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 $-0.45 \pm 0.07$ to $-0.27 \pm 0.07$; $P < .001$), but in controls, it increased the QTVI (from $-1.20 \pm 0.08$ to $-0.78 \pm 0.14$; $P < .001$). In these subjects and controls, oral sildenafil citrate induced a significant reduction in high frequency, expressed in absolute power (subjects with CHF: from $4.04 \pm 0.14$ to $3.43 \pm 0.16$ natural logarithm ms$^2$; $P < .001$; controls: from $5.61 \pm 0.44$ to $4.98 \pm 0.32$ 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 $1.3 \pm 0.12$ to $1.89 \pm 0.16$; $P < .001$) and low frequency expressed in normalized units ($P < .05$).

Sildenafil citrate caused no significant changes in the QT interval or dispersion. 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). 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.\(^1\)\(^2\)

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-
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 ms after sildenafil citrate).

Methods
Study subjects
For this study, we selected patients who had mild CHF (NYHA classification II) 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, 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 and arterial pressure variability.

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 ms after sildenafil citrate).

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-
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.

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.

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.\textsuperscript{20,27} 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.
yielded by the same trained operator. Intraobserver and measurement errors of QTc 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).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects with heart failure (n = 10)</th>
<th>Control subjects (n = 10)</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td>Age (y)</td>
<td>50 ± 2</td>
<td>49 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 1</td>
<td>26 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium (mEq/dL)</td>
<td>141 ± 2</td>
<td>142 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Potassium (mEq/dL)</td>
<td>4.32 ± 0.04</td>
<td>4.41 ± 0.03</td>
<td>NS</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 2</td>
<td>63 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>121 ± 5</td>
<td>130 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>71 ± 2</td>
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<td>326 ± 7</td>
<td>NS</td>
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<tr>
<td>QT interval max (ms)</td>
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<td>QTc interval max (ms)</td>
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<tr>
<td>QT dispersion (ms)</td>
<td>70 ± 5</td>
<td>51 ± 4</td>
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<td>Ejection fraction</td>
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<td>68% ± 5%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>161 ± 4</td>
<td>103 ± 3</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; QTc, QT intervals corrected for heart rate; LVMI, left ventricular mass index; NS, not significant.
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 QTm was significantly longer in patients with CHF than in control subjects (P < .001), QTc values in the 2 study groups overlapped. After oral sildenafil citrate, in patients with CHF, QTm increased (from 388 ± 4 ms to 396 ± 3 ms; P < .05) as did QTc (from 47 ± 2 ms to 55 ± 2 ms; P < .001), whereas in healthy subjects, QTm decreased (from 329 ± 4 ms to 326 ± 4 ms; P < .05) and QTc 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).

No significant changes were found between QT and RR signal coherence after drug and after placebo.
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 QTc measures in the various leads nor QT and QTc 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), whereas the dynamic tests measure temporal changes and therefore mainly depend on altered cardiovascular autonomic control. 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). 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. Further evidence confirming its reliability came in this study from the reduction in $\alpha$ HF, a spectral index of baroreflex sensitivity that correlates reasonably well with baroreflex sensitivity determined with the phenylephrine method. 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, considered a measure of increased sympathetic activity. 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), 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.

Despite the carvedilol-induced $\alpha$ 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 Ikr 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 CHF8 and with the presence of malignant tachycardias.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,9,11 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 pathophysiological conditions involving the autonomic nervous system, including hypertension,15,18,20,28 obesity,42,45 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