Cardiac Involvement by Yellow Fever (from the PROVAR+ Study)

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Incidence of Yellow Fever (YF) has increased in Brazil, and cardiac findings such as bradyarrhythmias and conduction abnormalities have been described. We aimed to perform a comprehensive cardiac evaluation of patients with YF, and to assess the association between cardiac involvement and disease severity. Patients hospitalized with YF from February to March 2018 underwent clinical and laboratory evaluation, focused bedside echocardiography (GE Vivid IQ), electrocardiogram and, in case of alterations, 24-hours Holter. Patients were divided into 2 groups according to YF severity. Five patients underwent magnetic resonance imaging and 3 had necropsy. Seventy patients had confirmed YF, 69% with severe form. Mean age was 48 ± 14 years, 63 (90%) were males and 5 (7%) died. Significant electrocardiogram abnormalities were present in 52% of patients with mild/moderate form of YF (G1) and 77% of those with severe form (G2), p = 0.046. Sinus bradycardia was observed in 24% (N = 17): G1 23% versus G2 25%, p = 0.67. Among 32 patients who underwent Holter, 14 (44%) had mean HR <60 beats per minute, being 8 from G2. Echocardiogram revealed left ventricular dysfunction in 4 (6%) patients, from G2. Left ventricular wall thickening with a hyper-refringent myocardial texture suggesting infiltration was observed in 17 patients (G1 18% vs G2 27%, p = 0.55). One magnetic resonance (G2) was suggestive of myocarditis, and one necropsy revealed areas of myocardial necrosis and acute myocarditis. In conclusion, cardiac involvement was observed in patients with YF, most commonly bradycardia and myocardial hyper-refringent texture suggestive of infiltration. **(Am J Cardiol 2019;123:833−838)**

Yellow Fever (YF) is an acute hemorrhagic fever caused by the infection of a Flavivirus (*Flaviviridae* family) transmitted by mosquitoes of the *Haemagogus* and *Aedes* genera.[1,2] YF is present in South America and Africa with well-established endemic zones, although its natural cycle involves periods of retractions and expansions.[3] Infected people are mostly asymptomatic, however 15% develop severe manifestations[4] including fever, vomiting, nausea, hepatitis with jaundice, hemorrhage, renal failure, shock and death[1,2] and, among these, the disease is fatal in 20% to 60%.[5] It is well established that the liver is the main impaired organ but, similarly to other arboviral diseases,[6] other structures are possibly affected, including the heart.[1,2] Bradycardia was firstly described in

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Funding: This study was funded by Edwards Lifesciences Foundation, USA and FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais), Brazil.

The funders did not have any relation with the conduct of the study, the collection, analysis, and interpretation of the data, and the preparation, review, or approval of this manuscript.

The abstract of this work was presented as a moderated poster at the *American Heart Association Scientific Sessions* 2018, November 10 to 12, 2018, in Chicago, IL.

See page 838 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2018.11.032

1822, while myocardial degeneration in infected monkeys was detected in 1931.[7] Viral antigens were found in the myocardium of 3 autopsied patients who died of YF from 1981 to 1985[8] and also in patients who evolved with post-vaccine viscerotropic disease.[9,10] Brazil and other South American countries have been facing the largest outbreak of YF observed in decades,[11] and a deeper understanding of the pattern of its cardiac manifestations may improve patient care.

We aimed to perform a comprehensive cardiac evaluation of patients with YF during the 2018 outbreak in Brazil, and to assess the association between cardiac involvement and disease severity.

Methods

The PROVAR+ program has been conducted since 2017 in the state of Minas Gerais, southeast Brazil, under the auspices of the Universidade Federal de Minas Gerais and the Telehealth Network of Minas Gerais,[12] in collaboration with the Children's National Health System, Washington DC. The program utilizes nonexperts for imaging acquisition and remote interpretation in different settings. Ethics approval was obtained from the institutional review boards of Universidade Federal de Minas Gerais and Hospital Eduardo de Menezes. The data analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure, from the corresponding author upon reasonable request.

In this study, consecutive patients admitted to a reference hospital for infectious diseases (Hospital Eduardo de Menezes, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, MG, Brazil) with clinical suspicion of arboviruses underwent a standardized clinical questionnaire and laboratory evaluation, including complete blood count, serology for YF (immunoenzymatic assay, IgM) and biochemistry (including liver function tests and inflammatory markers), analyzed in a central lab. All patients underwent a standard digitally recorded resting 12-lead ECG (ECG PC machine, TEB, São Paulo, Brazil). ECGs were classified by the Minnesota Code (MC) criteria.[13] The following were considered to be significant ECG abnormalities: sinus bradycardia (HR <60 bpm), old myocardial infarction (major Q-wave abnormalities [MC 1.1.x or 1.2.x]) or possible MI (minor Q-waves abnormalities with ST segment or T-wave abnormalities [MC 1.3.x and 4.1.x, 4.2, 5.1, or 5.2]), complete intraventricular blocks (MC 7.1, 7.2, 7.4, or 7.8), supraventricular or ventricular premature beats (MC 8.1.x, except 8.1.4), major isolated ST segment or T-wave abnormalities (MC 4.1.x, 4.2, 5.1 or 5.2), atrial fibrillation or flutter or supraventricular tachycardia (MC 8.3.x. or 8.4.2), other major arrhythmias (MC 8.2.x, except 8.2.1), major atrioventricular conduction abnormalities or pacemaker use (MC 6.1, 6.2.x, 6.4, 6.8, 8.6.1 or 8.6.2), major QT prolongation (>115%) and left ventricular hypertrophy (MC 3.1 together with [4.1.x, 4.2, 5.1, or 5.2]).[14]

Patients with one or more significant ECG abnormalities underwent 24-hour Holter monitoring, with 3-channel devices (Dynamics, Cardios, São Paulo, Brazil). ECGs and Holters were centrally analyzed at the Telehealth Center (Universidade Federal de Minas Gerais) by experienced cardiologists and visually inspected for technical errors.

Additionally, all patients underwent focused bedside echocardiography (Vivid IQ, GE Healthcare, Milwaukee, WI), with acquisition of standard parasternal and apical views by nonphysicians for further remote interpretation. Echocardiograms were uploaded to a dedicated reading system (EchoPAC, GE Healthcare) and reviewed by two experts cardiologists (MN and MLJ) according to the ASE guidelines,[15] and discrepancies were consensually solved. Significant heart disease was defined as moderate to severe valve disease (regurgitation or stenosis), ventricular dysfunction or hypertrophy, congenital heart disease, pericardial effusion or any wall-motion abnormalities (Appendix 1). Reports were promptly made available for clinical care by the hospital. A subset of patients who presented with cardiac abnormalities at admission underwent cardiac magnetic resonance imaging and 3 fatal cases were necropsied.

All data were entered to the SigTel online reporting system and exported to the RedCap database.[16] Statistical analysis was performed using SPSS software version 23.0 for Mac OSX (SPSS Inc., Chicago, Illinois). We included all consecutive patients admitted over 2 months (March and April, 2018), during the peak of the epidemic. Data are presented for all patients with confirmed positive serology for YF: categorical variables, expressed as numbers and percentages were compared between groups (mild or moderate vs severe presentation of YF, according to duration of illness, systemic symptoms and signs of liver dysfunction and shock[17]) using Fisher's exact test, whereas continuous data, expressed as mean ± standard deviation (SD) or median and Q1 to Q3 (25% to 75%), were compared using Student's unpaired *t* test or the Mann-Whitney *U* test, as appropriate. We further compared the prevalence of ECG abnormalities with data from a previously published cohort of >14,000 Brazilian adults (civil servants from public universities, including Universidade Federal de Minas Gerais) with matching age and sociodemographic composition.[13] A two-tailed significance level of 0.05 was considered statistically significant.

Results

A total of 103 patients with suspected arbovirosis were admitted over 2 months, and 70 had serological confirmation of YF; 69% (N = 48) evolved with the severe form. Mean age was 48 ± 14 years, and 63 (90%) were males. Demographic and clinical characteristics, including cardiovascular risk factors, were similar between patients with mild/moderate forms of YF (G1) and those with severe form (G2) (Table 1). Laboratory markers related to YF, including aspartate aminotransferase, creatinine, and bilirubin, were considerably higher in G2. No patients had elevated Troponin-I levels (Table 1).

Significant ECG abnormalities were present in 52% of patients and were more common among those with severe disease (G2) (G1, 52% vs G2, 77%, p = 0.046). Abnormal ventricular repolarization and sinus bradycardia without prolonged PR interval were the most frequent alterations.

Table 1
Baseline demographic, clinical and laboratorial characteristics of patients with Yellow Fever, according to disease severity

Characteristic	Overall (n = 70)	Yellow fever severity		p value
		Mild/Moderate YF (n = 22)	Severe YF (n = 48)	
Age (mean ± SD)	47.5 ± 14.3	45.5 ± 13.8	48.4 ± 14.5	0.42
Male	60 (90%)	19 (86%)	44 (92%)	0.67
Hypertension	14 (20%)	4 (18%)	20 (21%)	0.80
Diabetes *mellitus*	4 (6%)	1 (5%)	3 (6%)	0.78
Active smoker	13 (19%)	3 (16%)	10 (21%)	0.65
Alcohol drinker	13 (19%)	3 (16%)	10 (21%)	0.65
Prior CAD	0	0	0	N/A
Fever (days) (median, Q1 to Q3)	4.0 (3.0 to 5.0)	4.0 (3.0 to 5.0)	3.0 (3.0 to 6.0)	0.84
Hospitalization (days) (median, Q1 to Q3)	10.0 (7.0 to 17.0)	7.0 (5.5 to 9.0)	12.0 (9.0 to 19.0)	<0.001*
ICU stay	43 (61%)	3 (14%)	40 (83%)	<0.001*
ICU days (median, Q1 to Q3)	5.5 (3.0 to 8.5)	3.0 (2.0 to 4.0)	6.0 (3.0 to 9.0)	0.19
Mortality	5 (7%)	0	5 (10%)	0.23
Creatinine (mg/dl) (median, Q1 to Q3)	0.9 (0.7 to 1.5)	0.8 (06 to 0.9)	1.2 (0.8 to 2.2)	0.001*
Bilirubin total (mg/dl), (median, Q1 to Q3)	2.3 (0.8 to 5.3)	0.8 (0.5 to 1.0)	3.9 (1.4 to 7.6)	<0.001*
Bilirubin direct (mg/dl), (median, Q1 to Q3)	1.6 (0.5 to 4.5)	0.5 (0.4 to 0.7)	3.0 (3.0 to 6.0)	<0.001*
ALT (UI/l), (median, Q1 to Q3)	2,180 (652 to 4,259)	703 (343 to 1,091)	3,647 (2,092 to 7,011)	<0.001*

Abbreviations: ALT = Alanine aminotransferase; CAD = coronary artery disease; ICU = intensive care unit; Q1 to Q3 = quartiles 25% to 75%; SD = standard deviation.
* $p < 0.05$.

Bradycardia was mostly observed early during hospitalization. Baseline ECG variables were similar between groups (Table 2). The overall prevalence of significant ECG abnormalities (49.1% vs 9.5%, $p < 0.001$), abnormal ventricular repolarization (35.7% vs 3.9%, $p < 0.001$), QT prolongation (11.4% vs 1.2%, $p < 0.001$) and atrial fibrillation/flutter (2.9% vs 0.3%, $p < 0.001$) was higher than that observed in a cohort of Brazilian healthy adults.[13] In 24 hours Holter, conducted in 32 patients, parameters were similar between G1 and G2 (Table 2) with 44% of the cohort (n = 14) with mean heart rate <60 bpm (8 of which from G2), and 4 of those with pauses >2 seconds. Maximum heart rate tended to be higher in G2, but all other Holter variables were similar between groups (Table 2).

Bedside echocardiography revealed abnormalities in 27 patients (39%), but were more common in G2 (48%, $p = 0.012$). Overall, ventricular diameters and function were similar between groups (Table 2). Mild and moderate left ventricular (LV) dysfunction was observed in 4 (6%) patients, all in G2. LV wall thickening with a hyper-refringent myocardial texture, suggestive of an infiltrative pattern, was observed in 17 (24%) patients (G1 18% vs G2 27%, $p = 0.55$) (Figure 1), with full agreement between independent readers for this finding. Of those, 4 (24%) had mildly increased left atrial diameter. Among the 5 fatal cases, 4 had this pattern.

Among 5 patients with severe YF who underwent cardiac magnetic resonance, one, who also showed hyper-refringent myocardium in echo, had global diffuse hypokinesia of the LV, with areas of late enhancement involving the basal septal wall, suggestive of inflammatory process (myocarditis) (Figure 2). The other 4 patients (being one with hyper-refringent LV pattern) had preserved LV function, without significant structural abnormalities or late enhancement.

Among 3 patients who died and underwent postmortem examination, one (a patient who died after 11 hospital days,

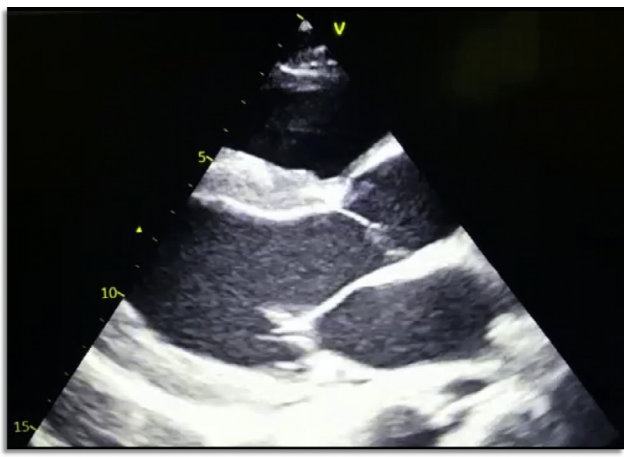

Figure 1. Echocardiographic view showing left ventricular wall thickening, with a hyper-refringent myocardial texture, suggestive of infiltration. A similar pattern was observed in other 16 patients.

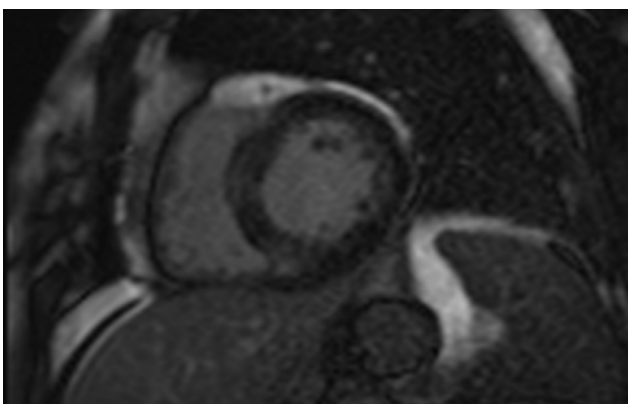

Figure 2. Cardiac magnetic resonance imaging (turboflash sequence) showing areas of late enhancement involving the basal septal wall segments, suggestive of inflammatory process (myocarditis).

Table 2
Baseline characteristics of 12-lead electrocardiogram, 24 hours Holter monitoring and echocardiogram of patients with Yellow Fever, according to disease severity

Characteristic	Overall (n = 70)	Yellow fever severity		p value
		Mild/Moderate YF (n = 22)	Severe YF (n = 48)	
Electrocardiogram (n = 70)				
Heart rate (bpm) (mean ± SD)	60.1 ± 14.4	59.4 ± 11.0	60.4 ± 15.8	0.78
Rhythm				0.67
• **Normal sinus**	50 (71%)	17 (77%)	33 (69%)	
• **Sinus bradycardia**	17 (24%)	5 (23%)	12 (25%)	
• **Atrial fibrillation**	2 (3%)	0	2 (4%)	
P wave (ms) (median, Q1 to Q3)	106 (99 to 111)	106 (98 to 114)	105 (100 to 108)	0.36
PRi (ms) (median, Q1 to Q3)	140 (132 to 158)	154 (140 to 164)	138 (132 to 148)	0.61
QRS (ms) (median, Q1 to Q3)	96 (90 to 102)	98 (93 to 105)	94 (87 to 101)	0.69
QTc (ms) (median, Q1 to Q3)	420 (407 to 439)	409 (401 to 431)	436 (409 to 445)	0.22
Prolonged PRi	0	0	0	N/A
Prolonged QTc	8 (11%)	1 (5%)	7 (15%)	0.22
Abnormal repolarization	25 (36%)	7 (32%)	18 (38%)	0.65
Left bundle branch block	1 (1%)	0	1 (2%)	0.50
Right bundle branch block	2 (3%)	0	2 (4%)	0.33
Abnormal ECG	47 (69%)	11 (52%)	36 (77%)	0.046*
24h Holter monitoring (n = 32):				
Median HR (bpm) (mean ± SD)	64.3 ± 15.6	65.0 ± 23.4	64.0 ± 11.2	0.90
Minimum HR (bpm) (mean ± SD)	44.9 ± 8.1	42.3 ± 4.7	46.0 ± 9.2	0.13
Maximum HR (bpm) (mean ± SD)	94.8 ± 22.8	84.7 ± 15.7	98.7 ± 24.2	0.07
SDNN (mean ± SD)	131.0 ± 50.6	139.5 ± 36.1	128.0 ± 55.3	0.51
Pauses >2 s	4 (13%)	0	4 (18%)	0.20
Mean HR < 60 bpm	14 (44%)	6 (60%)	8 (36%)	0.22
Echocardiogram (n = 70):				
LVEF (%) (mean ± SD)	65.5 ± 8.1	66.3 ± 6.0	65.0 ± 9.0	0.49
LVd (mm)	49.0 (46.0 to 51.0)	48.0 (46.0 to 51.0)	49.0 (45.0 to 51.0)	0.86
LVs (mm)	30.5 (28.0 to 34.0)	30.0 (28.0 to 32.0)	31.0 (27.0 to 34.0)	0.71
LA (mm)	37.0 (34.0 to 39.0)	37.0 (35.0 to 39.0)	36.5 (33.5 to 39.0)	0.64
LV dysfunction				0.39
• **Mild**	3 (4%)	0	3 (6%)	
• **Moderate**	1 (1%)	0	1 (2%)	
LV hypertrophy				0.45
• **Mild/moderate**	7 (10%)	1 (5%)	6 (13%)	
• **Severe**	1 (1%)	0	1 (2%)	
Mitral regurgitation				0.65
• **Mild**	37 (53%)	13 (59%)	24 (50%)	
• **Moderate**	1 (1%)	0	1 (2%)	
Aortic regurgitation (mild)	14 (20%)	8 (36%)	6 (13%)	0.02*
Pericardial effusion	10 (14%)	1 (5%)	9 (18%)	0.12
Hyper-refringent LV	17 (24%)	4 (18%)	13 (27%)	0.42
Abnormal echo	27 (39%)	4 (18%)	23 (48%)	0.012*

Abbreviations: ECG = electrocardiogram; HR = heart rate; LA: left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; LVd = left ventricle diastolic diameter; LVs = left ventricle systolic diameter; Q1 to Q3 = quartiles 25% to 75%; SD: standard deviation.
* $p < 0.05$.

with severe liver injury, renal failure and 3rd degree atrioventricular block) demonstrated multiple brownish-red areas of myocardial necrosis, inflammatory infiltrate, foci acute endocarditis and epicarditis, and thrombosis of the coronary branches. In these infarct areas, fungal hyphae were seen within thrombus in the intramyocardial branches of the coronary arteries and in the cardiac veins (Figure 3). Heart tissue examination of the other 2 patients showed only focal epicardial hemorrhage, without signs of active inflammatory activity.

None of the cardiovascular abnormalities required specific interventions other than supportive measurements, except for one patient with unfavorable outcome who developed advanced atrioventricular block and cardiogenic shock, requiring inotropes.

Discussion

Cardiac manifestations of arboviral infections remain incompletely understood. The recent YF outbreak in Brazil has provided an opportunity for intensive study in a large cohort of severely affected, hospitalized patients, revealing some particular patterns, such as paradoxical bradycardia in patients with prominent inflammatory

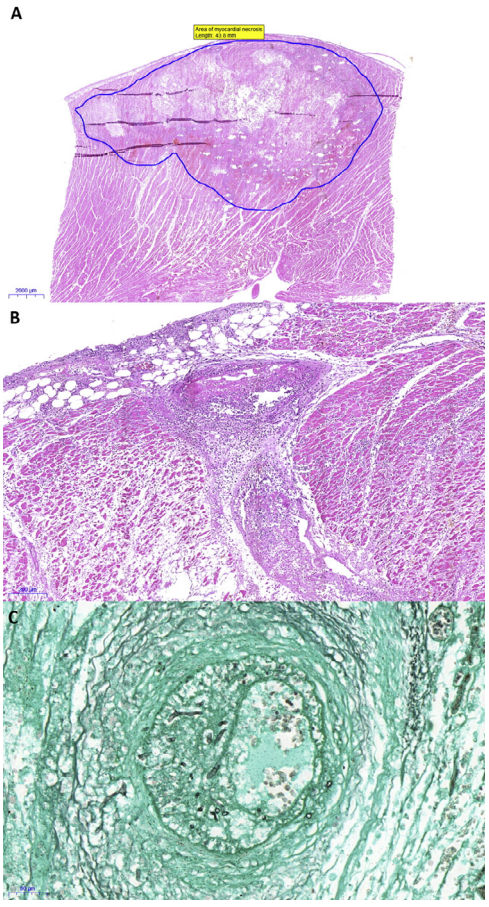

Figure 3. Representative histopathologic images. (A) Area of myocardial necrosis (Hematoxylin & Eosin stain at x0.5 magnification); (B) Thrombosis of the coronary branches, inflammatory infiltrate, and epicarditis (Hematoxylin & Eosin stain at x5 magnification); (C) In these infarct areas, fungal hyphae are observed within thrombus in the intramyocardial branches of the coronary arteries (Grocott's methenamine silver stain at x20 magnification).

response, a range of conduction and repolarization abnormalities and signs suggestive of infiltration and inflammation of the myocardium observed in the 2D echocardiogram, cardiac magnetic resonance and post-mortem examination.

The lethality associated with severe YF ranges from 20% to 50%.[18] Although our population consisted of hospitalized YF patients (therefore, with more severe manifestations of the disease) hospital mortality was lower than expected, probably because the epidemic had started earlier and better treatment strategies were developed, or maybe due to the high prehospital mortality during outbreaks.

More than half of YF patients demonstrated an ECG abnormality. Sinus bradycardia, the classical presentation,[6] abnormal ventricular repolarization and conduction abnormalities may reflect inflammation in the conduction pathways,[7] as seen clinically and histologically in YF-affected primates.[19] Contribution of an YF-triggered abnormal immune response has also been postulated.[20] Atrial fibrillation, as has previously been reported with the arbovirus Dengue,[21] also occurred in our cohort, but was uncommon. Further research is needed to more fully understand the mechanisms and prognosis of ECG abnormalities and arrhythmias associated with arboviruses.

As has been previously reported from other arboviral infections such as Dengue[21–23], Zika,[24] and Chikugunya,[20] YF in its severe forms may also be associated with impaired systolic function. It remains unclearly if this results from direct viral infection[8] or replication[19] leading to cytokine dysregulation,[25] as has been reported in adverse YF vaccine reactions, or as consequence of septic shock, itself elevating cytokine and inflammatory responses and leading secondary to myocardial dysfunction,[26] or perhaps a combination of these factors. Our MRI data showed no robust evidence of classical myocarditis and only rare late enhancement. In one fatal case, necroscopy revealed foci of myocardial necrosis, acute endocarditis, epicarditis, and thrombosis of coronary branches—a histopathological pattern not yet described in YF. The presence of fungal hyphae is possibly associated with the postinfection immunosuppression triggered by cytokine network signaling disorders indirectly associated with YF.[27]

Despite representing the largest sample of YF patients with systematic cardiovascular evaluation, our unicentric study is limited by the lack of longitudinal follow-up and cannot address persistence or regression of cardiovascular abnormalities. Cardiovascular abnormalities occurred more frequently than in the general population, but can only be considered correlated with YF, as our study was not designed to prove causation. More advanced cardiac diagnostic such as MRI and Holter monitoring were applied only in a few patients for logistic reasons, so findings are not representative of the entire cohort. Finally, the number of patients who underwent necropsy was also limited, and more accurate methods for viral detection in the cardiac tissue were not applied.

In conclusion, cardiac involvement was observed commonly in patients with YF—especially with the severe form—and ranged from asymptomatic conduction abnormalities to impaired systolic function. Our findings suggest that detailed cardiovascular examination and ECG should be considered in the assessment of patients with YF, in particular in its severe forms, however a recommendation for routine advanced imaging for all YF patients is not yet supported by literature. Further studies are necessary to understand longitudinal impact of YF on cardiovascular outcomes and to delineate the mechanisms of cardiovascular involvement by the disease.

Funding Statement

The PROVAR+ study is funded Edwards Lifesciences Foundation, US, with local complementary funding by FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais). Echocardiography equipment is provided by General Electric Healthcare. The Telehealth Network of Minas Gerais was funded by the State Government of Minas Gerais, by its Health Department (Secretaria de Estado da Saúde de Minas Gerais) and FAPEMIG (Fundação de Amparo à Pesquisa de Minas Gerais), and by the Brazilian Government, including the Health Ministry

and the Science and Technology Ministry and its research and innovation agencies, CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) e FINEP (Financiadora de Estudos e Projetos). Dr Ribeiro was supported in part by CNPq (Bolsa de produtividade em pesquisa, 310679/2016-8) and by FAPEMIG (Programa Pesquisador Mineiro, PPM-00428-17). Medical students received scholarships from the National Institute of Science and Technology for Health Technology Assessment (IATS, project: 465518/2014-1).

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.032.

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