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Cardiac involvement in antiphospholipid syndrome: The diagnostic role of noninvasive cardiac imaging

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ABSTRACT

Objectives: The antiphospholipid syndrome (APS) is an autoimmune disorder of acquired hypercoagulability characterized by vascular thrombosis, increased pregnancy morbidity, and elevated levels of antiphospholipid antibodies. Cardiac involvement in APS may be presented as heart valve disease affecting approximately a third of patients or less frequently as intracardial thombosis, pulmonary hypertension, right or left ventricular dysfunction, micro-vascular thrombosis, coronary artery, or micro-vascular disease with overt or silent clinical presentation.

Methods: Noninvasive cardiovascular imaging plays a crucial role in the evaluation of heart involvement in APS. Transthoracic or transoesophageal echocardiography enable early, accurate diagnosis and severity assessment of HVD as well as of ventricular dysfunction and pulmonary hypertension. Studies by echocardiography and nuclear imaging have detected abnormalities in myocardial perfusion in approximately 30% of primary APS. CT scan is the technique of choice for the assessment of pulmonary embolism and can effectively detect intracardiac thrombi. Myocardial perfusion defects have been detected by 13N-ammonia PET in 40% of APS. Cardiovascular magnetic resonance (CMR) has identified an unexpectedly high prevalence of occult myocardial scarring and endomyocardial fibrosis in APS, and is the technique of choice, if quantification of heart valve disease and stress myocardial perfusion-fibrosis is needed.

Results: Noninvasive, nonradiating imaging techniques, such as echocardiography and CMR are superior to CT or nuclear techniques and are of great value for the diagnosis and follow-up of both clinically overt and silent cardiac disease in APS.

Conclusions: The high incidence of cardiac involvement in APS demands early diagnosis/treatment and multimodality cardiovascular imaging is of great importance.

Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous, arterial, and/or small vessel thrombosis, pregnancy morbidity, and elevated levels of antiphospholipid antibodies (aPL), including lupus anticoagulant (LAC) and/or anticardiolipin antibodies (aCL), and/or anti-beta2-glycoprotein I (anti-β2GPI) antibodies [1]. The syndrome can be either primary or secondary, associated with an underlying condition, most commonly systemic lupus erythematosus (SLE).

Cardiac involvement in APS may be presented either as heart valve disease (HVD) or less frequently as nonvalvular disease, including intracardial thombosis, pulmonary hypertension, right or left ventricular dysfunction, and ischemic heart disease either due to coronary artery or micro-vascular disease with overt or asymptomatic clinical presentation [2–4]. Heart valve thickening and vegetations are the most common cardiac manifestations in patients with primary or SLE-related APS. Mitral valve is most frequently affected, followed by the aortic valve; regurgitation is more common than stenosis, but usually without severe hemodynamic significance. In most prospective echocardiographic studies in APS, valvular disease was persistent or progressive over time, independently of the use of anticoagulant or antiplatel treatment [3–5]. Most patients remain asymptomatic for years, while heart

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failure and valve replacement surgery are some of valve disease complications [6]. Libman–Sacks valvular lesions are sterile fibro-fibrinous vegetations that may develop anywhere on the endocardial surface of the heart, especially in the ventricular surface of the mitral valve [5,7,8] and may lead to significant regurgitation, and eventually to pulmonary hypertension. Libman–Sacks vegetations have been detected in 1 of 10 patients with SLE, and correlated with disease duration, disease activity, and the presence of anticardiolipin antibodies and antiphospholipid syndrome [8].

Right or left ventricular diastolic dysfunction has also been reported in the context of primary or SLE-related APS, regardless of the presence of valvular disease or systolic dysfunction [9–11]. Prospective echocardiographic studies have shown a progression of ventricular dysfunction during a long-term follow-up period [10,11]. Intracardiac thrombosis, in the form of single or multiple thrombi, is a rare cardiac manifestation of APS that may cause pulmonary and systemic emboli [12,13]. Pulmonary hypertension is another rare manifestation of APS, associated with pulmonary artery thrombosis or micro-vascular thrombosis and endothelial remodeling [9,14].

Myocardial involvement in APS includes myocardial infarction, or myocardial ischemia due to coronary vasospasm or micro-vascular thrombosis. In a European cohort of 1000 patients with APS, myocardial infarction was diagnosed in 5.5% of APS patients and was the presenting manifestation in 2.8% of them [2]. In a recent systematic review, the estimated frequency of antiphospholipid antibodies among patients with myocardial infarction in the general population was 11% [15]. Additionally, coronary vasospasm, known as Prinzmetal's angina or syndrome X, has been described in APS and may lead to myocardial ischemia without thrombosis [16,17]. Myocardial ischemia can also be caused by thrombotic cardiac micro-vascular disease; as a consequence, the ischemic subendocardium could act as a trigger for clot formation, especially, if there is concurrent LV dysfunction [18]. Kattwinkel et al. [19] described the case of a patient with primary APS, who was diagnosed with cardiac necrosis and normal coronary arteries. Endomyocardial biopsy showed a noninflammatory micro-vascular disease, characterized by bland thrombi and lack of inflammatory cells in the vessel wall. Finally, endomyocardial fibrosis (EMF) is another nonvalvular cardiac manifestation that has been reported in some cases with APS [20], with uncertain pathogenesis.

Noninvasive imaging techniques to assess cardiovascular involvement in APS

Echocardiography/ultrasonography

Echocardiography is the cornerstone of cardiac imaging and gives reliable information about valvular integrity, wall motion changes, right and left ventricular function, and assessment of pulmonary hypertension. Transthoracic echocardiography (TTE) and/or transoesophageal echocardiography (TEE) enable early and accurate diagnosis and severity assessment of HVD. The prevalence of valve disease in APS is about 30–40% in TTE studies, reaching the level of 82% in TEE studies [3–5,21]. In the context of APS, valve lesions are defined by (a) valve thickness >3 mm; (b) localized thickening involving the proximal or middle part of the leaflets; or (c) irregular nodules on the atrial face of the mitral valve and/or the vascular face of the aortic valve [22]. The application of real-time 3D echocardiographic imaging (RT3D) for the evaluation of Libman–Sacks vegetations' size can strengthen the already well established role of TTE and TEE; furthermore, the exact estimation of vegetations' size may influence the therapeutic interventions [23]. A prospective study including a 10-year echocardiographic follow-up of patients with APS and patients with SLE with or without aPL, documented that the coexistence of SLE and APS, and the disease duration were independent factors for valvular disease progression. In addition, ventricular diastolic dysfunction, primarily of the left ventricle, also progressed over the 10-year period while anticoagulation could not arrest the progression of both valvular disease and myocardial dysfunction [11].

TTE can also detect complex and irregular masses adherent to the endocardial surface of any cardiac chamber or great vessels, and TEE can provide details about their anatomy and pathophysiology [12,21,24,25]. For the detection of left ventricular thrombi, TTE has a sensitivity and a specificity of 86–95% [26–28]. TTE can not reliably visualize the left atrium or left atrial appendage (LAA), and has a sensitivity of only 39–63% for the detection of left atrial thrombi [29–31]. The diagnostic accuracy of TEE has been evaluated in patients undergoing surgery or autopsy. For the diagnosis of left ventricular thrombus, TEE has a sensitivity and specificity similar to those of TTE [32]. However, for the diagnosis of left atrial thrombi, TEE has a sensitivity of 100% and a specificity of 99% [33].

The presence of pulmonary hypertension is based on hemodynamic parameters estimated by TTE and confirmed by right heart catheterization [3,21]. In a recent study including 53 patients with primary and SLE-associated APS pulmonary hypertension was diagnosed using TTE in 11.3% of patients and it was the most common nonvalvular cardiac manifestation. Left myocardial disease and intracardiac thrombi were rare manifestations with a prevalence of 3.8% and 1.8% respectively [10].

A high level of agreement between contrast echocardiography and nuclear imaging for the assessment of myocardial perfusion was observed in a prospective study of patients with primary APS reporting a 30% prevalence of myocardial perfusion abnormalities by both techniques [34].

Ultrasonography is particularly useful for the assessment of common carotid arteries, where it is up to 10-fold more sensitive than magnetic resonance, displaying a resolution of 0.1–0.2 mm. Therefore, it can identify peripheral vessels' thrombosis, due to APS. Furthermore, premature atherosclerosis expressed as increased carotid intima media thickness (IMT), is a clinical feature of thrombotic primary APS and can be easily assessed by ultrasonography [35].

Echocardiography is a bedside, inexpensive, widely available, nonradiating technique. It is ideal for diagnosis and follow-up of cardiovascular involvement in APS patients. However, it is an operator-dependent technique and carries the limitation of poor acoustic window in a significant percentage of patients. Ultrasonography is also a highly operator-dependent method. Furthermore, while imaging is optimal in the common carotid and vertebral arteries, the assessment of proximal subclavian and distal internal carotid arteries is limited, due to overlying tissues. High-resolution US of the aorta could be an excellent alternative. However, high-resolution probes still have disadvantage of pour penetration and can not be used for evaluation of deep thoracic or abdominal vessels, especially in obese patients [36].

High-resolution computed tomography (CT)

A high-resolution cardiac computed tomography (CT) can confirm the presence of pseudotumours with or without partial calcification and the absence of contrast enhancement in cases of intracardiac thrombi in patients with APS [12,37]. CT scan is the technique of choice for the assessment of pulmonary embolism and pulmonary hypertension due to recurrent pulmonary emboli. CT scan may reveal bilateral patchy areas of ground-glass attenuation and pulmonary angiography moderately dilated central pulmonary arteries with or without pulmonary emboli.