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REVIEW

"How many times must a man look up before he can really see the sky?" Rheumatic cardiovascular disease in the era of multimodality imaging

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Abstract

Cardiovascular involvement in rheumatic diseases (RD) is the result of various pathophysiologic mechanisms including inflammation, accelerated atherosclerosis, myocardial ischemia, due to micro- or macro-vascular lesions and fibrosis. Noninvasive cardiovascular imaging, including echocardiography, nuclear techniques, cardiovascular computed tomography and cardiovascular magnetic resonance, represents the main diagnostic tool for early, non-invasive diagnosis of heart disease in RD. However, in the era of multimodality imaging and financial crisis there is an imperative need for rational use of imaging techniques in order to obtain the maximum benefit at the lowest possible cost for the health insurance system. The oligo-asymptomatic cardiovascular presentation and the high cardiovascular mortality of RD necessitate a reliable and reproducible diagnostic approach to catch early cardiovascular involvement. Echocardiography remains the routine cornerstone of cardiovascular evaluation. However, a normal echocardiogram can not always exclude cardiac involvement and/or identify heart disease acuity and pathophysiology. Therefore, cardiovascular magnetic resonance is a necessary adjunct complementary to echocardiography, especially in new onset heart failure and when there are conflicting data from clinical, electrocardiographic and echocardiographic evaluation of RD patients.

Key words: Echocardiography; Cardiovascular magnetic resonance; Nuclear imaging; Cardiovascular computed tomography; Myocardial perfusion-fibrosis; Coronary artery disease; Vasculitis; Rheumatic cardiovascular disease; Myocarditis

Core tip: The oligo-asymptomatic cardiovascular presentation and the high cardiovascular mortality of rheumatic diseases (RD) necessitate a reliable and

reproducible diagnostic approach to catch early cardiovascular involvement. Echocardiography, although being the cornerstone of cardiac evaluation, can not always exclude cardiac involvement and/or identify acuity and pathophysiology of cardiac lesions. Therefore, cardiovascular magnetic resonance is a necessary adjunct, complementary to echocardiography, especially in new onset heart failure and when there are conflicting data from clinical, electrocardiographic and echocardiographic evaluation of RD patients.

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INTRODUCTION

Cardiovascular involvement in rheumatic diseases (RD) is the result of various pathophysiologic mechanisms including systemic, myocardial, vascular inflammatory process, atherosclerosis, cardiac ischemia, due to micro and/or macrovascular lesions, abnormal coronary vasoreactivity and fibrosis[1,2]. RD patients may present with valvular, myocardial, pericardial, coronary artery or microvascular disease, vasculitis, systolic and diastolic heart failure, as well as pulmonary arterial hypertension. Symptoms of heart involvement in RD are usually subtle and underestimated, because they are attributed to the underlying systemic disease. The application of targeted treatment in RD led to a significant reduction of disease-associated mortality; however, the life expectancy of RD patients still remains lower, compared to general population[3], predominantly due to high incidence of cardiovascular disease[4-8].

RD with cardiovascular involvement include: (1) Rheumatoid arthritis and the spondyloarthropathies; (2) Systemic lupus erythematosus (SLE); (3) Systemic vasculitides; (4) Inflammatory myopathies; (5) Systemic sclerosis; (6) Mixed connective tissue diseases (MCTD); and (7) Sarcoidosis (SRC).

Non-invasive cardiovascular imaging, including echocardiography, nuclear techniques, cardiovascular computed tomography and cardiovascular magnetic resonance, represents useful diagnostic tool for early, non-invasive assessment of cardiac disease in RD. However, in the era of multimodality imaging and financial crisis there is an imperative need for rational use of the above mentioned techniques in order to obtain the maximum diagnostic benefit at the lowest possible cost for the health insurance system.

Applying the Bob Dylan's lyrics to cardiovascular evaluation of RD, it is clear that a careful and cost-effective evaluation of all available imaging techniques is needed, before to achieve the best diagnostic approach. The aim of this review is to present the value of various imaging techniques and propose an efficient diagnostic algorithm for early detection of cardiovascular involvement in RD.

NON-INVASIVE IMAGING TECHNIQUES

Echocardiography

Currently, the most commonly noninvasive, imaging technique, used in cardiovascular imaging, is echocardiography, due to high availability, portability, low cost, lack of radiation and high expertise among cardiologists. Transthoracic echocardiography (TE) allows an accurate evaluation of valvular morphology and function, assessment of pericardium and abnormalities of ventricular wall motion; by adding Doppler analysis, valuable information about left ventricular diastolic function, valvular flow and pulmonary pressure can be also obtained. Recently, it was documented that the definition of pulmonary hypertension obtained by echocardiography is useful to predict the 6-year mortality in SLE[9]. In another study evaluating patients with antiphospholid syndrome (APS), pulmonary hypertension was the most common finding in APS and was associated with thromboembolic disease; in contrary left ventricular disease and cardiac thrombi were rare[10]. Furthermore, in APS and SLE (with or without aPL), SLE/APS and disease duration were independent predictors for valvular disease progression and ventricular diastolic dysfunction in a 10-year follow-up echocardiographic evaluation[11]. In a meta-analysis, the presence of aPL in SLE was associated with high risk for heart valvular disease, including Libman-Sacks endocarditis. Therefore, systematic echocardiography evaluation in SLE with aPL should be always scheduled[12]. Echocardiography has been successfully used in both antiphospholipid syndrome[11,12] and asymptomatic patients with juvenile-onset SLE, who presented evidence of declining ventricular diastolic function with time[13]. Rexhepaj *et al*[14] found significant differences in early diastolic flow velocity (E), atrial flow velocity (A) and E/A ratios in rheumatoid arthritis (RA) compared with normals, suggesting that a subclinical lesion of left and right ventricular function is present in RA patients, although left ventricular parameters were still normal. Improvement of cardiac function was also shown by conventional echocardiography in RA after treatment with infliximab[15].

Another application is transthoracic dipyridamole stress echocardiography and coronary flow reserve (CFR) evaluation. CFR is assessed in the distal left anterior descending coronary artery expressed as ratio between peak diastolic velocity during stress and at baseline. It is an extremely sensitive marker (> 90%) for coronary artery disease (CAD)[16,17] and, if it was considered together with regional wall motion abnormalities, is even more specific[18]. A CFR < 2 is a very accurate index to predict the presence of CAD[17]. If coronary arteries are normal, CFR abnormalities show impairment of coronary microcirculation, as in

arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus, hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy and other diseases[19]. A reduced CFR reflects bad CAD prognosis[20]. Finally, we should emphasize that not only the binary (normal-abnormal) response in CFR, but also the continuous spectrum of CFR values is a strong independent predictor in known or suspected CAD[21]. Hirata *et al*[22] found a serious reduction of CFR in premenopausal SLE women compared with matched controls, due to microvascular disease that leads to decreased vasodilation during pharmacological stress. Turiel *et al*[23] detected a significant impairment of CFR in early RA without any anti-rheumatic therapy and disease duration < 1 year. The reduced CFR in the absence of wall motion abnormalities indicated abnormalities of coronary microcirculation, due to endothelial dysfunction.

Furthermore, exercise echocardiography (EE) using dobutamine was proven of great value for the evaluation of myocardial ischemia in RD. In a study by Saghir *et al*[24], RA was associated with a 2-fold higher risk for cardiac ischemia on EE and the risk was depending on RA disease duration; mortality rate was also higher in RA with ischemic EE study[24]. Furthermore, asymptomatic RA patients may present cardiac ischaemia at similar levels to DM patients but with low prevalence of obstructive coronary artery lesions and higher incidence of microvascular disease, due to increased inflammatory response[25].

Tissue Doppler imaging (TDI) is a new echocardiographic technique that allows the measurement of myocardial velocities and myocardial deformation. It is limited by the angle used, because only deformation along the ultrasound beam can be used from velocities evaluation; however, myocardium presents simultaneous deformation in 3 dimensions[24]. Birdane *et al*[26] demonstrated that RA patients had a significant impairment of TDI biventricular diastolic function compared with controls that was depended on age and steroids treatment. To overcome TDI limitations, speckle tracking analysis has been applied to evaluate myocardial strain along the longitudinal, circumferential and radial axes[27]. Recently, it was demonstrated that interleukin-1 inhibition contributes to a greater amelioration in endothelial, coronary and aortic function in addition to left ventricular myocardial deformation and twisting in RA patients with CAD than in those without[28]. Additionally, global longitudinal LV/RV strain was reduced in RA patients compared with controls and strain abnormalities were correlated with RA disease severity[29]. Furthermore, 3D-speckle tracking is a new method to detect early abnormalities in SLE patients with normal LV systolic function assessed by 2D echocardiography[30].

Another application of echocardiography which is very useful in systemic autoimmune diseases is transesophageal echocardiography (TOE). TOE is more sensitive compared with TE for the detection of valvular lesions and cardiac masses[31]. Turiel *et al*[32] detected a high prevalence (61%) of valvular abnormalities or vegetations as potential embolic causes using TOE in 56 patients with primary APS. Recently, the development of 3D TOE allows cross-sectional visualization of the mitral, aortic and tricuspid valves, improving the diagnostic sensitivity compared to traditional 2D imaging[33]. Its superiority over 2D echocardiography includes more accurate and reproducible calculation of LV volumes, mass and ejection fraction, more accurate identification of wall motion changes, more reliable evaluation of right ventricle and better assessment of valvular and subvalvular abnormalities[34].

Echocardiography represents the most versatile and popular cardiac imaging modality easily applicable in any patient from outpatient clinic to intensive care unit; however, it carries some limitations. It is operator dependent, has the limitation of the acoustic window, cannot perform detailed tissue characterization and cannot define the type of tissue lesions in patients with preserved diastolic or systolic function[35].

Nuclear techniques

Single-photon emission computed tomography: It is the most widely used nuclear technique to evaluate stress/rest cardiac perfusion. Maximal exercise or pharmacological stress can be used as a stressing factor and diffusible radiotracers injected during the peak stress allow the detection of myocardial stress perfusion defects[36]. Myocardial blood flow during stress increases about 3 to 5 fold compared with the values during rest. If there is a significant coronary stenosis, myocardial perfusion will not increase adequately in the territory supplied by the stenotic artery conducting to perfusion defect. The currently used single-photon emission computed tomography (SPECT) radiotracers are characterized by a myocardial uptake proportional to blood flow[37]. SPECT is considered as a very sensitive technique for the detection of myocardial ischemia[38]; however, its specificity is relatively lower[39], mainly due to soft-tissue attenuation artifacts. Additional disadvantages of SPECT include high cost and the use of radioactive materials[40].

Positron emission tomography: It has higher spatial resolution compared with SPECT and provides absolute quantitative information about the physiologic parameters of myocardium; moreover, it has high sensitivity and specificity for assessment of myocardial ischemia compared with SPECT. Recently, positron emission tomography (PET) with flurpiridaz F 18 was proven safe and superior to SPECT, due to better image quality, higher certainty during interpretation and generally better CAD diagnosis[41].

Myocardial perfusion by nuclear techniques is a useful tool for the detection of subclinical CAD in RD[42]. Silent myocardial infarction has been also diagnosed by myocardial perfusion SPECT in SLE[43]. Additionally, abnormal perfusion was identified in asymptomatic,

low risk for CAD in SLE patients using a technetium-99m sestamibi[44]. Finally, in SLE patients with cardiac symptoms an abnormal glucose metabolism of the myocardium was detected, shown as a pathological 18FDG scan, whereas perfusion appeared normal (reversed mismatch)[45]. In inflammatory myopathies, Technetium-99m pyrophosphate (99mTc-PYP) and gallium-67 scans had similar sensitivity, specificity and accuracy in the detection of skeletal muscle disease, compared with serum enzymes (70%, 100% and 80%, respectively). Compared with clinical parameters, 99mTc-PYP presented 70% and 67Ga 65% accuracy. Abnormal PYP and 67Ga cardiac uptake was observed in 57% and 15% of patients, respectively[46].

However, nuclear imaging techniques have the disadvantages of high cost, radiation, inability to perform tissue characterization and low spatial resolution, not allowing the assessment of subepicardial, intramyocardial or subendocardial fibrotic lesions, frequently found in RD[33].

Multislice computed tomography

Coronary artery calcification (CAC) occurs due to atherosclerotic process and reflects the total coronary atherosclerotic burden[47]. The Agatston coronary calcium score identifies the extent of calcification in the coronary arteries[48]. Electron-beam computed tomography (EBCT) is a very sensitive technique able to detect small depositions of calcium in the coronary arteries. The radiation dose during an EBCT is considerably lower compared with X ray coronary angiography[49]. Recently published studies, using multislice computed tomography (CT) with iodinate contrast agents to visualize the coronary artery lumen, demonstrated high accuracy in the early diagnosis of CAD[50]. This technique plays a diagnostic role not only for the detection of significant coronary artery stenosis, but also for tissue characterization of the atherosclerotic plaque. Moreover, it allows coronary calcium assessment along the coronary arteries[51]. CT requires iodinated contrast agents, which could provoke symptoms of intolerance and/or renal impairment. Furthermore, during the CT examination patients undergo ionizing radiation exposure. The prevalence of CAD using CTA in asymptomatic high-risk patients is high. If coronary artery calcium score is zero, it can not exclude CAD; however, a normal CTA is extremely accurate to exclude CAD. Total coronary plaque burden, even if only one segment is involved, are associated with high risk for cardiac events[52]. Finally, according to the recently published CONFIRM study, coronary CT angiography has incremental prognostic value for prediction of mortality and non-fatal myocardial infarction in asymptomatic patients with moderately high coronary artery calcium score (CACS), but not in lower or higher CACS[53].

Using CT, it was documented that SLE patients had significantly higher prevalence and/or extent of arterial calcification, compared with matched controls[54] and the disease activity was a potentially modifiable risk factor[55]. Finally, another CT study demonstrated that the calcification of cardiac valves is more prevalent in RA and SLE, compared with controls. The presence of mitral valve, but not aortic valve calcifications, independently predicted premature atherosclerosis in RA and SLE[56]. Furthermore, RA patients without CAD had higher prevalence and severity of all types of coronary plaque. Residual disease activity associates with higher incidence of non-calcified and mixed plaques contributing to future cardiac events[57]. In another CT study, it was also documented that coronary atherosclerosis was not uncommon in asymptomatic SSc patients[58]. Finally, CT scan is the technique of choice for assessment of pulmonary embolism and pulmonary hypertension secondary due to recurrent pulmonary emboli[59].

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) is a non-invasive, nonradiating, operator independent technique that can offer reliable and reproducible information about myocardial function, inflammation, perfusion, fibrosis and heart disease acuity; additionally, vascular disease acuity and vascular inflammation and/or stenosis can be also assessed.

Table 1 summarises the most frequent findings, advantages and disadvantages of each methodology.

The evaluation of rheumatic diseases by CMR can offer: (1) Angiography, imaging of vessel wall and cardiac evaluation (function, oedema, early, late gadolinium enhancement and stress CMR) in vasculitis. Techniques for angiography include both contrast-enhanced MR angiography (CE-MRA) as well as non-contrast methods. Pre-contrast T1W and T2W dark blood imaging but also post-gadolinium T1W imaging can reveal presence of inflammation, even when the disease is clinically under remission[60]; (2) Function, oedema, early, late gadolinium enhancement and stress CMR for RA, SLE, SSc and MTCD. Evidence of myocardial inflammation and/or fibrosis can be identified by STIR T2, early and late gadolinium enhancement, even if the rheumatic disease is under remission[61,62]; (3) Additionally, it is the gatekeeper for differential diagnosis between various types of scar: scar due to CAD that should motivate coronary artery evaluation (subendocardial or transmural scar following the distribution of coronary arteries in CAD) and scar due to inflammation or vasculitis (subepicardial or intramural scar not following the distribution of coronary arteries in inflammation and diffuse subendocardial fibrosis in case of diffuse subendocardial vasculitis)[61-63]; (4) Function, oedema, early and late gadolinium enhancement in inflammatory myopathies using SSFP, STIR T2, early and late gadolinium enhancement, even if the disease is under remission[64,65]; (5) Carotid angiography and vessel wall imaging in RA and SLE[60]; (6) Coronary angiography, oedema, early, late gadolinium enhancement, stress CMR and scar detection for Kawasaki disease[66]; and (7) Assessment of PAH includes information about

Table 1 Clinical findings, advantages and disadvantages of each technique

Noninvasive imaging techniques	Evaluation of	Advantages	Disadvantages
Rest echocardiography	Cardiac valves	Cheap	Operator dependent
	Pericardium	Widely available	Limitation due to poor acoustic window
	Ventricular function	Bedside	No tissue characterization
	Wall motion	No radiation	
	Pulmonary pressure		
Tissue doppler imaging	Measurement of myocardial velocities	The same as in rest echocardiography	Limited by angle-dependency
Stress echocardiography	CFR in LAD	The same as in rest echocardiography	The same as in rest echocardiography
	Myocardial ischemia		
Transesophageal echocardiography	Valvular lesions	The same as in rest echocardiography	The same as in rest echocardiography
	Intracardiac masses		Semi-invasive
SPECT	Myocardial ischemia	Widely available	Radiation
	Ventricular function	Reasonable sensitive	High cost
		Not very specific	Low spatial resolution
PET	Myocardial ischemia	Very sensitive	Radiation
	Ventricular function	Very specific	High cost
			Low spatial resolution
			Not widely available
CT	Great vessels	Fast	Radiation
	Coronary arteries/grafts	Widely available	High cost
			Iodinated contrast agent
CMR	Ventricular function	Highly reproducible	Not widely available
	Inflammation	Operator independent	High Cost
	Perfusion	No radiation	Claustrophobia
	Fibrosis	Tissue characterisation	Non MRI compatible devices can not be scanned
	Heart disease acuity	High spatial resolution	Low temporal resolution
	Vascular disease acuity		
	Vascular inflammation and/or stenosis		

SPECT: Single-photon emission computed tomography; PET: Positron emission tomography; CMR: Cardiovascular magnetic resonance; CFR: Coronary flow reserve; CT: Computed tomography; LAD: Left anterior descending.

right ventricular (RV) mass index, RV volumes-ejection fraction, late gadolinium enhancement (LGE) and phase contrast imaging, including average velocity (cm/s), retrograde flow (L/min) and percentage retrograde flow (%)[67]. These indexes have been shown to be prognostic of long-term outcomes. LGE at ventricular insertion points in PAH is due to altered intraventricular septal motion and not to elevated RV pressure or remodelling[68].

TOWARDS AN ALGORITHM ABOUT THE APPLICATION OF NONINVASIVE CARDIOVASCULAR IMAGING IN RHEUMATIC DISEASES

The first line and cornerstone of routine cardiac assessment in RD is echocardiography. However, it is unable to detect cardiac disease acuity, myocardial or vascular inflammation and scar in cases with normal LV function[69]. Nuclear techniques are also unable to detect small perfusion defects, commonly found in RD, due to low spatial resolution, to identify disease acuity and the exact location of the lesion (subendocardial, transmural or subepicardial) and to further guide risk stratification[70]. CT coronary angiography cannot be included in the routine assessment of cardiac involvement in RD, because it cannot answer all the relevant queries, raised in these diseases. Furthermore, high cost, the need of repetitive radiation in both nuclear techniques and CT and the use of iodinated contrast agents in CT constitute serious limitations for its routine use in diagnosis and follow up.

CMR is a non-invasive, nonradiating, highly reproducible technique, capable to answer queries about cardiac disease acuity, etiology of cardiac lesion, necessity for cardiac catheterization and persistence of myocardial involvement, although the systemic disease seems quiescent[69].

CONCLUSION

The oligo-asymptomatic cardiovascular presentation and the high cardiovascular mortality of RD necessitate a reliable and reproducible diagnostic approach to catch early cardiovascular involvement. Echocardiography remains the routine cornerstone of cardiac evaluation. However, a normal echocardiogram cannot always exclude cardiac involvement and/or identify acuity and pathophysiology of cardiac lesions. Therefore, CMR is a necessary adjunct, complementary to echocardiography, especially in new onset heart failure and when there are conflicting data from clinical, electrocardiographic and echocardiographic evaluation of RD patients.

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