Original Articles

HEART RATE VARIABILITY IN PATIENTS WITH MITRAL STENOSIS: A STUDY OF 20 CASES FROM KING ABDULAZIZ UNIVERSITY HOSPITAL

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Background: Left atrial enlargement in mitral stenosis predisposes to atrial fibrillation (AF). Analysis of heart rate variability (HRV) prior to the onset of an arrhythmia may show alterations in autonomic balance that are known to predispose to the development of AF. The aim of this study was to determine whether HRV in patients with rheumatic mitral stenosis (MS) is abnormal in comparison to normal controls, and to find the relationship between left atrial size and HRV in patients with MS in sinus rhythm and in AF.

Subjects and Methods: A series of 24-hour ambulatory Holter electrocardiogram recordings were obtained for 10 consecutive, newly diagnosed untreated subjects with pure mitral stenosis in sinus rhythm, 10 with mitral stenosis complicated by atrial fibrillation and 10 age-matched normal controls. Digitized records were processed using time domain and power spectral analysis.

Results: In patients with mitral stenosis in sinus rhythm, we observed significant decrease of the standard deviation of the RR intervals (SDRR), as well as of the root mean square of successive RR interval differences (RMSSD) and Edinburgh index (sNN50), while in patients with AF, the RMSSD and sNN50 were much larger than those in normal. The areas under all spectral bands were markedly increased in patients with AF compared with normal. Furthermore, the high low frequency/high frequency (HLF/HF ratio) ratio was very small compared to normal. HRV measures were independent of atrial size in both groups.

Conclusion: Decreased HRV in mitral stenosis patients with sinus rhythm suggests increased sympathetic activity in patients prone to atrial fibrillation, while marked increased of HRV in patients with AF may indicate that parasympathetic activity modulates the intrinsic behavior of the atrioventricular node during atrial fibrillation. The evaluation of HRV may be a useful tool for the identification of patients predisposed to AF.
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Atrial fibrillation (AF) is common in patients with mitral valve disease and left atrial enlargement. Because of the stenotic mitral valve, the left ventricle is not subject to an extensive load as is the case in mitral regurgitation.[1] These patients present an attractive model to study the genesis of AF. This is because mitral valve disease, particularly isolated or predominant mitral stenosis (MS), produces little ventricular dysfunction.[2] The patients are often young and, therefore, very unlikely to have coronary artery diseases. The only atrial abnormality is that of increased atrial size. The patient's heart rhythm goes from stable sinus rhythm to intermittent AF to chronic AF.

The analysis of heart rate variability (HRV) during the stages of stable sinus rhythm and AF may throw some light on the genesis of atrial fibrillation in these patients. It may show alterations in autonomic balance that are known to predispose to the development of AF.[3]

Literature review revealed no studies relating changes in HRV to the propensity to develop AF in MS. Interestingly, HRV may be useful in predicting the prognosis in patients with mitral regurgitation, a condition that invariably leads to left ventricular hypertrophy (LVH) and dysfunction.[4-5] When the ventricular rate was studied in patients with chronic non-ischemic AF due to mitral regurgitation, reductions in time-domain measurements of ultra low and high-frequency HRV predicted risk of mortality and requirement for mitral valve surgery.[6] Although patients who develop AF after coronary bypass surgery have warnings of atrial arrhythmia including supraventricular ectopic beats, paroxysmal supraventricular tachycardia, and episodes of nonsustained atrial fibrillation and flutter,[7] the value of HRV analysis in these patients is not known.

Analysis of HRV has not been applied in patients with mitral stenosis, especially patients associated with AF. This is probably because of the presumed absence of any form of pattering of the ventricular rhythm, particularly vagally mediated respiratory arrhythmia. In fact, HRV is not

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FIGURE 1. Example of RR interval series of A) normal subject; B) MS subject in sinus rhythm; and C) MS subject in atrial fibrillation.

FIGURE 2A. 3-D spectral analysis for a normal subject. The analysis was based on FFT using Del Mar Holter Analysis System. The different frequency peaks move around in a 3-D graph showing the true time-frequency distribution.

random even in patients with AF. HRV in patients with atrial fibrillation is related to vagal tone.[8] When patients with chronic AF were compared with controls, the patients had higher HRV. Analysis of HRV after the administration of propranolol and methylatropine showed that heart rate variability (ventricular rate) was affected by vagal tone even in the presence of AF.[8] Thus, the aim of this work was to study HRV in patients with pure or predominant mitral stenosis in sinus rhythm and AF, and correlate the finding with left atrial size.

Subjects and Methods

Following the local Ethical Committee approval, we studied 10 consecutive, newly diagnosed untreated subjects with pure mitral stenosis in sinus rhythm,10 with mitral stenosis complicated by atrial fibrillation, and 10 age-matched normal controls (Table 1). Informed consent was obtained from each subject. The patients were selected from King Abdulaziz University Hospital in Jeddah, under supervision of a consultant of cardiology who performed the echocardiography for patients and normal subjects, while the analysis of HRV was done in the Department of Physiology at the same university. We found no gender differences in any measure of HRV (data not shown), which is consistent with previous published work.[9]

Mitral stenosis was confirmed by echocardiography (Table 2). All subjects were normotensive, had no evidence of pre-existing cardiovascular disease, or previous history of ill health, and were taking no regular medication.

24-Hour ECG Recording

The 24-hour electrocardiogram (ECG) recordings were carried out using a two-channel tracker (DEL MAR Holter System). One channel records the ECG signal and the second channel records a time signal generated by the recorder. The time signal is used to correct variations in tape speed. Individuals went about their normal daily activities. A new cassette tape and battery were used for each recording. The electrodes were positioned in standard positions over the precordium. Replay, QRS detection and measurement of the RR interval was performed using DEL MAR ECG Analyzer.

Time Domain 24-Hour ECG Analysis

We measured several time-domain variables. The definitions and significance of these variables are summarized in Table 2.

Frequency Domain 24-Hour ECG Analysis

We used the Fast Fourier Transformation (FFT) technique to obtain the power spectral density estimation. Since the RR intervals are of variable length, the data points are linearly interpolated and then the signal is re-sampled at a fixed rate of 1 Hz to obtain the equispaced sampling frequency of the FFT. We then divided the sample record (24-hour ECG recordings) into six non-overlapping segments of equal time intervals (2000 data points), each selected randomly from the 24-hour ECG recordings. Finally, we averaged all PSD of individual segments to produce the final PSD and calculated the area within each spectral band (Table 3).[10]

Echocardiography was done for all subjects to determine the degree of mitral stenosis, presence or absence of mitral regurgitation, other cardiac abnormalities, LV mass, ejection fraction and left atrial size,

FIGURE 2B. The 3D spectral analysis for MS subject in atrial fibrillation. Note the marked increase in all frequencies compared to normal subject.

TABLE 1. *Age and sex of mitral stenosis (n=10), AF (n=10) and normal subjects (n=10). Values are mean ±1 SD and range.*

Group	N	M/F	Age(years)
MS	10	6/4	34.9±10.9 (17-54)
AF	10	7/3	51.2±13.7 (30-68)
N	10	5/5	34.2±6.4 (22-40)

MS=patients with mitral stenosis in sinus rhythm; AF=patients with mitral stenosis in atrial fibrillation; n=normal control.

Comparisons between data were made using Student's *t*-test for unpaired normally distributed values. However, because distributions of power spectrum values were skewed towards high values, these data were log transformed and then analyzed using Analysis Of Variance (ANOVA) test (general factorial model). $P<0.05$ was considered significant. Data were expressed as the mean ± 1 SD and range.

Results

Time Domain 24-Hour ECG Analysis/ Time Series

The first step in any time series analysis is to plot the time series, so a graph of X_t versus t was done. Doing so prevens rediscovering trivial aspects of the time series, and may immediately suggest useful or interesting hypotheses to test.

It has been reported that time series of RR intervals from patients with autonomic damage were noticeably smoother than those from normal subjects with large abrupt changes in heart rate.[10] The beat-to-beat variation is represented as a time series (Figure 1) in which the *Y*-axis is the time between beats (ms) and the *X*-axis is the number of beats. The RR interval time series illustrates the normal

pattern of fluctuations for the healthy adult (a), compared to the smooth pattern of interbeat intervals for a subject with mitral stenosis in sinus rhythm (b), and a more complex pattern in patients with mitral stenosis in AF (c).

Mean Heart Rate

MS subjects had significantly higher mean heart rate in comparison to normal subjects (MS 89±7 vs. normal controls, 79±3 beats/min ($P<0.001$)), while the mean heart rate of AF subjects (AF 72±15; normal 79±3 beats/min ([NS]) was not significantly different from the normals (Table 4).

Time-Domain Parameters of RR Intervals

The mean and standard deviation of RR intervals of MS subjects with sinus rhythm were significantly decreased in comparison to normal subjects (Table 4), while the mean and standard deviation of RR for patients with AF were not significantly different from the normals.

There was significant decrease in the sNN50 and the root mean square of successive RR interval differences (RMSSD) in patients with mitral stenosis in sinus rhythm, while patients with AF had a marked increase in sNN50 and RMSSD (Table 4).

Findings of Echocardiographic Examination

We measured mitral valve size, atrial size and ejection fraction (EF%) for all patients and normal control subjects. As expected, we found significant decrease in mitral valve size and EF% in both groups (MS and AF) compared to normal. Furthermore, the atrial size was significantly increased in diseased patients compared to normal (Table 5).

Correlation between Atrial Size and HRV

There was no significant correlation between echocardiographic parameters (atrial size, mitral valve size and EF%) and different HRV parameters in patients with sinus rhythm and patients with atrial fibrillation (results not shown).

Frequency Domain 24-Hour ECG Analysis

Figure 2 represents an example of multi-epoch spectral analysis in a 3-D display for (a) a healthy subject, and (b) MS subject in AF. The 3-D display for MS in sinus rhythm was much similar to normal (Figure not shown). In order to quantify the power spectrum for the whole population, we applied spectral analysis to six segments of each 24h recordings, and the area under power spectra were calculated. We observed that the areas under all spectral bands, including the low-low frequency (LLF) band were markedly increased in patients with MS in atrial fibrillation compared with normal controls. Furthermore, the HLF/HF

TABLE 2. *Different time domain measures of heart rate variability (HRV).*

Variable	Units	Definition	Significance
SDRR	ms	Standard deviation of normal RR intervals	Broad band measure
sNN50 counts	beats	The number of time that the difference between adjacent normal RR intervals greater than 50 ms, computed over the entire 24 hour recording (Bigger et al., 1989)	Vagal index
RMSSD	ms	Root mean square of successive RR intervals difference; the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals over the entire 24-our ECG recordings (10)	Vagal index
St. George's index	–	The St. George's index is calculated from the frequency histogram of 24-hour ECG recordings	Broad band measure

TABLE 3. *Components of spectral analysis.*

Variable	Units	Definition	Significance
Total power	s^2	Variance of NN intervals (0.0-0.5 Hz)	Broad band measure
LLF	s^2	Power in VLF range (0.0 -0.05 Hz)	Non-autonomic (hormonal, temperature regulation, etc.)
HLF	s^2	Power in LF range (0.05-0.15 Hz)	Mainly sympathetic
HF	s^2	Power in HF range (0.15-0.5 Hz)	Vagal index
HLF/HF	ratio	Ratio HLF (ms^2)/HF (ms^2)	Sympathovagal balance

TABLE 4. *Mean heart rate (MHR), standard deviation of RR intervals, sNN50, RMSSD and St. George's index of MS (n=10), AF (n=10) and normal subjects (n=10). Values are mean±1 SD and (range).*

Time domain parameters	Normal control (n=10)	MS (n=10)	AF (n=10)	*P*-values* (*t*-test)	
MHR (beats/min)	79±3	89±7	72±15	MS vs N	*P*=0.001
	(76-86)	(71-86)	(59-94)	AF vs N	NS
Mean RR (mes)	740±57	700±106	811±206	MS vs N	*P*=0.03
	(688-825)	(650-845)	(631-1058)	AF vs N	NS
SDRR (mes)	155±11	135±31	151±58	MS vs N	*P*=0.02
	(145-176)	(106-179)	(84-241)	AF vs N	NS
sNN50 count	15813±8335	10376±8173	22947±16847	MS vs N	*P*=0.01
	(3784-25820)	(5260-244910)	(5889-42469)	AF vs N	*P*=0.01
RMSSD (mes)	37±10	30±10	75±31	MS vs N	*P*=0.01
	(21-49)	(24-48)	(26-112)	AF vs N	*P*=0.01
St. George's index	40.7±6.2	37.3±10.7	32.7±8.5	MS vs N	NS
	(33.5-47.6)	(23.9-83.9)	(18.6-40)	AF vs N	NS

MS=patients with mitral stenosis in sinus rhytm; AF=patients with mitral stenosis in artial afibrilation; N=normal control; NS=not significant.

TABLE 5. *Size of mitral wave (MV), size of left atrium (LA) and ejection fraction (EF%) of MS (n=10), AF (n=10) and normal subjects (n=10). Values are mean±1 SD and (range).*

	Normal control (n=10)	MS (n=10)	AF (n=10)	*P*-values* (*t*-test)	
MV size/cm	4.8±0.8	1.5±0.5	2.9±0.9	MS vs N	0.0001
	(4-6)	(1-2.2)	(1.7-4)	AF vs N	0.0003
LA size/cm	4.2±1.2	5±0.2	5.1±0.2	MS vs. N	0.0001
	(3-6)	(4-6)	(4-7)	AF vs. N	0.0001
EF%	85.8±5.9	63.5±6.8	62.7±11	MS vs. N	0.0001
	(80-95)	(55-71)	(50-69)	AF vs. N	0.0002

TABLE 6. *Area under different power spectral bands*

Spectral bands	Normal control (n=10)	MS (n=10)	AF (n=10)	*P*-values* (ANOVA)	
LLF	2.4±1.2	3.1±1.2	3.5±0.8	MS vs. N	NS
(0.0-0.05 HZ)	(0.8-3.3)	(1.2-5.8)	(3.02-4.9)	AF vs. N	*P*=0.01
HLF	2.4±1.1	2.6±1.1	3.4±0.4	MS vs. N	NS
(0.05-0.15 HZ)	(0.2-3.3)	(0.07-4.1)	(3.1-3.4)	AF vs. N	*P*=0.003
HF	1.8±1.4	2.4±1.2	3.7±1	MS vs. N	NS
(0.15-0.5 HZ)	(0.06-3.04)	(0.3-4.04)	(2.8-5.4)	AF vs. N	*P*=0.002
TP	2.5±1.3	3.2±1.02	4.1±0.4	MS vs. N	NS
(0.0-0.5 HZ)	(0.8-3.7)	(0.9-4.8)	(3.8-4.9)	AF vs. N	*P*=0.001
HLF/HF	0.4±0.2	0.3±0.2	0.02±0.2	MS vs. N	*P*=0.01
	(0.1-0.9)	(0.06-0.7)	(0.03-0.3)	AF vs. N	*P*=0.001

ratio was very small in MS patients with AF (AF 0.02±0.2; normal controls 4.3±0.2; P=0.01). On the other hand, the areas under all spectral bands for MS patients with sinus rhythm were not significantly different from the normals (Table 6).

Discussion

The normal heart rate is determined by the dynamic interaction between the spontaneous pacemaker activity of the SA node and the antagonistic influences of the sympathetic and parasympathetic nervous system. Changes in vagal activity lead to immediate marked changes in heart rate (high frequency), whereas changes in sympathetic activity are associated with more gradual and slow changes (low frequency).[11] Measurements of HRV, which is the irregular cyclic changes in sinus rate over time, can be used to characterize the effect of efferent autonomic activity on the heart, and to evaluate the integrity of cardiovascular control system.[11] In fact, HRV assessment has become a widely used technique for noninvasive study of sympatho-vagal modulation of heart rate in a broad spectrum of cardiovascular disorder.[10] However, a review of the literature revealed that our work is the first study that evaluates HRV in patients with rheumatic mitral stenosis (MS) in sinus rhythm and in atrial fibrillation (AF).

Using time-domain analysis of HRV, our results showed that patients with MS in sinus rhythm had significant reductions in SDRR. The 24-hour SDRR depends not only on short-term variability but also on long-term variability and diurnal changes in mean RR level, reflecting not only vagal modulation but also changes in cardiac sympathetic tone.[11] Thus, the reduction in SDRR in patients with MS may indicate decreased autonomic modulation. Furthermore, the reduction of vagal indices (sNN50 and RMSSD) in these patient compared to normal may indicate decreased vagal tone (prone to atrial fibrillation). Thus, the sympathetic activity may take upper hand before the onset of atrial fibrillation. This is in agreement with previous findings of a significant reduction in HRV before the onset of tachyarrhythmias.[3] On the other hand, the marked increase of vagal indices (sNN50 and RMSSD) in patients with atrial fibrillations may indicate that during atrial fibrillation, the parasympathetic activity takes the upper hand.

The analysis of RR intervals by spectral analysis techniques enabled a decomposition of the RR interval variations into a number of frequency components. From Figure 2, one can clearly see the marked increase of HRV in MS patients in AF (Figure 2b) compared to a healthy subject (Figure 2a). There was individual variation between these patients, however, no single individual in the AF group was similar to a normal subject. The individual variation can be explained by the difference in the severity of atrial fibrillation and by the different daily activity between subjects which is also the source of variation between the healthy individuals.

Quantification of power spectrum in the whole population showed that patients with AF had marked increase in all spectral bands (Table 6), which is in agreement with previously published data.[12] The lack of differences of power spectral parameters between the normal subjects and patients with MS in sinus rhythm may indicate that these parameters are not sensitive enough to differentiate between the two groups. On other hand, the vagal indices (sNN50 and RMSSD) were highly sensitive to changes in vagal activity.

Since the autonomic imbalance is more important than the vagal or sympathetic drive alone, we determined the HLF/HF ratio, which is thought to express the sympathovagal balance, with HLF spectral component reflecting the sympathetic and HF component parasympathetic influences.[10] We have shown a significant reduction in the HLF/HF ratio in subjects with AF compared with normal controls. This shows that HRV in patients with AF is related to vagal tone. This is consistent with the observation of Van den Berg et al.[8] We observed a lack of correlation between different heart rate variability parameters and atrial size in both groups of patients. This may indicate that HRV variability is an independent measure for autonomic imbalance in patients with mitral stenosis.

Conclusion

Decreased HRV in mitral stenosis patients with sinus rhythm suggests increased sympathetic activity in patients prone to atrial fibrillation, while marked increased of HRV in patients with AF may indicate that the ventricular rhythm has a respiratory related periodicity, and predominant parasympathetic activity may modulate the intrinsic behavior of the atrioventricular node during atrial fibrillation. Our results also suggest that the evaluation of HRV is a useful tool for the identification of patients with rheumatic mitral stenosis who are prone to atrial fibrillation. However, the role of heart rate variability for diagnostic assessment and therapeutic decision-making in these patients remains to be clarified by further controlled studies.

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