Cardiovascular Magnetic Resonance for Evaluation of Heart Involvement in ANCA-Associated Vasculitis: A Luxury or a Valuable Diagnostic Tool?

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Abstract

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis is a systemic small-vessel vasculitis, including 3 clinical syndromes: granulomatosis with polyangiitis, known as Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA) and the Churg–Strauss syndrome (CSS). ANCA-associated vasculitis usually presents with life-threatening kidney failure or pulmonary hemorrhage, has a mortality rate of 28% at 5 years, and contributes to increased morbidity and mortality.

Cardiac involvement in this entity includes coronary vessels vasculitis, pericarditis, myocarditis, endocarditis, myocardial infarction and diffuse subendocardial vasculitis that can contribute to reduced life expectancy. Cardiovascular magnetic resonance using oedema and fibrosis imaging can reveal noninvasively and without radiation, early heart involvement during vasculitis, undetected by other imaging techniques and guide further risk stratification and treatment of these patients.

Keywords: Cardiovascular magnetic resonance; Systemic vasculitis; Coronary artery; Myocardial ischemia; Myocardial inflammation; Myocardial fibrosis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis is a systemic small-vessel vasculitis, including three clinical syndromes: granulomatosis with polyangiitis, known as Wegener’s granulomatosis (WG) [1] microscopic polyangiitis (MPA) and the Churg–Strauss syndrome (CSS) [2]. ANCA-associated vasculitis usually presents with life-threatening kidney failure or pulmonary hemorrhage, has a mortality rate of 28% at 5 years and contributes to increased morbidity and mortality of these patients [3].

WG is characterized by granulomatous inflammation of the respiratory system and by autoantibodies against the neutrophil granule serine protease proteinase 3 in 66% of patients (considered to have proteinase 3 ANCA–associated vasculitis) or against another neutrophil granule component, myeloperoxidase, in 24% of patients (considered to have myeloperoxidase ANCA–associated vasculitis) [4]. MPA is associated with myeloperoxidase ANCA in 58% of cases and with proteinase 3 ANCA in 26% of cases [4]. Some vasculitis patients are ANCA-negative [4], as in more than 50% of CSS [5].

Pathogenesis

There is evidence of an important genetic contribution to ANCA-associated vasculitis, including evidence of a familial association [6]. The most convincing association has been with the major histocompatibility complex (MHC), especially the locus HLA DPB1*0401.10 [6]. The pathogenesis of ANCA-associated vasculitis apart from a genetic component, shows also genetic distinctions between WG and MPA that are associated with ANCA specificity, and suggests that the response against the autoantigen proteinase 3 is a central pathogenic feature of proteinase 3 ANCA associated vasculitis [6]. Recent data support the concept that proteinase 3 ANCA–associated vasculitis and myeloperoxidase ANCA– associated vasculitis are distinct autoimmune syndromes [6].

Anti-neutrophil cytoplasmic antibodies (ANCAs) with specificity for proteinase-3 (PR3) or myeloperoxidase (MPO) are the hallmarks of ANCA vasculitis and play an important role in disease progression. In addition to ANCA, the cellular immune system also contributes to the pathogenesis of vasculitis. Initially, ANCA-mediated degranulation of neutrophils causes severe vasculitic damage. Then, T cells drive granuloma formation and further promote the vasculitic damage by using several different pathways and enhancing autoantibody production by B cells. Complementary PR3 and lysosomal membrane protein-2 were suggested as novel auto-antigens in ANCA associated vasculitis. Recent findings also support the importance of complement, danger-associated molecular patterns, and dendritic cells in this type of vasculitis [7]. In ANCA-associated vasculitis, the endothelium damage is located in the post-capillary venules [8]. Dead endothelial cells are leading to detachment, as it is evident by circulating detached endothelial cells that have been captured and quantified [9]. This denudation exposes the underlying basement membrane, initiating thrombosis and platelet deposition and results in occlusion of vessel lumen. In addition to this passive event, a more active process takes place. This involves the endothelial cells response to injury by expressing a pro-inflammatory phenotype, i.e. changes in adhesion molecule and cytokine patterns [10].

Clinical Presentation

WG, MPA and CSS share many common features, affecting kidneys, lungs and skin. However, granulomatous destruction of the respiratory tract is more common in WG, whereas eosinophilia and asthma support the diagnosis of CSS and MPA uncommonly involves the upper airways or the eyes. Although patients’ survival rates have

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Received March 22, 2013; Accepted April 06, 2013; Published April 08, 2013


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been improved to over 80% at 5 years, there is a considerable morbidity, involved with the current use of immunosuppressants [11].

**Documentation of Diagnosis**

The majority of patients with ANCA-associated vasculitis (90%) produce autoantibodies to neutrophil components termed ANCA (anti-neutrophil cytoplasm antibodies). The two major antigens for ANCA are: MPO (myeloperoxidase) and PR3 (proteinase 3), both expressed in the neutrophil granules. ANCA display two characteristic staining patterns when applied to ethanol fixed neutrophils. A perinuclear localization (pANCA) denotes an anti-MPO ANCA and is predominantly associated with MPA or CSS, whereas cytoplasmic distribution (cANCA) is due to anti-PR3 and is frequently linked to WG and, less frequently, to MPA. ANCA are also detected using ELISA. These two tests are usually combined to provide a higher degree of confidence and, when used in parallel with the clinical assessment and history contribute to diagnosis of ANCA-associated vasculitis. This is of great importance, because the disease treatment is highly toxic.

Tissue biopsy is also of great value to confirm the diagnosis of ANCA-associated vasculitis, before start of potentially toxic immunesuppressive treatment. In patients with haematuria, a renal biopsy may reveal a typical vasculitis glomerulonephritis. Biopsy of other involved tissues, such as nasal mucosa or lung tissue, may also be informative in selected patients.

Clinical disease activity is defined by a standardized system known as BVAS (Birmingham Vasculitis Activity Score). This utilizes a numerical scoring system, involving nine organs, which is weighted for importance. A high score denotes either critical organ involvement or multisystem effects and relates to mortality [12,13]. The damage caused by vasculitis or the use of drugs for its treatment is assessed using a complementary scoring system called the vasculitis Damage Index.

ANCA-associated vasculitis can be fatal, if left untreated. Adverse prognostic factors are: a) age b) renal impairment and c) pulmonary involvement. Relapses can occur frequently, if treatment is discontinued and usually long-term maintenance therapy is necessary [11].

**Cardiac Involvement in ANCA-associated Vasculitis**

**WG**

Clinically overt cardiac involvement is rare in WG, although ECG abnormalities, coronary artery vasculitis, cardiac arrhythmias, pericarditis, myocarditis, valvulitis, and myocardial infarction (MI) have been described [14-17]. However, histopathologic studies demonstrated cardiac involvement in 30%. Pericarditis was the most common cardiac involvement occurring in 50% of WGs, with the next 50% involving the coronary arteries. Pericarditis can be either diffuse or focal, but cases of pericardial effusions and cardiac tamponade have been also reported [18]. The endocardium (including valves), myocardium, and epicardium can be also affected by vasculitis (Figure 1). The epicardium has shown granulomatous inflammatory foci [18] and the myocardium granulomatous foci, peri-vascular inflammation and necrotizing arteriolitis. The endocardium and valves were also involved in several cases with inflammation, fibrinoid necrosis, and granulomatous formation of the mitral and, less commonly, tricuspid valves [19]. The incidence of atrioventricular conduction disease in WG has not been fully assessed. However, supraventricular are more common than ventricular arrhythmias [18].

Coronary vasculitis has been reported in 50% of WG autopsy. However, angina pectoris and MI are uncommon. The coronary vessels showed a spectrum of vasculitic changes, ranging from acute necrotizing to healing activity. Other potential mechanisms of ischemia include coronary artery embolism from aortic valvulitis [19] and aortitis-related ostial stenosis [20]. The association of WG with myocardial infarction without typical chest pain has been also described [14,15,19,21].

**MPA**

It shows a lower prevalence than Wegener’s disease, it affects more men than women and starts at the age of ≥ 50 years. The organs that are more commonly involved are the kidneys and the lungs. However, MPA may also involve the nervous system, the skin, the musculoskeletal system, the eye, the gastrointestinal system and also the heart contributing to heart failure [22,23]. Coronary ectatic disease and myocardial infarction can be also found in MPA (Figure 2) [24].

**CSS**

Although it is classified in ANCA-associated vasculitis, according to a recent study, P-ANCAs/MPO-ANCAs were present in only 38% of CSS. ANCA-positive patients were more likely to have disease manifestations, due to small-vessel vasculitis, including necrotising glomerulonephritis, mononeuritis and purpura, whereas ANCA-negative cases were more likely to have cardiac and lung involvement [25]. Cardiac involvement is common in patients with CSS, is associated with the absence of ANCA and high eosinophil counts and represents cardiac emergency. According to a recent study, endomyocarditis was found in the majority of CSS with cardiac symptoms, and was associated with impaired cardiac function and poor future outcome (Figure 3) [26].

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**Figure 1:** Diffuse subendocardial fibrosis in a WG patient.

**Figure 2:** Transmural fibrosis due to myocardial infarction in a MPA patient.
Risk Stratification and Treatment

To summarize, the diagnostic work-up of ANCA-associated vasculitis relies on an interdisciplinary approach including clinical assessment, imaging techniques and laboratory tests in order to evaluate disease stage and severity. However, the gold standard remains the histological proof of a necrotizing, pauci-immune small vessel vasculitis. Prior to effective treatment, ANCA-associated vasculitis had a mortality of 93% within 2 years, mainly due to renal and respiratory failure [27]. The introduction of glucocorticoids in 1948 and cyclophosphamide in the 1960s, together with adjunctive therapies such as antihypertensive drugs and renal replacement therapy, has transformed survival - with 5-year survival rates now approaching 80% [28]. Treatment must be individualised according to disease stage and extent; cyclophosphamide is the mainstay of therapy and in rapidly progressive glomerulonephritis with an imminent dialysis indication plasmapheresis should be performed additionally. Plasma exchange decreases the risk of progression to end-stage renal failure by 24% at 12 months, but had no effect on longer-term renal function or survival [29]. A remission, during the early systemic disease without organ- and life-threatening clinical manifestations and nearly normal kidney function, can be achieved with methotrexate. Methotrexate is not inferior at inducing remission, but remission is slower than with cyclophosphamide in those patients with more extensive disease or pulmonary involvement. Methotrexate provokes less leucopaenia, but more liver dysfunction and has a higher relapse rate.

In generalized forms of vasculitis, when vital organ function is already compromised, adjunctive therapies that include, plasma exchange, i.v. methylpredni-solone, intravenous immunoglobulin (IVIg) and TNFa blockade have been also considered.

When remission is achieved, usually after 3-6 months of induction treatment, cyclophosphamide is switched to azathioprine, as maintenance of remission drug. Alternative therapies are methotrexate, if kidney function is normal or Leflunomide in the long-term follow-up; unfortunately, the relapse rate in ANCA-associated vasculitis is approximately 50% in 5 years, irrespective of drug used for maintenance treatment. The relapse rate is significantly higher in WG than in MPA and CSS.

Rituximab is the best studied biological agent in ANCA associated vasculitis. The recently published randomised controlled trials RITUXVAS and RAVE have shown that rituximab is similar to cyclophosphamide, in terms of both efficacy and safety, for induction of remission in the short term. Subgroup analysis in the RAVE trial found the efficacy of rituximab to be superior to cyclophosphamide at 6 months for patients with relapsing disease. However, potential adverse effects of any new therapy must be carefully evaluated prior to recommendation of use [30].

How can Cardiovascular Magnetic Resonance Contribute to the Evaluation of ANCA-associated Vasculitis?

The most commonly applied non-invasive technique in routine cardiac practice is transthoracic echocardiography. It has the advantages of being easy, cheap, without radiation, widely available and the disadvantages of being an operator-dependent technique, of limited value in patients with bad acoustic window and unable to perform tissue characterization.

In contrary, cardiovascular magnetic resonance (CMR), although it needs high expertise and is more expensive, can overcome these limitations. CMR is the best and most reproducible technique to assess cardiac volumes and ejection fraction noninvasively and without contrast agent [31]. It is of great value for the assessment of the right ventricle, which is of special interest for rheumatic diseases and is not always adequately assessed by echocardiography. CMR provides 3-dimensional images of the heart, also feasible with 3D echocardiography. While CMR ejection fraction and volumes are more accurate and reproducible than other imaging techniques, there is a good correlation between CMR and these techniques [31].

CMR is the only non-invasive technique that can give early, reliable and reproducible information about myocarditis and myocardial vasculitis, commonly found in vasculitis patients [32-41]. Myocarditis during its early stages remains undetected by the commonly used imaging techniques (echocardiography or nuclear imaging techniques), because these techniques are unable to distinguish slight tissue structure changes (oedema, cell infiltration) that occur without associated changes in left ventricular ejection fraction, which is the most commonly detected parameter by echocardiography. Instead, the ability of MR to characterize tissue changes makes it extremely valuable for myocarditis detection. CMR contributes to the diagnosis of myocarditis using three types of images: T2-weighted (T2-W), early T1- weighted (EGE) images taken 1 min and delayed enhanced (LGE) images taken 15 minutes after the injection of contrast agent. T2-W is an indicator of tissue water content, which is increased in inflammation or necrosis, such as during myocardial infarction or myocarditis (oedema imaging). However, it is not possible to differentiate between necrosis and inflammation only by the use of T2-W images. To enhance the detection of pathology on CMR, images after early and delayed gadolinium injection should be obtained. Higher levels of early gadolinium enhancement (EGE) after gadolinium administration are due to increased membrane permeability or capillary blood flow. Membrane permeability is a major contributor as inflammation damages cell membranes through both T-cell perforin and B-cell antibody/complement-mediated processes. The third parameter, late gadolinium enhancement (LGE), is the result of the contrast agent deposition in the delayed images, due to myocardial necrosis in the acute phase that increases the gadolinium distribution. A combined CMR approach using T2-W, EGE and LGE has a sensitivity of 76%, a specificity of 95.5% and a diagnostic accuracy of 85% for the detection of myocarditis [32].

The detection of small vessels vasculitis in myocardium is based on the subendocardial pattern of myocardial involvement that can be easily detected by LGE, but not by echocardiography [38-42]. Existing data support the use of LGE and T2 myocardial imaging in defining the
presence, acuity and extent of cardiac involvement during the course of vasculitis [40,42-46].

Although coronary magnetic resonance angiography (cMRA) cannot achieve the resolution of X-Ray angiography for grading of stenoses, nor the resolution of CT coronary angiography to identify coronary artery calcifications, it is of value to evaluate coronary artery ectasia or aneurysm [47,48] and also coronary artery lumen [49,50]. The first multicenter coronary MRA trial using navigator techniques showed a high sensitivity for the detection of coronary artery disease (95%). Although the specificity was relatively low (34%), its negative predictive value for 3-vessel disease was high (90%), allowing to exclude high risk patients scheduled for surgery. However, accuracy was too low for a general clinical indication [50]. Two recently published studies using more sophisticated techniques showed a sensitivity of 78% and 82%, a specificity of 91% and 90% and an accuracy of 89% and 87% respectively [51,52]. Coronary MRA has been already successfully used for the evaluation of coronary arteries in Kawasaki disease [47-49] (Figure 3) and other vasculitis [24] and gave significant information about lesions in the coronary arteries and/or myocardium. Furthermore, the combination with the late gadolinium enhanced images allowed the detection of scar, which represents the most important risk factor for major cardiac events and mortality [24,47].

CMR can also perform ischemia evaluation:

a) By detection of wall motion abnormalities (abnormal wall motion and wall thickening) using the stress factor dobutamine (the same way as stress echo, but without the limitation of acoustic window). Compared to stress echo, stress CMR using dobutamine has better sensitivity (86% vs. 74%) and specificity (86% vs. 70%) [53-56]; b) By assessment of myocardial perfusion during the first pass of bolus of gadolinium, a T1-shortening contrast agent, (first-pass gadolinium) injected into a peripheral vein [57,58]. Data acquired during intravenous vasodilator-stress (most commonly with adenosine) delineate the under-perfused regions associated with myocardial ischemia. The spatial resolution of CMR perfusion imaging is around 2-3 mm and it is greatly superior to other imaging modalities, such as nuclear techniques, so that subendocardial ischemia can be more reliably identified [58,59].

The interpretation of CMR myocardial perfusion studies in clinical practice is most commonly visual, but also quantitative approaches are available [57,60-63] and have been validated against x-ray angiography, SPECT and PET [64-66]. The recent CE-MARC study is the largest, prospective, real world evaluation of CMR and has established CMR’s high diagnostic accuracy in coronary heart disease and CMR’s superiority over SPECT. Therefore, it should be adopted more widely than at present for the investigation of coronary heart disease [67].

However, the most important CMR contribution is its capability to perform tissue characterization and reveal early changes, undetected by other imaging techniques. In this context, CMR, using T2-Weighted sequences can detect myocardial oedema (oedema imaging) [68,69]; additionally, CMR is the most reliable imaging way to detect and quantify the scar or fibrotic tissue, due to irreversible myocardial damage (fibrosis imaging). The preferred imaging time for scar detection is between 10 and 20 minutes after contrast agent administration, when the differences between scar, normal myocardium and blood pool are maximal. This method is referred in the literature as late gadolinium enhanced CMR (LGE) and is the gold standard for the \textit{in vivo} assessment of myocardial scar. CMR can detect fibrosis in as little as 1 cm$^2$ of tissue, substantially less than other \textit{in vivo} methods, such as echocardiography and nuclear techniques. LGE has shown excellent agreement with histology in animal and human studies [70-73].

The most important information that CMR can give in ANCA-associated vasculitis is the evaluation of disease acuity using the combination of oedema and fibrosis imaging. If both parameters are increased, there is evidence of acute myocardial lesion [32]. If T2 is normal and only LGE is identified, the cardiac lesion is chronic. This information is of great diagnostic value, because cardiac involvement in ANCA-associated vasculitis is usually oligo-asymptomatic. Furthermore, CMR using the combination of T2-Weighted images, EGE and LGE can distinguish acute from chronic myocardial inflammation [33,34]. This approach has been already used for evaluation of myocardial inflammation in Kawasaki disease [34,35]. Additionally, by evaluating the LGE pattern, we can have information of pathophysiologic background of the lesion. In this context, subendocardial vasculitis presents with diffuse subendocardial fibrosis, myocarditis with intramural or subepicardial lesions not following the distribution of coronary arteries and myocardial infarction with subendocardial or transmural lesions following the distribution of coronary arteries [41,32-35].

There are an increasing number of publications about the role of CMR in ANCA-associated vasculitis [24-26,33-46]. CMR allows the identification of coronary artery ectasia and/or aneurysms in parallel with myocardial fibrosis evaluation [24]. Additionally, the excellent spatial resolution of CMR, allows the detection of subendocardial lesions missed by other imaging techniques [38]. Finally, CMR has the capability to early detect different types of cardiac damage (myocarditis, pericarditis, and impaired myocardial perfusion) that take place during ANCA-associated vasculitis, even before symptoms onset [24,38-46]. Early detection of cardiac damage enables faster implementation of aggressive treatment, which may significantly improve disease prognosis. The widespread, even routine, practice of CMR in patients with ANCA-associated vasculitis seems to be justified providing essential diagnostic and prognostic information and will guide patients risk stratification [41].

Currently more sophisticated techniques able to provide detailed information about both diffuse oedema and fibrosis became available. For this purpose, quantitative T2 mapping was proved reliable to identify myocardial oedema without the limitations encountered by T2-weighted short tau inversion recovery imaging and could offer the potential for increased accuracy in the detection of myocardial oedema [74]. Additionally, the application of T1 mapping, that has been recently used to identify diffuse fibrosis in heart failure, looks promising for the detection of diffuse fibrosis in myocarditis [75]. Additionally, ultra small superparamagnetic iron oxide (USPIO) particles have been used for detection of vascular inflammation. USPIO enhanced MR imaging proved promising to identify high risk atheromatous plaque inflammation in vivo in humans, in which areas of focal signal loss on MR imaging have been shown to correspond to accumulation of iron particles in \textit{ex vivo} specimens. USPIO accumulates predominantly in activated macrophages either at the shoulders or in the necrotic lipid core of ruptured and prone to rupture human atherosclerotic lesions. Signal loss on T$^*_1$ weighted imaging as a result of USPIO uptake may be used as a surrogate to measure of the extent of inflammation within vessels wall [76].

In conclusion, ANCA associated vasculitis are genetic type autoimmune diseases that can frequently involve the cardiovascular system. CMR, due to its excellent spatial resolution and high versatility, using different imaging sequences, can detect early cardiac lesions, undetected by other imaging techniques and contribute to patients risk stratification. Therefore, it should be included in the vasculitic diagnostic algorithm.  

References


This article was originally published in a special issue, Autoimmune Diseases handled by Editor(s). Dr. Kenneth Blum, University of Florida, USA