NON-INVASIVE CARDIOVASCULAR IMAGING FOR CARDIOVASCULAR RISK ASSESSMENT IN RHEUMATOID ARTHRITIS

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Disclosure: The authors have declared no conflicts of interest.
Received: 02.03.16 **Accepted:** 03.05.16
Citation: EMJ Rheumatol. 2016;3[1]:106-113.

ABSTRACT

People with rheumatoid arthritis (RA) are often under-recognised as a group with elevated risk of cardiovascular (CV) disease and increased morbidity from CV events. Standard clinical risk assessment tools, which take into account traditional CV risk factors such as smoking, diabetes, hypertension, hyperlipidaemia, and family history do not accurately predict CV risk in patients with autoimmune rheumatic disorders; therefore, there is an unmet need for other methods to assess their risk. Non-invasive CV imaging is evolving as a novel clinical tool to determine subclinical atherosclerotic coronary artery disease in patients with RA. Non-invasive imaging studies, such as tests of endothelial function (i.e. reactive hyperaemia index and flow-mediated dilation) and arterial stiffness (i.e. pulse-wave velocity), have been identified as a potential means for providing accurate assessment of early CV risk in the general population and are evolving in their utility for patients with RA. These types of non-invasive imaging have the potential to eliminate the current use of invasive assessments for identification of precursors to coronary artery disease, such as coronary angiography for early endothelial cell dysfunction. By combining the expertise of subspecialists in cardio-rheumatology clinics, the expectation is to pre-emptively identify RA patients with early coronary artery disease, allowing early modification of risk factors through either medical management or lifestyle modification.

Keywords: Cardio-rheumatology, endothelial cells, flow-mediated dilation (FMD), aortic pulse-wave velocity (aPWV).

INTRODUCTION

Rheumatoid arthritis (RA) is a common inflammatory autoimmune condition presenting in a symmetrical fashion in both large and small joints, and is defined by the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria as definite clinical synovitis in ≥1 joint and a score ≥6 in four domains: number/site of involved joints, serological abnormality, elevated acute phase response, and symptom duration of at least 6 weeks. The epidemiology of RA varies by geographic region and by ethnic/racial group with 1% of the worldwide population affected; RA develops in women 2 to 3-times more often than men, with the lifetime risk of RA being 3.6% in women and 1.7% in men.[1]

People with RA have increased mortality attributable to atherosclerotic cardiovascular disease (ASCVD) events,[2] and a 1.5 to 2-fold increased risk of developing ASCVD compared with the general population. A recent meta-analysis identified a 50% increased risk of death in patients with RA compared with the general population,[3,4] and at the time of RA diagnosis, patients in the study were >3-times as likely as the general population to have had a prior myocardial infarction. Standard CV risk assessment scores have been shown to markedly underestimate the risk of CV disease events in the RA population. In one study, the observed

CV risk was 2-fold higher in female RA patients than the Framingham Risk Score predicted, and was 65% higher in men.[4] The Reynolds Risk Score (which includes C-reactive protein [CRP]) was similarly deficient in estimating the risk.[4] While a heightened risk of CV events exists in patients with RA, we have yet to uncover an accurate method for estimating that risk. Lack of such knowledge is an important problem, given the poor survival rate and heightened mortality from ASCVD in patients with RA compared with the general population.

CARDIO-RHEUMATOLOGY

Cardio-rheumatology is an emerging field addressing the unmet clinical and research needs of identifying early atherosclerosis in patients with rheumatic disease.[2] These unmet needs include identification of silent, or 'subclinical', atherosclerosis, inability to predict CV risk in RA patients based on the traditional CV risk scores, and understanding the role of inflammation.[2] The use of non-invasive CV imaging for CV risk assessment is of interest in the field of cardio-rheumatology, and has been encouraging in its ability to detect early atherosclerosis and endothelial dysfunction in RA patients, thus enhancing the co-ordination of care of RA patients between cardiologists and rheumatologists.[2,3] Ideally, through the early identification of CV risk by non-invasive CV imaging, cardiologists will assist rheumatologists in the modification of risk factors in RA patients.

The typical presentation of CV symptoms is often under-recognised in patients with inflammatory autoimmune disease, and classic symptoms of cardiac angina and myocardial infarction often go unrecognised in RA patients.[5] Patients with RA are twice as likely as the general population to develop silent myocardial infarctions and sudden cardiac death, and receive less regular counselling for other traditional risk factors such as smoking, hypertension, and maintaining healthy activity levels.[2,3,5] As reviewed by Crowson et al.,[3] chronic glucocorticoid use, visceral adiposity, low muscle mass, elevated risk of venous thromboembolism, and low activity levels from debility are also important cardiac risk factors in RA patients. In persons with RA, early intervention for modifiable CV risk factors and recognition of subclinical accelerated atherosclerosis is desperately needed. Crowson et al.[3] found that only 55% of patients with RA in one study had lipid levels measured; management by rheumatologists was associated with less frequent lipid screening, showing that patients with RA generally have less primary and secondary preventative screening.[3,5] The hope of the joint endeavours in cardio-rheumatology clinical practice is to ameliorate the heightened morbidity from CV disease, and identify other non-invasive methods to assess CV risk that are different from the traditional risk scores.

CHALLENGES TO ASSESSING CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS

The accelerated and diffuse nature of subclinical atherosclerosis in patients with autoimmune disease is comparable to patients with diabetes mellitus; however, traditional risk factors (male sex, smoking, family cardiac history) seem to play a greater role in ASCVD associated with diabetes mellitus, whereas systemic inflammation appears to have greater significance in RA.[2] Patients with RA have greater underlying inflammation and lower lipid levels in comparison with the general population, exemplifying the many challenges in CV risk stratification and pharmacologic prevention in patients with autoimmune disease.[3] Lipid levels therefore have a paradoxical relationship with CV risk in RA patients, because lower lipid levels are typically associated with more severe systemic inflammation, which is associated with enhanced CV risk.[3] Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) appear to reduce vascular inflammation and have been tested for efficacy in the treatment of RA, but they present challenges in the RA patient because of drug interactions.[6] It is considered that statins may have a beneficial effect on endothelial function, arterial stiffness, and in improving high density lipoprotein-cholesterol anti-inflammatory properties in patients with RA.[3,5] Rollefstad et al.[6] performed an observational study using non-invasive imaging with carotid ultrasound within a cardio-rheumatology preventative clinic. Four hundred and twenty-six patients with inflammatory joint disease (257 RA, 108 ankylosing spondylitis, and 61 psoriatic arthritis) were stratified for subclinical CV risk using the systematic coronary risk evaluation (SCORE), which also included a bilateral carotid artery ultrasound to assess for the presence of plaque.

Table 1: Comparison of traditional and modified cardiovascular risk scores.

Prediction variables	Framingham (Revised 2008)	Reynolds CVD risk score for men 2008	QRISK® and QRISK®2	ACC/AHA pooled cohort hard CVD risk calculator	SCORE CVD death risk calculator 2003	ATP III hard CHD risk score 2002
Age	x	x	x	x	x	x
Gender	x		x	x	x	x
Total chol	x	x	x	x	x	x
HDL chol	x	x	x	x	x	x
Systolic BP	x	x	x	x	x	x
DM	x			x		
Current smoking	x	x	x	x	x	x
BP treatment	x		x	x		x
Family Hx CVD			x			
Parental history of MI before age 60 years		x				
Region of Europe					x	
Region of United Kingdom			x			
BMI kg/m^2			x			
Serum hs-CRP		x				

HDL: high density lipoprotein-cholesterol; BP: blood pressure; DM: diabetes mellitus; Family Hx: family history; CVD: cardiovascular disease; MI: myocardial infarction; BMI: body mass index; hs-CRP: high sensitivity C-reactive protein; chol: cholesterol; CHD: coronary heart disease; SCORE: Systemic Coronary Risk Evaluation; ATP: Adult Treatment Panel; ACC: American College of Cardiology; AHA: American Heart Association.

Typical CV risk factors included smoking status, diabetes mellitus, family history of premature CV disease, and patient history of peripheral vascular disease or transient ischaemic attack. In this study, 36.6% of patients had a SCORE <5%, and therefore did not require lipid lowering management, although half of the study population was identified as having plaque present on carotid ultrasound. The remainder of the study patients (n=270) went on to be treated with primary or secondary prevention with statin medication in accordance with guideline-recommended lipid targets. Even though several patients with inflammatory joint disease in the study had established coronary artery disease, many were not using lipid lowering treatment at the time of referral to the study, illustrating the need for improved CV risk factor management in patients with RA.[6] The Rollefstad et al.[6] study illustrates that one of the goals of the cardio-rheumatology collaboration is to modify the risk factors for ASCVD in RA patients with early recognition by including non-invasive imaging, such as carotid ultrasound, with the goal of initiating early therapy.[2,3,5,6] Although the heightened CV risk has been recognised in RA patients for several decades, providers are often hesitant to prescribe statin drugs for this population due to the concern of exacerbating myalgias and arthralgias. This study provides further evidence of the necessity of early statin drug initiation in this patient population.[6]

Table 2: Comparison of non-invasive cardiovascular imaging methods.[22]

Imaging methods	FMD	Brachial artery US	CIMT	aPWV	Aix
Arterial ultrasonography	x	x	x		
Arterial tonometry				x	x
Expensive		x			
Requires operator skill		x			
Early changes able to be identified?	x		x		
Measure of arterial stiffness?				x	x
Measures of vascular age?			x		x
Acts as a surrogate for atherosclerotic disease burden?			x		
Biomarker for endothelial function	x				
Microvascular function		x			

FMD: flow-mediated dilation; US: ultrasound; aPWV: aortic pulse-wave velocity; Aix: aortic augmentation index; CIMT: carotid intima media thickness.

REVIEW OF TRADITIONAL AND MODIFIED CARDIOVASCULAR RISK SCORES

A current limitation in identifying CV risk in patients with RA is that the degree of subclinical coronary atherosclerosis in patients with rheumatic disease is substantially under-recognised by current CV risk assessment scores, therefore making it difficult to pre-emptively identify RA patients who have a higher CV risk. Incidence of ASCVD events in patients with RA is underestimated by the CV scoring systems developed for use in the general population, such as the Framingham, Reynolds, American Heart Association/American College of Cardiology (AHA/ACC), and European Risk Scores, and QRISK®2 risk calculator (Table 1).[4] The Framingham Risk Score is designed for the general population anddoes not predict CV events accurately in patients with RA.[4] As reflected in the JUPITER (Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, it is notable that markers of acute phase response such as CRP are often elevated in RA patients, and are known risk markers for heart disease in the general population.[7] However, even with CRP taken into account using the Reynolds Risk Score, the risk of CV disease in patients is underestimated. Persons with RA are at a 1.5 to 2-fold increased risk of developing CV disease compared with the general population, a 2-fold risk of myocardial infarction, and a 10-year risk of CV events is 60% higher than that in the general population.[4] A recommendation by EULAR was that the traditional CV risk scores (Framingham) be multiplied by 1.5 in patients with RA (i.e. those who have disease duration of 10 years, positive rheumatoid factor [RF], or anti-citrullinated protein antibodies), to reflect their true risk of heart disease. However, implementation of the 1.5 multiplier failed to identify 88% of patients with carotid intima media thickness >0.9 mm and carotid plaques.[8] In fact, these modified traditional risk scores continue to underestimate ASCVD, especially in patients with older age, positive RF, and persistently elevated erythrocyte sedimentation rates and CRP levels.[9] Further studies have sought to identify other ways of assessing CV risk, andrecent developments through the use of non-invasive CV imaging studies, with a focus on endothelial dysfunction and arterial stiffness, have been fruitful (Table 2).[4]

ATHEROSCLEROSIS AND ITS SURROGATE MARKERS FOR CARDIOVASCULAR DISEASE

In autoimmune diseases, accelerated ASCVD occurs from an interplay of pro-inflammatory cytokines, immune and endothelial cell dysfunction, and general upregulation of adhesion molecules that remains incompletely understood.[2] In RA, chronic inflammation is known to be a key factor in escalating early atherosclerosis. Prasad et al.[2] discussed the activation of the nuclear factor kappa B pathway by interleukin-6, tumour necrosis factor alpha (TNF-α), and pro-inflammatory cytokines, causing enhanced leukocyte permeation and activation that leads to accelerated atherosclerosis. Interestingly, patients with RA have lower lipid levels in periods of severe systemic inflammation, and patients with autoimmune disease have been found to have higher levels of oxidised low density lipoprotein.[2,3] As reviewed by Crowson et al.,[3] these factors can lead to a decrease in apolipoprotein A1 and diminished high-density lipoprotein atheroprotective effects, which may result in enhanced ASCVD. Finally, the significance of RF and anti-citrullinated protein antibody-positivity in patients with rheumatic disease, and the relationship that these auto-antibodies play in affecting ASCVD is unclear.

ENDOTHELIAL DYSFUNCTION AS A PRECURSOR TO CORONARY ARTERY DISEASE

Coronary endothelial dysfunction exists in most patients with coronary artery disease, and is associated with adverse CV events.[10] Endothelial activation and dysfunction are precursors to atherosclerosis.[10,11] While traditional CV risk factors continue to be evaluated in clinical practice to predict the likelihood of atherosclerotic disease, non-invasive imaging methods that assess endothelial function in patients with early atherosclerosis to predict CV risk are in development.[10] Normal endothelium, which lines the vascular circulatory system, is a 'complex organ' with the purpose of vascular homeostasis, and it maintains an atheroprotective role through vasodilation and inhibition of platelet aggregation.[11] Reduction in levels of nitric oxide, an endothelium-derived vasodilator, results in endothelial dysfunction.[10] Nitric oxide mediates arterial vasodilation in response to shear stress caused by arterial flow. Cardiac catheterisation is an invasive method used for evaluating coronary endothelial function by using infusions into the peripheral vessels (like acetylcholine into the brachial artery); it is considered to be the gold standard invasive assessment of endothelial function.[10,11] The responses indicated by venous occlusion plethysmography, which measures volume change in the forearm, assume that endothelial dysfunction is both generalised and systemic, and can be used to establish if there is generalised endothelial dysfunction.[10,11] Endothelial dysfunction is proven to be reversible with aggressive lifestyle interventions such as weight loss, physical activity, smoking cessation, pharmacologic medications like anti-hypertensives, and statin use. Identification of endothelial dysfunction may thus help identify early coronary artery disease in patients with inflammatory diseases such as RA, and provide opportunities to initiate lifestyle modification.[9,10]

STUDIES OF NON-INVASIVE ARTERIAL HEALTH ASSESSMENTS

Non-invasive CV imaging methods to assess the diffuse and systemic nature of endothelial function are promising, and are based on characterising the atherogenic and atheroprotective function of the endothelium.[10] These methods include reactive hyperaemia peripheral arterial tonometry (RH-PAT) and flow-mediated vasodilation (FMD) (Table 2).[10-12] RH-PAT measures peripheral endothelial cell function using finger probes to measure pulse-wave amplitude at rest and during reactive hyperaemia.[12] This method employs the use of digital pulsatile volume changes, correlating with endothelial cell dysfunction, and is unique in that it reflects microvessel vasodilation.[13] Digital pulse volume is affected by levels of nitric oxide and therefore also depends on endothelial function.[10,12,13] Another non-invasive assessment, forearm FMD, is a biomarker of endothelial dysfunction that measures the diameter of the brachial artery at rest and during reactive hyperaemia, which is achieved by the release of a blood pressure cuff around the patient's arm after being inflated to above-systolic pressure for a few minutes and employing high resolution ultrasound imaging to assess the brachial artery endothelial function.[10,11] This artery is used due to ease of access, and the percentage of FMD is computed using the following formula:

(maximum diameter-baseline diameter)/baseline diameter x 100.[14]

Use of FMD to assess endothelial dysfunction was evaluated by Fichtlscherer et al.[15] when they studied patients with angiographically confirmed coronary artery disease, and assessed endothelial function 8 weeks after an episode of acute coronary syndrome, showing improvement in endothelial function. Likewise, Hamburg et al.[16] showed that abnormal FMD in a large community-based sample was also associated with elevated age, blood pressure, and higher body mass index, thus showing correlation between endothelial dysfunction and traditional CV risk factors. Bonetti et al.[12] investigated the relationship between RH-PAT in patients without obstructive coronary artery disease by performing RH-PAT and coronary angiography on the same day in 94 patients, and found that the RH-PAT index was higher in patients with normal coronary endothelial function, and was significantly lower in patients with endothelial dysfunction. This study revealed that RH-PAT could be an efficient non-invasive test to identify individuals with coronary endothelial dysfunction.[12]

FLOW-MEDIATED DILATION IN RHEUMATOID ARTHRITIS

With respect to RA, FMD has been used as a non-invasive assessment to show evidence of impaired conduit artery endothelial function. Typically, the finding of a higher FMD is associated with higher levels of inflammation; therefore, the percentage of FMD is higher in RA patients with high levels of disease activity. With respect to levels of disease activity, Watanabe et al.[14] evaluated 25 patients with RA who met the ACR 1987 revised criteria, and showed that the percentage of brachial FMD correlated with patients that had higher disease activity, as measured by the 28-joint disease activity score, DAS28. This study confirmed that a higher percentage of FMD correlated with higher inflammation, and therefore higher disease activity scores.[12]

The effects of RA treatment, such as traditional disease modifying anti-rheumatic drug (DMARD) therapy (methotrexate) and TNF inhibitors, have been assessed for their effect on measures of FMD.[17] Hansel et al.[17] hypothesised that switching from DMARD therapy to anti-TNF-α inhibitor therapy in patients with low disease activity would modify endothelial function. They tested vascular function at the endothelial level after infusing acetylcholine into the brachial artery at graded doses and measured forearm blood flow by a calibrated strain gauge plethysmograph.[17] This study demonstrated an impairment of endothelium-dependent vasodilation in young patients with a prolonged history of RA and low disease activity. This is interesting, because the results were obtained during a period of low inflammatory activity of the disease, and presence of endothelial dysfunction indicates endothelial damage from sustained cytokine stress. The study by Watanabe et al.[14] also echoed these findings, concluding that using anti-TNF therapies, such as infliximab, etanercept, and adalimumab correlated with the percentage of FMD in randomly selected RA patients, in addition to disease activity as mentioned previously. The percentage of FMD increased significantly in the group treated with anti-TNF therapy compared with the group treated with DMARD (methotrexate, bucillamine, and sulfasalazine) therapy, demonstrating that TNF inhibition improves endothelial function in patients with RA.[14] Vaudo et al.[18] showed that RA patients with low disease activity but without clinically obvious atherosclerotic disease or traditional CV risk factors have a lower mean brachial FMD compared with control subjects, as measured by non-invasive ultrasound. This study also identified that there was no difference in measures of brachial artery FMD in patients that had a positive RF or erosive disease.

PULSE-WAVE TRANSMISSION

Another marker of subclinical atherosclerosis is increased arterial stiffness, where the arterial wall becomes thickened and loses its elasticity due to chronic inflammation. Pulse pressure, which is one measure of arterial stiffness, can assess risk for adverse CV events. Widening of the pulse pressure, occurring when the systolic blood pressure increases and/or diastolic blood pressure decreases, is associated with heightened CV mortality. Large arteries, such as the aorta, have a constant transmission of the arterial pressure through the arterial wall, which is influenced by the elastic properties of that wall; the velocity of this pulse-wave transmission (PWV) is a measure of arterial stiffness (Table 2). The stiffer the artery, whether from age-related changes, or atherosclerotic disease, causes an increase of PWV. Aortic PWV, which measures the rate

at which aortic pressure waves travel, is a non-invasive method to assess arterial stiffness, an independent predictor of CV risk.[13] It is performed by use of a tonometry probe to compress the patient's radial artery, recording multiple waveforms in sequence, and using computer software that analyses the average central waveform, providing a measure of aortic augmentation index (Aix).[13] Klocke et al.[13] evaluated the Aix as a measure of arterial stiffness in 14 RA patients with no cardiac disease and found that the mean Aix was higher in the RA group than the control group, but interestingly did not correlate with DAS28 scores. This suggests that Aix may be a sensitive marker for early CV disease in patients with RA and provides a non-invasive assessment tool to assess CV risk. Malik et al.[19] and Kullo et al.[20] investigated the association of forearm microvascular and brachial artery function assessed by brachial artery ultrasound, with measures of PWV to assess central arterial stiffness in subjects with subclinical coronary artery disease. Their findings of higher resting shear stress with greater pulse pressure and aortic PWV suggest that elevated shear stress in the brachial artery may be a marker of greater arterial stiffness. Ambrosino et al.[21] conducted a systemic review and meta-analysis which showed that more severe inflammation in patients with RA caused significantly higher aortic PWV, even in the early stages of RA.

CONCLUSION

People with RA have higher case fatality after an acute myocardial infarction than the general population, with higher morbidity from subclinical CV disease. Well-known CV risk assessment tools, such as the Framingham or Reynolds Risk Scores, do not accurately predict CV risk in patients with RA. Given the increased risk of premature atherosclerosis, aggressive control of traditional risk factors is particularly important in patients with inflammatory joint disease and early identification of subclinical atherosclerotic disease using novel non-invasive CV risk assessment tools such as FMD, RH-PAT, and aortic PWV is promising. The widespread screening of patients with RA for endothelial dysfunction is not currently recommended due to limited supporting data on the efficacy of these tools, small size of research investigations, lack of standardisation of tools, and potential cost. Nonetheless, these novel imaging tools are promising as a means of identifying patients with RA and other rheumatic diseases who are at increased risk of ASCVD. Future research will determine if non-invasive cardiac imaging to identify subclinical atherosclerotic disease is a cost-effective approach to diminish mortality risk in patients with rheumatic diseases.

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