

Subclinical Cardiovascular Involvement in Autoimmune Diseases: Role of Coronary Flow Reserve

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Abstract

Many published papers have analysing the close relationship between atherosclerosis and systemic autoimmune diseases because atherogenesis and its complications play a major role in the cardiovascular morbidity and mortality of such patients. It is also important to underline the pivotal role of specialists in the early diagnosis of pre-clinical abnormalities as this allows the timely implementation of appropriate therapeutic and preventive measures, which should form the operational backbone of the work of the teams involved in studying and treating systemic autoimmune diseases. In particular, primary prevention is essential in order to avoid cardiovascular events such as acute coronary syndrome, myocardial infarction and sudden death.

The aim of this review was to highlight the central role of an echocardiographic stress examination and the non-invasive assessment of coronary flow reserve as a means of detecting endothelial dysfunction and sub-clinical atherosclerosis with the final objective of improving the prognosis and outcomes of even asymptomatic patients with or without overt cardiovascular diseases.

Keywords: Coronary flow reserve; Systemic autoimmune diseases; Sub-clinical atherosclerosis

Introduction

Patients with autoimmune disorders are characterised by immune responses directed against their own tissues that cause prolonged inflammation and subsequent tissue destruction [1]. These immune/inflammatory responses activate and injure the vascular endothelium, and it is well known that inflammation and endothelial dysfunction are key mechanisms in the pathogenesis of atherosclerosis (ATS) as the endothelium is the main regulator of vascular wall homeostasis [2].

Physiologically, endothelial cells maintain relaxed vascular tone and low levels of oxidative stress by releasing mediators such as nitric oxide (NO), prostacyclin and endothelin-1 to control local angiotensin II activity [3]. Considerable published evidence suggests that endothelial dysfunction occurs early in the process of atherogenesis and contributes to the formation, progression and complications of atherosclerotic plaque [4].

Patients with systemic autoimmune diseases (SADs) are affected by a number of extra-articular causes of mainly cardiovascular (CV) morbidity and mortality [5,6] in which endothelial dysfunction plays an important role and, as the onset of CV abnormalities is frequently asymptomatic, an early diagnosis is a fundamental goal [7]. The many parameters that can be used to evaluate endothelial dysfunction and early ATS include arterial distensibility and stiffness [8], which are mainly assessed by measuring intima-media thickness (IMT) and pulse wave velocity (PWV) [9]. It has also recently been suggested that asymmetric dimethylarginine (ADMA) may be involved in endothelial dysfunction because it is the main endogenous inhibitor of all three NO synthases [10].

We have used various methods of assessing endothelial dysfunction in patients with SADs such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and systemic sclerosis (SSc), including transthoracic echocardiography and the non-invasive evaluation of coronary flow reserve (CFR), which is capable of estimating cardiac macro- and microcirculation [11]. The CFR of the left anterior descending coronary

artery (LAD) is a strong and independent indicator of mortality, and has additional prognostic value over wall motion analysis in patients with known or suspected coronary artery disease (CAD) [12].

Coronary microvascular dysfunction is a term that has been introduced to describe abnormalities in the regulation of myocardial blood flow (MBF) that cannot be attributed to epicardial CAD. Recio-Mayoral et al. [13] carried out a case-control study in which positron emission tomography (PET) was used to study MBF and CFR at rest and during adenosine-induced hyperemia in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). All of the patients also underwent coronary angiography, which showed the absence of any significant epicardial stenosis, but they had a lower CFR and less MBF during hyperemia.

CFR is therefore a very interesting and important means of diagnosing CAD and detecting microvascular dysfunction, but it can also be considered a novel link between chronic inflammation and sub-clinical cardiovascular (CV) damage to the coronary circulation, and may play a crucial role in reducing the higher CV morbidity and mortality rates associated with autoimmune disorders [14]. In the above cited article of Kerekes et al., CFR is presented as a validated methods to assess CV involvement and especially subclinical atherosclerosis and moreover, we should consider that manuscript as a sort of "bible" of all CV diagnostics in SADs.

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However, there are still no specific reviews of this aspect of CFR, the aim of this study was to bridge this critical gap. Therefore, our choice will be especially addressed on a single marker of ATS expression such as CFR rather than on indicators as troponin, BNP, etc. which are not usually used in SADs patients analysis concerning cardiovascular problems (especially coronary artery disease field).

Finally, you will may see a review regarding only three (3) subgroups of SADs pts because they represent more frequent clinical conditions in that field.

CFR Evaluation

Of the various methods that can be used to measure CFR, transthoracic stress echocardiography with dipyridamole has the advantages of being simple, non-invasive and inexpensive [15-17], and dual imaging of LAD wall motion and CFR is the current state-of-the-art technique as it provides better diagnostic and prognostic information than standard stress testing.

CFR can be measured during high-dose dipyridamole administration (up to 0.84 mg/kg over six minutes) in combination with 12-lead electrocardiographic monitoring. Coronary flow in the mid-distal portion of LAD is assessed in the low parasternal long-axis view under the guidance of colour Doppler flow mapping, and is defined as the ratio between hyperemic and basal peak diastolic coronary flow velocity. There is no doubt that the three-coronary approach would be more fruitful, but it is still too technically challenging for large-scale assessments.

The presence of ischemia can be determined on the basis of CFR and stress-induced new and/or worsening pre-existing wall motion abnormalities. A CFR value of ≤ 2 is generally considered pathological because it indicates a coronary stenosis of $>70\%$ and allows the risk stratification of patients with intermediate coronary stenosis or normal or nearly normal coronary arteries. A higher CFR cut-off value of ≤ 2.5 is used in the case of patients with SADs because values of <2 are highly pathological there is a "grey zone" at values of 2-2.5 and outcomes may vary widely [18]. It also has to be remembered that, although CFR cannot distinguish micro- and macrovascular coronary disease, it is important because of its additional diagnostic value over conventional wall motion analysis.

At the end of the international stress protocol described, intravenous aminophylline 125-250 mg is administered to counteract the effects of dipyridamole [19].

Our transthoracic echocardiographic images were recorded using a commercially available ultrasound unit (IE33, Philips Medical Systems, città, Stato, USA) equipped with 1-2 MHz (S5) transducer capability and a 3-8 MHz broad-band high-frequency transthoracic transducer (S8) with second harmonic. LV diameters and wall thicknesses were measured from the 2D targeted M-mode echocardiographic trace in accordance with the recommendations of the American Society of Echocardiography [20]. The LV was divided into 16 segments, and segmental wall motion was graded as 1=normal, 2=hypokinetic, 3=akinetic, or 4=dyskinetic, after which a wall motion score index was obtained by dividing the sum of the segment scores by the number of visualised segments [21]. The images and loop recordings of all of the studies were digitally stored in order to simplify their further off-line analysis and measurement.

Finally, we'd like to underline that in our studies such as other referral groups we usually have been using dipyridamole rater

than adenosine because the choice of dipyridamole is always more cheaper (fundamental in crisis times!) and better suitable for patients' compliance.

CFR in Systemic Autoimmune Diseases

CFR in rheumatoid arthritis (RA)

RA is a disabling systemic autoimmune disease of unknown etiology that is characterised by a chronic inflammatory process affecting the synovial membrane of the diarthrodial joints. Morbidity and mortality rates are higher in RA patients than in the general population not only because of infectious, gastrointestinal, renal or pulmonary complications, but also because of cardiovascular diseases. All of the cardiac structures can be affected by RA, probably because the chronic state of inflammation causes cardiac complications such as pericarditis, myocardial fibrosis, arrhythmias, alterations in conduction, valvular diseases, pulmonary hypertension, as well as coronary disease leading to a higher risk of acute myocardial infarction and sudden death. The cardiac involvement is often asymptomatic in the early stages of the disease, and so it is very important to detect it during the sub-clinical phase.

Ciftci et al. [22] found that RA patients have increased IMT and a reduced CFR. Moreover, Chung et al. showed that patients with a longstanding RA have a higher prevalence of more severe coronary calcifications than those with early rheumatoid arthritis (ERA, a disease duration of ≤ 12 months in the absence of anti-rheumatic therapy), and Del Rincon et al. [23] demonstrated that patients with long-lasting established RA are more likely to have ATS than healthy controls. The importance of recognising and treating patients in the early stages of RA is due to the risk that active disease may lead to progressive joint and CV damage.

We studied 25 ERA patients before and after treatment with disease-modifying anti-rheumatic drugs (DMARDs) [7] and 25 healthy volunteers with no history or current signs of CAD or other traditional risk factors. CFR was evaluated by means of dipyridamole transthoracic stress echocardiography and the IMT of the common carotid arteries by means of carotid ultrasonography; ADMA levels were also measured. CFR was significantly reduced in the ERA patients (six of whom had a CFR of <2 , which is consistent with potentially dangerous coronary impairment), who also showed greater IMT and had higher plasma ADMA levels. When the patients' CFR was measured again after 18 months of DMARD treatment, it had significantly improved probably because of the drugs' anti-inflammatory effects.

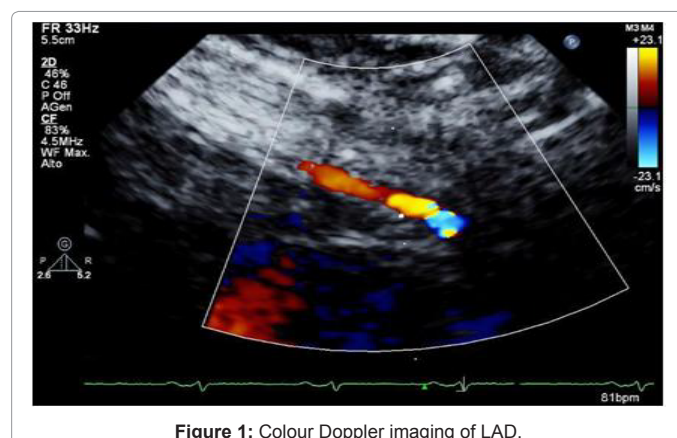


Figure 1: Colour Doppler imaging of LAD.

RA patients are at higher risk of developing CV diseases than the general population and, in our experience, the non-invasive echo-Doppler evaluation of CFR can be considered an early marker of functional damage [11,14]. Consequently, careful screening for impaired coronary microcirculation is essential from the earliest stages of RA even in the absence of any signs or symptoms of CV involvement [24].

CFR in psoriatic arthritis (PsA)

Psoriasis is a chronic inflammatory disease associated with several CV conventional risk factors. Both ATS and psoriasis are characterized by T helper 1 (Th1) and Th17 activation, and reduced T regulatory cell (Treg) function, and there are striking similarities in the immuno-inflammatory mechanisms of the two diseases.

A number of published studies have shown that PsA patients without conventional CV risk factors or clinically evident CV disease have endothelial dysfunction and a higher prevalence of increased carotid artery IMT than controls [25].

Moreover, we found sub-clinical cardiac involvement in a group of 22 outpatients with satisfying the CIASsification of Psoriatic ARthritis study group criteria for PsA without a history of CV disease, who were compared with 35 controls [26]. Although the patients did not have any signs of, or risk factors for CV disease, they had higher ADMA levels and a significantly reduced CFR. The significant correlation between the reduced CFR and increased ADMA levels may be indicative of endothelial dysfunction and impaired coronary microcirculation, and confirm that active PsA is a risk factor for CV disease as recently demonstrated by Wakkee et al. [27].

In 2010, Ahlehoff et al. [28] conducted a cohort study of the entire Danish population, including 34,371 subjects with mild psoriasis, 2,621 with severe disease and 607 with PsA. CV events were more frequent in the psoriasis patients, and the rate increased with disease severity

and decreased with age at the time of onset. The risk was similar in the subjects with severe skin affection alone and those with PsA.

Given the high CV burden mainly related to endothelial dysfunction and ATS, an early diagnosis is clearly fundamental in patients with PsA [29].

CFR in systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a multi-system disease characterised by vasculopathy, organ fibrosis and endothelial cell injury, and may increase the risk of coronary ATS. The vascular involvement is probably the result of an immuno-inflammatory process that injures the vascular endothelium, and it is known that inflammation and endothelial dysfunction are key mechanisms in the pathogenesis of ATS in SSc patients [30,31].

SSc-associated vasculopathy typically affects the small vessels, but macrovascular involvement has also been demonstrated and there is still controversy concerning the predominant mechanism [32].

In 2003, Montisci et al. [33] enrolled 27 SSc pts without any evidence of ischemic heart disease and 23 control subjects. LAD CFR was evaluated using the new non-invasive method of contrast(Levovist®)-enhanced transthoracic Doppler echocardiography during adenosine infusion, and it was found that CFR was severely reduced in 14 of the SSc patients.

One year later, Sulli et al. [34] confirmed this finding (Figures 1 and 2).

Our group recently enrolled 20 patients fulfilling the American College of Rheumatology criteria for SSc without any signs or history of coronary artery disease, and 20 healthy volunteers [35], all of whom underwent dipyridamole echocardiography and the calculation of CFR. The SSc patients had a significantly lower CFR than controls,

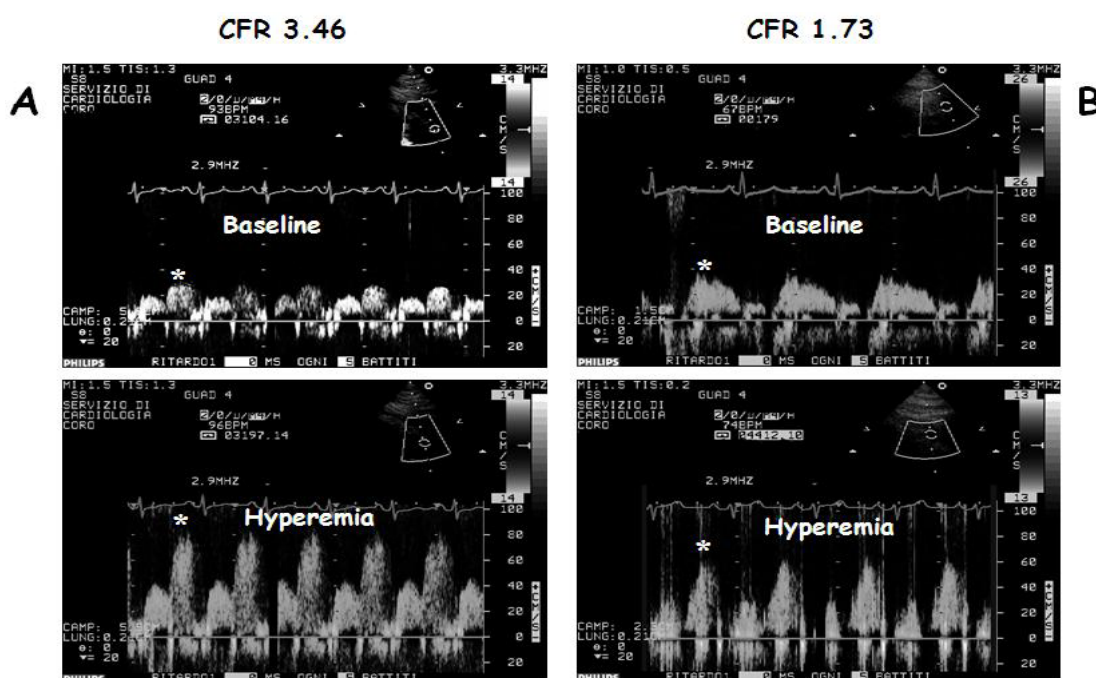


Figure 2: Pulse-wave (PW) Doppler sampling of LAD with evaluation of CFR.
 A) A healthy subject at baseline (top) and after the intravenous administration of dipyridamole to induce hyperemia (bottom)
 B) An outpatient with SAD at baseline (top) and after the intravenous administration of dipyridamole to induce hyperemia (bottom)

which seems to support the hypothesis of sub-clinical CV involvement in subjects with diffuse SSc.

Finally, Vacca et al. [36] have very recently confirmed our data in a group of 41 patients with SSc who were asymptomatic for CAD using transthoracic Doppler echocardiography with adenosine infusion to study the microcirculation and dobutamine stress echocardiography to search for left ventricular wall motion abnormalities. CFR was reduced in 19 SSc patients, and 16 showed wall motion abnormalities.

All of the above findings confirm the importance of using non-invasive methods to detect abnormal coronary microcirculation at a sub-clinical stage.

Conclusions

The studies described in this review suggest that CFR may be a useful marker of sub-clinical cardiac damage in SAD patients and allows the early detection of any pre-clinical involvement of the coronary microcirculation.

As SAD patients are at higher risk of developing CV diseases than the general population, it is essential to detect endothelial dysfunction and impaired coronary microcirculation especially in asymptomatic subjects. Coronary angiography remains the gold standard for diagnosing coronary stenosis, but new, non-invasive and more reliable diagnostic techniques have been introduced into clinical practice to detect sub-clinical abnormalities in the microcirculation. Echocardiography and its many variables (including CFR) seems to be the most appropriate screening technique as it non-invasively, reliably, sensitively and specifically identifies pre-clinical cardiac involvement in patients with SADs. Common carotid IMT measured by means of carotid ultrasonography can provide additional information that is useful for stratifying CV risk in SAD patients but increased IMT reflects a later stage of the atherosclerotic process when anatomical changes have already occurred, whereas impaired CFR is an earlier marker identifying functional damage. It is therefore important to stress that a functional injury is potentially reversible and this allows a better prevention strategy than a later diagnosis made after the occurrence of anatomical abnormalities.

Its relatively low cost means that measuring CFR can be considered a modern gold-standard for detecting and controlling ATS in SADs patients even in this time of economic constraint.

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