louis
254 PUBLICATIONS   **11,799** CITATIONS

ELSEVIER

Vagal modulation and aging

Ronald Edmond De Meersman [a,*], Phyllis K. Stein [b]

[a] Department of Rehabilitation Medicine, Columbia University Medical Center and The Department of Biobehavioral Sciences,
Teachers College, Columbia University, New York, NY 10032, United States
[b] Division of Cardiology, Washington University School of Medicine, St. Louis, MO 63110, United States

Dedicated to my mentor, Dr. John Alexander Downey, M.D., D. Phil.

Abstract

Cardiovascular disease accounts for approximately 30% of all deaths worldwide, and will only worsen as the world's population ages. It is well-established that age, per se, is a major risk factor and contributor to all cardiovascular morbidities and mortalities. However, environmental factors, including a lack of exercise, appear to play a critical role in the onset and progression of cardiovascular disease. This paper reviews the literature on cardiac variability and aging and addresses risk factors associated with aging that can be modified and possibly attenuate the decline of heart rate variability with aging, including exercise training to increase vagal modulation. Thus, results of the studies described in this review support a potential benefit of increasing or maintaining fitness in order to slow the decline of parasympathetic control of HR with normal aging.
© 2006 Elsevier B.V. All rights reserved.

Keywords: Cardiac vagal control; Cardiac vagal tone; Vagal modulation and aging; Autonomic nervous system; Heart rate variability; Exercise; Aging; Cardiovascular disease

1. Autonomic dysfunction and cardiovascular disease

Cardiovascular disease accounts for approximately 30% of all deaths worldwide. This death rate will soon surpass the infectious diseases as the leading cause of mortality. This epidemic will only worsen as the world's population ages. In the United States alone there are over 35 million people over 65 years old and it is projected that this number will double by the year 2030. It is well-established that age, per se, is a major risk factor and contributor to all cardiovascular morbidities and mortalities. Furthermore, automation has altered our lifestyle and therefore greatly contributed to this cardiovascular disease epidemic. Support for this notion that environmental factors, including a lack of exercise, account for the majority of our cardiovascular diseases has been provided by a number of cohort studies. Ultimately, all of these cardiovascular diseases are associated with a common denominator, namely a "perturbed autonomic balance" in which there is either a decrease in vagal modulation, an increase in sympathetic modulation or a combination of both. It is tempting, therefore, to hypothesise that preservation of cardiac autonomic function by lifestyle or interventions should be associated with a marked reduction in the risk of cardiovascular disease and death.

This review will focus on one component of cardiac autonomic balance, namely vagal modulation of heart rate. Its purpose will be: (1) to describe the effects of normal aging and gender on vagal modulation of HR as quantified by indices of heart rate variability (HRV) and to provide normative data for each decade of adult life, (2) to describe the effects of changes in physical fitness and body weight on vagal modulation of HR, and (3) to discuss the associations of various pathologies (heart disease, depression and metabolic syndrome) upon vagal modulation of HR. This review is not all inclusive; however we have attempted to provide an unbiased selection of scientific papers. We apologize for the omission of many pertinent and current references.

2. Heart rate variability measure reflecting vagal modulation

To familiarize the reader with the various time and frequency-domain measures of HRV that reflect vagal (i.e.,

Table 1
Definitions of time-domain and frequency-domain measures reflecting vagal modulation of HR

pNN50 (%)	Percent of differences between adjacent normal RR intervals that are greater than 50 ms, computed from short-term recordings or over the entire 24 h electrocardiogram recording. These measures strongly reflect vagal modulation
rMSSD (ms)	Root mean square successive difference, the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals from short-term recordings or from the entire 24 h electrocardiogram recording. This time-domain measure strongly reflects vagal modulation
SDSD (ms)	The standard deviation of successive differences between adjoining normal cycles
sNN50 (or counts)	Absolute number of adjacent normal RR intervals differing by >50 ms. Less commonly used in current studies
Low frequency power (LF)	Low frequency modulations of heart rate variability represent the variance of the heart period spectrum between 0.03 and 0.15 Hz. Both sympathetic and parasympathetic contributions are involved during rest. Usually computed per 5 min or sometimes over a shorter period. Usually averaged per 5 min for a 24 h recording
High frequency power (HF)	High frequency modulation of heart rate variability represents the variance of the heart period spectrum centered at the respiratory frequency of a range between 0.15 and 0.4 Hz and has been accepted as a marker of vagal modulation of HR. Usually computed per 5 min or sometimes over a shorter period. Usually averaged per 5 min for a 24 h recording
LF/HF	Ratio of low to high frequency power or sympathovagal balance. Changes from one time point to the next can reflect changes in the balance between sympathetic and parasympathetic modulation of HR. Usually computed per 5 min or sometimes over a shorter period. Usually averaged per 5 min for a 24 h recording

parasympathetic) modulation of HR, definitions for some commonly used measures are shown in Table 1. At this time, no definitive conventions for these time and frequency-domain measures exist, so the reader may encounter different abbreviations and subscripts in the literature.

For the papers cited in this review the definitions above apply. It is important to note that no units are presented for the frequency-domain measures. In general, frequency-domain HRV is natural log transformed to permit parametric statistical evaluation. Also, frequency-domain HRV can be normalized in various ways to try to capture the proportion that is accounted for by HF or LF. Since normalized HRV is calculated in different ways, caution should be used in comparing results of different studies. Furthermore, the term HRV is used interchangeably for studies that are based on long-term Holter monitoring and for those based on very short recordings. Therefore, we will try to indicate the recording period in the studies described below.

3. Stability of heart rate variability measures

If 24 h or short-term HRV is to be used for risk stratification or to assess the efficacy of an intervention, it must be reproducible. Gerritsen et al. (2003) studied the stability of short duration (1–3 min) HRV measures as part of the Hoorn study. Stability in a sub-sample was moderate to high. To improve stability they recommended standardization of measurement conditions with particular attention to time of day in order to eliminate diurnal rhythms (Gerritsen et al., 2003). More recently, our group demonstrated significant correlations between short duration epoch measurements of HRV measures obtained from 2 consecutive data collections in older (mean age 62.5 years) chronic obstructive pulmonary disease patients (Bartels et al., 2004). The stability of heart rate variability as a measure of parasympathetic activity is of particular interest in clinical medicine. Nolan and co-workers determined the reproducibility of parasympathetic activity of 24 h duration electrocardiograms from normal participants and ischemic heart disease patients during follow-up periods ranging from 2 to 16 weeks. Their

coefficients of repeatability showed excellent long-term reproducibility (Nolan et al., 1996). Short-term (2 weeks) and long-term (7 months) reproducibility of 10 min ECG derived time and frequency-domain heart rate variability measurements were evaluated by Pitzalis and co-workers in normal participants. Vagal-modulated time-domain measurements showed intraclass correlation coefficients (ICC) > or =0.75. The frequency-domain measures obtained by means of either Fourier transformations or autoregressive methods showed similar reproducibility (Pitzalis et al., 1996). Therefore, it appears that both short- and long-term time and frequency-domain measures provide acceptable reproducibility in normal participants and in diseased populations.

4. HRV indices of vagal modulation of HR over the lifespan in healthy participants

Table 2 represents time-domain measures of vagal modulation of heart rate per decade of life in a normal healthy population. Results were based on 24 h Holter recordings. This study was chosen as an example of normative data because of the very stringent inclusion criteria (absence of coronary artery disease, diabetes, overweight, hypertension, neurological and psychiatric disorders and the use of chronic medication except for oral contraceptives). Shift workers were excluded from the study as well (Bonnemeier et al., 2003).

Table 3 provides another set of normative data by decade for vagally-modulated 24 h HRV time-domain measures from Umetani et al. (1998).

Table 2
Effects of aging on vagally-modulated 24 h HRV parameters by decade (Bonnemeier et al., 2003)

Decade	rMSSD (ms)	sNN50
20–29	46.3 (17.9)	810.1 (395.6)
30–39	35.5 (15)	555.1 (419.6)
40–49	26.1 (9.1)	273.7 (208.9)
50–59	24.2 (10.9)	218.3 (279.8)
60–70	18.8 (6.8)	109.4 (155.8)

Table 3
Normative time-domain measures of vagally-modulated 24 h heart rate variability (Umetani et al., 1998)

Age (year)	rMSSD (ms)	pNN50 (%)
20–29	43 (19)	18 (13)
30–39	35 (11)	13 (9)
40–49	31 (11)	10 (9)
50–59	25 (9)	6 (6)
60–69	22 (6)	4 (5)
70–79	24 (7)	4 (5)
80–99	21 (6)	3 (3)

Table 4
Normative data of log-transformed short-term frequency-domain measures

Age group	30–39	40–49	50–59	60–69
HF(ln) (ms^2)				
Male	4.5 (1.2)	4.3 (0.7)	3.9 (1.0)	3.4 (1.3)
Female	5.0 (1.2)	4.5 (1.0)	4.1 (1.2)	3.9 (0.8)
LF(ln) (ms^2)				
Male	5.4 (1.2)	5.4 (1.0)	5.2 (1.0)	4.6 (1.1)
Female	5.4 (0.9)	4.8 (1.3)	5.0 (0.9)	4.6 (1.1)

Values are mean ± S.D. HF, high frequency; LF, low frequency, both are log-transformed.

Fukusaki and co-workers also investigated the relationship of age and HRV in a population-based sample of 373 participants. In this study, HRV was derived from short-term, resting recordings. They used factor analysis to eliminate coupling between age and other variables (fitness, triglycerides, total cholesterol, high-density lipoprotein, glucose and systolic blood pressure). They concluded that age-related changes in HF modulation, i.e., vagal modulation of HR, was primarily mediated by aging per se and less so by physiologic changes associated with aging (Fukusaki et al., 2000). Results are shown in Table 4.

As can be seen from these tables, vagally-modulated HRV continues to decline with advancing age, at least until the sixth decade of life. Although data suggest that this decline is then stabilized, it is possible that the continuing decline in vagally-modulated HRV is masked by an increased prevalence of more random HR patterns which also elevate rMSSD and pNN50 (Stein et al., 2005).

5. Centenarians and heart rate variability

Finally, heart rate variability in centenarians was studied by Shimizu et al. (2002). Twenty-seven people aged 100 years or more in 1992 underwent a 24 h ambulatory electrocardiogram. In 1996, a follow-up study was conducted on the 10 survivors of the above cohort. Frequency-domain analyses were carried out on all data and logistic regression indicated that decreased values for the LF/HF ratio was among the variables predicting mortality among the centenarians (Shimizu et al., 2002). Piccirillo and co-workers studied heart rate variability in ultra-centenarians and found that high-frequency (HF) values of RR-intervals were higher when compared to 41–60, 61–80 and 81–100 age groups. This difference reached significance between the 81 and 100 age groups and the over 100 age group. Thus HF power was lower with each advancing age bracket through the 80–90 year old group, but not among those over 100 years of age, who showed higher HF power than the younger group. However, these data may reflect a selection bias, particularly since all studies are of a cross-sectional nature. The study by Piccirillo and co-workers concluded that the relationship of HF exhibits a U-shaped curve (Piccirillo et al., 1998). They concluded that increased spectral high-frequency power of heart rate variability could reflect a neuroautonomic pattern that helps protect individuals over 100 years of age from sudden death. However, the increased prevalence of a high degree of randomness in HR patterns which elevates HF power, as previously described, could also explain both findings, and this possibility was not tested in either study. Indeed, in the Rotterdam study, based on 10 s ECG strips, both decreased HRV and increased HRV, in a pattern that did not appear to reflect respiratory sinus arrhythmia, were significantly associated with increased death from ischemic heart disease (De Bruyne et al., 1999).

6. Effect of gender on vagal modulation of HR

As seen in Table 4, gender has a strong effect on HRV, with men, generally, having higher HRV than women. Umetani and co-workers found that gender differences are age and measure dependent. Heart rate variability of young female participants is lower than that of age-matched male participants (age 10–29 years). Gender differences decrease with age and disappear by age 50 years. The age of disappearance varies dependent upon what measure is being used. The most pronounced differences in young participants occur with pNN50. Heart rate variability of young male participants was 53% higher than that of age-matched female participants. All other measures demonstrate smaller, but still significant gender differences (Umetani et al., 1998). Differing effects of gender were also investigated by Stein et al. (1997). Twenty-four hour Holter recordings were obtained from two groups of men and women, differing in approximately 35 years of age.

Differences between younger men and younger women (mean age for both groups was 33 years) were present during the daytime, with pNN50 and rMSSD being significantly higher for men than for women. However this difference was not seen at night. When comparing older men to older women (mean age for both groups was 67 years) no statistically significant differences between the groups were found in any of the standard HRV indexes. However, the finding of no difference in HRV between older men and women could be a function of the sample size. Indeed, in the Cardiovascular Health Study where HRV was measured in 1273 adults, 65 years and older gender difference in HRV persisted with mean differences similar to those reported by Umetani et al. attaining statistical significance (Stein, unpublished data). In summary, the above studies underscore the importance of taking the effects of aging and gender on cardiac vagal modulation into consideration when between participants evaluating differences.

7. The consequences of age-associated changes in vagal modulation

It is well-established that loss of HRV occurs with aging; moreover, lower levels of vagally-modulated HRV have been demonstrated to be associated with increased cardiovascular morbidity and mortality in the elderly (Tsuji et al., 1994). Therefore, the question arises, "Are there perhaps some risk factors associated with aging that can be modified and possibly attenuate the decline of heart rate variability as we age?" The following sections will describe cross-sectional and prospective results from studies of the relationship of two of these modifiable risk factors (sedentary lifestyle and increased body weight) that are also associated with aging.

8. Association of functional capacity on vagal modulation of HR

Several cross-sectional studies have shown a strong positive relationship between functional capacity and heart rate variability within populations and in comparisons of athletes and matched sedentary controls. Exercise tolerance and 24 h HRV were assessed in 296 participants aged 30–50 years (Antelmi et al., 2004). When participants were divided into low, moderate and high fitness groups, there was a strong association between functional capacity and heart rate variability. However, after adjustment for heart rates, differences between groups were no longer statistically significant. When 9 physically active post-menopausal women (age 53 ± 1 year) were compared with 11 age-matched controls, LF and HF power from short-term HRV recordings and well as vagally-modulated baroreflex sensitivity were higher in the active women (Davy et al., 1996). In another cross-sectional study by De Meersman in which 72 male runners, ages 15–81 were compared to 72 age and weight matched sedentary individuals, breathing-associated heart rate variability, which is vagally-modulated was assessed. The overall results between the two groups showed that the physically active or runners group had significantly higher fitness levels, as assessed by maximal oxygen consumption tests (VO_2max) and significantly higher levels of breathing-associated heart rate variability, when compared with their sedentary counterparts (De Meersman, 1993). However, it is well-known that the increase in cardiovascular fitness in response to aerobic training varies across individuals. Hautala et al. (2003) tested the possibility that baseline cardiac autonomic function might influence the magnitude of this effect by performing 24 h Holter monitoring and VO_2 peak testing in 39 males, aged 35 ± 9 years. Holter monitoring and exercise testing were repeated after 8 weeks of 6 session/week at 70–80% of maximum HR. The training response correlated with both age ($r = -0.39$, $p = 0.007$) and with HF spectral power ($r = 0.46$, $p = 0.002$). Even after adjustment for age, HF power was still associated with the magnitude of the training response. Thus high vagal modulation of HR is associated with a greater improvement in exercise capacity in healthy sedentary participants and might help explain the higher heart rate variability in trained athletes.

9. Heart rate variability and cardiovascular fitness in senior athletes

Senior athletes provide a good model for testing the hypothesis that physical fitness can reduce the aging-associated loss of vagal modulation of HR. Fifteen senior athletes were compared to 14 sedentary persons of similar age (mean age 69 years) by Yataco et al. (1997). The maximal aerobic capacity (VO_2max) of the athletes was 58% higher than the sedentary men (41 ml O_2/kg/min versus 24 ml O_2/kg/min) and body mass index for the athletes was 23 compared to 31 for the sedentary individuals. Twenty-four hour Holter recordings were analyzed for time and frequency-domain measures, and comparisons were statistically adjusted for body mass index. The main findings were that senior competitive athletes have increased overall HRV and vagal modulation of HR when compared with their sedentary counterparts. HRV parameters had a positive correlation with aerobic fitness and a negative correlation with obesity. Results were compared to normalized data from 2 h recordings in younger, untrained individuals who were part of the Framingham heart study. HF power, in the senior athletes was comparable to the values in the Framingham participants <40 years of age (Yataco et al., 1997). Hunt and co-workers investigated the effects of long-term physical activity on neural vagal modulation in older physically active men. They compared integrated cardiovagal baroreflex gain, determined as the relationship between the slowing of heart rate per millimeter of blood pressure rise, between 10 young untrained men, 6 older untrained men and 12 older, physically active men. Findings in this investigation indicated that the integrated gain in older active men across groups was comparable to that in untrained young men and that long-term physical activity attenuates the neural decline in vagal control (Hunt et al., 2001). However, limitations associated with cross-sectional studies include the assumption that the only difference between those who do and do not exercise is the choice to be active, and therefore caution is needed about extrapolations to causative factors. Moreover, it should be pointed out that there is a large genetic component associated with both physical fitness and heart rate variability. Researchers estimate that the combined effects of genetics and familial environment raise the upper limit of genetic determination to about 50% for VO_2max (Bouchard et al., 1998). In addition, the contribution of genetics to rMSSD, based on twin studies, has been estimated at 40–48% (Kupper et al., 2004).

10. Effect of exercise training on vagal modulation of HR

The potential for exercise training to increase HRV has been shown in several studies. For example, Pichot and co-workers studied the effects of a 14-week program of intensive interval training on elderly men. Following the training period, functional capacity (VO_2max) increased 18.6% while the nocturnal indices for vagal modulation (rMSSD, pNN50, HF power) also increased. Thus, their findings demonstrated a significant improvement in vagal modulation associated with

intensive interval training in elderly men (Pichot et al., 2005). Jurca and co-workers investigated the effects of an 8-week moderate intensity training program on heart rate variability in post-menopausal women. After 8 weeks, women randomly assigned to the exercise group improved their vagal modulation of HR based on 10 min resting ECGs. Findings in this investigation indicate that aerobic exercise training at moderate intensity (50% of VO_2max) is sufficient to improve vagal modulation (Jurca et al., 2004). However, Stein et al. (1999) found that 12 months of supervised exercise training increased VO_2 max and decreased HR, especially at night, but had no effect on indices of vagal control of HR in 16 adults aged 66 ± 4 years. Twenty-four hour HR and HRV did not change over the same period in a control group of older adults who did not alter their activity level. Finally, in a recent meta-analysis, Sandercock et al. (2005) reported that the decrease in HR in response to exercise training was less in older adults, but the increase in HF power was more consistent across age groups. Also, a greater effect size was seen in 24 h recordings, possibly because, as seen in the Stein et al. study, the strongest effect of exercise training may be seen during the nighttime. Thus, results of the studies described above support a potential benefit of increasing or maintaining fitness in order to slow the decline of parasympathetic control of HR with normal aging.

11. Obesity and autonomic modulation

Obesity is America's most rapidly proliferating and treatment-resistant disease. Obesity is the most visible mark of a complex physiologic derangement that can include hypertension, insulin resistance, alterations in cardiac output and even increased inflammation. There is a growing consensus that obesity is associated with a reduced sympathetic response to glucose ingestion (Quilliot et al., 2005; Matsumoto et al., 2001; Laederach-Hofman et al., 2002), but there are surprisingly few studies comparing indices of vagal modulation in obese and non-obese participants. Karason et al. (1999) reported, based on 24 h Holter monitoring, that obese participants had lower HF values than lean participants. However, Quillot et al. (2001) found no relationship between obesity and vagal control of HR as quantified by short-term standardized measures of normalized HF power. Consistent with this, Petretta et al. (1995) did not find any difference in HF power on 24 h Holters between 10 young obese women and 10 controls; although LF power (reflecting a combination of sympathetic and parasympathetic control of HR) was slighter lower in the obese participants.

Considerably more data on the positive effect of weight reduction on vagally-modulated HRV are found in the literature, although in many cases the intervention included both weight loss and exercise. A decrease in heart rate is a general finding. Franchini and coworkers studied changes of autonomic cardiac profiles after a 3-week body weight reduction program in severely obese patients. HRV was from an 18 h Holter recording obtained before and at the end of the third week. The 3-week body weight reduction program reduced BMI (from 41.4 ± 4.6 to $39.5 \pm 4.3 \text{ kg/m}^2$). Significant changes in

vagal modulation of HR were observed both in the time and frequency-domain (mean squared successive difference (MSSD): +16.7%; pNN50: +31.8%; low frequency power (LF): +17.1%; HF: ±18.2%). Thus, a short-term, integrated body weight reduction program was able to favorably modify the autonomic profile in a population of normotensive, severely obese participants (Facchini et al., 2003). Results were consistent with the findings of Akehi et al. (2001) that using a very low calorie diet resulted in a mean 18% weight loss over an average of 40 days of inpatient treatment. Patients did not exercise. Twenty-four hour Holter monitoring was performed at baseline and on the final day of the program. Significant increases were seen in all vagally-modulated HRV indices.

Combining exercise and weight loss, as is generally recommended, has been reported to have similar positive effects on vagal control of HR as either intervention alone. We are not aware of any studies that attempted to separate out these potential effects. Amano and coworkers showed that following12 weeks of exercise training in which 18 obese middle-aged men and women significantly reduced their BMI and percent body fat, there was a concomitant increase in vagal modulation of HR while at rest (Amano et al., 2001). Poirier and co-workers described 8 severely obese participants (BMI $> 40.0 \text{ kg/m}^2$) who underwent a 3 month weight loss program followed by 3 month reduced-weight maintenance regimen. After the diet regimen, there was a 10% decrease in weight. HRV was derived from a 24 h Holter monitoring. The authors concluded that after weight loss, there was an increase in high-frequency modulation of heart rate variability, showing a significant increase in cardiac vagal modulation (Poirier et al., 2003). The effects of exercise and mild calorie restriction on heart rate variability (HRV) were also investigated in 12 mildly obese, normotensive Japanese women aged 45.8 ± 4.2 years with a body mass index (BMI) of $27.3 \pm 0.4 \text{ kg/m}^2$. Participants participated in a 3 month program aimed at increasing physical activity and modifying eating behavior (intervention group). The control group consisted of 12 women (age 50.1 ± 4.8 years, BMI $27.2 \pm 0.6 \text{ kg/m}^2$) who did not attend the program. Frequency-domain HRV was calculated from 5-min supine Holter recordings. After 3 months, BMI decreased significantly to $25.0 \pm 0.5 \text{ kg/m}^2$ in the intervention group. The mean and SD of the RR intervals, low and high frequency power of HRV significantly increased after the intervention, whereas no significant changes were seen for the controls. The changes in these HRV variables (calculated by subtracting the baseline values from the follow-up values) negatively correlated with the change in waist circumference, with the Pearson correlation coefficients being between -0.50 and -0.62 ($p < 0.05$). Thus, the combination of exercise and mild calorie restriction led to changes in HRV indicative of an improvement in parasympathetic modulation (Ito et al., 2001).

Finally, the work by Arone and co-workers indicates that in both animals and humans the autonomic nervous system (ANS) responds to short-term changes in systemic energy balance. Specifically, the ANS response to weight change was examined by sequential blockade of cardiac autonomic innervation with parasympathetic (atropine) and sympathetic (esmolol) blockers.

Changes in heart period (interbeat interval) from baseline after atropine defined the amount of parasympathetic control (PC). The subsequent change after esmolol defined the amount of sympathetic control (SC). In non-obese participants, weight gain to 10% above initial body weight resulted in a decrease in PC and an increase in SC, and conversely, weight loss to 10% below initial weight resulted in an increase in PC and a decrease in SC. In obese participants, weight loss resulted in the same pattern of changes in PC and SC. The major autonomic effects of weight changes were in the parasympathetic arm of the ANS (Arone et al., 1995). These findings support the hypothesis that the ANS acts to oppose weight change and may be a major influence in weight control. However, the studies described above are all relatively short-term. Laaksonen et al. (2003) conducted a 1-year study that involved both weight loss and weight maintenance in 41 obese men and women with the metabolic syndrome. Despite successful weight maintenance, the initial increase in para-sympathetically modulated HRV gradually attenuated during 1 year of follow-up.

It appears from the findings in the above mentioned investigations that acute and/or long-term weight reductions are associated with favorable changes in cardiac autonomic modulation through both parasympathetic and concomitant sympathetic modulation effects. Thus, weight reduction among the obese or maintenance of a normal weight among those who are not, appear to be potential ways to reduce aging associated declines in parasympathetic control of HR.

12. Heart disease and cardiac vagal modulation

It has been clearly shown in numerous studies that cardiac patients have significantly decreased HRV compared to healthy controls. This difference has been less consistent for indices that reflect vagal control of HR (Bigger et al., 1995) because, as previously mentioned, of the increased prevalence of sinus arrhythmia of non-respiratory origin in the elderly and among cardiac patients (Stein et al., 2005). A number of studies have asked whether aerobic exercise training could improve cardiac vagal control in patients recovering from an acute cardiac event or in patients with congestive heart failure. Significant improvements in time and frequency-domain measures of heart rate variability have been shown for post-MI patients who exercise when compared to a matched sedentary control group (Stahle et al., 1999; Malfatto et al., 1996). Moreover, it appears that exercise training performed for 8 weeks after a myocardial infarction, modifies the sympathovagal balance control of HRV toward a persistent increase in vagal modulation (Stahle et al., 1999). In a very recent study, Garet and co-workers evaluated the influence of daily physical activity on established HRV prognostic indices in patients with varying severity of congestive heart failure (CHF). They hypothesised that if mean habitual daily physical activity assessed by daily energy expenditure correlated with established prognostic HRV indices, it would further strengthen the determinant role of adopting an active lifestyle, even after myocardial infarction with altered left ventricular ejection fraction. Based on the results of their study, moderate to intensive daily physical

activity might be recommended to CHF patients, under medical supervision, in order to preserve their autonomic function (Garet et al., 2005). The prognostic role of such an improvement in daily activity still needs to be determined. More precisely, rather than daily energy expenditure, moderate to intensive physical activity appears to be the minimal intensity level required to counteract the decline in HRV observed with increasing severity of heart failure. However, another recent study reported that long-term low intensity exercise training had no effect on autonomic function (Uusitalo et al., 2004). In light of these above findings it might be important to determine the effects of daily free-living physical activity on autonomic function. As total activity time was not statistically different between the three groups, the intensity of the performed daily activities appeared to be a determinant factor influencing heart rate variability. In summary, the preponderance of studies suggests that aerobic exercise exerts a beneficial effect upon autonomic function in patients with cardiovascular disease.

13. Depression and heart rate variability in cardiac patients

Although the hypothesis that depression should have an adverse effect of on the autonomic nervous system makes sense, the evidence that this is the case is suggestive (see Rottenberg, this issue), except in the case of patients with cardiovascular disease. Depression has been shown to be a significant risk factor for first and recurrent cardiac events and for mortality in such patients. A significant number of patients, estimated to be from 20 to 50%, who die from myocardial infarction, appear to be significantly depressed prior to the infarction (Glassman and Shapiro, 1998; Greene et al., 1972; Lebovits et al., 1967). Furthermore, major depression doubles the risk that patients with newly diagnosed coronary heart disease (CHD) will experience an adverse cardiovascular event within 12 months; and its predictive value is independent of the extent of disease (Carney et al., 1988). Compared to non-depressed individuals, patients with depression are at a much greater risk of death due to cardiac-related events for up to 10 years following the diagnosis of established CHD (Barefoot et al., 1996). Even after accounting for risk factors such as arrhythmias and history of previous myocardial infarction, major depression is a significant predictor of mortality in patients at both 6 and at 18 months following myocardial infarction (Barefoot et al., 1996; Frasure-Smith et al., 1993). The predictive value of major depression for subsequent cardiovascular events is equivalent to that of left ventricular dysfunction (Barefoot et al., 1996), history of previous myocardial infarction (Frasure-Smith et al., 1993) and continued smoking (Booth-Kewley and Friedman, 1987). Depression, at least in cardiac patients, may perhaps be conceptualized to influence cardiovascular function via neuroimmunomodulatory autonomic dysregulation. Auto-nomic function is altered in depression, evidenced by reduced heart rate variability, impaired baroreflex sensitivity and increases in heart rate. These changes may influence the

pathogenesis of diseases that affect the cardiovascular system (Grippo and Johnson, 2002). It is not uncommon for all three factors, old age, coronary heart disease and depression to be clustered in the elderly, and a disturbance in cardiac autonomic modulation is the common linkage. Decreased HRV at around the time of MI has been reported in depressed versus non-depressed patients, and this decrease (using only one measure of HRV) has been calculated to explain 27% of the elevated risk of mortality in depressed patients (Carney et al., 2005). The same group has also shown that treatment of depression using cognitive behavioral therapy alone resulted in significant decreases in heart rate and increases in some HRV indices, including rMSSD during the daytime, in patients with known coronary artery disease (Carney et al., 2000). There was no change in HRV in the untreated control group. Finally, although there is not much information about the effect of treatment with selective serotonin reuptake inhibitors (SSRIs) in cardiac patients, there is evidence that treatment of depression with SSRIs enhances survival among post-MI patients (Taylor et al., 2005). Perhaps then a treatment-related improvement in cardiac autonomic function among depressed patients could play a major role in reducing risk.

14. Human model of accelerated aging and the metabolic syndrome

Prior work by Bauman et al. in a human model of accelerated aging, namely the spinal cord injured individual (SCI), suggests that the metabolic syndrome or the clustering of hypertension, dyslipidemia and hyperinsulinemia significantly contributes to accelerated cardiovascular aging (Bauman and Spungen, 1994; Bauman et al., 1998A,B, 1999). Within this model there is a consistent disruption in autonomic modulation which appears to be a common denominator in linking these co-morbidities (Grimm et al., 1995, 1997). From a public health perspective, individuals who manifest this clustering of metabolic and autonomic impairments are at a significantly higher risk for overall cardiovascular morbidity and mortality (DeVivo et al., 1989; Hartkopp et al., 1997). Furthermore, these cardiovascular risk factors have been documented in our human model of accelerated aging, the spinal cord injured (SCI) individual. Specifically, improvements in clinical care immediately post-injury and throughout life have significantly increased the lifespan of persons sustaining a spinal cord injury. Consequently, as this population ages, cardiovascular disease is the leading cause of death (46%) (DeVivo et al., 1989). Moreover, others have reported that the incidence and onset of cardiovascular disease in spinal cord injury was 14.9 times higher when compared to the general population (Hartkopp et al., 1997). In regards to the SCI populations' autonomic profile, Inoue et al. reported both the absence of the low-frequency and high-frequency component of HRV in individuals with quadriplegia when compared to a non-spinal cord injured (non-SCI) control group (Inoue et al., 1990). These investigators concluded that the interruption of sympathetic innervations to the heart may be a contributor to the downregulation of vagal modulation in this population.

Considering the above observations in the aging model it is prudent to speculate that in the normal aging population there appears to be a gradual and sustained downregulation of vagal modulation to the heart. This gradual loss of vagal modulation has been shown to be in part responsible for the increased cardiovascular morbidity and mortality in the aging population at large (Kleiger et al., 1987). These investigators concluded that the interruption of sympathetic innervations to the heart may be a contributor to the downregulation of vagal modulation in this population.

15. Summary

Vagal control of heart rate, as assessed by analysis of specific heart rate variability parameters, provides significant information about the functioning of the cardiac autonomic nervous system. Vagal control of heart rate decreases with advancing age and is generally lower among women. In the elderly, heart rate variability measures must be interpreted with caution because increased randomness of heart rate patterns can elevate these measures and make it appear that vagal modulation of the heart is better than it really is. Increased vagal control of heart rate is associated with higher levels of physical fitness and data suggest that exercise may help protect against the adverse autonomic effects of aging. Similarly, obesity and the development of the metabolic syndrome appear to have adverse effects on cardiac vagal control and weight loss helps restore autonomic balance. Cardiac vagal control is reduced in cardiovascular disease, especially after MI and in heart failure. Exercise training may help ameliorate this situation. Finally, at least among cardiac patients, psychiatric depression is associated with reduced cardiac vagal modulation and at the same time associated with markedly increased mortality. Very limited data suggest that treatment of depression in post-MI patients may improve heart rate variability and also improve survival. The use of markers of cardiac vagal modulation, especially in intervention studies, has the potential to further understanding of who may benefit and of the mechanisms by which benefit might occur.

References

Akehi, Y., Yoshimatsu, H., Kurokawa, M., Sakata, T., Eto, H., Ito, S., Ono, J., 2001. VLCD weight loss improves heart rate variability in moderately obese Japanese. Experimental Biology and Medicine 226 (5), 440–445.

Amano, M., Kanda, T., Ue, H., Moritani, T., 2001. Exercise training and autonomic nervous system activity in obese individuals. Medicine and Science in Sports and Exercise 33 (8), 1287–1291.

Antelmi, I., de Paula, S.R., Shinzato, A.R., Peres, C.A., Mansur, A.J., Grupi, C.J., 2004. Influence of age, gender, body mass index and functional capacity on heart rate variability in a cohort of subjects without heart disease. The American Journal of Cardiology 93, 381–385.

Arone, L.J., Mackintosh, R., Rosenbaum, M., Leibel, R.L., Hirsch, J., 1995. Autonomic nervous system activity in weight gain and weight loss. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology 269, R222–R225.

Barefoot, J.C., Helms, M.J., Mark, D.B., Blumenthal, J.A., Califf, R.M., Haney, T.L., O'Connor, M., Siegler, I.C., Williams, R.B., 1996. Depression and long-term mortality risk in patients with coronary artery disease. The American Journal of Cardiology 78, 613–617.

Bartels, M., Jelic, S., Gonzalez, J., Kim, W., De Meersman, R., 2004. Reproducibility of heart rate and blood pressure variability in patients with chronic obstructive pulmonary disease. Clinical Autonomic Research 14, 194–196.

Bauman, W.A., Adkins, R.H., Spungen, A.M., Kemp, B.J., Waters, R.L., 1998A. The effect of residual neurological deficit on serum lipoproteins in individuals with chronic spinal cord injury. Spinal Cord 36, 13–17.

Bauman, W.A., Adkins, R.H., Spungen, A.M., Maloney, P., Gambino, R., Waters, R.L., 1998B. Ethnicity effect on the serum lipid profile in persons with spinal cord injury. Archives of Physical Medicine and Rehabilitation 79, 176–180.

Bauman, W.A., Adkins, R.H., Spungen, A.M., Waters, R.L., 1999. The effect of residual neurological deficit on oral glucose tolerance in persons with chronic spinal cord injury. Spinal Cord 37, 765–771.

Bauman, W.A., Spungen, A.M., 1994. Disorders of carbohydrate and lipid metabolism in veterans with paraplegia or quadriplegia: a model of premature aging. Metabolism 43 (6), 749–756.

Bigger, J.T., Fleiss, J.L., Steinman, R.C., Rolnitzky, L.M., Schneider, W.J., Stein, P.K., 1995. RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. Circulation 91, 1936–1943.

Bonnemeier, H., Wiegand, U.K.H., Brandes, A., Kluge, N., Katus, H.A., Richardt, G., Potratz, J., 2003. Circadian profile of cardiac autonomic nervous modulation in healthy subjects. Journal of Cardiovascular Electrophysiology 14 (8), 791–803.

Booth-Kewley, S., Friedman, H.S., 1987. Psychological predictors of heart disease: a quantitative review. Psychological Bulletin 101, 343–362.

Bouchard, C., Daw, E.W., Rice, T., Perusse, L., Gagnon, J., Province, M.A., Leon, A.S., Rao, D.C., Skinner, J.S., Wilmore, J.H., 1998. Familial resemblance for VO₂max in the sedentary state: The Heritage family study. Medicine and Science in Sports and Exercise 30 (2), 252–258.

Carney, R.M., Blumenthal, J.A., Freedland, K.E., Stein, P.K., Howells, W.B., Berkman, L.F., Watkins, L.L., Czajkowski, S.M., Hayano, J., Domitrovich, P.P., Jaffe, A.S., 2005. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. Archives of Internal Medicine 165 (13), 1486–1491.

Carney, R.M., Freedland, K.E., Stein, P.K., Skala, J.A., Hoffman, P., Jaffe, A.S., 2000. Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosomatic Medicine 62 (5), 639–647.

Carney, R.M., Rich, M.W., Freedland, K.A., Saini, J., teVelde, A., Simeone, C., Clark, K., 1988. Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosomatic Medicine 50, 627–633.

Davy, K.P., Miniclier, N.L., Taylor, J.A., Stevenson, E.T., Seals, D.R., 1996. Elevated heart rate variability in physically active postmenopausal women: a cardioprotective effect? American Journal of Physiology 271 (2 Pt 2), H455–H460.

De Bruyne, M.C., Kors, J.A., Hoes, A.W., Klootwijk, P., Dekker, J.M., Hofman, A., van Bemmel, J.H., Grobbee, D.E., 1999. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. American Journal of Epidemiology 150 (12), 1282–1288.

De Meersman, R., 1993. Heart rate variability and aerobic fitness. American Heart Journal 125, 726–731.

DeVivo, M., Kartus, P., Stover, S., Rutt, R., Fine, P., 1989. Cause of death for patients with spinal cord injuries. Archives of Internal Medicine 149, 1761–1766.

Facchini, M., Malfatto, G., Sala, L., Silvestri, G., Fontana, P., LaFortuna, C., Sartorio, A., 2003. Changes of autonomic cardiac profile after a 3-week integrated body weight reduction program in severely obese patients. Journal of Endocrinological Investigation 26 (2), 138–142.

Frasure-Smith, N., Lespérance, F., Talajic, M., 1993. Depression following myocardial infarction: impact on 6-month survival. The Journal of the American Medical Association 270, 1819–1825.

Fukusaki, C., Kawakubo, K., Yamamoto, Y., 2000. Assessment of the primary effect of aging on heart rate variability in humans. Clinical Autonomic Research 10, 123–130.

Garet, M., Degache, F., Pichot, V., Duverney, D., Costes, F., Da Costa, A., Isaaz, K., 2005. Relationship between daily physical activity and ANS activity in patients with CHF. American College of Sports Medicine 37 (8), 1257–1263.

Gerritsen, J., Ten Voorde, B.J., Dekker, J.M., Kingma, R., Kostense, P.J., Bouter, L.M., Heethaar, R.M., 2003. Measures of cardiovascular autonomic nervous function: agreement, reproducibility, and reference values in middle age and elderly subjects. Diabetologia 46, 330–338.

Glassman, A.H., Shapiro, P.A., 1998. Depression and the course of coronary artery disease. The American Journal of Psychiatry 155, 4–11.

Greene, W.A., Goldstein, S., Moss, A.J., 1972. Psychological aspects of sudden death. A preliminary report. Archives of Internal Medicine 129, 725–731.

Grimm, D., De Meersman, R., Almenoff, P., Spungen, A.M., Bauman, W., 1997. Sympathovagal balance of the heart in subjects with spinal cord injury. American Journal of Physiology 272, H142–H143 (Heart and Circulatory Physiology 41).

Grimm, D., De Meersman, R., Garofano, R., Spungen, A.M., Bauman, W., 1995. Effect of provocative maneuvers on heart rate variability in subjects with quadraplegia. American Journal of Physiology 268, H2239–H2245 (Heart and Circulatory Physiology 38).

Grippo, A.J., Johnson, A.K., 2002. Biological mechanisms in the relationship between depression and heart disease. Neuroscience and Biobehavioral Reviews 26, 941–962.

Hartkopp, A., Bronnum-Hansen, H., Seidenschnur, A.-M., Biering-Sorensen, F., 1997. Survival and cause of death after traumatic spinal cord injury a long term epidemiological survey from Denmark. Spinal Cord 35 (2), 76–85.

Hautala, A., Torkkell, S., Raty, K., Junnari, T., Kantola, J., Mantsala, P., Hakala, J., Ylihonko, K., 2003. Cardiovascular autonomic function correlates with the response to aerobic training in healthy sedentary subjects. American Journal of Physiology. Heart and Circulatory Physiology 285 (4), H1747–H1752.

Hunt, B.E., Farquhar, W.B., Taylor, J.A., 2001. Does reduced vascular stiffening fully explain preserved cardiovagal baroreflex function in older, physically active men? Circulation 103 (20), 2424–2427.

Inoue, K., Miyake, S., Kumashiro, M., Ogata, H., Yoshimura, O., 1990. Power spectral analysis of heart rate variability in traumatic quadriplegic humans. American Journal of Physiology 258, H1722–H1726 (Heart and Circulatory Physiology 27).

Ito, H., Ohshima, A., Tsuzuki, M., Ohto, N., Yanagawa, M., Maruyama, T., Kaji, Y., Kanaya, S., Nishioka, K., 2001. Effects of increased physical activity and mild caloric restriction on heart rate variability in obese women. Japanese Heart Journal 42 (4), 459–469.

Jurca, R., Church, T.S., Morss, G.M., Jordan, A.N., Earnest, C.P., 2004. Eight weeks of moderate-intensity exercise training increases heart rate variability in sedentary postmenopausal women. American Heart Journal 147 (5), e21.

Karason, K., Molgaard, H., Wikstrand, J., Sjostrom, L., 1999. Heart rate variability in obesity and the effect of weight loss. The American Journal of Cardiology 83 (8), 1242–1247.

Kleiger, R.E., Miller, J.P., Bigger, J.T., 1987. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. The American Journal of Cardiology 59, 256–262.

Kupper, N.H., Willemsen, G., van den Berg, M., de Boer, D., Posthuma, D., Boomsma, D.I., de Geus, E.J., 2004. Heritability of ambulatory heart rate variability. Circulation 110, 2792–2796.

Laaksonen, D.E., Laitinen, T., Schonberg, J., Rissanen, A., Niskanen, L.K., 2003. Weight loss and weight maintenance, ambulatory blood pressure and cardiac autonomic tone in obese persons with the metabolic syndrome. Journal of Hypertension 21 (2), 261–262.

Laederach-Hofman, K., Kupferschmid, S., Mussgay, L., 2002. Links between body mass index, total body fat, cholesterol, high-density lipoprotein, and insulin sensitivity in patients with obesity related to depression anger and anxiety. The International Journal of Eating Disorders 32 (10), 58–71.

Lebovits, B.Z., Shekelle, R.B., Ostfeld, A.M., Paul, O., 1967. Prospective and retrospective psychological studies of coronary heart disease. Psychosomatic Medicine 29, 265–272.

Malfatto, G., Facchini, M., Bragato, R., Branzi, G., Sala, L., Leonetti, G., 1996. Short and long term effects of exercise training on the tonic autonomic regulation of HRV after myocardial infarction. European Heart Journal 17 (4), 532–538.

Matsumoto, T., Miyawaki, C., Ue, H., Kanda, T., Yoshitake, Y., Moritani, T., 2001. Comparison of thermogenic sympathetic response to food intake between obese and non-obese young women. Obesity Research 9 (2), 78–85.

Nolan, J., Flapan, A.D., Goodfield, N.E., Prescott, R.J., Bloomfield, P., Neilson, J.M., Ewing, D.J., 1996. Measurement of parasympathetic activity from 24-h ambulatory electrocardiograms and its reproducibility and sensitivity in normal subjects, patients with symptomatic myocardial ischemia, and in patients with diabetes mellitus. The American Journal of Cardiology 15 (77(2)), 154–158.

Petretta, M., Bonaduce, D., de Filippo, E., Mureddu, G.F., Scalfi, L., Marciano, F., Bianchi, V., Salemme, L., de Simone, G., Contaldo, F., 1995. Assessment of cardiac autonomic control by heart period variability in patients with early-onset familial obesity. European Journal of Clinical Investigation 25 (11), 826–832.

Piccirillo, G., Bucca, C., Bauco, C., Cinti, A.M., Durante, M., Fimognari, L.F., Cacciafesta, M., Marigliano, V., 1998. Power spectral analysis of heart rate in subjects over a hundred years old. International Journal of Cardiology 63, 53–61.

Pichot, V., Roche, F., Denis, C., Garet, M., Duverney, D., Costes, F., Barte-helemy, J.C., 2005. Interval training in elderly men increases both heart rate variability and baroreflex activity. Clinical Autonomic Research 15 (2), 107–115.

Pitzalis, M.V., Mastropasqua, F., Massari, F., Forleo, C., Di Maggio, M., Passantino, A., Colombo, R., Di Biasi, M., Rizzon, P., 1996. Short- and long-term reproducibility of time and frequency domain heart rate varia-bility measurements in normal subjects. Cardiovascular Research 32 (2), 226–233.

Poirier, P., Hernandez, T.L., Weil, K.M., Shepard, T.J., Eckel, R.H., 2003. Impact of diet-induced weight loss on the cardiac autonomic nervous system in severe obesity. Obesity Research 11, 1040–1047.

Quilliot, D., Zannad, F., Ziegler, O., 2005. Impaired response of cardiac autonomic nervous system to glucose load in severe obesity. Metabolism 54 (7), 966–974.

Sandercock, G.R., Bromley, P.D., Brodie, D.A., 2005. Effects of exercise on heart variability: inferences from meta-analysis. Medicine and Science in Sports and Exercise 37 (3), 433–439.

Shimizu, K., Arai, Y., Hirose, N., Yonomoto, T., Wakida, Y., 2002. Prognostic significance of heart rate variability in centenarians. Clinical and Experi-mental Hypertension 24 (1–2), 91–97.

Stahle, A., Nordlander, R., Bergfeld, L., 1999. Aerobic group training improves exercise capacity and HRV in elderly patients with a recent coronary event: a randomized controlled study. European Heart Journal 20 (22), 1638–1646.

Stein, P.K., Domitrovich, P.P., Hui, N., Rautaharju, P., Gottdiener, J., 2005. Sometimes higher heart rate variability is not better heart rate variability: results of graphical and non-linear analyses. Journal of Cardiovascular Electrophysiology 6, 1–6.

Stein, P.K., Kleiger, R.E., Rottman, J.N., 1997. Differing effects of age on heart rate variability in men and women. The American Journal of Cardiology 80 (3), 302–305.

Stein, P.K., Ehsani, A.A., Domitrovich, P.P., Kleiger, R.E., Rottman, J.N., 1999. Effect of exercise training on heart rate variability in healthy older adults. American Heart Journal 138 (3 Pt 1), 567–576.

Taylor, C.B., Youngblood, M.E., Catellier, D., Veith, R.C., Carney, R.M., Burg, M.M., Kaufmann, P.G., Shuster, J., Mellman, T., Blumenthal, J.A., Krishnan, R., Jaffe, A.S., the ENRICHD Investigators, 2005. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Archives of General Psychiatry 62 (7), 711–712.

Tsuji, H., Venditti, F., Manders, E., Evans, J., Larson, M., Feldman, C., Levy, D., 1994. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 90, 878–883.

Umetani, K., Singer, D.H., McCraty, R., Atkinson, M., 1998. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. Journal of the American College of Cardiology 31, 593–601.

Uusitalo, A.L., Laitinen, T., Vaisanen, S.B., Lansimies, E., Rauramaa, R., 2004. Physical training and heart rate and blood pressure variability: a 5-yr randomized trial. American Journal of Physiology (Heart Circulatory Physiology) 286, H1821–H1826.

Yataco, A.R., Fleisher, L.A., Katzel, L.I., 1997. Heart rate variability and cardiovascular fitness in senior athletes. The American Journal of Cardiol-ogy 8, 1389–1391.