Electrocardiogram in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Patients Without Any Clinical Evidence of Coronary Artery Disease
A Case-Control Study

Rodica Cumurciuc, MD; Patrick Henry, MD, PhD; Claire Gobron, MD; Eric Vicaut, MD, PhD; Marie-Germaine Bousser, MD; Hugues Chabrier, MD, PhD; Katayoun Vahedi, MD

Background and Purpose—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited systemic arteriopathy caused by highly stereotyped mutations in NOTCH3. The clinical expression of CADASIL is confined to the central nervous system with characteristic recurrent subcortical infarcts and vascular dementia. However, cases have been reported with associated circulatory small vessel abnormalities in the retina or the myocardium and with myocardial infarction. Classical cardiovascular risk factors may influence such circulatory abnormalities. Thus, we conducted a case control study to determine the frequency of electrical abnormalities on a 12-lead resting ECG in CADASIL patients without classical atherosclerotic risk factors.

Methods—Twenty-three CADASIL patients (mean age±SD; 55.1±11 years) free of any classical cardiovascular risk factors except for hypercholesterolemia were recruited from 1 neurology department and compared with 23 sex- and age-matched healthy controls (mean age±SD; 54.7±9.5 years). A resting supine 12-lead ECG was recorded at inclusion and analyzed later by 2 reviewers. Signs of myocardial infarction or ischemia, conduction, and rhythm disturbances were looked for.

Results—We found no ECG sign evoking myocardial infarction or myocardial ischemia. CADASIL patients had, compared with healthy controls, a significantly higher heart rate and a significantly lower Sokolow index, but these values remained in the normal ranges.

Conclusions—In this case-control study, we found no ECG evidence for myocardial infarction or ischemia, conduction disturbances, or arrhythmias in CADASIL patients compared with healthy controls. (Stroke. 2006;37:1100-1102.)

Key Words: CADASIL • electrocardiography • myocardial infarction • small vessel disease

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small vessel disease caused by highly stereotyped mutations in NOTCH3. This genetic abnormality is responsible for characteristic alterations of vascular smooth muscle cells all along the arterial tree. Despite this, the clinical manifestations of the disease are confined to the central nervous system and include mainly migraine with aura, recurrent subcortical infarcts, mood disturbances, and dementia. Interestingly, silent retinal microvascular circulatory changes have been reported in CADASIL patients as well as high frequency of myocardial infarction in a single series of Dutch patients, suggesting that ischemic heart disease may be part of the manifestations of CADASIL. However, classical cardiovascular risk factors were frequently present in these patients, which may interfere with the results.

Herein we report the results of a case-control study that we conducted to determine the frequency of cardiac abnormalities on a 12-lead resting ECG in CADASIL patients without classical cardiovascular risk factors.

Patients and Methods

Patients
We analyzed clinical and ECG data of 23 CADASIL patients (11 women; mean±SD age; 55.1±11 years; range 39 to 75) who participated in a case-control study of skin microvascular reactivity. Patients were included if they had a characteristic NOTCH3 mutation, had no past history of cardiovascular diseases including coronary heart disease, hypertension or diabetes mellitus, heavy past

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or current tobacco smoking, were not severely demented, and if they
gave their written informed consent. Because it was extremely
difficult to recruit CADASIL patients without hypercholesterolemia
in addition to the other selection criteria, we included those with
treated hypercholesterolemia or low-density lipoprotein (LDL) cholesterol >4.2 mmol/L (n=9). However, LDL cholesterol level
was considered in the statistical analysis by splitting the patients
into 2 subgroups of patients with hypercholesterolemia (if treated
hypercholesterolemia or LDL cholesterol >4.2 mmol/L) or without
hypercholesterolemia.

Controls
CADASIL patients were compared with 23 age- and sex-matched
healthy subjects free of any known cerebrovascular or cardiovascular
diseases, including any previous history of coronary heart disease,
hypertension, diabetes mellitus, hypercholesterolemia, or tobacco
use on the basis of the medical history and a careful medical
examination before inclusion (11 women; mean±SD age; 54.7±9.5
years; range 40 to 74).

A regional ethic committee approved the study (CCPRPB/40-01/
Pitié–Salpêtrière), and all participants signed an informed consent.
Each participant had at inclusion a complete physical and neuro-
logical examination and a fasting blood examination, including serum
total cholesterol, LDL, and high-density lipoprotein (HDL) choles-
terol, triglycerides, and homocysteine. The systolic and diastolic
blood pressures were measured after resting for 10 minutes in a
sitting position.

Electrocardiogram
A resting supine 12-lead ECG was recorded at inclusion in each participant at a paper speed of 25 mm/s and an amplification of
10 mm/mV. The ECGs were later, blindly analyzed by 2 reviewers
including a board-certified cardiologist (P.H.). Prespecified signs of
myocardial infarction or myocardial ischemia, conduction distur-
ances, and arrhythmias were looked for. Pathological Q waves
signifying myocardial infarction were defined as a first negative
deflection exceeding 0.04-s duration and a depth exceeding 33% of
the following R wave, provided the R wave itself was <5 mm in 2
consecutive derivations. Signs suggesting myocardial ischemia were
defined as the presence of ST segment depression >1 mm and
abnormal T-wave inversion in 2 consecutive leads. Conduction and
rhythm analysis were also conducted. Complete right or left bundle
branch block was considered when QRS complex duration exceeded
120 ms. Other conduction disturbances such as atrioventricular block
or incomplete right or left bundle branch block were systematically
assessed as well as cardiac rhythm abnormalities including sinus
bradycardia or tachycardia, extrasystolic beats, atrial fibrillation,
or flutter.

Electrocardiographic signs of left ventricular hypertrophy defined
as the joint occurrence of isolated high R waves in combination with
either ST depression or T-wave morphology change in lateral leads
were recorded. The Sokolow index was calculated as the sum of the
largest R wave of the V5 or V6 derivation plus S wave in V1. Values
≥35 mm were considered as pathological in favor of left ventricular
hypertrophy.

QT-corrected interval was calculated according to Bazett’s for-
mula (QTc=QT divided by √ interval between 2 R waves).

Statistical Analysis
The data analysis was computed using the JMP statistical software
(Abacus Concepts). Descriptive statistics were obtained for the main
clinical features and ECG data in each of the studied groups.
Comparisons between groups were tested using the χ² or Student t
tests. P values <0.05 were considered statistically significant.

Results
The patient and control baseline characteristics including
demographics, risk factors and concomitant medications
are shown in Table 1. No significant differences were
found between CADASIL patients and controls for sex, age,
systolic and diastolic blood pressure, pulse pressure, LDL and
HDL cholesterol, serum homocysteine, and glucose (Table 1). The triglycerides level was significantly higher in CADASIL
patients compared with controls (Table 1).

Nine of 23 CADASIL patients had treated or untreated
hypercholesterolemia and formed the hypercholesterol-
emic group. Hypercholesterolemic patients were signifi-
cantly older than those with normal cholesterol (mean±SD; 61±10 versus 51±10 years; P=0.04). They also had more
dilated diastolic blood pressure (mean±SD; 78±8 versus
71±6 mm Hg; P=0.04).

Among the CADASIL patients, 18 had a previous ischemic
stroke, 9 had migraine with aura, 12 had mood disturbances,
5 were demented according to the Diagnostic and Statistical
Manual of Mental Disorders, Fourth Edition, criteria, and 2
had epileptic seizures. Four of 23 patients were functionally
dependent (modified Rankin score >3 and Barthel index
<75). The use of antiplatelets and statines were more
frequent in CADASIL patients than in controls (Table 1).

The heart rate was significantly higher in CADASIL
patients than in controls (mean±SD; 70±11 bpm versus
56±7 SD bpm; P<0.001; Table 2). The difference remained
significant in each group of CADASIL patients (either
hypercholesterolemic [mean±SD; 69±9 bpm versus 55±6
bpm; P=0.017] or normocholesterolemic [mean±SD;
71±12 bpm versus 56±8 bpm; P=0.0009]). There were no
differences in other conduction parameters such as P-R
interval, P waves, QRS duration, Q-T, and corrected QT
intervals between patients and controls. There was a slight
difference in Sokolow index between the 2 groups, but it
remains in the normal range in both groups (mean±SD;
15.4±6.76 mm in CADASIL patients versus 18.9±5.07 mm
in controls; P=0.04). No subjects, either cases or controls,

<table>
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<th>TABLE 1. Patient Demographics and Risk Factors</th>
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<td>Age±SD, y</td>
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<td>Use of antiplatelet agents, n (%)</td>
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<td>Hypercholesterolemia, n (%)</td>
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<td>Use of statines, n (%)</td>
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Values are mean±SD.
had ECG signs of myocardial infarction. Incomplete right bundle branch block was found in 6 patients and in 5 controls, whereas incomplete left bundle branch block was found in 3 patients and in 1 control (Table 2).

Discussion
In this case-control study, 12-lead resting ECG parameters did not differ between CADASIL patients and their age- and sex-matched healthy controls except for a significantly higher heart rate and a significantly lower Sokolow index in CADASIL patients. However, the values of the heart rate in both patients and controls correspond to those in a cohort of CADASIL patients.12

Further prospective longitudinal cohort studies will be needed to better understand the issue of the role of classical vascular risk factors in the ischemic consequences of NOTCH3 mutations both in the cerebral tissue and the myocardium.

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