Effects of sildenafil citrate (Viagra) on cardiac repolarization and on autonomic control in subjects with chronic heart failure

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Background Cases of sudden death associated with sildenafil citrate use have been reported in men with coronary artery disease. The aim of this study was to investigate the drug's effect on cardiac repolarization and sinus autonomic and vascular control in men with mild chronic heart failure (CHF; New York Heart Association classification II). Changes in these variables could predispose patients to malignant ventricular arrhythmias.

Method We measured QT dispersion, the QT-RR slope, and the index of QT variability (QTVI) and analyzed spectral power of RR and systolic blood pressure variability in 10 men with dilated cardiomyopathy and in 10 control subjects after administration of a single 50-mg oral dose of sildenafil citrate or placebo at rest (not followed with any attempt at intercourse).

Results In both groups, oral sildenafil citrate decreased the systolic blood pressure (P <.05) and increased the heart rate (P <.05). In subjects with CHF, it also increased the QT-RR (P <.001) and QTVI (from −0.45 ± 0.07 to −0.27 ± 0.07; P <.001), but in controls, it increased the QTVI (from −1.20 ± 0.08 to −0.78 ± .014; P < .001). In these subjects and controls, oral sildenafil citrate induced a significant reduction in high frequency, expressed in absolute power (subjects with CHF: from 4.04 ± 0.14 to 3.43 ± 0.16 natural logarithm ms^2; P <.001; controls: from 5.61 ± 0.44 to 4.98 ± 0.32 natural logarithm ms^2; P <.05) and in normalized units (P <.05). In subjects with CHF but not in controls, it also significantly increased the low frequency to high frequency ratio (from 1.3 ± 0.12 to 1.89 ± 0.16; P <.001) and low frequency expressed in normalized units (P <.05).Sildenafil citrate caused no significant changes in the QT interval or dispersion.

Conclusion These findings indicate that, in men with heart failure, sildenafil citrate reduces vagal modulation and increases sympathetic modulation, probably through its reflex vasodilatory action. The autonomic system changes induced with sildenafil citrate could alter QT dynamics. Both changes could favor the onset of lethal ventricular arrhythmias. At the dose usually taken for erectile dysfunction, sildenafil citrate has no direct effect on cardiac repolarization (QT interval or dispersion). (Am Heart J 2002;143:703-10.)

Many men with cardiac disease have impotence, and sildenafil citrate is an extremely useful drug in erectile dysfunction. Yet, for various reasons, sildenafil citrate is an inappropriate choice in patients with heart disease. The risk arises mainly from the combination of sildenafil citrate with drugs that can potentiate systemic vasodilatation (nitrates) or interfere with sildenafil citrate metabolism (for example, digitalis, statin, amiodarone, and calcium-channel blockers).[1] Despite recommendations for caution in the prescription of sildenafil citrate to patients with cardiovascular disease, some cases of sudden death have been reported, not all of them explainable with preexisting heart disease.[1,2]

From the Dipartimento di Scienze, dell-Invecchiamento.
Submitted July 4, 2001; accepted August 17, 2001.
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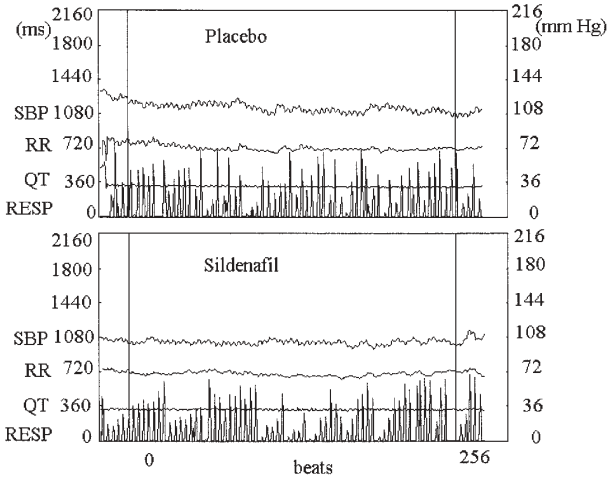
0002-8703/2002/$35.00 + 0 ***4/1/121547***
doi:10.1067/mhj.2002.121547

Recent reports in vitro have observed that sildenafil citrate induces a dose-dependent block of the rapid component (I_{kr}) of the delayed rectifier potassium current.[3] At high plasma concentrations, sildenafil citrate therefore acts as a classification III antiarrhythmic drug.[3] Hence, some cases of sudden death could be explained by the onset of malignant ventricular arrhythmias induced by prolonged cardiac repolarization,[3] for example, in the long QT syndrome. Nonetheless, confirmation of these data is lacking in vivo. Furthermore, the plasma sildenafil citrate concentrations necessary to induce these changes would be higher than those normally reached when the drug is taken to induce an erection.

Thus, our aim in this study was to investigate the effect of sildenafil citrate on cardiac repolarization in subjects with an altered phase. We studied repolarization noninvasively at rest and QT_c intervals and their dispersion[4] and by determining the following dynamic QT variables: the QT-RR slope[5-7] and the index of QT variability (QTVI).[8-11] We assessed these variables in men who had New York Heart Association (NYHA) clas-

Figure 1



Simultaneous 256-beat recordings of systolic blood pressure *(SBP)*, of heart rate expressed as RR interval *(RR)*, QT interval *(QT)*, and respiratory frequency *(RESP)*. *Top panel,* After placebo; *lower panel,* after oral sildenafil citrate. After sildenafil citrate administration, SBP decreased (from mean 114 mm Hg during placebo to 102 mm Hg after sildenafil citrate). Mean RR intervals shortened (from 720 ms after placebo to 695 ms after sildenafil citrate). Mean QT interval lengthened (from 315 ms after placebo to 324 after sildenafil citrate).

sification II chronic heart failure (CHF) as the result of ischemic dilated cardiomyopathy and in healthy control subjects with similar general characteristics.

Furthermore, because a recent report observed that sildenafil citrate induces an increase of sympathetic activity,[12] we then also investigated drug-induced changes in arterial pressure, heart rate, and autonomic control. Autonomic nervous system control was assessed with spectral analysis of RR[13-15] and arterial pressure variability.[13,15-18]

Methods

Study subjects

For this study, we selected patients who had mild CHF (NYHA classification II) as the result of ischemic dilated cardiomyopathy and healthy volunteer controls from among staff in the clinic. Patients were excluded if they had had a myocardial infarction within 6 months before enrollment or had recently undergone revascularization procedures or coronary angioplasty. Patients had stable symptoms of heart failure; none had been hospitalized, had manifested worsening symptoms, or had changed therapy during the past 3 months. None of the patients had atrial fibrillation, frequent extrasystole (1 extrasystole per minute was permitted), branch block, or other arrhythmias likely to interfere with assessments.

All subjects underwent a complete history, physical examination, routine laboratory investigation, electrocardiography, 2-dimensional echo-Doppler scan study of the vessels, and echocardiography. During echocardiography, data were obtained to determine the left ventricular mass index and ejection fraction.

Patients with CHF were taking standard medications for heart failure, including enalapril (10 mg/day), furosemide (25 mg/day), spironolactone (25 mg/day), carvedilol (12.5 mg/day), and acetylsalicylic acid. Those taking nitrates or other drugs that can interfere with sildenafil citrate plasma concentrations were excluded.[1]

All participants gave their informed consent to the procedures, and the local ethics committee approved the study. The study complied with the ethical rules for human experimentation stated in the Declaration of Helsinki.

Study protocol and data acquisition

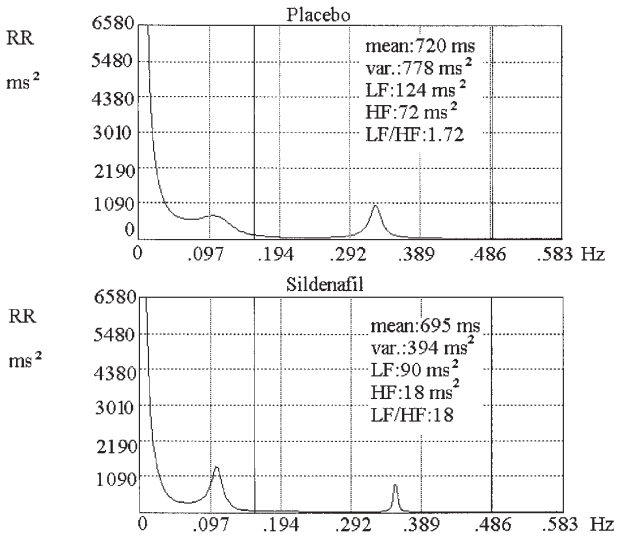
Because the aim of the study was to assess cardiac repolarization and autonomic control, in single-blind design, after administration of placebo or a 50-mg tablet of sildenafil citrate, all subjects underwent a 12-lead electrocardiographic recording at a speed of 50 mm/s and simultaneous beat-to-beat recording of the electrocardiographic trace in the second lead (Telemetria Mortara Rangoni, Bologna, Italy), of systolic blood pressure (SBP; Finapres, Ohmeda, Englewood, NJ), and respiratory frequency (strain-gauge belt). This recording lasted 10 minutes. The first recording was used for measurement of QT duration and dispersion, and the second for autonomic assessment and determination of QT dynamics. Each session comprised the 2 assessments: after placebo and after drug. To avoid possible changes in the electrode placement, adhesive electrodes were used. They were placed when the study began and removed only when it ended. The 12-lead electrocardiography was recorded 50 minutes after administration of drug or placebo, and the 10-minute recording began 55 minutes after administration of drug or placebo. During the 10-minute recording, subjects breathed at a frequency of 20 breaths/min (0.33 Hz) in time with a metronome.

The 3 analogic signals (electrocardiography, SBP, and respiratory frequency) were acquired simultaneously and digitally converted with a custom-designed card (Keithley Metrabyte–DAS 1200 Series, Cleveland, Ohio) at a sampling frequency of 500 Hz per channel with 12-bit precision. For recognition and measurement of the RR and QT interval, SBP, and respiratory rate we used a software program developed in our laboratory on the basis of an automated derivative/threshold algorithm. To calculate the QT interval and to make the end of the T wave easier to identify, we used a software program on the basis of the algorithm for quantification of beat-to-beat fluctuations in QT interval variability proposed by Berger et al.[8-11] From both 10-minute recordings, we selected a stationary continuous 256-beat segment (Figure 1) for the determination of RR, QT, and SBP variability (Figure 1).

RR and systolic blood pressure variability

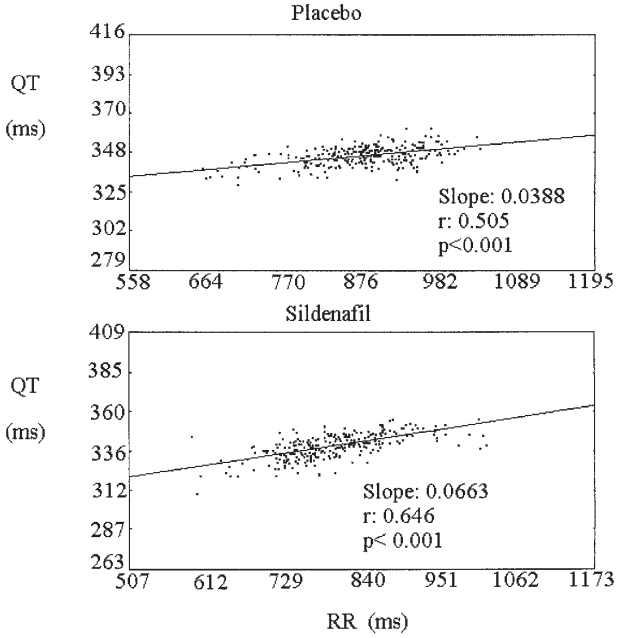
For RR and SBP, we calculated the following spectral components: high-frequency (HF) component, from 0.15 to 0.42 Hz; and low-frequency (LF) component: from 0.03 to 0.15 Hz (Figure 2). The spectral components were transformed into their natural logarithm (ln) and into normalized units (normal-

Figure 2



RR interval spectra recorded after placebo and after sildenafil citrate. High-frequency spectral component *(HF)* from 0.292 to 0.389 Hz represents respiratory (vagal) modulation of sinus activity. Low-frequency spectral component *(LF)* oscillates around 0.097 Hz. Reduction in HF is index of reduced sinus vagal modulation. Increase in LF/HF ratio corresponds to increased sinus sympathetic modulation.

Figure 3



QT-RR slope after placebo and after sildenafil citrate in representative subject. Oral sildenafil citrate in this subject increased slope.

ized unit LF = LF/total Power – very-low-frequency × 100; normalized unit HF = HF/total Power – very-low-frequency × 100).[14,15,19,20] Last, we calculated the ratio between LF and HF powers of RR variability (LF/HF).[14,15,19-22]

Software for data acquisition and storage and for spectral analysis were designed and produced by our research group and have been described in detail elsewhere.[15,19,20] The α index was calculated by dividing the square root of the spectral density of the heart rate by the square root of the corresponding spectral density of arterial pressure, as described by Robbe et al[23] and later by other investigators[15-18,24,25]: αLF = √ LF RR/√ LF SBP; α HF = √ HF RR/√ HF SBP.

The coherence function of the various spectral components then was estimated. Coherence expressed the fraction of power at a given frequency in either time series that could be explained as a linear transformation between the 2 signals. Recordings showing <0.5 coherence in LF and HF[16] between the SBP and RR variability signals were discarded. The phase of systolic pressure and RR interval relation was –45° ± 5° in LF and –30° ± 7° in HF. These results suggest that systolic pressure variations precede RR interval variations.[18]

Spectra of the respiratory trace were analyzed on the signal sampled once every cardiac cycle. These spectra were used as a reference to identify heart rate oscillations caused by respiratory sinus arrhythmia. The RR interval and respiratory signal recordings were also used for cross-spectral analysis. The software program automatically calculated the respiratory frequency for each cycle.

QT interval dynamic and variability index

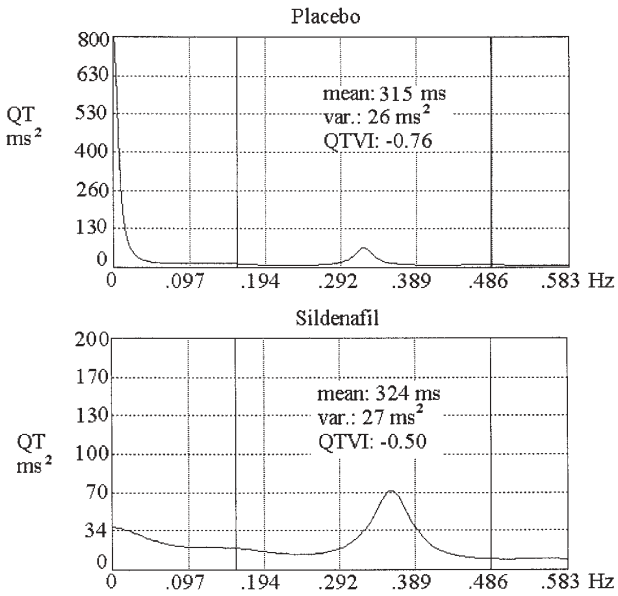
QT interval was calculated from Q wave to the end of the T wave. From stationary 256-beat segments recorded before and after drug administration, we calculated the mean (QT_m) and variance (QT_v) of the QT intervals and the QT-RR slope (Figure 3). QT_v and QT_m also were used to calculate the QTVI (Figure 4) with the following formula: $QTVI = \log_{10}\{(QT_v)/(QT_m)^2]/[(RR_v)/(RR_m)^2]\}$,[8-11] where RR_m is the mean and RR_v is the variance of the 256 RR intervals.

The 256 QT segments also were analyzed spectrally (Figure 4) and with cross-spectral analysis with RR. The last variable determined was coherence, calculated from the spectral region between 0 and the end of the respiratory peak (Figure 4).

Measurement of QT intervals and dispersion

The duration of the QT interval was measured at each lead of the 12-lead surface electrocardiogram for 2 consecutive cycles. Interval dispersion was calculated with the Perkiomaki method.[26,27] QT intervals were measured from the onset of the QRS to the end of the T wave with a tangential method. When U waves were present, the tangent was also used to measure the QT to the nadir of the curve between the T and U waves. Variables were measured manually by a trained operator blinded to each subject's clinical and spectral data. Bazett's formula was used to obtain QT intervals corrected for heart rate (QT_c). QT_c dispersion was defined as the difference between the respective maximum and minimum QT_c, and the mean value of 2 consecutive cycles was calculated. Interobserver measurement error was avoided with measurements

Figure 4



QT interval spectra recorded after placebo and after sildenafil citrate. QT variability index *(QTVI)* was increased after sildenafil citrate.

Table I. General characteristic of study subjects

Variables	Subjects with heart failure (n = 10)	Control subjects (n = 10)	*P* value
Age (y)	50 ± 2	49 ± 2	NS
BMI (kg/m²)	26 ± 1	26 ± 0.4	NS
Sodium (mEq/dL)	141 ± 2	142 ± 1	NS
Potassium (mEq/dL)	4.32 ± 0.04	4.41 ± 0.03	NS
Heart rate (bpm)	65 ± 2	63 ± 2	NS
SBP (mm Hg)	121 ± 5	130 ± 6	NS
DBP (mm Hg)	71 ± 2	75 ± 5	NS
QT interval min (ms)	340 ± 8	326 ± 7	NS
QT interval max (ms)	400 ± 8	375 ± 6	<.05
QT_c interval min (ms)	375 ± 7	374 ± 7	NS
QT_c interval max (ms)	445 ± 6	425 ± 5	<.05
QT dispersion (ms)	60 ± 2	49 ± 3	<.05
QT_c dispersion (ms)	70 ± 5	51 ± 4	<.05
Ejection fraction	38% ± 2%	68% ± 5%	<.001
LVMI (g/m²)	161 ± 4	103 ± 3	<.001

BMI, Body mass index; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; QT_c, QT intervals corrected for heart rate; *LVMI,* left ventricular mass index; *NS,* not significant.

yielded by the same trained operator. Intraobserver and measurement errors of QT_c dispersion were defined.

Statistical analysis

All data were evaluated with database SPSS-PC+ (SPSS-PC+ Inc, Chicago, Ill). All results are expressed as mean ± standard error. One-way analysis of variance was used to compare the general characteristics and other data, including QTVI data, in the 2 groups.

Paired *t* test was used to evaluate the differences between the data measured during placebo or drug. A *P* value of <.05 was considered to indicate statistical significance.

Results

No significant differences were found between patients with mild CHF and healthy subjects for age, sex, body mass index, or other general characteristics. The only variables that differed between groups were the ejection fraction and QT duration, dispersion, and variability (Table).

Oral sildenafil citrate significantly lowered the mean beat-to-beat SBP in both groups (in patients with CHF, from 107 ± 3 to 100 ± 2 mm Hg; in controls, from 112 ± 2 to 103 ± 2 mm Hg; *P* <.05). The percentage reduction was slightly, although not significantly, larger in patients (6% ± 2% and 8% ± 2%). Conversely, sildenafil citrate had no effect on diastolic blood pressure in patients with CHF but slightly reduced this variable in controls (*P* <.05).

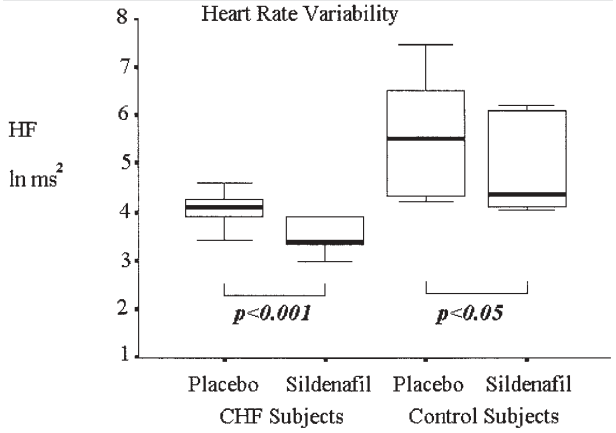
Sildenafil citrate increased the mean heart rate in both groups (in patients with CHF by 13% ± 3% and in controls by 8% ± 3%; *P* <.05). None of the men had adverse reactions that could be attributed to sildenafil citrate.

RR and systolic blood pressure variability

The spectral analysis of RR variability showed that after sildenafil citrate and after placebo men with CHF had lower variability (variance) and total spectral power (TP) than did controls (*P* <.05). By contrast, their LF values, expressed as the ln and in normalized units, were higher than those of controls (*P* <.05). HF was invariably significantly lower in patients with CHF (Figure 5). By contrast, the LF/HF ratio was higher in patients with CHF (*P* <.05; Figure 6).

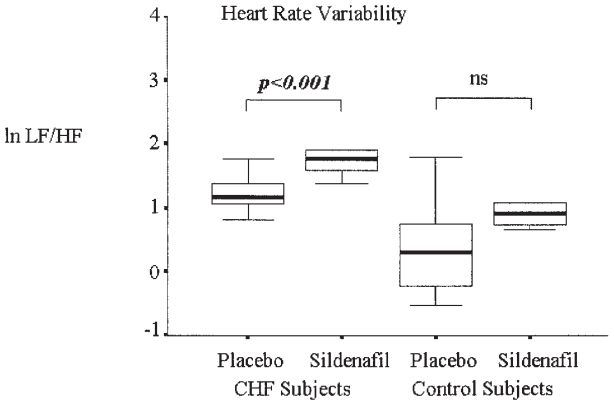
In subjects with CHF and controls, oral sildenafil citrate induced a significant reduction in HF, expressed in ln (subjects with CHF: from 4.04 ± 0.14 ln ms² to 3.43 ± 0.16 ln ms²; *P* <.001; controls: from 5.61 ± 0.44 ln ms² to 4.98 ± 0.32 ln ms²; *P* <.05; Figure 5) and in normalized units (*P* <.05). In subjects with CHF but not in controls, it also significantly increased the LF/HF ratio (from 1.3 ± 0.12 to 1.89 ± 0.16; *P* <.001; Figure 6) and LF expressed in normalized units (*P* <.05). Both groups had higher LF power of SBP, expressed in the absolute form (mm Hg²) and in normalized units, after sildenafil citrate (*P* <.001). α LF and α HF were both lower in patients. In both groups, the drug also decreased the α HF index (patients with CHF: from 5.81 ± 0.75 ms/mm Hg to 4.50 ± 0.45 ms/mm Hg; *P* <.05; controls: from 15.88 ± 3.88 ms/mm Hg to 10.80 ± 2.4 ms/mm Hg; *P* <.05).

Figure 5



Changes in natural logarithm *(ln)* high-frequency spectral component *(HF)* of RR variability in men with chronic heart failure *(CHF)* and control subjects. In this and subsequent box plots, *central line* represents median distribution, each *box* spans from 25th to 75th percentile points, and *error bars* extend from 10th to 90th percentile points (with analysis of variance and paired *t* test). Note that men with CHF after placebo (*P* <.05) and after oral sildenafil citrate (*P* <.001) invariably had lower ln of HF. In both groups, drug significantly reduced this spectral component.

Figure 6



Changes in natural logarithm low-frequency/high-frequency spectral component *(LF/HF)* of RR variability in men with chronic heart failure *(CHF)* and control subjects (with analysis of variance and paired *t* test). Note that men with CHF had higher natural logarithm LF/HF after placebo (*P* <.05) and after oral sildenafil citrate (*P* <.05). In men with CHF, sildenafil citrate induced significant increase in these spectral indices (with analysis of variance and paired *t* test).

No significant changes were found for coherence between SBP and RR signals after placebo or after drug. No subjects were excluded because of reduced signal coherence, but men with CHF had significantly lower coherence for these 2 variables (*P* <.05)

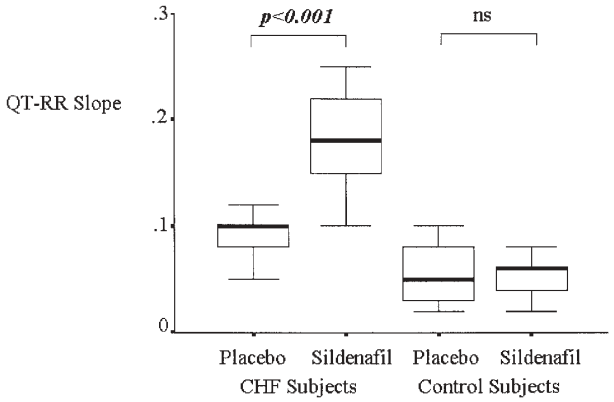
QT interval dynamic and variability index

Whereas QT_m was significantly longer in patients with CHF than in control subjects (*P* <.001), QT_v values in the 2 study groups overlapped. After oral sildenafil citrate, in patients with CHF, QT_m increased (from 388 ± 4 ms to 396 ± 3 ms; *P* <.05) as did QT_v (from 47 ± 2 ms to 55 ± 2 ms; *P* <.001); whereas in healthy subjects, QT_m decreased (from 329 ± 4 ms to 326 ± 4 ms; *P* <.05) and QT_v increased (from 47 ± 5 ms to 55 ± 4 ms; *P* <.05).

Patients with CHF invariably had higher regression slope values than did control subjects (*P* <.05; Figure 7). Their slope values also increased significantly after sildenafil citrate (from 0.09 ± 0.01 to 0.18 ± 0.01; *P* <.001), whereas those of control subjects remained practically unchanged (from 0.05 ± 0.01 to 0.05 ± 0.01; not significant; Figure 7).

Patients with CHF invariably had higher QTVI values than did control subjects (Figure 8). Oral sildenafil citrate increased the QTVI in both groups (subjects with CHF: from −0.45 ± 0.07 to −0.27 ± 0.07; *P* <.001; control subjects: from −1.20 ± 0.08 to −0.78 ± 0.14; *P* <.001; Figure 8).

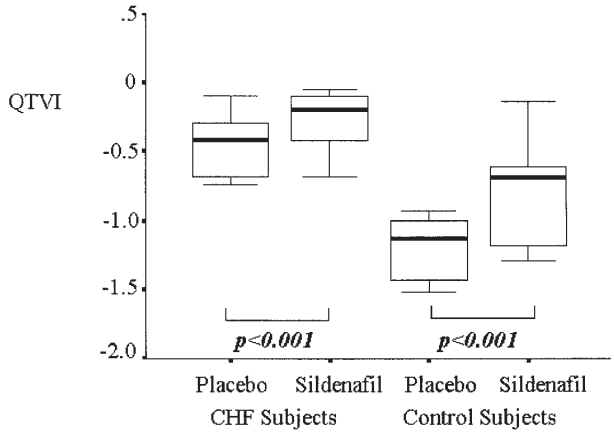
Figure 7



Changes in QT-RR slope in patients with chronic heart failure *(CHF)* and control subjects (with analysis of variance and paired *t* test). Note that in men with CHF after placebo (*P* <.05) and after oral sildenafil citrate (*P* <.001) QT-RR slope was always higher in men with CHF than in control subjects. In addition, drug caused significant increase in this variable but did so only in men with CHF.

No significant changes were found between QT and RR signal coherence after drug and after placebo.

Figure 8



QT variability index (QTVI) changes in patients with chronic heart failure (CHF) and control subjects (with analysis of variance and paired *t* test). Note that after placebo ($P < .001$) and after oral sildenafil citrate ($P < .001$) QTVI was always higher in patients with CHF. Oral sildenafil citrate significantly increased this variable in both groups.

Patients had significantly lower coherence for this pair of signals ($P < .05$).

QT interval dispersion

QT values remained statistically unchanged after oral sildenafil citrate. Notably, neither the duration of the various QT and QT_c measures in the various leads nor QT and QT_c dispersion changed. Intraobserver variability was 3 ms.

Discussion

Our data in this study show that oral sildenafil citrate induces changes in some of the variables that dynamically assess cardiac repolarization. Notably, in men with mild CHF, it increased the QT-RR slope and the QTVI. Yet, it left the QT interval and QT dispersion unchanged. This result is hardly surprising insofar as both these QT variables predominantly reflect structural changes (including hypertrophy, dilatation, infarction, and genetically induced alterations in potassium or sodium channels),[4,25-29] whereas the dynamic tests measure temporal changes and therefore mainly depend on altered cardiovascular autonomic control.[5,30-35] Accordingly, both tests yielded higher baseline values in patients with CHF than in healthy subjects. Hence, the changes in the duration of cardiac repolarization induced by the I_{kr} blockage, which can induce a prolonged pharmacologic QT, probably occur at higher blood concentrations (possibly 100-fold higher) than those achieved by the dose normally needed to induce an erection and used in this study (50 mg).[3] Presumably, the concentrations used in vitro could also induce in vivo changes in the duration of cardiac repolarization and hence in QT dispersion.

Oral sildenafil citrate induced changes in autonomic cardiovascular control that might cause secondary alterations in cardiac repolarization. In particular, the drug exerted a mild systemic vasodilatory action that slightly lowered pressures, thus causing a reflex increase in the heart rate. The increased heart rate could depend either on a drug-induced reduction of sinus vagal modulation or increased sympathetic modulation or on both phenomena. Evidence that healthy subjects reduced vagal modulation alone comes from the reduction in HF measured in the absolute form and in normalized units (Figure 5). HF, especially when obtained with controlled breathing, provides a reliable index of parasympathetic sinus modulation.[13-20,28] Further evidence confirming its reliability came in this study from the reduction in α HF, a spectral index of baroreflex sensitivity that correlates reasonably well with baroreflex sensitivity determined with the phenylephrine method.[17,24,25,36] Conversely, in men with CHF, we also observed a reduction in HF RR after sildenafil citrate and a significant increase in the LF/HF ratio. This variable, is generally, though not unanimously,[35-38] considered a measure of increased sympathetic activity.[11-20,26] This result is confirmed also by the increased LF of RR measured in normalized units. With these experimental circumstances, the use of normalized units is more appropriate because normalization reduces the influence of TP (see Methods),[14,19] namely, the total RR variability expressed as variance. Thus, by reducing the mean RR interval (tachycardia), oral sildenafil citrate reduced TP and thus lowered LF and HF. But in relative terms (normalized units), LF tended to increase. These data suggest that, in men with CHF, as sinus vagal modulation diminishes sinus sympathetic modulation increases. Besides, the increased LF of SBP indicates a drug-induced increase in vascular sympathetic activity. Hence, in men with mild CHF, who, despite chronic carvedilol therapy at small doses, had increased baseline sympathetic activity linked to their disease, oral sildenafil citrate further increased sinus sympathetic modulation, thus resulting in vagal withdrawal, and concomitantly lowered baroreflex sensitivity. A plausible reason for the finding that sildenafil citrate increased sympathetic activity—already high in persons with heart failure—is that the men we studied had only mild CHF. Men in higher NYHA classifications, hence with lower ejection fractions, would probably be unable to augment LF power.[36,39-41]

Despite the carvedilol-induced α adrenergic receptor inhibition and enalaprin-induced formation of angiotensin II in patients, sildenafil citrate induced a similar systemic vasodilatory effect in the 2 groups.

Hence, at these plasma concentrations, the drug is hemodynamically tolerated. Furthermore, the pressure-induced effects in patients with CHF had no influence on diastolic blood pressure, probably because these patients' peripheral resistance is modulated by the use of carvedilol and enalapril but mainly by the autonomic nervous system.

These autonomic changes, probably more than the effect of the I_{kr} blockage, induce a dynamic change in cardiac repolarization that increases the QT-RR slope and QTVI. The autonomic nervous system response characterized by vagal withdrawal along with enhanced sympathetic activity and the increase in the QT-RR slope and QTVI, providing evidence of a temporal inhomogeneity in cardiac repolarization, are risk factors for sudden death.[5-10,29] More important, the increased QTVI correlates with an increase in the severity of CHF[8] and with the presence of malignant tachycardias and ventricular arrhythmias.[9]

Our data need further clarification. In the healthy men we studied, sildenafil citrate did not alter both indexes of ventricular repolarization in a similar manner. Whereas the QTVI significantly increased, the QT-RR slope remained unchanged after drug administration. The most likely explanation for this discrepancy is that the QTVI increases also as a function of the reduction in RR variance (see Methods), an indirect index of altered autonomic control,[8-11] whereas the QT-RR slope is influenced by RR variance. In other words, the sildenafil citrate–induced reduction in RR variance could increase the QTVI. QT dynamics expressed as the QT-RR slope would be altered only in persons with severely defective autonomic control, such as those with CHF. In healthy subjects, the vagal reduction induced at a normal sildenafil citrate dose leaves the QT-RR slope unchanged.

Finally, we consider that men wishing to take sildenafil citrate, especially those with CHF and pathophysiologic conditions involving the autonomic nervous system, including hypertension,[15,18-20,28] obesity,[42,43] anxiety neurosis,[20,28,44,45] or aging,[19,45-49] should undergo dynamic assessment of cardiac repolarization. Dynamic monitoring of the electrocardiogram during sexual activity after a sildenafil citrate–induced erection could be extremely useful to assess the risks of sildenafil citrate therapy.

References

1. Cheitlin MD, Hattler AH, Brindis RG, et al. Use of sildenafil (Viagra) in patients with cardiovascular disease. J Am Coll Cardiol 1999;33:273-82.
2. Zusman RM, Morales A, Glasser DB, et al. Overall cardiovascular profile of sildenafil citrate. Am J Cardiol 1999;83:35C-44C.
3. Geelen P, Drolet B, Rail J, et al. Sildenafil (Viagra) prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current. Circulation 2000;102:275-7.
4. Day CP, McComb JM, Campbell RWF. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J 1990;63:39-41.
5. Maison-Blanche P, Coumel P. Changes in repolarization dynamicity and the assessment of arrhythmic risk. Pacing Clin Electrophysiol 1997;20:2614-24.
6. Singh JP, Sleight P, Kardos A, et al. QT interval dynamics and heart rate variability preceding a case of cardiac arrest. Heart 1997;77:375-7.
7. Govren-Segal D, Radai MM, Sivan Y, et al. Real-time PC-based system for dynamic beat-to-beat QT-RR analysis. Comput Biomed Res 1999;32:336-54.
8. Berger RD, Kasper EK, Baughman KL, et al. Beat-to-beat QT interval variability. Novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation 1997;96:1557-65.
9. Atiga WL, Calkins H, Lawrence JH, et al. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. J Cardiovasc Electrophysiol 1998;9:899-908.
10. Atiga WL, Fananapazir L, Mc Areavey D, et al. Temporal repolarization lability in hypertrophic cardiomyopathy caused by β-myosin heavy-chain gene mutation. Circulation 2000;101:1237-42.
11. Piccirillo G, Cacciafesta M, Lionetti M, et al. The influence of age, the autonomic nervous system and anxiety on QT interval variability. Clin Sci. 2001;101:429-38.
12. Phillips BG, Kato M, Pesek CA, et al. Sympathetic activation by Sildenafil. Circulation 2000;102:3068-73.
13. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178-93.
14. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standard of measurements, physiological interpretation and clinical use. Circulation 1996;93:1043-65.
15. Piccirillo G, Bucca C, Durante M, et al. Heart rate and blood pressure variability in salt-sensitive hypertension. Hypertension 1996;28:944-52.
16. Pagani M, Somers V, Furlan R, et al. Changes in autonomic regulation induced by physical training in mild hypertension. Hypertension 1988;12:600-10.
17. De Toma G, Nicolanti V, Plocco M, et al. Baroreflex failure syndrome after bilateral carotid body tumor: an understimated problem. J Vasc Surg 2000;31:806-10.
18. Piccirillo G, Viola E, Nocco M, et al. Autonomic modulation of heart rate and blood pressure in normotensive offspring of hypertensive subjects. J Lab Clin Med 2000;135:145-52.
19. Piccirillo G, Fimognari FL, Munizzi MR, et al. Age-dependent influence on heart rate variability in salt-sensitive hypertensive subjects: power spectral analysis during rest and head-up tilt. J Am Geriatr Soc 1996;44:530-8.
20. Piccirillo G, Santagada E, Viola E, et al. Autonomic modulation of heart rate and blood pressure in hypertensive subjects with symptoms of anxiety. Clin Sci 1998;95:43-52.
21. Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation 1997;95:1441-8.
22. Montano N, Cogliati C, Porta A, et al. Central vagotonic effects of atropine modulate spectral oscillation of sympathetic nerve activity. Circulation 1998;38:1394-9.

23. Robbe HWJ, Mulder LJM, Rüddel H, et al. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension 1987;10:538-43.
24. Lucini D, Pagani M, Mela S, et al. Sympathetic restraint of baroreflex control of heart period in normotensive and hypertensive subjects. Clin Sci 1994;86:547-56.
25. Pitzalis MV, Mastropasqua F, Passantino A, et al. Comparison between noninvasive indices of baroreceptor sensitivity and the phenylephrine method in post myocardial infarction patients. Circulation 1998;97:1362-7.
26. Perkiomaki JS, Koistinen MJ, Yli-Mayry, et al. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. J Am Coll Cardiol 1995;26:174-9.
27. Perkiomaki JS, Ukahemio MJ, Pikkujamsa SM, et al. Dispersion of QT interval and autonomic modulation of heart rate in hypertensive men with and without left ventricular hypertrophy. Hypertension 1996;28:16-21.
28. Piccirillo G, Viola E, Nocco M, et al. Autonomic modulation and QT interval dispersion in hypertensive subjects with anxiety. Hypertension 1999;34:242-6.
29. Coumel PL, Maison-Blanche P, Badilini F. Dispersion of ventricular repolarization. Realty? Illusion? Significance. Circulation 1998;97: 2491-3.
30. Singh JP, Musialek P, Sleight P, et al. Effect of Atenolol or Metoprolol on waking hour dynamics of the QT interval in myocardial infarction. Am J Cardiol 1998;81:924-6.
31. Dawidowski TA, Wolf S. The QT interval during reflex cardiovascular adaptation. Circulation 1984;69:22-5.
32. Browne KF, Zipes DP, Heger JJ, et al. Influence of autonomic nervous system on the Q-T interval in man. Am J Cardiol 1982;50:1099-103.
33. Kautzner J, Hartikainen JEK, Heald S, et al. The effects of reflex parasympathetic stimulation on the QT interval and QT dispersion. Am J Cardiol 1997;80:1229-32.
34. Sarma JSM, Singh N, Schoenbaum MP, et al. Circadian and power spectral changes of RR and QT intervals during treatment of patients with angina pectoris with nadolol providing evidence for differential autonomic modulation of heart rate and ventricular repolarization. Am J Cardiol 1994;74:131-6.
35. Cappato R, Alboni P, Codecà L, et al. Direct and autonomic mediated effects of oral quinidine on RR/QT relation after an abrupt increase in heart rate. J Am Coll Cardiol 1993;22:99-105.
36. Piccirillo G, Leonetti Luparini R, Celli V, et al. Carvedilol effects on heart rate and blood pressure variability in subjects with chronic heart failure. Am J Cardiol 2000;86:1392-5.
37. Parati G, Saul JP, Di Rienzo M, et al. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension 1995;25:1276-86.
38. Eckberg DL. Sympathovagal balance. A critical appraisal. Circulation 1997;96:3224-32.
39. Mortara A, La Rovere MT, Signorini MG, et al. Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation. Br Heart J 1994;71:422-30.
40. Guzzetti S, Cogliati C, Turiel M, et al. Sympathetic predominance followed by functional denervation in the progression of chronic heart failure. Eur Heart J 1995;16:1100-7.
41. Van de Borne P, Montano N, Pagani M, et al. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. Circulation 1997;95:1449-54.
42. Piccirillo G, Vetta F, Viola E, et al. Heart rate and blood pressure variability in obese normotensive subjects. Int J Obes 1998;22: 741-50.
43. Piccirillo G, Vetta V, Fimognari FL, et al. Power spectral analysis of heart rate variability in obese subjects: evidence of decreased cardiac sympathetic responsiveness. Int J Obes 1996;20:825-9.
44. Piccirillo G, Viola E, Bucca C, et al. QT interval dispersion and autonomic modulation in subjects with anxiety. J Lab Clin Med 1999; 133:461-8.
45. Piccirillo G, Santagada E, Bucca C, et al. Abnormal passive head-up tilt test in subjects with symptoms of anxiety power spectral analysis study of heart rate and bood pressure. Int J Cardiol 1997; 60:121-31.
46. Piccirillo G, Fimognari FL, Viola E, et al. Age-adjusted normal confidence intervals for heart rate variability in healthy subjects during head-up tilt. Int J Cardiol 1995;50:11724.
47. Colosimo A, Giuliani A, Mancini AM, et al. Estimating a cardiac age by means of heart rate variability. Am J Physiol Soc 1997; 273:H1841-7.
48. Giuliani A, Piccirillo G, Marigliano V, et al. A novel explanation for aging induced changes in heart beat dynamics. Am J Physiol Soc 1998;275:H1455-61.
49. Piccirillo G, Bucca C, Bauco C, et al. Power spectral analysis of heart rate in subjects over a hundred years old. Int J Cardiol 1998; 63:53-61.