Chagasic Cardiomyopathy Is Independently Associated With Ischemic Stroke in Chagas Disease

Francisco Javier Carod-Artal, MD, PhD; Antonio Pedro Vargas, MD; Thomas Anthony Horan, MD, FRCSC; Luiz Guillerme Nadal Nunes, MSc

Background and Purpose—Chagasic cardiomyopathy is independently associated with ischemic stroke in Chagas disease. American trypanosomiasis, Chagas disease (CD), is a major public health problem in South America. We sought to evaluate prevalence of vascular risk factors for stroke in patients with stroke caused by CD.

Methods—Ninety-four consecutive CD stroke patients and 150 consecutive nonchagasic stroke patients were studied. CD was confirmed when both immunofluorescence and hemagglutination serology were positive. Data collected included age, sex, vascular risk factors, diagnostic stroke subtype (TOAST classification), and echocardiography findings. Fasting plasma levels of protein C, protein S, antithrombin III, homocysteine, activated protein C resistance, IgG anticardiolipin antibodies, lupus anticoagulant, and genetic tests for the factor V Leiden and the C677T methylene tetrahydrofolate reductase gene mutation were determined.

Results—CD patients had a mean age of 56.31 years compared with 61.59 years for non-CD stroke patients (P=0.0002). Cardioembolism occurred in 56.38% of CD stroke patients compared with 9.33% in controls (P=0.000), whereas atherothrombotic strokes occurred in 8.51% of CD strokes versus 20% in controls (P=0.016), and small-vessel stroke in 9.57% of CD stroke patients versus 34.67% in controls (P=0.000). Apical aneurysm (37.23% versus 0.67%; OR, 88.39), left ventricular dilatation (23.4% versus 5.33%; OR, 5.42), mural thrombus (11.7 versus 2%; OR, 6.49) and abnormal electrocardiography (ECG) (66% versus 23.3%; OR, 2.87) were significantly higher in the group of chagasic stroke patients. No statistical differences were observed in thrombophilia between both groups. The significant variables that predicted CD stroke patients on a stepwise logistical regression model were apical aneurysm, cardiac insufficiency, ECG arrhythmia, female gender, and hypertension.

Conclusions—Chagasic cardiomyopathy is independently associated with ischemic stroke, whereas hypercoagulable states do not appear to be major contributors to the excess stroke risk seen in patients with CD. (Stroke. 2005;36:965-970.)

Key Words: aneurysm • Chagas disease • stroke • thrombophilia

A merican trypanosomiasis, Chagas disease (CD), is a major public health problem and a major cause of cardiomyopathy in South America.1 It is an emerging medical problem in the United States. CD is an acute or chronic infection caused by the flagellate protozoan Trypanosoma cruzi (T. cruzi), transmitted by bugs of the family Reduviidae, subfamily Triatominae.2,3

T. cruzi infection is widespread from southern Chile, Argentina, and Brazil, throughout South and Central America, extending to southern Texas. Geographic strain differences result in distinct tissue tropism, virulence, and clinical manifestations.4 Up to 8% of the population in South America is seropositive, but only 10% to 30% of these will have symptomatic disease.1 The emigration of several million people from T. cruzi-endemic countries to the United States has raised concerns regarding a possible increase in cases of Chagas heart disease, as well as an increased risk of transfusion-transmitted T. cruzi.5,6

Irreversible damage to the heart can appear 10 to 20 years after chagasic infection.7 Heart-related diseases in CD includes cardiomegaly, dysrhythmia, heart failure, and sudden cardiac death.8 Pathologic studies of the brain have shown cerebral infarction in 9.4% and 26.3%9,10 of patients with the chronic form of CD. Previous studies described a predominant cardioembolic cause of ischemic stroke in CD.11,12 The influence of other vascular risk factors on the appearance of ischemic stroke is not fully defined.

The aim of this study is to: (1) evaluate vascular risk factors of ischemic stroke in CD, compared with a control nonchagasic stroke patients; and (2) analyze the prevalence of a thrombophilic state in patients with stroke caused by CD. Associated vascular risk factors were analyzed to identify the variables that could predict higher risk of stroke in both the chronic and latent forms of CD.

Materials and Methods

All patients consecutively admitted to the Department of Neurology at Sarah hospital, in Brasilia DF, Brazil, during the 18 months from...
January 2003 through June 2004 with the clinical diagnose of ischemic stroke and a positive Chagas serology were included in the study. A prospective case-control analysis design was developed. Collected data on vascular risk factors and thrombophilia were compared with a control group of 150 nonchagasic stroke patients consecutively admitted at hospital between April 2003 and September 2003. During the study (January 2003 to June 2004), all patients with ischemic stroke admitted to hospital received a serologic test for CD.

Data were collected on vascular risk factors, location of brain lesion, diagnostic stroke subtype, electrocardiography, and echocardiography findings. Demographic variables included age, sex, previous history of stroke, and vascular risk factors. All chagasic and nonchagasic stroke patients underwent a diagnostic protocol for stroke including ECG, chest radiograph, carotid echo Doppler, transcranial Doppler, bubble test transthoracic Doppler, transesophageal echocardiogram, and a brain computerized tomography. Brain MRI was used when necessary in 23% patients. Thrombophilia studies were also determined in all case and control subjects. These included fasting plasma levels of protein C, protein S, antithrombin III, levels of homocysteine, activated protein C resistance, IgG anticardiolipin antibodies, and lupus anticoagulant. Genetic tests for the factor V Leiden and the C677T methylene tetrahydrofolate reductase gene mutation were obtained in all subjects. Additional biochemical studies included Veneral Disease Research Laboratory serology and antinuclear antibodies. CD immunofluorescence and hemagglutination were positive. Diagnosis of stroke was confirmed by clinical and/or radiological findings. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria was used to define stroke subtype: large-artery atherosclerosis, small-vessel occlusion, cardioembolism, other determined causes, and undetermined causes. For the purpose of the study, we considered only ischemic strokes, as defined by TOAST criteria, in patients who had both a positive Chagas serology with suspected latent CD or chronic symptomatic cardiac CD. Patients with cerebral hemorrhage were excluded from the study. Chagasic patients were divided into 2 groups: patients with previous history of symptomatic chagasic cardiomyopathy and patients with chronic asymptomatic forms of CD to establish differences in the prevalence of vascular risk factors in both groups.

The topographical classification of stroke followed the Oxfordshire classification. Total anterior circulation infarctions included large strokes (but not bilateral carotid occlusions) in the anterior circulation territory. Partial anterior circulation infarctions included small strokes (not lacunae) in the same territory. Lacunar syndromes and posterior circulation infarctions were also studied.

Statistical analysis was performed using SPSS. Risk factor comparison for subjects with and without CD was performed using t tests for continuous variables and \( \chi^2 \) test and Fisher exact test for categorical variables. A 2-tailed \( P < 0.05 \) was considered statistically significant. Odds ratio (OR) and 95% limit confidence interval (CI) were performed. A forward logistic regression analysis was done for significant variables observed on univariate analysis.

**Results**

During the study, 478 patients (251 females and 227 males; mean age, 57 years, SD 15.8 years) were admitted with the diagnosis of ischemic stroke. Of these stroke patients, 94 (19.66%) had positive CD serology (55 women [58.51%] and 39 men [41.49%]). Control group consisted of 150 nonchagasic stroke patients, 58.6% males and 41.1% females. Chagasic stroke patients were younger than the control group (mean age, 56.31 years versus 61.59 years; \( P = 0.002 \)) and had a preponderance of females (58.51 versus 41.43; \( P = 0.009 \)). Mean age in CD stroke patients was not statistically different between sexes (CD men 53.74 versus CD women 58.15).

Table 1 describes the demographic characteristics of stroke patients, and their associated vascular risk factors.
85.1% of CD stroke patients had at least 1 defined vascular risk factor (94% in control group; \( P = 0.021 \)), with the most frequent being hypertension (61.7%), followed by congestive heart failure (27.6%) and hyperlipidemia (19.1%). A past history of stroke was identified in 22.3% of CD stroke patients and 20% of controls.

Vascular risk factors in stroke patients showed a significantly higher frequency of hypertension (88% versus 61.7%; \( P = 0.0004 \)) and hypercholesterolemia (19.1% versus 33.3%; \( P = 0.016 \)) in the control group. Whereas congestive heart failure (27.6% versus 2.6%; \( P = 0.000 \)) and atrial fibrillation (13.8% versus 5.3%; \( P = 0.021 \)) were significantly more frequent in the Chagasic stroke group.

Table 2 describes the ECG and echocardiogram findings in stroke patients. 67% of CD patients and 23.3% of control group had an abnormal ECG (\( P = 0.000 \)). Ten chagasic patients had previous pacemaker insertion, whereas there was just one nonchagasic stroke patient (\( P = 0.000 \)). All stroke patients underwent an echocardiogram, either transthoracic (58.5% versus 71%) or transthoracic and transesophageal ones (41.49% versus 28.86%). A normal echocardiogram was obtained in only 34% of CD patients. Left ventricular (LV) diastolic dysfunction was the most frequent echocardiography finding in CD stroke patients (48.94% versus 58.66%).

We found an apical aneurysm in 35 CD stroke patients. Apical aneurysm appeared in 19 patients with cardiac symptoms of chagasic cardiomyopathy and in 16 patients with chronic undetermined form of CD. 23 CD stroke patients with apical aneurysm had an arrhythmia on ECG, whereas 12 patients with apical aneurysm had a normal ECG. No significant difference in CD patients with or without apical aneurysm by age (mean age, 53.53 years with versus 58 years without). Gender of CD patients did not show significant difference in frequency of apical aneurysm (19 females [54.3%] versus 16 males [45.7%]).

Table 3 describes characteristics of the strokes experienced by our study population. According to TOAST criteria, we defined 56.38% of CD stroke patients as cardioembolism (with a clear source of embolus), 8.51% as atherothrombotic stroke, 9.57% as small-vessel stroke, and 25.53% as stroke of undetermined cause. Cardioembolism (56.38% versus 9.33%; \( P = 0.000 \)) was significantly more frequent in the CD stroke group, whereas large-artery atherosclerosis (8.51% versus 20%; \( P = 0.031 \)) and small-vessel occlusion (9.57% versus 34.66%; \( P = 0.000 \)) were significantly more frequent in nonchagasic stroke group.

The most frequent stroke syndromes in CD patients and stroke control group were, respectively, partial anterior circulation infarctions (48.94% versus 32%; \( P = 0.008 \)) followed

### Table 2. Electrocardiographic and Echocardiographic Findings of the Stroke Population

<table>
<thead>
<tr>
<th></th>
<th>Chagasic Stroke Group, ( n = 94 )</th>
<th>Control Group, ( n = 150 )</th>
<th>( P, \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrocardiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>63 (67)</td>
<td>35 (23.33)</td>
<td>0.000</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>33 (35.1)</td>
<td>15 (10)</td>
<td>0.000</td>
</tr>
<tr>
<td>Left Hiss fascicular block</td>
<td>16 (17)</td>
<td>9 (6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14 (14.89)</td>
<td>7 (4.667)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pacemaker rhythm</td>
<td>10 (9.4)</td>
<td>1 (0.667)</td>
<td>0.000, Fisher</td>
</tr>
</tbody>
</table>

| **Echocardiographic findings** |                                    |                                 |                |
| Apical aneurysm         | 35 (37.23)                         | 1 (0.667)                      | 88.39 (12.53–1774) |
| Mural thrombus          | 11 (11.7)                          | 3 (2)                          | 6.49 (1.62–30.26) |
| LV diastolic dysfunction | 46 (48.94)                         | 88 (58.667)                    | NS             |
| LV systolic dysfunction | 15 (15.96)                         | 3 (2)                          | 9.3 (2.43–41.78) |
| Right-left shunt        | 11 (11.7)                          | 16 (10.667)                    | NS             |
| Pulmonary HTA           | 6 (6.38)                           | 1 (0.667)                      | 10.16 (1.19–227.61) |
| LV hypocinesia          | 3 (3.19)                           | 1 (0.667)                      | NS             |
| Atrial septum aneurysm  | 1 (1.06)                           | 4 (2.667)                      | NS             |
| Interarterial communication | 2 (2.13)                        | 1 (0.667)                      | NS             |
| Aortic plaques          | 3 (3.19)                           | 4 (2.667)                      | NS             |
| Mitral valve prolapse   | 0 (0)                              | 1 (0.667)                      | NS             |
| Mitral prosthesis       | 1 (1.06)                           | 1 (0.667)                      | NS             |
| Valvuloplasty           | 4 (4.25)                           | 5 (3.33)                       | NS             |
| Left ventricle hypertrophy | 4 (4.25)                         | 26 (17.33)                     | 0.21 (0.06–0.67) |

LV indicates left ventricular; HTA, hypertension.
by total anterior circulation infarctions (36.17% versus 28%; nonsignificant) and posterior circulation infarctions (5.32% versus 11.22%; nonsignificant). Only 9.57% CD stroke patients presented with lacunar syndromes, whereas 28.66% of stroke controls did (P < 0.000). Middle cerebral artery was the most frequently affected vascular territory in CD stroke patients (87.23% versus 63%; P < 0.000%), whereas internal capsule infarctions (4.25% versus 12%; P = 0.04) were more frequent in the control group. A right–left shunt on bubble test transcranial Doppler was observed in 20.21% of chagasic stroke patients and 20.67% of nonchagasic stroke patients. Vascular epilepsy appeared during follow-up in 18.08% of chagasic patients and in 10.66% of nonchagasic stroke patients (P = 0.09).

Table 4 shows prevalence of thrombophilia states in chagasic and nonchagasic stroke patients. We did not observe differences in prevalence of thrombophilia states, such as protein C or S deficiency, antithrombin III deficiency, APR resistance, factor V Leyden mutation, lupus anticoagulant, or anticardiolipin antibodies. Sickle cell anemia (6.38% versus 1.33%; Fisher exact test 0.039) was significantly more frequent in CD patients. Hyperhomocysteinemia was significantly more frequent in nonchagasic stroke patients (55.33% versus 36.17%; P = 0.004). Nonchagasic stroke patients had significantly higher levels of homocysteine (mean homocysteine: 17.43% versus 13.25%; 2-tail Student t 0.000). Distribution of mutation of the gene of the methylene tetrahydrofolate reductase gene mutation was similar in both groups of

### TABLE 3. Stroke Characteristics in Chagasic and Nonchagasic Patients

<table>
<thead>
<tr>
<th>Etiology of Stroke, TOAST</th>
<th>Chagasic Stroke Group, n=94</th>
<th>Control Group, n=150</th>
<th>P, χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolism</td>
<td>53 (56.38%)</td>
<td>14 (9.33%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>8 (8.51%)</td>
<td>30 (20%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Small-vessel occlusion</td>
<td>9 (9.57%)</td>
<td>52 (34.66%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Undetermined cause</td>
<td>24 (25.53%)</td>
<td>53 (35.33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other causes</td>
<td>0 (0%)</td>
<td>1 (0.67%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke Syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACI</td>
<td>46 (48.94%)</td>
<td>48 (32%)</td>
<td>0.008</td>
</tr>
<tr>
<td>TACI</td>
<td>34 (36.17%)</td>
<td>42 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>LACI</td>
<td>9 (9.57%)</td>
<td>43 (28.66%)</td>
<td>0.000</td>
</tr>
<tr>
<td>POCI</td>
<td>5 (5.32%)</td>
<td>17 (11.22%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular Territories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>82 (87.23%)</td>
<td>110 (63%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Internal capsula</td>
<td>4 (4.25%)</td>
<td>18 (12%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Semiovale center</td>
<td>3 (3.19%)</td>
<td>0 (0)</td>
<td>0.056, Fisher</td>
</tr>
<tr>
<td>PCA</td>
<td>1 (1.06%)</td>
<td>4 (2.66%)</td>
<td>NS</td>
</tr>
<tr>
<td>ACA</td>
<td>1 (1.06%)</td>
<td>4 (2.66%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pons</td>
<td>1 (1.06%)</td>
<td>8 (5.33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>2 (2.12%)</td>
<td>6 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid Findings on Echo-doppler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis &gt;70%</td>
<td>1 (1.06%)</td>
<td>5 (3.33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>6 (6.38%)</td>
<td>18 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>Plaques</td>
<td>31 (32.98%)</td>
<td>63 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Normal</td>
<td>56 (59.57%)</td>
<td>86 (57.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same Territory</td>
<td>5 (5.32%)</td>
<td>14 (9.396)</td>
<td>NS</td>
</tr>
<tr>
<td>Different Territory</td>
<td>17 (18.08%)</td>
<td>17 (11.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular Epilepsy</td>
<td>17 (18.08%)</td>
<td>16 (10.667)</td>
<td>NS</td>
</tr>
<tr>
<td>Right-left Shunt on TCD</td>
<td>19 (20.21%)</td>
<td>31 (20.667)</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet Drugs</td>
<td>65 (69.15%)</td>
<td>140 (93.33%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>29 (30.85%)</td>
<td>10 (6.66)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; LACI, lacunar infarction; MCA, middle cerebral artery; PACI, partial anterior circulation infarction; PCA, posterior cerebral artery; POCI, posterior circulation infarction; TACI, total anterior circulation infarction.
stroke patients. Secondary prevention with oral anticoagu-
lants was significantly more prevalent at hospitalization in the
group of chagasic stroke patients (30.85 versus 6.66; 
$P < 0.000$).

In a subanalysis, we placed chagasic patients in 2 groups. 
Group A consisted of any CD stroke patient with previous 
symptoms of chagasic cardiopathy, including heart failure, 
cardiomyopathy, atrial fibrillation, or use of pacemaker; 
group B consisted of latent CD or chronic CD without clinical 
symptoms of cardiopathy but included persons with asymptomatic 
right bundle block. The distribution of the following variables 
and vascular risk factors was similar in both groups: age, 
history of previous stroke, diabetes, hypertension, smoking, 
dyslipidemia, and apical aneurysm. The cardioembolism 
subtype of stroke predominated in group A, whereas the 
undetermined etiology and small-vessel occlusion subtypes 
were significantly more frequent in group B. Prevalence of 
thrombophilia was similar in both groups.

Significant variables on univariate analysis (stroke age, 
sex, vascular risk factors, hypertension, smoking, cardiac 
arrhythmia, dyslipidemia, arrhythmia on ECG, apical aneu-
rysm, mural thrombus, LV dysfunction, dilated cardiomyop-
athy, cardiac insufficiency) were further analyzed in a step-
wise forward logistic regression model. Final logistic model 
was well-adjusted to sample observations (Hosmer–Leme-
show goodness of fit test, $P = 0.772$). The statistically signif-
icient variables in CD stroke in this final model were apical 
aneurysm (OR, 86; CI, 10.5 to 705.5), ECG arrhythmia (OR, 
5.6; CI, 2.7 to 11.8), cardiac insufficiency (OR, 8.6; CI, 2.4 to 
30.5), female gender (OR, 2.2; CI, 1.1 to 4.6), and hyperten-
sion (OR, 0.2; CI, 0.1 to 0.4).

Statistical analysis of prevalence of vascular risk factors 
and thrombophilia was done within the subgroup of nonhy-
pertensive chagasic patients. In the stepwise regression anal-
ysis model, significant variables associated with CD stroke in 
nonhypertensive CD stroke patients were apical aneurysm, 
LV dysfunction, dysrhythmia on ECG, and female sex.

**Discussion**

Chronic cardiomyopathy is the most common clinical form of 
CD. $^{16}$ The apical region of the LV is a critical region in the 
chagasic heart, where aneurysm, thrombus, or both occur 
with high frequency. In a retrospective study of 1345 CD 
autopsy reports, $^{17}$ frequency of a cardiac thrombus was 36% 
in severe heart disease patients and 15% in the cases of 
sudden death. The frequency of apical aneurysm in CD 
patients studied by echocardiography have been reported to 
be in the range of 20% to 35%. $^{18}$ A previous report of cerebral 
embolism and stroke observed a rate of 12.7% of apical 
lesions of the LV. $^{19}$ In our study, prevalence of apical 
aneurysm in CD stroke patients of 37% is considerably higher 
than controls and occurred in 44% of nonhypertensive CD 
stroke patients. A bias selection about prevalence of apical 
aneurysm in our group of CD stroke patients cannot be ruled 
out, because this is a hospital study and not a population study 
CD stroke seems to be lower in patients with mild to 
moderate heart failure. $^{20}$ A survival advantage for women 
presenting with heart failure has been reported in the Fra-
mingham heart study. If this assumption is true as well in CD 
patients, chagasic women affected by a CD cardiomyopathy 
might be expected to have a longer survival. Thus, they 
would also be at greater risk of embolic stroke. This hypo-
thesis may explain the higher frequency of CD stroke that we 
observed in chagasic women. Other authors have described 
the same phenomenon. $^{12,21}$
Clinical implications derived from this study suggest that South American stroke patients should perform an indirect immunofluorescence test to rule out CD. We did not find a higher frequency of thrombophilia in chagasic patients. Thus, no special attention to thrombophilia studies is recommended in this population. We demonstrated that at least 56.3% of chagasic strokes are caused by cardioembolism and 25.53% are of undetermined cause. We therefore encourage the use of transesophageal echocardiography in all patients with chagasic stroke. The appearance of apical aneurysm demands consideration of the institution of oral anticoagulation in such patients.

Although in the chronic chagasic form the appearance of LV dysfunction and apical aneurysm seem to represent a clear embolic source, it is not as clear why asymptomatic patients experience stroke. Prevalence of undetermined form of stroke seems to be similar in chagasic and nonchagasic stroke patients. However, we recognized the possibility that chagasic patients with no LV dysfunction might have experienced a stroke because of underlying systemic arterial hypertension. Some experimental works in the acute phase of experimental infection by T. cruzi have showed aortic endothelial cell changes. The relevance of endothelial dysfunction of the microcirculation as a potential cause of stroke in chagasic patients with no LV systolic dysfunction remains unknown.

In conclusion, apical aneurysm, cardiac insufficiency, and ECG arrhythmia seem to be important risk factors in the genesis of ischemic stroke related to CD, whereas hypercoagulable states are unlikely to be major contributors to the excess stroke risk seen in CD.

References

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