Background and Purpose—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited systemic microangiopathy with prevalently cerebral manifestations. Among the causes of death, sudden unexpected death seems to occur in a significant number of CADASIL patients. Because potential causes of sudden unexpected death may include cardiac arrhythmias and myocardial infarction, we evaluated risk factors for life-threatening arrhythmias, such as reduced heart rate variability, sympathetic overactivity and QT interval (QTc) prolongation, in 23 CADASIL patients. The relationship of these changes with brain MRI pattern was also investigated.

Methods—Frequency domain measures of heart rate variability (10 minutes recordings) and QTc interval were recorded in 23 CADASIL patients (17 males, 6 females) and 22 healthy age- and sex-matched control subjects. The following heart rate variability spectral parameters were considered at rest during spontaneous and controlled breathing (Cb): total power, very-low-frequency component, low-frequency component, high-frequency component, low-frequency/high-frequency ratio, and Cb-total power, Cb–very-low-frequency component, Cb–low-frequency component, Cb–high-frequency component, Cb–low-frequency/high-frequency ratio. R-to-R wave and QTc interval were also analyzed. All data were statistically compared between CADASIL and control subjects. Conventional brain MRI was performed in patients with CADASIL and T1-weighted and T2-weighted lesion volumes, and were compared with each spectral component of the tachogram.

Results—During spontaneous and controlled breathing, total power spectrum and all spectral components (very low frequency component, high-frequency component, low-frequency component) of heart rate variability were significantly reduced in CADASIL patients with respect to controls ($P<0.05$). The low-frequency/high-frequency component ratio was significantly higher in CADASIL patients than in controls. No significant correlation between heart rate variability spectral parameters and other variables including total brain T2-weighted and T1-weighted lesion volumes were observed in CADASIL subjects.

Conclusions—We found a statistically significant reduction in all frequency domain parameters of heart rate variability associated with a higher low frequency/high frequency ratio for CADASIL patients with respect to normal subjects. These data are consistent with autonomic derangement and suggests that CADASIL patients may be at risk for life-threatening arrhythmias. This could at least in part explain their higher recurrence of sudden unexpected death and should be taken into account in planning therapy. (Stroke. 2007;38:276-280.)

Key Words: arrhythmias • CADASIL • heart rate • sudden unexpected death

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited systemic microangiopathy, caused by mutations in the Notch3 gene. The main clinical manifestations of CADASIL include recurrent strokes, migraine with aura, cognitive impairment and psychiatric disturbances. The clinical course is highly variable and can lead to premature death. Among the causes of death, sudden unexpected death (SUD) seems to occur in a significant number of CADASIL patients. SUD may be caused by a number of factors, including cardiac arrhythmias and myocardial infarctions. It is well
demonstrated that abnormalities in cardiac autonomic control, as measured by heart rate variability (HRV), are an independent predictor of cardiac arrhythmias and sudden death after myocardial infarction.\(^8\) In particular, reduced HRV has been associated with increased risk of life-threatening arrhythmias caused by autonomic derangement.\(^9\) Stroke\(^10\) has also been shown to produce changes in cardiac autonomic balance and several studies report increased susceptibility to SUD after acute cerebral ischemic events.\(^11\)

Although acute myocardial infarction and electrocardiography-related abnormalities have been reported in CADASIL,\(^12\) specific studies on risk factors that could explain the high incidence of SUD in CADASIL have not been addressed in these patients. By considering this background, we evaluated risk factors for life-threatening arrhythmias, such as reduced HRV, sympathetic overactivity, and QTc prolongation, in 23 CADASIL patients. The relationship of these changes to brain MRI pattern was also investigated.

Materials and Methods

Subjects
Twenty-three CADASIL patients (17 males, 6 females; mean age, 49 years, range, 25 to 69 years) from 15 families were recruited consecutively. Mutations in the Notch3 gene were found in all patients except 1, who had skin biopsy evidence of granuloschismic materials. None of the patients had experienced acute vascular events in the 3 months preceding the study. None had a history of concomitant central or peripheral nervous abnormalities, diabetes, and heart or pulmonary diseases, possibly affecting autonomic nervous system function. None of them received treatment with \(\beta\)-blockers. The following clinical features were recorded: age of onset, age at examination, overall cognitive performance evaluated with convenient access to the information in both data sets while returning to the T-P baseline. When U waves were present, QT was measured to the nadir of the curve between the T and U waves. The QT interval, determined by the longest hand-measured QT interval in any lead, was corrected for heart rate by the Bazett method to yield the QTc. It was calculated by dividing the QT interval by the square root of the R-R interval, excluding intervals shorter than 521 ms and longer than 1111 ms; values outside this range are considered unreliable. The QTc interval was considered abnormal if it was >0.44 seconds.\(^18\)

MRI Examination and Analysis

The MRI examination of the brain for quantitative analysis of T2-weighted (T2-W) and T1-weighted (T1-W) lesion volume (LV) was performed in 21 of 23 CADASIL patients. All these patients were examined using the same MR protocol using a Philips Gyroscan operating at 1.5 T (Philips Medical Systems). A sagittal survey image was used to identify the anterior commissure and posterior commissure. A dual-echo, turbo spin-echo sequence (repetition time/echo time 1/echo time 2=2075/30/90 ms, 256\(\times\)256 matrix, 1 signal average, 250-mm field of view, 50 contiguous 3-mm slices) yielding proton density-weighted and T2-W images was acquired in the transverse plane parallel to the line connecting the anterior commissure and posterior commissure. Subsequently, a T1-W gradient echo sequence (repetition time/echo time=35 ms/10, 256\(\times\)256 matrix, 1 signal average, 250-mm field of view, 50 contiguous 3-mm slices) was acquired.

The quantitation of LV was performed in each patient by a single observer, unaware of subject identity, using a segmentation technique based on user-supervised local thresholding. For the T2-W LV classification, lesion borders were determined primarily on proton density-weighted images, but information from T2-W and T1-W images were also considered as the software used (Jim 3.0, Xinapse System, Leicester, UK) offered the ability to toggle between the proton density and T2-W and T1-W images, providing the operator with convenient access to the information in both data sets while defining lesions. Hypointense white matter T1-W lesions were defined as those lesions with signal intensity between that of the gray matter and the cerebrospinal fluid on T1-weighted scans.\(^19\) In both T2-W and T1-W images, the value of total brain LV was calculated by multiplying lesion area by slice thickness.

Statistical Analysis

The following variables of the tachogram, at rest during spontaneous and controlled breathing (Cb), respectively, were considered for analysis: total power, VLF, LF, HF, LF/HF, RR, and CB-total power, CB-VLF, CB-LF, CB-HF, CB-LF/HF, and CB-RR. The QTc interval was also considered. Each statistical variable (HRV spectral parameters
and QTc interval) was compared between CADASIL patients and normal subjects using either the Student t test (for equal or unequal group variance) or the nonparametric Mann-Whitney test depending, respectively, on normal or not normal variable distribution. Normality was tested on sample data using the Kolmogorov-Smirnov test. Equality of group variances was tested by Levene statistics.

For CADASIL cases, the correlation of the total power variables, VLF, LF, HF, and LF/HF, with brain LV in T1 and T2-W images was also investigated by Pearson statistics. P<0.05, corresponding to a significance level 95%, was chosen for all statistical computing. Statistical analysis was performed with the SPSS computer package.

Results

Demographic and Clinical Characteristics (Table 1)
The age at onset of the first symptom ranged from 17 to 66 years. Four patients were currently asymptomatic (ages 48, 45, 27, and 25 years). The following cardiovascular risk factors were found: hypertension, 4 of 23; hyperhomocystinemia, 5 of 23; hypercholesterolemia, 2 of 23; current smokers, 5 of 23; and ex-smokers, 2 of 23. No diabetes, significant heart or pulmonary abnormalities, or carotid stenosis were found. Four patients were in treatment with angiotensin-converting enzyme-inhibitors during the study, which does not interfere with LF or HF components of the tachogram. At recruitment, stroke/transient ischemic attacks occurred in 17 of 23 patients and dementia (Mini-Mental-Status Examination corrected for age and educational variables <23) in 9 of 23. Only 3 patients were moderately disabled (Rankin=3); most were mildly disabled (15 patients, Rankin=1 to 2) or normal (5 patients, Rankin=0).

Brain MRI Lesion Load
A brain MRI examination for quantitation of visible white matter lesions was performed in 21 of 23 CADASIL patients. In this group of CADASIL patients, the T2-W LV was 65±53 cm³ and the T1-W LV was 24±20 cm³. Visible brain stem lesions were identified in 12 of 21 patients.

HRV Findings
During spontaneous and controlled breathing, total power spectrum and all spectral components of HRV were significantly reduced in CADASIL patients with respect to controls.

Table 1. Phenotypic and Genetic Profile

<table>
<thead>
<tr>
<th>Patient (sex)</th>
<th>Age/Onset</th>
<th>Mutation</th>
<th>TIA/Stroke</th>
<th>Risk Factors</th>
<th>Rankin Score</th>
<th>MRI MRI Brain Stem</th>
<th>T1W L-L (cm³)</th>
<th>T2W L-L (cm³)</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG (m)</td>
<td>60/31</td>
<td>R110C</td>
<td>+</td>
<td>Homocysteine</td>
<td>3</td>
<td>28.1</td>
<td>63.7</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>PN (m)</td>
<td>31/17</td>
<td>R110C</td>
<td>+</td>
<td>Homocysteine</td>
<td>2</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>PPG (m)</td>
<td>25/—</td>
<td>R110C</td>
<td>+</td>
<td>Homocysteine</td>
<td>0</td>
<td>0.0</td>
<td>1.46</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>FR (m)</td>
<td>42/23</td>
<td>C183S</td>
<td>+</td>
<td>Homocysteine</td>
<td>1</td>
<td>35</td>
<td>67.03</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>DPM (f)</td>
<td>55/48</td>
<td>*Fs aa127–158</td>
<td>+</td>
<td>Ex-smoker</td>
<td>1</td>
<td>65.1</td>
<td>122.1</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>TG (m)</td>
<td>69/66</td>
<td>R607C</td>
<td>+</td>
<td>Hypertension</td>
<td>3</td>
<td>44.3</td>
<td>124.28</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>TGB (m)</td>
<td>47/42</td>
<td>R1006C</td>
<td>+</td>
<td>Hypertension</td>
<td>1</td>
<td>4.6</td>
<td>15.03</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>SS (m)</td>
<td>57/48</td>
<td>R607C</td>
<td>+</td>
<td>Homocysteine</td>
<td>2</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>TA (m)</td>
<td>51/40</td>
<td>R1076C</td>
<td>+</td>
<td>Homocysteine</td>
<td>1</td>
<td>19.1</td>
<td>39.9</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>TS (m)</td>
<td>45/38</td>
<td>R1076C</td>
<td>+</td>
<td>Homocysteine</td>
<td>1</td>
<td>1.4</td>
<td>11.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>FD (m)</td>
<td>49/36</td>
<td>R332C</td>
<td>+</td>
<td>Smoker</td>
<td>2</td>
<td>31.4</td>
<td>123.9</td>
<td>+</td>
<td></td>
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<tr>
<td>FF (m)</td>
<td>33/30</td>
<td>R332C</td>
<td>+</td>
<td>Smoker</td>
<td>1</td>
<td>63.8</td>
<td>132.2</td>
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<tr>
<td>GP (f)</td>
<td>64/64</td>
<td>C174Y</td>
<td>+</td>
<td>Homocysteine</td>
<td>1</td>
<td>24.1</td>
<td>65.3</td>
<td>+</td>
<td></td>
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<tr>
<td>MG (f)</td>
<td>59/56</td>
<td>R169C</td>
<td>+</td>
<td>Homocysteine</td>
<td>1</td>
<td>53.0</td>
<td>179.5</td>
<td>+</td>
<td></td>
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<tr>
<td>GV (f)</td>
<td>69/62</td>
<td>R141C</td>
<td>+</td>
<td>Homocysteine</td>
<td>2</td>
<td>32.0</td>
<td>109.9</td>
<td>+</td>
<td></td>
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<tr>
<td>JF (m)</td>
<td>50/44</td>
<td>C511Y</td>
<td>+</td>
<td>Hypertension</td>
<td>3</td>
<td>28.4</td>
<td>122.9</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>SmS (m)</td>
<td>67/63</td>
<td>R1076C</td>
<td>+</td>
<td>Smoker</td>
<td>1</td>
<td>21.1</td>
<td>75.8</td>
<td>+</td>
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<tr>
<td>CP (m)</td>
<td>37/34</td>
<td>O65Y</td>
<td>+</td>
<td>Smoker</td>
<td>1</td>
<td>5.3</td>
<td>18.3</td>
<td>—</td>
<td></td>
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<tr>
<td>SG (f)</td>
<td>54/17</td>
<td>R207C</td>
<td>+</td>
<td>Ex-smoker</td>
<td>1</td>
<td>40.0</td>
<td>69.3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>TM (m)</td>
<td>45/—</td>
<td>R1076C</td>
<td>+</td>
<td>Homocysteine</td>
<td>0</td>
<td>2.5</td>
<td>4.6</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>AA (m)</td>
<td>27/—</td>
<td>R169C</td>
<td>+</td>
<td>Smoker</td>
<td>0</td>
<td>2.2</td>
<td>5.3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>SM (m)</td>
<td>48/—</td>
<td>R207C</td>
<td>+</td>
<td>Homocysteine</td>
<td>0</td>
<td>1.7</td>
<td>13.3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>LG (f)</td>
<td>38/37</td>
<td>C108S</td>
<td>+</td>
<td>Homocysteine</td>
<td>0</td>
<td>5.4</td>
<td>20.9</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*Heterozygous deletion of 5bp (Del 458_462TTGTG) in exon 4 of Notch3 gene; (Stop codon aa159); †skin biopsy evidence of GOMs. f indicates female; m, male; L-L, lesion load; NP, not performed; +/-, yes/no.
In addition, the LF/HF ratio was significantly higher in CADASIL patients than controls. No significant differences in RR or QTc interval (<0.44 seconds) were observed between the 2 groups.

Only variables CbHF and CbLF/HF did not pass the Kolmogorov-Smirnov test of normality (P<0.05). Their differences were therefore evaluated with the Mann-Whitney test. Descriptive statistics, including mean and standard deviation, of all HRV variables showing statistically significant differences (P<0.05) between CADASIL and controls are shown in Table 2. CADASIL patients showed a significant reduction of all HRV spectral parameters during spontaneous and controlled breathing (total power, 1157±1259; VLF, 501±528; LF, 410±530; HF, 200±267; LF/HF, 3.49±3.64; Cb total power, 1461±1007; CbVLF, 823±561; CbLF, 254±176; CbHF, 319±316; CbLF/HF, 1.52±0.98) with respect to control subjects (total power, 3077±1483; VLF, 1388±980; LF, 715±424; HF, 844±554; LF/HF, 1.06±0.56; Cb total power, 4604±3396; CbVLF, 3243±3132; CbLF, 461±379; CbHF, 2438±3026; CbLF/HF, 1.01±2.05). Pearson correlation analysis did not show any significant linear association between HRV spectral parameters and total brain T2-W and T1-W LV.

### Discussion

SUD has been reported to account for 26% of cases of premature mortality in patients with CADASIL.6 To explain such a high incidence of SUD, we investigated risk factors for life-threatening arrhythmias (reduced heart rate variability, sympathetic overactivity, and QTc prolongation) in these patients.

The results of this study showed statistically significant reduction in all HRV frequency-domain parameters associated with a higher LF/HF ratio in CADASIL patients compared with normal subjects. These data are consistent with autonomic derangement and suggest that sympathetic and parasympathetic autonomic cardiovascular regulatory systems may both be impaired in these patients.20 Transient or persistent abnormalities in sympathetic–parasympathetic interactions have been shown to favor arrhythmia in patients with heart disease as well as in the general population.21 In this respect, primary sympathetic hyperactivity and vagal tone suppression may both predispose to life-threatening cardiac arrhythmia and sudden death.22 Suppression of HRV and prevalence of sympathetic tone are considered an independent predictor of increasing cardiovascular mortality after myocardial infarctions.8,23 Various mechanisms, such as changes in geometry of the beating heart that may induce sympathetic overflow, have been postulated to explain the cardiac origin of this autonomic derangement after cardiac events. They may attenuate vagal tone of the sinus and atrioventricular nodes, facilitating sympathetic preponderance and arrhythmokinesia. Furthermore, persistent sympathetic excitation may functionally saturate the sinus node, drastically decreasing its responsiveness to neural input and predisposing to cardiac electrical instability.14

Because coronary vessels are affected by the typical pathological changes in CADASIL, a possible cardiac origin of HRV derangement in these patients should be considered. In line with this, increased occurrence of myocardial infarction and ECG-related abnormalities have been observed in several Dutch CADASIL pedigrees.12 However, these features were not confirmed in a recent case control study aimed to determine the frequency of ECG abnormalities or in our series of patients, in which ECG evidence of myocardial infarction, subclinical ischemia, conduction disturbances, and arrhythmias were excluded.

Alternatively, changes in HRV behavior caused by abnormal cardiovascular autonomic balance may have a central origin.25 Nonfatal cardiovascular abnormalities and cerebrogenic sudden death can complicate various brain diseases. HRV is reported to be reduced in patients with cerebellar and pontine lesions as well as in those with subarachnoid or intracerebral hemorrhage.26 Many studies have also provided strong evidence of depression in HRV and increased risk of SUD in the acute poststroke phase as well as in long-term poststroke course,27 particularly when the insular cortex is involved.28

Emerging data suggest that the insular cortex, amygdala, lateral hypothalamus, and various brain stem nuclei form the main network controlling autonomic nervous system and cardio regulatory functions. The pathways linking this network have not yet been clarified in detail.26

CADASIL is a typical form of subcortical ischemic vasculopathy in which cortical infarctions are usually absent. This suggests that it may be worthwhile considering other, especially subcortical, mechanisms. Although studies on HRV behavior in sporadic forms of subcortical ischemic
vasculopathies are substantially lacking, autonomic nervous system dysfunctions have been demonstrated indirectly. In CADASIL, patients, autonomic system dysfunctions have been postulated, because 24-hour blood pressure monitoring studies showed higher nondipping behavior and a reduced blood pressure profile.

Although we failed to demonstrate significant correlations between global volume of white matter changes and HRV spectral parameters, we were unable to rule out disconnections between cortical–subcortical structures controlling cardiac autonomic balance, secondary to white matter damage. Alternatively, the HRV derangement found in these patients may be caused by discrete subcortical lesions in specific structures controlling the autonomic system, especially within the brain stem. Brain stem lesions common in CADASIL were demonstrated in most of our patients.

In conclusion, our results show that significant reduction of HRV may be evident in CADASIL patients. Although no conclusions can be drawn about the origin of HRV dysfunction, our results strongly suggest that CADASIL patients may be at risk for life-threatening arrhythmias. This could at least partly explain the higher occurrence of SUD in this disease and should be taken into account in planning therapy.

Sources of Funding
Research partly financed by a grant from Region of Toscana to A.F. and by a grant from Fondazione MPS to M.T.D.

Disclosures
None.

References
Cardiac Autonomic Nervous System and Risk of Arrhythmias in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

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Stroke. published online January 11, 2007;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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