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Comparing low frequency heart rate variability and preejection period: Two sides of a different coin

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Abstract

It has been hypothesized that the ratio of heart rate variability in the low- (LF) and high- (HF) frequency bands may capture variation in cardiac sympathetic control. Here we tested the temporal stability of the LF/HF ratio in 24-h ambulatory recordings and compared this ratio to the preejection period (PEP), an established measure of cardiac sympathetic control. Good temporal stability was found across a period of 3.3 years ($.46 < r < .78$), but the LF/HF ratio did not show the expected negative correlation to PEP, either between or within subjects. We conclude that the evidence to support the LF/HF ratio as a potential marker of cardiac sympathetic control in epidemiology-scaled research is currently insufficient.

Descriptors: LF/HF ratio, PEP, Sympathetic, Ambulatory monitoring

Because activity of the sympathetic nervous system (SNS) may be paramount to the detrimental effects of stress on cardiovascular health (Kamarck & Lovallo, 2003; Palatini & Jullius, 2004) cardiovascular psychophysiologists need reliable and valid methods to measure SNS activity in humans. Ideally, such measures should be noninvasive, unobtrusive, and cheap to allow ambulatory assessment in epidemiology-scaled samples. In response to this need, Pagani and coworkers have suggested that spectral power of the heart period time series in the lower frequencies centered around 0.1 Hz (LF) divided by the power in the higher frequencies centered around the respiratory frequency (HF) may reliably capture changes in the ratio of sympathetic to vagus nerve traffic to the heart (Malliani, Pagani, Lombardi, & Cerutti, 1991; Pagani et al., 1986, 1991, 1997). Because recording of the heart period time series requires nothing more complicated than a three-lead ECG recording, spectral-power-derived LF/HF ratios can be obtained in ambulatory paradigms in huge numbers of subjects at very modest costs.

Although its use has become widespread, the LF/HF ratio is not without controversy (Eckberg, 1997). The strongest concern about the validity of the LF/HF ratio comes from studies that directly compare it against invasive measures of sympathetic activity, like direct recording of action potentials from superficial sympathetic nerves or assessment of cardiac norepinephrine spillover by radioactive tracers. Most of these studies did not find a correlation between the LF/HF ratio and these sympathetic measures across a range of clinical contexts, as reviewed by Grassi and Esler (1999).

In defence of the LF/HF power it must be noted that these studies were often performed in nonecological physiological contexts; for example, within-subject variance in sympathetic activity was usually induced by infusion of nitroprusside or phenylephrine (Pagani et al., 1997; Saul, Rea, Eckberg, Berger, & Cohen, 1990). Secondly, they were mostly performed on small sample sizes that required the correlations to be in the .60–.80 range to be considered "significant." It is unlikely, however, that LF/HF reflects cardiac sympathetic control that closely. Whereas HF power relatively purely reflects cardiac vagal control over the heart (Task Force of the European Society of Cardiology and the North American Society of Pacing, 1996), it is fully acknowledged that LF power is influenced by *both* sympathetic and vagal activity. Hence, the LF/HF ratio will not yield a perfect indicator of cardiac sympathetic control. Even so, it may still retain sufficient explanatory and predictive power to be useful in epidemiology-scaled research.

In this study, we recorded ambulatory LF and HF power in 64 subjects and reassessed these powers after an average of 3.3 years to establish temporal stability of the ambulatory LF/HF ratio. We next compared the LF/HF ratio, both within and between subjects, to an alternative measure of cardiac sympathetic control, the preejection period (PEP), which can be obtained by ambulatory recording of the thoracic impedance cardiogram (Kupper, Willemsen, Boomsma, & de Geus, 2006; Riese et al., 2003). Changes in PEP reflect changes in

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β-adrenergic inotropic drive to the left ventricle, provided subjects are compared in the same posture (Houtveen, Groot, & de Geus, 2005; Sherwood et al., 1990). If the LF/HF ratio is a valid measure of cardiac sympathetic control, it should show a negative correlation to the PEP, such that longer PEPs are associated with lower LF/HF ratios.

Methods

Participants

Participants were all registered with the Netherlands Twin Register (NTR). They came from families that participated in a genetic linkage study searching for genes influencing personality and cardiovascular disease risk, which is described elsewhere (Boomsma et al., 2000). Out of the 1,332 twins and siblings who participated in the linkage study, 816 were also willing to participate in cardiovascular ambulatory monitoring (Kupper et al., 2006). To establish temporal stability, 65 volunteers (20 male, 45 female) were re-recruited for a second ambulatory recording day after an average of 3 years 4 months (minimum of 2 years 1 month and maximum of 4 years 8 months). These 65 subjects with two repeated test days form the basis of the current study. At the first test day their ages ranged from 18 to 62 years (mean = 30.7, $SD = 9.7$).

Procedure

A detailed description of the ambulatory monitoring procedure has been provided elsewhere (Goedhart, Kupper, Willemsen, Boomsma, & de Geus, 2006; Goedhart, van der Sluis, Houtveen, Willemsen, & de Geus, 2007; Kupper et al., 2006). Briefly, subjects were fitted with the Vrije Universiteit Ambulatory Monitoring System that recorded the electrocardiogram (ECG) and the impedance cardiogram (ICG) continuously during a 24-h period (daytime and sleep) through six disposable, pregelled Ag/AgCl electrodes. During the daytime and evening, participants were regularly prompted to give a chronological account of posture, physical activity, physical load, location, and social situation during the last 30-min period. Using the activity diary entries in combination with a visual display of an in-built vertical accelerometer signal, the entire 24-h recording was divided into fixed periods coded for posture (e.g., lying, sitting, standing), ongoing activity (e.g., desk work, eating/drinking, meetings, watching TV), physical activity (no, light, medium, and heavy), location (e.g., work, home, outside), and social situation (e.g., alone, with colleagues, with friends). An average of 27 coded periods was created per subject with a mean duration of 30 min (minimum 5 min, maximum 60 min).

PEP and LF/HF Registration

Large-scale ensemble averaging of the ICG signals was performed to obtain the mean PEP per coded period as outlined in detail by Riese et al. (2003) and Kupper et al. (2006). From the ECG and the dZ, we obtained the heart period time series and respiration signal (Goedhart et al., 2007; Houtveen et al., 2005). In keeping with PEP scoring, mean LF and HF powers were computed across the entire coded period. We used a Wavelet approach, which has some advantages over the more common Fourier approach as discussed elsewhere (Houtveen & Molenaar, 2001). The LF power was computed as the variance in the 0.0625–0.125-Hz window and HF power as the variance in the 0.125–0.5-Hz window. From these, the LF/HF ratio was computed as well as the LF power in normalized units (LFnu), which is the LF power divided by the sum of the LF and HF powers. Although it has been suggested that LFnu and LF/HF ratio can be considered equivalent carriers of information (Burr, 2007), we present full data on absolute LF, LFnu, and LF/HF ratio for completeness.

Results

Table 1 presents the untransformed means and standard deviations for PEP and the heart rate variability measures separately during sleep, awake sitting, and mild physical activity. Because the LF/HF ratio and the LF, HF, and LFnu power distributions were skewed, their natural logarithms were used in all further analyses.

Table 1 also reports the temporal stability that was assessed by intraclass correlation, computed separately for nighttime sleep, sitting during the day, and mild physical activity (standing/walking). Good temporal stability for LF, HF, and LFnu powers and the LF/HF ratio was found over an average period of 3 years 4 months during sitting and sleep. Correcting HF power for changes in respiration rate (residualized HF powerHFres) did not further improve stability. Physical activity, which is inherently less comparable across repeated test days, produced lower estimates.

Table 2 show the within-subject correlations of PEP and the heart rate variability measures during sitting activities across the

Table 1. *Means (SD) of PEP and Heart Rate Variability Measures and Temporal Stability across the Two Test Days (N = 64)*

Condition	PEP (ms)	LF (ms^2)	HF (ms^2)	LF/HF	LFnu
Sleep					
Test day 1	105.39 (11.62)	1023.75 (804.09)	1080.64 (1039.62)	1.26 (.66)	51.41 (11.61)
Test day 2	107.53 (13.18)	975.72 (1025.26)	901.74 (1093.50)	1.43 (.79)	54.30 (11.52)
Temporal stability	**.71**	**.80**	**.79**	**.64**	**.72**
Sitting					
Test day 1	97.43 (12.42)	829.59 (556.60)	666.57 (723.62)	1.74 (.82)	59.39 (8.92)
Test day 2	97.11 (13.18)	764.68 (580.30)	592.72 (658.77)	1.76 (.75)	59.81 (8.69)
Temporal stability	**.80**	**.82**	**.79**	**.70**	**.70**
Mild physical activity					
Test day 1	98.58 (11.94)	689.29 (400.47)	578.83 (553.61)	1.69 (.78)	58.47 (10.41)
Test day 2	96.33 (13.36)	666.96 (412.77)	444.36 (346.64)	1.93 (.79)	61.58 (8.14)
Temporal stability	**.76**	**.62**	**.57**	**.53**	**.53**

Note: Correlations significant at $p < .05$ are in bold.

Table 2. *Within-Subject Correlations between PEP and HRV Measures during the Posture Sitting*

Participant no.	Age	*N*	PEP-LF	PEP-HF	PEP-HFres	PEP-LF/HF	PEP-LFnu	LF-HF	LF-HFres
1	18.0	26	.04	.03	.06	−.01	.00	**.82**	**.80**
2	18.9	40	−.07	**−.51**	**−.53**	**.56**	**.52**	**.67**	**.60**
3	18.9	26	−.20	.08	.03	−.15	−.24	.68	.68
4	20.2	23	.13	−.03	−.03	.14	.11	.42	.40
5	21.9	31	.36	.28	.25	.08	.07	**.64**	**.60**
6	23.0	30	.01	−.03	−.07	.05	.06	.09	.10
7	23.0	14	−.04	−.30	−.30	.36	.34	**.66**	.59
8	23.1	16	−.01	.41	.39	−.34	−.32	**.57**	.52
9	23.5	33	−.10	−.01	−.07	−.08	−.07	.37	**.36**
10	23.9	23	**.61**	**.80**	**.80**	**−.78**	**−.77**	**.87**	**.87**
11	24.0	27	.18	.04	−.05	.24	.26	**.84**	**.80**
12	24.6	32	.31	.30	.18	.07	.10	**.63**	**.62**
13	24.7	32	−.34	−.38	−.31	.09	.06	**.83**	**.77**
14	24.9	43	.26	.17	.30	.19	.19	**.70**	**.59**
15	25.2	17	.30	.32	.22	−.09	−.05	**.83**	**.79**
16	25.6	28	.13	.28	.32	−.33	−.33	**.86**	**.85**
17	26.6	21	.27	.10	.09	.25	.19	**.87**	**.84**
18	26.8	23	.17	−.01	.05	.30	.30	**.81**	**.81**
19	27.1	40	.06	−.30	**−.43**	.37	.36	**.46**	**.43**
20	27.5	36	.33	.12	.10	.22	.25	**.62**	**.61**
21	28.0	40	.29	.30	.27	.04	.08	**.86**	**.85**
22	28.5	27	**.58**	.47	**.50**	.06	.06	**.55**	**.52**
23	28.5	16	.31	.29	.25	−.08	−.04	**.71**	**.72**
24	28.6	29	.10	.18	.16	−.14	−.14	**.51**	**.51**
25	29.5	23	**.61**	.26	.28	.52	**.67**	**.85**	**.86**
26	30.0	29	−.13	.25	.27	−.39	−.39	**.55**	**.51**
27	30.7	23	.04	.52	**.53**	**−.61**	**−.66**	**.67**	**.65**
28	31.2	23	.11	.47	.52	−.51	−.46	**.58**	**.55**
29	32.7	25	−.12	.23	.26	−.47	−.49	**.73**	**.74**
30	32.9	25	.62	**.55**	**.53**	−.33	−.29	**.92**	**.90**
31	32.9	20	.27	.20	.22	.10	.08	**.95**	**.94**
32	35.3	21	.16	−.11	−.14	.33	.34	**.73**	**.71**
33	36.6	29	.14	.12	.12	.09	.08	**.89**	**.87**
34	40.3	21	.53	.24	.18	.23	.33	**.76**	**.71**
35	42.1	32	.08	.02	−.05	.06	.07	**.70**	**.65**
36	42.1	36	**.44**	.28	.27	−.02	.07	**.70**	**.67**
37	42.7	30	.17	.27	.27	−.28	−.26	**.76**	**.73**
38	44.0	26	.09	.20	.17	−.09	−.08	.31	.35
39	44.1	22	.02	−.26	−.14	.30	.28	.42	.40
40	47.3	28	.15	−.07	−.13	.29	.30	**.71**	.39
41	47.5	37	**.44**	.38	.40	−.18	−.22	**.95**	**.94**
42	48.3	26	−.06	.11	.16	−.23	−.27	**.83**	**.82**
43	48.4	23	**.59**	**.72**	**.72**	−.30	−.31	**.95**	**.94**
44	62.3	32	.05	.42	.37	−.44	−.45	**.70**	**.69**
45	19.5	30	.42	.43	.46	−.08	−.01	**.49**	**.47**
46	19.7	22	.15	.24	.23	−.19	−.13	**.74**	**.73**
47	20.5	30	.37	.36	.34	−.21	−.04	.34	.33
48	22.5	24	.38	.44	.44	−.18	−.19	**.96**	**.96**
49	24.7	33	.41	**.45**	**.52**	−.07	−.05	**.61**	**.58**
50	25.0	25	.08	.02	.04	.04	.10	**.79**	**.78**
51	25.1	46	.12	−.27	−.26	**.46**	**.49**	**.69**	**.68**
52	25.3	21	**.62**	.54	.51	−.22	−.16	**.91**	**.89**
53	25.4	30	.19	.16	.19	.09	.08	**.89**	**.86**
54	25.8	24	.01	−.06	.03	.08	.11	**.87**	**.86**
55	27.0	15	.05	−.07	−.08	.28	.32	**.94**	**.94**
56	27.8	37	.22	.05	.03	.16	.14	**.43**	.38
57	28.0	23	.37	.11	.13	.39	.41	**.78**	**.77**
58	28.5	19	.05	.38	.33	−.31	−.29	.35	.31
59	31.4	28	.07	.25	.20	−.32	−.24	**.68**	**.61**
60	33.0	27	.14	.41	.45	**−.55**	**−.52**	**.84**	**.82**
61	38.6	32	.02	.06	.01	−.06	−.05	**.80**	**.78**
62	45.6	28	−.03	.13	.21	−.26	−.22	**.74**	**.73**
63	47.1	25	.31	.35	.27	.06	.06	**.74**	**.74**
64	50.8	30	−.01	−.03	.09	.01	.03	**.68**	**.65**
Median	30.9	27	.15	.20	.19	.00	.05	.72	.71

Note: Bold signifies that the correlation is significant at the .01 level.

two 24-h measurements. The median within-subject correlation between PEP and the LF/HF ratio was exactly zero. Only 3 out of 64 subjects showed a significant correlation in the expected (negative) direction. For absolute LF power, not a single subject showed the expected significant negative correlation. Inspection of each test day separately also failed to reveal significant LF/HF to PEP correlations.

Median within-subject correlations between LF and HF power were unanimously high (LF and HF, $r = .72$). Correction for within-subject changes in respiration barely influenced this correlation (LF and HFres, $r = .71$).

Table 3 shows the between-subject correlations separately within each of the three main ambulatory conditions for both test days. Partial correlations were computed controlling for the effect of sex and age. During sleep, none of the correlations between PEP and the heart rate variability measures were significant. During sitting and physical activity on Day 2 a significant correlation between PEP and the LF power was found, but the direction was opposite to the expectation.

Between-subject correlation for LF and HF all exceed .79 in all three conditions on both test days, indicating high overlap between the two measures of heart rate variability. Again, partialling out respiration rate barely affected the LF–HF correlation.

Discussion

The notion has been advanced that a single ratio, spectral power of the heart period time series in the lower frequencies centered around 0.1 Hz (LF) divided by the power in the higher frequencies centred around the respiratory frequency (HF), may capture differences in cardiac sympathetic control, even if imperfectly (Malliani et al., 1991; Pagani et al., 1986, 1991, 1997). Here we used prolonged ambulatory recordings on two test days to establish temporal stability of the LF/HF ratio and to test whether it was correlated within and between subjects with the PEP, an established measure of cardiac sympathetic control.

Although good temporal stability was found across a period of 3.3 years, the LF/HF ratio did not show the expected negative correlation to PEP, either between or within subjects. The most parsimonious conclusion from these results is that PEP and LF/HF do not measure the same physiological phenomenon; they appear to be "two sides of a different coin." The important question then becomes which of the two measures reflects cardiac sympathetic control best. Studies using manipulations known to increase cardiac sympathetic activity like mental stress and exercise currently suggest that the PEP outperforms the LF/HF ratio as an index of sympathetic control. Mental or emotional stress increases the LF power in some studies (Langewitz & Ruddel, 1989) but not in all (Hoshikawa & Yamamoto, 1997; Tulen, Boomsma, & Veld, 1999), whereas these stressors systematically shorten the PEP (Berntson et al., 1994; de Geus, Kupper, Boomsma, & Snieder, 2007; Houtveen et al., 2005; Sherwood et al., 1990). Furthermore, cardiac sympathetic activation induced by exercise sometimes evokes a decrease in LFnu power rather than the expected increase (Ahmed, Kadish, Parker, & Goldberger, 1994), whereas systematic and dose-dependent shortening of the PEP is seen during exercise (Houtveen, Rietveld, & de Geus, 2002; Smith et al., 1989). Finally, PEP shows more specificity in response to autonomic blockade than the LF/HF ratio. Acute β-adrenergic blockade does not give rise to the expected reduction in LF power (Pagani et al., 1986) and may even cause an increase in LF power (Jokkel, Bonyhay, & Kollai, 1995) whereas cholinergic blockade by atropine causes a substantial reduction or even elimination of LF fluctuations (Akselrod et al., 1981; Jokkel et al., 1995). In contrast, acute

Table 3. *Between-Subject Corrrelation between PEP and Heart Rate Variability Measures*

Condition	Day	*N*	PEP-LF	PEP-HF	PEP-HFres	PEP-LFHF	PEP-LFnu	LF-HF	LF-HFres
Sleep	1	58	.26 (.19)	.17 (.10)	.16 (.08)	.12 (.17)	.11 (.16)	**.87 (.89)**	**.86 (.89)**
	2	57	.22 (.24)	.18 (.16)	.16 (.13)	.02 (.08)	.03 (.10)	**.89 (.91)**	**.90 (.91)**
Sitting	1	64	.24 (.25)	.24 (.19)	.23 (.18)	− .13 (. − 04)	− .09 (− .01)	**.87 (.88)**	**.84 (.85)**
	2	64	**.38 (.39)**	**.35 (.34)**	**.34 (.32)**	− .14 (− .12)	− .07 (− .05)	**.90 (.90)**	**.89 (.89)**
Mild physical activity	1	64	.18 (.22)	.29 (.27)	.27 (.25)	− .27 (− .21)	− .27 (− .22)	**.81 (.81)**	**.79 (.79)**
	2	64	**.35 (.35)**	**.32** (.31)	.29 (.27)	− .13 (− .11)	− .05 (− .03)	**.88 (.85)**	**.88 (.84)**

Note: Bold signifies that the correlation is significant at the .01 level. Correlations after partialling out age and sex are in parentheses.

β-receptor blockade always prolongs PEP (Cacioppo et al., 1994; Sherwood et al., 1990; Winzer et al., 1999) whereas atropine leaves it unchanged (Cacioppo et al., 1994).

In conclusion, we find that in ambulatory data the PEP and the LF/HF ratio are uncorrelated, either within or between subjects. The predictive power of both LF and HF power for cardiovascular disease is beyond question (Dekker et al., 2000; Tsuji et al., 1996), as is the usefulness of ambulatory recording of these two aspects of heart rate variability. However, the evidence to support ambulatory LF/HF ratio as a potential marker of cardiac sympathetic nerve control may be insufficient.

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