Coll. Antropol. **29** (2005) 1: 295–300
UDC 612.172:616.1
Original scientific paper

Low to High Frequency Ratio of Heart Rate Variability Spectra Fails to Describe Sympatho-Vagal Balance in Cardiac Patients

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A B S T R A C T

Heart rate variability (HRV) reflects an influence of autonomic nervous system on heart work. In healthy subjects, ratio between low and high frequency components (LF/HF ratio) of HRV spectra represents a measure of sympatho-vagal balance. The ratio was defined by the authorities as an useful clinical tool, but it seems that it fails to summarise sympatho-vagal balance in a clinical setting. Value of the method was re-evaluated in several categories of cardiac patients. HRV was analysed from 24-hour Holter ECGs in 132 healthy subjects, and 2159 cardiac patients dichotomised by gender, median of age, diagnosis of myocardial infarction or coronary artery surgery, left ventricular systolic function and divided by overall HRV into several categories. In healthy subjects, LF/HF ratio correlated with overall HRV negatively, as expected. The paradoxical finding was obtained in cardiac patients; the lower the overall HRV and the time-domain indices of vagal modulation activity were the lower the LF/HF ratio was. If used as a measure of sympatho-vagal balance, long-term recordings of LF/HF ratio contradict to clinical finding and time-domain HRV indices in cardiac patients. The ratio cannot therefore be used as a reliable marker of autonomic activity in a clinical setting.

Key words: *heart rate, nervous system, autonomic, heart disease*

Introduction

Heart rate variability (HRV) is a physiological phenomenon that reflects an influence of autonomic nervous system on sinus node activity, through changes in the length of consecutive RR intervals by breathing and in the heart rate by daily activities. The decreased HRV is found to be a risk factor for the onset of malignant arrhythmias in cardiac patients, related to their sympathetic overactivity[1].

Besides influence of vagal and sympathetic tone on heart rate, some of spectral components of HRV are comprehended as a reflection of possibilities of autonomic nervous system to modulate heart rate. High frequency HRV spectra component (HF) was defined as a representative of vagal modulation activity Low frequency component (LF) defined as a representative of sympathetic or of mixed sympathetic and vagal modulation activities[1]. With a certain suspicion[2], there is general opinion that the ratio between low and high frequency components of HRV spectra (LF/HF ratio) represents a measure of balance of sympatho-vagal activity[3]. In a wide spectrum of cardiac patients, long-term values of LF/HF ratio higher than 4.8 were considered to reflect predominant sympathetic and those lower than 1.3 predominant vagal modulation activity[4].

The method seems to be useful when considering short term recordings under controlled conditions in healthy population[1], but there are indices that HRV spectra might fail to summarise sympatho-vagal balance in clinical practice, when long term Holter recordings are analysed[5]. LF/HF ratio was found to be useless in determination of sympatho-vagal balance in patients with advanced stages of cardiac disease and seriously decreased overall HRV with significant sympathetic overactivity[2,6–12] (Figure 1). In these subjects, LF/HF ratio is usually as low as that in healthy subjects with predominant vagal modulation. An attempted explanation of this finding was the hypothesis that an oversaturation of sympathetic tone might suppress its modulatory activities[13].

Received for publication February 11, 2005

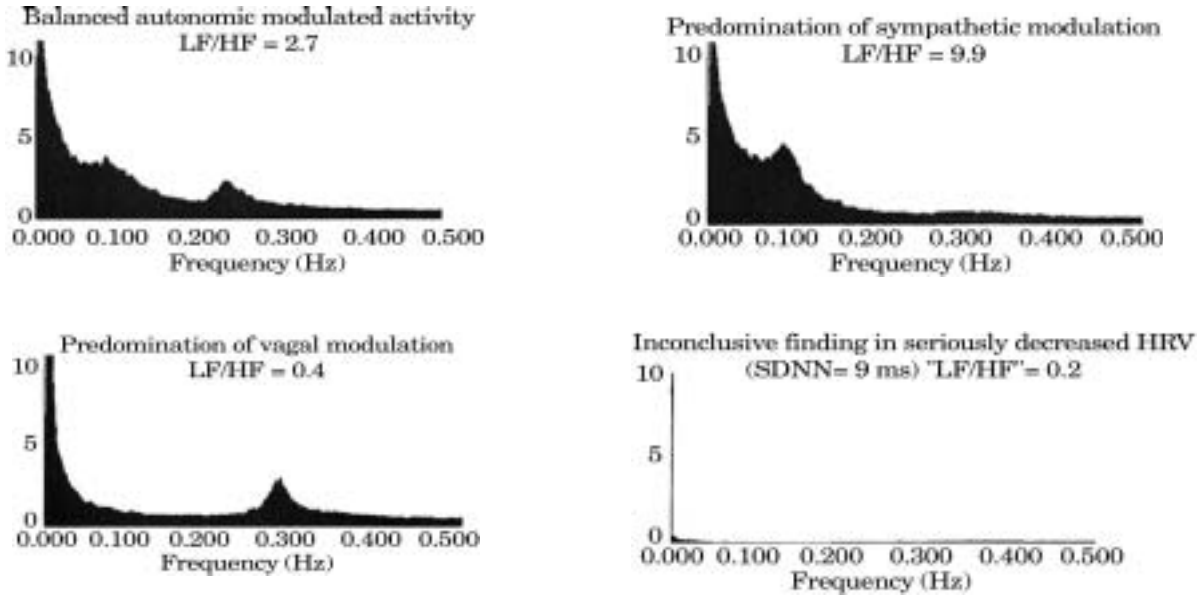

Figure 1. HRV spectra provide valuable data on sympathovagal balance in healthy subjects (first three charts), but the method fails in seriously diseased patients (right bottom chart).

However, the problem of assessing sympatho-vagal balance and the doubts related to the value of LF/HF ratio may be extended to other cardiac patients too, not only the most serious cases mentioned above. Our previous analysis[14] showed that cardiac out-of-hospital patients have no lower LF/HF ratio (i.e. more pronounced vagal modulation) than in-hospital patients, despite better preserved overall HRV and less severe disease. A »sympathetically stimulated« out-of-hospital environment could explain that finding in part, but the doubts still remain. Our clinical impression was that LF/HF ratio is unable to reflect autonomic activities in most cardiac patients, regardless of form and stage of disease.

As clinical experience differs from the authorities' official statement[1], modalities of HRV spectra related to the »sympatho-vagal balance« were re-analysed in several categories of cardiac patients.

Subjects and Methods

Heart rate variability was analysed in 132 healthy subjects (aged 51±9 years, 67% male), 1495 consecutive out-of-hospital patients (aged 51±12 years, 49% male) and 664 consecutive in-hospital patients (aged 56±11 years, 79% male). The out-of-hospital group was a mixture of mildly to moderately ill patients, heterogeneous by diagnoses, while in-hospital group consisted of patients with 3 weeks to 3 months old myocardial infarction or coronary artery bypass grafting who underwent stationary cardiac rehabilitation. All patients and healthy subjects were in sinus rhythm, with no sinus sick syndrome or atrioventricular block of a degree greater than first. The in-hospital patients were divided by gender, median of age (55 years), diagnosis of myocardial infarction (75%) or coronary artery bypass grafting (25%) and by left ventricular systolic function (low if ejection fraction ≤ 40%, high if ejection fraction ≥ 50%; determined by Simpson rule; taken from echocardiographical apical 2- and 4-chamber view). They were furthermore divided by overall HRV into four categories. Heart rate variability was considered low if standard deviation of all normal R-R intervals (SDNN) was lower or equal to 52 ms (16 pts), moderately diminished if SDNN was 53 to 81 ms (91 pts), normal if SDNN was 82 to 160 ms (454 pts) and high if SDNN was equal to or higher than 161 ms (103 pts). Cut-points were determined on this sample previously[14].

HRV was calculated from 24-hour Holter ECG. A commercial system (Oxford Instruments) was used. R-R intervals that included ectopic beats were excluded and extrapolated by linear interpolation. The spectral analysis was computed using fast Fourier transformation. Ten-minutes epochs were repeatedly transformed and averaged over the entire 24-hour period. Details were published elsewhere[14]. Time domain analysis included mean of R-R intervals for normal beats (mean RR), standard deviation of all normal R-R intervals (SDNN), square root of the mean of the squared successive differences in R-R intervals (rMSSD) and percentage of R-R intervals that are at least 50 ms different from the previous interval (pNN50). Frequency domain analysis covered total power (0.0–0.5 Hz) (TP), low (0.04–0.15 Hz) (LF) and high (0.15–0.40 Hz) (HF) frequency components, with low to high frequency ratio (LF/HF). SDNN and TP were used as representatives of overall HRV (overall autonomic activity). LF was used as representative of sympathetic modulation activity (predominantly), while HF, rMSSD and pNN50 were used as representatives of vagal modulation activity. LF/HF ratio was used

as a reflection of sympatho-vagal balance. The meaning and calculations of parameters used are described in details elsewhere.[1] Most of the HRV variables fit in best with the logarithmic distribution[14], so median values are given and variables were log transformed for correlations. Mann Whitney test and, after logarithmic transformation, ANOVA were used to compare HRV between subgroups of patients. Analytical tool was SPSS for Windows, version 7.5.

Results

In comparison to the in-hospital patients, the out-of-hospital patients had faster heart rate (RR of 797 vs 840 ms) and higher SDNN (138 vs 119 ms;), rMSSD (32 vs 27 ms), pNN50 (5.7 vs 3.7%), TP (3160 vs 2388 ms^2), LF (523 vs 377 ms^2) and HF (204 vs 137 ms^2) ($p<0.01$ for all variables), indicating better preserved overall HRV, stronger sympathetic tone and more pronounced both sympathetic and vagal modulation activity in the out-patients group. The LF/HF ratio was equal (2.7) in two groups. Median values of LF/HF ratio did not differ among the out-patients when they were divided by SDNN into quartiles; they were 2.6, 2.7, 2.7 and 2.7 (NS).

Among the in-patients subgroups (Table 1), those with higher overall HRV were characterised by slower heart rate and higher values of rMSSD and pNN50. These findings were consistent with better preserved vagal tone and vagal modulation of heart rate. However, in these patients the LF/HF ratio was higher than that in patients with more deteriorated HRV, falsely indicating more pronounced sympathetic modulated activity. That was the result of a greater reduction of the power of LF component than of HF component along with the reduction on HRV. When the patients were divided by the level of HRV into four categories, the following rule became evident: the lower the overall HRV, the lower the LF/HF ratio. The progressive reduction of LF/HF ratio was paradoxically paralleled with the progressive reduction in the vagaly mediated time-domain parameters as mean RR, rMSSD and pNN50. The reduction of LF/HF ratio could be interpreted as an indirect evidence of shift of sympatho-vagal balance toward predominant vagal modulatory activity, while the reduction of time domain parameters clearly indicated a diminished vagal activity and sympathetic predominance.

In healthy subjects, LF/HF ratio correlated with overall HRV negatively as expected ($r = –0.46$ for SDNN and –0.39 for TP; $p<0.01$ for both correlations), there were no correlation in the out-patients ($r = 0.02$ for both, SDNN and TP), while the correlation became positive when comparing values measured in the in-patients ($r = 0.36$ for SDNN and 0.42 for TP; $p<0.01$ for both correlations). It is interesting to note that the extent of correlation between LF/HF ratio and overall HRV has been in-

TABLE 1
THE DECREASE IN OVERALL HRV AND IN VAGAL TIME-DOMAIN INDICES IS PARALLELED BY THE »PARADOXICAL« DECREASE OF LF/HF RATIO

	RR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms^2)	LF (ms^2)	HF (ms^2)	LF/HF ratio
age < median	829	128	29	4.8	3105	561	168	3.30
age ≥ median	845	111	25	2.9	1845	258	114	2.30
difference	*–2%*	*13%**	*14%**	*40%**	*41%**	*56%**	*32%**	*30%**
male	849	120	27	3.7	2605	397	140	2.91
female	811	111	25	3.1	1592	233	120	1.87
difference	*4%**	*8%**	*7%*	*16%*	*39%**	*41%**	*14%*	*36%**
myocardial infarction	863	123	27	4.7	2812	479	152	2.50
coronary surgery	826	96	23	2.9	1570	210	108	2.21
difference	*5%**	*22%**	*15%**	*38%**	*44%**	*56%**	*29%**	*12%*
high ejection fraction	914	121	29	5.0	3316	420	156	2.70
low ejection fraction	802	81	24	2.5	1291	172	87	1.94
difference	*12%†*	*33%**	*15%†*	*50%†*	*61%**	*59%**	*44%†*	*26%†*
SDNN ≥ 161 ms	917	186	45	10.6	5142	947	291	3.00
SDNN 81–160 ms	849	119	26	3.7	2537	385	140	2.78
SDNN 51–80 ms	745	72	19	1.2	916	123	60	1.90
SDNN ≤ 50 ms	686	47	15	0.3	239	28	32	0.73
difference	*	*	*	*	*	*	*	*

* – $p < 0.01$; † – $p < 0.05$;
Median values are given
Mann Whitney test was used for the first four comparisons and ANOVA for the last one (four SDNN categories)

creased with the magnitude of decrease in HRV. In patients with high overall HRV, LF/HF ratio did not correlate with SDNN and TP (r = 0.05 and –0.08, respectively), in those with normal HRV the correlation was mild (r = 0.22 and 0.25, respectively; p<0.01 for both correlations) whereas in those with moderately diminished HRV the correlation was moderate (r = 0.30 and 0.50, respectively; p<0.01 for both correlations).

Discussion

Task Force on Heart rate variability of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology proposed low value of LF/HF ratio of HRV spectra as a practical sign of predominant vagal modulation activity. Considering that, positive correlation between LF/HF ratio and overall HRV, found in the in-hospital patients, would suggest an enhancement of vagal modulation with the progression of cardiac disease. Such paradoxical finding contradicts to a general clinical impression, time domain HRV analysis presented herein and to neural[6,9] and hormonal[15] evidences of sympathetic predominance in such patients, displayed elsewhere.

A reduction in LF/HF ratio has been reported in association with a reduction of left ventricular systolic function, as well as in most clinical conditions characterised by a decrease in overall HRV[7,10,16–20], but such »paradoxical« findings were not addressed by their authors. In the study made by Bigger and co-workers[16], healthy subjects, patients with old and those with recent myocardial infarction, who had SDNN of 141, 112 and 81 ms, respectively, had LF/HF ratio of 4.6, 3.6 and 2.8 respectively. In patients with coronary artery disease and heart failure, Casolo et al.[17] found progressive decrease in SDNN by worsening of heart failure, and a simultaneous decrease in LF/HF ratio. By increased NYHA class from II to IV (four categories of heart failure progression), median value of LF/HF ratio decreased from 4.3 to 1.4. All those »paradoxical« results are in accordance with the finding of Kienzle et al.[6]. They showed that neural and humoral signs of sympathetic excitation correlate more negatively with LF spectra than with HF band, at least in patients with congestive heart failure.

The present study showed that, as a rule, the lower the overall HRV, the lower the LF/HF ratio, and the higher positive correlation between the two parameters. This finding contradicts the traditional interpretation of LF/HF ratio as a representative of sympatho-vagal balance, not only in patients with seriously decreased HRV[12], whose sympathetic tone perhaps suppresses its modulation activity[13], but in those with moderately or even mildly decreased HRV as well. Even more, the LF/HF ratio is disqualified as representative of sympatho-vagal balance in those among cardiac patients who had normal HRV. Healthy subjects showed an expected negative correlation between 24-hours measured HRV and LF/HF ratio, although there are data suggesting to the positive role of LF/HF ratio as an indicator of autonomic balance only in younger cohort of healthy population[21].

It is well known that the low value of LF spectra component or of LF/HF ratio independently predict higher mortality risk[18,20,22–27], in the same way as low overall HRV does. That fact discards the proposed value of the LF/HF ratio in the detection of sympatho-vagal balance furthermore; it could not be expected from »vagal predominance« to trigger sudden cardiac death.

Different modalities of HRV spectra are poorly explained. For patients with advanced stages of cardiac disease and sympathetic overactivity, whose »paradoxically« decreased LF/HF ratio mimics vagal predominance, Malik and Camm[13] suggested following explanation: oversaturated sympathetic tone suppresses sympathetic modulatory activities reflected in LF band. Suppressed vagal tone in such case results in some extent in reduction of vagal modulation activity (HF component), but less pronounced than the reduction of LF. LF amplitude may also be affected by vagal mechanisms[28], which has to lead to an additional reduction of a LF fluctuations. By this, LF spectral component decreases during an illness much more than HF spectral component, resulting with decrease of LF/HF ratio in patients with a clear sympathetic predominance.

However, this interpretation has never been validated and it fails to explain many other conditions in which a paradoxical reduction in LF/HF ratio has been observed – in patients with just mildly or moderately diminished HRV whose level of background sympathetic activity is unlikely to suppresses its modulatory component. It is possible that a disease changes expression of autonomic nervous system and that either sympathetic or vagal, or even both components change frequency of their impulses formation, speed of propagation etc. By this, sympathetic and vagal activities would reflect through HRV spectra frequencies different from LF and HF[29]. That idea is the topic of the forthcoming analyses.

While searching for the adequate method, and in the evaluation of it – an issue of general importance in scientific validation of various aspects of practical cardiology[30,31] – it is often necessary to change the focus of the analytical tool or even to change the tool. The chaos theory or the catastrophe theory model are sometimes used to explain physiological or pathological cardiac changes[32], but it seems that some new model has to be established to explain the spectral HRV changes during the process of cardiac disease.

The long-term (24-hour) HRV measurements utilised in this study and many others with commercial instrumentations[16,17,19,20,24] are considered less accurate then short-term measurements due to a problem of stationarity[1]. That might be a limitation of the study, but only long-term HRV measurements may provide a comprehensive evaluation of autonomic profile. That can not be obtained by a single, five- or ten-minute recording at rest and under unphysiological resting controlled conditions.

In conclusion, the »established« HRV spectral measures of sympatho-vagal balance do not correspond to clinical findings in most of cardiac patients, indicating that at least long-term measured LF/HF ratio cannot be used as a reliable marker of autonomic activity in clinical setting. These findings have some important clinical implications, but further attempts are yet to be made to elucidate the role of HRV spectral analysis in the exploration of ANS.

Acknowledgements

The study was supported by the Project 0219163 of the Ministry of Science, Education and Sport of the Republic of Croatia.

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OMJER NISKO I VISOKO FREKVENTNE AKTIVNOSTI VARIJABILNOSTI SRČANOG RITMA NE ODRAŽAVA SIMPATIČKO-VAGALNI BALANS U SRČANIH BOLESNIKA

SAŽETAK

Varijabilnosti srčanog ritma (VSR) označava utjecaj autonomnog živčanog sustava na rad srca. Snižena VSR je činitelj rizika za nastup malignih aritmija u srčanih bolesnika, vezano uz prekomjernu simpatičku stimulaciju. U zdravih ispitanika, omjer između komponenti niske i visoke frekvencije (LF/HF) spektra VSR predstavlja mjeru balansa između simpatičke i vagalne modulacijske aktivnosti; više vrijednosti upućuju na predominaciju simpatikusa, niže vagusa. U znanstvenoj je zajednici LF/HF definiran kao korisno kliničko oruđe. Nasuprot tome, prema našim iskustvima spektar VSR ne uspijeva prikazati simpato-vagalni balans u kliničkoj praksi. To nas je motiviralo da preispitamo zajednički stav svjetskih autoriteta, pa smo analizirali modalitete spektra VSR u nekoliko kategorija kardioloških bolesnika. Dvadesetčetiri-satna VSR analizirana je u 132 zdrava ispitanika, 1495 kardioloških ambulantnih bolesnika i 664 kardiološka rehabilitacijska bolesnika. Bolnička je skupina podijeljena po spolu, medijanu dobi, dijagnozi infarkta miokarda ili aorto-koronarnom premoštenju, sistoličkoj (dis) funkciji lijeve klijetke i u više

kategorija prema ukupnoj VSR. VSR je analizirana u vremenskom i frekvencijskom području. U zdravih je ispitanika LF/HF korelirao negativno s ukupnom VSR, kao što je očekivano. Što je bila jača vagalna modulacija srčanog rada, to je bila bolja ukupna VSR. Nasuprot tome, u bolesnika je LF/HF omjer bio to niži što je bila niža ukupna VSR, sugerirajući »paradoksno« naglašeniju vagalnu modulacijsku aktivnost u bolesnika sa znacima predominacije simpatikusa. Uvriježene mjere simpatičko-vagalnog balansa izvedene iz spektralne domene VSR su u kontradikciji s kliničkim nalazom i s mjerama izvedenim iz vremenske domene VSR, što potvrđuje da LF/HF ne može biti korišten kao adekvatna mjera autonomne aktivnosti u kardioloških bolesnika.