JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 11, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jcmg.2017.08.017

Cardiac Tissue Characterization and Imaging in Autoimmune Rheumatic Diseases

Sophie I. Mavrogeni, MD, PhD,[a] Petros P. Sfikakis, MD, PhD,[b] Loukia Koutsogeorgopoulou, MD, PhD,[c] George Markousis-Mavrogenis, BSc (Hons),[a] Theodoros Dimitroulas, MD, PhD,[d] Genovefa Kolovou, MD, PhD,[a] George D. Kitas, MD, PhD[e]

ABSTRACT

Inflammation, microvascular and macrovascular ischemia, valvular disease, and fibrosis are the main causes of cardiovascular disease (CVD) in autoimmune rheumatic diseases (ARDs). The silent presentation and the high mortality and/or morbidity of CVD in ARDs necessitate a reliable tool for early diagnosis. Noninvasive cardiovascular imaging, including echocardiography, nuclear imaging, cardiovascular computed tomography (CT), cardiac magnetic resonance (CMR), and hybrid imaging modalities, constitutes the main tool for monitoring of CVD in ARDs. Echocardiography is the cornerstone for CVD evaluation, but it is operator-dependent and cannot perform tissue characterization. Nuclear imaging and CT, although promising, have the disadvantage of ionizing radiation. CMR can assess inflammation, ischemia, and fibrosis without ionizing radiation, thus making it a necessary adjunct, which is especially relevant for ARDs with new-onset heart failure, conflicting data from other imaging modalities, and recent onset of chest pain and/or arrhythmias. Recently, hybrid imaging with positron emission tomography (PET)/CT and PET/CMR has shown promise in ARDs, although these modalities currently have prohibitive costs. (J Am Coll Cardiol Img 2017;10:1387–96) © 2017 by the American College of Cardiology Foundation.

In autoimmune systemic connective tissue diseases, the main pathophysiological phenomenon is autoimmune reactivity that targets connective tissues. Connective tissues may be defined as a collection of diverse cell groups located inside a tissue-specific extracellular matrix, externally bounded by the basal lamina of overlying epithelia, muscle cells, or glial cells (1). Currently, the term "autoimmune rheumatic disease" (ARD) is considered more preferable than the older term "connective tissue disease," because disease pathology is not limited to the connective tissues. ARDs are characterized by multiorgan involvement due to systemic inflammation caused by inappropriate activation of the immune system, with subsequent tissue damage. Women are more commonly affected than men, and associations between both genetic and environmental factors and the observed immune dysregulation have been identified (1). ARDs with potential cardiovascular involvement include: 1) systemic lupus erythematosus (SLE); 2) rheumatoid arthritis (RA) and seronegative arthritides; 3) systemic sclerosis (scleroderma) (SSc); 4) mixed connective tissue disease; 5) inflammatory myopathies, including dermatomyositis, polymyositis, and inclusion body myositis; 6) vasculitis of large, medium, and small vessels; and 7) sarcoidosis (SRC).

New targeted treatments used in the management of ARDs have resulted in significant reductions of disease-associated mortality. However, ARDs continue to convey a lower life expectancy compared with the general population (1), with an excess of cardiovascular risk being heavily implicated as the culprit (2–6). Cardiovascular disease (CVD) in patients with ARDs is the endpoint of various pathophysiological processes occurring during their disease course. These include systemic and/or cardiovascular inflammation, perfusion defects due to microvascular

From the [a]Onassis Cardiac Surgery Center, Athens, Greece; [b]First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece; [c]Department of Pathophysiology, Laikon Hospital, Athens, Greece; [d]4th Department of Internal Medicine, School of Medicine, Hippokration Hospital, Aristotle University of Thessaloniki, Greece; and the [e]Arthritis Research UK Epidemiology Unit, Manchester University, Manchester, United Kingdom. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 4, 2017; revised manuscript received August 25, 2017, accepted August 29, 2017.

ABBREVIATIONS AND ACRONYMS

ARDs = autoimmune rheumatic diseases

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CT = computed tomography

ECV = extracellular volume

LGE = late gadolinium enhancement

PET = positron emission tomography

RA = rheumatoid arthritis

SLE = systemic lupus erythematosus

SPECT = single-photon emission computed tomography

SRC = sarcoidosis

SSc = systemic sclerosis

and/or macrovascular disease combined with abnormal vasoreactivity, diffuse or replacement fibrosis, coagulation abnormalities, pulmonary hypertension due to primary cardiac or lung involvement, valvular diseases, and side effects of immunosuppressive medication (7,8). **Table 1** presents the most common pathophysiological phenomena that occur in ARDs with cardiac involvement.

Despite etiology, symptoms of CVD in ARD patients are usually subtle and are often underestimated or dismissed as constitutional symptoms of the underlying systemic disease. Clinically overt cardiovascular signs and symptoms present late in the course of CVD in patients with ARDs and carry a poor prognosis because they indicate advanced stages of cardiovascular damage and/or decompensation (9). The latter underlines a pressing need for diagnostic tools that are capable of characterizing cardiovascular tissues before the onset of overt CVD manifestations.

In addition, the multifaceted nature of CVD in ARDs stresses the requirement for a high-resolution diagnostic imaging modality for evaluating cardiovascular pathology. Echocardiography, nuclear imaging modalities, and x-ray coronary angiography still remain the cornerstones of cardiovascular imaging in clinical cardiology. However, these modalities are hampered by serious limitations concerning the early diagnosis of CVD in ARD patients because they cannot reliably detect cardiovascular inflammation, fibrosis, and microvascular disease in pre-clinical nonovert stages (10,11). Cardiac magnetic resonance (CMR) has recently been proposed as a potent diagnostic tool for pre-clinical tissue characterization and monitoring of early cardiovascular involvement in ARD patients (12). Recently, hybrid imaging with positron emission tomography (PET)/computed tomography (CT) and PET/CMR have been also proposed as a potential useful diagnostic tool in ARD (13).

The aim of this review is to evaluate the role of noninvasive imaging modalities for cardiac tissue characterization in ARDs.

IMAGING MODALITIES FOR CARDIAC TISSUE CHARACTERIZATION IN ARDs

Cardiovascular imaging modalities are the "sine qua non" of clinical cardiology because of their ability to noninvasively evaluate pathophysiological phenomena that occur during the course of cardiac disease. Routinely used imaging modalities in cardiology include echocardiography, nuclear imaging modalities, and x-ray coronary angiography. However, despite their adequate performance in the evaluation of coronary artery disease (CAD), they are suboptimal in the assessment of myocarditis, microvascular disease, and cardiomyopathy. When assessing these conditions, the only valuable information these modalities can provide are some abnormalities of imaging indexes, without further detail regarding myocardial edema, microvascular dysfunction, or diffuse myocardial fibrosis, which constitute the core of cardiovascular pathophysiology in ARDs.

ECHOCARDIOGRAPHY. Currently, the most commonly employed noninvasive imaging modality used in cardiovascular imaging is echocardiography, due to its high availability, portability, low cost, lack of ionizing radiation exposure, and high expertise among cardiologists. It can reliably identify morphological, functional, and valvular alterations both at rest and stress; however, image quality is strongly dependent on the acoustic window of the patient and the expertise of the operator. Furthermore, classic echocardiographic indexes do not address the aforementioned necessity for cardiac tissue characterization (12).

Tissue Doppler imaging, a relatively new echocardiographic technique, allows for measurement of myocardial systolic and diastolic velocities and represents a reliable tool for the assessment of myocardial deformation. However, it is limited by angle dependency because only deformation along the 2-dimensional plain, as defined by the ultrasound beam, can be derived from the evaluated velocities, whereas the myocardium deforms simultaneously in all 3 dimensions (14). Birdane et al. (15) demonstrated that RA patients had a significant impairment of tissue Doppler imaging biventricular diastolic functional parameters compared with healthy control subjects, which was dependent on age and corticosteroid treatment. To overcome the limitations of tissue Doppler imaging, speckle tracking analysis was used to evaluate myocardial strain along the longitudinal, circumferential, and radial axes (16). 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 CAD (17). In addition, global longitudinal left ventricular and right ventricular strain were reduced in RA patients compared with control subjects, and strain abnormalities were correlated with RA disease severity (17). Furthermore, 3-dimensional speckle