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Impact of Acute Respiratory Stress on Cardiac Autonomic Control in Young Healthy Subjects Explored by Time and Frequency Domain Methods

Subbalakshmi Narsajana Krishnadasa, Basha Ahamed, and Ramesh Bhat

Department of Physiology, Center for Basic Sciences, Kasturba Medical College, Mangalore 575004 Karnataka, India

Abstract

To find the possible utility of analysis of heart rate variability in quantifying transient cardiac autonomic modulation, we assessed the impact of breath holding-induced acute respiratory stress on heart rate variability parameters and blood pressure in young healthy subjects. In ten healthy subjects aged between 22-24 years of either sex, R-R intervals and blood pressure were recorded for one minute under resting state, during breath holding and immediately after withdrawal from breath holding. Heart rate variability was quantified by time and frequency domain methods. Mean differences in values were compared separately between resting and during breath holding, during and following withdrawal from breath holding; resting and following withdrawal from breath holding employing paired 't' test. Blood pressure and standard deviation of R-R intervals (SDNN) significantly increased during breath holding and decreased following withdrawal from it. Low frequency power in normalized units (LF nu) significantly decreased, while the high frequency power in normalized units (HF nu) significantly increased with a resulting decrease of the LF/HF ratio following withdrawal from breath holding compared to during breath holding. During the recovery phase only the LF% power significantly decreased as compared with the resting state. Thus, blood pressure and SDNN appeared to better quantify the ability of the heart to meet changing situational demands. LF nu and HF nu or LF/HF ratio reflected the behavior of sympathetic and parasympathetic limbs in adapting to changing situational demand.

Key Words: breath holding, acute stress, sympathovagal balance, heart rate variability, spectral analysis, standard deviation of R-R intervals

Introduction

The autonomic nervous system plays an important role not only in physiological situations, but also in various pathological settings such as diabetic neuropathy (8, 12), myocardial infarction (19, 20) and congestive heart failure (4, 5). Autonomic imbalance associating increased sympathetic activity and reduced vagal tone has been strongly implicated in the pathophysiology of arrhythmogenesis and sudden cardiac death (6, 16). Among the different available noninvasive techniques for assessing the autonomic status, heart rate variability (HRV) has emerged as a simple and noninvasive method to evaluate the sympathovagal balance at the sino-atrial level (22). The ability of HRV analysis to assess overall cardiac health and the state of the autonomic nervous system responsible for regulating cardiac activity underlies its promise as a major new tool in the diagnostic and monitoring armamentarium (14).

There are two approaches to measurement of heart rate variability: analysis in the time or in the

Corresponding author: Dr. N.K. Subbalakshmi, Department of Physiology, Center for Basic Sciences, Kasturba Medical College, Mangalore 575004, Karnataka, India. Tel: (91) 984 513 0905, Fax: (91) 824 242 8183, E-mail: rao.subbalakshmink@rediffmail.com
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frequency domain. Time domain analysis addresses how much variability there is. Time domain values result from simple statistical calculations performed on the set of interbeat intervals. Frequency domain analysis is used to partition the total variance of the heart rate into the variance accounted for by underlying groups of frequencies (21). These measures are based on the analysis of interbeat intervals of normal beats determined usually from a routine 24-h ambulatory electro-cardiogram. However HRV is also thought to reflect the heart's ability to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli (7). Thus, it is quite natural to ask if time or frequency domain methods of analysis of heart rate variability measure transient and rapid changes in autonomic activity and provide insight into cardiovascular autonomic regulation under changing situation. Hence, the present study was undertaken to investigate the utility of heart rate variability parameters obtained from time and frequency domain methods of analysis of heart rate variability in assessing the physiological effects of acute respiratory stress induced by one minute breath holding on cardiovascular system.

Materials and Methods

Subjects

Ten healthy subjects of either sex (5 males and 5 females) in the age range of 22-24 years took part in this study programme.

The parameters considered were systolic and diastolic blood pressure, resting heart rate and heart rate variability (HRV) parameters measured by time and frequency domain methods.

Procedures

The study protocol was completed in the morning between 10-11A.M. Before beginning the test procedures, subjects were familiarized with the details of the study protocol. ECG was then recorded in supine position for one minute during the following conditions:

1. Spontaneous normal breathing.
2. Breath held in inspiratory phase for 1 min.
3. Immediately after withdrawal from breath holding (during recovery phase).
4. Breathing in controlled manner matched for breathing rate measured immediately after withdrawal from the breath holding (that is during recovery phase).

To avoid artifacts in electrocardiogram (ECG) tracing, blood pressure was recorded separately in supine position during these maneuvers using sphygmomanometer.

Data Acquisition: The ECG was recorded continuously at a speed of 25 mm/second connected to the limb lead II. Concurrently, ECG signals were picked up by the digital acquisition system and fed into a computer. HRV parameters were then estimated by time and frequency domain methods of analysis of HRV.

Frequency Domain Analysis: Analysis of tachogram was done by power spectral density. Fast Fourier transform method was used to calculate power spectral density. The power spectrum obtained were High Frequency (Frequency range-0.015-0.400 Hz), Low Frequency (Frequency range-0.040-0.015), Very Low Frequency (frequency range-0.001-0.040) and Total Power (TP). The Low Frequency (LF power), High Frequency (HF power) and Very Low Frequency (VLF power) values were expressed in absolute power (ms^2). High Frequency and Low Frequency power were also expressed in normalized units (HF norm. and LF norm. respectively). Power spectral components were as well expressed in fraction namely fraction Low Frequency (LF% Power), fraction High Frequency (HF% Power) and fraction Very Low Frequency (VLF% Power). In addition, the Low Frequency-to-High Frequency ratio (LF/HF Ratio) was also obtained.

Time Domain Method: The indices of HRV included in this study were standard deviation of the R-R intervals (SDNN) and the root-mean square of the difference of successive R-R intervals (RMSSD). Values were expressed in milliseconds.

Statistical Analyses

As the power spectra obtained was highly skewed data were log transformed. Data were then analyzed by repeated measures of analysis of variance and paired '*t*' test. Statistical significance was taken to be at $P < 0.05$.

Results

Cardiovascular autonomic modulation due to breath holding was initially evaluated by dependent multi-means comparisons of blood pressure, heart rate and HRV parameters under resting, during and at the recovery phase of breath holding. Comparison of mean differences between the phases was then considered.

Dependent multi-means comparison revealed very highly significant effect of breath holding on systolic blood pressure ($F = 33.85$, $P = 0.0005$), diastolic blood pressure ($F = 6.51$, $P = 0.007$) and

Table 1. Cardiovascular changes during breath holding compared to resting state in healthy subjects

Parameter	Before BH* (Means ± SD)	During BH* (Means ± SD)	Mean difference	*t*	*P*
Resting Heart Rate (beats/min)	71.1 ± 5	69.3 ± 6.76	1.8	1.04	NS
Systolic Blood Pressure (mmHg)	108 ± 7.88	117.8 ± 7.56	-9.8	49	0.0001
Diastolic Blood Pressure (mmHg)	74 ± 8.43	78 ± 6.32	-4	2.44	< 0.05
SDNN (milliseconds)	1.69 ± 0.17	1.86 ± 0.16	-0.17	2.55	< 0.05
RMSSD (milliseconds)	1.65 ± 0.21	1.65 ± 0.24	0.001	0.01	NS
Total Power (ms^2)	3.38 ± 0.46	3.5 ± 0.49	-0.12	0.86	NS
HF Power (ms^2)	2.24 ± 0.56	2.76 ± 0.69	-0.52	2.007	NS
HF Power (n. u.)**	1.44 ± 0.25	1.16 ± 0.41	0.27	1.90	NS
HF% Power	1.39 ± 0.26	0.99 ± 0.58	0.40	2.04	NS
LF Power (ms^2)	3.15 ± 0.45	3.22 ± 0.42	-0.06	0.54	NS
LF Power (n. u.)**	1.82 ± 0.11	1.88 ± 0.11	-0.06	1.53	NS
LF% Power	1.77 ± 0.10	1.71 ± 0.16	0.05	0.98	NS
VLF Power (ms^2)	2.77 ± 0.58	2.49 ± 0.79	0.27	1.68	NS
VLF% Power	0.85 ± 0.44	1.26 ± 0.52	-0.40	1.81	NS
LF/HF Ratio	0.37 ± 0.36	0.72 ± 0.51	-0.34	1.84	NS

* BH = breath holding; ** n.u. = normalized units

Table 2. Cardiovascular changes following withdrawal from breath holding

Parameter	During BH* (Means ± SD)	After BH* (Means ± SD)	Mean difference	*t*	*P*
Resting Heart Rate (beats/min)	69.3 ± 6.76	68.7 ± 5.03	0.6	0.34	NS
Systolic Blood Pressure (mmHg)	117.8 ± 7.56	111 ± 11.005	6.8	4.15	< 0.01
Diastolic Blood Pressure (mmHg)	78 ± 6.32	73 ± 8.23	5	3	< 0.02
SDNN (milliseconds)	1.86 ± 0.16	1.67 ± 0.19	0.19	5.25	< 0.001
RMSSD (milliseconds)	1.65 ± 0.24	1.56 ± 0.29	0.09	1.28	NS
Total Power (ms^2)	3.5 ± 0.49	3.30 ± 0.46	0.20	1.87	NS
HF Power (ms^2)	2.76 ± 0.69	2.37 ± 0.42	0.39	2.21	NS
HF Power (n. u.)**	1.16 ± 0.41	1.53 ± 0.26	-0.21	2.47	< 0.05
HF% Power	0.99 ± 0.58	1.43 ± 0.36	-0.44	3.38	< 0.01
LF Power (ms^2)	3.22 ± 0.42	2.96 ± 0.46	0.26	2.81	< 0.05
LF Power (n. u.)**	1.88 ± 0.11	1.75 ± 0.18	0.13	2.62	< 0.05
LF% Power	1.71 ± 0.16	1.65 ± 0.14	0.05	0.98	NS
VLF Power (ms^2)	2.49 ± 0.79	2.73 ± 0.73	-0.24	1.62	NS
VLF% Power	1.26 ± 0.52	1.07 ± 0.43	0.19	1.38	NS
LF/HF Ratio	0.72 ± 0.51	0.22 ± 0.43	0.5	3.42	< 0.01

* BH = breath holding; ** n.u. = normalized units

SDNN (F = 7.28, *P* = 0.005). There was moderate evidence for influence of breath holding on HF norm. (F = 5.64, *P* = 0.012), HF% Power (5.29, *P* = 0.016), LF norm. (F = 4.01, *P* = 0.036) and LF/HF ratio (F = 5.61, *P* = 0.013). There was only suggestive evidence for influence of breath holding on LF Power (F = 2.27, *P* = 0.08), HF Power (F = 3.11, *P* = 0.069), LF% Power (F = 3.36, *P* = 0.057). No evidence of effect of breath holding on resting heart rate, RMSSD and Total Power was observed.

Data on comparison of mean differences between the phases in blood pressure, heart rate and HRV parameters done separately between normal breathing and during breath holding, during breath holding and immediately after breath holding, normal spontaneous breathing and immediately after withdrawal from breath holding (that is during recovery phase). Computed values for mean and standard deviation in each state along with mean difference between the phases are provided in Table 1, Table 2 and Table 3

Table 3. Blood pressure and heart rate variability during recovery phase *vs*. resting state

Parameter	Before BH* Means ± SD	After BH* Means ± SD	Mean difference	*t*	*P*
Respiratory Rate	17.7 ± 1.63	20 ± 2.10	2.3	7.66	< 0.0001
Resting Heart Rate (beats/min)	71.1 ± 5	68.7 ± 5.03	2.4	1.58	NS
Systolic Blood Pressure (mmHg)	108 ± 7.88	111 ± 11.005	3	1.96	NS
Diastolic Blood Pressure (mmHg)	74 ± 8.43	73 ± 8.23	1	1	NS
SDNN (milliseconds)	1.69 ± 0.17	1.67 ± 0.19	0.02	0.34	NS
RMSSD (milliseconds)	1.65 ± 0.21	1.56 ± 0.29	0.09	1.26	NS
Total Power (ms^2)	3.38 ± 0.46	3.30 ± 0.46	0.07	0.68	NS
HF Power (ms^2)	2.24 ± 0.56	2.37 ± 0.42	-0.13	0.63	NS
HF Power (n. u.)**	1.44 ± 0.25	1.53 ± 0.26	-0.08	1.13	NS
HF% Power	1.39 ± 0.26	1.43 ± 0.36	0.03	0.35	NS
LF Power (ms^2)	3.15 ± 0.45	2.96 ± 0.46	0.19	1.5	NS
LF Power (n. u.)**	1.82 ± 0.11	1.75 ± 0.18	0.06	1.43	NS
LF% Power	1.77 ± 0.10	1.65 ± 0.14	0.11	4.18	< 0.01
VLF Power (ms^2)	2.77 ± 0.58	2.73 ± 0.73	0.03	0.28	NS
VLF% Power	0.85 ± 0.44	1.07 ± 0.43	-0.21	1.38	NS
LF/HF Ratio	0.37 ± 0.36	0.22 ± 0.43	0.15	1.32	NS

* BH = breath holding; ** n.u. = normalized units

Table 4. Effect of higher respiratory rate on cardiovascular parameters

Parameter	Resting Resp. Rate* (Means ± SD)	Higher Resp. Rate* (Means ± SD)	Mean difference	*t*	*P*
Resting Heart Rate (beats/min)	71.1 ± 5	76.1 ± 9.19	5	1.82	NS
Systolic Blood Pressure (mmHg)	108 ± 7.88	108 ± 7.88	0	–	NS
Diastolic Blood Pressure (mmHg)	74 ± 8.43	74 ± 8.43	0	–	NS
SDNN (milliseconds)	1.69 ± 0.17	1.69 ± 0.18	0.0009	0.01	NS
RMSSD (milliseconds)	1.65 ± 0.21	1.63 ± 0.25	0.02	0.30	NS
Total Power (ms^2)	3.38 ± 0.46	3.35 ± 0.38	0.02	0.33	NS
HF Power (ms^2)	2.24 ± 0.56	2.42 ± 0.71	-0.17	0.55	NS
HF Power (n. u.)**	1.44 ± 0.25	1.27 ± 0.55	0.16	1.13	NS
HF% Power	1.39 ± 0.26	1.06 ± 0.61	0.32	1.95	NS
LF Power (ms^2)	3.15 ± 0.45	2.96 ± 0.27	0.19	2.10	NS
LF Power (n. u.)**	1.82 ± 0.11	1.88 ± 0.11	-0.06	1.53	NS
LF% Power	1.77 ± 0.10	1.60 ± 0.23	0.16	1.80	NS
VLF Power (ms^2)	2.77 ± 0.58	2.74 ± 0.79	0.03	0.12	NS
VLF% Power	0.85 ± 0.44	1.39 ± 0.54	-0.53	2.52	< 0.05
LF/HF Ratio	0.37 ± 0.36	0.40 ± 0.74	-0.02	0.11	NS

* Resp. Rate = respiratory rate; ** n.u. = normalized units

respectively.

Mean difference in measured parameters between normal breathing and raised respiratory rate matched for respiratory rate during recovery phase is shown in Table 4.

Both systolic and diastolic blood pressure were significantly higher during breath holding compared to normal resting level (t = 49, P = 0.0001, t = 2.44, P < 0.5 respectively, Table 1). Among the HRV parameters measured only SDNN was significantly higher during breath holding compared to normal resting level (t = 2.55, P < 0.05, Table 1). HF Power (*i.e.* expressed in absolute power) was appreciably higher but not statistically significant during breath

holding compared to normal resting level (t = 2.007, Table 1). A clear trend of decline (but not statistically significant) was observed in HF% Power during breath holding (t = 2.04, Table 1). Slight insignificant rise in LF norm, TP and LF/HF ratio was observed (Table 1). Slight insignificant decline was seen in resting heart rate, HF norm and LF% Power (Table 1).

Both systolic and diastolic blood pressures declined significantly during the recovery phase (t = 4.15, $P < 0.01$; t = 3, $P < 0.02$ respectively, Table 2). Among the time domain HRV parameters only mean difference in SDNN between during and recovery phase was significant (t = 5.25, $P < 0.001$, Table 2). Among the spectral power components LF Power (*i.e.* expressed in absolute power), LF norm and LF/HF ratio was significantly less during recovery phase compared to during breath holding phase (t = 2.81, $P < 0.05$; t = 2.62, $P < 0.05$; t = 3.42, $P < 0.01$ respectively, Table 2). Non-significant but a clear trend of decline in HF Power was observed (t = 2.21, Table 2). HF norm and HF% Power were significantly higher during recovery phase compared to during the breath holding phase (t = 2.47, $P < 0.05$; t = 3.38, $P < 0.01$ respectively, Table 2).

No significant difference in blood pressure and HRV parameters except LF% Power was observed between resting state and recovery phase (t = 4.18, $P < 0.01$, Table 3). No change in RMSSD was observed during any of the three phases (Table 1, 2, and 3).

The respiratory rate was significantly higher during recovery phase compared to pre-breath holding resting phase (t = 7.66, $P < 0.0001$, Table 3). Influence of respiratory rate on cardiovascular parameters was analyzed by comparing the mean difference in measured parameters between pre-breath holding resting respiratory rate phase and during raised respiratory rate state (matched for recovery phase). VLF% Power was significantly higher in raised respiratory rate phase (respiratory rate matched for recovery phase) compared to pre- breath holding phase (t = 2.52, $P < 0.05$ Table 4). LF Power (in absolute values, ms^2) was higher during raised respiratory rate phase compared to resting phase but was not statistically significant (t = 2.10). Blood pressure and all the other measures of HRV did not show significant differences (Table 4).

Discussion

Although the analysis of HRV has gained popularity as a simple and non-invasive tool for assessing autonomic function in both normal subjects and in patients in a variety of clinical settings, the potential of this tool in evaluating the transient changes in cardiac autonomic modulation in response to physiological or pathological stimuli has not been elucidated adequately. Our study examined the utility of time and frequency domain methods of analysis of HRV in assessing cardiac autonomic response to acute respiratory stress induced by holding breath in inspiratory phase for one minute.

Dependent multiple comparisons revealed highly significant influence of breath holding on blood pressure. A separate comparison of the mean differences of blood pressure between the phases showed significant rise of blood pressure during breath holding (Table 1) and immediate decline of it towards base line value following withdrawal from breath holding (Table 2). This finding demonstrates that the acute respiratory stress initiates transient rapid changes in cardiovascular autonomic function.

Among the measured time domain indices of heart rate variability, significant variations were observed only in SDNN during and following phases of breath holding maneuver. SDNN reflects all the cyclic components responsible for variability in the period of recording (21). It is influenced both by parasympathetic and sympathetic effects (15). To put it another way SDNN represents both the sympathetic and parasympathetic influences on heart rate. Thus, the significant variation observed in SDNN during and following phase of breath holding suggests that SDNN could be a suitable parameter for quantifying transient changes in overall cardiac autonomic nervous system modulation.

Spectral analysis of the RR tachogram is typically used to estimate the effect of the sympathetic and parasympathetic modulation of the RR-intervals. Previous studies have indicated that a shift in the autonomic balance was associated with a redistribution of the power between the LF and the HF bands, and it was suggested that normalized power units (LF_{nu} and HF_{nu}) or LF/HF were efficient means for detecting shifts in autonomic balance (11, 17). Accordingly, we observed in our present study that LF_{nu} decreased and HF_{nu} increased and LF/HF ratio decreased during withdrawal phase compared to during breath holding phase.

Increase in LF norm and concomitant decrease in HF norm and visa versa observed in our study were also noted in humans and animals under different experimental conditions indicative of sympathetic arousal such as mental stress, mild exercise, upright position (11, 18) and coronary artery occlusion (10). However there are certain differences present between our study findings in this study and studies on upright position and mild exercise. In the upright position total power decreased and mild exercise caused a rise in heart rate, whereas breath holding did not bring about these changes.

Along with HF_{nu}, HF% also increased signifi-

cantly in withdrawal phase compared to during breath holding phase. This finding suggests that HF% could be another index of parasympathetic activity. However known parasympathetic activity index HF expressed in absolute units (21) or time domain measure of parasympathetic activity namely RMSSD (21) did not show significant variations in any phase of breath holding maneuver.

LF is reported to be associated with vasomotor oscillations, and it has been suggested that it reflects both parasympathetic and sympathetic modulations of heart rate (1). However in the present study following withdrawal from the breath holding LF expressed in absolute power decreased significantly along with LF_{nu} a suggestive of index of sympathetic activity.

In the present study LF% alone remained significantly lower following withdrawal from the breath holding compared to pre-breath holding state. In addition to LF/HF ratio, some researchers consider LF% as an index of sympathovagal balance (11, 17). Thus, it appears that LF% might reflect some aspects related to sympathovagal balance which is not reflected in LF/HF ratio.

There is an important effect of respiratory rate on HRV (2, 9, 13). A previous study by Brown *et al*. (3) has demonstrated that the amplitude of HF Power and LF Power regresses with higher respiratory rates (3). However rise in respiratory rate from the mean spontaneous breathing rate of 17.7 to the raised rate of 20 (matched for recovery phase) did not influence any of the HRV parameters significantly except VLF% (Table 4). It could be said that the changes observed in heart rate variability parameters were mainly due to the physiological effect of breath holding on cardiac autonomic modulation independent of raised respiratory rate.

In the present study, the known indicators of vagal activity namely HF expressed in absolute power and RMSSD did not display significant variations although other indices of vagal activity exhibited significant variations. Similarly the significant variation in two indicators of sympathovagal balance, the namely LF/HF ratio and LF% was displayed not in the same phase but in the different phases of breath holding maneuver. It, thus appears that although the heart rate variability parameters of time and frequency domain measure sympathetic and parasympathetic activity directed towards heart, the phenomenon responsible for modulating the activity is different. These heart rate variability parameters are probably not quantifying the same phenomenon responsible for the same.

However it could be concluded based on our findings that blood pressure and SDNN appeared to better in quantifying the ability of the heart to meet changing situational demands. LF nu and HF nu or LF/HF ratio reflected the behavior of sympathetic and parasympathetic limbs in adapting to changing situational demand.

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