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Heart Rate Variability and Inflammation: A Meta-Analysis of Human Studies

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Abstract

The inflammatory reflex is known as the body's primary defense against infection and has been implicated in a number of diseases. The magnitude of the inflammatory response is important, as an extreme or insufficient response can be differentially harmful to the individual. Converging evidence suggests that the autonomic nervous system (ANS) regulates the inflammatory reflex. Heart rate variability (HRV) can be separated into components that primarily reflect parasympathetic (PNS) or vagal activity (i.e., indices of vagally mediated HRV) and a combination of both sympathetic (SNS) and PNS influences. Given the physiological relation between the vagus and inflammatory processes, one would expect to find higher HRV, especially indices of vagally-mediated HRV, to be associated with decreased levels of inflammation via the cholinergic anti-inflammatory pathway. However, existing findings here are mixed, such that studies have also shown a positive association between indices of HRV and markers of inflammation. Therefore, the present meta-analysis aimed to synthesize existing studies, estimating the general direction and strength of the relationship between different indices of HRV and inflammatory markers. A systematic search of the literature yielded 2,283 studies that were screened for inclusion eligibility (159 studies eligible for inclusion); in sum, 51 studies reported/provided adequate information for inclusion in meta-analyses. Results generally showed negative associations between indices of HRV and markers of inflammation. In this regard, the standard deviation of R-R intervals (SDNN) and power in the high frequency band of HRV (HF-HRV) showed the strongest and most robust associations with inflammatory markers compared to other time- and frequency-domain measures of HRV. Overall, we propose that indices of HRV can be used to index activity of the neurophysiological pathway responsible for adaptively regulating inflammatory processes in humans.

Keywords: inflammation; heart rate variability; vagal tone; autonomic nervous system; cholinergic anti-inflammatory pathway

1. Introduction

In the presence of attack or injury to the human body, a reflexive and localized response sets into motion an inflammatory process that alerts the brain to eliminate the pathogenic threat. As such, the inflammatory reflex is known as the body's primary defense against infection and its malfunction has been implicated in several diseases. The magnitude of the inflammatory response is important, as an extreme or insufficient response can be differentially harmful to the individual (Elenkov, et al., 2005; Pavlov & Tracey, 2005; Pavlov & Tracey, 2012; see Tracey, 2002, *for a review*). It is theorized that the autonomic nervous system (ANS) is largely involved in the regulation of the inflammatory reflex; it constantly monitors inflammation to ensure that cytokines do not spill into the blood stream by administering a reflexive and quick anti-inflammatory process (Tracy, 2002). The ANS executes this by way of the central nervous system (CNS); following an inflammatory response, afferent signals travel via the vagus nerve (primary nerve of the parasympathetic nervous system (PNS)) to the nucleus of the solitary tract. A subsequent efferent signal via the vagus inhibits pro-inflammatory cytokine synthesis via the neurotransmitter acetylcholine. In sum, a core set of physiological structures that involve the vagus nerve are responsible for a quick reflexive action in response to inflammation, known as the *cholinergic anti-inflammatory pathway* (Pavlov et al., 2003; Pavlov & Tracy, 2005; Tracey, 2007).

Empirical evidence supports the proposed mechanisms of this bi-directional pathway, and highlights the important role of the ANS, specifically the PNS (vagus nerve), in adaptively regulating inflammatory processes (e.g., Borovikova et al., 2000; Bernik, et al., 2002). In regards to the sympathetic nervous system (SNS), influence from this pathway can both increase and decrease inflammation; however, the effects are often context dependent, and slower in

comparison to the PNS. Therefore, the vagus nerve is considered the primary interface between local inflammation and CNS action (Tracey, 2002).

Heart rate variability (HRV), defined as the variability between heartbeats, can be separated into various indices of measurement, reflecting ANS influence on cardiac control. For example, using frequency-domain analyses, the high frequency power component of HRV (HF-HRV; 0.15-0.4 Hz) detects quick beat-to-beat fluctuations in a heart period time series, primarily reflecting PNS activity – such measures are indices of *vagally-mediated* HRV (Task Force, 1996; Thayer, Hansen, and Johnsen, 2010). The low frequency power component of HRV (LF-HRV; 0.04-0.15 Hz) has been theorized to represent general ANS (Berntson et al.,1997), especially SNS (Malliani, Pagani, Lombardi, and Cerutti, 1991) activity, although this stance is not without controversy (see Goldstein, Bentho, Park, and Sharabi, 2011, *for example*). The very low frequency power component of HRV (VLF-HRV; 0.003-0.04 Hz) has been associated with thermoregulation in response to ambient temperature changes (Sollers et al., 2002). It is important to note that all indices are thought to have some PNS influence despite the primary autonomic mechanism thought to underlie each HRV index, (Thayer, et al., 2010).

Given the physiological relation between the PNS and inflammatory processes, one would expect to find higher HRV (all indices), especially vagally-mediated HRV, to be associated with lower levels of inflammation. Some research supports this idea, reporting an inverse relationship between pro-inflammatory cytokines and vagally-mediated HRV using both short-term (< 1 hour; e.g., Soares-Miranda et al., 2010; Young et al., 2014) and long-term (> 1 hour; e.g., Araújo et al., 2006; Janszky et al., 2004) recordings of HRV. Prospective studies have also found similar results, showing vagally-mediated HRV to negatively predict inflammation four years into the future (Jarczok, et al., 2014). Moreover, a review revealed an overall negative association between

indices of HRV and markers of inflammation in both healthy individuals and patients with cardiovascular disease (Haensel et al., 2008). However, studies also show mixed or positive associations between indices of HRV and inflammation (e.g., Guinjoan et al., 2009; Pellissier et al., 2014; Schaefer et al., 2015). For example, while Singh and colleagues (2009) reported a negative correlation between vagally-mediated HRV and inflammation at baseline, results showed higher inflammation to predict higher vagally-mediated HRV two years into the future (Singh et al., 2009). Given these inconsistencies in the existing literature, a meta-analysis is warranted to better understand the general direction and strength of reported associations between indices of HRV and markers of inflammation.

The following series of meta-analyses therefore seeks to quantify the association between ANS activity, as measured by different indices of HRV, and inflammatory processes. If the vagus is indeed a mechanism underlying inflammatory responses, and indices of HRV can reflect such activity, we expect indices of HRV reflecting vagal activity, to show a general negative association with markers of inflammation. Overall, we sought to investigate the possibility that different indices of HRV, especially vagally-mediated HRV, can index the (in)adequate function of the inflammatory reflex, as indexed by markers of inflammation.

2. Methods

2.1 Literature Search

A systematic search of the literature (through 7/19/15) was performed using the electronic databases *PubMed*, *Cinahal*, *PSYCHINFO*, and *Web of Science* (*see* Appendix A for search

strategy by database). After removing duplicates, initial hits were hand searched and all abstracts were screened with inclusion criteria of an empirical investigation in (i) humans that measured both (ii) an inflammatory marker and (iii) an index of HRV and (iv) was conducted following the year 1996, when guidelines on measuring HRV were first published (Task Force, 1996). Empirical investigations were defined as studies involving active data collection. Conference abstracts and full-reports were included. Reviews, meta-analyses, comments, or single-case reports were not included. The number of studies meeting the pre-defined inclusion criteria, the number of studies excluded, and reasons for exclusion were recorded. Studies that fit the criteria were noted with later attempts to retrieve the full text. All reports, including both peer-reviewed manuscripts and "grey literature" (e. g., theses/dissertations, conference abstracts, etc.), were included.

Where available, information extracted from studies included title and author, the country in which the study was conducted, sample size (n), sample health status (dichotomous and continuous), mean age (in years), age range (in years), sex (% females from total sample), the length of HRV recording (dichotomous and continuous), and if associations were adjusted for covariates (coded as unadjusted *vs* adjusted). Health status was recorded as healthy *vs* non-healthy individuals, in addition to percentage of non-healthy individuals. With respect to HRV recording length, short-term recordings were defined as recordings that had a recording duration between 3 minutes and 1 hour. Long-term recordings were defined as recordings with a duration between 1 hour and 24 hours. Recordings were also coded in minutes.

2.2 Variables of interest

Time-domain indices of HRV included the standard deviation of R-R intervals (SDNN | ms), the count of consecutive R-R intervals that differed more than 50 milliseconds (NN50 | count), the percentage of NN50 (pNN50 | %), and the root mean of the square successive differences

(RMSSD | ms). Heart rate (HR | beats per minute) was also collected where possible. Frequency-domain indices of HRV included VLF-HRV (0.003-0.04 Hz | ms2), LF-HRV (0.04-0.15 Hz | ms2), HF-HRV (0.15-0.4 Hz | ms2), and the LF/HF ratio. Given that the influence of the PNS branch of the ANS in regulating HR produces rapid changes in the beat-to-beat timing of the heart (Uijtdehaage & Thayer, 2000), of these measures, NN50, RMSSD, pNN50, and HF power measures are thought to reflect PNS activity (Thayer et al., 2010). SDNN is thought to reflect total variability (i.e., both SNS and PNS contribution) (Berntson et al., 1997; Thayer et al., 2010). RMSSD and HF-HRV are considered primary indices of vagally-mediated HRV (Thayer et al., 2010). LF-HRV is thought to reflect the influence of both the SNS and PNS; however, this stance is not without controversy, as LF-HRV has also been shown to reflect other cardiac mechanisms such as baroreflex sensitivity (e.g., Goldstein et al., 2011). Despite controversy surrounding LF-HRV, some studies suggest an association between the LF/HF ratio and ANS balance (Williams et al., 2016, 2017). VLF is thought to reflect activity of the renin-angiotensin system and thermoregulation in response to ambient temperatures (Thayer et al., 2010). Markers of inflammation included interleukin-1 (IL-1), 2 (IL-2), 4 (IL-4), 6 (IL-6), and 10 (IL-10), C-Reactive Protein (CRP), white blood cell (WBC) count, fibrinogen, Interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α).

Only baseline data (i.e., free of any manipulation) for inflammation and HRV were included in the series of meta-analyses. For studies that fit the criterion but did not provide sufficient statistical information, data requests were sent to 116 authors who listed contact information in order to obtain the respective information.

2.3 Quantitative Analysis

Meta-analytic computations were performed using *MedCalc* software (MedCalc Software bvba, Ostend, Belgium). When available, we obtained correlation coefficients (*r*), partial (adjusted) correlation coefficients, and standardized betas. If possible, we tried to use measures of association from adjusted analysis to provide a more conservative estimate of the true effect. In order to pool data and examine relationships across as many studies as possible, standardized betas were transformed to correlation coefficients using a simple imputation formula proposed by Peterson & Brown (Peterson & Brown, 2005) where $r = \beta + .05\lambda$. λ is an indicator variable that equals 1 when β is nonnegative and 0 when β is negative. The Hedges-Olkin (1985) method was used (random-effects model, REML), and correlation coefficients of each study were z-transformed (Fisher's Z), 95% confidence intervals were calculated, and average z-transformed correlation coefficients were converted back into a "true effect correlation coefficient" value. Similar to meta-analysis on group differences, heterogeneity was assessed using the standard I^2 index (Higgins & Thompson, 2002). Substantial heterogeneity was assumed if I^2 was greater than 50%, indicating that 50% of the variability in the outcome cannot be explained by sampling variation. For meta-regression, we tested the direct impact of several covariates on the relationships between HRV and inflammation; such relationships were included in meta-regression if available comparisons (k) were greater than or equal to 10. Indices subjected to meta-regression included IL-6 with SDNN, LF, and HF, in addition to CRP with SDNN, RMSSD, VLF, LF, HF, and LF/HF. Continuous covariates included sample-mean age (in years), sex (% of females), health status (% of non-healthy individuals), and the recording length of HRV (in minutes). Nominal regression tests were used to test the impact dichotomous covariates may have on the above HRV-inflammation relationships. Dichotomous covariates included HRV recording length as either long (> 1hr) or short (< 1hr), whether the study included covariates, and whether

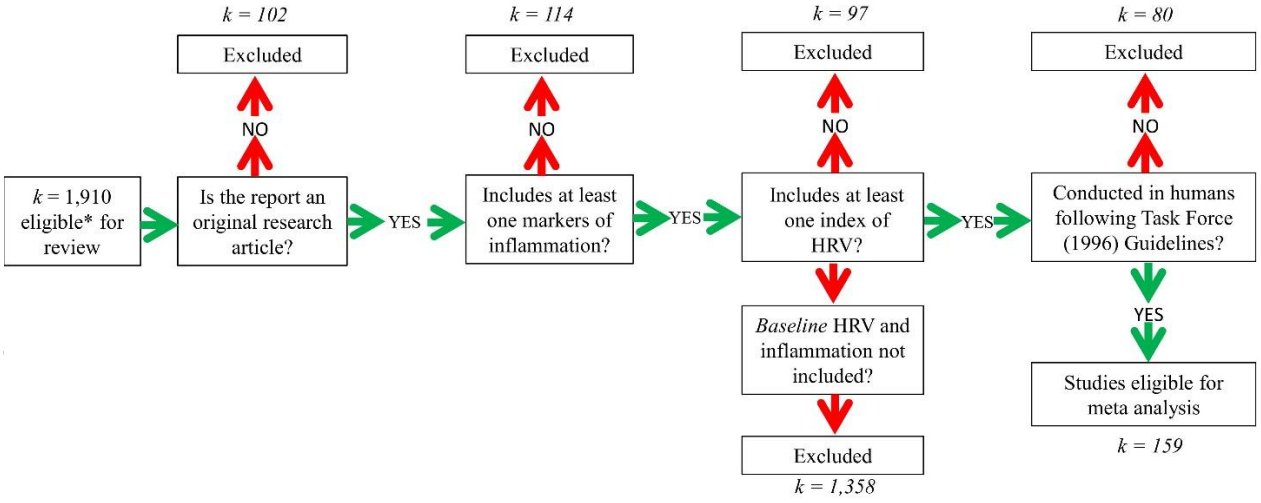
the study included non-healthy individuals. All tests were two-tailed and were analyzed using a set level of significance of $p < .05$.

3. Results

3.1 Search Results

A systematic search identified a total of 2,283 titles and abstracts. After excluding duplicates, 1,910 abstracts were screened for inclusion. A final count of 159 studies were eligible for inclusion (see *Figure 1* for details). Forty-three studies included a statistical index of the degree to which the HRV index and the inflammatory marker were related. We received eight eligible responses to data requests, yielding a final total of 51 eligible studies. It is important to note that three studies reported demographic and statistical information split by sample (i.e., healthy controls *vs* non-healthy individuals). Thus in these studies, each sample was considered its own investigation, and was notated in the data.

Figure 1. Flow Chart of Inclusion Criterion and Search Results



Note: This figure includes a flowchart for search results and inclusion criterion. A hit of 2,298 studies were screened for duplicates (which were removed), leaving 1,910 studies eligible for review. A final count of 159 studies were eligible for inclusion.

3.2 Tests of heterogeneity

On average, tests of heterogeneity showed moderate to high Q and I^2 values (near or above 50%; *Table 1*), particularly with relationships that included greater than 10 studies. Thus, substantial heterogeneity of studies is assumed.

3.3 Meta-Analytic Associations between HRV and Inflammation

Table 1 depicts statistics for all available associations.

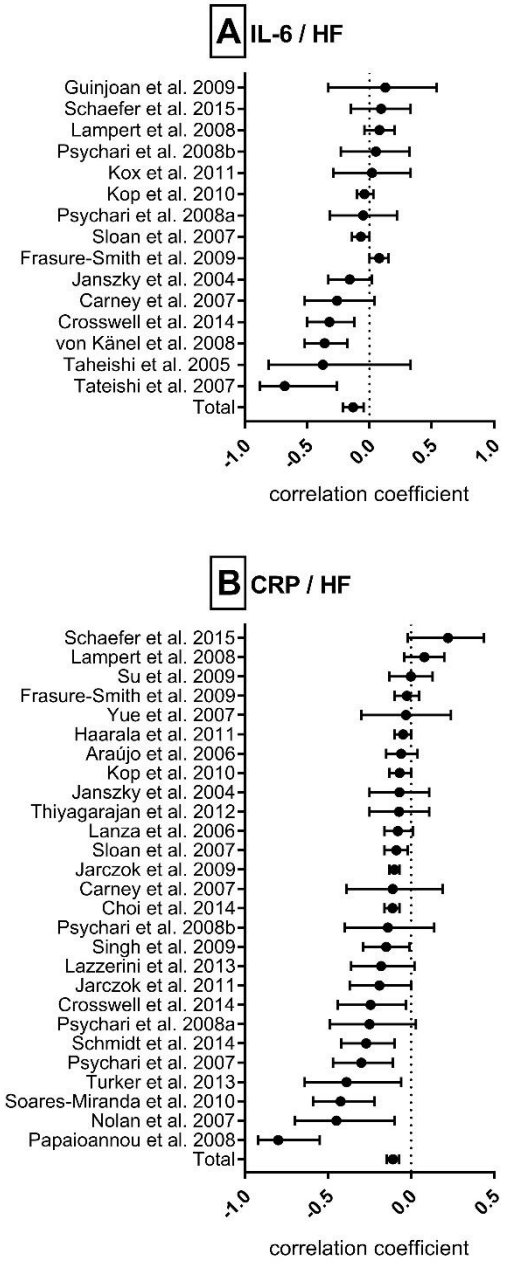
Table 1: Meta-Analysis Statistics for Associations between Markers of both HRV and Inflammation

	Cardiac marker	Inflammation marker	*n*	*k*	RELM Coeff	Lower CI	Upper CI	z	*p*	Tests of heterogeneity	Q	*p*	I^2 (%)
TNF	SDNN	TNF	267	5	-.196	-.434	.068	-1.41	.144		15.64	**.003**	74.42
	RMSSD	TNF	207	3	-.131	-.296	.041	-1.50	.135		2.73	.255	26.80
	LF	TNF	144	3	-.126	-.486	.271	-1.03	.540		11.03	**.004**	81.87
	HF	TNF	340	7	-.144	-.351	.076	-.1.29	.199		21.60	**.001**	71.51
	LF/HF	TNF	404	5	.249	-.026	.489	1.77	.076		30.31	**< .001**	86.81
IL-1	SDNN	IL1	161	2	-.102	-.254	.060	-1.26	.202		0.40	.529	0.00
	LF	IL1	293	3	0.080	-.367	.497	2.53	.736		28.66	**<.001**	93.02
	HF	IL1	293	3	-.198	-.401	.678	0.68	.530		51.83	**<.001**	96.14
IL-6	HR	IL6	2,011	5	.052	.008	.096	2.30	**.020**		0.61	.962	0.00
	SDNN	IL6	7,752	11	-.146	-.187	-.104	-6.78	**< .001**		19.86	**.030**	49.65
	PNN50	IL6	1,810	3	.002	-.433	.049	0.12	.904		0.86	.651	0.00
	RMSSD	IL6	5,253	7	-.064	-.182	.117	-1.04	.298		35.03	**<.001**	82.87
	VLF	IL6	1,437	6	-0.19	-.281	-.095	-3.91	**< .001**		9.82	.081	49.09
	LF	IL6	3,145	13	-.231	-.176	-.107	-4.28	**< .001**		80.79	**< .001**	85.15
	HF	IL6	3,249	15	-.132	-.214	-.048	-3.08	**< .001**		55.30	**< .001**	74.68
	LF/HF	IL6	403	6	.166	.097	.407	1.24	.216		32.19	**< .001**	84.47
WBC	HR	WBC	2,739	2	.107	.069	.144	5.61	**< .001**		0.45	.501	0.00
	SDNN	WBC	7,329	4	-.129	-.186	-.070	-4.30	**< .001**		15.94	**.001**	81.18
	PNN50	WBC	3,350	3	-.068	-.125	-.011	-2.33	**< .001**		5.06	.080	60.47
	RMSSD	WBC	7,944	5	-.093	-.131	-.054	-4.67	**< .001**		9.96	**.041**	59.84
	LF	WBC	6,686	3	-.086	-.110	-.063	7.10	**< .001**		0.77	.679	0.00
	HF	WBC	6,686	3	-.062	-.086	-.038	-5.08	**< .001**		1.03	.060	0.00
					]								

FIBR	RMSSD	FRIB	1,473	3	-.156	-.221	-.089	-4.56	< **.001**		2.78	.247	28.52
	VLF	FRIB	906	2	-.295	-.706	.264	-1.04	.300		13.55	<**.001**	92.62
	LF	FRIB	161	3	-.229	-.516	-.105	-1.35	.177		8.89	**.011**	77.51
	HF	FRIB	808	4	-.175	-.242	-.107	-4.99	< **.001**		2.25	.521	0.00
	LF/HF	FRIB	117	2	.084	-.101	.264	.891	.373		0.02	.883	0.00
CRP	HR	CPR	5,900	8	.118	.093	.144	9.13	< **.001**		6.65	.467	0
	SDNN	CRP	17,421	24	-.202	-.252	-.151	-7.59	< **.001**		196.76	<**.001**	88.31
	PNN50	CRP	4,447	6	-.109	-.182	-.035	-2.87	**.005**		26.02	**<.001**	80.79
	RMSSD	CRP	16,450	19	-.107	-.140	-.074	-6.31	**< .001**		54.50	**<.001**	66.98
	VLF	CRP	2,856	11	-.239	-.257	-.187	-5.87	**< .001**		37.34	**<.001**	73.22
	LF	CRP	11,791	20	-.137	-.173	-.100	-7.28	**< .001**		47.11	**<.001**	59.66
	HF	CRP	12,531	25	-.109	-.147	-.071	-5.5	**< .001**		64.6	**<.001**	73.45
	LF/HF	CRP	4,580	11	.100	-.009	-.208	1.79	.074		88.49	**<.001**	88.70

Note. This table gives statistical information on the observed associations between variables of interest split by inflammatory marker. Cardiac markers are as follows: heart rate (HR), the standard deviation of R–R intervals (SDNN), the percentage of R–R intervals that differed more than 50 milliseconds (pNN50), the root mean of square of the successive differences (RMSSD), very low frequency HRV (VLF), low frequency HRV (LF), high frequency HRV (HF), and the ratio between the LF-HRV and HF-HRV (LF/HF). CRP: C-reactive protein; FIBR: fibrinogen; IL-1: interlukin-1; IL-6: interlukin-6; TNF: tumor necrosis factor; WBC: white blood cell count. Total number of individuals observed for each relationship is represented as "*n*" and total number of included studies for each relationship is represented as "*k*". The random effects linear model (RELM) correlation coefficient is represented as "r", and includes associated confidence intervals (lower and upper bound as "lower CI" and "upper CI", respectively), z value, and *p* value. Bolded *p* values represent significant associations ($p < .05$) between the respective HRV and inflammatory marker. The final three columns are tests of homogeneity that include both a Q and I^2 index, with an associated p value for the Q index. Bolded *p* values represent significant Q statistics ($p < .05$).

Figure 2. Forest Plots for the Association between HF-HRV and both IL-6 and CRP



Note: This figure depicts forest plots for all available associations between high-frequency heart rate variability (HF-HRV) and both interleukin-6 (IL-6 | Figure 2A) and c-reactive protein (CRP | Figure 2B). Confidence intervals (95%) are calculated using sample size and correlation coefficients.

TNF-α showed no significant associations with SDNN, RMSSD, LF power, HF power, or the LF/HF ratio (each $p > .05$; see *Table 1*). It is important to note that effect sizes here were of similar magnitude to other inflammatory markers, however sample sizes were much smaller. Not enough studies reported/provided associations between TNF-α and HR, PNN50, and SDNN for meta-analyses. IL-1 showed no significant associations with SDNN, LF power, or HF power (each $p > .05$; see *Table 1*). Not enough studies reported/provided associations between IL-1 and HR, pNN50, RMSSD, VLF power, and the LF/HF ratio for meta-analyses. IL-6 showed a significant positive association with HR (n = 2,011, k = 5, r = .052, p = .020) and was negatively associated with SDNN (n = 7,752, k = 11, r = -.146, $p < .001$), VLF-HRV (n = 1,437, k = 6, r = -.190, $p < .001$), LF-HRV (n = 3,145, k = 13, r = -.231, $p < .001$), and HF-HRV (n = 3,249, k = 15, r = -.132, $p < .001$; Figure 2A). No significant associations were found between IL-6 and pNN50, RMSSD, or the LF/HF ratio (each $p > .05$; see Table 1). WBC showed a significant positive association with HR (n = 2,739, k = 2, r = .107, $p < .001$). WBC also showed significant negative associations with SDNN (n = 7,329, k = 5, r = -.129, $p < .001$), pNN50 (n = 3,350, k = 3, r = -.068, $p < .001$), RMSSD (n = 7,944, k = 5, r = -.093, $p < .001$), LF (n = 6,686, k = 3, r = -.086, $p < .001$), HF (n = 6,686, k = 3, r = -.062, $p < .001$). Not enough studies reported/provided associations between WBC and both VLF power and the LF/HF ratio for meta-analyses. Fibrinogen showed significant negative associations only with RMSSD (n = 1,473, k = 3, r = -.156, $p < .001$) and HF power (n = 808, k = 4, r = -.175, $p < .001$). No significant relationship was found between fibrinogen and VLF power, LF power, and the LF/HF ratio (each $p > .05$; see *Table 1*). Not enough studies reported/provided associations between fibrinogen and HR, SDNN, and pNN50 for meta-analyses. CRP showed a significant positive association with HR (n = 5,900, k = 8, r = .118, $p < .001$), and negative associations with SDNN (n = 17,421, k = 24, r = -.202, $p < .001$), pNN50 (n = 4,447, k =

6, r = -.109, p = .005), RMSSD (n = 16,450, k = 19, r = -.107, p < .001), VLF- HRV (n = 2,856, k = 11, r = -.239, p < .001), LF-HRV (n = 11,791, k = 20, r = -.137, p < .001), and HF-HRV (n = 12,531, k = 25, r = -.109, p < .001; Figure 2B). No significant association was found between CRP and the LF/HF ratio (n = 4,580, k = 11, r = .100, p = .074). Not enough studies reported/provided data to yield statistics on the relationships between indices of HRV and IL-2, IL-4, IL-10, and IFN-γ.

3.4 Meta-regression for Primary Correlations

Results indicated that sample-mean age significantly moderated the negative association between CRP and RMSSD (B = .004 (.002), [.000, .007], p = .028), such that as age increased, the negative association became weaker. Sex was a significant moderator to the negative association between CRP and VLF (B = .003 (.001), [.000, .006], p = .028), such that a higher percentage of females in the study was associated with a weaker negative association. No other regression coefficients for covariates were significant, all meta-regression statistics for all continuous covariates are displayed in Table 2. No significant results were found with regard to dichotomous variables.

Table 2: Meta-Regression Statistics and Results

Associations	Covariate	B	SE	Lower CI	Upper CI	*p*
IL-6 – SDNN	Age	-.001	.004	-.001	.008	.785
	Sex	-.002	.002	-.005	.002	.327
	Health Status	.000	.001	-.003	.002	.798
	Recording Length	.000	.000	.000	.000	.441
IL-6 – LF	Age	-.001	.004	-.011	.023	.423
	Sex	-.002	.003	-.008	.003	.386
	Health Status	-.001	.002	-.005	.002	.384
	Recording Length	.000	.000	.000	.000	.264
IL-6 – HF	Age	.010	.005	-.001	.021	.062
	Sex	-.002	.002	-.007	.002	.223
	Health Status	-.001	.001	-.004	.002	.494
	Recording Length	.000	.000	.000	.000	.919
CRP – SDNN	Age	.001	.003	-.005	.006	.842

	Sex	.000	.002	-.004	.004	.940
	Health Status	-.001	.001	-.003	.001	.414
	Recording Length	.000	.000	.000	.000	.490
CRP – RMSSD	**Age**	**.004**	**.002**	**.000**	**.007**	**.028**
	Sex	-.002	.001	-.004	.001	.143
	Health Status	.000	.001	-.001	.001	.904
	Recording Length	.000	.000	.000	.000	.528
CRP – VLF	Age	.000	.005	-.011	.011	.971
	Sex	**.003**	**.001**	**.000**	**.006**	**.028**
	Health Status	.000	.001	-.002	.002	.727
	Recording Length	.000	.000	.000	.000	.989
CRP – LF	Age	.001	.002	-.003	.005	.520
	Sex	-.001	.001	-.002	.001	.539
	Health Status	-.001	.001	-.003	.001	.196
	Recording Length	.000	.000	.000	.000	.767
CRP – HF	Age	.004	.002	-.001	.008	.120
	Sex	-.002	.001	-.004	.001	.145
	Health Status	-.001	.001	-.003	.001	.244
	Recording Length	.000	.000	.000	.000	.590
CRP – LF/HF	Age	-.007	.003	-.015	.001	.083
	Sex	.004	.003	-.003	.010	.221
	Health Status	-.001	.002	-.006	.004	.657
	Recording Length	.000	.000	-.001	.000	.498

Note. This table gives meta-regression statistics on the observed associations with studies (k) greater than or equal to 10. Cardiac markers are as follows: the standard deviation of R–R intervals (SDNN), the root mean of square of the successive differences (RMSSD), very low frequency HRV (VLF), low frequency HRV (LF), high frequency HRV (HF), and the ratio between the LF-HRV and HF-HRV (LF/HF). Interlukin-6 (IL-6) and C-reactive protein (CRP) were the inflammatory variables. Covariate coding is as follows: mean sample age in years (age), sample sex as percentage of females (sex), health status as percentage of non-healthy individuals (health status), and HRV recording length in minutes (Recording Length). Statistics include unstandardized beta coefficients (B), standard error (SE), confidence intervals (lower and upper bound as "Lower CI" and "Upper CI", respectively), and *p* values. Bolded *p* values represent significant covariates ($p < .05$)

4. Discussion

Converging theoretical and empirical evidence suggests an inverse relationship between indices of HRV, especially vagally-mediated HRV, and markers of inflammation. However, recently several studies provided conflicting results, suggesting the opposite (e.g., Singh et al., 2009), such that higher HRV was associated with greater inflammation; the present series of meta-analyses sought to address these inconsistencies. Using a meta-analytical approach, we found a general negative association between HRV, including indices of vagally-mediated HRV (e.g., HF power), and markers of inflammation. Of these inflammatory markers, both CRP and WBC showed the most robust and consistent negative associations across different indices of HRV. For

time domain indices of HRV, SDNN – an index of HRV thought to reflect the contribution of both the PNS and SNS – showed the strongest and most consistent negative associations across markers of inflammation. For the frequency-domain indices of HRV, HF-HRV showed the strongest and most consistent negative associations across markers of inflammation. Overall, our data lend support for the theorized action of the cholinergic anti-inflammatory pathway (Tracey, 2002) and further suggests that the activity of this pathway can be indexed using measures of HRV.

4.1 Implications and Future Directions

Health status, sex, statistical adjustment, mean age, and HRV recording length were not significant covariates in most of our observed relationships. However, mean age and sex were significant contributors to the association between CRP-RMSSD and CRP-VLF, respectively. Two previous studies reported significant sex differences in the association between HRV and inflammatory markers and suggested that the effect was larger in women than in men (Thayer & Fischer, 2008; Von Känel et al., 2009). Consistent with current US NIH recommendations, future studies are needed that report the associations between ANS indices and inflammatory markers separately by sex.

As it relates to indices of vagally-mediated HRV, both HF-HRV and RMSSD are consistently related to markers on inflammation, with HF-HRV being more strongly associated with all inflammatory markers except for WBC. When examining all HRV indices, SDNN showed a stronger and more consistent association with markers of inflammation (e.g., IL-6 and WBC) compared to all other indices, including HF-HRV. A previous review of the literature (Haensel et al., 2008) highlighted similar patterns, such that SDNN was more strongly, negatively correlated

with markers of inflammation in comparison to HF-HRV and RMSSD. In sum, results were particularly robust for SDNN (PNS and SNS influence) and inflammatory markers compared to that of primarily PNS influence (RMSSD and HF power). Only one study examined the association between HRV and inflammatory markers after controlling for SNS activity; results indicated an independent association between vagally-mediated HRV and inflammation (Thayer & Fischer, 2008). Given the finding of the current study that mixed PNS/SNS indices were more strongly and consistently related to inflammatory indices, future studies that measure both PNS and SNS markers are needed to assess the independent contributions of each branch of the ANS to these associations. It is important to note that while various indices of HRV may reflect activity of various autonomic mechanisms, each measure includes one common pathway – the vagus. Therefore, as theory would suggest (Tracey, 2002; Thayer and Sternberg, 2006, 2010), the vagus is likely the common mechanism underlying consistent negative relationships between HRV and inflammation.

Nevertheless, these patterns of results are interesting to consider from a physiological standpoint, as the slower-acting SNS (via epinephrine and norepinephrine) may indeed have a significant influence as it relates to systemic inflammatory markers such as IL-6 and CRP. For example, both initial (by PNS withdrawal via acetylcholine) and prolonged (via SNS hyperactivity) inflammatory responses may be best captured via SDNN – a measure of HRV thought to reflect activity of both SNS and PNS pathways. In this regard, additional research is also needed on the relationship between indices of HRV and "first-responder" inflammatory markers (i.e., those that promote systemic inflammation) such as TNF- α and IFN-γ. Such work will inform us if the relationship between indices of HRV and markers of inflammation vary as a function of the physiological nature of each measure. To give a specific example, upon the

detection of a pathogen macrophages release TNF-α; these site-specific responses produce classic signs of infection such as swelling and pain (Tracey, 2002). TNF-α therefore serves as a "warning signal" that defenses should be mobilized in an attempt to fight infection and/or injury. Importantly, TNF-α responses can prolong the inflammatory response via other pro-inflammatory cytokines released such as IL-6, thus causing widespread cytokine responses. As SDNN is more closely related to CRP, IL-6, and WBC as systemic markers of inflammation, HF-HRV and RMSSD may be more related to inflammatory markers that are site specific, such as TNF- α and IL-1 compared to that of SDNN; however not enough studies reported these associations to make such comparisons. In sum, it is possible that vagally-mediated HRV measures may be more closely related to "first-responder" inflammatory markers such as TNF-α. We stress the importance of additional research in this area.

4.2 Limitations and Future Directions

One limitation of the current study is that many eligible studies for inclusion were not analyzed due to inadequate reporting of the relationships of interest despite our attempt to contact all authors for additional information. Therefore, it is necessary that future studies that include both markers of inflammation and HRV should examine and provide full reporting on the association between these factors for meta-analytical research.

The mixed relationship reported here between immune/inflammatory measures and aspects of HRV reflecting activation of the sympathetic and parasympathetic systems, is consistent with autonomic regulation of immunity. The immune/inflammatory measures examined in this meta-analysis, including WBC, CRP, IL-6, fibrinogen, TNF alpha, IL-1 each come into play at different stages of immune/inflammatory activation, each of which are differentially regulated by both the

SNS and PNS. Thus, a measure of total WBC likely includes neutrophils, lymphocytes, and other immune cells, each of which are regulated by the SNS and PNS at different stages of immune activation (Bellinger and Lorton, 2014; Madden, 2017; Pavlov and Tracey 2017). For example, in addition to the PNS-mediated inflammatory reflex (Tracey, 2002) the sympathetic nervous system regulates mobilization of immune cells as well as circadian fluctuations, primarily affecting NK cells and granulocytes, with minimal effects on lymphocyte numbers. The association of WBC counts with SDNN, reflecting both SNS and PNS activation, would be consistent with this mixed autonomic regulation of WBCs. In order to tease out the precise relationships between different aspects of inflammatory/immune responses and different components of HRV, more detailed studies would need to be performed, for example, under controlled conditions and challenges, such as exercise (Simpson et al., 2015). This complex regulation of different aspects of inflammatory/immune responses likely explains the mixed findings in the literature to date assessing the relationship between HRV and immune measures.

4.3 Conclusions

The current series of meta-analyses supports the importance of the vagus nerve in regulating and controlling the inflammatory response, as there was an overall *negative* relationship found between HRV and markers of inflammation. We conclude by stressing the need for continued research in this area to better understand the potential complexities underlying these associations. Specifically, research is needed to address if measures of HRV may be associated with markers of inflammation differentially as a function of both the primary autonomic mechanism associated with the HRV measure, and the cascade position of the inflammatory marker.

*****aterisks denote references included in the meta-analysis

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Appendix A

Overall Search Strategy

inflamm* OR interleuk* OR IL-6 OR IL-8 OR IL-2 OR IL-1 OR C reactive protein OR CRP OR white blood cell* OR WBC OR leukocytes OR fibrinogen OR myeloperoxide OR MPO OR tumor necrosis factor OR TNF OR TNF-α OR interferon gamma OR IFNy or ICAM or VCAM OR α1-antichymotrypsin OR (ACT) AND heart rate variability OR HRV OR heart period variability OR respiratory sinus arrhythmia OR RSA OR vagal OR vagus

Pubmed: 1,449 results found

(Inflamm* OR interleukin* OR IL-6 OR IL-8 OR IL-2 OR IL-1 OR c reactive protein OR CRP OR white blood cells OR WBC OR leukocytes OR fibrinogen OR myeloperoxidase OR MPO OR tumor necrosis factor OR TNF OR tnf-alpha OR interferon gamma OR icam OR vcam OR alpha1-antichymotrypsin OR ACT) AND ("heart rate variability" OR HRV OR "heart period variability" OR "respiratory sinus arrhythmia" OR RSA OR vagal OR vagus) AND

Cinahal: 263 results found

(inflamm* OR interleuk* OR IL-6 OR IL-8 OR IL-2 OR IL-1 OR C reactive protein OR CRP OR white blood cell* OR WBC OR leukocytes OR fibrinogen OR myeloperoxide OR MPO OR tumor necrosis factor OR TNF OR TNF-α OR interferon gamma OR IFNy or ICAM or VCAM OR α1-antichymotrypsin OR ACT) AND ("heart rate variability" OR HRV OR "heart period variability" OR "respiratory sinus arrhythmia" OR RSA OR vagal OR vagus)

Web of Science: 385 results found

TITLE:((Inflamm* OR interleukin* OR IL-6 OR IL-8 OR IL-2 OR IL-1 OR “c-reactive protein” OR CRP OR “white blood cells” OR WBC OR leukocytes OR fibrinogen OR myeloperoxidase OR MPO OR “tumor necrosis factor” OR TNF OR tnf-alpha OR “interferon gamma” OR icam OR vcam OR “alpha1-antichymotrypsin” OR ACT) AND ("heart rate variability" OR HRV OR "heart period variability" OR “respiratory sinus arrhythmia” OR RSA OR vagal OR vagus))

Psychinfo: 201 results found

((Inflamm*) OR (interleukin*) OR (IL-6) OR (IL-8) OR (IL-2) OR (IL-1) OR (c reactive protein) OR (CRP) OR (white blood cells) OR (WBC) OR (leukocytes) OR (fibrinogen) OR (myeloperoxidase) OR (MPO) OR (tumor necrosis factor) OR (TNF) OR (tnf-alpha) OR (interferon gamma) OR (icam) OR (vcam) OR (alpha1-antichymotrypsin) OR (ACT)) AND (("heart rate variability") OR (HRV) OR ("heart period variability") OR (respiratory sinus arrythmia) OR (RSA) OR (vagal) OR (vagus))

Highlights:

Heart Rate Variability and Inflammation: A Meta-Analysis of Human Studies

- A general negative association exists between indices of heart rate variability (HRV) and markers of inflammation.
- The strength of these associations differ based on the inflammatory and HRV variables of interest.
- The standard deviation of R-R intervals (SDNN) and power in the high frequency band of HRV (HF-HRV) showed the most robust associations with markers of inflammation.
- HRV can be used to index the activity of inflammatory processes.