Beat-to-Beat Heart Rate and QT Variability in Patients with Congestive Cardiac Failure: Blunted Response to Orthostatic Challenge

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Background: Congestive cardiac failure is associated with increased sympathetic activity and impaired baroreflex function. We sought to test the hypothesis that these patients also have blunted response of beat-to-beat QT interval variability during orthostatic challenge.

Methods: We compared beat-to-beat heart rate and QT interval data in 17 patients with congestive cardiac failure and 17 age-matched normal controls in supine normal breathing, supine controlled breathing, and standing controlled breathing conditions. The ECG data were acquired in lead II configuration at a sampling rate of 1000 Hz.

Results: Supine controlled breathing was associated with an increase in spectral HF power (0.15–0.5 Hz) of HR and QT interval time series compared to spontaneous breathing condition only in controls. While there were significant changes in HR, HR LF power, HR LF/HF ratios, and QT variability measures in standing posture in controls, there were no such changes in patients.

Conclusions: This impairment of postural changes of HR variability is most likely due to an impaired baroreceptor function in patients with congestive heart failure. The etiology of this is likely due to an increased cardiac sympathetic and a decreased vagal function. However, the relationship of postural changes in beat-to-beat QT interval variability and baroreflex need further investigation.

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Patients with congestive heart failure exhibit abnormal autonomic function including a decrease in vagal function, an increase in sympathetic function, and a decreased baroreceptor reflex responsiveness.[1–11] Patients with heart failure have impaired baroreceptor function that is associated with sympathetic activation.[9,10] Successful treatment also improves HR variability implying a recovery of parasympathetic and baroreceptor function.[12,13]

Cardiac repolarization lability plays an important role in causing sudden death and an increase in sympathetic activity and a decrease in cardiac vagal activity make the myocardium vulnerable to fatal arrhythmias.[14–16] A recent measure, beat-to-beat QT interval variability appears to be an important and independent measure of cardiac mortality and severity of illness in patients with heart disease and also in coronary patients with effort angina pectoris.[17–19] We have found that the beat-to-beat QT interval variability significantly increases during challenges associated with an increase in cardiac sympathetic activity including a change from supine to standing posture and administration of intravenous isoproterenol.[20–23] These studies have used QTvi, which is an index of QT interval variability corrected for mean QT squared divided by heart rate variability corrected for mean heart rate squared. Our recent study comparing QTvi

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between patients with congestive heart failure and normal controls has shown that the patients have a significantly higher QTvi in supine posture during controlled breathing and during follow-up, there was a significant decrease of nonlinear indices of QT variability only in those who showed clinical improvement.[24] This report again supports an increased cardiac sympathetic activity at baseline. To our knowledge, there are no reports on the effects of posture on QT variability measures in these patients.

Though R-R interval drives the QT interval to some extent, in all the previous studies on beat-to-beat QT variability, even in normal controls, the coherence between R-R/HR and QT interval series was 0.3 to 0.7 at the most.[17,20,21] Thus, this leaves a lot of variance in QT that is not explained by changes in R-R interval.

In normal controls, there is a significant increase in LF/HF (LF: 0.04–0.15 Hz; HF: 0.15–0.5 Hz) ratios of HR during postural challenge.[25] In the present study, we sought to test the hypothesis that heart failure is associated with no significant changes in HR LF/HF ratios and QT TP and QTvi during postural challenge.

METHODS

Subjects

Table 1 gives the demographic data on all the patients. There were some missing data, as some did not have an echocardiogram. The subjects were outpatients who were consecutively recruited from the hospital with a diagnosis of congestive heart failure. We used mean ± SD (standard deviation) throughout the text and tables in this report. Age-matched control subjects were recruited from the staff working in the hospital and their relatives. There were 17 patients (16 males and 1 female; age: 53 ± 13 years) and 17 normal controls (13 males and 4 females; age: 52 ± 12 years). These studies were approved by the ethics committee at the M.S. Ramaiah Hospital, Bangalore, India.

Medications

Most of the patients were on the following medications: digoxin, enalapril, lisinopril, metoprolol, ranitidine, perindopril, ameloride, 1-carnitine, trimetazadine, aspirin, antioxidants, clopidogrel, carvedilol, nitrate, pantoprazole, furosemide, thiazide, spironolactone, and losartan.

Table 1. Descriptive Data on Patients

Patient	NYHA Classification	LVEF (%)
1	III	45
2	III	36
3	IV	23
4	III	40
5	III	20
6	III	40
7	IV	44
8	III	41
9	III	38
10	IV	27
11	III	29
12	III	48
13	III	35
14	III	35
15	IV	27
16	III	–
17	III	–

LVEF = Left ventricular ejection fraction.

Data Acquisition

Electrocardiogram (ECG) was continuously acquired in lead II configuration in a noise-free environment. All subjects were asked to breathe normally to auditory cues from a cassette player at 12 per minute. The ECG signal was digitized at 1000 Hz and the data were saved on Zip diskettes for later analyses. The subjects lied down quietly for at least 5 minutes before the supine data were acquired. After 10 minutes of spontaneous breathing in supine condition, they were asked to breathe normally at 12 per minute for 5 minutes. The subjects breathed to auditory cues from a cassette player at regular intervals. At the end of this period, the subjects were asked to stand up slowly and the standing records were obtained after an adaptation period of at least 3 minutes. Fourteen controls and 12 patients also had data during spontaneous breathing and controlled breathing.

QT Variability

This QT variability algorithm has been described by Berger and coworkers in detail and has been used by his and our groups in previous studies,[17,20–23] This was performed on a PC using Solaris Desktop Unix software (Sunsoft, Mountainview, CA, USA). This uses a graphical interface of digitized ECG (sampled at 1000 Hz that

gives a precision of 1 msec to measure the R-R and QT intervals) where the time of the R-wave is obtained using a peak-detection algorithm. Then the operator provides the program with the beginning and the end of the QT wave template. This algorithm finds the QT interval for each beat using the time-stretch model. If the operator chooses a longer QT template, all the QT intervals will be biased accordingly. The output of this algorithm contains beat-to-beat R-R intervals and QT intervals.

The HR (beats per minute; bpm: 60,000/R-R in msec) time series were sampled at 4 Hz using the technique of Berger et al.[26] The QT intervals were also constructed at 4 Hz using linear interpolation. The reason to sample the HR and the QT intervals was to ensure that the same length of time was used for the analysis as the instantaneous HR and QT were equidistant sampled at 0.25 seconds. We used HR time series free of ventricular premature beats and noise. The HR and QT data were then detrended by using the best-fit line prior to the computation of spectral analyses.

The mean HR (HRm), detrended HR variance (HRv), mean QT interval (QTm), detrended QT variance (QTv) of HR, and QT interval were calculated from the instantaneous HR and QT time series of 1024 points (256 seconds). Mean HR is in bpm and mean QT is in msec. The powers are corresponding squared values.

A normalized QT variability index was calculated as suggested by Berger et al.[17]

$$QTvi = Log_{10}[(QTv/QTm^2)/(HRv/HRm^2)]$$

This index represents the log-ratio between the QT interval and the HR variabilities (detrended), each normalized for the corresponding mean. We used 256 seconds of data in supine as well as standing postures.

Spectral Analyses

The QT time series (256 seconds at 4 Hz = 1024 points) was subjected to spectral analyses and the power spectrum was computed with the Blackman Tukey method.[17] The powers were integrated in the following bands: TP (total power: 0–0.5 Hz), VLF (very low frequency power: 0.0–0.04 Hz), LF (low frequency power: 0.04–0.15 Hz), and HF (high frequency power: 0.15–0.5 Hz).

Statistical Analysis

As the data were normally distributed, we use natural logarithmic transformation for the statistical analyses. However, we present the median and ranges of all the values in Tables 2 and 3. We used 2-way ANCOVA (analysis of covariance) for repeated measures using patients versus controls as the grouping factor and supine versus standing conditions as the repeated measures with gender as a covariate. All significant effects or trends toward significance ($P < 0.1$) were followed up by ANCOVA with gender as the covariate. A probability level of ≤ 0.05 was accepted as significant. We used paired *t*-tests to compare the supine normal and controlled breathing conditions for the HR and QT HF power. We also compared the males separately in each group.

Table 2. HR and QT Variability Measures of Patients with Congestive Cardiac Failure and Normal Controls

	CONTROLS		PATIENTS	
	Supine-NB	**Supine-CB**	**Supine-NB**	**Supine-CB**
HR-HF (0.15–0.5 Hz) (bpm^2)				
Mean ± SD	0.5 ± 1.3	1.4 ± 1.0*	−0.72 ± 1.32	0.43 ± 2.1***
Median	0.4	1.0	−1.0	0.8
Range	−1.4 to 3.1	0.15–3.2	−1.8 to 1.4	−1.4 to 2.3
QT-HF (0.15–0.5 Hz) (msec^2)				
Mean ± SD	2.3 + 0.6	2.7 + 0.7**	2.9 ± 1.2	3.7 ± 1.1****
Median	2.2	3.0	3.9	3.9
Range	1.5–3.3	1.4–3.8	1.1–5.2	2.3–5.9

HF = 0.15–0.5 Hz; NB = normal breathing; CB = controlled breathing.
*$P < 0.02$; **$P = 0.05$; ***$P = 0.11$; ****$P = 0.22$.
Significant difference between supine-NB and supine-CB ($P < 0.05$).

Table 3. HR Variability Measures of Patients with Congestive Cardiac Failure and Normal Controls

	CONTROLS		PATIENTS	
	Supine-CB	**Standing-CB**	**Supine-CB**	**Standing-CB**
HRm (bpm)				
Mean	80.0 ± 11.0	91.0 ± 10.0***	83.4 ± 15.6	85.1 ± 13.1
Median	77	88	83	86
Range	61–102	72–105	61–105	63–115
HR-TP (0–0.5 Hz)				
Mean	2.4 ± 0.9	2.5 ± 0.9	1.5 ± 1.2	1.6 ± 1.3
Median	2.2	2.5	2.2	2.5
Range	0.8–3.7	1.5–3.9	0.8–6	1.4–3.9
HR-VLF(0–0.04 Hz)				
Mean	1.2 ± 1.1	1.6 ± 0.9	0.5 ± 1.0	0.9 ± 1.2
Median	1.5	1.6	0.7	1.4
Range	−1 to 2.6	0.1–3.4	−1.6–3.1	−1.2 to 5.0
HR-LF (0.04–0.15 Hz)				
Mean	0.73 ± 1.1	1.2 ± 1.1*	−0.1 ± 1.4	0.03 ± 1.6
Median	0.4	1.6	−.02	0.18
Range	−0.6 to 2.8	−0.12 to 3.0	−0.31 to 4.5	−3.2 to 5.0
HR-HF (0.15–0.5 Hz)				
Mean	1.4 ± 0.9	0.8 ± 0.2*	0.21 ± 1.6	0.10 ± 1.6
Median	1.3	0.58	0.82	0.73
Range	0.15–3.0	−0.9 to 3.0	−2.7 to 5.4	−2.5 to 5.5
HR LF/HF				
Mean	0.6 ± 0.5	1.8 ± 2.1**	1.0 ± 0.8	1.2 ± 0.8
Median	0.8	1.6	0.6	1.6
Range	0.14–1.6	0.4–9.4	0.3–2.8	0.4–3.0

CB = Controlled breathing.
HRm (HR mean) is in beats per minute.
Powers for HR are in Ln of bpm^2.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.005$; significant difference between supine-CB and standing-CB. Degrees of freedom for the paired *t*-tests = 16.

RESULTS

The results remained the same after adjusting for gender even though there was a higher proportion of females in the control group. The results were also similar when the comparisons included only the male subjects in each group. Table 2 shows the HR and QT HF powers in supine posture during spontaneous and controlled breathing conditions. Tables 3 and 4 show the data of HR and QT variability measures of patients and controls in supine and standing postures during controlled breathing at 12 per minute. Table 5 shows the results of ANCOVA for patients and controls between supine and standing posture with gender as the covariate. While there were significant increases in HR HF and QT HF powers during controlled breathing in normal controls, there were no such increases in the patient group. The results of 2-way ANCOVA for the HR and QT variability measures were essentially similar to the ones obtained for the ANOVA. There were significant increases in HR LF and HF powers and LF/HF ratios only in the control group. There were also significant increases in QT LF and HF powers and QTvi only in the control group.

DISCUSSION

To our knowledge, this is the first study to examine the effects of controlled breathing and postural challenge on beat-to-beat QT variability measures in patients with heart failure. The main findings of this study are impaired response of HR and HRv measures, including LF/HF ratios, and also an impaired response of QT variability measures during the change from supine to standing posture in patients compared to controls. There was also no significant increase in HR and QT HF power in patients during controlled breathing, which is most likely due to an impaired vagal function in the patients. In all our previous reports, there was

Table 4. QT Variability Measures of Patients with Congestive Cardiac Failure and Normal Controls

	CONTROLS		PATIENTS	
	Supine-CB	**Standing-CB**	**Supine-CB**	**Standing-CB**
QTm (msec)				
Mean	371 ± 30	357 ± 33**	471 ± 77	464 ± 91
Median	361	359	433	465
Range	331–418	296–400	349–580	335–590
QT-TP (0–0.5 Hz)				
Mean	3.3 ± 0.6	3.7 ± 0.5*	4.6 ± 1.2	4.8 ± 1.3
Median	3.3	3.5	4.4	5.0
Range	1.8–4.1	3.0–4.4	2.3–9.0	3.1–7.6
QT-VLF(0–0.04 Hz)				
Mean	1.5 ± 0.6	1.8 ± 0.7	2.8 ± 0.8	2.7 ± 1.1
Median	1.7	1.6	2.8	3.2
Range	−0.5 to 2.6	0.7–3.2	1.0–4.1	0.7–5.7
QT-LF (0.04–0.15 Hz)				
Mean	1.7 ± 0.7	2.2 ± 0.6***	2.9 ± 0.7	3.1 ± 1.0
Median	1.4	2.3	2.8	3.5
Range	0.42–2.6	1.14–3.0	0.5–4.5	1.8–6.5
QT-HF (0.15–0.5 Hz)				
Mean	2.7 ± 0.7	3.2 ± 0.5**	3.7 ± 0.7	3.9 ± 0.7
Median	2.4	2.9	3.7	4.1
Range	1.4–3.9	2.4–4.0	1.2–5.5	2.7–6.8
QTvi				
Mean	−0.9 ± 0.5	−0.62 ± 0.3**	−0.22 ± 0.6	−0.07 ± 0.5
Median	−1.05	−0.57	−0.32	−0.04
Range	−1.5 to 0.3	−1.2 to −0.29	−0.5 to 0.41	−0.64 to 0.86
HR-QT Coherence (0–0.5 Hz)				
Mean	0.20 ± 0.06	0.19 ± 0.06	0.22 ± 0.10	0.21 ± 0.10
Median	0.19	0.20	0.20	0.21
Range	0.12–0.29	0.09–0.29	0.12–0.35	0.1–0.31

CB = Controlled breathing; QTvi = QT variability index.
QTm (QT interval mean) is in msec. Not corrected for R-R interval.
Powers for QT are in Ln of $msec^2$.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.005$; significant difference between supine-CB and standing-CB. Degrees of freedom for the paired *t*-tests = 16.

a highly significant increase in QT variance and also QTvi in standing posture compared to the supine condition in normal adults.[20] The lack of such a response in cardiac failure patients is most likely due to the heightened sympathetic activity in supine posture and a lack of further increase in standing posture. As we reported in our previous study,[24] patients with heart failure had an increased QT variance and QTvi compared to controls in supine posture, which decreased after treatment. This implies that these patients have an increased cardiac sympathetic activity at baseline, and thus, there are no further changes in standing posture. We do not have enough data to answer the question whether clinical improvement with treatment would normalize these orthostatic changes.

Previous studies on HRv show that the power spectrum shows a peak around 0.1 Hz (LF power) related to baroreflex mechanisms and another at respiratory frequency between 0.15 and 0.5 Hz (HF power).[25,27,28] There is strong evidence showing an increase in LF/HF ratios of HRv in humans in standing posture.[25] This is due to a relative increase in LF power and a decrease in HF power during standing posture. This study shows that patients with heart failure had an impaired response of LF/HF ratios of HRv during orthostatic challenge. We speculate that the impaired postural responses of HR LF/HF ratios may in part be related to the impaired baroreflex response in these patients. These results should also be interpreted with caution, as there was no significant increase in HR TP in control group in standing posture. It is also premature to relate the

Table 5. Results of 2-way ANCOVA (with Gender as a Covariate) for HR and QT Variability Measures of Patients with Congestive Cardiac Failure and Normal Controls

	Time Effect (Posture)	Interaction Effect
HRm (bpm)	$F = 15$; $P < 0.0005$	$F = 8.0$; $P < 0.008$
HR-TP (0–0.5 Hz)	NS	NS
HR-VLF(0–0.04 Hz)	NS	NS
HR-LF (0.04–0.15 Hz)	$F = 6.0$; $P < 0.05$	NS
HR-HF (0.15–0.5 Hz)	$F = 4.2$; $P < 0.05$	$F = 4.3$; $P < 0.05$
HR LF/HF	$F = 8.0$; $P < 0.01$	NS
QTm (msec)	$F = 3.0$; $P < 0.1$ (Trend)	NS
QT-TP (0–0.5 Hz)	$F = 4.5$; $P < 0.05$	NS
QT-VLF(0–0.04 Hz)	NS	NS
QT-LF (0.04–0.15 Hz)	$F = 25.0$; $P < 0.00001$	$F = 13.0$; $P < 0.001$
QT-HF (0.15–0.5 Hz)	$F = 8.0$; $P < 0.01$	NS
QTvi	NS	$F = 6.0$; $P < 0.05$
HR-QT coherence (0–0.5 Hz)	NS	NS

QTvi = QT variability index.
HRm (HR mean) is in beats per minute; QTm (QT interval mean) is in msec.
Powers for HR are in Ln of bpm^2 and for QT, $msec^2$.
Degrees of freedom for time and interaction effects: 1.32.

impairment of QT variability measures during postural challenge to baroreflex response. Majority of the patients had idiopathic-dilated cardiomyopathy. Two patients had thyrotoxicosis-associated cardiomyopathy and two drug-induced cardiomyopathy. We did not address the issue of etiology in this article due to the small sample size. Most of the medications the patients were receiving are supposed to improve the cardiac condition and some of them may even improve baroreceptor sensitivity. Thus, medication effects may not have been responsible for the present findings.

Limitations

We did not have any direct measure of baroreflex sensitivity to correlate with QT variability measures, thus limiting any conclusions relating postural changes in QT variability to baroreflex response. We also did not record the respiratory signal and it is possible that patients may not have been able to breathe as effectively as controls to auditory cues. Due to the small number of subjects and different groups of medications that the subjects were on, these results should be interpreted with caution and should be considered preliminary.

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