European Heart Journal (1998) **19,** 1334–1341 Article No. hj981084

Heart rate variability and heart rate in healthy volunteers

Is the female autonomic nervous system cardioprotective?

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Aims Heart rate variability has been proposed as an indicator of cardiovascular health. Since women have a lower cardiovascular risk, we hypothesized that there are gender differences in autonomic modulation.

Methods and Results In 276 healthy subjects (135 women, 141 men) between 18 and 71 years of age, 24 h heart rate and heart rate variability were determined. All heart rate variability parameters, except for pNN50 and high frequency power, were higher in men. After adjustment for heart rate, we obtained gender differences for: the standard deviation ($P=0{\cdot}049$), the standard deviation of the 5 min average ($P=0{\cdot}047$), low frequency power (absolute values, $P=0{\cdot}002$; normalized units, $P<0{\cdot}001$) and ratio low frequency/high frequency ($P<0{\cdot}001$). There were no significant gender differences in heart rate variability parameters denoting vagal modulation. Gender differences were confined to age categories of less than 40 years of age. The majority of heart rate variability parameters decreased with age. Only in men, was a higher body mass index associated with a higher heart rate and with lower heart rate variability parameters ($P<0{\cdot}001$).

Conclusion Cardiac autonomic modulation as determined by heart rate variability, is significantly lower in healthy women compared to healthy men. We hypothesize that this apparently paradoxical finding may be explained by lower sympathetic activity (low frequency power) in women. This may provide protection against arrhythmias and against the development of coronary heart disease.
(Eur Heart J 1998; 19: 1334–1341)

Key Words: Autonomic nervous system, heart rate variability, vagal activity, sympathetic activity, gender, age.

Introduction

Heart rate variability measurements are used as markers of autonomic modulation of the heart. Time domain analysis of heart rate variability uses statistical methods to quantify the variation of the standard deviation or the differences between successive RR intervals. Frequency domain analysis of heart rate variability enables us to calculate the respiratory dependent high frequency and the low frequency power. High frequency power is mediated by vagal activity[1], while low frequency power has been suggested to represent predominantly sympathetic modulation[2,3]. The most important clinical application of heart rate variability lies in post-myocardial infarction risk stratification. The relation between reduced heart rate variability and an increased risk of arrhythmic death in coronary heart disease has been firmly established[4–6].

Compared to their male counterparts, women are at less risk of coronary heart disease[7,8], and of serious arrhythmias[9,10], with women lagging behind men in the incidence of sudden death by 20 years[11]. Only a few studies, with rather conflicting results, have focused on the influence of gender on cardiac autonomic modulation. These studies have several limitations: some report on only a small number of healthy subjects[12,13], or restrict their population to a certain age category such as the middle-aged[14–16]. Furthermore, the special report on the standards of measurement of heart rate variability by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[17] was published only recently. With previous studies using a multitude of approaches[12,15,16,18] to calculate heart rate variability, their comparison and interpretation remains troublesome. The purpose of this study was to test the hypothesis that heart rate variability is higher in healthy women

Revision submitted 17 March 1998, and accepted 24 March 1998.

Some of the results on heart rate variability calculations were used in a previous study to test the association between cardiac autonomic function and stress-coping style[37].

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0195-668X/98/091334+08 $18.00/0

than in healthy men. If confirmed, this points to a possible mechanism protecting women against cardiovascular disease. For measurements of heart rate variability, we have applied the recommended standards in a sufficiently large number of healthy subjects between adolescence and old age.

Methods

Study population

Two-hundred and seventy-six healthy subjects were recruited at two centres of occupational medicine (Medi Leuven and IDEWE, Leuven, Belgium) and in a group of volunteers of the Christelijke Mutualiteiten (health insurance institution, Leuven, Belgium): 135 women and 141 men between 18 and 71 years of age, with at least 40 participants per 10 years age category. A detailed medical history was obtained from each participant. Subjects with diabetes, hypertension, cardiovascular, neurological or psychiatric diseases were excluded. Smoking behaviour, height, weight and education level were registered.

Data collection

After informed consent, a Holter recorder was attached to the patient for 24 h between 0800 and 0900. The morning after, any sleep disturbance due to the Holter recorder was noted. Only recorders with time tracking were used.

Heart rate variability analysis

Heart rate variability was calculated in general agreement with the standards of measurement recently proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[17]. Power spectral analysis was included to study the interrelationship between time domain and frequency domain indices. Another reason to include power spectral analysis was the absence of a time domain parameter corresponding to low frequency power. The Holter recordings were digitized at a rate of 200 samples . s^{-1} on a PC-based platform and analysed for arrhythmic events. Correct manual annotation was made and premature supraventricular and ventricular beats, missed beats and pauses were filtered, with omission of one subsequent beat and linear interpolation of the corresponding periods. Subsequently heart rate variability parameters were calculated for 24 h, between 0800–2100h in the day and 2300–0600h at night. We calculated the standard deviation of the normal-to-normal (NN) intervals (SD), the standard deviation of the 5 min average of NN intervals (SDANN), the percentage of NN intervals with a cycle length over 50 ms different from the previous interval (pNN50), and the square root of squared successive differences in NN intervals (rMSSD) in the time domain. Power spectral density (Fast Fourier Transform) was computed on 256 s tachograms, with a 50% overlapping function and multiplication by a Hanning window. In the frequency domain, total power (0·01–1·00 Hz), low frequency power (0·04–0·15 Hz), high frequency power (0·16–0·40 Hz) and low frequency/high frequency ratio were calculated.

Statistical analysis

Statistical analysis was performed with SPSS for Windows Release 7.5 (Scientific Packages for Social Sciences, Inc., Chicago, IL, U.S.A.). The Kolmogorov–Smirnov goodness of fit test was used to test normality. Because of their skewed distribution, rMSSD, total power, low frequency power, high frequency power and low frequency/high frequency ratio were transformed by calculating their natural logarithm. For pNN50 we used the square root as transformation. All transformed heart rate variability parameters showed a normal distribution. The spectral parameters low frequency and high frequency power were also transformed to normalized units[3,19]. By definition, this means that every statistical result on low frequency power (in normalized units) yields the same result for high frequency power (in normalized units).

Differences between groups were analysed by Student's t-test (two-tailed), or by analysis of variance with control for confounding variables; this conducted separately for the two periods, day and night (see above). To test the association between the different heart rate variability indices, a two-tailed Pearson correlation coefficient (r) was calculated for the whole population and separately in men and women. Since heart rate variability decreases with age[20,21], partial correlation coefficients, controlling for age, were calculated. Correlations from 0 to 0·25 (or $-0{\cdot}25$) were disregarded since, in biomedical sciences, they indicate only little or no relationship[22].

Results

Normal values — influence of gender, diurnal variation, age, and weight

The mean values of 24 h heart rate and the different heart rate variability indices for all 276 volunteers are depicted in Table 1. Except for pNN50 and high frequency power in absolute values, all heart rate variability indices were higher in men (Table 1). After the introduction of heart rate as a covariate, we found only the following gender differences: SDANN ($P=0{\cdot}047$), SD ($P=0{\cdot}049$), total power ($P=0{\cdot}014$), low frequency power (absolute values, $P=0{\cdot}002$) and the ratio low

Table 1 Normal values of 24 h heart rate variability indices, with gender differences and correlations with age (Pearson correlation coefficients, all P<0·001)

	Men (n=141)				Women (n=135)				Gender difference	
	Mean	Standard deviation	Percentile 05–95	Correlation with age	Mean	Standard deviation	Percentile 05–95	Correlation with age	Without adjustment for basal HR	With adjustment for basal HR
Age (years)	40·8	14·4	23–67	/	42·6	14·8	23–66	/	/	/
BMI ($kg . m^{-2}$)	24·9	3·1	20–31	0·27	23·4	3·8	18–31	0·56	***	***
Heart rate ($beats . min^{-1}$)	74·3	8·9	59·5–91·3	ns	79·1	8·2	65·2–92·1	−0·31	***	/
Time domain HRV										
pNN50 (%)	11·8	10·1	6–32·1	−0·61	9·5	7·6	1·0–27·1	−0·41	ns	ns
rMSSD (ms)	41·8	22·9	14·1–91·6	−0·50	35·4	16·2	17·1–70·1	−0·32	*	ns
SDANN (ms)	141·4	44·9	76·2–220·9	−0·51	124·6	29·2	72·8–168·7	ns	***	*
SD (ms)	157·1	45·1	87·0–235·5	−0·54	138·6	29·3	86·2–185·4	ns	***	*
Freq domain HRV										
tot power (ms^2)	2690	1712	579–6382	−0·61	1834	1125	596–4267	−0·53	***	*
LF power (ms^2)	1073	701	175–2528	−0·64	704	466	188–1726	−0·59	***	***
in NU	81·7	9·1	61·5–92·2	ns	78·2	8·4	61·9–88·5	ns	***	***
HF power (ms^2)	281	322	29–774	−0·52	218	237	40–692	−0·44	ns	ns
in NU	18·3	9·1	7·8–38·5	ns	21·8	8·4	11·5–38·1	ns	***	***
LF/HF	5·7	3·1	1·6–11·9	ns	4·2	1·9	1·6–7·7	ns	***	***

For abbreviations see Methods. NU=normalized units. For statistical analysis pNN50, rMSSD, total power, low frequency power, high frequency power, and low frequency/high frequency were tranformed to obtain normality, as described in the Methods. Significance of gender difference: *$P<0·05$, **$P<0·01$, ***$P<0·005$. ns=non-significant.

Table 2 Day/night changes in HR and heart rate variability indices

	Day			Night			Day/night difference	
	Mean	Standard deviation	Percentile 05–95	Mean	Standard deviation	Percentile 05–95	Without adjustment for basal HR	With adjustment for basal HR
Heart rate (beats . min $^{-1}$)	83·9	10·2	68·2–101·5	65·0	8·6	52·6–80·5	***	/
Time domain HRV								
pNN50 (%)	7·4	7·3	0·3–23·5	17·5	15·5	0·8–49·6	***	ns
rMSSD (ms)	31·5	16·6	13·7–63·4	48·9	29·9	16·6–109·6	***	**
SDANN (ms)	82·9	31·3	44·9–144·7	74·9	33·8	35·9–153·3	***	***
SD (ms)	104·3	33·1	63·1–179·0	110·6	40·1	60·3–196·9	*	***
Freq domain HRV								
tot power (ms^2)	2010	1424	552–4747	2846	2319	607–7247	***	***
LF power (ms^2)	817	572	174–1850	1086	983	191–2881	***	***
in NU	82·8	8·7	65·6–92·4	74·8	11·9	51·9–89·7	***	***
HF power (ms^2)	187	246	28–619	433	626	37–1368	***	ns
in NU	17·2	8·7	7·6–34·4	25·2	11·9	10·3–48·1	***	***
LF/HF	6·2	3·5	1·9–12·2	4·0	2·7	1·1–8·7	***	***

For abbreviations see Methods. NU = normalized units. For statistical analysis pNN50, rMSSD, total power, low frequency power, high frequency power, and low frequency/high frequency were tranformed to obtain normality, as described in the Methods. Significance of day/night difference: *P<0·05, **P<0·01, ***P<0·005. ns = non-significant.

frequency/high frequency (P<0·001). The expression of low frequency power in relative terms (i.e. normalized units) did not affect the gender difference (P<0·001). There were no significant gender differences for the heart rate variability parameters denoting vagal modulation, such as pNN50, rMSSD and high frequency power in absolute values.

During the night, heart rate was lower, and all heart rate variability indices related to vagal modulation were higher (Table 2). Low frequency power exhibited higher absolute values during the night but a higher relative contribution (normalized units) during the day. These diurnal variations were present in both men and women and in all age categories. The relatively small day/night differences in SDANN, SD and low frequency power, however, did not always reach statistical significance in these smaller groups. The day/night changes in vagal modulation (high frequency power, pNN50) were linked to the day/night changes in basal heart rate (correlation between differences in day/night heart rate and day/night high frequency power $r = -0{\cdot}45$, P<0·001), which explains the absence of day/night differences in these parameters after adjustment for basal heart rate.

Analysis of the gender difference in heart rate and heart rate variability for the day and night separately, showed basically the same patterns for all time domain indices and for the spectral indices expressed in absolute values. Examination of the spectral indices after transformation to normalized units revealed that the gender difference in low frequency power is more pronounced during the night (P<0·001 vs non-significant (ns) during the day). This is not surprising, since the absolute values of high frequency power are much lower during the day. In this way they contribute less to the normalization process. After adjustment for basal (day or night) heart rate some other minor differences emerged. Night-time high frequency power was slightly higher in women (P = 0·044). Both night and day low frequency power (in normalized units) were higher in men after the introduction of heart rate as a covariate (P<0·001 and P = 0·005, respectively).

Further analysis per age category of 10 years demonstrated that gender differences were confined to the categories of less than 40 years of age. At higher ages, heart rate, SDANN, SD, and the absolute values of total power and low frequency power of women and men converged, and the gender difference disappeared (Fig. 1). Day and night heart rate variability showed the same pattern. The relative contribution of low frequency and high frequency power to cardiac autonomic modulation also presented a clear gender difference, especially during the night, with higher low frequency power (in normalized units) and consequently lower high frequency power (in normalized units) in men, and this in all age categories except those below the age of 30 and above 60 (Fig. 2).

The majority of heart rate variability parameters decreased with age (Table 1, Fig. 1). Increasing age was associated with a higher heart rate only in women. However, in women, the inverse association between age and time domain heart rate variability indices was less solid and was even absent for SD and SDANN. The mean body mass index was higher in our male population (Table 1). Adjustment of the statistical analysis for body mass index did not change the age and gender differences. In men, a higher weight and body mass index were both highly significant (P<0·001) associated with a higher mean heart rate (r = 0·33) and lower heart rate variability indices (e.g. for body mass index $r = -0{\cdot}39$ with pNN50, $-0{\cdot}42$ with rMSSD, $-0{\cdot}39$ with SD, $-0{\cdot}33$ with SDANN, $-0{\cdot}41$ with total power,

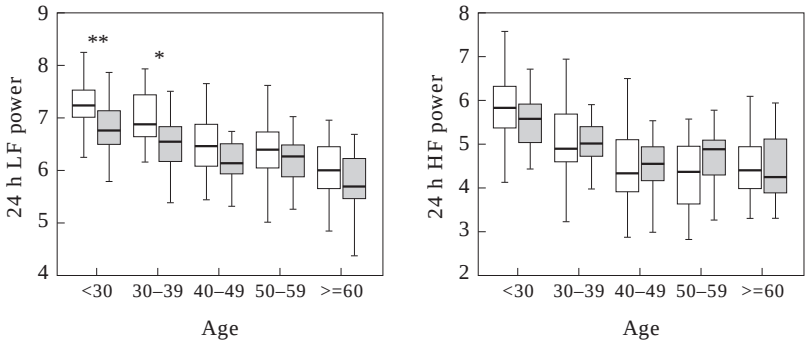

Figure 1 **Gender differences in absolute values of 24 h low frequency power and high frequency power per age decade (□ = male; ▨ = female). Both low frequency and high frequency power were tranformed by calculating their natural logarithm as described in Methods. The boxes represent the 75th percentile, median, and 25th percentile. The whiskers show the largest and smallest observed values which are not outliers. Significance of gender difference *****P*** **< 0·001, ****P*** **< 0·005.**

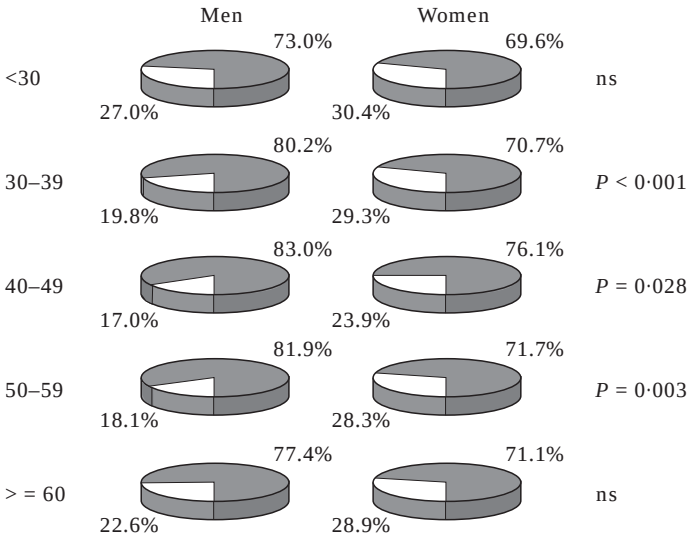

Figure 2 **Gender differences in relative contributions of night-time low frequency power (▨) and high frequency power (□) per age decade. Both low frequency and high frequency power were transformed to normalized units, as described in Methods.**

$-0{\cdot}37$ with low frequency power (in ms^2), and $-0{\cdot}41$ with high frequency power (in ms^2)). In women there were no significant correlations between heart rate or heart rate variability indices and weight or body mass index.

Correlations between heart rate and heart rate variability and between different heart rate variability indices

For the whole population, an inverse association between 24 h mean heart rate and the majority of heart rate variability parameters existed (Table 3, first column). The correlation with spectral parameters was highly significant for total power ($r = -0{\cdot}68$), low frequency power ($r = -0{\cdot}58$), and high frequency power ($r = -0{\cdot}49$). Sub-analysis per sex category demonstrated similar results in men and women. Sub-analysis per age category, however, showed that the relation between heart rate and heart rate variability indices is lost with increasing age (data not shown).

As expected, the different time domain vagal indices pNN50 and rMSSD correlated very well ($r = 0{\cdot}92$), as did the global variability reflecting time domain parameters SD and SDANN ($r = 0{\cdot}95$). rMSSD correlated better with the frequency domain high frequency power than did pNN50 ($r = 0{\cdot}91$ vs $0{\cdot}83$). The frequency domain parameter total power showed a

Table 3 Partial Pearsons correlation coefficients, controlling for age, between heart rate variability indices and between heart rate and heart rate variability indices

	Heart rate	pNN50	rMSSD	SDANN	SD	tot power	LF power (in ms^2)	LF power (in NU)	HF power (in ms^2)
pNN50	−0·66								
rMSSD	−0·62	0·92							
SDANN	−0·48	0·53	0·51						
SD	−0·60	0·66	0·64	0·95					
tot power (in ms^2)	−0·68	0·80	0·83	0·55	0·69				
LF power (in ms^2)	−0·58	0·70	0·72	0·49	0·60	0·96			
LF power (in NU)	ns	−0·51	−0·63	ns	ns	ns	ns		
HF power (in ms^2)	−0·49	0·83	0·91	0·43	0·54	0·83	0·74	−0·72	
LF/HF	ns	−0·50	−0·60	ns	ns	ns	ns	0·98	−0·70

NU = normalized units. For statistical analysis pNN50, rMSSD, total power, low frequency power, high frequency power, and low frequency/high frequency were tranformed to obtain normality, as described in the Methods. Statistical significance all $P<0·001$. ns = non-significant or $-0·25<r<0·25$. For abbreviations, see Methods.

strong association with low frequency power ($r=0·96$) and with high frequency power ($r=0·83$). Low frequency power was only moderately associated with high frequency power ($r=0·74$). The ratio low frequency/high frequency correlated very well with low frequency power expressed in normalized units ($r=0·98$).

Discussion

Heart rate variability, a marker of cardiac autonomic function, is considered a parameter of cardiovascular health. Because women live longer and develop cardiovascular illness at a later age than men, it was postulated that healthy women would have greater heart rate variability than healthy men. Our findings in 141 men and 135 women show that none of the heart rate variability parameters were higher in women. Moreover, global autonomic activity (SD, SDANN, total power) and especially low frequency power, even after normalization, were higher in men compared to women. The heart rate variability parameters reflecting vagal modulation, such as pNN50, rMSSD and high frequency power, showed no statistically significant differences after adjustment for mean heart rate. Introduction of heart rate as a covariate in the statistical analysis is justified since heart rate, together with age, has been identified as a major determinant of heart rate variability[23].

The mechanisms underlying the paradoxal gender difference in cardiac autonomic function are obscure. One has to take into account the physiological background of the different heart rate variability indices. There is a general agreement that high frequency power, which is related to respiration, is a marker of vagal modulation[24–26]. The high frequency power correlates with pNN50 and rMSSD in the time domain[27]. Our results therefore suggest that vagal modulation is similar in both sexes. The physiological substrate of the low frequency power is still controversial[17,28]. It has been proposed as an index for sympathetic modulation (especially when expressed in normalized units), because it increases during mental stress[29], postural tilt[30] and in experimental conditions that lead to tonic increases in sympathetic efferent activity[31]. Therefore, it is a tempting hypothesis that the higher low frequency power (in absolute values as well as in normalized units), and the higher low frequency/high frequency ratio which we have observed in our male population can be attributed to higher sympathetic activity in men.

Higher sympathetic activity has been related to a higher susceptibility to fatal arrhythmias and to the development of coronary heart disease[32]. Therefore hypothetically, the reduced low frequency power in women could protect against the development and incidence of coronary heart disease and arrhythmia. It remains to be proven, however, that the difference in behaviour of the cardiac autonomic nervous system in men and women substantially contributes to the large gender differential in morbidity and mortality of heart disease, which cannot be explained by the presently known standard risk factors[33]. The rates of coronary heart disease in women increase in the fifth decade of life, suggesting that younger women have a protective factor which is lost after the fifth decade[34]. Our results show a narrowing and disappearance of the gender difference in cardiac autonomic function between the age of 40 and 50. Because most women become menopausal during this age range, it is speculated that the protective factor may be the female hormone oestrogen. Higher female longevity has also been linked to the protective effect of oestrogens against the development of coronary heart disease[35]. The exact impact of the female neurohumoral axis, physical activity[36], and of psychological[37] factors on the cardiac autonomic nervous system, next to other coronary heart disease risk factors, remains to be elucidated.

To our knowledge, only a few publications have focused on sex differences in cardiac autonomic function in healthy subjects in a significant number of study

subjects of different age categories. Based on spectral analysis and approximate entropy calculation on 8 min ECG segments in standardized conditions during quiet and metronomic breathing, Ryan *et al*.[12] concluded that vagal high frequency power was higher in women (n = 27) than in men (n = 40). They showed that these differences are most apparent for young (20–39 years) and middle-aged (40–64 years) subjects. Recently, Umetani *et al*.[18], based on their findings of time domain heart rate variability in 102 men and 132 women, also suggested that this gender difference was secondary to higher levels of parasympathetic activity in men. Our results in 141 men and 135 women between 18 and 71 years of age contradict their findings. Cowan *et al*.[20]. described, based on 24 h Holter recordings, a lower heart rate variability in healthy women (n = 71, age 52 ± 15 years) compared to healthy men (n = 40, age 57 ± 15 years). Every gender difference in the heart rate variability parameters was lost when baseline heart period was introduced as a covariate. Bigger[14] described similar findings in middle-aged (40–60 years of age) persons (202 men, 75 women) with a higher low frequency power in men. No adjustment was made for baseline heart rate. The studies of Yamasaki *et al*.[13] and Molgaard *et al*.[15] both focused on the circadian variation of heart rate variability and both described a higher low frequency power in men in 105 (aged 20–78 years, 63 men and 42 women) and 104 (aged 40–77 years, 65 men and 39 women) healthy subjects respectively. The ARIC study[16] reported, based on only 2 min beat-to-beat heart rate data, that women had lower low frequency power in a population of 1984 healthy subjects, aged 45 to 64 years.

The implications of this gender difference is of paramount importance in all heart rate variability research, since the lack of an age- and sex-matched control group can be sufficient to generate significant differences. However, the use of heart rate variability in post-myocardial infarction risk stratification and in the detection of diabetic neuropathy, the two established areas of clinical applicability of heart rate variability, is independent of age and gender[38].

The discrepancy between a higher mean absolute and relative low frequency power and a lower mean basal heart rate in men is unexplained, but may derive from different neurohumoral and central autonomic mechanisms in men and women rather than solely from differences in autonomic outflow. The higher basal heart rate in women can also be related to a lower stroke volume.

Our results confirm earlier reports on the reduction of heart rate variability indices with increasing age. However, this relation was less stable than presumed and again showed an obvious gender difference. In men, nearly all heart rate variability parameters decreased with age. In women SD and SDANN showed no correlation at all with age. The other parameters, including those reflecting vagal modulation, decreased with increasing age.

The major criticism against heart rate variability is that heart rate analysis, by itself, could provide more or less the same information because it reflects the sympathovagal modulation of the intrinsic heart rate. Indeed, heart rate and heart rate variability parameters are no independent variables, as demonstrated by significant inverse correlations in a relatively small number of young male volunteers[39]. In this study, we demonstrated that the relationship between heart rate and heart rate variability is less unequivocal: at higher ages, the relation between heart rate and heart rate variability weakens. Besides this, a number of pathological conditions are characterized by a decreased correlation between heart rate variability and heart rate[40]. Heart rate variability indices are therefore by no means redundant and spectral analysis of heart rate variability in particular, provides a high order measurement that visualizes the dynamics of cardiac autonomic modulation. Heart rate should ideally be included in all heart rate variability measurements and statistical analysis should include an adjustment for baseline heart rate.

Some limitations of this study should be considered. Respiratory rate was not measured simultaneously with the Holter recording. Therefore it cannot be excluded that a reduction in high frequency power can be attributed to less frequent respiration at a frequency above 0·16 Hz, and not solely to a reduction in vagal activity. Furthermore, we did not quantify the exact physical activity or the exercise capacity of the participants. Even mild levels of physical activity markedly affect heart rate and heart rate variability. Regular physical training reduces resting heart rate, has a distinct impact on heart rate variability with a shift towards vagal predominance, and enhances the physiological synchronization between heart rate and respiratory rate[41]. Another matter of concern, particularly in the older male sub-population, is the possible presence of sub-clinical cardiovascular diseases. Future studies should deal with the question of which, preferably non-invasive, techniques are able to definitively exclude subclinical coronary heart disease. Future studies should also consider the timing in the menstrual cycle, since there is increasing evidence that women undergo marked autonomic changes during the menstrual cycle[42].

In summary, we describe a highly significant gender difference in heart rate and heart rate variability. Heart rate variability indices, denoting vagal activity, were not significantly different between men and women, whereas the spectral indices low frequency power and low frequency/high frequency ratio were significantly higher in men. We believe that these findings may reflect a higher sympathetic activity in men compared to women.

We are indebted to Y. Bourgeois of the Bakken Research Center, Maastricht, The Netherlands, for his guidance and support; to A. Leplat, MD, N. de Beauffort, R. De Keyzer, N. Mondelaers, B. Nevens (medical staff Interbrew-Medi Leuven); D. Lahaye, MD, G. Helsen, MD, S. Luyts, MD, G. Van Rompuy, MD, and C. Verbeek, MD (medical staff IDEWE) for their assistance; to D. Van Edom and J. Vankrunkelsven (Christelijke Mutualiteiten Leuven) for their active participation in the recruitment of volunteers.

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