Systemic Lupus Erythematosus: Review of Cardiovascular Aspects

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune condition with a complex pathophysiological process in which its inflammatory activity is an enhancer of coronary disease by systemic inflammation, endothelial dysfunction and predisposition to thrombosis. The cardiovascular involvement in SLE is not a diagnostic criterion and is considered only as damage established in the long-term of the disease. The objective of this study is to highlight the importance of clinical vision for the early identification of cardiovascular involvement in SLE. A critical analysis of the cardiac approach in SLE, with emphasis on clinical aspects, cardiovascular biomarkers and genetics and rational request of additional tests. The particularity of patients with lupus nephritis and antiphospholipid antibody syndrome is also highlighted. The perception of subclinical cardiac damage is critical for interrupting the cycle of myocardial injury and to avoid progression of heart disease.

Keywords: Lupus erythematosus, systemic; Cardiovascular diseases; Inflammation

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune condition with a complex pathophysiological process involving genetic, environmental and, possibly, infection factors. The main components of the innate and adaptive, cellular and humoral immune system have influence on the disease and can affect organs and tissues in different ways.

The diagnostic criteria of SLE have been recently revised in order to increase diagnostic accuracy (Chart 1), where the presence of four or more clinical and laboratory criteria defines SLE.

The SLICC index (Systemic Lupus International Collaborating Clinics, 2012) is validated for the outpatient treatment of patients with SLE to represent cumulative damage by the disease. In this classification, cardiac involvement is determined by the presence of pulmonary hypertension, history of angina or angioplasty, previous myocardial infarction, diagnosis of cardiomyopathy, valvular disease, pericarditis for more than six months or pericardiectomy or vascular claudication for more than six months.

The first description of cardiac involvement by SLE is attributed to William Osler in 1895. The cardiovascular involvement in SLE is not a diagnostic criterion (ACR) and is considered only as damage established in the long-term (SLICC index). Pericarditis is included in the criteria of serositis, but does not include other forms of aggression to the heart. At some point in the progression of the disease, myocardial impairment begins and that early detection will address the myocardial disease and improve outcomes for cardiovascular morbidity and mortality.

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ABBREVIATIONS AND ACRONYMS

• **CAD** — coronary artery disease
• **ECG** — electrocardiogram
• **HF** — heart failure
• **NT-proBNP** — brain natriuretic peptide
• **CRP** — C-reactive protein
• **SAF** — antiphospholipid antibody syndrome
• **SLE** — systemic lupus erythematosus
• **SLICC** — Systemic Lupus International Collaborating Clinics

The frequency of SLE is variable in the population and may reach 1:200 black women. Its prevalence is well established in countries of Europe and Central America, with rates ranging from 20 to 200 per 100,000 people. Epidemiological data in Latin American countries are scarce and controversial.

Despite the large impact on the quality of life of patients, the incidence and prevalence of SLE in Brazil were rarely described, and there are few studies with data at the national level. The epidemiology of SLE in Brazil follows the universal tendency to predominate in women of childbearing age — third decade of life, with a current estimate of 16-80,000 cases diagnosed in the country. In the southern region, 4.8 cases/100,000 inhabitants/year were estimated, with predominance of females and age group in the fourth decade of life; international benchmarks show an incidence ranging from 1.15 to 9.3 cases per 100,000 inhabitants/year. Regional assessments described similar clinical presentations, with a predominance of skin and joint manifestations. Studies of medical records in the northern region of the country identified renal involvement in 62.5%, but there was no specific documentation of cardiac damage.

In this series of Hospital Universitário Antônio Pedro (HUAP), there is a prevalence of nephritis in 40.0% of patients with SLE and cardiac abnormalities in more than 50.0% of patients (unpublished data), but the proportion of these patients presenting incipient or established cardiovascular disease (CVD) is not known.
There is no established protocol in the literature for cardiac evaluation of patients with SLE. The objective of this manuscript is to highlight the importance of clinical vision for the early identification of cardiovascular involvement in SLE. The history and clinical examination may lead to suspicion of cardiovascular involvement in patients who have predominant clinical manifestations in other systems — osteoarticular, renal, hematologic, and allow better control of cardiovascular morbidity and mortality in LES\textsuperscript{10-13}.

**Methods**

Non-systematic review of the literature to find studies on cardiovascular manifestations of SLE. The search was conducted in the databases PubMed, Medline and Google Scholar up to February 20, 2015. The filters used were manuscripts of international relevance and not before 1980. The following descriptors and terms in English were applied: “Systemic lupus erythematosus and cardiovascular disease”, and “Systemic lupus erythematosus and cardiovascular disease and nephritis”.

The search returned 1334 manuscripts, 614 of which with emphasis on cardiovascular findings. After analyzing the abstracts of the manuscripts, we excluded those in duplicity or not related to the subject, with the result of 51 manuscripts in English, French, Italian and Portuguese.

**Cardiac manifestations in SLE**

Cardiovascular disease is the leading cause of morbidity and mortality in patients with SLE. The most prevalent diseases are coronary heart disease (12-90.0%), myocardial diseases (40-60.0%) and pericardium (25-50.0%), heart failure (5-31.0%), valvular heart diseases (13-65.0%) and conduction disorders (3-16.0%) (Chart 2)\textsuperscript{13}. It is estimated that 50% of patients with SLE have cardiac abnormalities, mostly oligosymptomatic but detectable when investigated with high-sensitivity imaging methods\textsuperscript{10}. There is prevalence of hypertension in up to 2/3 of patients with SLE, which contributes to accelerated atherosclerosis and increased cardiovascular risk\textsuperscript{11}. Despite this importance, there is no cardiac criteria established in the classification of SLICC criteria, which emphasizes the need for clinical perception by the doctor.

Autoimmune activity of SLE may induce epicardial, endocardial or pericardial disease (the most common one) with spectrum of clinical manifestations ranging from asymptomatic patients to scenarios of acute left ventricular failure requiring hemodynamic support\textsuperscript{12}. Valvular heart diseases are less common and have prevalence similar to the general population\textsuperscript{11}. The perception of subclinical cardiac damage is essential to stop the myocardial injury cycle and prevent the progression of heart disease\textsuperscript{14,15}.

An ischemic heart disease in SLE patients without obstructive identifiable coronary artery disease (CAD) has been recently described. Ishimori et al.\textsuperscript{10} described, in patients with SLE and angina pectoris, a prevalence of 44.0% of alterations in cardiac magnetic resonance imaging tests with assessment of myocardial perfusion on stress, with reduced coronary perfusion reserve index with normal coronary angiography\textsuperscript{10,11}. The most likely hypothesis is that the perfusion deficit results from microvascular coronary dysfunction\textsuperscript{12}.

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium</td>
<td>Pericardial effusion, pericarditis</td>
</tr>
<tr>
<td>Myocardium</td>
<td>Heart failure, myocarditis</td>
</tr>
<tr>
<td>Valve disorders</td>
<td>Endocarditis (infectious and non-infectious)</td>
</tr>
<tr>
<td>Conduction system</td>
<td>Atrioventricular block, sinus tachycardia</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Stable angina, acute coronary syndrome</td>
</tr>
</tbody>
</table>

**Chart 2**

**Cardiovascular manifestations in patients with SLE**
With early diagnosis of CAD, the survival of these patients increases, as well as improves the prognosis of patients who develop heart failure (HF). Clarke et al.\textsuperscript{14} reported an average cost of treatment of SLE higher than US$ 10,000 per year, which is higher than that of other collagen diseases. The lack of epidemiological data in Brazil prevents an accurate estimate, but the impact on public health spending certainly exists.

In addition to Framingham’s classic risk factors for DAC\textsuperscript{15,16}, the SLE inflammatory activity has become one more enhancer of coronary disease through systemic inflammatory activity, endothelial dysfunction, and predisposition to thrombosis, in addition to cardiovascular side effects of drugs used, especially glucocorticoids\textsuperscript{17-19}. For this reason, it is considered that the Framingham classification underestimates cardiovascular risk in patients with SLE\textsuperscript{15-20}.

Bartels et al.\textsuperscript{20} demonstrated that patients with SLE have a greater chance of cardiovascular morbidity and mortality in the two years preceding the diagnosis of SLE. This strengthens the hypothesis of SLE inflammatory activity as a cardiovascular risk factor\textsuperscript{15-20}.

The antiphospholipid antibody syndrome (APS) is associated with SLE and has high cardiovascular morbidity. Its diagnosis depends on clinical criteria: arterial or venous thrombosis and pregnancy morbidity; and laboratory criteria: positivity for lupus anticoagulant and presence of anticardiolipin antibodies and antiβ2-glycoprotein-I. Myocardial damage may occur by direct mechanisms (immune-mediated) or indirect mechanisms (thrombosis), and the most prevalent cardiac manifestation in APS are the valvular diseases, followed by ischemic diseases (Chart 3).

<table>
<thead>
<tr>
<th>Clinical presentation</th>
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<tbody>
<tr>
<td>Accelerated atherosclerosis</td>
</tr>
<tr>
<td>Atherosclerosis of central and splanchnic vessels.</td>
</tr>
<tr>
<td>Valve disorders</td>
</tr>
<tr>
<td>Mitral regurgitation (common) and stenosis (rare); thickening of leaflets, vegetation (marantic endocarditis).</td>
</tr>
<tr>
<td>Myocardium</td>
</tr>
<tr>
<td>Ventricular hypertrophy, systolic or diastolic dysfunction, myocarditis, heart failure.</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Embolization or atherosclerosis, angina, acute myocardial infarction, microvascular damage.</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Embolism or thrombosis of pulmonary vessels, pulmonary hypertension.</td>
</tr>
<tr>
<td>Systemic arterial embolism</td>
</tr>
<tr>
<td>Thrombosis of the aorta or carotid, axillary, mesenteric, hepatic, pancreatic, splenic, iliac, femoral or popliteal arteries.</td>
</tr>
</tbody>
</table>

ASP — antiphospholipid antibody syndrome

Cardiologic approach in SLE
- Clinical approach
Cardiovascular dysfunction may be evident both in the initial presentation of the disease with acute HF\textsuperscript{21} and in the context of volemic overload due to acute or chronic renal failure due to lupus nephritis\textsuperscript{22}. Other factors such as hypoalbuminemia (secondary to nephrotic syndrome or inflammatory state) may also contribute to hemodynamic overload even in young patients. Gladman and Urowitz\textsuperscript{23} demonstrated in patients with SLE a prevalence of angina in up to 12.0%, history of acute myocardial infarction in 16.0% and sudden death in 8.0%. These patients are also at increased risk of progressing with metabolic syndrome, with decreased correlation with complement C3 fraction, duration of disease and corticosteroid use as independent risk factors\textsuperscript{22-24}. Mucocutaneous clinical signs suggest disease activity, and extracardiac vascular manifestations such
as telangiectasias, vasculitis, livedo reticularis, Raynaud’s phenomenon and thrombophlebitis may be clinical evidence that the patient has an increased risk of cardiac vascular involvement.

Increased risk of CAD, cardiotoxicity by drugs (mainly cyclophosphamide and hydroxychloroquine) and lupus myocarditis should guide the management of these patients in a context of acute cardiopulmonary symptoms. Clinical suspicion of cardiac involvement in SLE, either in the initial presentation or in the outpatient setting, will define the use of complementary tests in these patients.

Chen et al. described the presentation of patients in the emergency room with signs and symptoms suggesting acute HF with no history of cardiopulmonary disease or traditional risk factors. The LES is a possible diagnosis.

- Cardiovascular biomarkers and genetics

Autoantibodies (anti-phospholipid, anti-SSA/RO, endothelial anticells) correlate with cardiac injury in autoimmune diseases. In patients with SLE, antibodies against heart contractile proteins, membrane receptors, mitochondrial proteins and structural proteins are described. Due to the coexistence of nephritis and hemodynamic overload, in addition to prolonged use and high doses of corticoids and other cytotoxic drugs, there may be a combination of causes for the development of heart failure in these patients.

Although the presence of traditional risk factors in these patients is often documented, Liu et al. indicate that there would be other causes for the higher global cardiovascular risk and thrombosis in autoimmune diseases. The dynamics of atherosclerosis, thrombosis and inflammation is combined to the factors related to lupus: inflammation and endothelial dysfunction, nephropathy, lupus phenotype, autoantibodies and genetic predisposition.

The autoantibodies mostly related to vascular inflammation are the antiphospholipid antibody and antiphosphorylcholine. Analysis of traditional risk factors in patients with SLE demonstrated higher percentage of hypertension and dyslipidemia — increased total cholesterol, triglycerides and low-density lipoprotein (LDL-c), and decreased high-density lipoprotein (HDL-c) compared to control groups.

Ultrasensitive C-reactive protein (CRP) is an inflammatory biomarker with evidence of correlation with increased risk for coronary plaque rupture. CRP studies in patients with SLE showed no association with disease activity, number of diagnostic criteria or specific damage of organs, but correlated with traditional risk factors: body weight, blood pressure and apoprotein-I.

Cardiac-specific troponin-I is a myocardial injury biomarker that can be high in chronic inflammatory diseases, in which the prototype is rheumatoid arthritis, even in the absence of heart failure or cardiovascular risk factors. The subclinical myocardial injury in patients with systemic inflammatory diseases is associated with increased risk of myocarditis and vasculitis of coronary vessels in these patients — conditions where there is high troponin-I.

Brain natriuretic peptide (NT-proBNP) is associated with cardiovascular morbidity and mortality in the general population. Patients with SLE have higher levels of NT-proBNP even in the absence of clinically detectable atherosclerotic disease. There is a correlation of NT-proBNP with cumulative damage and SLE diagnosis time and this mechanism may be explained by the association with chronic inflammation. NT-proBNP can be high in the absence of clinically detectable heart disease, but it indicates the propensity of these patients to develop myocardial disease.

Vitamin D is a biomarker related to modulatory effects of the immune response and in the renin-angiotensin-aldosterone system, and its deficiency correlates with higher mortality from cardiovascular events — heart failure, acute myocardial infarction, sudden death, stroke, atrial fibrillation and vascular peripheral disease. Patients with SLE and low levels of 25(OH) vitamin D have a greater association with cardiovascular risk factors and increased disease activity by SLE.

The pathogenesis of SLE is multifactorial and is based on a hereditary polygenic model in which the concurrence of susceptibility genes raises the risk of developing the disease. Molecular studies have demonstrated the relationship of SLE with defects in the intracellular elimination of nucleic acids and subsequent activation of interferon-I from the innate immune system.

The activation of inflammatory mediators, particularly matrix 2 (MMP-2) and 9 (MMP-9) metalloproteinase and
oxidative stress are involved in the process of chronic inflammation and may also be related to cardiovascular disease\(^41\). MMP-9 -C1562 T and MMP-2 -G1575A alleles were identified as indicators of three times higher risk of developing SLE, and also correlated with higher blood pressure levels and LDL cholesterol and lower HDL cholesterol levels\(^42\).

**The heart in lupus nephritis**

Among the visceral manifestations of SLE, secondary renal disease is described in 25-60.0% of patients in whom complete remission of nephritis is reached after two years in 25-50.0% of cases\(^43,44\); and 5-20.0% progress to renal replacement therapy over a period of ten years after diagnosis\(^43,44\). Lupus nephritis is defined by clinical and laboratory parameters (persistent proteinuria above 500 mg/24 hours, cellular and rheumatic cylinders) and/or renal biopsy\(^45\). Biopsy may be considered in all lupus patients with evidence of nephritis, especially in the first episode\(^44,45\). Patients diagnosed with lupus nephritis have lower survival rates than the general population with SLE without nephritis due to correlation with cardiovascular morbidity\(^49,50\).

The prevalence of ischemic myocardial disease in patients with SLE and nephritis is higher than the population with SLE without renal involvement and its early detection may change morbidity and mortality of this subgroup through specific treatment of the condition.

**Clinical applicability of laboratory tests**

The rational use of cardiovascular imaging studies in SLE depends on the clinical manifestations and is relevant because the mortality of these patients associated with CVD has not improved over time, unlike other causes of mortality, such as lupus nephritis\(^48,51\).

The great challenge of clinical cardiologists is to diagnose cardiovascular disease in asymptomatic patients without other risk factors besides the SLE. Following a growing complexity of tests, 12-lead electrocardiogram (ECG) is important to show signs of left ventricular hypertrophy and rhythm disorders\(^9\) and chest X-ray can reveal indirect signs of pulmonary congestion, pulmonary hypertension, and pericardial effusion (Figure 1). Initial findings will guide the clinical decision toward the next steps in the rational use of other complementary tests as a method for assessing disease activity. ECG (Figure 2) is the initial test of cardiac evaluation, and the most prevalent findings are signs of left ventricular hypertrophy and sinus tachycardia, and conduction blocks (usually associated with neonatal SLE)\(^9\). One proposal of use of complementary tests in the management of these patients is shown in Figure 3.

Doppler echocardiogram is the most accessible test to assess cardiac function. Tissue Doppler allows to evaluate the degree of ventricular dysfunction and estimate pulmonary artery pressure (SPAP)\(^52,53\). The most common echocardiographic abnormalities are pericardial effusion or thickening, increased left chambers, abnormal left ventricular shortening fraction and identification of intracavitary thrombi\(^7\). Of valve changes, the most common finding in SLE is the thickening of left chamber valves, and the most characteristic findings are valve nodes and non-infectious marantic endocarditis (Libman-Sacks), which is a proliferative fibrosis of the valvular endocardium, mainly mitral, with risk of embolization or infection\(^53\). The speckle tracking technique allows the identification of subclinical structural heart disease by identifying bright intramyocardial points (speckles) and accompanies them during the cardiac cycle (tracking)\(^54\) and demonstrate early findings of remodeling and left ventricular dysfunction on echocardiography. Patients with SLE have left ventricular mass index and reduction of all strain components\(^55,56\). The use of three-dimensional echocardiography is also promising for analyzing early and subclinical left ventricular dysfunction.
Figure 2
ECG of a 26-year-old patient with SLE without classical cardiovascular risk factors.
Signs of increased left chambers and left ventricular hypertrophy.
ECG — electrocardiogram; SLE — systemic lupus erythematosus

Anamnesis:
- Risk factors (traditional risk factors and those related to SLE);
- Emphasis on cardiosystemic symptoms;
- Attention to extra-articular manifestations (hematological, renal).

Clinical tests:
- Signs of hemodynamic overload (B3, jugular swelling, HJR);
- Pulmonary hypertension (P2 > A2);
- Anasarca and/or cavitary effusion.

Figure 3
Complementary tests in cardiology evaluation of patients with SLE.
SLE — systemic lupus erythematosus; B3 — third heart sound; HJR — hepatojugular reflux; P2 — pulmonary component of the second heart sound; A2 — aortic component of the 2nd heart sound; MRI — magnetic resonance imaging; PET-CT — positron emission computed tomography; US — ultrasound
Carotid Doppler ultrasound evaluates the intima-media layer thickness and the presence of vascular plaques. These findings correlate with increased risk for cerebrovascular events and suggest the presence of vascular systemic disease. Studies on patients with SLE showed that there is a correlation between carotid vascular disease findings with the presence of other cardiovascular risk factors.

Computed angiography tomography with calcium score of coronary arteries can identify perfusion defects and correlate with myocardial ischemia with performance similar to that of patients without SLE, but with other cardiovascular risk factors (Figure 4). The presence of autoantibodies (anticardiolipin IgG and antiβ2-glycoprotein IgG) correlate with four times higher chances of coronary calcification.

Myocardial perfusion imaging with technetium 99m-sestamibi executed in phases of rest and stress is sensitive to detect myocardial perfusion abnormalities and Sella et al. showed changes in up to 40-60% of the tests in asymptomatic patients with SLE from the cardiovascular point of view. Low levels of HDL-c and diabetes mellitus were correlated with abnormalities in myocardial perfusion in these patients, suggesting that perfusion defects may represent an early stage of subclinical atherosclerosis. Scintigraphy with gallium-67 is useful in identifying myocardial inflammatory disease that, in the case of SLE patients, can occur in 3-15.0% of patients at some point in the evolution of the disease.

Positron emission tomography (PET-CT) uses a radiopharmaceutical (usually fluorodeoxyglucose) to quantify their concentration in the tissues. The presence of pericarditis and myocarditis can induce uptake of the radiotracer, and the intensity of this uptake allows defining, with 100% sensitivity and specificity, the diagnosis of acute myocarditis in comparison with endomyocardial biopsy when the test is done within two weeks from the onset of the disease.

Myocardial magnetic resonance imaging offers heart structure details and is sensitive to abnormalities that characterize lupus myocarditis, especially in the T2 sequence (myocardial edema) and the early and late gadolinium enhancement with sensitivity of 76.0% and specificity of 95.5% for detection of inflammation. Besides that, it allows assessing left ventricular size, function and mass and can correlate imaging findings with disease activity and duration, inflammatory state and antiphospholipid antibodies.

Recent studies with nuclear imaging methods have described different cardiac involvement standards that, in general, are more prevalent in patients with other risk factors for coronary disease, and usually correlated with microvascular coronary disease. Because it employs radioactivity of a very short half-life, radiation exposure is low and acceptable in view of the testing quality. Other methods, such as optical coherence tomography, invasive magnetic resonance imaging and coronary angioscopy are promising for the study of the morphology and microstructure of coronary plaques, but have not yet been studied in this group of patients.

Coronary angiography is the test that is most available to study the coronary anatomy with the possibility of intervention. Given the high prevalence of obstructive atherosclerotic disease, many young patients are referred for coronary angiography, which is a procedure that involves risks and has limited application in patients with impaired renal function.

**Comments**

Although it is not part of the diagnostic criteria, cardiac involvement in SLE may occur alone in any phase of
the disease, as an isolated damage or concomitantly with other events (especially nephropathy), which enhances the risk of cardiovascular mortality. The rational approach of heart diseases in the context of a systemic disease may allow more effective care to these patients at increased risk of cardiovascular disease.

Urowitz et al.\(^7\) described a bimodal pattern of mortality in SLE that is still recognized, where there is a peak in the first year due to intense disease activity (mainly renal), and another peak at a later point in time (after eight years)\(^7\) in which more recent studies show the participation of coronary disease as an etiologic predominant factor.\(^10,11,12\) Patients with SLE have incidence of CAD up to seven times higher, even when adjusted for cardiovascular risk factors.\(^10,11,14\) Because of this, it is worth noting that CAD must be investigated even in young patients with chest pain without traditional risk factors. The cardiologist should be aware of subclinical manifestations and make a decision about stratifying these patients.

The identification and fight against cardiovascular risk factors are a constant concern of cardiologists. The SLE has relevant prevalence in the Brazilian environment, and early clinical suspicion of cardiovascular involvement in this clinical syndrome is of utmost importance. The proper approach and rational request of complementary tests can reduce morbidity and mortality and contribute to the quality of life of these patients. More studies are needed to determine the Brazilian population with SLE and its cardiovascular profile.

### Potential Conflicts of Interest
No relevant potential conflicts of interest.

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### Academic Association
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