Echocardiographic Evaluation of Late Cardiac Abnormalities Caused by the Chikungunya Fever

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Abstract

Background: **Chicungunya fever causes highly debilitating joint pains. Complications are rare and may affect the cardiovascular system.**

Objective: **To evaluate, with echocardiography and two-dimensional strain, the cardiovascular changes in the chronic phase of the Chikungunya infection.**

Methods: **The study included 32 patients, mean age 56 ± 14 years divided into Group A, with < 12 months evolution (12 patients) and Group B, with ≥ 12 months evolution (20 patients). The cardiac dimensions, left ventricular end-diastolic volume indexed to body surface, left ventricular ejection fraction, left ventricular global longitudinal strain and left atrial longitudinal strain were determined. The groups were compared using unpaired analysis. The p significance was < 0.05.**

Results: **Most Group A patients presented diffuse hypocontratility and decreased left ventricular ejection fraction (45.5 ± 10.4%) with normal left ventricular diastolic indexed volume (58.7 ± 24.9 mL/m²). Most Group B patients presented diffuse hypocontratility (ejection fraction 38.2 ± 6.4%) and increased left ventricular diastolic indexed volume (88.3 ± 26.4 mL/m²). There was segmental changes in 22% of the patients, and hypertrophy or remodelling in seven cases of each Group. There was decreased global longitudinal strain in both Groups (-11.9 ± 4.4% in Group A and -10.3 ± 3.8% in Group B). Lef atrial longitudinal strain were 37.9 ± 17.3% in Group A and 27.5 ± 15.2% in Group B. Patients with pericarditis had normal left ventricular dimensions and function.**

Conclusion: **The cardiac complications of Chikungunya fever was diffuse hypocontratility with left ventricular normal size observed in the first year of chronic evolution and diffuse hypocontratility with left ventricular dilation observed in later evolution. Patients with pericardial thickening did not present myocardial issues. Echocardiography can be used as an important tool in patients with Chikungunya fever, since it can detects early abnormalities in the cardiovascular system. (Arq Bras Cardiol: Imagem cardiovasc. 2018;31(3):183-190)**

Keywords: **Echocardiography. Longitudinal Strain. Chikungunya fever.**

Introduction

Chikungunya, "those who bend." This word comes from the Makonde language, spoken by tribes inhabiting northern Mozambique and southern Tanzania. It represents a condition of intense joint pain produced by an African virus disease, an infection caused by an arbovirus of the *Togaviridae* family and genus Alphavirus transmitted by mosquitoes of the genus Aedes (*Aedes aegypti* and *Aedes albopictus*). It is similar to dengue, zika and yellow fever.[1] It was first isolated in 1952 in Tanzania,[2] and its first occurrence was in South Asia and India. The second occurrence was in Kenya in 2004, where it spread to Indonesia, India and Southeast Asia. In 2013, it arrived to the Caribbean islands and, in 2014, it was detected in Brazil, in Oiapoque (State of Amapá). It spread through several states. The Northeast was the most affected area. There is a single serotype of the Chikungunya virus (CHIKV) and three genotypes: West Africa, East/Central/South Africa (ECSA), and the Asian and Indian Ocean lineages, probably originating from the ECSA. The CHIKV genotypes found in Brazil are of Asian lineage, in Amapá, and from the ECSA, in Bahia. In 2014, 2,772 cases were confirmed, most of which in the state of Amapá;[3] In 2015, there were 6,784 confirmed cases, most of which in the State of Bahia;[4] in 2016, 146,914 cases were confirmed, with 159 deaths;[5] As of September 2017, 121,734 cases had been confirmed, with 99 deaths.[6]

CHIKV infection after the incubation period, which lasts from 3 to 7 days, produces a sudden febrile syndrome, with intense highly debilitating joint pain, affecting more than 80% of the patients, lasting from 10 to 15 days – but it may last months and even years. Post-infection manifestations include persistent joint pain and even rheumatoid arthritis, which affects 5% of patients.[7] Elderly and neonates may

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Manuscript received January 21, 2018; revised February 1, 2018; accepted June 4, 2018.

DOI: 10.5935/2318-8219.20180027

have neurological impairment, with high mortality due to encephalopathy. There are also records of maternal-fetal vertical transmission during labor.[8]

CHIKV infection progresses in three phases: acute or febrile phase, lasting up to the tenth day after the incubation period; subacute phase, lasting up to 3 months; and chronic phase, which can last for months and even years. In its chronic form, the disease can cause atypical complications, such as heart failure, respiratory failure, meningoencephalitis, hepatitis, skin lesions and renal failure. The incidence of atypical cardiovascular complications was estimated at 12.8% for segmental myocardial abnormalities and 9.4% for heart failure.[9]

Myocardial involvement, in the form of ventricular dysfunction and pericardial thickening, can be observed in the acute phase, but it is in the chronic form that it occurs with greater severity. Some observers have found myocardial impairment in more than half of the patients with complications.[10] This is the most frequent condition second only to joint pain.[11,12]

The mechanism of myocardial impairment by CHIKV is by virus penetration into the myocytes, producing direct cell damage in myofibrils, inflammatory response and infiltration, followed by secondary damage caused by hypersensitivity and necrosis, usually with no signs of infarction. Viral impairment leaves the myocardium vulnerable to infection by other viruses, favoring the evolution of the disease, with dilatation of the cavity.[13]

Objective

To evaluate the echocardiographic abnormalities in patients with chronic Chikungunya virus infection, who presented clinical signs of cardiac impairment.

Methods

Of 35 patients referred for echocardiography, examination was conducted on 32 who had confirmed CHIKV infection, whose symptoms started more than 5 months prior (range of 5 to 25 months, averaging 13.6 months), mean age 55.6 ± 14.3 years, and 15 of them were female. Two patients, whose echocardiogram was inadequate to calculate the left ventricular ejection fraction (LVEF) by Simpson's double-plane method, were excluded, and one patient whose number of myocardial segments required for left ventricular (LV) global longitudinal strain (GLS) analysis could not be detected was also excluded.

All patients presented laboratory diagnosis for CHIKV by IgM and IgG titration by the Enzyme-Linked Immunosorbent Assay (ELISA), as recommended by the Brazilian Society of Rheumatology (SBR) for atypical complications.[14] The patients observed the criteria of the Declaration of Helsinki.[15]

The LV wall dimensions and thickness and the right ventricular (RV) inflow tract diameter, the LV systolic function by LVEF, the mass index and the relative thickness of the walls, and the aorta and left atrial (LA) diameters were taken. The criterion to determine LV dilatation was LV diastolic volume index (LVDVi) for the body surface, using the cutoff values > 74 mL/m^2 for males and > 61 mL/m^2 for females, corresponding to two standard deviations from the value specified in the cavity quantification guideline. LVEF was considered decreased when < 54% for the female sex and < 52% for the male sex.[16]

The left ventricular pressure ratio (dP/dt), using Doppler flowmetry, was used to assess the LV systolic function where there was mitral regurgitation, and was considered decreased when < 800 mmHg/s.[17] LV diastolic function was assessed by mitral E-wave velocity, E/A ratio, e' septal wave velocity and lateral velocity of the mitral annulus with tissue Doppler, and the lateral E/e' ratio (except in cases of pericarditis, in which the septal E/e' ratio was used).[18] The tricuspid regurgitation velocity was determined with spectral Doppler and the mitral annular velocity with tissue Doppler. In RV, the tricuspid annular plane systolic excursion (TAPSE) was assessed. With the methods that analyze myocardial strain, the GLS was estimated using the mean of 16 myocardial segments evaluated by 4, 2 and 3-chamber apical views,[19] and the LA longitudinal strain (LALS) was estimated by 4-chamber apical view. The cutoff values were < -16.6% for GLS[20] and < 22% for LALS.[21] Patients who had more than three myocardial segments not suitable for strain analysis or two contiguous myocardial segments[19] (Figure 1) were excluded.

Once it was found that there was greater LV dilation the later the evolution of the CHIKV infection, the patients were arbitrarily divided into two groups: Group A, with duration of CHIKV infection < 12 months, consisting of 12 patients, and Group B, with disease duration ≥ 12 months, consisting of 20 patients. The data were tabulated and the mean and standard deviation of the mean were calculated. To compare Groups A and B, unpaired analysis was used. The regression equation was used to correlate LVGLS and LALS with LVEF. The statistical data were considered significant when $p < 0.05$.

To conduct the tests, Eko7, Samsung Electronics with P2-4BA transducer, and the Speckle Tracking software for myocardial strain analysis were used.

Results

The patients were referred by reference Cardiology services because they presented clinical signs of some sort of myocardial impairment and their most frequent symptoms were dyspnea, orthopnea, fatigue and decreased functional capacity on the 6-minute walk test.

Among the demographic data, age was significantly lower in Group B patients ($p = 0.02$) and height and body surface area were significantly higher ($p = 0.001$ and $p = 0.02$, respectively). The sociodemographic data are shown in Table 1.

LV diastolic and systolic diameters were significantly higher in Group B ($p = 0.0002$ and $p = 0.0003$, respectively), and the septal and LV wall thickness, as well as the aortic diameter, did not show any significant differences. LA diameter ($p = 0.005$), RV inflow tract diameter ($p = 0.004$), and RV wall thickness ($p = 0.05$) were increased in Group B. LV and RV dimensions are shown in table 2.

Group A patients had significantly lower LV and LVDVi than those of Group B ($p = 0.0002$ and $p = 0.002$, respectively). Ventricular mass was significantly higher in Group B patients ($p = 0.03$), but the mass index had no significant difference.

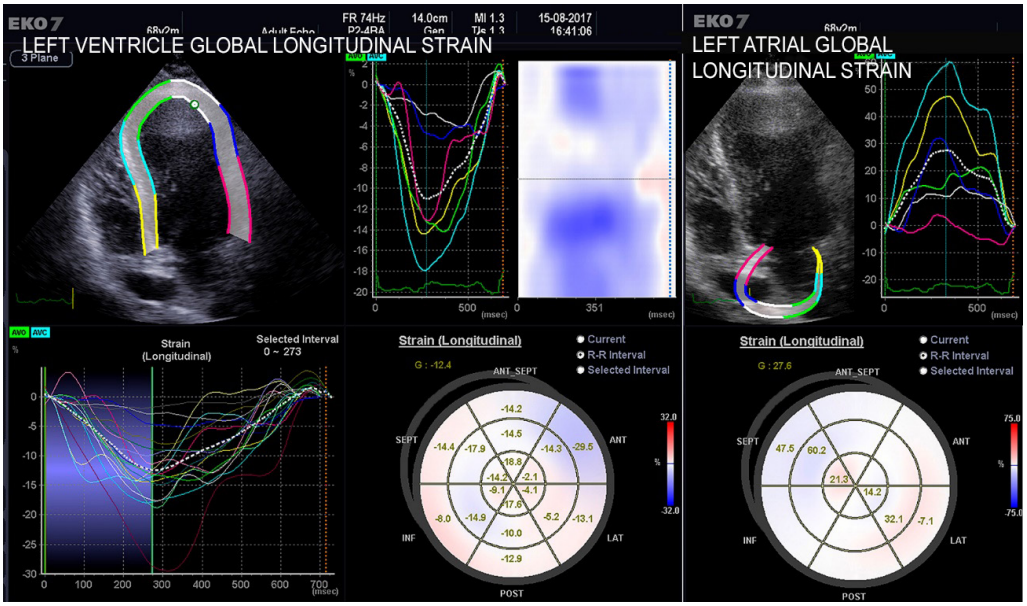

Figure 1 – *Patient with Chikungunya virus infection, chronic phase. Determination of global longitudinal strain in 16 myocardial segments (left). Determination of left atrial longitudinal strain by 4-chamber apical view.*

Table 1 – Demographic data

Group	n	Gender		Age (years)	Chronic phase duration (months)	Weight (kg)	Height (cm)	Body surface area (m²)
A	12	Female: 8	M	62.08	8.75	67.08	156.08	1.66
		Male: 4	SD	15.09	1.66	19.87	9.52	0.26
B	20	Female: 7	M	51.65	16.50	74.40	165.30	1.81
		Male: 13	SD	12.58	4.14	14.00	6.46	0.16
Probability amount				0.02	< 0.0001	0.12	0.001	0.02

M: mean; SD: standard deviation.

The relative wall thickness was significantly lower in Group B patients (p = 0.002). The AE volume was higher in Group B patients (p = 0.04), but when indexed to the body surface, there was no significant difference. LV volumes and myocardial mass are shown in Table 3.

LVEF was significantly lower in Group B patients (p = 0.001), and dP/dt, obtained in ten patients from Group A and in 17 patients from Group B, did not show any significant difference.

TAPSE and tricuspid regurgitation velocity did not present any significant differences between the groups.

GLS was decreased in both groups, but there was no significant difference between them. Compared to LVEF by the linear regression equation in all patients, SLG showed a significant correlation (r = 0.74; r^2 = 0.55; p < 0.00001). In Group A, the correlation between LVEF and GLS was significant (r = 0.70, r^2 = 0.49, p = 0.01) and, in Group B, it presented a more significant correlation (r = 0.79; r^2 = 0.62; p < 0.00001).

LALS was significantly decreased in Group B (p = 0.04). When evaluated in all patients, LALS showed a significant correlation with LVEF, as evidenced by the geometric correlation (r = 0.71; r^2 = 0.51; p < 0.00001). In Group B, LALS was decreased in 30% of patients with a significant correlation with LVEF (r = 0.78; r^2 = 0.61, p = 0.00001). In Group A, LALS decrease in 21% of the patients did not show any significant correlation with LVEF (r = 0.55; r^2 = 0.30; p = 0.06). The LV and RV function data are shown in table 4.

In Group A, diastolic function was normal in four patients, indeterminate in one, grade 1 in five, and grade 2 in two. In Group B, diastolic function was indeterminate in two patients, grade 1 in three, grade 2 in nine, and grade 3 in six. Mitral E wave velocity did not present any significant difference between the groups. E/A ratio was significantly higher in Group B (p = 0.02). Lateral e' wave, septal e' wave and E/e' ratio did not show significant differences between the groups. Mitral flow data and tissue Doppler velocities are shown in table 5.

Table 2 – Left ventricular (LV) and right ventricular (RV) dimensions

Group		LVDd (mm)	LVSd (mm)	DST (mm)	DWT (mm)	AoD (mm)	LA (mm)	RVDD (mm)	RVWT (mm)
A	M	45.83	32.33	9.00	8.75	31.00	31.33	30.77	5.81
	SD	8.01	7.67	1.48	1.36	3.95	6.92	3.78	0.88
B	M	56.00	42.40	8.95	8.80	32.25	37.45	34.63	5.33
	SD	6.39	6.74	1.70	1.51	4.01	5.51	3.73	0.71
Value of probability		0.0002	0.0003	0.5	0.5	0.20	0.005	0.004	0.05

LVDd: left ventricular diastolic diameter; LVSd: left ventricular systolic diameter; DST: diastolic septal thickness; DWT: diastolic wall thickness; AoD: aortic diameter; LA: left atrial diameter; RVDD: right ventricular diastolic diameter; RVW: right ventricular thickness; M: mean; SD: standard deviation.

Table 3 – Left ventricular (LV) and left atrial (LA) volumes and LV mass

Group		EDV (mL)	EDVi (mL/m²)	Mass (g)	LV mass index (g/m²)	Relative wall thickness	LA volume (mL)	LAVoli (mL/m²)
A	M	96.43	58.73	143.83	86.94	0.40	56.92	34.52
	SD	38.72	24.87	62.71	37.31	0.07	23.07	13.29
B	M	159.01	88.32	193.18	106.22	0.32	72.50	40.04
	SD	46.06	26.38	71.00	35.53	0.07	24.73	13.59
Value of probability		0.0002	0.002	0.03	0.08	0.002	0.04	0.1

EDV: left ventricular end-diastolic volume; EDVi: end-diastolic volume indexed to body surface; LAVoli: left atrial volume indexed to body surface; M: mean; SD: standard deviation.

In two patients of Group A and five patients of Group B, there was a segmental contractility abnormality of irregular distribution associated with diffuse hypocontratility of the walls, with akinesia or dyskinesia in some segments. The segments that presented the greatest number of impairments were, in order of frequency: medial anterolateral and lateral apical; basal anteroseptal and basal inferoseptal; medial inferoseptal, inferior basal and basal inferolateral; and anterior medial, medial anteroseptal, anterior apical, apical septal and inferior apical (Figure 2). No patient had a history of precordial pain or coronary disease in the clinical history, nor clear signs of myocardial infarction on the electrocardiogram (ECG), as reported by the service that requested the echocardiogram. Seven patients (four from Group A) were being treated for hypertension; two patients from Group A and two from Group B received treatment for type 1 diabetes mellitus.

LV eccentric hypertrophy and concentric remodeling of the walls were observed in 14 patients (Group A: four patients with concentric remodeling and three with eccentric hypertrophy; Group B: one patient with concentric remodeling and six patients with eccentric hypertrophy).

Pericardial thickening, observed in three patients, did not present any abnormalities in systolic function when evaluated by LVEF. In a patient with pericardial thickening, there were signs suggestive of restricted right ventricular filling, respiratory variation of the tricuspid flow greater than 20%, dyspnea, hepatomegaly, decreased LV GLS (-14.3%), decreased TAPSE (1.34 cm) and decreased lateral e' wave (7 cm/s) with normal septal e' wave (9 cm/s).

Regarding valve regurgitation, in Group A, four patients had moderate or severe valve insufficiency (one patient with severe mitral regurgitation, one with severe tricuspid regurgitation and two with moderate aortic regurgitation). The other patients had no regurgitation or it was considered discrete. In Group B, five patients had moderate regurgitation (three mitral and two aortic regurgitations). The other patients had no regurgitation or it was considered discrete. No patient presented valve stenosis.

One patient from Group A and another from Group B had atrial fibrillation. Four patients from Group A and five from B presented other types of arrhythmia, mainly extrasystoles.

Discussion

Although there are few data in the literature, the atypical complications of Chikungunya fever, described as infrequent, are very important because of the high prevalence of the disease in epidemic periods. More than half of the atypical complications are cardiovascular, producing significant and, apparently, progressive and permanent myocardial damage.[10,12] In this study, we found that the diffuse hypocontratility of LV with preserved cavity size was the most common form in the first year of the chronic form (78% of cases without considering patients with pericardial thickening), and cavity dilatation with diffuse hypocontratility was more frequent in later evolution (90% of cases). Probably both are evolutionary forms of the infectious process. Literature studies, in cases of systolic dysfunction without cavity dilatation, showed, through CMRI[22] and myocardial biopsy,[23] myocardial inflammation compatible with myocarditis. Cases with cavity dilatation with decreased LV systolic function parameters present criteria compatible with dilated cardiomyopathy.[24,25]

Table 4 – Left ventricular (LV) and right ventricular systolic function data. Parameters of LV and left atrial (LA) strain.

Group		LVEF (%)	dP/dt (mmHg/s)	TAPSE (cm)	Tricuspid regurgitation velocity (m/s)	LVGLS (%)	LALS (%)
A	M	45.58	823.30	1.89	2.51	-11.91	37.91
	SD	10.45	321.30	0.44	0.25	4.41	17.29
B	M	38.25	663.29	1.87	2.72	-10.33	27.55
	SD	6.41	123.27	0.55	0.28	3.76	15.19
Value of probability		0.001	0.08	0.46	0.08	0.14	0.04

LVEF: left ventricular ejection fraction; dP/dt: left ventricular pressure increase ratio; TAPSE: tricuspid annular plane systolic excursion; GLS: global longitudinal strain; LALS: left atrial longitudinal strain; M: mean; SD: standard deviation.

Table 5 – Mitral flow and tissue Doppler

Group		Mitral E wave (cm/s)	E/A ratio	Lateral e' wave (cm/s)	Septal e' wave (cm/s)	E/e' ratio
A	M	77.58	0.84	10.92	8.70	7.75
	SD	27.50	0.27	3.58	2.67	3.62
B	M	72.53	1.60	9.76	7.95	8.01
	SD	17.99	1.45	3.21	3.50	2.88
Value of probability		0.27	0.02	0.18	0.29	0.41

M: mean; SD: standard deviation.

All patients studied were in the chronic phase of the CHIKV infection, with an evolution time ≥ 5 months. They were referred for echocardiography as they had some symptom of cardiac impairment without any previous screening. It is, therefore, an observational study in a selected group of patients, not representative of the general population of CHIKV-infected patients, but of great importance because it shows serious and apparently progressive cardiac issues.

The separation into Groups A and B, according to the evolution time greater or shorter than 12 months, was performed arbitrarily, based on the observation of the predominance of preserved LV diastolic dimension before the first year of evolution and dilation of the cavity in the later evolution. This finding was reported by other authors.[10]

The differences found in the mean age, height and body surface of patients from Groups A and B may be due to the small size of the sample studied, and there are no other causes for such variation.

Increased LV diameters, with change to the wall thickness, and increased LA size, RV inflow tract, and RV wall thickness, as found in Group B, suggest greater myocardial impairment in the later stages of chronic evolution of CHIKV infection. This seems to be corroborated by the increase in LV end-diastolic volume and LVDVi, maintenance of mass index, decreased relative thickness of the walls and significant decrease in LVEF, some parameters that indicate cavity dilatation without compensatory hypertrophy, with severe systolic dysfunction. It should be noted that three patients with pericardial thickening from Group A had normal LVEF. The absolute volume of LA was increased in Group B, but when indexed, there was no significant difference between the groups, probably due to the dispersion around the mean and the effect of greater body surface found in this group. Although LV dP/dt is lower in Group B, did not have a significant difference compared to Group A, probably due to the influence of preload (increased LA pressure in cases with grade 2 and 3 diastolic dysfunction). TAPSE showed no difference between the groups, suggesting preserved RV systolic function, even with greater cavity diameter and greater wall thickness, suggesting remodeling of this chamber, which may be related to increased tricuspid reflux velocity observed in Group B.

The decrease in GLS was observed in both groups, with no significant difference between them. Two patients from Group A who had signs of pericardial thickening and one patient from Group B who had decreased LVEF had normal LV GLS. In a case of pericardial thickening in Group A that had normal LVEF, LV GLS was decreased. This patient presented signs of pericardial constriction, with respiratory variation of the tricuspid flow, decreased lateral e' wave with maintenance of the septal e' wave and decreased TAPSE. This patient also had neurological impairment manifested by frequent seizures.

The cases of left ventricular hypertrophy in the form of eccentric hypertrophy or concentric remodeling were frequent (65.6% of the patients), with the association of diffuse hypocontratility of the walls and, in some cases, arrhythmias (34.4% of the patients), which has also been found in the literature.[12] Ventricular hypertrophy in the form of concentric remodeling was more frequent in Group A patients (58% of the patients; four with concentric remodeling and three with eccentric hypertrophy) and less frequent in Group B patients (35% of patients, one with concentric remodeling and six with

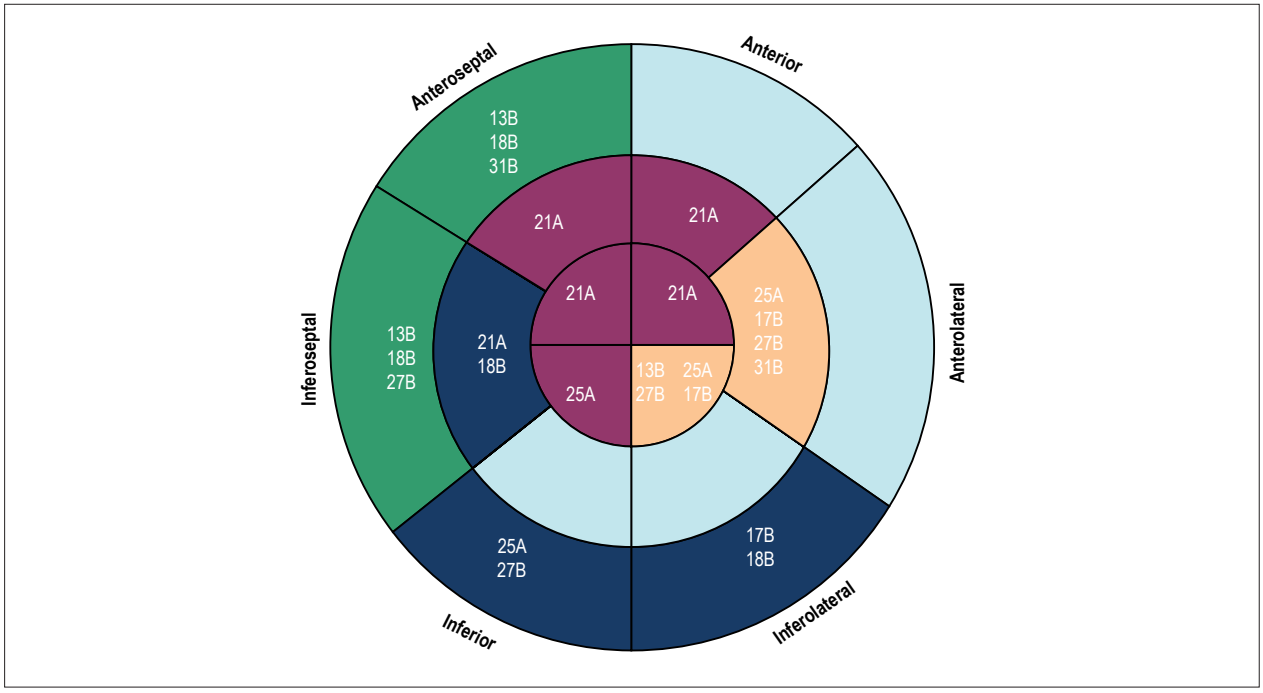

Figure 2 – *Polar map of the 16 myocardial segments with the segmental abnormalities observed in seven patients. The number and letter in each segment indicate the number and group of each case.*

eccentric hypertrophy). Although the cause of hypertrophy is unclear, myocardial inflammatory reaction and interstitial edema may be contributing factors.

In some cases (22% of patients), there was segmental alteration in contractility, but with no clear evidence of association with territories of myocardial irrigation. No patient had a previous history of precordial pain or known coronary disease, according to the clinical history provided by the services that referred the patients. This seems to corroborate the literature findings, which do not associate segmental abnormalities to myocardial infarction in the chronic form in similar virus infections.[25,26] In the acute form, myocardial infarction was found in 1% of atypical complications, half as much in previously healthy patients.[27,28]

The most common comorbidities were hypertension and type 1 diabetes, all in clinical treatment.[29]

Regarding diastolic function, we observed a prevalence of normal diastolic function or abnormal relaxation in Group A, in addition to a greater number of patients with pseudonormal dysfunction, restrictive filling in Group B, suggesting that the patients with longer course of CHIKV infection present higher myocardial dysfunction and higher atrial pressure.

The right ventricular function, as evaluated by TAPSE, was decreased in 31% of patients with chronic CHIKV infection (25% in Group A and 35% in Group B), with increased RV dimensions and RV free wall thickness in Group B patients. These data suggest biventricular impairment in a significant number of cases.

Mitral and aortic valve regurgitation (most moderate) were found in several patients in both groups, and an association with myocardial contractility issues could not be established.

Limitations

The main limitation was the selection of patients, performed by direct request of the echocardiography, only in patients who had some type of cardiovascular symptom detected in specialized Cardiology services, where patients under treatment in public services are referred. Another limitation was the non-inclusion of patients in the acute phase, mainly due to late diagnostic confirmation and later appearance of cardiovascular symptoms. The limited number of patients, considering the epidemic nature of the disease, was due to the regional context of patient selection from specialized centers, not directly from primary care centers.

We do not have any records of myocardial issues in the chronic phase of CHIKV infection because these patients were not followed up. As the CHIKV mechanism of action is a combination of cell destruction, inflammatory process and great vulnerability to myocardial involvement with other viruses and microorganisms, it may be an irreversible process.

Conclusion

The decrease in left ventricular systolic function parameters, as evidenced by decreased left ventricular ejection fraction and global longitudinal strain, was found in most patients with chronic Chikungunya virus infection, except where there was pericardial thickening, in the which left ventricular function was preserved. In the first year of chronic evolution, the left ventricular dimensions were normal and, after one year of evolution, most patients presented cavity dilatation. Other important data were left ventricular concentric remodeling, more frequent in the first year, and eccentric hypertrophy, more common after one year of evolution.

Segmental abnormalities without correlation with territories of myocardial irrigation were observed in almost one quarter of the cases, as well as high incidence of arrhythmias. All of these findings, accompanied by clinical symptoms of cardiac involvement, suggest the progressive nature of the disease.

Echocardiography plays an important role in the detection of cardiovascular issues caused by Chikungunya fever and should be used as a first-line diagnostic method after confirmation of infection to initiate appropriate treatment in the acute phase, which should probably minimize the deleterious effects of the disease.

Authors' contributions

Research creation and design: Del Castillo JM; Data acquisition: Del Castillo JM, Alencar GMP, Nóbrega MVD, Mazzarollo C, Diniz JV; Data analysis and interpretation: Del Castillo JM, Alencar GMP; Statistical analysis: Del Castillo JM, Sena ADM; Manuscript writing: Del Castillo JM; Critical revision of the manuscript as for important intellectual content: Del Castillo JM, Alencar GMP, Nóbrega MVD, Mazzarollo C, Diniz JV, Albuquerque ES, Sena ADM, , Silveira CAM, Osella OFS; Collection of references: Alencar GMP, Nóbrega MVD.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

Sources of Funding

This study had no external funding sources.

Academic Association

This study is not associated with any graduate program.

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