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Cerebral infarct topography of atrial fibrillation and Chagas disease

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ABSTRACT

Background: Chagas disease (CD) and ischemic stroke (IS) have a significant but poorly understood correlation. There is paucity of evidence regarding secondary prophylaxis of IS and etiological causes.
Objectives: To compare arterial stroke topography and the respective morbidities and mortality in patients with CD of undetermined and cardioembolic etiologies and with cardioembolic IS (atrial fibrillation [AF]).
Methods: We compared vascular topography and outcomes using data obtained from the electronic medical records of all patients with IS with either CD (with cardioembolic or undetermined etiology) or AF, admitted to SARAH Hospital Brasilia between 2009 and 2013.
Results: A total of 115 patients were investigated: 49 involving AF, 23 involving CD of unclear etiology, and 43 involving CD of cardioembolic etiology. Middle cerebral artery stroke was predominant in all groups, although more frequent in patients with CD of undetermined etiology. No significant difference was found in the arterial territories. Hemodynamic stroke was predominant among CD patients who experienced cardioembolic events. AF patients had worse modified Rankin scale scores upon admission and a higher mortality rate than CD patients in both categories.
Conclusions: Stroke topography is not useful in determining the etiological diagnosis. Patients with AF and IS are more likely to have worse outcomes than are those with CD and IS. The autonomic nervous system could be affected in patients with CD.

1. Introduction

Chagas disease (CD) is a vector borne disease with multi-organ involvement and is endemic in regions such as Asia and South America [1–3]. A correlation and causal association was observed between CD and ischemic stroke (IS) [2–4]. Several studies that used different methodologies have addressed this association; however, gaps in knowledge were still observed [5–10].

Cardiac involvement comprises most etiological causes of IS in these populations; however, several patients were still diagnosed with an unknown cause even after an extensive etiologic investigation [11–14]. In our series of patients with CD and stroke, 45% of the cerebral infarcts were of undetermined etiology [4]. Some attempts were made to determine the cause of stroke in patients with CD. For example, the evaluation of cardiac function using magnetic resonance imaging (MRI) may reveal ventricular changes not easily observed on echocardiography [15].

Comparing cerebrovascular lesion topography in patients with CD and stroke of undetermined causes with that of patients with different types of cardioembolic stroke (e.g., atrial fibrillation [AF] and cardiopathy secondary to CD) may help identify an infarct pattern that could be useful in defining the etiological diagnosis. For instance, similarity in the characteristics of ischemic lesions in patients with CD and those with undetermined etiology to those of patients with CD and cardioembolic stroke and patients with IS and AF might indicate that occult AF or alternative causes of cardiac thrombi could play a role in patients with CD and stroke of unknown cause. Conversely, a difference in the pattern of infarcts and etiology between CD patients (non cardioembolic etiology) and those with cardioembolic stroke may be an indication that other mechanisms, such as inflammation and atherosclerosis, are risk factors for IS in these patients [9].

Furthermore, it has been argued that different cardiopathies may be

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associated with a diverse stroke size and severity [16]. A possible explanation is that some cardiopathies may lead to larger thrombi than others. Therefore, it would be interesting to compare lesions secondary to cardiopathies due to AF and CD.

The present study aimed to compare the vascular topography of cerebral lesions in patients with CD and stroke of an undetermined cause with that of patients with cardioembolic causes, involving both CD and cardioembolic mechanisms, and of patients with IS and AF. Moreover, the lesion pattern in patients with IS and AF and in those with IS and CD due to cardiac causes was evaluated, and the baseline characteristics, stroke outcome, and recurrence in these groups were assessed.

2. Methods

This was a retrospective case-control study that used data obtained from the electronic medical records of the patient cohort who presented with IS and concomitant CD or IS with AF but without CD. All patients who were admitted to the neurological rehabilitation service at SARAH Hospital Brasília and were diagnosed between January 2009 and December 2013 were included in the analysis, and the patients were followed-up until 2017. If a patient missed the last consultation, one of the researchers makes contact via telephone to determine recurrence and/or mortality. A new medical consultation using neuroimaging in either our institution or another health center/hospital was required to confirm recurrence. The ethics committee of the SARAH Network of Hospitals approved our study protocol, and the requirement for patient consent was waived by the committee.

For the CD group, we included the cohort in our previous research [4]. Moreover, 59 patients with AF and IS who were consecutively admitted to our service during the same time period were selected from the database. The patients were not matched for age and sex.

The inclusion criteria were as follows: patients evaluated during the study period at the SARAH Hospital Brasília, those with a diagnosis of CD for the cases and AF for the controls, and those with confirmed IS on neuroimaging (computed tomography [CT] scan or MRI). CD was confirmed via two different serological tests (enzyme-linked immunosorbent and hemagglutination assay). AF was diagnosed by the presence of arrhythmia on an electrocardiogram (ECG) or Holter monitoring. The exclusion criteria were as follows: those with conflicting serological results for CD, those who lack a confirmed diagnosis of IS, and those aged < 18 years. Patients with AF and another potential etiological cause for IS (i.e., evidence of coexisting stroke) were also excluded. Therefore, all patients in the AF group exhibited a cardioembolic etiology for stroke.

Data recorded included the following vascular risk factors: age; dyslipidemia as defined by the elevation of total cholesterol level > 190 mg/dL and/or low-density lipoprotein level > 100 mg/dL and triglyceride levels > 150 mg/dL; hypertension; obesity; diabetes mellitus; history of smoking up to 1 year prior to the diagnosis of IS; and alcoholism according to the World Health Association criteria defined as continuous or periodic: impaired control during drinking, alcohol preoccupation, use of alcohol despite adverse consequences, distortions in thinking, and most notably denial. All these variables are routinely obtained during admission of patients in the rehabilitation program. We also evaluated the recurrence of IS, presence of hemorrhagic transformation, and history of hemorrhagic stroke. Cognitive decline was measured using the criteria described elsewhere [17].

Etiological investigation of patients included a battery of tests, such as transthoracic echocardiography (TTE), chest radiograph, ECG, neuroimaging (MRI or CT scan), non-invasive intracranial vascular studies (magnetic resonance angiography, CT angiography, and transcranial Doppler), transesophageal echocardiography (TEE), and 24-h Holter monitoring, which were performed per the discretion of the attending neurologist responsible for the patient's condition. The investigation of thrombophilia was performed in patients with negative results for the initial investigation and cardiological examinations (including TEE and 24-h Holter monitoring). However, the result was negative in all patients tested. In cases of stroke recurrence, new etiological investigation, including all of the above-mentioned steps, was repeated in the undetermined cases.

Stroke etiology was classified by two independent neurologists using a computerized system (available at https://ccs.mgh.harvard.edu/ccs_title.php) based on the Stop Stroke Study Causative Classification System Trial of ORG 10172 in Acute Stroke Treatment [18,19]. Disagreements between investigators were resolved through discussion and consensus. Undetermined cardioembolic etiology was classified based on this classification system. The cases were considered of undetermined etiology only after extensive negative investigation results (including those for all above-mentioned tests and hypercoagulable condition screenings).

To determine the modified Rankin scale (mRS) score, the data of the patients obtained upon admission were used in the rehabilitation program.

For vascular topographical determination, two neurologists independently analyzed the neuroimaging results and determined the site of the vascular lesion. Both neurologists were blinded to the stroke etiology and CD serology results when evaluating the images. We classified the lesions in one of the following 10 groups based on classical stroke templates [20]: (1) superior middle cerebral artery (MCA) territory, (2) inferior MCA territory, (3) complete MCA territory, (4) anterior cerebral artery territory, (5) posterior cerebral artery territory, (6) vertebrobasilar arteries territory, (7) watershed territory, (8) more than one territory (non-lacunar) at once, (9) deep middle cerebral artery (comma shaped), and (10) lacunar stroke.

2.1. Statistical analysis

All statistical analyses were performed using the IBM® Statistical Package for the Social Sciences software version 23. Continuous variables were expressed as mean with a standard deviation for normally distributed variables and as median and interquartile ranges for non-normally distributed variables. The kappa coefficient was used as a measure of agreement/concordance between the two neurologists who determined the etiological and vascular topography diagnosis.

Comparison of the vascular topography and mRs between the cases (IS and CD with undetermined and cardioembolic etiologies) and control patients (IS and AF) was performed using the chi-square test. For mortality and recurrence, we used the Kaplan–Meier method and the log-rank test. The analysis of variance test and Kolmogorov–Smirnov test (test of normality) were used for continuous variables. *P*-values ≤.05 were considered significant.

3. Results

A total of 115 patients from the SARAH Network database were included in the analysis. Of these, 49 had AF without CD as the cause of IS (AF without CD group), and 66 had CD, of which 23 presented with an undetermined etiology (CD-undetermined group) and 43 with a cardioembolic etiology (CD-cardio group). The last medical evaluation of all patients in the AF group was in 2017. Among the CD populations, 20% missed the last medical appointment, and assessment of outcomes, such as mortality and recurrence, were conducted via telephone, in all required cases. The kappa coefficient of agreement for etiological classification between the two neurologists was 0.909. TTE and ECG were performed in all patients in the three groups; CT scan, in 64%; MRI, in 26%; and both CT scan and MRI, in 10% of patients. Holter monitoring was performed in 20% of the participants (55% of patients in the AF-no CD group), and non-invasive intracranial studies were performed in 30% of the patients. Among the patients with CD of cardioembolic etiology, only two had documented AF and were included in the CD-cardio group. Cardiac changes in the CD-cardio group included

Table 1
Baseline characteristics and outcome.

	Cardioembolic etiology UE			P-value[a]	P-value[b]
	AF-no CD (*n* = 49)	CD-cardio (*n* = 43)	CD-undetermined (n = 23)		
Mean age ± SD	63.3 (± 14.3)	58.9 (± 9.6)	57.3 (± 13.1)	0.086	0.195
Sex, n (%)					
Male	27 (55%)	16 (37%)	9 (39%)	0.086	0.512
Female	22 (45%)	27 (63%)	14 (61%)		
SAH, n (%)	39 (80%)	32 (74%)	14 (61%)	0.555	0.111
DM, n (%)	10 (20%)	4 (9%)	3 (13%)	0.139	0.793
Dyslipidemia, n (%)	23 (47%)	23 (56%)	13 (56%)	0.531	0.576
Smoking, n (%)	19 (39%)	20 (46%)	11 (48%)	0.454	0.638
Alcoholism, n (%)	11 (22%)	17 (39%)	10 (43%)	0.076	0.321
Obesity, n (%)	1 (2%)	1 (2%)	4 (17%)	0.926	0.003
Epilepsy, n (%)	6 (12%)	12 (28%)	4 (17%)	0.059	0.813
Antiplatelet use, n (%)	23 (47%)	23 (53%)	23 (100%)	0.531	0.000
Statin use, n (%)	40 (82%)	22 (51%)	18 (78%)	0.002	0.311
Anticoagulant use, n (%)	26 (53%)	20 (47%)	0 (0.0%)	0.097	0.000
Cognitive deficit, n (%)	25 (51%)	9 (21%)	5 (22%)	0.003	0.168
Death, n (%)	13 (26%)	1 (2%)	1 (4%)	0.001	0.441
Stroke recurrence, n (%)	6 (12%)	4(10%)	3 (15%)	0.098	0.073
Hemorrhagic transformation	10 (20%)	10 (25%)	2 (10%)	0.168	0.010
Hemorrhagic stroke	1 (2%)	2 (5%)	0 (0%)	0.177	0.001
mRs (mean)	3.5	3.2	3	0.033	0.010

CD: Chagas disease, AF: atrial fibrillation, DM: Diabetes Mellitus; SAH: systemic arterial hypertension; UE: undetermined etiology; mRs: Modified Rankim scale.
[a] comparison between AF and cardioembolic CD patients.
[b] comparison between undetermined CD and both AF and cardioembolic CD.

a reduced ejection fraction (*n* = 11), hypokinesia/akinesia (*n* = 23), dilated cardiomyopathy (*n* = 9), apical aneurysm (*n* = 7), intracavitary thrombus (*n* = 3), and AF (n = 2). For the CD-undetermined group, the most common findings were diastolic dysfunction (*n* = 12), normal examination results (*n* = 10), increased atrial volume (*n* = 5) in TTE and right bundle block (*n* = 15), and alteration of ventricular repolarization (n = 10) on ECG.

The average time from IS to hospital admission for the CD group was 3 years, and that for the AF-no CD group was 2.5 years. Although the groups were not matched for age, a similarity was observed in the mean age at stroke onset. The population characteristics are shown in Table 1. When the patients with CD of no etiologic cause were compared to patients with cardioembolic stroke (both AF-no CD and CD cardio groups), a higher frequency of obesity in the CD-undetermined group (17% vs. 2%, *P* = .003) and use of medication were observed. None of the participants in the CD-undetermined group used anticoagulants compared to half of the patients in the other groups (*P* = .000). No differences were observed in terms of mortality and stroke recurrence among the groups, although a higher mortality rate was more likely to be observed in the AF group, as shown on Figs. 1 and 2 (online only), respectively, depicting the Kaplan–Meier curves of recurrence and mortality. When both groups of patients with cardioembolic stroke were compared (AF-no CD and CD cardio groups), a higher number of patients in the AF-no CD group used statins (82% vs. 51%, *P* = .002) and had severe stroke (mRS: 3.5 vs. 3.2, *P* = .03) and cognitive deficit (51% vs. 21%, *P* = .003). Moreover, mortality was higher in this group (28% vs. 2%, *P* = .001).

MCA was the predominant topography in AF-no CD, CD-cardio, and CD-undetermined groups. If we include all the subdivisions of the MCA (superior division, inferior division, and deep and complete territory), two-thirds of the lesions were localized in these areas. Overall, no significant difference was observed in the territories involved in the three groups (Table 2), although watershed lesions were more likely to be observed in the CD-cardio group (32%) than in the AF-no CD group (4%) and the CD-undetermined group (10%) (*P* = .06).

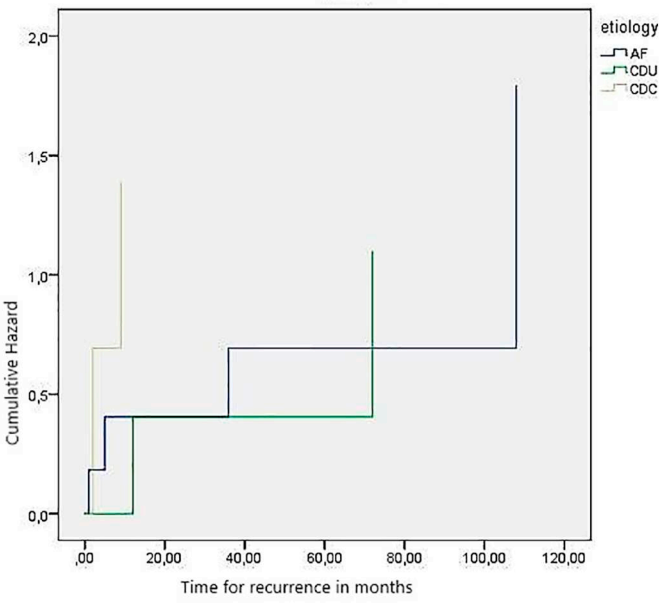

Fig. 1. Kaplan–Meier curve depicting the recurrence of stroke among the three groups. Time measured in months. The Chagas disease undetermined (CDU) and atrial fibrillation (AF) groups showed a pattern of crossing lines, and Chagas disease cardioembolic (CDC) was more likely to recur at an earlier stage of follow-up.

4. Discussion

Our findings indicated that no differences were observed in the arterial topographic involvement in patients with IS and AF and CD of both undetermined and cardioembolic etiologies. A predominant involvement of the MCA territory was noted in both patients with AF and CD, which is not surprising since it is generally the most common territory involved in ischemic stroke. Moreover, even when we compared the subdivisions of the MCA, no significant difference was observed between the groups.

It was interesting to observe that inferior division of the MCA and deep MCA territories was observed in over half of the patients with CD and an undetermined etiology. These findings are important as the inferior branch of the MCA may be associated with cardiac emboli,

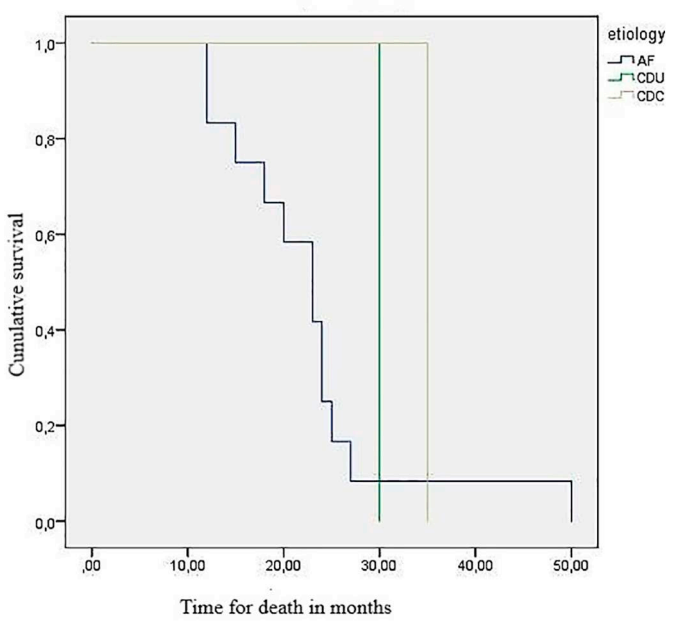

Fig. 2. Kaplan–Meier curve depicting mortality between the three groups. Time measured in months. The Chagas disease undetermined (CDU), Chagas disease cardioembolic (CDC), and atrial fibrillation (AF) groups showed a pattern of crossing lines; however, a higher incidence of mortality was more likely to be observed in the latter group.

Table 2
Topography comparisons between all three groups.

			Etiology		
			AF – no CD	CD-Undetermined	CD- Cardio
Topography	Superior middle cerebral artery	n	8	3	5
		%	16%	13%	11%
	Lacunar	n	3	0	0
		%	6%	0%	0%
	Inferior MCA artery	n	7	5	10
		%	14%	22%	23.%
	Complete MCA territory	n	9	4	6
		%	18%	17%	14%
	Anterior cerebral artery	n	1	0	0
		%	2%	0%	0%
	Posterior cerebral artery	n	4	0	1
		%	8%	0%	2%
	Vertebrobasilar arteries	n	3	2	2
		%	6%	9%	5%
	Watershed	n	5	1	14
		%	10%	4%	33%
	More than one territory non lacunar	n	2	1	0
		%	4%	4%	0%
	Deep middle cerebral artery	n	7	7	5
		%	14%	30%	12%
Total		n	49	23	43
		%	100%	100%	100%
Pearson's chi-square χ^2 (exact) = 25.19 *P*-value = .064					

CD C: Chagas Disease cardioembolic, CD U: Chagas Disease undetermined, AF C: atrial fibrillation cardioembolic, MCA middle cerebral artery.

possibly due to anatomical and hemodynamic factors [21,22]. This finding may suggest that cardiac causes that are not easily diagnosed, such as intermittent AF or other causes of cardiac thrombi, may be present in this subgroup. More intensive investigations (e.g., prolonged cardiac monitoring and cardiac MRI) should be conducted to evaluate these patients. Moreover, a clinical trial comparing antiplatelet agents with anticoagulants in patients with CD and stroke of unknown cause must be conducted.

Another interesting finding was that a higher number of patients with CD and cardiac abnormalities presented with watershed lesions, although this was not statistically significant in our study, probably because of the small sample size. Patients with CD and cardiomyopathy were more likely to present with autonomic dysfunction than patients with AF or CD but without cardiopathy. This hypothesis is supported by previous studies of neuronal depopulation in the parasympathetic ganglia in individuals with CD and scattered sympathetic denervation [23].

Our study showed that patients with AF and IS were more likely to have a worse functional outcome and higher mortality than patients with CD. The extremely low mortality rate (2.3%) even in patients with cardioembolic CD contributed to this difference. Although no difference was observed in the involved territories, we did not measure the size of the lesion that could be larger in patients with AF than in those with other cardiopathies. This could be potentially explained by the larger embolus size in patients with AF than in those with CD [16]. Worse functional outcomes and higher mortality rates in AF patients with IS compared with those with other stroke causes are well described in the literature [24–26]. Alternatively, patients with AF and IS may present with other complications, such as arrhythmias, which could also contribute to higher mortality rates. Since age did not differ among the groups, this variable may adequately explain these findings. Another potential explanation is that patients with AF may exhibit more comorbidities than patients with CD. Although the prevalence of classical risk factors was similar between groups, diseases are not considered, or frailty could have hypothetically justified the worse outcome observed in patients with AF.

In our cohort, cognitive decline was more frequently observed in patients with AF than in patients with CD, which could be explained by the larger ischemic lesions discussed previously. Furthermore, several studies have shown the association of AF to dementia, both the vascular type and that caused by Alzheimer's disease. AF is associated with dementia even in patients without stroke, possibly due to increased inflammatory status and impairment in cerebral blood flow [27,28].

In our study population, none of the patients in the undetermined CD used anticoagulant drugs as secondary prevention, as possibly determined by the physician, as current guidelines do not support the routine prescription of anticoagulant drugs to these patients [26]. An increased recurrence of stroke was more likely to be observed in this subgroup than in the other two groups (15% vs. both 10% in the CD-cardio group and 12% in the AF-no CD group, $P = .06$). An explanation for this phenomenon is that some patients classified with undetermined cause may have an occult cardiac etiology for stroke.

A higher frequency of hemorrhagic events, both hemorrhagic transformation and stroke, was observed in patients with cardioembolic etiology (AF-no CD and CD cardio groups) compared with those with an undetermined etiology (25% vs. 10% for both, $P = .01$). This difference may be partially attributed to the use of anticoagulant drugs in patients with known cardiac causes. Alternatively, as hemorrhagic transformation is a marker of recanalization of the cardiac emboli [16], its low frequency in the group of patients with CD and undetermined etiology may indicate that atherosclerosis and inflammation, rather than cardiac embolization, are the main mechanisms of stroke in this subgroup.

Our study has some strengths. First, it was performed in a quaternary multicentric rehabilitation network setting ensuring a reasonable etiological investigation and follow-up of patients. Thus, a significant number of patients could be enrolled. Second, a defined etiological investigation protocol for IS is used at our institution.

However, the study also had some limitations. First, it is a retrospective study; second, there was a prolonged time lapse between IS and hospitalization, which could have led to a selection bias. Third, convenience sampling was used, with no sample size calculation nor

matching of important variables, such as age and sex, which could have led to a type II error.

5. Conclusions

Patients with CD and stroke of unknown cause had similar patterns of cerebral involvement compared to patients with AF or CD and cardiac diseases. This finding may be an evidence showing that cardiac diseases are not easily diagnosed as intermittent AF or other causes of cardiac thrombi may be present in this subgroup. The number of patients with CD and known cardiac mechanisms who presented with hemodynamic infarcts was higher than that of patients with AF. A possible explanation is that a more extensive autonomic nervous system involvement was observed in patients with CD and cardiopathy. Finally, patients with IS and AF showed a higher morbidity, mortality, and frequency of cognitive impairment than patients with CD. This could be secondary to the presence of large ischemic lesions or comorbidities/frailty in patients with AF.

Ethical standards

This study was approved by the ethics committee of SARAH hospital and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Declarations of interest

None.

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References

[1] J.E. Pitella, Ischemic cerebral changes in the chronic chagasic cardiopathy, Arq. Neuropsiquiatr. 42 (1984) 105–115.
[2] J. Oliveira-Filho, L.C. Viana, R.M. Vieira de Melo, et al., Chagas disease is an independent risk factor for stroke: baseline characteristics of a Chagas disease cohort, Stroke. 36 (2005) 2015–2017.
[3] L.C. Paixão, A.L. Ribeiro, R.A. Valaccio, A.L. Teixeira, Chagas disease: independent risk factor for stroke, Stroke. 40 (2009) 3691–3694.
[4] V.V.A. Montanaro, C.M. Silva, C.V.V. Santos, M.I.R. Lima, E.M. Negrão, G.R. de Freitas, Ischemic stroke classification and risk of embolism in Chagas disease, J. Neurol. 263 (2016) 2411–2415.
[5] A.S. Sousa, S.S. Xavier, G.R. De Freitas, A. Hasslocher-Moreno, Prevention strategies of cardioembolic ischemic stroke in Chagas disease, Arq. Bras. Cardiol. 91 (2008) 280–284.
[6] G.L. Mandell, J.E. Bennett, R. Dolin, Principles and Practice of Infectious Disease, 7, Churchill Linvingstone, USA, 2010.
[7] J.P. Andrade, J.A.M. Neto, A.A.V. Paola, et al., Latin American guidelines for the diagnosis and treatment of Chagas' heart disease: executive summary, Arq. Bras. Cardiol. 96 (2011) 434–442.
[8] C. Chagas, New human tripanozomiase: studies in the morphology and the evolutionary cycle of the *Schizotrypanum cruzi* n. Gen., n. SP etiologic agent of new morbid entity in man, Mem. Inst. Oswaldo Cruz 1 (1909) 159–218.
[9] F.J. Carod Artal, J. Gascon, Chagas disease and stroke, Lancet Neurol. 9 (2010) 533–542.
[10] M.C.P. Nunes, A. Beaton, H. Acquatella, et al., Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association, Circulation. 138 (2018) e169–e209.
[11] World Health Organization, Making health research work for poor people, Seventeenth Programme Report UNDP/TDR, 17 2005, pp. 30–34.
[12] F.J. Carod-Artal, Policy implications of the changing epidemiology of Chagas disease and stroke, Stroke. 44 (2013) 2356–2360.
[13] C. Bern, S. Kjos, M.J. Yabsley, S.P. Montgomery, *Trypanosoma cruzi* and Chagas' disease in the United States, Clin. Microbiol. Rev. 24 (2011) 655–681.
[14] E.N. Cardoso, F.Y.B. Macedo, M.N. Garcia, et al., Chagas cardiomyopathy is associated with higher incidence of stroke: a meta-analysis of observational studies, J. Card. Fail. 20 (2014) 931–938.
[15] H.T. Moreira, G.J. Volpe, J.A. Marin-Neto, B. Ambale-Venkatesh, C.C. Nwabuo, H.S. Trad, Evaluation of right ventricular systolic function in Chagas disease using cardiac magnetic resonance imaging, Circ. Cardiovasc. Imaging. 10 (2017), https://doi.org/10.1161/CIRCIMAGING.116.005571.
[16] O. Inaba, Y. Yaumauichi, M. Sekigawa, et al., Atrial fibrillation types maters: greater infarct's volume and worse neurological defects seen in acute cardiogenic cerebral embolism due to persistent or permanent rather than paroxysmal atrial fibrillation, EP. Europace. (2017), https://doi.org/10.1093/europace/eux346.
[17] V.V.A. Montanaro, T.F. Hora, C.M. Silva, et al., Mortality and stroke recurrence in a rehabilitation cohort of patients with cerebral infarcts and Chagas disease, Eur. Neurol. 79 (2018) 177–184.
[18] H. Ay, T. Benner, E.M. Arsava, et al., A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system, Stroke. 38 (2007) 2979–2984.
[19] H. Ay, Causative classification system for ischemic stroke, https://ccs.mgh.harvard.edu/ccs_title.php. (Accessed from 15 January to 10 May 2016).
[20] L. Tatu, T. Moulin, J. Bogousslavsky, H. Duvernoy, Arterial territories of the human brain: cerebral hemispheres, Neurology. 50 (1998) 1699–1708.
[21] M. Hennereci, M. Daffertshofer, L. Jakobs, Failure to identify cerebral infarcts mechanisms from topography of vascular territory lesions, Am. J. Neuroradiol. 19 (1998) 1067–1074.
[22] J. Bougousslavsksky, R. Martín, Embolic versus non embolic causes of ischemic stroke, Cerebrovasc. Dis. 5 (1995) 70–74.
[23] O. Nasario-Junior, P.R. Benchimol-Barbosa, R.C. Pedrosa, J. Nadal, Assessment of autonomic function by phase rectification of R-R interval histogram analysis in Chagas disease, Arq. Bras. Cardiol. 104 (2015) 450–456.
[24] S. Karayannides, P. Lundman, L. Friberg, A. Norhammar, High overall cardiovascular risk and mortality in patients with atrial fibrillation and diabetes: a nationwide report, Diab. Vasc. Dis. Res. 15 (2017) 31–38.
[25] H.H.G. Castro, A.P. Alencar, I.M. Benseñor, P.A. Lotufo, A.C. Goulat, Multimorbidities are associated to lower survival in ischaemic stroke: results from a Brazilian stroke cohort (EMMA study), Cerebrovasc. Dis. 44 (2017) 232–239.
[26] M. Alkhouli, F. Alqhatani, S. Aljohani, M. Alvi, D.R. Holmes, Burden of atrial fibrillation-associated ischemic stroke in the United States, JACC Clin. Eletrophys. 4 (2018) 618–625.
[27] M.F. Lima-Costa, E. Castro-Costa, E. Uchôa, et al., A population-based study of the association between *Trypanosoma cruzi* infection and cognitive impairment in old age (the Bambui study), Neuroepidemiology. 32 (2009) 122–128.
[28] M. Ding, C. Qiu, Atrial fibrillation, cognitive decline and dementia: an epidemiologic review, Curr. Epidemiol. Rep. 5 (2018) 252–261.