International Journal of Cardiology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors

Julian F. Thayer [a,b,*], Shelby S. Yamamoto [b], Jos F. Brosschot [c]

[a] The Ohio State University, Department of Psychology, 1835 Neil Avenue, Columbus, Ohio 43210, USA
[b] Mannheim Institute of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, Heidelberg University, Ludolf-Krehl-Str. 7-11, D-68167, Mannheim, Germany
[c] Leiden University, Division of Clinical and Health Psychology, Department of Psychology, Leiden University, P.O. Box 9555; 2300 RB Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 15 July 2009
Accepted 9 September 2009
Available online xxxx

Keywords:
Heart rate variability
Risk factors
Work stress
Heart disease
Hypertension

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide. The understanding of the risk factors for CVD may yield important insights into the prevention, etiology, course, and treatment of this major public health concern. Autonomic imbalance, characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system, is associated with various pathological conditions. Over time, excessive energy demands on the system can lead to premature aging and diseases. Therefore, autonomic imbalance may be a final common pathway to increased morbidity and mortality from a host of conditions and diseases, including cardiovascular disease. Heart rate variability (HRV) may be used to assess autonomic imbalances, diseases and mortality. Parasympathetic activity and HRV have been associated with a wide range of conditions including CVD. Here we review the evidence linking HRV to established and emerging modifiable and non-modifiable CVD risk factors such as hypertension, obesity, family history and work stress. Substantial evidence exists to support the notion that decreased HRV precedes the development of a number of risk factors and that lowering risk profiles is associated with increased HRV. We close with a suggestion that a model of autonomic imbalance may provide a unifying framework within which to investigate the impact of risk factors, including psychosocial factors and work stress, on cardiovascular disease.

© 2009 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Recent research has strongly suggested that negative affective states, dispositions and work stress are associated with diseases and ill health [1–7]. Work stress, in particular, has been associated with substantial economic consequences, including increased absenteeism, increased worker turnover, decreased worker job satisfaction and associated decreases in worker productivity [8,9]. Stress at work is also a major public health risk associated with cardiovascular morbidity [10,11]. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both men and women. This is particularly true in developed countries [12,13]. A wide range of risk factors for CVD have been identified but as yet a unified model that can account for this diversity of risk factors has not been put forward.

A recent report from the Whitehall Study [11] has shown that work stress is associated with decreased heart rate variability (HRV). Decreased HRV is an independent risk factor for morbidity and mortality. The important role that the vagus nerve plays in health and disease has been known for some time [14]. However, only relatively recently have researchers and clinicians started to investigate how this knowledge can be incorporated into a greater understanding of the etiology, manifestations, course, outcomes, and treatment of disease.

In this illustrative review we show that autonomic imbalance, in which vagal inhibitory influences are deficient, is associated with increased morbidity and all-cause mortality. We also review evidence linking vagal function to established and emerging risk factors including work stress, for CVD and mortality. Importantly, we discuss evidence that factors that increase HRV are associated with decreased risk and an improved health profile. Thus, the model of autonomic imbalance may provide a unified approach to the understanding of the role of HRV in the risk for cardiovascular disease and all-cause mortality.

2. Autonomic imbalance and disease

There is growing evidence for the role of the autonomic nervous system (ANS) in a wide range of diseases. The ANS is generally conceived to have two major branches—the sympathetic system, associated with energy mobilization, and the parasympathetic system, associated with vegetative and restorative functions. Normally, the activity of these branches is in dynamic balance. However, the activity of the two branches can be rapidly modulated in response to changing environmental demands. Conceptions of organism function based on complexity theory hold that organism stability, adaptability, and health

* Corresponding author. The Ohio State University, Department of Psychology, 1835 Neil Avenue, Columbus, Ohio 43210, USA. Tel.: +1 614 688 3450; fax: +1 614 688 8261.
E-mail address: Thayer.39@osu.edu (J.F. Thayer).

0167-5273/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2009.09.543

ARTICLE IN PRESS

are maintained through variability in the dynamic relationship among system elements [1,15–17]. Thus, patterns of organized variability, rather than static levels, are preserved in the face of constantly changing environmental demands. Because the system operates "far-from-equilibrium," the system is always searching for local energy minima to minimize the energy requirements of the organism.

Another corollary of this view is that autonomic imbalance, where one branch of the ANS dominates over the other, is associated with a lack of dynamic flexibility and health. Empirically, there is a large body of evidence to suggest that autonomic imbalance, in which typically the sympathetic system is hyperactive and the parasympathetic system is hypoactive, is associated with various pathological conditions [18]. In particular, when the sympathetic branch dominates for long periods of time, the energy demands on the system become excessive and ultimately cannot be met, eventuating in death. On the way to death, however, premature aging and disease characterize a system dominated by autonomic imbalance. Thus, autonomic imbalance may be a final common pathway to increased morbidity and mortality from a host of conditions and diseases, including cardiovascular disease.

Heart rate variability can be used to assess autonomic imbalances, diseases and mortality. Parasympathetic activity and HRV have been associated with immune dysfunction and inflammation, which have been implicated in a wide range of conditions including CVD, diabetes, osteoporosis, arthritis, Alzheimer's disease, periodontal disease, and certain types of cancers as well as declines in muscle strength and increased frailty and disability [3,19]. Measures of heart rate variability (HRV) in both the time and frequency domains have been used successfully to index vagal activity. In the time domain, the standard deviation of the interbeat intervals (IBI), standard deviation of R to R intervals (SDNN), the root mean square successive differences (RMSSD), and measures of baroreflex sensitivity (an index of the responsiveness of the cardiovascular system to changes in blood pressure) have been shown to be useful indices of vagal activity. In the frequency domain both low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.40 Hz) spectral powers have been used as indices of vagal activity, although there is some debate over the branch of the autonomic system that affects these measures [20]. Whereas there is little contention concerning HF power reflecting primarily parasympathetic influences, LF power has been shown to reflect both sympathetic and parasympathetic influences. Nevertheless, while there are some differences among studies, the consensus is that lower values of these indices of vagal function are associated prospectively with death and disability.

3. Heart rate variability and mortality

In one of the first studies to investigate the relationship between indices of HRV and mortality, Kleiger et al. [21] showed in almost 900 post-myocardial infarction (MI) patients that HRV was a significant independent predictor of mortality in this high risk group. Numerous studies have since supported the notion that decreased vagal activity, as indexed by HRV, predicts mortality in high risk as well as low risk populations. In an elderly sub-sample of the Framingham Heart Study (FHS), frequency domain measures were significantly associated with all-cause mortality after controlling for other risk factors. A total of 736 men and women with an average age of 72 years provided ambulatory time and frequency domain HRV data [22]. Eight measures of HRV were examined including five frequency domain measures. All five frequency domain measures were significantly associated with all-cause mortality and all but the LF/HF ratio (a putative measure of sympathovagal balance where higher numbers indicate greater relative sympathetic dominance) remained so after controlling for other risk factors. A one standard deviation (SD) difference in the log transformed LF power was associated with a 1.7 times greater relative risk of all-cause mortality in this sample [22]. Similarly, in the Hoorn Study, a prospective study of glucose tolerance in the general population, several time and frequency domain indices of HRV were calculated and five were associated with all-cause mortality during the nine-year follow-up period at least at the $p<0.10$ level after controlling for age, gender, and glucose tolerance [23]. This finding was strongest for those at high risk because of diabetes, hypertension, or cardiovascular disease.

In the Atherosclerosis Risk in Communities (ARIC) study, the association between HRV and mortality was investigated in 11,654 men and women with an average age of 54 years [24]. Two minutes of supine resting beat-to-beat heart rate data were collected and a number of time and frequency domain indices of HRV calculated. The lowest quartile of HF power was associated with incident MI, incident coronary heart disease (CHD), fatal CHD, and fatal non-CHD deaths in those with diabetes with hazard ratios ranging from 1.27 to 2.03 over the eight-year follow-up period [24] In those individuals without diabetes the effects were much less consistent. However, examination of LF power indicated results consistent with the Framingham Study such that those non-diabetics in the lowest quartile had a 1.33 greater risk of non-CHD mortality than those in the highest LF power quartile. The effect was even larger for fatal CHD with those in the lowest LF power quartile having a 1.92 greater risk than those in the highest quartile. In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRIMI) study, 1284 patients with a recent MI (within the last 28 days) were investigated using 24-h recordings [25]. For the time domain measure of the SDNN and an abnormal score cut point of SDNN < 70 ms, a 3.2 greater risk of mortality was found in the two-year follow-up period. Additionally, in a study of men and women post-MI with depressed left ventricular function (LVF), the HRV triangular index was used with an HRV cut point of <20 as an indicator of high risk [26]. In the placebo group, low HRV was a significant independent predictor of mortality with a relative risk of 1.46 after controlling for age, gender, LV ejection fraction, New York Heart Association class, diabetes, and beta-blocker use. Thus, numerous studies have supported the notion that decreased vagal activity, as indexed by HRV, predicts mortality in high risk as well as low risk populations. However, an important caveat about all of these studies is that to date, few studies have examined the association between HRV indices and mortality in asymptomatic persons.

4. Heart rate variability and the etiology and progression of cardiovascular disease risk

The evidence for an association between reduced HRV and mortality appears to be quite strong. Most of these studies examined the association after controlling for other known risk factors such as diabetes and hypertension. However, there is also evidence to suggest that reduced HRV leads to such risk factors. Thus, those studies that control for those known risk factors for which there exists evidence that reduced HRV might lead to those risk factors may, in fact, be underestimating the role of vagal function in death and disease.

The National Heart, Lung, and Blood Institute of the US National Institutes of Health list eight risk factors for heart disease and stroke, six of which are modifiable. Three of these modifiable risk factors are associated with what could be called biological factors. They are high blood pressure (hypertension), diabetes, and abnormal cholesterol. Three others listed as modifiable could be considered lifestyle factors and include tobacco use (smoking), physical inactivity (exercise), and obesity. The two non-modifiable risk factors are age and family history of early heart disease or stroke. It is interesting to note that there is at least some data to suggest that each of these risk factors is associated with decreased heart rate variability.

4.1. Modifiable biological risk factor: hypertension

Perhaps the single most important risk factor for CVD is hypertension. Numerous studies have documented the association between cardiac autonomic function and hypertension (Table 1). This association

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

Table 1
Heart rate variability and hypertension studies.

CVD risk factors	Studies	Subject and sample size	Effects investigated	Controlled variables	Association
Hypertension	Liao et al.[27]	$n=2061$; 32% hypertensive	HRV and hypertension	Age, race, gender, current smoking, diabetes, and education	Adjusted OR (95% CI): 1.00,1.46 (0.61–3.46), 1.50 (0.65–3.50) and 2.44 (1.15–5.20) from highest to lowest quartile of HRV–HF and incident hypertension
Hypertension	Singh et al. [28]	$n=2024$; 17% incident cases of hypertension	HRV and hypertension	Age, BMI, smoking, alcohol consumption, base systolic and diastolic blood pressure	Adjusted OR (95% CI): Men 1.38 (1.04–1.83), Women 1.12 (0.86–1.46) for LF and new-onset hypertension
Hypertension	Schroeder et al. [29]	$n=11{,}061$; 28% incident cases of hypertension	HRV, hypertension and blood pressure	Age, sex, race, study center, diabetes, smoking, education, and BMI	Adjusted hazard ratio (95% CI): SDNN 1.24 (1.10–1.40); RMSSD 1.36 (1.21–1.54); RR interval 1.44 (1.27–1.63) for incident hypertension

HRV = heart rate variability.
OR = odds ratio.
CI = confidence interval.
HF = high frequency.
BMI = body mass index.
LF = low frequency power.
SDNN = standard deviation of normal-to-normal RR intervals.
RMSSD = root mean square of successive differences.
RR interval = cycle between two consecutive R waves.

has been found in both cross-sectional and prospective analyses. Liao et al. [27] examined the association between two minutes of supine HRV and hypertension in a stratified random sample of 2061 black and white men and women from the ARIC study. During the three year follow-up period only 64 individuals developed hypertension. However, baseline HF power was inversely related to the development of hypertension among these individuals. In cross-sectional analyses, HF power adjusted for age, race, gender, smoking, diabetes, and education was significantly lower in the hypertensive group (both treated and untreated) than in the normotensive group. Additionally, those in the lowest HRV quartile had a 2.44-fold greater risk of hypertension than those in the highest quartile.

In the Framingham Heart Study (FHS), Singh et al. [28] examined the association between two hours of ambulatory HR recordings and hypertension in men and women in cross-sectional and prospective analyses. Cross-sectional analyses indicated that after adjustment for age, BMI, smoking, and alcohol consumption several measures of both time and frequency domain indices of HRV were significantly lower in hypertensive men and women than in normotensives. During the four year follow-up period 119 men and 125 women developed hypertension. These analyses showed that low LF power was associated with the development of hypertension in men but not in women.

In a recent report the association between HRV, hypertension, and blood pressure was examined in 11,061 men and women from the ARIC study [29]. HRV was assessed by 2-min and 6-min recordings separated by nine years. Consistent with previous reports HRV adjusted for age, race, study center, diabetes, smoking, education, and BMI was lower at baseline among those persons with hypertension. Importantly among the 7099 persons without hypertension at baseline the lowest quartile of HRV as indexed by RMSSD adjusted for relevant covariates was associated with a hazard ratio for the development of hypertension nine years later of 1.36 compared to those in the highest quartile.

These findings from large, epidemiological studies provide strong evidence that vagal tone, as measured by HRV, is lower in persons with hypertension than in normotensives even after adjustment for a range of covariates. Importantly, these studies suggest that decreases in vagal tone may precede the development of this critical risk factor for cardiovascular disease.

4.2. Modifiable biological risk factor: diabetes

Diabetes, another important risk factor for CVD, has also been associated with decreased HRV (Table 2). In the first population-based study to examine the relationship between vagal tone, serum insulin, glucose, and diabetes, Liao et al. [30] investigated 154 diabetic and 1779 non-diabetic middle-aged men and women in the ARIC study. Two minute supine resting HR recordings were used to compute HF power as an index of vagal tone while fasting insulin, glucose, and diagnosed diabetes were used to index diabetes and diabetes risk. Consistent with previous cross-sectional studies these researchers found that diabetics had lower vagal tone than non-diabetics after adjustment for age, race, and gender. In the non-diabetics, an inverse relationship was found between HF power, fasting insulin and fasting glucose, suggesting that reduced vagal tone may be involved in the pathogenesis of diabetes. However, after adjustment only the relationship between HRV and insulin remained significant. This was the first study to examine the relationship between HRV and insulin and glucose in a general population and suggests that reduced vagal tone may be involved in the pathogenesis of diabetes.

Singh et al. [31] examined the relationship between HRV and blood glucose levels in 1919 men and women from the FHS. The first two hours of ambulatory HR recordings were used to calculate a number of time and frequency domain indices of HRV. Fasting glucose levels were used to classify individuals as having normal or impaired fasting glucose, as well as to identify those with diabetes (in addition to those with diabetic diagnosis). Several indices of HRV including LF and HF power in the FHS were inversely associated with fasting glucose levels and were significantly reduced in diabetics and those with impaired fasting glucose compared to those with normal fasting glucose levels [31]. The association between reduced HRV and diabetes remained significant after adjustment for age, gender, HR, BMI, antihypertensive and cardiac medications, blood pressure, smoking, and alcohol and coffee consumption. Similarly, middle-aged men and women from the ARIC study in the lowest LF power quartile had a 1.2 greater fold risk of developing diabetes compared to those in the highest quartile, after adjustment for age, race, gender, study center, education, alcohol use, smoking, heart disease, physical activity, and BMI [32]. Those with HR in the highest quartile had 1.4 greater risk of diabetes than those in the lowest HR quartile with similar results for analyses restricted to those with normal fasting glucose.

4.3. Modifiable biological risk factor: cholesterol

To date few studies have examined the relationship between HRV and cholesterol (Table 3). Of those that have studied this relationship,

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

ARTICLE IN PRESS

Table 2
Heart rate variability and diabetes studies.

CVD risk factors	Studies	Subject and sample size	Effects investigated	Controlled variables	Association
Diabetes	Liao et al. [30]	$n=1933$; 8% diabetics	HRV, diabetes, fasting serum insulin and glucose	Age, race, gender	Adjusted geometric means $(\text{beats/min})^2$: 0.78 for HF of diabetics and 1.27 for HF of non-diabetics (mean difference $p<0.01$); 1.34 (lowest quartile) and 1.14 (highest quartile) of fasting serum insulin and HF ($p<0.01$ for trend) for diabetics and non-diabetics
Diabetes	Singh et al. [31]	$n=1919$; 4% diabetics	HRV and blood glucose levels	Age, gender, HR, BMI, antihypertensive and cardiac medications, blood pressure, smoking, and alcohol and coffee consumption	Mean ln LF: 6.74 for normal fasting glucose subjects and 6.54 for diabetes mellitus subjects ($p=0.008$) Mean LF/HF: 1.22 for normal fasting glucose subjects and 1.08 for diabetes mellitus subjects ($p=0.02$)
Diabetes	Carnethon et al. [32]	$n=8185$; 13% diabetics	HRV and Type 2 diabetes	Age, race, gender, study center, education, alcohol use, smoking, heart disease, physical activity, and BMI	Adjusted RR (95% CI): 1.2 (1.0–1.4) for LF and 1.4 (1.2–1.7) for HR in comparisons of the lowest and highest quartiles

p = probability.
LF/HF = low frequency/high frequency power ratio.
RR = relative risk.
HR = heart rate.

evidence exists that low HRV is associated with high cholesterol levels. Christensen et al. [33] examined the association between 24-h HRV and cholesterol in 47 men with heart disease and 38 healthy men. In both groups total cholesterol and low-density lipoprotein (LDL) were inversely associated with 24-h HRV. The association between HRV and cholesterol remained significant in both groups after adjustment for age and BMI.

The above results were also echoed in a study by Kupari et al. [34]. Researchers investigating the association between short-term HRV and cholesterol among a random sample of 41 men and 47 women without heart disease found that the RMSSD was inversely related to LDL cholesterol. Significance also remained after adjustment for other potential confounders including physical activity, smoking, and alcohol consumption.

4.4. Modifiable lifestyle-related risk factors: smoking, physical inactivity, and being overweight

Poor lifestyle choices, including a lack of physical activity and the abuse of tobacco, alcohol, and drugs have also been associated with autonomic imbalance and decreased parasympathetic activity [35–38] as well as CVD. Of the modifiable lifestyle-related risk factors for CVD (Table 4), perhaps the single most controllable risk is smoking. Hayano et al. [39] reported that both acute and chronic smoking was associated with decreased vagal tone. Likewise, smoking was associated with a significantly increased LF/HF ratio within five minutes of exposure in taxi drivers under ordinary working conditions [40]. Nighttime smoking, in particular, appeared to have a more potent, acute effect on cardiac modulation than daytime smoking. The authors also suggest that the sympathomimetric and parasympatho-withdrawal response of smoking may have an additional role in increasing cardiac risk [40]. In a very recent study, researchers have also found a link between maternal smoking during pregnancy and heart rate variability among infants. Prenatal smoking was associated with lower RMSSD during quiet sleep in the first three days of life [41].

Minami et al. [42] showed that indices of vagal tone increased after one week of smoking cessation in a group of habitual male smokers. Hayano et al. [39] reported that both acute and chronic smoking was associated with decreased vagal tone. Importantly, Minami et al. [42] showed that indices of vagal tone increased after one week of smoking cessation in a group of habitual male smokers. Moreover, in a study that examined the time course of the increase in vagal tone with smoking cessation Yotsukura et al. [43] also reported that indices of vagal tone increased within 24 h of smoking cessation. Interestingly, increases in vagal tone remained elevated for the one-month follow-up period in a group of male habitual smokers. Thus, smoking and smoking cessation have immediate and reversible effects on vagal tone.

A large number of cross-sectional as well as training studies have examined the effects of habitual exercise on cardiovascular function. The single most replicable effect of aerobic training on cardiac function is a decreased resting HR. Whereas there is some ongoing debate about the nature of the autonomic nervous system changes that accompany regular physical activity numerous studies have implicated increased vagal tone in the salubrious effects of exercise [44]. We have reported in a cross-sectional study that habitual physical activity was associated with greater levels of vagally mediated HRV in both men and women [37]. In 2334 men and 994 women from the Whitehall II study of British civil servants, moderate and vigorous physical activity was associated with greater vagal tone (in men) and lower resting HR (in men and women) compared to those that reported low levels of physical activity after adjustment for age, smoking and alcohol consumption [45]. Another study among young adults also found that HF power rose after 12 weeks of aerobic conditioning among men but not women, which returned to pre-training levels after deconditioning [46]. Taken together numerous studies report that physical inactivity, an important lifestyle risk factor for CVD, is associated with decreased vagal tone. Importantly, it also appears that increased physical activity may decrease resting HR and increase vagal tone.

Studies have also documented reduced HRV among overweight and obese individuals. In a study of 10 women with early-onset familial obesity and 10 non-obese women, several indices of HRV were reduced in the obese women [47]. Karason et al. [48] studied 28 obese patients referred for gastroplasty, 24 obese patients using a lifestyle dietary modification approach, and 28 non-obese persons. At baseline both obese groups had reduced HF values relative to the non-obese participants. After one year of follow-up, those persons that had undergone gastroplasty had an average weight loss of 28% and showed evidence of increased vagal function as indicated by increased HF power. Additionally, several studies of obesity in children and adolescence have also found that vagal function is reduced in obese individuals compared to non-obese individuals [49–51]. In all of these studies several indices of vagal function such as HF power were reduced in the obese individuals.

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

Table 3
Heart rate variability and cholesterol studies.

CVD risk factors	Studies	Subject and sample size	Effects investigated	Controlled variables	Association
Cholesterol	Christensen et al. [33]	$n=85$; 55% with heart disease (men)	HRV and cholesterol	Gender, age	Mean SDNN index among men with IHD dichotomized into cholesterol groups: 57 (low cholesterol), 38 (high cholesterol) ($p<0.05$) Mean RMSSD among men with IHD dichotomized into cholesterol groups: 59 (low cholesterol), 32 (high cholesterol) ($p<0.05$) Mean SDNN index among healthy men dichotomized into cholesterol groups: 75 (low cholesterol), 61 (high cholesterol) ($p<0.05$) Mean RMSSD among healthy men dichotomized into cholesterol groups: 41 (low cholesterol), 32 (high cholesterol) ($p<0.05$)
Cholesterol	Kupari et al. [34]	$n=88$; none clinical with heart disease	HRV and LDL cholesterol	Physical activity, smoking, alcohol consumption	Multiple regression coefficients (β): RR interval root mean square difference −0.22 ($p=0.008$), total RR interval power −0.25 ($p=0.007$) for LDL cholesterol

IHD = ischaemic heart disease.
LDL = low-density lipoprotein.

The results of these studies of lifestyle-related risk factors all indicate that decreased HRV is associated with poor risk factor profiles. Importantly, they also indicate that these risk profiles can be modified, which can lead to changes in HRV. As shown with obesity, weight loss was accompanied by increases in heart rate variability.

4.5. Non-modifiable risk factors: age and family history

Whereas the exact mechanism is still open to debate, studies have shown that increasing age is associated with decreasing HRV [52]. Age is often used as a covariate such as in the ARIC, FHS, and Whitehall studies. In those studies that have specifically investigated the relationship between age and cardiac function, consistent evidence supports this relationship [53]. For example Antelmi et al. [52] investigated the association between age and vagal tone in 292 men and 361 women aged from 14 to 82 years. They found that RMSSD decreased on average 3.6 milliseconds per decade.

Associations with reduced HRV have been found in individuals with a family history of CVD risk factors like hypertension and diabetes [54]. Piccirillo et al. [55] examined normotensive men and women with and without a family history of hypertension. Vagal tone, as indexed by baroreflex sensitivity and HRV, were reduced in those with a family history compared to those without a family history of hypertension. Recently, Maver et al. [56] also found that those with a positive family history of hypertension had lower vagal function as indexed by HF power and baroreflex sensitivity compared to those with a negative family history. These studies suggest that decreased vagal function is evident in persons with a family history of hypertension.

Similar results have been recorded in persons with a family history of diabetes. De Angelis et al. [57] found that individuals with a family history of diabetes had reduced vagal tone compared to those that had a negative family history. These results were also confirmed in another study by Lindmark et al. [58] comparing healthy persons with a family history of type 2 diabetes and persons with a negative family history of diabetes. HRV was analyzed during a number of conditions including rest and controlled breathing. The results indicated that total spectral power and HF power were lower during controlled breathing in those with a positive family history compared to those with a negative family history of diabetes. Again, these results indicate that decreased vagal function is evident in persons with a positive family history of diabetes compared to those with a negative family history.

Taken together, these findings suggest that non-modifiable risk factors such as age and family history of disease are associated with reduced HRV. Evidence suggests that both modifiable and non-modifiable risk factors for cardiovascular disease and death are preceded by indicators of autonomic imbalance and especially decreased vagal function. Decreased vagal function may be associated with the development of these known risk factors for cardiovascular disease and death. Data suggests that decreased vagal function is associated with degree of coronary artery occlusion [59] and plaque rupture [60]. Recent data also indicate that decreased vagal function is associated with increased markers of inflammation [61,62].

5. Emerging risk factors: psychosocial factors including work stress

Psychosocial factors such as stressful life events, general stress, hostility, depression, and anxiety are also emerging as risk factors for CVD [10,63–71]. Decreased HRV has been associated with several psychosocial conditions and states [1,2,66,67,72–75]. Another emerging psychosocial factor associated with CVD and HRV is work stress.

In terms of work stress, several studies have found significant associations with changes in indices of HRV (Table 5), although some have not [76]. A study by Tsaneva and Dukov [77] investigated hearing changes among miners using AHRV (analysis of heart rate variability) indices. An important finding of the study was that chronic exposure to work-related stress factors was associated with measures of HRV in workers. Likewise, Hintsanen et al. [78] found that higher effort-reward imbalances (ERI) or a larger ratio of higher efforts to rewards, was associated with lower levels of RMSSD and pNN50 in young Finnish women, although no association was observed for men. This suggests that autonomic activation could be one of the pathways that high ERI may lead to higher risks of CHD among women [78]. In another study among male shipyard workers, specific job characteristics were not found to be associated with cardiovascular risk factors. However, SDNN was significantly lower among those categorized in the high job strain group. Importantly, metabolic syndrome was also significantly related to decreased SDNN in the high job strain group. Thus, although not direct indicators of disease, the combination of sympathetic over-activity and low HRV in the high strain group, as suggested by the authors, may be useful indicators for potential cardiovascular dysfunctions associated with the onset of heart disease [2]. This was also the finding of Vrijkotte et al. [79] in a study among

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

ARTICLE IN PRESS

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

Table 4
Heart rate variability and lifestyle risk factors.

CVD risk factors	Studies	Subject and sample size	Effects investigated	Controlled variables	Association
Smoking	Hayano et al. [39]	$n=9$; male smokers (short-term effects) $n=81$; males, 69% smokers (long-term effects)	HRV and short and long-term smoking	Age, gender	Mean HF: decrease after 1 cigarette ($p=0.0061$) CCV_{MWSA}: increase after 10–17 minutes ($P<0.0001$) after smoking CCV_{RSA}: smaller in young heavy smokers compared to young non and moderate smokers ($P<0.0078$)
Smoking	Yotsukura et al. [43]	$n=20$; male smokers	HRV and smoking cessation	Gender	TF: 49.8 (precessation), 60.6 (post-cessation) ($p<0.01$) LF: 31.6 (precessation), 38.6 (post-cessation) ($p<0.01$) HF: 31.6 (precessation), 38.6 (post-cessation) ($p<0.01$)
Smoking	Minami et al. [42]	$n=39$; male smokers	HRV, HR, BP and short-effects of smoking cessation	Gender	24-h pNN50: 10.0 during smoking period, 15.6 during non-smoking period ($p<0.0001$) 24-h LF/HF: 0.90 during smoking period, 0.77 during non-smoking period ($p<0.01$)
Smoking	Kobayashi et al. [40]	$n=20$; male taxi drivers	LF/HF ratio and smoking	Age, gender, working on night duty for ≥ 1 year and smoking ≥ 1 year	Mean LF/HF during night shift: 3.83 at baseline vs. 4.32 after 5 min of smoking ($p<0.05$)
Smoking	Fifer et al. [41]	$n=271$; infants	HR, HRV and prenatal smoking and alcohol	Age, alcohol consumption and smoking before or during pregnancy	Baseline RMSSD: 9.6 ± 0.7 ($p=0.009$) during quiet sleep
Physical inactivity	Rossy and Thayer, [37]	$n=40$; 53% men	HRV and physical activity	Gender, BMI	MSD mean: 57 (low fit individuals), 84 (high fit individuals) ($p<0.05$) %BB50 mean: 11 (low fit individuals), 21 (high fit individuals) ($p<0.05$) HF mean: 1313 (low fit individuals), 2710 (high fit individuals) ($p<0.05$)
Physical inactivity	Rennie et al. [45]	$n=3328$; 70% men	HRV and physical activity	Age, smoking, alcohol consumption	SDNN: 33.4 (lowest quartile); 36.1 (highest quartile) for vigorous physical activity ($p<0.05$) LF: 304.6 (lowest quartile); 362.5 (highest quartile) for vigorous physical activity ($p<0.01$) HF: 107.1 (lowest quartile); 131.0 (highest quartile) for vigorous physical activity ($p<0.01$)
Physical inactivity	Sloan et al. [46]	$n=149$; men and women between 18–45 years	HRV and aerobic activity and strength training	Age, gender, BMI	SDNN increase: 0.12 ln ms (men after training) HF increase: 0.39 ln ms^2 (men after training) SDNN decrease: -0.20 ln ms (men after deconditioning HF decrease: -0.54 ln ms^2 (men after deconditioning)
Obesity	Petretta et al. [47]	$n=20$; 50% early-onset familial obesity	Heart period variability and obesity	Gender, age, alcohol consumption, smoking, oral contraceptives	ULF: 8.67 (control subjects), 8.43 (obese subjects) VLF: 7.57 (control subjects), 7.37 (obese subjects)
Obesity	Karason et al. [48]	$n=80$; 35% obese for gastroplasty, 30% obese for lifestyle dietary modification, 35% non-obese	HRV, BMI and norepinephrine secretion	Age, gender, smoking and antihypertensive treatment	Mean RR: 832 (gastroplasty individuals), 770 (obese control individuals) after 1 year follow-up ($p=0.016$) SDNN: 130 (obese individuals), 154 (lean individuals) at baseline ($p=0.003$); 139 (gastroplasty individuals), 121 (obese control individuals) after 1 year follow-up ($p=0.037$). Norepinephrine excretion rate (nmol/24 h): 360 (obese individuals), 273 (lean individuals) at baseline ($p=0.006$); 279 (gastroplasty individuals), 343 (obese control individuals) after 1 year follow-up ($p=0.047$)

CCV_{MWSA} = coefficient of component variance reflecting Mayer wave sinus arrhythmia.
CCV_{MWSA} = coefficient of component variance reflecting respiratory sinus arrhythmia.
pNN50 = % differences between adjacent RR intervals >50 ms.
TF = total frequency.
MSD = mean successive differences.
%BB50 = % heart period differences >50 ms.
Mean RR = mean of RR interval.
ULV = ultra low frequency.
VLF = very low frequency.

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

Table 5
Heart rate variability and work stress.

CVD risk factors	Studies	Subject and sample size	Effects investigated	Controlled variables	Associations
Work stress	Hintsanen et al. [78]	$n=863$; men and women between 24 and 39 years	ERI, heart rate and HRV	Educational level, occupational group, smoking, alcohol, coffee, physical activity, social support, BMI, SBP, DBP	ERI and RMSSD: -0.09 ($p=0.05$) ERI and pNN50: -0.10 ($p=0.03$)
Work stress	Kang et al. [2]	$n=169$; male shipyard workers	HRV and metabolic syndrome	Gender	SDNN: 39.6 (low strain group without metabolic syndrome), 31.1 (high strain group with metabolic syndrome) ($p=0.04$) logVLF: 6.4 (low strain group without metabolic syndrome), 5.9 (high strain group with metabolic syndrome) ($p=0.04$)
Work stress	Riese et al. [76]	$n=159$; female nurses	Job strain, blood pressure, heart rate and HRV	Gender, socioeconomic status, work characteristics	No effect of job strain on IBI, RMSSD, SBP or DBP including interactions with social support
Work stress	Tsaneva and Dukov [77]	$n=25$; miners, 48% Group 1 (mean age 37.9 and length of employment <15 years), 52% Group 2 (mean age of 47.7 and length of employment ≥15 years)	HRV and hearing balance	Age, length of employment	Correlation between SDNN and 4000 Hz frequency: 0.873 ($p<0.01$) in group 1; 0.592 ($p<0.01$) in group 2 Correlation between Amo% and 4000 Hz frequency: 0.367 ($p<0.01$) in group 1; 0.484($p<0.01$) in group 2 Correlation between HI and 4000 Hz frequency: 0.413 ($p<0.01$) in group 1; 0.420 ($p<0.01$) in group 2
Work stress	van Amelsvoort et al. [80]	$n=135$; 84% male workers	Noise, job strain, physical activity, shift work and HRV	Gender, age, smoking, physical activity	SDNNi during sleep: 69.3 ms vs 85.8 ms, $p<0.05$, shift vs. daytime workers
Work stress	Vrijkotte et al. [79]	$n=109$; male white-collar workers	Effort-reward imbalance, overcommitment, blood pressure, heart rate and vagal tone	Gender, age, work characteristics, waist circumference, cigarette smoking, alcohol consumption, physical activity	Adjusted OR (95% CI): heart rate during sleep 1.95 (1.02–3.77); lnRMSSD 2.67 (1.24–5.75) for incident mild hypertension

ERI = effort-reward imbalance.
SDNNi = mean of standard deviations of all NN intervals for all segments of recording (ms).
lnRMSSD = natural logarithm of root mean square of successive differences.
Amo = amplitude of the mode.
HI = homeostatic index.
logVLF = log transformation of very low frequency.
IBI = interbeat interval.
SBP = systolic blood pressure.
DBP = diastolic blood pressure.

white-collar workers. One of the main results was that a one standard deviation increase in heart rate during sleep or a one standard deviation decrease in lnRMSSD was associated with significantly increased risk of mild hypertension.

Similarly, a cohort study conducted among workers from the integrated circuit manufacturing industry, waste incinerator plants and hospitals showed that various occupational factors were related to HRV [80]. Shift workers had significantly decreased SDNNi (mean of the standard deviation of all NN intervals for all 5-min segments of the entire recording, in milliseconds), and increased %LF and HR levels during work compared to daytime workers. These workers also had significantly decreased SDNNi levels during sleep compared to daytime workers. Shift workers reporting acute high noise levels compared to low work noise levels also had elevated adjusted %LF means during work. This suggests that cardiovascular regulation is less successful among this group and could explain the excess cardiovascular disease risk among these workers. An additional finding related to work stress was that significantly elevated %LF means during work adjusted for mean values during sleep were recorded among those in low job demand, low job control (77.9, $p<0{,}01$), high demand, high job control (77.7, $p<0{,}05$) and high demand, low job control (77.7, $p<0.05$) groups compared to a control group, after adjusting for sleep [80]. These results suggest that chronic disturbance of the autonomic cardiac balance favoring sympathetic dominance may be one reason for the effects of workplace stress on CVD risk. The authors conclude that HRV can be a very useful tool to study work-related stress and their accompanying physiological effects.

Numerous studies have now reported that work stress is associated with increased risk of coronary heart disease (CHD) [11,81,82]. We also have previously shown that work-related worries were associated with the largest increases in HR and decreases in HRV [83,84]. Thus work-related stress as measured by job strain [2], effort-reward imbalance [11], and ecological momentary assessments [84] have been linked to decreased HRV.

6. Heart rate variability and the prevention of cardiovascular disease

There are several pathways via which the deleterious effects of modifiable factors such as work stress can be prevented or minimized. All of these pathways involve efforts to increase HRV. As noted above, smoking cessation, physical exercise, and weight loss are all associated with increased HRV. Dietary changes including the consumption of fruits and vegetables, moderate alcohol consumption, and intake of omega-3 fatty acids and vitamin D through fish or nut consumption are also effective approaches for which there is some suggestive evidence linking them to increased HRV [85,86]. Stress and worry reduction via meditation or worry postponement may provide effective ways to prevent or minimize the effects of work stress [87]. Another possible approach as suggested by Tiller et al. [88], based on 24-h HRV recordings during normal working days, is the use of positive emotions to alter sympathovagal balance. They suggest that this could be beneficial in terms of hypertension treatment and also reduce the risk of sudden death in those with congestive heart failure or coronary artery disease. Currently, however, there is a lack of studies investigating the impact of such interventions on both HRV and disease. These types of studies could provide greater insight into the effects of autonomic imbalance and new perspectives on the treatment and prevention of related diseases.

7. Summary

In this paper we have tried to provide an overview of some of the evidence for the role of HRV in cardiovascular disease risk and mortality. Although not exhaustive, this review shows that there is a large body of data to suggest that decreased vagal function is an independent risk factor for all-cause mortality. In addition, we examine evidence that decreased vagal function is a common factor in all of the major risk factors for CVD, both modifiable and non-modifiable. Furthermore, we showed that decreased vagal function characterizes emerging psychosocial risk factors. Importantly, the evidence presented here also strongly suggests that work stress is associated with decreased HRV. Work stress itself is a major risk factor for cardiovascular morbidity and research suggests that one of the major pathways involves decreased HRV. We also note that the effects of modifiable risk factors might be prevented or minimized by engaging in behaviors that might increase HRV. Moreover, studies that include indices of both sympathetic and parasympathetic activity are necessary to provide a more complete picture of the role of the ANS in health and disease [89]. Finally, we suggested that autonomic imbalance might be the final common pathway linking a host of disorders and conditions to death and disease. Thus, behaviors that alter this autonomic imbalance toward a more salubrious profile may serve to prevent or at least minimize the effects of certain factors on the risk for cardiovascular disease and death.

Acknowledgements

We would like to thank Tammy N. Sadle for her assistance with the tables. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [90].

References

[1] Friedman BH, Thayer JF. Autonomic balance revisited: panic anxiety and heart rate variability. J Psychosom Res 1998;44:133–51.
[2] Kang MG, Koh SB, Cha BS, Park JK, Woo JM, Chang SJ. Association between job stress on heart rate variability and metabolic syndrome in shipyard male workers. Yonsei Med J 2004;45:838–46.
[3] Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Annu Rev Psychol 2002;53: 83–107.
[4] Krantz DS, McCeney MK. Effects of psychological and social factors on organic disease: a critical assessment of research on coronary heart disease. Annu Rev Psychol 2002;53:341–69.
[5] Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55:580–92.
[6] Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
[7] Verrier RL, Mittleman MA. The impact of emotions on the heart. Prog Brain Res 2000;122:369–80.
[8] Duijts SF, Kant I, Swaen GM, van den Brandt PA, Zeegers MP. A meta-analysis of observational studies identifies predictors of sickness absence. J Clin Epidemiol 2007;60:1105–15.
[9] Harter JK, Schmidt FL, Hayes TL. Business-unit-level relationship between employee satisfaction, employee engagement, and business outcomes: a meta-analysis. J Appl Psychol 2002;87:268–79.
[10] Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953–62.
[11] Chandola T, Britton A, Brunner E, et al. Work stress and coronary heart disease: what are the mechanisms? Eur Heart J 2008;29:640–8.
[12] Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from disease injuries and risk factors in 1990 and projected to 2002. Boston, MA: Harvard School of Public Health; 1996.
[13] Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104:2746–53.
[14] Darwin C. The expression of emotion in man and animals. New York: Oxford University Press; 1998.
[15] Friedman BH, Thayer JF. Anxiety and autonomic flexibility: a cardiovascular approach. Biol Psychol 1998;49:303–23.
[16] Thayer JF, Friedman BH. The heart of anxiety: a dynamical systems approach. Amsterdam: Springer Verlag; 1997.
[17] Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 2000;61:201–16.
[18] Malliani A, Pagani M, Lombardi F. Methods for assessment of sympatho-vagal balance: power spectral analysis. Armonk, New York: Futura; 1994.
[19] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 2000;51:245–70.

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

ARTICLE IN PRESS

[20] Electrophysiology TFotESoCatNASoP. Heart rate variability: standards of measurement physiological interpretation and clinical use. Circulation 1996;93:1043–65.
[21] Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.
[22] Tsuji H, Venditti Jr FJ, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994;90:878–83.
[23] Gerritsen J, Dekker JM, TenVoorde BJ, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. Diabetes Care 2001;24:1793–8.
[24] Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. Diabetes 2002;51:3524–31.
[25] La Rovere MT, Bigger Jr JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (autonomic tone and reflexes after myocardial infarction) investigators. Lancet 1998;351:478–84.
[26] Camm AJ, Pratt CM, Schwartz PJ, et al. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 2004;109:990–6.
[27] Liao D, Cai J, Barnes RW, et al. Association of cardiac autonomic function and the development of hypertension: the ARIC study. Am J Hypertens 1996;9:1147–56.
[28] Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. Hypertension 1998;32:293–7.
[29] Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Hypertension 2003;42:1106–11.
[30] Liao D, Cai J, Brancati FL, et al. Association of vagal tone with serum insulin, glucose, and diabetes mellitus—the ARIC Study. Diabetes Res Clin Pract 1995;30:211–21.
[31] Singh JP, Larson MG, O'Donnell CJ, et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol 2000;86:309–12.
[32] Carnethon MR, Fortmann SP, Palaniappan L, Duncan BB, Schmidt MI, Chambless LE. Risk factors for progression to incident hyperinsulinemia: the Atherosclerosis Risk in Communities Study, 1987–1998. Am J Epidemiol 2003;158:1058–67.
[33] Christensen JH, Toft E, Christensen MS, Schmidt EB. Heart rate variability and plasma lipids in men with and without ischaemic heart disease. Atherosclerosis 1999;145:181–6.
[34] Kupari M, Virolainen J, Koskinen P, Tikkanen MJ. Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. Am J Cardiol 1993;72:897–903.
[35] Ingjaldsson JT, Laberg JC, Thayer JF. Reduced heart rate variability in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking. Biol Psychiatry 2003;54:1427–36.
[36] Reed SF, Porges SW, Newlin DB. Effect of alcohol on vagal regulation of cardiovascular function: contributions of the polyvagal theory to the psychophysiology of alcohol. Exp Clin Psychopharmacol 1999;7:484–92.
[37] Rossy LA, Thayer JF. Fitness and gender-related differences in heart period variability. Psychosom Med 1998;60:773–81.
[38] Weise F, Krell D, Brinkhoff N. Acute alcohol ingestion reduces heart rate variability. Drug Alcohol Depend 1986;17:89–91.
[39] Hayano J, Yamada M, Sakakibara Y, et al. Short- and long-term effects of cigarette smoking on heart rate variability. Am J Cardiol 1990;65:84–8.
[40] Kobayashi F, Watanabe T, Akamatsu Y, et al. Acute effects of cigarette smoking on the heart rate variability of taxi drivers during work. Scand J Work Environ Health 2005;31:360–6.
[41] Fifer WP, Fingers ST, Youngman M, Gomez-Gribben E, Myers MM. Effects of alcohol and smoking during pregnancy on infant autonomic control. Dev Psychobiol 2009;51:234–42.
[42] Minami J, Ishimitsu T, Matsuoka H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. Hypertension 1999;33:586–90.
[43] Yotsukura M, Koide Y, Fujii K, et al. Heart rate variability during the first month of smoking cessation. Am Heart J 1998;135:1004–9.
[44] Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. Sports Med 2003;33:33–46.
[45] Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am J Epidemiol 2003;158:135–43.
[46] Sloan RP, Shapiro PA, DeMeersman RE, et al. The effect of aerobic training and cardiac autonomic regulation in young adults. Am J Public Health 2009;99:921–8.
[47] Petretta M, Bonaduce D, de Filippo E, et al. Assessment of cardiac autonomic control by heart period variability in patients with early-onset familial obesity. Eur J Clin Invest 1995;25:826–32.
[48] Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999;83:1242–7.
[49] Riva P, Martini G, Rabbia F, et al. Obesity and autonomic function in adolescence. Clin Exp Hypertens 2001;23:57–67.
[50] Nagai N, Matsumoto T, Kita H, Moritani T. Autonomic nervous system activity and the state and development of obesity in Japanese school children. Obes Res 2003;11: 25–32.
[51] Rabbia F, Silke B, Conterno A, et al. Assessment of cardiac autonomic modulation during adolescent obesity. Obes Res 2003;11:541–8.
[52] Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 2004;93:381–5.
[53] Reinhardt F, Drexler H, Bickel A, et al. Electrophysiological investigation of central, peripheral and autonomic nerve function in workers with long-term low-level exposure to carbon disulphide in the viscose industry. Int Arch Occup Environ Health 1997;70:249–56.
[54] Pitzalis MV, Iacoviello M, Massari F, et al. Influence of gender and family history of hypertension on autonomic control of heart rate, diastolic function and brain natriuretic peptide. J Hypertens 2001;19:143–8.
[55] Piccirillo G, Viola E, Nocco M, Durante M, Tarantini S, Marigliano V. Autonomic modulation of heart rate and blood pressure in normotensive offspring of hypertensive subjects. J Lab Clin Med 2000;135:145–52.
[56] Maver J, Strucl M, Accetto R. Autonomic nervous system and microvascular alterations in normotensives with a family history of hypertension. Blood Press 2004;13:95–100.
[57] De Angelis C, Perelli P, Trezza R, et al. Modified autonomic balance in offsprings of diabetics detected by spectral analysis of heart rate variability. Metabolism 2001;50:1270–4.
[58] Lindmark S, Wiklund U, Bjerle P, Eriksson JW. Does the autonomic nervous system play a role in the development of insulin resistance? A study on heart rate variability in first-degree relatives of Type 2 diabetes patients and control subjects. Diabet Med 2003;20:399–405.
[59] Huikuri HV, Jokinen V, Syvanne M, et al. Heart rate variability and progression of coronary atherosclerosis. Arterioscler Thromb Vasc Biol 1999;19:1979–85.
[60] Kennedy HL. Beta blockade, ventricular arrhythmias, and sudden cardiac death. Am J Cardiol 1997;80:29J–34J.
[61] Lampert R, Bremner JD, Su S, et al. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am Heart J 2008;156:759.e1–7.
[62] Stein PK, Barzilay JI, Chaves PH, et al. Higher levels of inflammation factors and greater insulin resistance are independently associated with higher heart rate and lower heart rate variability in normoglycemic older individuals: the Cardiovascular Health Study. J Am Geriatr Soc 2008;56:315–21.
[63] Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–13.
[64] Kubzansky LD, Kawachi I. Going to the heart of the matter: do negative emotions cause coronary heart disease? J Psychosom Res 2000;48:323–37.
[65] van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med 2004;66:814–22.
[66] Sheps DS, Sheffield D. Depression, anxiety, and the cardiovascular system: the cardiologist's perspective. J Clin Psychiatry 2001;62(Suppl 8):12–6 discussion 7–8.
[67] Ward HE. Depression and cardiovascular disease. Curr Opin Psychiatry 2003;16: 221–5.
[68] Yan LL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI. Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. JAMA 2003;290:2138–48.
[69] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
[70] Everson-Rose SA, House JS, Mero RP. Depressive symptoms and mortality risk in a national sample: confounding effects of health status. Psychosom Med 2004;66:823–30.
[71] Macleod J, Davey Smith G, Heslop P, Metcalfe C, Carroll D, Hart C. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. BMJ 2002;324:1247–51.
[72] Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry 1996;39:255–66.
[73] Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res 2002;53:897–902.
[74] Cohen H, Matar MA, Kaplan Z, Kotler M. Power spectral analysis of heart rate variability in psychiatry. Psychother Psychosom 1999;68:59–66.
[75] Thayer JF, Friedman BH. A neurovisceral integration model of health disparities in aging. Washington, D.C: The National Academies Press; 2004.
[76] Riese H, Van Doornen LJ, Houtman IL, De Geus EJ. Job strain in relation to ambulatory blood pressure, heart rate, and heart rate variability among female nurses. Scand J Work Environ Health 2004;30:477–85.
[77] Tsaneva L, Dukov R. Correlations between certain hearing changes and vegetative balance in miners. Cent Eur J Public Health 2004;12:49–52.
[78] Hintsanen M, Elovainio M, Puttonen S, et al. Effort-reward imbalance, heart rate, and heart rate variability: the Cardiovascular Risk in Young Finns Study. Int J Behav Med 2007;14:202–12.
[79] Vrijkotte TG, van Doornen LJ, de Geus EJ. Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. Hypertension 2000;35:880–6.
[80] van Amelsvoort LG, Schouten EG, Maan AC, Swenne CA, Kok FJ. Occupational determinants of heart rate variability. Int Arch Occup Environ Health 2000;73:255–62.
[81] Aboa-Eboule C, Brisson C, Maunsell E, et al. Job strain and risk of acute recurrent coronary heart disease events. JAMA 2007;298:1652–60.
[82] Belkic KL, Landsbergis PA, Schnall PL, Baker D. Is job strain a major source of cardiovascular disease risk? Scand J Work Environ Health 2004;30:85–128.
[83] Brosschot JF, Van Dijk E, Thayer JF. Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. Int J Psychophysiol 2007;63:39–47.
[84] Pieper S, Brosschot JF, van der Leeden R, Thayer JF. Cardiac effects of momentary assessed worry episodes and stressful events. Psychosom Med 2007;69:901–9.
[85] Mozaffarian D, Stein PK, Prineas RJ, Siscovick DS. Dietary fish and omega-3 fatty acid consumption and heart rate variability in US adults. Circulation 2008;117:1130–7.
[86] Park SK, Tucker KL, O'Neill MS, et al. Fruit, vegetable, and fish consumption and heart rate variability: the Veterans Administration Normative Aging Study. Am J Clin Nutr 2009;89:778–86.

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543

ARTICLE IN PRESS

[87] Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. J Psychosom Res 2006;60:113–24.
[88] Tiller WA, McCraty R, Atkinson M. Cardiac coherence: a new, noninvasive measure of autonomic nervous system order. Altern Ther Health Med 1996;2:52–65.
[89] Thayer JF, Fischer JE. Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. J Intern Med 2009;265:439–47.
[90] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.

Please cite this article as: Thayer JF, et al, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.09.543