Cardiac inflammation and ventricular tachycardia in Chagas disease

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Introduction

Chagas disease (CD) is an infection that can affect many different organ systems; in the heart, CD is known to cause cardiac fibrosis, conduction abnormalities, cardiomyopathy (CM), ventricular tachycardia (VT), and sudden cardiac death (SCD). Active inflammation is known to occur in acute infection[1]; however, what role inflammation plays in chronic disease once CM has developed is not well understood. What is known is that CD patients with CM are at risk for monomorphic VT and have a higher mortality compared with other patients with nonischemic CM of other etiologies.[2] The drivers of this increased mortality are not well understood. We postulate that patients with Chagas CM may have ongoing inflammation, in addition to fibrosis/scar (Figure 1), that might contribute to risk of VT.

In this case report, we retrospectively reviewed 2 CD patients cared for at the Olive View–UCLA Center of Excellence for Chagas Disease that were referred to Ronald Reagan UCLA Medical Center for epicardial and endocardial mapping and ablation of VT after recurrent VT storm resistant to antiarrhythmic medications. Each patient underwent an 18F-fluoro-2-deoxy-D-glucose-positron emission tomography (18-FDG PET) as part of their clinical evaluation based on previous data from our center on inflammatory cardiomyopathies.[3]

A diagnosis of CD, with or without known cardiac involvement, was based on serologic testing done through the Centers for Disease Control. All samples underwent immunofluorescence assay and enzyme-linked immunosorbent assay (Chagatest ELISA recombinate v. 3.0, Wiener Laboratorios, Rosario, Argentina) tests. Ischemic CM was ruled out with coronary angiography.

Results

Patient 1

Patient 1 was a 50-year-old man, originally from El Salvador, with a history of hypertension that was first evaluated at our center in 2009 after VT arrest, resulting in anoxic brain injury. He was admitted to the hospital, had a negative left heart catheterization, and was eventually diagnosed with Chagas CM. He underwent implantable cardioverter-defibrillator (ICD) implantation during that hospitalization and was discharged on amiodarone. The patient did well for several years without ICD therapy. His amiodarone was eventually discontinued when he began to develop liver and thyroid issues, and these subsequently stabilized. He underwent ICD battery replacement in August of 2013 and experienced 2 subsequent, appropriate ICD shocks: the first for VT at a rate of 215 beats per minute, the second for VT at a rate of 187 beats per minute. Both events occurred spontaneously at rest.

The patient was therefore admitted to the hospital, where he underwent transthoracic echocardiogram, which showed a left ventricular ejection fraction of 45%-50% without any focal wall motion abnormalities. He subsequently underwent 18-FDG PET imaging, which was significant for areas of intense FDG uptake in the left ventricle (LV), most prominently in the inferobasal and anteroapical segments. He then underwent epicardial and endocardial mapping and ablation of VT. Low-voltage areas were found in the right ventricular outflow tract (RVOT) epicardium, the epicardial basal anterolateral LV, and the LV endocardium below the left coronary cusp. These sites correlated with some, but not all, of the VTs induced during the study. Extensive substrate modification of all abnormal potentials was undertaken. VT ablation was acutely successful and he was discharged from the hospital. However, 10 weeks later, VT recurred with a new slow VT not previously seen (Figure 2), and the patient underwent bilateral stellate ganglionectomy and has subsequently been free of ICD shocks.

Patient 2

Patient 2 was a 46-year-old man, originally from Mexico, who was diagnosed with CD in 2012 after being found to have sick sinus syndrome, first-degree atrioventricular block, and bifascicular block. He had an ICD placed in 2012 for primary prevention after his ejection fraction decreased to 20%. He was subsequently started on amiodarone for VT.

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KEY TEACHING POINTS

- In Chagas disease patients, ongoing inflammation is present even in late-stage cardiomyopathy.
- Inflammation may contribute to ventricular tachycardia in these patients and may be associated with increased mortality.
- 18F-fluoro-2-deoxy-D-glucose-positron emission tomography imaging is useful for identifying these areas of cardiac inflammation.

He presented to the hospital in 2015 for recurrent VT storm, which required treatment with continuous lidocaine drip. He was therefore transferred to UCLA for orthotopic heart transplant consideration and possible VT ablation. He underwent 18-FDG PET, which showed FDG uptake concerning for inflammation in the mid inferior septum. During electrophysiologic study, the only inducible VT arose from the RVOT, not near the mid inferior septal area of inflammation noted on PET. An RVOT VT ablation was attempted but was complicated by RVOT perforation and the procedure was terminated. In the days following, the patient developed subsequent spontaneous VT, and it was noted that this VT had morphology consistent with possible origin from the region of inflammation seen on 18-FDG PET imaging that had not been ablated (Figure 3). The patient's hospital course was unfortunately complicated by septic shock and multiorgan failure, and he died while still in the hospital.

Discussion

The major findings of the present study are as follows:

(1) Active cardiac inflammation appears to continue even during "end-stage" CM secondary to Chagas disease.
(2) Areas of inflammation, as noted by regions of abnormal 18-FDG PET uptake, may contribute to clinical VT, complicating and potentially decreasing the success of VT ablation in this group of patients.

CD, caused by the protozoan *Trypanosoma cruzi*, was previously estimated by the World Health Organization to affect some 16-18 million people throughout North, South, and Central America,[4] including over 300,000 people in the United States, based on a 2009 estimate.[5] Heart disease is the most frequent clinical manifestation of CD, affecting approximately 30% of infected individuals within 20 years after initial exposure.[6] Cardiac involvement is characterized by conduction system abnormalities, CM, VT, and SCD.[6]

Conduction system disturbances, most commonly right bundle branch block and left anterior fascicular block, precede the development of CM by many years, and these findings are thought to be the earliest makers of cardiac involvement. There is known to be a significantly increased mortality in this population by the time conduction system disease develops, even prior to the development of CM.[7] Data from Rassi et al[8] further reinforces that the increased risk of cardiac events in CD patients is not entirely explained by depressed ejection fraction/CM.

Though there is clearly a driver of risk that is present prior to the development of CM, once patients develop CM there is even further increased risk of VT and SCD. Work from our

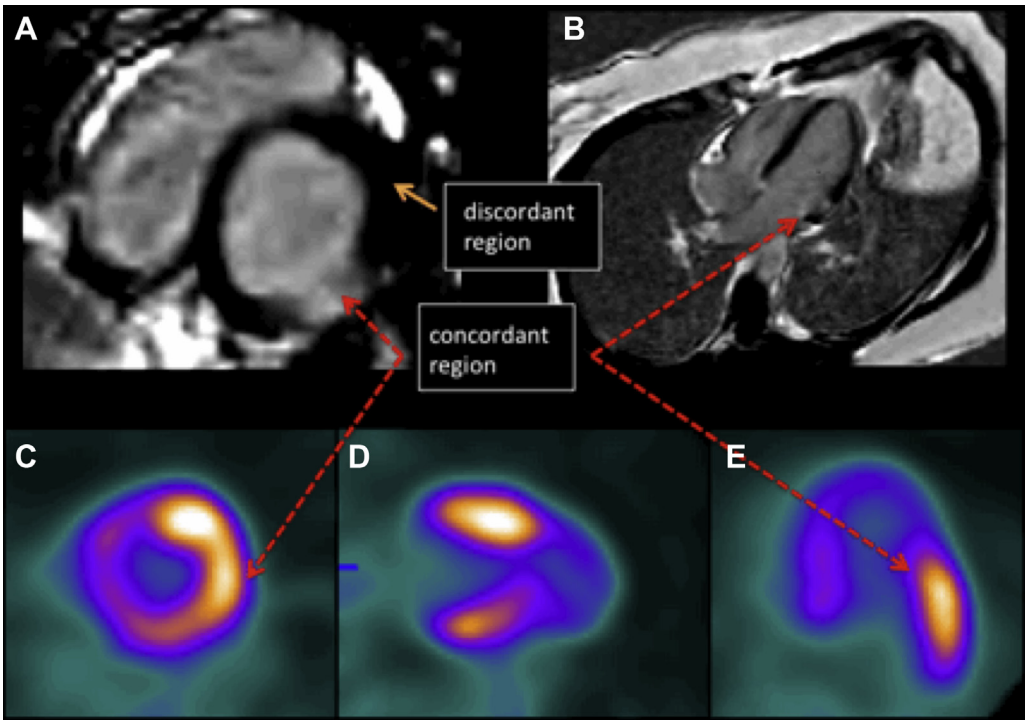

Figure 1 Evidence of cardiac magnetic resonance imaging delayed enhancement consistent with scar in a patient with Chagas disease (**A, B**) and 18F-fluoro-2-deoxy-D-glucose-positron emission tomography (PET) findings (**C-E**), with some regions of overlap (concordant) and others where there is no delayed enhancement but abnormal PET findings (discordant).

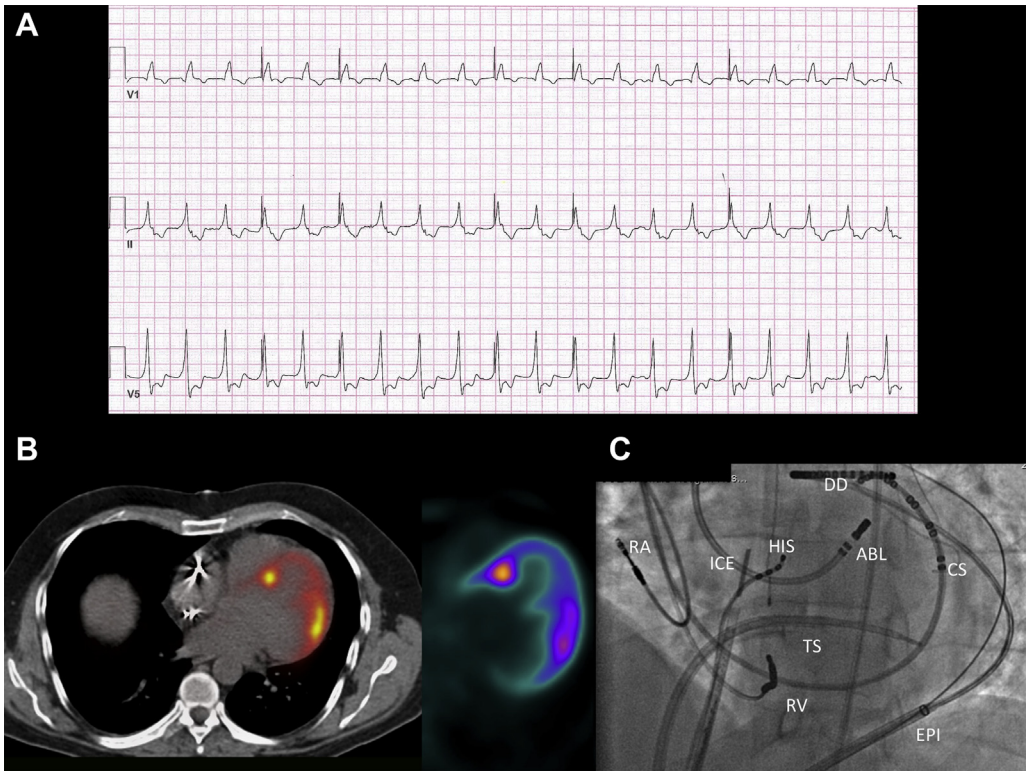

Figure 2 The fluoroscopic left anterior oblique image catheter position during epicardial and endocardial ventricular tachycardia (VT) ablation of Patient 1 is shown (**C**). The patient subsequently returned with sustained slow VT, shown on 3-lead rhythm strip (**A**). The previously obtained 18F-fluoro-2-deoxy-D-glucose-positron emission tomography–computed tomography and associated abnormalities (**B**) are shown. ABL = ablation catheter; CS = coronary sinus; DD = duodecapolar mapping catheter; EPI = epicardial sheath; HIS = HIS bundle catheter; ICE = intracardiac echo catheter; RA = right atrial lead; RV = right ventricular lead; TS = transseptal catheter.

group[9] demonstrates that, in a cohort of CD patients with CD-related, nonischemic CM living in the Unites States, there was a significantly higher risk of mortality (36% vs 10%, $P = .001$) compared with patients with other etiologies of nonischemic CM. Thus, the risk of cardiac mortality in CD patients cannot be explained by CM alone.

To date, the increased SCD rate in the CD population is not completely understood. One theory posits that, in addition to the late-occurring structural abnormalities in the CM subpopulation, there is also a potential autonomic component owing to destruction of parasympathetic innervation[10] that may lead to a mismatch of sympathetic and parasympathetic innervation. Although autonomic dysregulation may certainly play a role, we postulate that persistent cardiac inflammation may also contribute to the increased SCD risk by providing a substrate for VT, before fibrosis develops or in combination with already present fibrosis/scar. Active inflammation alone is not a likely substrate for reentrant VT. However, it may provide a trigger for reentry within adjacent scar, or be a substrate for focal VT.

At present, CD patients are not routinely screened for cardiac inflammation. Further, techniques to assess ongoing inflammation in this population are limited. Electrocardiographic and echocardiographic parameters cannot adequately assess inflammation. Delayed-enhancement cardiac magnetic resonance imaging (MRI) is best suited for assessing fibrosis and scar and has been described in CD.[11] As expected, increased fibrosis appears to be correlated with increased risk of VT in CD,[11] but, as fibrosis and scar are typically representative of late-stage disease, additional modalities that assess early-stage disease and concomitant inflammation during late-stage disease are needed.

In cardiac MRI, dedicated T2 edema imaging[12] may enhance the sensitivity of this imaging modality for identifying inflammation without fibrosis. As such, cardiac MRI has been used in the assessment of acute myocarditis[12] and for differentiating acute from chronic myocardial infarction.[13] However, there are limited data thus far on using cardiac MRI for screening for inflammation in CD patients, and, to date, this technique is not routinely performed at many centers. Further, given that many patients with CD and cardiomyopathy have ICDs or pacemakers in place, MRI is not an option available for CD patients at most centers. Therefore, alternative imaging techniques are needed to identify cardiac inflammation in CD patients.

Until this paper, 18-FDG PET imaging had not been used in the evaluation of CD patients presenting with VT, but it is a validated imaging modality in other cardiac diseases. Specifically, 18-FDG PET imaging has been found to be useful for prognostic assessment of risk of VT and death in patients with cardiac sarcoidosis.[12] Given that CD can cause similar presentations of cardiac inflammation and fibrosis to those seen in cardiac sarcoidosis, and given our finding of potential relationships between areas of inflammation on PET and VT

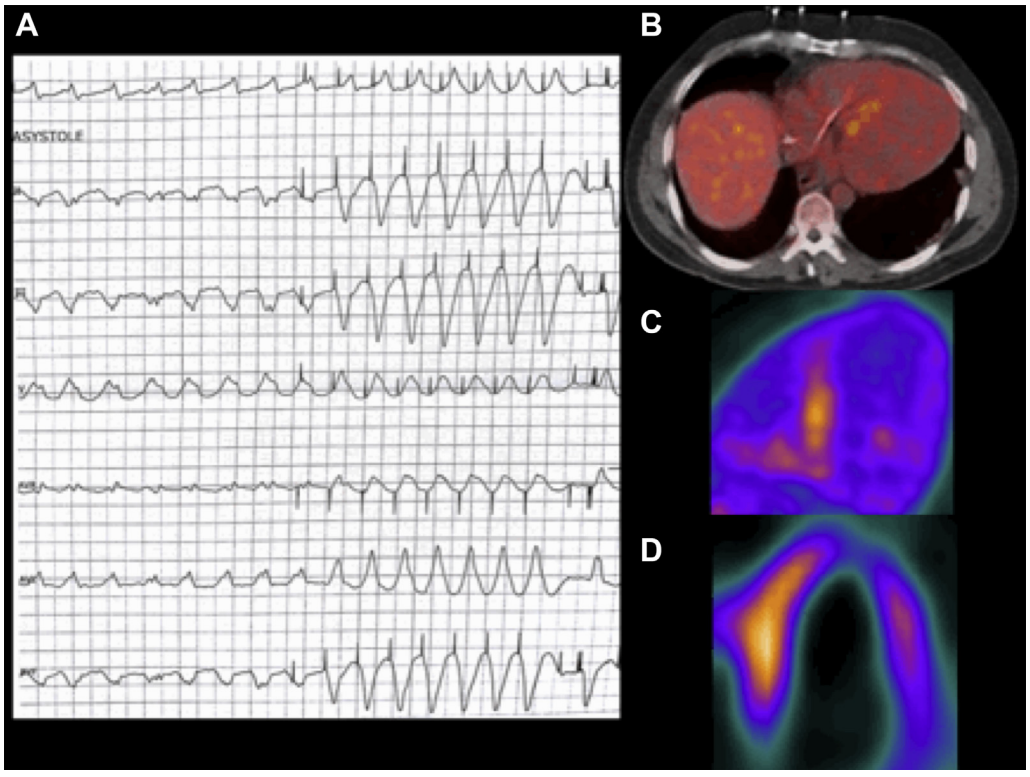

Figure 3 **A:** Electrocardiogram demonstrating inferoseptal ventricular tachycardia (VT) and successful antitachycardia pacing therapy. VT appears to be originating from the corresponding anatomic region of the abnormal 18F-fluoro-2-deoxy-D-glucose-positron emission tomography uptake (**B–D**).

site of origin, we believe 18-FDG PET may provide important clinical data. To our knowledge, the present study is the first to utilize 18-FDG PET imaging in CD.

Limitations

This is a case report from a single center. Signs of abnormal inflammation on 18-FDG PET imaging can be from multiple causes, and therefore we cannot be certain that the abnormal findings were directly related to the diagnosis of CD. VT site of origin cannot be fully determined based on electrocardiogram morphology. The VT exit site can be approximated, but critical sites of origin/reentry may be distant from the exit site.

Conclusions

The 2 cases provided are hypothesis generating: persistent inflammation, not fibrosis in isolation, may play a role in the risk of ventricular arrhythmias in CD patients. Further, 18-FDG PET imaging may provide a useful assessment of the extent of active cardiac inflammation in CD patients. Better understanding of the cardiac abnormalities responsible for the development of VT and/or SCD and proper identification of subclinical cardiac CD may provide novel treatment and risk stratification opportunities.

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