



Published in final edited form as:

Psychoneuroendocrinology. 2008 November ; 33(10): 1305–1312. doi:10.1016/j.psyneuen.2008.08.007.

The relationship between heart rate variability and inflammatory markers in cardiovascular diseases

Alexander Haensel^{a,b,*}, Paul J. Mills^b, Richard A. Nelesen^b, Michael G. Ziegler^c, and Joel E. Dimsdale^{b,c}

^aDepartment of General Internal Medicine, University Hospital Berne, Switzerland ^bDepartment of Psychiatry, University of California, San Diego, USA ^cDepartment of Medicine, University of California, San Diego, CA, USA

Summary

Introduction—Recent evidence implicates a cholinergic anti-inflammatory pathway. Because vagus nerve activity mediates some heart rate variability (HRV), this qualitative review examines the literature concerning circulating cytokines and HRV in cardiovascular function in humans. This qualitative review examines the literature concerning circulating cytokines and HRV in cardiovascular function in humans.

Methods—Thirteen studies on HRV, inflammation, and cardiovascular function were located by electronic library search and descriptively reviewed.

Results—The relationship between HRV and inflammation was studied in healthy controls, patients with acute or stable coronary heart disease (CHD), patients with metabolic syndrome or impaired glucose tolerance and patients with kidney failure. Investigations focused mainly on Interleukin-6 (IL-6) and C-reactive peptide (CRP). The majority of reviewed studies reported that parasympathetic nervous system tone as inferred from heart rate variability is inversely related to inflammatory markers (*r* values between -0.2 and -0.4). The relationships with inflammatory markers were similar whether derived from ECG signals as short as 5–30 min or from 24-h ECG readings for HRV analyses. While inflammatory markers appear to be related to HRV, it is a mistake to assume that the traditional “vagal measures” of HRV (such as high frequency heart rate variability) are the driving factors. Indeed, low frequency heart rate variability, a complex measure reflecting both parasympathetic and sympathetic activity, is the more commonly associated measure linked to inflammatory markers.

Discussion—Heart rate variability is inversely correlated with inflammatory markers in healthy individuals as well as in those with cardiovascular diseases.

*Corresponding author at: Department of General Internal Medicine, University Hospital Berne, Inselspital, 3010 Bern, Switzerland. Tel.: +41 31 6320249; fax: +41 31 3821184. Alexander.haensel@insel.ch, saschahaensel@hotmail.com (A. Haensel).

Conflicts of interest

All coauthors have no financial conflicts or other conflicts of interest in this area.

Keywords

Autonomic nervous; system; Vagal nerve; Heart rate variability; Coronary heart disease; Inflammation

1. Introduction

Cytokine production by the immune system has an important role in pathophysiological processes. Excessive expression of pro-inflammatory cytokines can lead to the development of tissue injury and damage, as is evident in chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, and atherosclerosis. In these diseases, therapies that target specific cytokines can ameliorate signs and symptoms (Elliott et al., 1994; Targan et al., 1997; Kraaijeveld et al., 2007).

Recently, research has demonstrated that the central nervous system can decrease cytokine production via parasympathetic or vagal nerve activity. Stimulation of the vagus nerve significantly inhibits tumor-necrosis-factor- α (TNF- α) release in animals (Borovikova et al., 2000). Furthermore, experimental models studying sepsis, myocardial ischemia and pancreatitis have documented an inhibition of cytokine activity through vagus nerve stimulation (Mioni et al., 2005; Saeed et al., 2005; van Westerloo et al., 2006).

The mechanism for this vagal inhibition involves acetylcholine, the neurotransmitter of the vagal nerve, and an acetylcholine-receptor (AChR) on macrophages. Studies have found, for instance, that the administration of agonists to the $\alpha 7$ subunit of the nicotinic AchR, results in a reduced production of TNF- α , Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Interleukin-8 (IL-8) (Wang et al., 2004). As a result of these and other observations, the connection between brain, vagus nerve and immune system has been named the “cholinergic anti-inflammatory pathway” (Tracey, 2002).

The activity of the autonomic nervous system can be studied through analysis of heart rate variability (HRV). HRV quantifies changes in intervals between sinus heart beats as the heart rate oscillates around a mean value. These oscillations are modulated by the autonomic nervous system and can be analyzed by different measures. The majority of research uses time and frequency domains (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Alternative measures include geometric and non-linear measures (Kleiger et al., 2005). In time-domain analysis, the intervals of subsequent normal R waves (NN intervals) are measured over the period of recording. The most commonly used index of time domain is SDNN, the standard deviation of intervals between two successive R waves. Because some heart rate oscillations are faster than others, frequency-domain approaches distinguish between high frequency (HF: 0.15–0.40 Hz), low frequency (LF: 0.04–0.15 Hz), and very low frequency (VLF 0.0033–0.04 Hz) bands. Table 1 provides an overview of commonly employed time-domain and frequency-domain variables.

If a normal sinus rhythm and atrioventricular-nodal function are present, time-domain indices that quantify parasympathetic heart rate modulation include the mean square of the

successive differences in interbeat intervals (rMSSD), the absolute count of differences between successive intervals >50 ms (NN50), and the percentage of interbeat interval differences >50 ms (pNN50). In the frequency domain, HF is an index of vagal activity. The LF band is mediated by sympathetic and parasympathetic influences because parasympathetic influences are present over the whole range of the HRV spectrum whereas sympathetic influence considerably diminishes at about 0.15 Hz (Saul, 1990). Thus, some authors control LF for parasympathetic activity by forming a ratio of LF/HF, which is a reasonable approximation of sympathetic tone (Pagani et al., 1986).

Heart rate variability is regulated by central nervous signals sent to the heart via sympathetic and parasympathetic nerves. Only a small fraction of the vagus nerve innervates the heart; indeed, most vagal nervous endings are located in the gastrointestinal tract. The major anticholinergic effect of the vagal nerve on cytokine production seems to converge in the spleen, although there is no direct parasympathetic innervation to it (Huston et al., 2006; Nance and Sanders, 2007).

Interpretation of parasympathetic actions on heart rate variability has to bear in mind that the relationship is not linear (Goldberger et al., 2001). Goldberger et al. (2001) observed an ascending limb where HRV increased with increasing parasympathetic effect, followed by a plateau level. After that, HRV decreased with increasing parasympathetic effect. Thus, a newer and possibly promising way to analyze heart rate variability includes non-linear and chaos system theory to measure, for instance, fractal-like correlation properties of the dynamic system (Goldberger, 1996). Fractal analysis of heart rate variability is a highly significant predictor for subsequent mortality in patients after an acute myocardial infarction (Tapanainen et al., 2002). An accurate explanation of these methods is beyond the focus of the present paper. However, an excellent overview of the different methods to analyze HRV is provided by Kleiger et al. (2005).

An excellent overview of the current state of knowledge on cardiac vagal control, emotion, psychopathology, and health is offered by a special issue in *Biological Psychology* in February 2007 edited by John J.B. Allen and Andrea S. Chambers.

This review focuses on studies that analyzed associations between heart rate variability and inflammation in healthy subjects as well as in patients with cardiovascular disease.

2. Methods

We performed an electronic library search (PubMed) using 'heart rate variability', 'inflammation' and 'cardiovascular function' as key words and 'humans' and 'English', 'French', and 'German' as limitations for publications as of September 2007. Overall, 61 papers were found. We excluded 48 papers for the following reason: (1) primary interest involved effects of medication (beta-blocker, statins) or nutritional supplements (omega-3 fatty acid) on inflammation and/or clinical outcome ($n = 4$); (2) no study of inflammatory markers other than erythrocyte sedimentation rate ($n = 7$); (3) letter, case report, review or consensus statement ($n = 12$); (4) studies of air pollution ($n = 5$); (5) studies in neonatal sepsis or mortality ($n = 10$); and (6) studies of patients with infectious disease ($n = 4$). Since

we were interested in examining how HRV measurements were obtained, we excluded three studies that provided no information on duration of recorded ECG. We excluded two papers studying HRV in obese children because we were primarily interested in adult physiology. Finally, one paper was excluded that did not report statistical data. Thus, this review summarizes information from the 13 remaining studies.

3. Results

We found 13 studies which met the criteria, the first being published in 2002 (see Table 2). The effect of vagal activity was mainly studied on Interleukin-6 (IL-6) and C-reactive peptide (CRP). Six studies reported on subjects with known or suspected coronary heart disease (CHD) (Hamaad et al., 2005; Lanza et al., 2006; Madsen et al., 2007; Nolan et al., 2007; Psychari et al., 2007; Yue et al., 2007), four studies investigated the association of HRV and inflammation in healthy population (Owen and Steptoe, 2003; Sajadieh et al., 2004; Kon et al., 2006; Sloan et al., 2007). Two papers analyzed inflammatory markers and HRV in metabolic syndrome and impaired glucose tolerance, respectively (Brunner et al., 2002; Diakakis et al., 2005). One study evaluated patients with moderate and severe chronic kidney disease with/without dialysis (Psychari et al., 2005).

3.1. Results analyzed by studied population

3.1.1. Known or suspected CHD—Three groups analyzed associations of circulating inflammatory markers and HRV in acute coronary syndromes within 24 h of onset or admission to the hospital (Hamaad et al., 2005; Lanza et al., 2006; Psychari et al., 2007). The participants were mainly male (69%), with a mean age >60 years. All investigations found a modest correlation between CRP and HRV ($r < 0.2$ – 0.4). In the paper of Lanza et al. (2006), HRV was the strongest predictor of CRP levels in multiple regression models. Psychari et al. (2007) reported a strong inverse relation between several HRV indices (SDNN, SDNNindex, TP, HF, and LF) and CRP, which remained after adjustment for left ventricular function.

The remaining three papers analyzed patients with suspected and stable CHD (Madsen et al., 2007; Nolan et al., 2007; Yue et al., 2007). The percentage of males (71%) in these studies was similar to the studies of acute CHD; mean age was over 60 years as well. In these patients with stable CHD, however, the results were mixed. While one group found a highly significant correlation between CRP and HRV indices using 24-h ECG signals, another group did not find statistically significant data. The latter study used 5-min of ECG while patients were resting in supine position (Yue et al., 2007). The third group compared a small CHD sample ($n = 29$) who represented a high and low quartile of CRP distribution of a bigger population (Nolan et al., 2007). Here, ECG assessment lasted 10 min and high-frequency power was statistically decreased in the high-CRP group.

3.1.2. CHD-free samples—Research in CHD-free subjects featured the biggest sample size with 2434 people (1227 male, 1207 female). Two investigations studied people between 55 and 75 years of age; participants in the other two studies were between 33 and 45 years old. All studies used a relatively short-time ECG reading for HRV evaluation (2–30 min). Findings differed across these studies. While two investigations reported a significant

inverse relationship with the inflammatory markers CRP and IL-6, one study demonstrated higher CRP levels only in the group of the lowest HRV quartile (Kon et al., 2006). The remaining group tested inflammatory markers and HRV during and after a mental stress test and found no relationship between immune responses and heart rate variability (Owen and Steptoe, 2003).

3.1.3. Metabolic syndrome and impaired glucose tolerance—Because patients with metabolic syndrome and/or diabetes have elevated risk for cardiovascular disease, two papers were included in this review that focused on such patients. One paper compared 30 male subjects with metabolic syndrome to 153 controls (Brunner et al., 2002). Mean age was 52 years. HRV was measured during 5 min of rest. IL-6 was inversely correlated with HRV ($p < 0.02$). The other paper compared patients with impaired glucose tolerance with healthy controls (Diakakis et al., 2005). Although patients showed significantly higher levels of TNF- α , TNF- α -Receptor-II, and IL-6 as well as a higher mean heart rate, statistical analysis did not find significant correlations between HRV indices and inflammatory markers.

3.1.4. Chronic kidney disease—Because of the association of chronic kidney disease with hypertension and with other cardiovascular diseases, we also reviewed one paper that compared 51 patients on hemodialysis with 53 patients with moderate to severe chronic kidney disease who were not on hemodialysis (Psychari et al., 2005). Twenty-four-hour ECG readings were obtained. Heart rate variability did not differ between the two groups, but patients without hemodialysis demonstrated an inverse correlation between HRV indices and IL-6.

3.2. Results of studied inflammatory marker

Eleven of the 13 studies assessed CRP; 3 studies examined values for IL-6 as well. One study tested for IL-6 and TNF- α ; one also included TNF- α -Receptor-II (see also Table 2).

3.3. Results of evaluation of heart rate variability

Five papers evaluated HRV by time domain, three papers by frequency-domain measures only. The remaining five groups analyzed both time- and frequency-domain measures. The time-domain readings (SDNN, SDNNindex, and SDANN) were inversely associated with CRP and/or IL-6. The frequency-domain analysis found VLF and LF negatively associated with inflammatory marker. The paper by Nolan et al. (2007) reported decreased HF power in the high-CRP group.

Concerning the duration of ECG reading, six studies used 24-h Holter monitoring for HRV analysis. The remaining seven studies examined 5–30 min periods. HRV and inflammatory markers were reported as inversely related in the majority of these papers, but three investigations did not find a statistical significant relationship. Two of the investigations with a negative finding used a short-time reading, and one negative finding was based on a 24-h measurement.

4. Discussion

This qualitative review confirms the hypothesis that decreased heart rate variability is associated with on-going, subclinical inflammation. In populations with acute as well as chronic coronary heart disease, inflammatory markers are inversely correlated with HRV and correlation coefficients ranged from -0.2 to -0.5 . In the study with the biggest sample size of CHD patients, HRV variables were the strongest predictors of CRP levels in a regression model that included most important clinical and laboratory variables ($r = -0.23$, Lanza et al., 2006). Since one study in patients with metabolic syndrome found a significant inverse correlation between HRV and IL-6, such measures of HRV activity may highlight a prognostic factor in the emergence of arteriosclerosis because IL-6 promotes plaque proliferation and instability and elevated IL-6 levels predict future myocardial infarction in healthy subjects (Ridker et al., 2000; Koukkunen et al., 2001; Lobbes et al., 2006).

Although two investigations in patients with suspected or stable CHD reported a positive association between CRP and HRV (Nolan et al., 2007; Madsen et al., 2007), the study by Yue et al. (2007) found no significant association. Measurements of HRV and inflammatory factors are by definition sensitive to stressors. It could well be that other life stressors confound the detection of associations between HRV and inflammation. Similarly, transient asymptomatic ischemic events in such patients can alter HRV; indeed some studies report that CHD patients show decrease heart rate variability (HF and LF power) even 10 min in advance of asymptomatic ischemic events associated with ST-segment depression (Kop et al., 2001). Moreover, in such patients the decrease in HRV persists even after the ischemic episode. Hence, tracking the association of HRV and inflammation in patients with CHD is subject to numerous confounding factors.

Diakakis et al. (2005) found no significant difference in indices of HRV between patients with impaired glucose tolerance and controls but found significantly increased inflammatory markers as well as an overall increased heart rate in patients with impaired glucose tolerance. The authors did not report a power calculation. It is possible that a study with a larger sample size would have found statistically significant results since higher baseline heart rate is normally associated with less vagal activity.

The Whitehall II cohort, an important multicenter epidemiologic investigation, included over 5000 subjects, and two of the reviewed paper used subsamples of this study to examine heart rate variability. Sloan found in a sample of 757 people an inverse correlation between HRV and IL-6 and CRP (Sloan et al., 2007). Using a very different design, Owen and Steptoe (2003) examined the effect of mental stress on HRV and inflammation in 211 subjects. They found no association between the two measures of stress reactivity. There are several other studies which also could not document an association between stressors and HRV (Hoshikawa and Yamamoto, 1997; Garde et al., 2002; Wahlstrom et al., 2002). On the other hand, such associations have been detected in other studies, including a recent report which found a reduction in HF component of HRV and an increase in LF/HF-ratio in the stress situation (Hjorskov et al., 2004). The differing effects of mental stress on the relationship between inflammatory markers and HRV may reflect differences in the reactivity protocols, particularly differences in the level of task demand in the stress setting.

The reviewed study population consisted mainly of men with sparse representation of women. It is therefore important to mention one investigation that studied only women (Janszky et al., 2004). In a sample of 121 women who were hospitalized for acute CHD or for revascularization procedure, IL-6 showed an inverse association with HRV measures even after controlling for confounding factors such as smoking, diabetes, BMI, menopause, and education. Thus, the link between higher parasympathetic control and inflammation seems comparable across both genders.

It is important to note that most of the reviewed articles did not find a significant correlation between inflammatory markers and the 'classical' HRV index for parasympathetic function (pNN50 and rMSSD for time domain, and HF power for frequency domain). However for several other HRV indices (such as SDNN, SDNNindex, and SDANN for time-domain measures and TP, VLF, and LF for frequency-domain measures), significant associations were reported between HRV and inflammatory markers.

The interesting finding by Nolan et al. (2007) that HF power was decreased in the high-CRP subgroup of the original studied population might guide future work if replicated.

It is practically impossible to study a parasympathetic effect on inflammation or cardiovascular disease without considering sympathetic function. For instance, LF is modulated by baroreflexes with a combination of efferent sympathetic and parasympathetic signals to the sinoatrial node. The peak of LF can be abolished by atropine and beta blockade prevents the LF increase caused by standing up (Kleiger et al., 2005). Also, the physiologic basis for VLF power is far less clear than HF power, but VLF has proven to be a powerful risk predictor in cardiovascular disease (Bigger et al., 1992). Thus, future studies of the link between vagal activity and inflammation must consider the probably confounding effects of sympathetic nervous system effects on HRV. Furthermore, there is evidence that sympathetic nervous system also modulates the production of cytokines (Nance and Sanders, 2007). A more extensive review of how sympathetic or parasympathetic system activity contribute to modulation of cytokine production is beyond the scope of this article.

Our review has several limitations. Both inflammatory and autonomic nervous systems have a circadian variation that is influenced, for instance, by activity of the hypothalamic-pituitary-adrenal axis. The explanatory power of correlating HRV activity and inflammation may be limited by the time frame of the analysis. HRV varies throughout the day, and for many inflammatory markers, it is similarly difficult to be confident that a single blood sample represents the daily inflammatory activity. Furthermore, important confounders of heart variability such as depressive symptoms and anxiety were not controlled for in most of the reviewed studies. Evidence shows that between 12 and 20% of hospitalized cardiac patients meet diagnostic criteria for current major depression, and posttraumatic stress disorder is found in nearly 15% of patients following acute myocardial infarction (Frasure-Smith and Lespérance, 2006; Gander and von Känel, 2006). Thus, it will be crucial to consider psychiatric diagnosis in future studies of the role of parasympathetic activity and low-grade inflammatory processes.

In conclusion, data from a variety of sources suggest an interaction between inflammation and parasympathetic physiology. In order to understand what this means for cardiovascular diseases, future studies will need to consider the following: (1) studying treatments that increase vagal activity in patients with CHD and documented low parasympathetic activity; (2) studying correlation of HRV, coded by the newer, non-linear methods, and progression of atherosclerosis, and (3) investigating interaction between parasympathetic activity and hypothalamus-pituitary-adrenal axis; (4) possible confounding effects of psychiatric diagnoses or short-term stress responses.

Acknowledgments

Role of funding sources

This work was supported by NIH grants HL44915, HL36005, RR00827, CA23100 and by the grant PBBSB115117 from the Swiss National Foundation. The grant organizations did not have any impact on the manuscript.

References

- Bigger JT, Kleiger RE, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992; 85:164–171. [PubMed: 1728446]
- Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000; 405:458–462. [PubMed: 10839541]
- Brunner EJ, Hemingway H, Walker BR, Page M, Clarke P, Juneja M, Shipley MJ, Kumari M, Andrew R, Seckl JR, Papadopoulos A, Checkley S, Rumley A, Lowe GD, Stansfeld SA, Marmot MG. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. *Circulation*. 2002; 106:2659–2665. [PubMed: 12438290]
- Diakakis GF, Parthenakis FJ, Mavrakis HE, Patrianakos AP, Zacharis EA, Nyktari EG, Ganotakis ES, Vardas PE. Association of impaired glucose tolerance with increased heart rate and subclinical inflammation. *Hellenic J. Cardiol*. 2005; 46:394–401. [PubMed: 16422126]
- Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet*. 1994; 344:1105–1110. [PubMed: 7934491]
- Frasere-Smith N, Lespérance F. Depression and coronary artery disease. *Herz*. 2006; 31:64–68. [PubMed: 17575807]
- Gander ML, von Känel R. Myocardial infarction and posttraumatic stress disorder: frequency, outcome, and atherosclerotic mechanisms. *Eur. J. Cardiovasc. Prev. Rehabil*. 2006; 13:165–172. [PubMed: 16575268]
- Garde AH, Laursen B, Jorgensen AH, Jensen BR. Effects of mental and physical demands on heart rate variability during computer work. *Eur. J. Appl. Physiol*. 2002; 87:456–461. [PubMed: 12172887]
- Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet*. 1996; 347:1312–1314. [PubMed: 8622511]
- Goldberger JJ, Challapalli S, Tung R, Parker MA, Kadish AH. Relationship of heart rate variability to parasympathetic effect. *Circulation*. 2001; 103:1977–1983. [PubMed: 11306527]
- Hamaad A, Sosin M, Blann AD, Patel J, Lip GY, MacRadyen RJ. Markers of inflammation in acute coronary syndromes: association with increased heart rate and reductions in heart rate variability. *Clin. Cardiol*. 2005; 28:570–576. [PubMed: 16405201]
- Hjorskov N, Rissen D, Blangsted AK, Rallentin N, Lundberg U, Sogaard K. The effect of mental stress on heart rate variability and blood pressure during computer work. *Eur. J. Appl. Physiol*. 2004; 92:84–89. [PubMed: 14991326]

- Hoshikawa Y, Yamamoto Y. Effects of Stroop color-word conflict test on the autonomic nervous system responses. *Am. J. Physiol.* 1997; 272:1113–1121.
- Huston JM, Ochani M, Rosas-Ballina M, Liao H, Ochani K, Pavlov VA, Gallowitsch-Puerta M, Ashok M, Czura CJ, Rox-well B, Tracey KJ, Ulloa L. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. *J. Exp. Med.* 2006; 10:1623–1628. [PubMed: 16785311]
- Janszky I, Ericson M, Lekander M, Blom M, Buhlin K, Geor-giades A, Ahnve S. Inflammatory markers and heart rate variability in women with coronary heart disease. *J. Intern. Med.* 2004; 256:421–428. [PubMed: 15485478]
- Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. *Ann. Noninvasive Electrocardiol.* 2005; 10:88–101. [PubMed: 15649244]
- Kon H, Nagano M, Tanaka R, Satoh K, Segawa T, Nakamura M. Association of decreased variation of R–R interval and elevated serum c-reactive protein level in a general population in Japan. *Int. Heart J.* 2006; 47:867–876. [PubMed: 17268121]
- Kop WJ, Verdino RJ, Gottdiener JS, O’Leary ST, BaireyMerz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events. *J. Am. Coll. Cardiol.* 2001; 38:742–749. [PubMed: 11527627]
- Koukkunen H, Penttila K, Kempainen A, Halinen M, Penttila I, Rantanen T, Pyorala K. C-reactive protein, fibrinogen, interleukin-6 and tumour necrosis factor-alpha in the prognostic classification of unstable angina pectoris. *Ann. Med.* 2001; 33:37–47. [PubMed: 11310937]
- Kraaijeveld AO, de Jager SC, van Berkel TJ, Biessen EA, Jukema JW. Chemokines and atherosclerotic plaque progression: towards therapeutic targeting? *Curr. Pharm. Des.* 2007; 13:1039–1052. [PubMed: 17430167]
- Lanza GA, Sgueglia GA, Cianflone D, Rebuzzi AG, Angeloni G, Sestito A, Infusino R, Crea R, Maseri A. SPAI (Stratifica-zione Prognostica dell’Angina Instabile) Investigators 2006. Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. *Am. J. Cardiol.* 2006; 97:1702–1706. [PubMed: 16765117]
- Lobbes MB, Lutgens E, Heeneman S, Cleutjens KB, Kooi ME, van Engelshoven JM, Daemen MJ, Nelemans PJ. Is there more than C-reactive protein and fibrinogen? The prognostic value of soluble CD40 ligand, interleukin-6 and oxidized low-density lipoprotein with respect to coronary and cerebral vascular disease. *Atherosclerosis.* 2006; 187:18–25. [PubMed: 16360159]
- Madsen T, Christensen JH, Toft E, Schmidt EB. C-reactive protein is associated with heart rate variability. *Ann. Noninvasive Electrocardiol.* 2007; 12:216–222. [PubMed: 17617066]
- Mioni C, Bazzani C, Giuliani D, Altavilla D, Leone S, Rerrari A, Minutoli L, Bitto A, Marini H, Zaffe D, Botticelli AR, Iannone A, Tomasi A, Bigiani A, Bertolini A, Squadrito R, Guarini S. Activation of an efferent cholinergic pathway produces strong protection against myocardial ischemia/reperfusion injury in rats. *Crit. Care Med.* 2005; 33:2621–2628. [PubMed: 16276189]
- Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987–2007). *Brain Behav. Immun.* 2007; 21:736–745. [PubMed: 17467231]
- Nolan RP, Reid GJ, Seidelin PH, Lau HK. C-reactive protein modulates vagal heart rate control in patients with coronary artery disease. *Clin. Sci.* 2007; 112:449–456. [PubMed: 17134377]
- Owen N, Steptoe A. Natural killer cell and proinflammatory cytokine responses to mental stress: associations with heart rate and heart rate variability. *Biol. Psychol.* 2003; 63:101–115. [PubMed: 12738402]
- Pagani M, Lombardi R, Guzzetti S, Rimoldi O, Rurlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell’Orto S, Piccaluga E, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. *Circ. Res.* 1986; 58:178–193. [PubMed: 2874900]
- Psychari SN, Apostolou TS, Iliodromitis EK, Kourakos P, Liakos G, Kremastinos DT. Inverse relation of C-reactive protein levels to heart rate variability in patients after acute myocardial infarction. *Hellenic J. Cardiol.* 2007; 48:64–71. [PubMed: 17489343]
- Psychari SN, Sinos L, Iatrou C, Liakos G, Apostolou TS. Relations of inflammatory markers to lipid levels and autonomic tone in patients with moderate and severe chronic kidney disease and in patients under maintenance hemodialysis. *Clin. Nephrol.* 2005; 64:419–427. [PubMed: 16370154]

- Ridker P, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000; 101:1767–1772. [PubMed: 10769275]
- Saeed RW, Varma S, Peng-Nemeroff T, Sherry B, Balakhaneh D, Huston J, Tracey KJ, Al-Abed Y, Metz CN. Cholinergic stimulation blocks endothelial cell activation and leukocyte recruitment during inflammation. *J. Exp. Med.* 2005; 201:1113–1123. [PubMed: 15809354]
- Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JR. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. *Eur. Heart J.* 2004; 25:363–370. [PubMed: 15033247]
- Saul JP. Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News Physiol. Sci.* 1990; 5:32–37.
- Sloan RP, McCreath H, Tracey KJ, Sidney S, Liu K, Seeman T. RR interval variability is inversely related to inflammatory markers: the CARDIA study. *Mol. Med.* 2007; 13:178–184. [PubMed: 17592552]
- Tapanainen JM, Thomsen PE, Køber L, Torp-Pedersen C, Mäkikallio TH, Still AM, Lindgren KS, Huikuri HV. Ractal analysis of heart rate variability and mortality after an acute myocardial infarction. *Am. J. Cardiol.* 2002; 90:347–352. [PubMed: 12161220]
- Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TR, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N. Engl. J. Med.* 1997; 337:1029–1035. [PubMed: 9321530]
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*. 1996; 93:1043–1065. [PubMed: 8598068]
- Tracey KJ. The inflammatory reflex. *Nature*. 2002; 420:853–859. [PubMed: 12490958]
- van Westerloo DJ, Giebelen IA, Rlorquin S, Bruno MJ, Larosa GJ, Ulloa L, Tracey KJ, van der Poll T. The vagus nerve and nicotinic receptors modulate experimental pancreatitis severity in mice. *Gastroenterology*. 2006; 130:1822–1830. [PubMed: 16697744]
- Wahlstrom J, Hagberg M, Johnson PW, Svensson J, Rempel D. Influence of time pressure and verbal provocation on physiological and psychological reactions during work with a computer mouse. *Eur. J. Appl. Physiol.* 2002; 87:257–263. [PubMed: 12111287]
- Wang H, Liao H, Ochani M, Justiniani M, Lin X, Yang L, Al-Abed Y, Wang H, Metz C, Miller EJ, Tracey KJ, Ulloa L. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat. Med.* 2004; 10:1216–1221. [PubMed: 15502843]
- Yue W, Schneider A, Ruckerl R, Koenig W, Marder V, Wang S, Wichmann HE, Peters A, Zareba W. Relationship between electrocardiographic and biochemical variables in coronary artery disease. *Int. J. Cardiol.* 2007; 119:185–191. [PubMed: 17141341]

Table 1

Abbreviations of heart rate variability indices

Time-domain	
RR	Mean value of all normal-to-normal interbeat (N–N) intervals
SDNN	Standard deviation of all N–N intervals
SDNNindex	Average of the standard deviations of N–N intervals for each 5-min period
SDANN	Standard deviation of the average N–N intervals for each 5-min period over 24 h
NN50	Number of N–N intervals differing by >50 ms from the preceding interval
pNN50	Percentage of adjacent cycles that are >50 ms apart
RMSSD	Root mean square successive differences in milliseconds
Frequency-domain	
TP	Total power (0.0–0.5 Hz)
VLF	Very low frequency (0.0033–0.04 Hz)
LF	Low frequency (0.04–0.15 Hz)
HF	High frequency (0.15–0.40 Hz)
LF/HF	Ratio of low to high frequency

Table 2

Studies on heart rate variability and inflammatory marker in alphabetical order

Paper	Population	Study design	Duration and index of HRV measurement	Inflammatory marker	Confounding variables	Results
Brunner et al.	30 men with metabolic syndrome, 153 controls	Case-control	5 min, time and frequency domain	IL-6, CRP		Serum IL-6 inversely correlated with HRV, $r = -0.20$, $p < 0.02$
Diakakis et al.	45 patients with impaired glucose tolerance, 28 controls	Case-control	24-h, time domain	IL-6, TNF- α , sTNF-RII		No differences in time-domain indices
Hamaad et al.	100 patients with acute CHD ($n = 100$), follow-up $n = 51$, healthy controls ($n = 29$)	Case-control	20 min, time and frequency	IL-6, CRP	Age, gender, smoking, hypertension, diabetes	IL-6 and CRP negative related to SDNN, SDNNindex, VLF, LF (r between -0.23 and -0.27 , $p < 0.05$)
Kon et al.	823 subjects without heart disease	Cross-sectional	2 min, time domain	CRP	Age, gender, heart rate, coronary risk factors	CRP independently predicted low SDNNindex (OR = 3.11, $p < 0.02$)
Lanza et al.	531 patients with unstable CHD	Prospective, multicenter	24-h, time and frequency domain	CRP	Age, gender, family history, smoking, hypercholesterolemia, diabetes, previous CHD	CRP inversely correlated to SDANN ($r = -0.23$, $p < 0.001$) and VLF ($r = -0.22$, $p < 0.001$)
Madsen et al.	269 with suspected CHD	Cross-sectional	24 h, time domain	CRP	Gender, age, use of beta-blocker	Upper CRP quartile correlated with higher SDNN, SDNNindex, SDANN ($p < 0.002$)
Nolan et al.	29 patients with CHD	Case-control	5 min, frequency domain	CRP		HF decreased in high-CRP group ($p = 0.003$)
Owen and Steptoe	211 healthy subjects	Cross-sectional	20–30 min, time domain	IL-6, TNF- α		No relationship between IL-6, TNF- α and HRV
Psychari et al.	98 patients with acute CHD	Cross-sectional	24-h, time and frequency domain	CRP	Left ventricular function	Inverse relation between CRP and HRV (r between -0.31 and -0.46 , $p < 0.01$)
Psychari et al.	51 patients with moderate and severe chronic kidney disease, 53 patients on dialysis	Cross-sectional	24-h, time and frequency domain	IL-6, CRP	Hemoglobin, left ventricular EF	IL-6 related to SDNN and VLF ($r = -0.4$, $p < 0.01$), SDNNindex ($r = -0.5$, $p < 0.01$), and LF ($r = 0.35$, $p < 0.05$)
Sajadieh et al.	643 subjects without CHD	Cross-sectional	24-h, time domain	CRP	Age, gender	SDNN predictor of CRP (OR = 0.9, $p = 0.03$)
Sloan et al.	757 young healthy adults	Prospective, multicenter, epidemiologic	10 min, frequency domain	CRP, IL-6	Systolic blood pressure, BMI, physical activity, smoking	IL-6 and CRP inversely correlated with HF and LF ($p < 0.001$)
Yue et al.	52 patients with CHD	Cross-sectional	5 min, frequency domain	CRP		No association between frequency-domain and inflammatory marker

Abbreviations: coronary heart disease (CHD), C-reactive peptide (CRP), Interleukin-6 (IL-6), Tumor-necrosis-factor- α (TNF- α), soluble tumor-necrosis-factor- α -Receptor-II (sTNF-RII).