REVIEW ARTICLE

Cardiac Imaging in Systemic Diseases: What the Clinician should Know

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Abstract: *Importance*: Systemic diseases that affect the cardiovascular system constitute a diagnostic and therapeutic challenge for all specialists involved; imaging tools along with clinical suspicion play an essential role in their evaluation. These entities share neurological, immunological, renal, hematologic, oncologic, infectious and endocrine processes, all of which may have associated cardiac involvement.

Observations: Recent advances in cardiac ultrasound, Computed Tomography (CT), cardiac Magnetic Resonance (CMR) and nuclear scintigraphy have impacted the management of these conditions when involving the heart since they provide valuable anatomical and functional information while avoiding the use of invasive techniques.

For this review, bibliographic sources were gathered from diverse databases, including PubMed, Cochrane, EBSCO and Google Scholar, concentrating on English language publications dealing with the clinical use of these tools.

Conclusion: Clinical suspicion should always guide the use of imaging since in many instances, these techniques only play a supportive role rather than representing a diagnostic gold standard. Early diagnosis is critical due to the fact that cardiac manifestations are commonly a late phenomenon.

1. INTRODUCTION

Systemic diseases often involve several organs and the cardiovascular system is one of the most affected. It is not yet entirely clear how they can damage cardiac tissue, but various theories suggest intracellular and extracellular interactions, genetic mutations, autoimmune reactions and inflammatory modulators as possible mechanisms [1].

Chronic conditions may provoke endothelial dysfunction and vascular injury due to disruption of homeostatic mechanisms of the blood vessels mediated by proinflammatory molecules such as Tumor Necrosis Factor-alpha (TNF-α) and interleukins (IL-1, IL-6) [1]. These can further activate macrophages and other inflammatory cells responsible for the accelerated atherosclerosis seen in some of these illnesses or induce granuloma formation such as in the case of cardiac sarcoidosis [2]. Deposition of immune complexes in the vasculature may aggravate the endothelial injury and might be related to the aseptic valvular vegetations present in

Systemic Lupus Erythematosus (SLE) [3]. Inflammatory molecules and related growth factors (*i.e.* fibroblast and platelet-derived growth factors) may also trigger periadventitial fibrosis and narrowing of the microvasculature with subsequent ischemia as seen in systemic sclerosis [4].

This review will discuss entities of high clinical interest, either by their frequency or phenotypic complexity, emphasizing the role played by different imaging methods in their clinical approach.

2. CARDIAC SARCOIDOSIS

Cardiac sarcoidosis represents a syndrome of unknown etiology whose clinical expression results from non-caseating granulomas infiltrating the myocardium of the inferior, anterior, lateral and septal segments of the Left Ventricle (LV) as well as the papillary muscles and right ventricle. Granulomas may also cause ventricular arrhythmias and disorders of the Atrioventricular (AV) conduction system and His bundle [2].

Cardiac involvement is found at autopsy in up to 30% of patients with extra-cardiac sarcoidosis. Its incidence varies between genders and ethnic groups, women younger than 50 years, Japanese, Scandinavian and African Americans being

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affected the most [2]. Cardiac involvement should be suspected in middle-aged adults with extra-cardiac sarcoidosis associated with persistent AV block, idiopathic monomorphic Ventricular Tachycardia (VT), ventricular aneurysms or systolic dysfunction. Heart failure (40-60%), advanced AV block (20-50%), VT (23%), syncope (31%), sudden death as the initial symptom (40%) and atrial arrhythmias (20%) are the most common clinical presentations according to some reports [5].

The diagnostic approach should include a complete history and physical, chest X-ray, Electrocardiogram (ECG), Holter monitoring and an echocardiogram as an initial imaging tool. It is generally accepted that for the definitive diagnosis of cardiac sarcoidosis, two major criteria or one major and at least two minors must be met [6]. Major criteria include: myocardial accumulation of gallium-67, advanced AV block, an Ejection Fraction (EF) lower than 50%, and marked thinning of the basal portion of the interventricular septum. Minor criteria include: arrhythmias, ECG abnormalities such as pathological Q waves, conduction disorders other than AV block, segmental LV dysfunction on echocardiography, myocardial perfusion defects detected with thallium-201 or technetium-99 diphosphate, and Late Gadolinium Enhancement (LGE) on CMR. Although not included in diagnostic guidelines, increased uptake of 18 fluorodeoxyglucose (18F-FDG) in a diffuse or focal pattern in Positron Emission Tomographic (PET) imaging is a very sensitive sign of active cellular inflammation; this tool is recommended in cases of high clinical suspicion without confirmation by other modalities [7].

Additional findings in sarcoidosis include valvular insufficiency, ventricular aneurysms particularly in those treated with steroids, diastolic dysfunction with altered myocardial deformation and pulmonary hypertension as a late manifestation. The combination of thinning of the basal septum, significant mitral regurgitation, distortion of the papillary muscles and regional systolic dysfunction in a pattern without coronary distribution is strongly suggestive of cardiac sarcoidosis [2] (Fig. (**1**); video 1).

CMR is a useful diagnostic modality in this entity because of its high spatial resolution and tissue characterization capabilities [7, 8]; it allows early detection of regional inflammatory activity, assessment of tissue response to steroid treatment and optimizes the quantification of ventricular volumes and function [9]. It also provides prognostic information since the presence of fibrosis suggests a late and irreversible phase of the disease. In these cases, LGE appears in a fibrotic patchy pattern sparing the sub-endocardium (Fig. **2**; A and B, video 2).

Watanabe *et al*. [10] analyzed duration and characteristics of cardiac sarcoidosis and their relationship with LV function. Images in 17 out of 19 patients in this series showed LGE primarily in the sub-epicardial layer. When CMR was
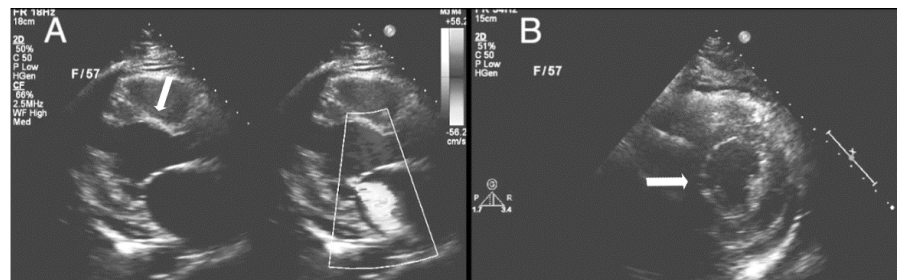

Fig. (1). A. Parasternal long axis echocardiographic images of a 56-year-old woman with uveitis and pulmonary sarcoidosis. Note a small pericardial effusion, left atrial dilation, mild to moderate mitral regurgitation, and reduced ejection fraction. Thinning of the basal segment of the interventricular wall caused by fibrosis and granulomatous infiltration (arrow) is also seen. **B**. Parasternal short axis view shows systolic dysfunction and thickening of the posterior papillary muscle (arrow).
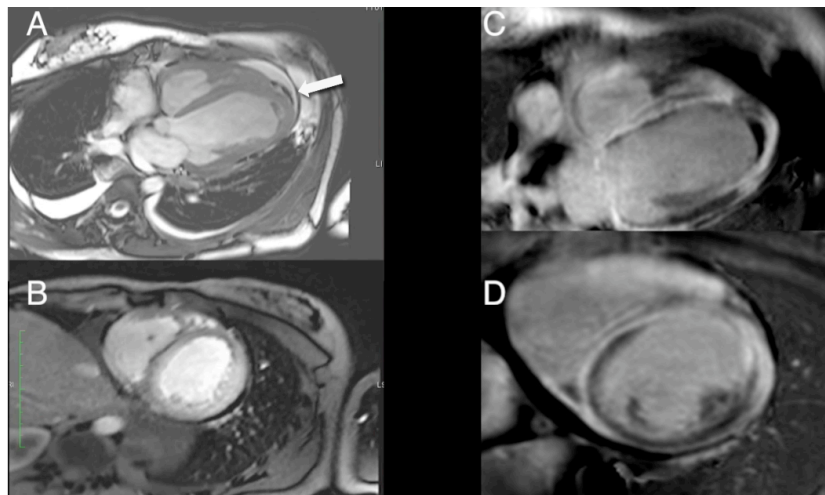

Fig. (2). CMR of a patient with advanced sarcoidosis revealing severe systolic dysfunction, biventricular dilation and apical thrombus (arrow) (**A**), diffuse scarring of the ventricular walls including the apex (**B, C D**) and thickening of the mitral sub-valvular apparatus.

added to the classic JMHW (Japanese Ministry of Health and Welfare) diagnostic criteria, cardiac sarcoidosis was detected in 26% of cases in contrast to 12% when only classic JMHW criteria were applied. LGE was also associated with higher adverse events including cardiac death, with a 20-fold increased risk, as validated in a larger case series recently published by Greulich [11].

Although PET scanning offers the advantage of measuring the extent of cardiac and extra-cardiac inflammation, it must be recognized that increased 18F-FDG uptake may be non-specific since it can be seen in other cardiac conditions associated with active inflammation as well [12]. Recently, Vita *et al.*, proved that in selected patients with suspected cardiac sarcoidosis, the combination of CMR and PET findings offers complementary value for the diagnosis and management of the disease. They found that when PET results were added to CMR, 45% of patients were reclassified to having a higher or lower likelihood of cardiac sarcoidosis, with 11% being reclassified to having highly probable (*e.g.*, >90%) involvement. However, not all patients being evaluated for this condition need both CMR and PET imaging; individuals who are most likely to benefit from either include those with equivocal or negative CMR findings in the setting of high clinical suspicion and those with high probability of cardiac sarcoidosis by CMR, in which cases, FDG PET could serve to identify inflammation/potential role for immunosuppressive therapies [13].

Patients with suspected cardiac sarcoidosis benefit from simultaneous PET/MR imaging (hybrid imaging) as the result of improved spatial resolution of LGE sequences. Better defined areas of myocardial infiltration can be further characterized by their metabolic activity on PET images as inflammatory or scar-related, supplementing the less specific MR sequences. PET also offers a complete whole-body assessment of extracardiac involvement that is less accessible by MR imaging alone [14].

3. CARDIAC AMYLOIDOSIS

The Amyloidoses represent distinct entities characterized by deposition of proteinaceous materials that may involve several organs including the heart. Cardiac involvement varies depending on the particular type but usually plays a significant role in the morbidity and mortality of the affected individual. Light chain immunoglobulin (AL) amyloidosis involves the heart in 50% of cases and its etiology is related to excessive production and deposition of monoclonal light chain immunoglobulin, as it may occur in multiple myeloma and benign gammopathies. Both myocardial architecture and tissue function are eventually lost, leading to irreversible heart failure. Life expectancy is often poor once symptoms develop, especially in cases with concomitant systemic disease [15].

Hereditary transthyretin-related amyloidoses (ATTR) subclassified in mutant (ATTRm) and wild-type (ATTRwt) tend to affect the heart in a very different pattern than the other variants of the disease; also known as familial amyloid polyneuropathy. They are transmitted as an autosomal dominant trait and caused by a transport protein primarily synthesized by the liver with predominant neurological and cardiac clinical manifestations [16].

Generally, cardiac amyloidosis should be suspected on echocardiography in the presence of a thickened myocardium in subjects without a history of systemic hypertension and with low voltage on ECG, although the latter has a poor sensitivity (25% in ATTR and 50% in AL). Patients may develop heart failure, conduction disorders and infiltrative changes in the peripheral arterial system responsible for the orthostatic hypotension commonly found in this condition. Obtaining extra-cardiac tissue in systemic involvement and myocardial biopsy for diagnostic confirmation was previously the only method available, however with the development of advanced imaging techniques, mainly CMR, histological sampling may not be needed in many cases [16].

Echocardiographic findings are usually not specific enough to confirm the diagnosis. Frequently, thickened LV walls with a granular appearance, atrial dilation, thickening of valvular tissue and interatrial septum wall and occasionally pericardial effusion can be found. In more advanced stages of amyloidosis, reduced EF, mitral and tricuspid regurgitation and patterns of restrictive LV filling may also appear [17].

Patients with any form of cardiac amyloidosis reveal a typical pattern of distortion in longitudinal myocardial deformation parameters as seen on echocardiographic speckle tracking strain imaging mainly affecting the basal segments of the LV and sparing the apex. These changes initially occur at the expense of sub-endocardial fibers dysfunction that leads to a fall in longitudinal strain with preserved ejection fraction. They carry diagnostic and prognostic implications independent of clinical findings and biomarkers, such as troponin and NT-proBNP, that have also been used as predictors of therapeutic response [18, 19].

In the presence of heart failure with preserved EF and left ventricular hypertrophy, it is necessary to maintain a high level of suspicion for amyloidosis in the differential diagnosis. In most cases, LGE on CMR allows the differentiation between hypertensive cardiomyopathy, amyloidosis and hypertrophic cardiomyopathy [15] (Figs. **3** and **4**, and videos 3 and 4).

Amyloid deposition within the cellular structure alters the distribution of gadolinium kinetics between blood and myocardium, consequently in most patients with amyloidosis shortening of subendocardial longitudinal relaxation time in T1 and the difference between the signal shown in T1 and blood (which indicates rapid uptake of contrast in the deposits and their rapid return to the circulation) become useful parameters. Typically, LGE appears in a diffuse pattern of global enhancement with subendocardial predominance that correlates with amyloid deposits with a specificity of up to 97% compared with biopsy [16].

It is important to recognize that patients with amyloidosis can have significant renal involvement and the use of gadolinium contrast may be restricted given the potential risk for systemic nephrogenic fibrosis. In these instances, the quantification of myocardial interstitial volume expansion caused by amyloid can be done through software modifications of CMR and time image acquisition protocols obviating the risk involved with gadolinium. These early changes in subclinical
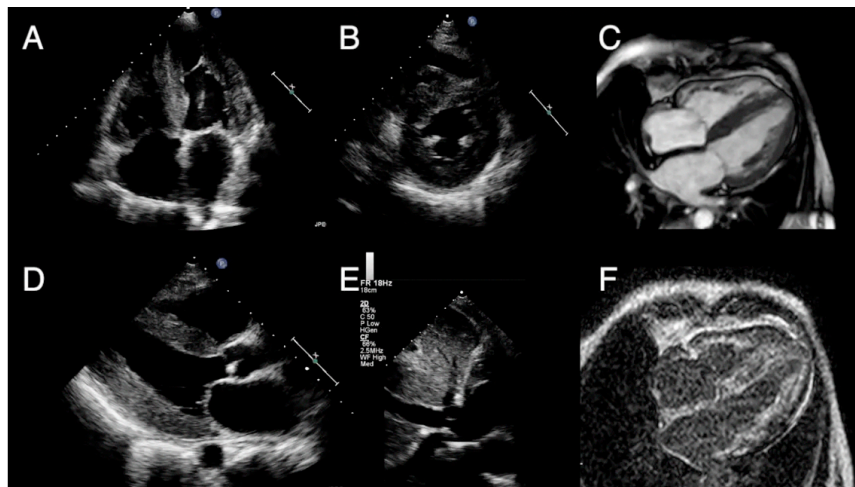
Fig. (3). Typical findings of amyloidosis with cardiac infiltration: (**A**) Apical 4 chamber view of an echocardiogram showing dilation of both atria and thickening of the mitral valve leaflets and both ventricles. (**B**) Parasternal short axis view depicting a preserved LV ejection fraction. (**C**) CMR demonstration of biatrial dilatation, AV valve insufficiency, biventricular and interatrial septal thickening. (**D**) Parasternal long axis view revealing a myocardial granular pattern. (**E**) Subcostal window indicating dilation and diminished excursion of the IVC compatible with elevation of right heart pressures. (**F**) CMR showing LGE in a global and diffuse pattern, including the interatrial septum, without a coronary distribution.
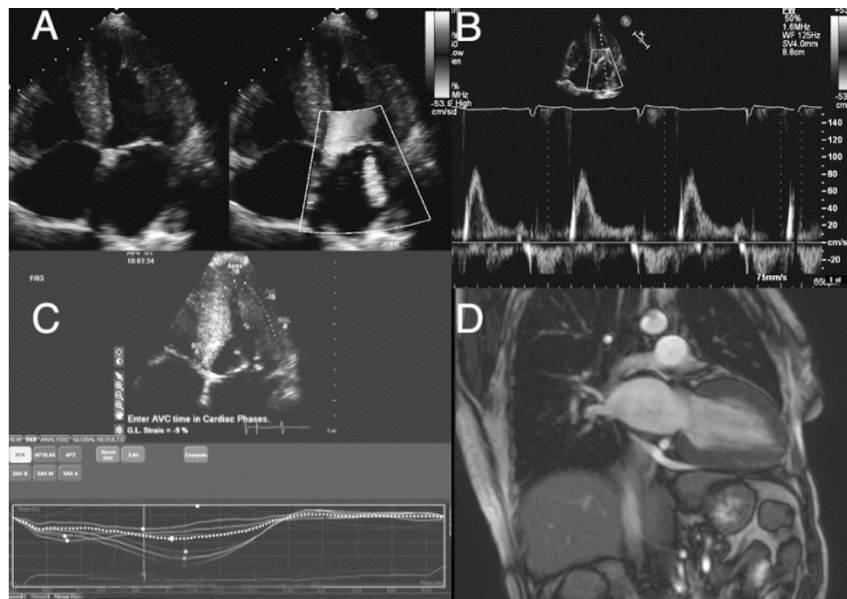

Fig. (4). Cardiac Amyloidosis: (**A**) Apical 4 chamber view of an echocardiogram showing biventricular wall thickening, systolic dysfunction and mild AV valvular insufficiency. (**B**) Transmitral pulsed waved Doppler revealing a 'restrictive' filling pattern (prominent E wave and shortened deceleration time). (**C**) Strain curve with reduced longitudinal deformation of the inferior basal and septal myocardial segments. (**D**) Two chamber view on CMR illustrating a small pericardial effusion, systolic dysfunction and elevation of the right sided venous pressures.

disease could have significant implications on management and prognosis [15].

It has been suggested that multimodal nuclear imaging with $_{123}$I- metaiodobenzylguanidine (MIBG) could be a helpful tool in the detection of early cardiac amyloidosis, even sooner than other imaging modalities. This tracer works as an analog to norepinephrine and shares similar uptake and storage in sympathetic nerve endings. However, unlike norepinephrine, MIBG suffers little enzymatic degradation. Due to these characteristics, it has been FDA approved for the assessment of myocardial sympathetic innervation in patients with New York Heart Association (NYHA) class II or class III heart failure and LVEF lower than 35% [20].

Similarly, radiolabeled tracers such as ^{99m}Tc-PYP and ^{99m}Tc-DPD are very useful in the differentiation of AL from transthyretin cardiac amyloidosis [20]. In AL amyloidosis, ^{99m}Tc-DPD uptake is absent or weak, as opposed to ATTR where the opposite occurs, a finding proven to be quite sensitive and specific. ^{99m}Tc-PYP uptake can also be seen in subacute myocardial infarction and therefore concurrent SPECT perfusion imaging will be useful for accuracy enhancement [21]. This imaging method is generally performed

with planar imaging and is limited to patients with large body index or claustrophobic, otherwise gated SPECT is recommended whenever possible [22]. In a recent study published by Bokhari *et al.*, 45 subjects (12 AL, 16 ATTRwt, 17 ATTRm) with biopsy proven amyloidosis underwent 99mTc-PYP SPECT. Images were evaluated with both a semi-quantitative visual score in relation to bone uptake (0 = no cardiac uptake to 3 = high uptake greater than bone) and applying quantitative analysis by drawing a region of interest (ROI) over the heart and calculating a heart-to-contralateral ratio (H/CL). LV wall thickness and mass correlated to the degree of cardiac tracer retention in the heart similar to what has been reported for 99mTc-DPD. Individuals with ATTR cardiac amyloid had notably higher semi-quantitative cardiac visual scoring and quantitative score than the AL cohort. With a H/CL ratio >1.5, meaning intensely diffuse myocardial tracer retention, a 97% sensitivity and 100% specificity has been described for identifying ATTR cardiac amyloidosis [23] (Fig. **5**). A positive phosphate scanning translates to a high number of amyloid fibrils in the heart, and this finding facilitates an earlier diagnosis, management and improved prognosis. Different to ^{99m}Tc-PYP, MIBG does not bind directly to amyloid deposits, as a result $_{123}$I-MIBG scintigraphy may reveal the extent of damage caused by amyloid deposition in cardiac nerve endings [16].

Of the bone seeking radiotracers, 99mTc-DPD has been the most studied to evaluate its use for cardiac amyloid imaging. Currently, this isotope is not approved by FDA and consequently not available for clinical use in the United States [20]. In 2005, Perugini *et al.* performed 99mTc-DPD imaging on 25 patients with cardiac amyloidosis (10 ATTRm, 5 ATTRwt, 10 AL) biopsy proven with typical echocardiographic appearance. A strong myocardial uptake of 99mTc-DPD was seen in all 15 ATTR subjects while no

uptake was observed in AL patients with 99mTc-DPD myocardial uptake being 100% sensitive and 100% specific for diagnosing ATTR cardiac amyloidosis. This tracer uptake also has prognostic significance leading to its widespread use among amyloid centers in Europe [24].

4.   GRANULOMATOSIS WITH POLYANGIITIS (WEGENER´S)

This is a rare form of vasculitis first described in 1936, which affects small and medium vessels predominantly in the upper respiratory tract and kidneys. Cardiac involvement at autopsy occurs in 30% of cases with clinical disease, prevalence ranging between 6% and 12%. Other series have shown that 40-60% of patients with granulomatosis with polyangiitis (GPA) have histological lesions that are indicative of heart involvement [25, 26].

A wide range of cardiovascular complications have been described including cardiomyopathy, pericarditis, coronary arteritis, conduction abnormalities and valvular disease [26]. In most instances, the myocardium and pericardium are compromised with valvular disease being extremely rare. Since the initial description of its impact on the cardiovascular system, many cases have been reported limited to isolated lesions in the mitral and aortic valves causing regurgitation with or without dilation of the aortic root [25].

Although the morphology of the valvulopathy in Wegener´s simulates conditions as diverse as endocarditis and myxomas, histopathological analysis is usually diagnostic and typically shows myxoid degeneration. It is important to consider this condition in the differential diagnosis of valvular pathology of uncertain cause since treatment with steroids may obviate the need for surgery [25] (Figs. **6** and **7**; video 5).
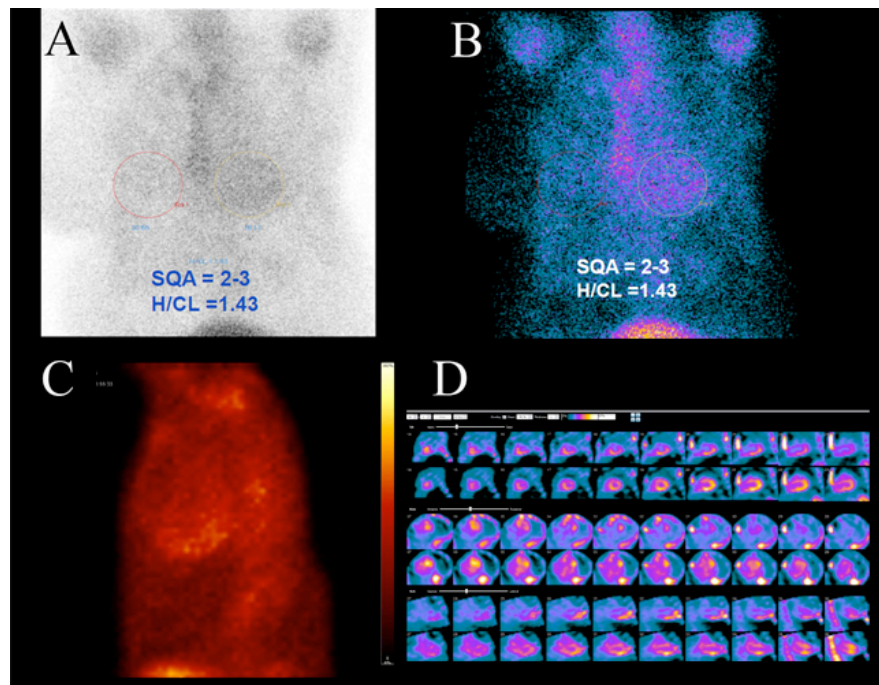

Fig. (5). Cardiac amyloidosis. ^{99m}Tc-PYP bone seeking tracer image obtained in an 87-year-old female. Planar anterior and left lateral projections of semi-quantitative visual analysis showing score 2-3: moderate to high uptake equal or greater than bone (**A, B, C**). SPECT imaging acquired according to Dorbala *et al.* [37] (**D**).
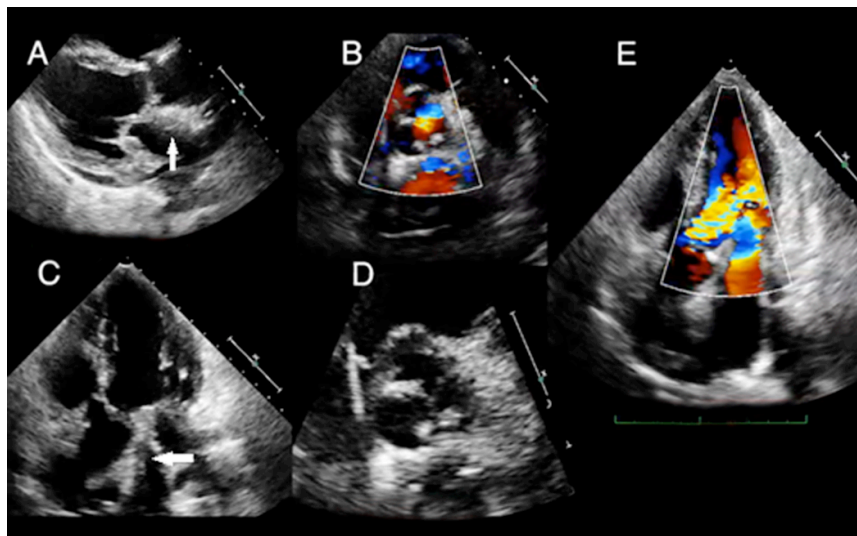
Fig. (6). Elderly patient with Wegener's presenting with Heart Failure. Notice thickening and invasion of the left atrial wall (**A, C**) (arrow), mitral and aortic valves causing severe insufficiency (**B, D, E**).

Fig. (7). CT scan of the patient described in Fig. (**6**) showing the extent of infiltration in the left atrial wall (arrows).

Interestingly, Walsh *et al.* [27] reported that 5.7% of 535 patients with recently diagnosed GPA with cardiovascular findings had a significantly higher rate of disease relapse than patients without cardiac disease. More recent publications have addressed findings on imaging modalities and their relationship with clinical manifestations. Pugnet *et al.*, [28] found that 61% of patients with GPA had at least one abnormality on CMR compared with 31% seen by echocardiography; disease duration over 18 months was associated with hypokinesia affecting multiple cardiac segments or with LGE. Similarly, symptomatic subjects and those with relapsing disease had more CMR abnormalities than new-onset GPA patients suggesting a correlation between extent of vasculitis and impairment of LV function.

5. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE is an autoimmune disease of chronic nature with intermittent episodes of exacerbation and a prevalence of 1:2500. Like rheumatoid arthritis, its cardiac manifestations include early vascular compromise secondary to progressive atherosclerosis without *in situ* thrombosis as well as direct effects on the cardiac valves and pericardial tissue. Advanced age, duration and severity of the disease and use of corticosteroids and immunosuppressive therapies are some of the factors that can change the course of SLE [29].

SLE patients with chest pain and no obstructive CAD on cardiac CT represent a diagnostic challenge. Ishimori *et al.*, [30] suggested that chest pain in this setting is due to myocardial ischemia owing to microvascular dysfunction as demonstrated by perfusion abnormalities on stress CMR identified in 44% of patients compared with none among control subjects. In a recent series, Varma *et al.*, [31] suggested that visualization of coronary vessel wall contrast enhanced with LGE may represent a potential new indicator of subclinical remodeling allowing early recognition of coronary involvement on SLE patients before the presentation of symptomatic disease. Although coronary vasculitis may lead to clinical events, more frequently "traditional" atherosclerosis is seen on the coronary arteries implying an accelerated progression of the disease among SLE victims. Furthermore, CMR is capable of measuring plaque composition and inflammatory activities allowing clinicians to identify atherosclerotic changes that are characteristic of SLE [32].

The typical valve lesion in SLE is Libman-Sacks "endocarditis" secondary to infiltration of the endocardial tissue
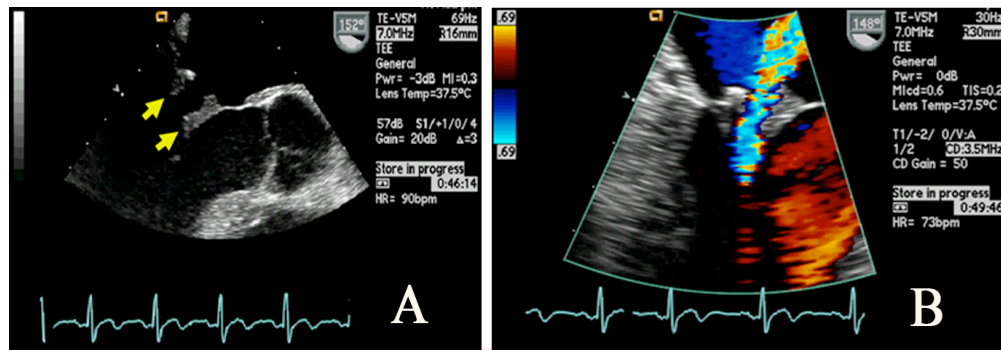
Fig. (8). Transesophageal echocardiographic still-frame images (**A** and **B**) depicting marked thickening of the atrial surface of both mitral leaflets (lupus vegetations) and associated functional regurgitation.

(Fig. **8**), it classically thought to be present in a third of cases and today is a relatively uncommon clinical finding thanks to advances in treatment. These lesions are present in up to 60% of autopsies of SLE patients and involve atrial, mitral and aortic valves surfaces. They are also frequently associated with antiphospholipid syndrome (7-15% in the case of mitral involvement and 3-19% in aortic). Pericardial disease (subclinical or overt) is a common manifestation of SLE evident in 20-50% of patients and usually occurs in the presence of active disease with small or moderate pericardial effusions without hemodynamic compromise except in cases of chronic nephritis [33].

A contemporary study revealed a significant link between mitral and tricuspid valve regurgitation and positive anti-double-stranded DNA (antidsDNA) antibodies, a finding that supports the previously known association between mitral regurgitation and anticardiolipin antibodies, lupus anticoagulant and anti-β2-glycoprotein. Therefore, asymptomatic SLE patients who have clinically inactive disease, but abnormal serology should be screened for the presence of structural cardiac abnormalities with noninvasive tools such as echocardiography [34]. Of note, reports utilizing multiparametric CMR imaging have shown that patients free of cardiac symptoms may have subclinical abnormalities in cardiac structure and function despite seemingly preserved systolic function [35].

6. CARCINOID SYNDROME

Carcinoid tumors are rare and their systemic expression as a syndrome occur in 5% of cases; they derive from the enterochromaffin cells of the gastrointestinal or bronchial tract being capable of secreting vasoactive substances, notably serotonin. Although the mechanisms related to carcinoid heart are not completely understood, increased levels of 5-hydroxyindoleacetic acid (5-HIAA) seem responsible for the clinical manifestations of diarrhea, flushing, bronchoconstriction, telangiectasia and right heart disease. Therefore, increased urinary 5-HIAA raises the diagnostic suspicion [36].

Once the presence of carcinoid syndrome has been established, echocardiography is the most useful imaging method revealing abnormalities not only of diagnostic value but that also correlate with disease progression. CMR may be used to evaluate valvular lesions otherwise not detected on echocardiography as well. Right heart involvement appears in 20-66% of patients and includes thickening, restriction and shortening of the tricuspid valve (97%); tricuspid regurgitation (90%) with a pattern of early peak and rapid decline on Doppler or prolonged pressure half-time and thickening of the pulmonic valve (50%) with predominance of regurgitation over stenosis (Fig. **9**). In the presence of intracardiac shunts and bronchial carcinoid there may be secondary involvement of the left sided valves (7%) [36, 37].

7. ENDOMYOCARDIAL FIBROSIS (EMF)

Endomyocardial fibrosis is a restrictive cardiomyopathy prevalent in equatorial Africa and other regions of the world that after a latent phase following a febrile illness may lead to biventricular fibrosis and thrombosis. Symptoms are related to anatomical involvement. Its etiology involves ge-
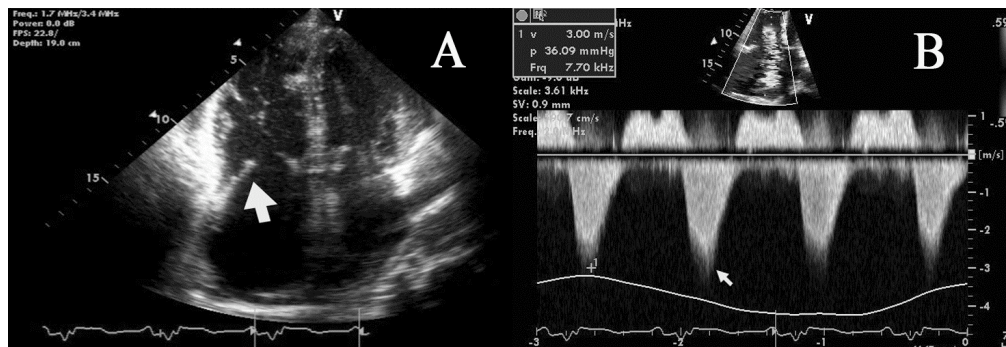

Fig. (9). Carcinoid heart disease. Apical 4 chamber view echocardiogram **(A)** demonstrating right atrial enlargement, thickening, shortening and restriction of the tricuspid valve causing both obstruction and regurgitation as demonstrated in the Doppler image (**B**). Note the rapid decay of the tricuspid regurgitation velocity commonly seen in this condition.
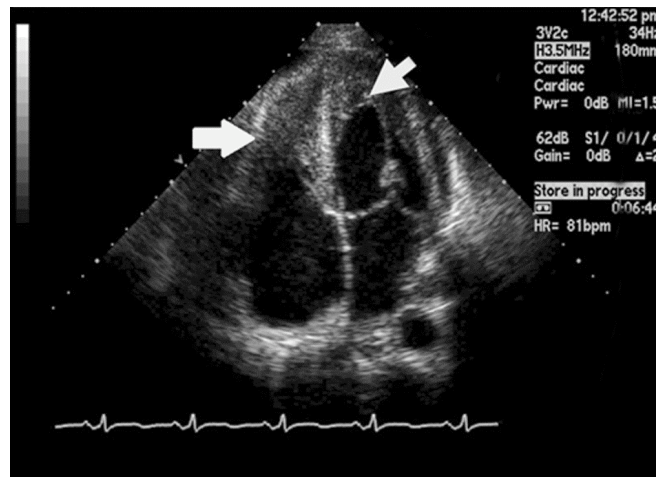
Fig. (10). Apical 4 chamber echocardiographic view showing marked endocardial fibro-thrombotic thickening of both ventricles (arrows) in a Brazilian patient affected by EMF.

Table 1.   Imaging Tools in Systemic Diseases Involving the Heart.

-	Echocardiography	CMR	Isotope Tracers	PET	CT
Sarcoidosis	++	++	++	++	-
Amyloidosis	+++	+++	++	+	-
Wegener's Granulomatosis	++	++	-	-	+
Lupus	+++	+	-	-	+
Carcinoid	+++	++	-	-	-
Endomyocardial Fibrosis	+++	++	-	-	-

CMR: Cardiac magnetic resonance; PET: Positron emission tomography; CT: Computed tomography.

netic (ethnic), dietary and various infectious and autoimmune/ inflammatory processes that could transiently share features of the hypereosinophilic syndromes. Apical fibrosis or thrombi off the left ventricle (Fig. **10**), tethering of the atrioventricular valves papillary muscles, giant atrial enlargement and a restrictive filling pattern on Doppler recordings may be seen [38-40].

Right ventricular Endomyocardial Biopsy (EMB) has been part of the EMF diagnostic workup allowing diagnosis and excluding other restrictive (infiltrative and storage) cardiomyopathies, albeit with a poor specificity. Recent data suggest that CMR may be the ideal noninvasive tool for the diagnosis of EMF. Salemi *et al.*, [41] compared EMB and LGE patterns in 36 patients with EMF and demonstrated a strong diagnostic agreement.

CONCLUSION

Systemic diseases affecting the cardiovascular system have myriad presentations and constitute a diagnostic challenge for the cardiologist given their multi-organ involvement. Early diagnosis is critical since cardiac manifestations are commonly a late phenomenon. Clinical suspicion should always precede the use of imaging tools since in many instances, these play a supportive role rather than being diagnostic gold standard. The specific role of advanced cardiac

imaging in these conditions will need to be further validated in larger series particularly considering technologic advancements that to this date continue to evolve. We have summarized their relative value in Table **1**.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

SUPPLEMENTAL DATA LEGENDS

Video 1. A. Parasternal long axis echocardiographic images of the patient described in Fig. (**1**) showing a small pericardial effusion, left atrial dilation, mild to moderate mitral re-

gurgitation, and reduced ejection fraction. Note thinning of the basal segment of the interventricular wall caused by fibrosis and granulomatous infiltration. **B**. After implantation of a pacemaker a short axis view shows systolic dysfunction and thickening of the posterior papillary muscle.

Video 2. CMR of a patient with advanced sarcoidosis revealing severe systolic dysfunction, biventricular dilation and apical thrombus (**A**), diffuse scarring of the ventricular walls including the apex (**B, C D**) and thickening of the mitral sub-valvular apparatus.

Video 3. Typical findings of amyloidosis with cardiac infiltrations: (**A**) Apical 4 chamber view of an echocardiogram showing dilation of both atria and thickening of the mitral valve leaflets and both ventricles. (**B**) Parasternal short axis view depicting a preserved LV ejection fraction. (**C**) CMR showing dilation of both atria, AV valve insufficiency, biventricular and interatrial septal thickening. (**D**) Parasternal long axis view revealing a myocardial granular pattern. (**E**) Subcostal window indicating dilation and diminished excursion of the IVC compatible with elevation of right heart pressures. (**F**) CMR showing LGE in a global and diffuse pattern, including the interatrial septum, without a coronary distribution.

Video 4. Cardiac amyloidosis: (**A**) Apical 4 chamber view of an echocardiogram showing biventricular wall thickening, systolic dysfunction and mild AV valvular insufficiency. (**B**) Transmitral pulsed waved Doppler revealing a 'restrictive' filling pattern (prominent E wave and shortened deceleration time). (**C**) Strain curve with reduced longitudinal deformation of the inferior basal and septal myocardial segments. (**D**) Two chamber view on CMR illustrating a small pericardial effusion, systolic dysfunction and elevation of the right sided venous pressures.

Video 5. Elderly patient with Wegener's presenting with heart failure. Notice thickening and invasion of the left atrial wall (**A, C**), mitral and aortic valves causing severe insufficiency (**B, D**).

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