Review Article

What Is Important in the Echocardiographic Evaluation of Patients With Cardiac Sarcoidosis?

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Abstract

Sarcoidosis is a systemic condition, of unclear etiology, associated with the formation of non-necrotizing granulomas in several organs, and thoracic involvement in 90% of the cases. Cardiac impairment is detected in approximately 10% of the patients, reaching 25% in autopsy studies. It is in charge of about half the deaths in patients with sarcoidosis, and an important prognostic factor. Interventricular septum and the left ventricle free wall are the most affected regions, especially in the subepicardial portion. The development of changes in conduction (including atrioventricular block and ventricular arrhythmia) and heart failure are the most common manifestations. Diagnosis is challenging and often requires more advanced imaging examinations, such as positron emission tomography or late-enhancement cardiac magnetic resonance imaging. However, these examinations have high cost and are not so available. The conventional transthoracic echocardiography, on the other hand, is widely accessible, but presents later and little specific findings. The most important ones are the reduction of the left ventricle ejection fraction < 50% and the presence of abnormal tapering of the basal interventricular septum. Other segmental changes, especially when not correspondent to coronary territories, and aneurisms, are also relevant. Besides, there may be diastolic dysfunction, pericardial effusion and right ventricular dysfunction, both due to impairment primary or secondary to pulmonary hypertension. The most advanced ultrasound techniques, such as myocardial strain, myocardial work and elastography, are promising in the search of an earlier diagnosis at a lower cost.

Introduction

Sarcoidosis is a systemic condition, of unclear etiology, with a probable autoimmune component, associated with the formation of non-necrotizing granulomas in several organs and tissues.[1] Its prevalence is about 0.05%[2] and, in about 70% of the cases, it affects individuals aged between 25 and 40 years, with a second peak of incidence in women aged more than 50 years.[3]

Clinical manifestations are diverse, as well as the clinical course of the disease, which can be self-limited or chronic. Thoracic involvement occurs in 90% of the cases, with hilar adenopathy and/or diffuse pulmonary micronodules, especially along lymphatic structures.[1]

Cardiac impairment is clinically detected in about 10% of the patients; however, prevalence reaches 25% in autopsy studies.[4] The interventricular septum and the left ventricle free wall are the most affected regions, especially in the subepicardial portion. The most common clinical manifestations are the development of conduction changes (including atrioventricular blocks and potentially fatal ventricular arrhythmias) and cardiomyopathy, leading to heart failure.[4] Patients may be asymptomatic or present with palpitation, dyspnea, syncope or even sudden cardiac death as a first manifestation.[4]

Cardiac impairment is associated with granulomatous infiltration, and progressive evolution to cicatricial fibrosis. It is responsible for about 50% of the deaths in patients with sarcoidosis,[5] being an important factor for poor prognosis in the disease. Therefore, all patients diagnosed with sarcoidosis should be actively questioned about cardiovascular symptoms and undergo a resting electrocardiogram, with individualized indication for transthoracic echocardiography and a 24-hour Holter test.[6]

There are specific criteria for the diagnosis of cardiac sarcoidosis, both in its isolated form and associated with systemic impairment.[7,8] Such criteria require, in most cases, the performance of advanced imaging examinations, such as gallium[6,7] scintigraphy, ^{18}F-FDG PET/CT (^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography) or late-enhancement cardiac magnetic resonance (CMR) (Figure 1). However, these are expensive and less available examinations, rarely used as initial diagnostic methods. Transthoracic echocardiography, on the other hand, is widely available and has low cost. In this article, we will discuss the main diagnostic and prognostic ultrasound findings associated with cardiac sarcoidosis, as well as the use of more advanced techniques as way to increase diagnostic sensitivity.

Conventional echocardiography evaluation

From the diagnostic point of view, the most important findings are reduced left ventricle ejection fraction (LVEF) < 50% and the presence of abnormal tapering of the basal interventricular septum. Other segmental changes, especially if not correspondent to coronary territories, including the presence of aneurisms, are also relevant. Such findings, despite being associated with more advanced impairment,

Keywords

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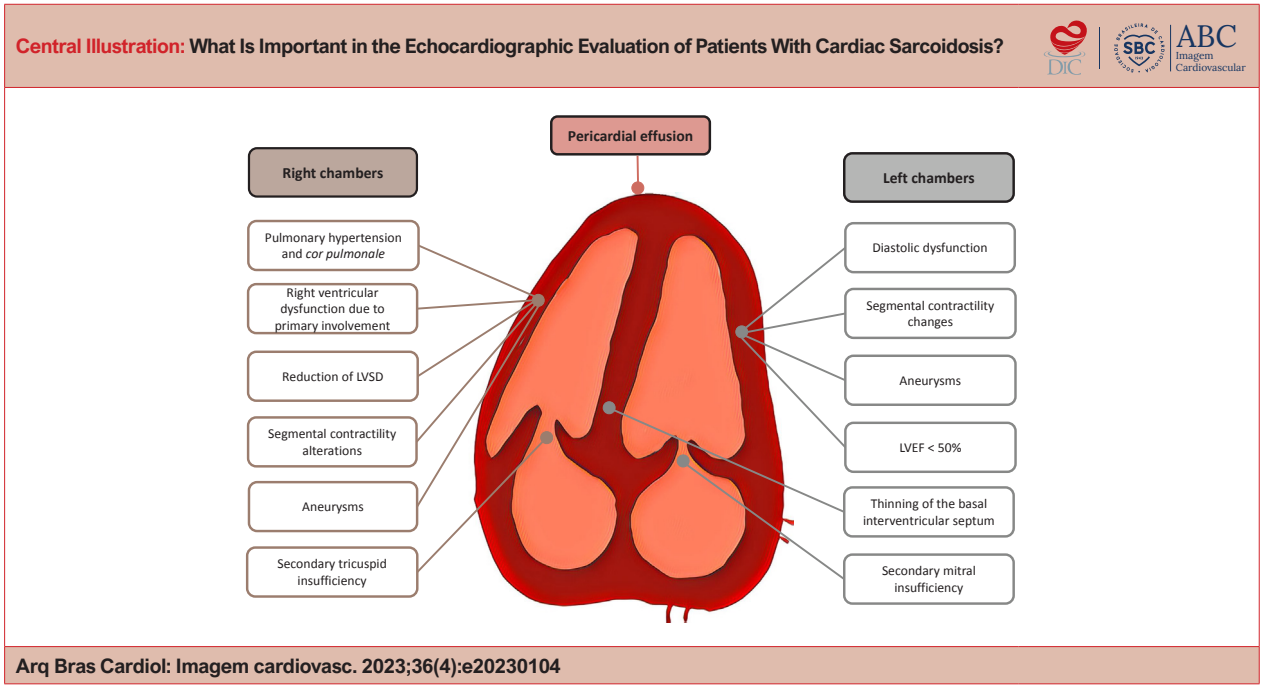

Main echocardiographic findings in sarcoidosis. RV: right ventricle; RV GLS: right ventricle global longitudinal strain; LVEF: left ventricle ejection fraction.

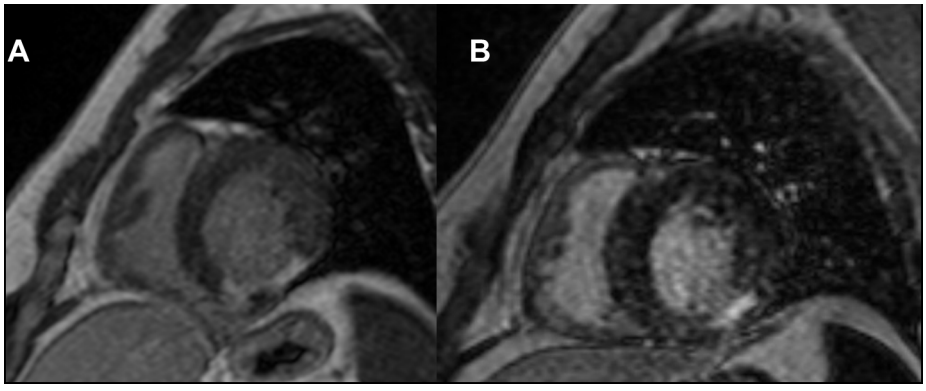

Figure 1 – *Images of a cardiac magnetic resonance of a patient with cardiac sarcoidosis showing akinesia (A) and fibrosis using transmural late enhancement (B) in the inferior lateral and inferior walls, cross-sectional view.*

are contemplated as larger criteria by the main diagnostic algorithm used nowadays.[8] Figures 2 to 4 show these changes in examinations of patients diagnosed with cardiac sarcoidosis.

Diastolic dysfunction, despite not being specific for diagnosis, appears in earlier stages in comparison to the previously mentioned findings, and may suggest an additional investigation in patients with an established systemic diagnosis, or at the presence of suggestive clinical condition. According to a study published in 2019, diastolic dysfunction of the left ventricle was present in 26% of the 77 patients with confirmed diagnosis of systemic sarcoidosis.[9] Therefore, routine echocardiography, according to previously established criteria for other diseases, is essential.

Another important aspect is the analysis of the pericardium, once its direct involvement, after primary myocardial dysfunction, is described in 20% of the patients with cardiac sarcoidosis.[10] The most frequent finding is the presence of small-volume pericardial effusion, but evolution is also described for constrictive pericarditis and cardiac tamponade.

Left ventricular impairment may be primary, due to granulomatous myocardial infiltration, or secondary, due to pulmonary hypertension associated with lung impairment; its analysis is essential using quantitative parameters. The estimated systolic pressure of the pulmonary artery, in echocardiography, showed correlation with the measurements shown by the right catheterization in patients with pulmonary sarcoidosis.[11] Peak

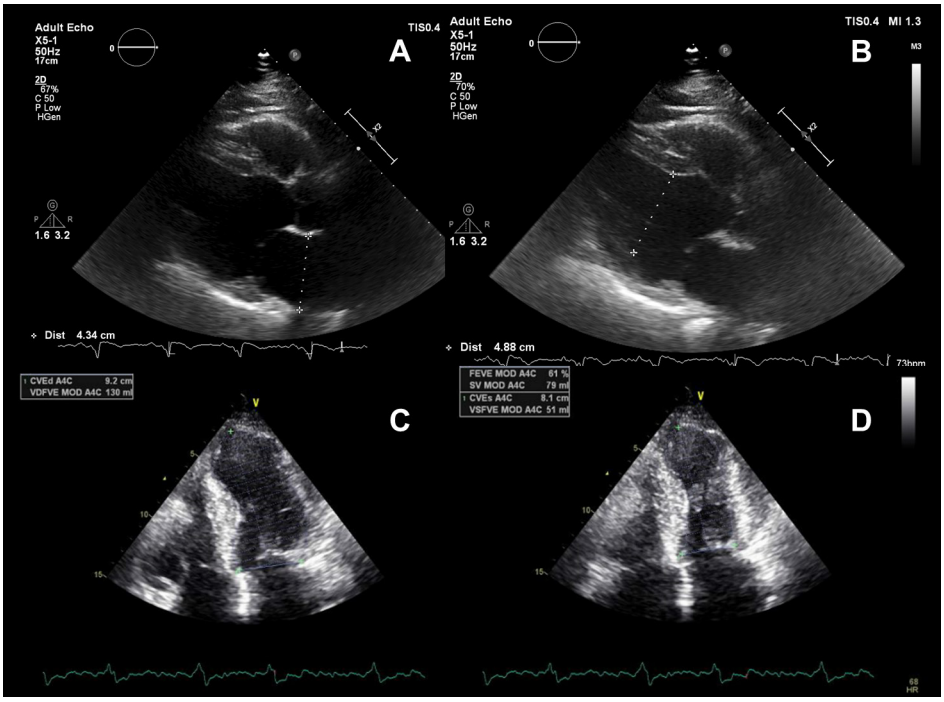

Figure 2 – *Images in transthoracic echocardiography in patient with cardiac sarcoidosis. It is possible to see tapering and akinesia of the basal interventricular septum in the longitudinal parasternal view (A and B). Another patient with cardiac sarcoidosis and dyskinesia of the apical region in apical 4 chamber view (C and D).*

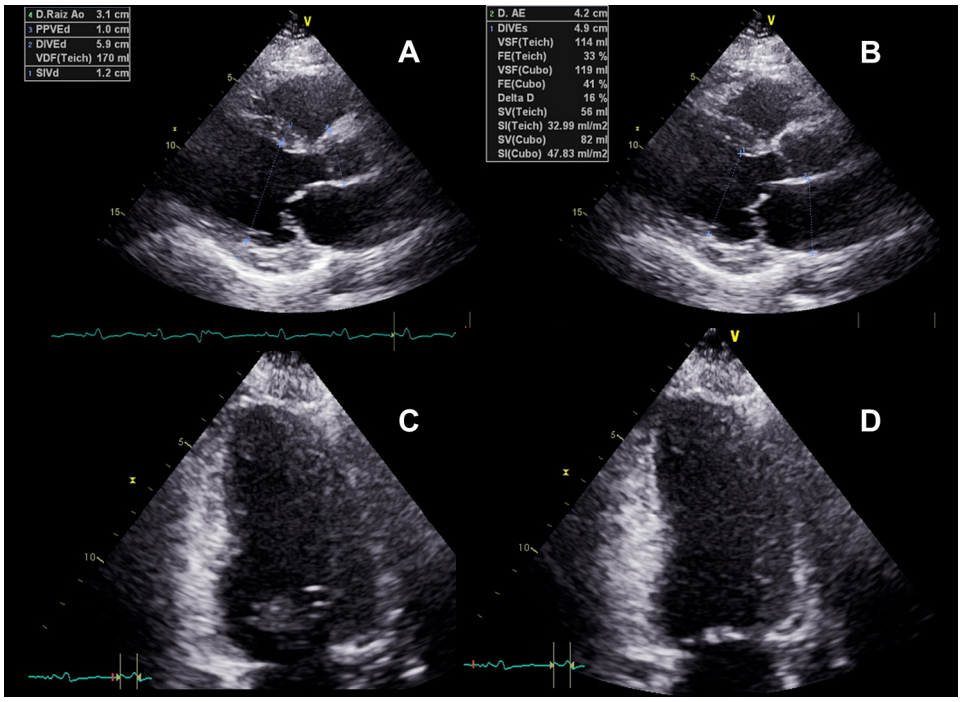

Figura 3 – *Images in transthoracic echocardiography in patient with cardiac sarcoidosis. There is increased refringency and akinesia of the basal segment of the interior lateral wall in the longitudinal parasternal view (A, diastole; and B, systole). The same patient presents akinesia of the basal segment of the inferior wall in apical 2 chamber view (C, diastole; and D, systole).*

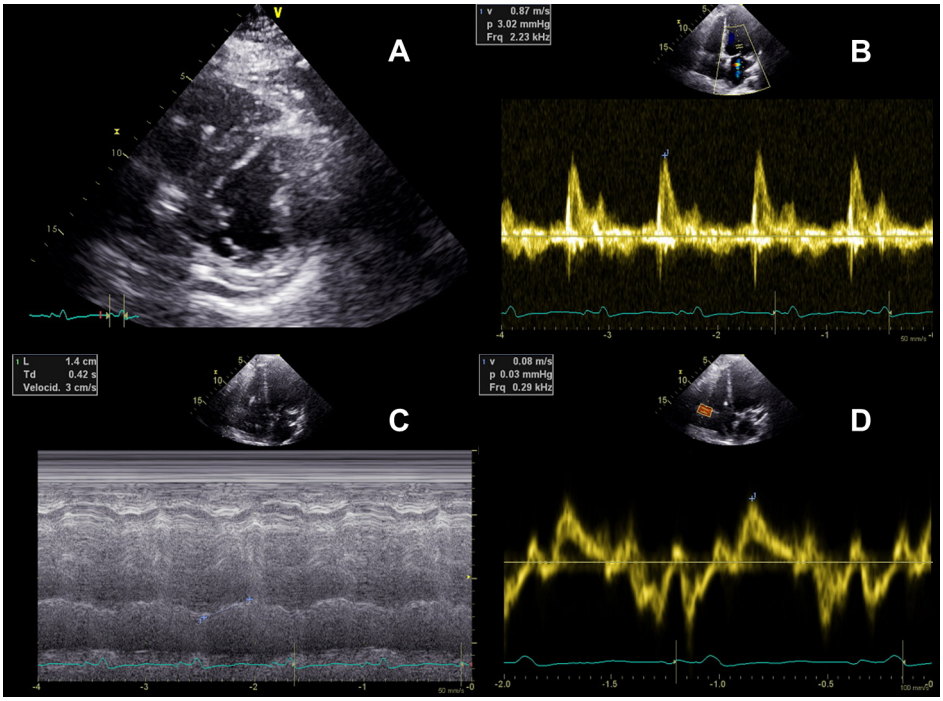

Figure 4 – *Images in the transthoracic echocardiography of patient with cardiac sarcoidosis. There is rectification of the ventricular septum, in the cross-sectional parasternal view, due to pressure overload and pulmonary hypertension, besides mild pericardial effusion in cross-sectional parasternal view (A). There are signs of diastolic function in mitral Doppler, with E/A ratio > 2, and shortened time of deceleration (B), besides systolic dysfunction of the right ventricle, assessed by the reduced tricuspid annular plane systolic excursion (TAPSE = 14 mm; abnormal if < 16 mm), and reduced s' wave of the right ventricular free wall (s' wave = 8 mm/s; abnormal if < 9,5 mm/s).*

tricuspid regurgitation velocity < 2.9 m/s was verified to rule out pulmonary hypertension in these patients, whereas values > 3,4 m/s considerably increase the chances of pulmonary hypertension by invasive measurement.[12]

The central illustration represents the main echocardiography findings associated with cardiac sarcoidosis.

Despite theoretically affecting any portion of the heart, endocardial and valve impairment is less reported. However, a recently published study demonstrated that 68% of the patients with cardiac sarcoidosis and moderate or major mitral insufficiency, presented hypercaptation of some level in papillary muscles, usually both, even when mitral insufficiency was classified as functional.[13] Besides, 61% of the patients presented improvement of at least one grade of mitral insufficiency after treatment with immunosuppressants,[13] raising the hypothesis that inflammation can be more relevant than considered before.

Advanced echocardiography techniques

Among the advanced echocardiography techniques, the evaluation of myocardial strain using the speckle tracking technique is the most analyzed one. Absolute left ventricular global longitudinal strain (LV GLS) lower than 16.3% showed 82.2% sensitivity and 81.2% specificity for the diagnosis of cardiac sarcoidosis in patients with confirmed systemic diagnosis, whereas absolute right ventricular global longitudinal strain (RV GLS) lower than 19.9% showed 88.1% sensitivity and 86.7% specificity.[14]

A meta-analysis published in 2020 assessed 589 patients with confirmed extracardiac sarcoidosis and 378 controls, showing consistent reduction of longitudinal and circumferential global strain in this group of patients, associated with cardiovascular outcomes, such as all-cause mortality, hospitalization due to heart failure, implantable cardioverter defibrillator (ICD) or appropriate therapy with that device.[15]

Myocardial strain was also compared with other imaging methods, and had correlation with the late enhancement findings in CMR.[16] When compared to ^{18}F-FDG PET/CT,[16] there was also an association with the number of myocardial segments with perfusion changes, and both methods had prognostic value.[17]

These data strengthen the use of the strain as a diagnostic and prognostic evaluation tool in these patients, with potential for earlier detection in relation to conventional echocardiographic findings.

Other advanced techniques are currently being analyzed by the Cardiomyopathy Group at Instituto do Coração (InCor). The evaluation of myocardial work and myocardial elastography in patients with confirmed cardiac sarcoidosis and sarcoidosis with no cardiac involvement is ongoing.

Myocardial elastography is an ultrasound modality that allows non-invasive assessment of myocardial stiffness by measuring the

speed of propagation of shear waves naturally generated by the closure of the mitral valve. In media with a known density, it is known that this speed is directly proportional to the tissue stiffness.[18] This technique has already been shown to be feasible in the evaluation of patients with cardiac amyloidosis.[19]

Myocardial work is an approach deriving from myocardial strain, which represents the volume-pressure curve area of the left ventricle, built with data from LV GLS and the non-invasive blood pressure verification. Thus, it incorporates the effects of load variation, not contemplated by other methods, such as LVEF and LV GLS,[18] also being a promising technique for diagnostic and prognostic purposes.

Tridimensional echocardiography (3D Echo) is still little available in transthoracic studies due to the learning curve to perform the examination, besides the costs associated with the specific transducer. The 3D Echo provides more accurate measurements of heart chambers and LVEF, with numbers that are comparable with those obtained in the CMR. This technique was used in patients with sarcoidosis and no diagnosed cardiac impairment, and showed reduction in the left atrial emptying fraction,[20] and increased systolic dissinchrony index (SDI)[21] when compared to control individuals, generating the hypothesis of other possible early markers for cardiac impairment.

Prognostic evaluation by the echocardiography

The most important prognostic factor is the presence of left ventricular dysfunction, related to the extension of cardiac impairment. Besides reduced LVEF, the extension of late myocardial enhancement through CMR and the number of segments with changes in perfusion in PET follow the same reasoning and are associated with negative cardiovascular outcomes.[22]

Another prognostic data that is easy to verify is the thickness measurement of the interventricular septum basal portion $\leq$ 4 mm, which was considered as an independent predictor of adverse events (all-cause mortality, heart failure leading to hospitalization and severe symptomatic arrhythmias).[23]

As previously discussed, myocardial strain presents prognostic value in many studies. LVEF lower than 14% was significantly related to hospitalization and heart failure.[14]

Challenges in echocardiography assessment

Conventional echocardiography findings are often unspecific or late. Besides, the differential diagnosis with other cardiomyopathies, or even with coronary artery disease, can be challenging. Therefore, the development of advanced techniques that can be incorporated to conventional examination, without substantial increase in cost, is very relevant.

Some technical aspects related to the method also made evaluation difficult, such as limitation in the acoustic window of patients with excess weight, often associated with the chronic use of corticoids, or extensive lung impairment. In these situations, the use of ultrasound enhancement agents can facilitate the evaluation of segmental dysfunction, tapering and aneurism, and should be used when available.

Conclusion

Despite the limitations, transthoracic echocardiography has several benefits and is indispensable in the clinical practice of the cardiologist, including to evaluate patients with cardiac sarcoidosis.

The detailed evaluation of biventricular function, searching for the findings that are most suggestive of cardiac impairment caused by sarcoidosis, is essential, especially in cases of clinical suspicion or patients that have already been diagnosed with the systemic form of the disease, leading it to more specific imaging examinations. In this context, the use of myocardial strain with speckle tracking should be encouraged and performed whenever technically possible.

In the future, the domain of advanced ultrasound techniques by the echocardiographer promises to increment the diagnostic and prognostic evaluation of these patients, allowing earlier treatment and better clinical outcomes.

Author Contributions

Conception and design of the research: Santorio NC; acquisition of data and writing of the manuscript: Santorio NC, Santorio PT, Hotta VT; critical revision of the manuscript for intellectual content: Fernandes F, Hotta VT.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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