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REVIEW

Evaluation of Endothelial Function by Flow-Mediated Dilation: a Comprehensive Review in Rheumatic Disease

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Abstract Flow-mediated dilation (FMD) represents a non-invasive marker of endothelial function to evaluate vascular homeostasis, which reflects the effects of several mechanisms, including vessel tone regulation, cell proliferation, and inflammatory responses. Beyond classical atherosclerotic risk factors such as arterial hypertension, diabetes mellitus, smoking, obesity, and dyslipidemia, chronic inflammation contributes to the endothelial dysfunction causing plaque formation and there is growing evidence of a significantly higher cardiovascular morbidity associated with autoimmune diseases. The endothelium reacts to several endogenous and exogenous stimuli, through surface receptors and intracellular signalling, and releases numerous vasoactive substances, including endothelins, prostacyclins, and nitric oxide (NO). Chronic inflammatory rheumatic diseases are commonly associated with decreased endothelial NO production, vascular damage, and premature atherosclerosis. Despite partially eclipsed by pulse wave velocity measure in the modern scientific literature, we provide a comprehensive overview and critically discuss the available data supporting FMD as a surrogate marker of endothelial function and, therefore, its potential role in predicting early atherosclerosis in patients with rheumatic diseases.

Keywords Cardiovascular risk · Chronic inflammation · Rheumatoid arthritis · Psoriatic arthritis · Connective tissue disease · Autoantibody

Abbreviations

APS	Anti-phospholipid syndrome
aPL	Anti-phospholipid antibodies
CVD	Cardiovascular disease
EDHF	Endothelium-derived hyperpolarizing factor
eNOS	Endothelial NO synthase
FMD	Flow-mediated dilation
MCTD	Mixed connective tissue disease
MTX	Methotrexate
NO	Nitric oxide
oxLDL	Oxidized low-density lipoproteins
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SpA	Spondyloarthropathies
SSc	Systemic sclerosis

Introduction

Systemic autoimmune diseases are characterized by the occurrence of premature atherosclerosis and cardiovascular disease, and are associated with vascular damage (Roman et al. 2003; Skeoch and Bruce 2015). The link between atherosclerosis and inflammation is well established and chronic inflammatory diseases share, as a common

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pathologic factor, the response to injury process, ultimately leading to endothelial dysfunction (Murdaca et al. 2012). Indeed, accelerated atherosclerosis has been associated with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or spondyloarthropathies (SpA), while obliterative vasculopathy may rather be characteristic for systemic sclerosis (SSc) or mixed connective tissue disease (MCTD). Anti-phospholipid antibodies (aPL) have been implicated in vascular injury underlying SLE, primary antiphospholipid syndrome, RA, and MCTD. A great variability is seen also in the biohumoral profile with respect to risk factors. Nitric oxide (NO), released from the endothelium in response to increased shear-stress and certain pharmacologic stimuli, may work as an endogenous antiatherogenic molecule by maintaining low arterial tone at rest, inhibiting leukocyte-endothelial interactions, attenuating platelet aggregation, and inhibiting smooth-muscle cell proliferation (Celermajer 1997). Aging, diabetes, dyslipidemia, and hypertension are characterized by reduced NO availability and by the production by the endothelium, as a compensatory mechanism, of endothelium-derived hyperpolarizing factor (EDHF), which has a vasodilating effect mediated by hyperpolarization of vascular smooth-muscle cell (Taddei et al. 1999). The reduction of NO availability, furthermore, interferes with the mobilization of circulating endothelial progenitor cells (EPCs), an alternative mechanism for maintenance and repair of the endothelium (Op den Buijs et al. 2004). EPCs are peripheral blood mononuclear cells derived from different tissues, expressing cell surface markers that are similar to mature endothelial cells. The discovery of EPCs has led to new insights in vascular repair and atherosclerosis, and also produced a new hypothesis for immunological aging. EPCs from the bone marrow contribute to vascular repair by migrating to distant vessels to differentiate into mature endothelial cells and replace old and injured endothelial cells. The ability of EPCs to repair vascular damage depends on their number and functionality. Thus, such mechanisms may be impaired in patients with classical cardiovascular risk factors (Altabas et al. 2016) and significant abnormalities in the number and function of these cells were reported in patients with RA and SLE. Inflammatory cytokines including interferon-α and tumor necrosis factor (TNF)-α are capable to impair EPCs function ex vivo and may, therefore, contribute to the elevated cardiovascular disease (CVD) risk in these patients (Reynolds et al. 2014).

Endothelial dysfunction is a widely used term to describe any form of abnormal functional and reversible alteration based on endothelial cells, leading to an abnormal response to physiological stimuli and to a shift of the actions of the endothelium toward reduced vasodilation, proinflammatory state, and proliferative and prothrombotic properties (Daiber et al. 2016).

Endothelial dysfunction, especially the reduction in the bioavailability of endothelium-derived NO, is a key early event in atherogenesis, appearing long before the formation of structural atherosclerotic changes (Celermajer et al. 1992). The increased expression of adhesion molecules, proinflammatory cytokines, prothrombotic factors, oxidative stress upregulation, and abnormal vascular tone modulation are the main factors involved in this "atherogenic cascade" (Murdaca et al. 2012).

The most widely used and validated technique for measuring endothelial function is based on flow-mediated dilation (FMD) (Celermajer et al. 1992; Peretz et al. 2007). It is a non-invasive method introduced in 1992 (Celermajer et al. 1992) that consists in studying flow-mediated changes in the brachial artery diameter. Flow-mediated changes in conduit artery diameter are caused by shear-stress induced generation of endothelial derived vasoactive mediators, in particular NO. Since the arterial dilator response to shear-stress can be almost completely blocked by pre-treatment with NO synthase inhibitors (Joannides et al. 1995), it has been suggested that the phenomenon is predominantly due to endothelial release of this molecule (Raitakari and Celermajer 2000). Indeed, Endothelium-independent dilator response can be tested by low-dose sublingual nitroglycerin (Ghiadoni et al. 2001). The endothelial state of activation, assessed by this method, significantly correlates with the results of more invasive coronary functional tests representing the gold standard (Takase et al. 1998) and strongly predicts future cardiovascular events. Median FMD was the best independent predictor of long-term cardiovascular adverse events in a cohort of 618 consecutive healthy subjects with no apparent heart disease (Shechter et al. 2014).

FMD has been studied widely in clinical research as it enables serial evaluation of young subjects, including children. It also permits testing of lifestyle and pharmacological interventions on endothelial biology at an early preclinical stage, when the disease process is most likely to be reversible (Deanfield et al. 2007). However, some practical challenges need to be overcome before this technique becomes suitable for use in routine clinical practice (Corretti et al. 2002; Deanfield et al. 2007). These challenges include the need for trained operators, the cost of the equipment and also the care required to minimize the effect of environmental or physiological influences. It is important to note that technical variations, such as the position of the occluding cuff and duration of the inflation, may produce results that are less representative of local NO activity, since FMD is determined, in part, also by the magnitude of post-ischemic forearm vasodilatation, which is a measure of microcirculatory function. Finally, due to the variability and degree of response, large study populations are required for clinical studies (Ghiadoni et al. 2008).

Atherosclerosis and Immune Mechanisms

An alteration of the endothelial function is an early marker of atherosclerosis, also contributing to the development of atherosclerotic lesions and later clinical complications (Ghiadoni et al. 2008). Early in the development of atherosclerosis, low-density-lipoprotein cholesterol becomes oxidized, which results in endothelial cell dysfunction and the expression of vascular cell adhesion molecules and chemokines. In response to these adhesion molecules, monocytes are recruited; these differentiate into macrophages and endocytose (through interactions with scavenger receptors) into the vessel wall. These macrophages then take up oxidized low-density-lipoprotein cholesterol and become foam cells, which subsequently produce growth factors and cytokines that lead to the proliferation of vascular smooth-muscle cells and the development of plaques. T cells, predominantly type 1 T-helper lymphocytes, are also recruited to the subendothelial space where they produce cytokines that can promote a systemic inflammatory response. The lipoproteins are often associated with proteoglycan molecules in the extracellular space of the intima (Sherer and Shoenfeld 2006).

The endothelium is a large paracrine organ that regulates the vascular tone, cell growth, platelet/leukocyte interactions, and thrombogenicity (Corretti et al. 2002). It synthesizes at least three different vasodilator factors: i.e., NO, prostacyclin, and EDHF. However, under several pathological conditions, vasoconstricting factors, including endothelin, superoxide, and vasoconstrictor prostaglandins can be produced by endothelium, as well. Animal and human studies have demonstrated that several mechanisms are involved in endothelial dysfunction in atherosclerosis (Dhawan et al. 2005; Hathaway et al. 2002; Li et al. 2015; Maas et al. 2008; Orlandi et al. 2006; Tabas et al. 2015; Vanhoutte et al. 2009), including a reduced or impaired endothelial signal transduction, the reduced availability of L-arginine, the reduced endothelial NO synthase (eNOS) expression, reduced co-factors for eNOS, NO inactivation increased by superoxide anion derived from macrophages, concomitant release of endothelium-derived contracting factors, intimal thickening, and smooth-muscle vascular response. eNOS is one of three enzymatic isoforms that synthesize NO, a small gaseous and lipophilic molecule that is primarily responsible for the generation of NO in the vascular endothelium. NO produced by eNOS in the vascular endothelium plays a crucial role in regulating vascular tone, cellular proliferation, leukocyte adhesion, and platelet aggregation (Forstermann and Munzel 2006). Therefore, a functional eNOS is essential for a healthy cardiovascular system and eNOS pathophysiology is the key topic to understand how endothelial dysfunction results in FMD reduction.

Atherosclerosis may result from systemic and/or local vascular inflammation also in non-rheumatic diseases, but a more pronounced chronic inflammatory infiltration in media and inner adventitia was found in specimens from patients with inflammatory rheumatic diseases (Hollan et al. 2007). Moreover, higher level of pentraxin 3, a key component of innate immunity and novel biomarker of inflammation, was found in patients sera with coronary artery disease associated to inflammatory arthritides (Hollan et al. 2010).

Inflammatory mechanisms leading to atherosclerosis are intricate and quite specific of disease spectrum. Cytokines, such as TNF-α or interleukin 6, and immune complexes are mainly involved in arthritides, such as RA, SpA, as well as in SLE. On the other hand, specific autoantibodies including anti-oxidized-low-density lipoproteins (oxLDL), anticardiolipin, and anti-β2-glycoprotein (anti-β2-GPI) are rather involved in SLE- and anti-phospholipid syndrome (APS)-related vascular disease (Soltesz et al. 2011). The most important cytokines involved in atherosclerosis are summarized in Table 1. β2-GPI inhibits oxLDL engulfment via scavenger receptors, but if bound to oxidized forms of cholesteryl linoleate on LDL can be recognized by anti-β2-GPI antibodies and the complexes uptaken by macrophages via the Fc-γ receptors (Matsuura et al. 2002). Not only oxLDL but also high-density lipoproteins (HDL) may be detrimental by losing their athero-protective properties in case of qualitative modifications and turning to proinflammatory HDL. These macromolecular changes can actually cause increased oxidation of LDL as seen in 45% of women with SLE compared to 20% of RA and 4% of controls (McMahon et al. 2006; Watanabe et al. 2012). Moreover, in a study by Ronda et al. (2012), impairment of serum capacity to promote cholesterol efflux from macrophages shows different patterns in RA and SLE, not only demonstrating a dysfunction and loss of athero-protective activity of HDL, but also pointing to the existence of specific underlying mechanisms in each disease, possibly beyond inflammation and correlating with disease activity (Rader 2006).

FMD Measurement Tools

The measure of the target artery diameter is obtained by high-resolution vascular ultrasonography in response to an increase in blood flow, causing shear-stress, during reactive hyperemia (Joannides et al. 1995). Numerous factors affect flow-mediated vascular reactivity, including temperature, food, drugs, and sympathetic stimuli, among others. Therefore, subjects should fast for at least 8–12 h before the study, and they should be studied in a quiet, temperature-controlled room. All vasoactive medications should be withheld for at least four half-lives, if possible. In addition,

Table 1 Cytokines involved in atherosclerosis

Cytokine	Expressed by	Induced by	Receptor(s)	Target cells	Biological function	Evidence for role in atherosclerosis	References
TNF-α	Endothelial cells T cells B cells Monocytes Foam cells Mesenchymal cells	LPS IFN-γ Inhibited by HDL	TNFRI (inflammatory) TNFRII (apoptotic)	Neutrophils NK cells T cells Fibroblasts Macrophages	Activates endothelium Activates macrophages Increases adhesion molecules Increases SAA Increases MCP-1	Increased TNF-α levels increase ATH risk	Barter et al. (2004), Ponthieux et al. (2004)
IL-1	Monocytes Macrophages Foam cells	LPS TNF-α Inhibited by HDL	IL-1R1 IL-1R2 (not signalling) IL-1ra (natural antagonist)	T cells Fibroblasts Macrophages	Activates macrophages Increases adhesion molecules Increases SAA Increases MCP-1 Drives angiogenesis	Increased IL-1 levels increase ATH risk	Astry et al. (2013), Barter et al. (2004), Brennan et al. (1989), Ponthieux et al. (2004), Schurgers et al. (2011)
IL-6	T cells B cells Mesenchymal cells Smooth-muscle cells Macrophages Endothelial cells	IL-1	Gp130 IL-6R	T cells B cells Macrophages Chondrocytes	Autoantibody production Induces acute phase proteins	Plaque development Plaque destabilisation	Astry et al. (2013), Schuett et al. (2009)
IFN-γ	T cells NK cells Foam cells	Viral RNA T cells	IFN-γR	T cells B cells	Th1 differentiation Inhibits SMCs, ECs, collagen, LPL Increases plaque instability Increases TNF-α, IL-1 Primes macrophages for activation Increase CD40L	Increases IFN-γ in unstable angina	Fernandes et al. (2004), Hansson (2001), Schurgers et al. (2011), Szabo et al. (2003)
IL-12	Macrophages Smooth-muscle cells Endothelial cells	LPS CD40 IFN-γ OxLDL	IL-12R	Macrophages NK cells T cells	Th1 differentiation Increases IFN-γ production	Increased levels observed in ATH plaques	Fernandes et al. (2004), Uyemura et al. (1996)

IFN interferon, *IL* interleukin, *ATH* atherosclerosis, *SAA* serum amyloid A, *MCP-1* monocyte chemoattractant protein-1, *LPS* lipopolysaccharide, *SMC* smooth-muscle cells, *ECs* endothelial cells, *LPL* lipoprotein lipase

subjects should not exercise, which should not ingest substances that might affect FMD such as caffeine, high-fat foods, and vitamin C or use tobacco for at least 4–6 h before the study (Corretti et al. 2002). The investigator should be cognizant of the phase of the subject's menstrual cycle, as it too may affect FMD (Hashimoto et al. 1995).

The subject is supine with the arm in a comfortable position for adequate imaging of the brachial artery above the antecubital fossa on the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall is selected for continuous 2D grayscale imaging (Corretti et al. 2002). When a sphygmomanometer cuff placed on the forearm distal to the brachial artery is inflated to 200 mmHg and subsequently released 5 min later, FMD occurs as a result of local endothelial release of NO (Ghiadoni et al. 2007; Joannides et al. 1995). The artery diameter is measured on two phases: at baseline and during reactive hyperaemia. It is possible to finally get a third-phase imaging after administration of sublingual nitroglycerin using a normal antianginal dose of 400 μg (which causes endothelium-independent smooth-muscle-mediated vasodilation) (Raitakari and Celermajer 2000). The cuff inflation period of 5 min was initially decided to produce adequate hyperaemia and to allow

FMD, but not to compromise patient comfort. Shorter inflation periods do not seem to produce significant FMD (Corretti et al. 1995).

A B-mode ultrasound image of the brachial artery is obtained, with focus of the near wall (Celermajer et al. 1992). Ultrasound transducers with a frequency of 7.0 MHz or greater should be used. The ideal vessel size is 2.5–5.0 mm (90% of the brachial arteries among adult population). Most investigators have found this technique accurate and reproducible (Leeson et al. 1997; Sorensen et al. 1995; Uehata et al. 1997), although some groups have reported poor inter-operator comparability (Hardie et al. 1997). With regard to the problem of FMD normal range, a rigorous meta-regression by Bots et al. (2005), comprehensive of 219 papers, 412 study groups and 16,680 subjects, found a FMD mean value of $6.4 \pm 3.6\%$ for healthy subjects.

As a matter of fact, mean FMD differs widely between studies and there is a great overlap between populations (healthy, chronic heart disease, and diabetics), owing to technical different aspects of the measurements, location, and duration of the occlusion. However, as seen in the following paragraphs, clinical significance of FMD arises interestingly if intra-population and case–control differences are considered.

FMD and Atherosclerosis in Autoimmune Diseases

Risk of cardiovascular events has been found to be increased in many autoimmune rheumatological diseases and especially in RA (Jacobsson et al. 1993; Liang et al. 2006; Turesson et al. 2007), SLE (Bertoli et al. 2006b; Erkan 2006; Manzi et al. 1997) and APS (Meroni et al. 2007; Vaarala et al. 1995). Since this was demonstrated, flow-mediated dilatation has been studied also in this setting (Cugno et al. 2010; Stamatelopoulos et al. 2009) and demonstrated to be a reliable marker of endothelial function (Soltesz et al. 2009). Detection of early endothelial dysfunction in this selected population may have a beneficial role in preventing cardiovascular events, to date, the leading cause of death in the Western World (Doria et al. 2005; Shoenfeld et al. 2005).

Our literature review was conducted to verify if FMD can be a reliable method to assess preclinical atherosclerosis in systemic autoimmune diseases. Structured literature searches were done from June 2015 and subsequently updated until November 2016 in PubMed/Medline database, using the following medical subject headings (MeSH): autoimmune diseases, rheumatic diseases, RA, psoriatic arthritis (PsA), SLE, anti-phospholipid (syndrome), and SSc, combined with "flow-mediated dilation", which is not included in MeSH database. Titles and abstracts were screened to determine if they were potentially relevant. Included in the review were both cross-sectional and interventional studies either comparatively assessing FMD in rheumatic patients and healthy controls or evaluating its changes after treatment. Articles not concerning rheumatic diseases, editorials, and articles in languages other than English or involving children were excluded.

RA and PsA

RA is a chronic autoimmune disease characterized by persistent synovitis, systemic inflammation, and autoantibodies (particularly to rheumatoid factor and citrullinated peptide) (Scott et al. 2010).

RA represents the "model disease" when talking about atherosclerosis and autoimmunity like a two-faced coin. From a biological point of view, B cells and citrullinate proteins are found in the adventitia infiltrates only in RA atherosclerotic patients (Sokolove et al. 2013). Cardiovascular disease accounts for 30–50% of deaths in patients with RA (DeMaria 2002; Kitas and Erb 2003) and the magnitude of cardiovascular risk in RA is comparable to that of diabetes mellitus (Peters et al. 2009). Significant RA-related risk factors for cardiovascular death are the total inflammatory burden, presence of vasculitis, and lung disease (Maradit-Kremers et al. 2005).

The decreased endothelium-dependent macrovascular function, assessed with FMD, appears to be evident within 1 year of RA diagnosis, but does not appear to be further influenced by disease duration (Van Doornum et al. 2003; Vaudo et al. 2004). Chatterjee Adhikari et al. (2012) more recently confirmed the association between subclinical atherosclerosis and early RA. A positive association between disease activity using erythrocyte sedimentation rate, C-reactive protein and Disease Activity Score (DAS-28) and FMD in RA, was described in higher quality studies (Arosio et al. 2007; Pingiotti et al. 2007; Vaudo et al. 2004). The association was not recapitulated by other groups, whose data were not fully shown in the paper (Sodergren et al. 2010; Van Doornum et al. 2003). A positive correlation of FMD with rheumatoid factor was also reported (Chatterjee Adhikari et al. 2012) as well as with the HLA-DRB1*04 shared epitope (Gonzalez-Juanatey et al. 2003), while an inverse correlation with the CCR5Δ32 polymorphism was reported (Rodriguez–Rodriguez et al. 2011). This latter association suggests the potential role of genetic susceptibility in facilitating inflammation-related cardiovascular morbidity.

Treatments may play a role in both increasing and preventing cardiovascular morbidity. Nonsteroidal anti-inflammatory drugs and cyclooxygenase (COX)-2 selective inhibitors in particular can worsen endothelial function

by producing the well-known prostaglandin/thromboxane mismatch (Hawkey 2001) leading to a higher thrombosis risk (Mukherjee et al. 2001). However, FMD is unlikely to be affected by COX-1 and COX-2 inhibition (Wong et al. 2007).

In addition, corticosteroids increase cardiovascular risk with a dose-related profile (del Rincon et al. 2004) by their action on arterial pressure, glycaemia control, weight gain, and lipid balance. However, Veselinovic et al. (2012) demonstrate that RA patients who used low doses of corticosteroids have, statistically, significantly better FMD, than those steroid-free. This would be related to better control of inflammation in treated patients, with limited side effects of small doses of corticosteroids.

Disease-modifying antirheumatic drugs significantly improve FMD in a 1-year noncontrolled follow-up study (Guin et al. 2013). Despite the concerns about homocysteine production (Landewe et al. 2000), methotrexate (MTX) reduces overall mortality and cardiovascular risk in RA (Choi et al. 2002; Krause et al. 2000), and the same for sulphasalazine and hydroxychloroquine (van Halm et al. 2006). Folate supplementation during MTX appears to have no effect on cardiovascular mortality. No data about leflunomide are available, probably due to its second-line therapy profile.

Myocardial infarction and stroke risk are affected by biological therapies (Nadareishvili et al. 2008; Weisman et al. 2007), likely by improving endothelial function with FMD improvement as observed with rituximab (Gonzalez-Juanatey et al. 2008; Hsue et al. 2014), tocilizumab (Protogerou et al. 2011), and anti-TNF-α (Bilsborough et al. 2006; Hurlimann et al. 2002; Kerekes et al. 2011), in this last case likely with a sustained effect (Capria et al. 2010; Sidiropoulos et al. 2009) or transitory during the loading phase of therapy, suggesting an enhanced and persistent TNF generation within the arterial wall (Bosello et al. 2008; Gonzalez-Juanatey et al. 2004). No data on abatacept are available.

PsA is a multigenic autoimmune disease that involves synovial tissue, entheseal sites, and skin, and that may result in significant joint damage (Fitzgerald and Winchester 2009). An increased cardiovascular morbidity and mortality is reported in patients with PsA as well (Gladman et al. 2009; Li et al. 2012). Endothelial dysfunction and subclinical atherosclerosis seem to underlie this association also in the absence of an overt cardiovascular disease (Gonzalez-Juanatey et al. 2007). In several reports, a lower FMD was found in patients compared to controls (Contessa et al. 2009; Di Minno et al. 2015; Garg et al. 2016; Yilmazer et al. 2015). As in RA, also in PsA, there are concerns about the long-term response to TNF-α blockers on endothelial dysfunction via FMD assessment (Mazzoccoli et al. 2010; Ramonda et al. 2014). Ustekinumab appears to be neutral on cardiovascular risk despite there may be a long-term effect (Hugh et al. 2014), but there are no data of its influence on endothelial function. No data on possible athero-protective effects of apremilast are available yet.

SLE and APS

SLE is a pleomorphic condition with features ranging from skin rash and arthritis through anaemia and thrombocytopenia to serositis, nephritis, and neurological signs and symptoms (Rahman and Isenberg 2008). Atherosclerosis occurs prematurely in SLE and is independent of classical Framingham risk factors. The clinical profile of patients with SLE and atherosclerosis suggests a role for disease-related factors in atherogenesis (Roman et al. 2003). Heightened endothelial cell apoptosis may represent a common pathway for abnormal vascular function and thrombosis propensity (Rajagopalan et al. 2004).

The risk of thrombosis for a patient with SLE is significantly higher than for the general population, especially in the first year from diagnosis and cardiovascular events accounts for one-third of deaths in SLE. The inflammatory burden, the presence of renal disease, vasculitis, aPL positivity, and high-dose corticosteroids are further risk factors in this setting (Bertoli et al. 2006a; Erkan 2006).

APS may cause venous, arterial and small-vessel thrombosis, pregnancy loss and preterm delivery for patients with severe pre-eclampsia or placental insufficiency. Other clinical manifestations are cardiac livedo reticularis, heart valvular disease, microthrombotic nephropathy, thrombocytopenia, haemolytic anaemia, and cognitive impairment. aPL promote activation of endothelial cells, monocytes, and platelets in addition to overproduction of tissue factor and thromboxane A2 (Ruiz-Irastorza et al. 2010).

The link between arterial thrombotic events and aPL has widely been established by Euro-phospholipid Project (Cervera et al. 2002, 2015) in a cohort of 1000 patients. In this study population, the prevalence of stroke was 13.1%, myocardial infarction 2.8%, TIA 7%, and amaurosis fugax 2.8%. Smaller studies confirmed this strong association with micro- and macrovascular morbidity (Brey et al. 2001; Meroni et al. 2007). Furthermore, the presence of aPL has been associated also with accelerated atherosclerosis (Pierangeli et al. 2008) inducing a proinflammatory and procoagulant phenotype and cross reacting with oxLDL in SLE-related APS (Vaarala et al. 1993). Moreover, immunolocalizing of β2-GPI I in atherosclerotic plaques and β2-GPI-reacting T cells suggest this further mechanism of disease in humans (Conti et al. 2014; George et al. 1999; Tincani et al. 1996). However, Roman et al. (2003) and other groups revealed, in clinical studies, the absence of association between aPL positivity and plaque formation

in SLE patients compared to primary APS (Manzi et al. 1999).

The FMD percent was significantly lower in adults with SLE compared to controls in many studies (Wang et al. 2014) and appears to be related to the total antioxidant status (Sincer et al. 2015), myocardial diastolic function (Chin et al. 2014) and vascular atherosclerotic complications (Kiss et al. 2006). Significant differences were also found in SLE patients with and without nephritis, showing lower FMD in nephritis group, whereas no difference in carotid-intima-media thickness was reported (Sharma et al. 2016). It is outstanding that disease-related risk factors might be counterbalanced by the traditional cardio-protective behaviours like physical activity without worsening disease activity (dos Reis-Neto et al. 2013).

FMD supported early onset of subclinical atherosclerosis in APS (Cugno et al. 2010; Mercanoglu et al. 2004; Stalc et al. 2011) with only one case–control study on 20 patients by Gresele et al. (2009) not confirming the association between aPL positivity and endothelial dysfunction.

In nearly all studies (Kosch et al. 2003), cyclosporine and other calcineurin inhibitors have demonstrated to ameliorate FMD in renal transplantation recipients (Akoglu et al. 2013), and the same for sirolimus and mycophenolate (Joannides et al. 2010), but no data of such treatment regimens in SLE are available. Similarly, there are no data about FMD changes with azathioprine, cyclophosphamide, or belimumab in SLE.

Systemic Sclerosis

Systemic sclerosis (SSc) is a complex disease in which extensive fibrosis, vascular alterations, and autoantibodies against various cellular antigens are among the main hallmarks (Gabrielli et al. 2009). Accelerated atherosclerosis has been described in patients with SSc and this occurred despite of the absence of classical vascular risk factors (Cerinic et al. 2003). Whether endothelial dysfunction at a macrovascular level is present in very early stages of SSc remain uncertain (Domsic et al. 2014; Rollando et al. 2010; Roustit et al. 2008), but FMD is reduced in correlation with disease duration and capillaroscopic damage progression (Rosato et al. 2013). In addition to blunted peripheral vascular reactivity and endothelial function, patients with SSc have significantly smaller brachial artery diameter compared to healthy controls and FMD is associated with digital ulcers development (Frech et al. 2015) and recurrence (Silva et al. 2015). Pulmonary arterial hypertension is predicted by low FMD in limited cutaneous SSc but not in diffuse cutaneous SSc (Frech et al. 2015; Takahashi et al. 2014).

Assessment of FMD in the pre-atherosclerotic stage may have a beneficial diagnostic, prognostic, and therapeutic relevance (Szucs et al. 2007). Endothelial dysfunction and reduced FMD are associated with prostanoid cyclic therapy. This effect occurs together with a concomitant increase in expired NO, suggesting its direct positive influence on endothelial function. It may also partially explain the clinical beneficial effect of this treatment in SSc (Giannattasio et al. 2007). An improvement of FMD in SSc patients after therapy with bosentan has also been described (Sfikakis et al. 2007), while neither data on macitentan nor riociguat and FMD are available. Only in one small case series of two patients, a benefit of cyclophosphamide pulses was demonstrated on endothelial function in parallel with improvement of SSc-related interstitial lung disease (Takahashi et al. 2012).

Concluding Remarks

Prevention of CVD requires risk stratification and treatment of classical risk factors, such as smoking, hypertension, hypercholesterolemia, and diabetes. Nevertheless, classic risk stratification might be not sufficient in the presence of a non-modifiable factor like a chronic inflammatory disease.

Several vascular markers obtained by ultrasound and other non-invasive techniques have been proposed for this aim (Bruno et al. 2014). Although greater evidence is becoming available for other vascular functional tests like pulse wave velocity (Ben-Shlomo et al. 2014) and carotid-intima-media thickness measurement (O'Leary and Bots 2010), FMD may be most cost-effective to stratify rheumatic patients based on their cardiovascular risk. Standardization is, however, the ultimate factor when using this method that is operator-dependent and affected by many non-disease-related factors. In chronic rheumatic diseases, FMD appears as a useful and reliable technique to assess endothelial function and to predict atherosclerosis and cardiovascular risk that is, to date, the first cause of morbidity and mortality in these patients. It is then of paramount importance to better define long-term disease-related prognostic factors, being autoimmune diseases increasingly curable nowadays.

As seen in Table 2, mean or median FMD shows a considerable variation among different settings and study populations (range 3.2–11.0%), but shows an almost universal significance in defining case/control differences in assessing the treatment outcome. Moreover, it well correlates with undebated atherosclerosis predictors like carotid artery intima-media thickness as seen in RA (Veselinovic et al. 2012) and SLE (El-Magadmi et al. 2004).

FMD resulted, therefore, a good surrogate marker of chronical vascular injury in autoimmune rheumatic

Table 2 Available reports on FMD in rheumatological disorders

Disease	References	*N*	FMD	Comments
Rheumatoid arthritis	Hurlimann et al. (2002)	11	Mean baseline 3.2%, SEM 0.4% After 12 weeks of anti-TNF-α 4.1%, SEM 0.5% ($p=0.018$)	Slight improvement after anti-TNF
	Van Doornum et al. (2003)	25	Mean RA 7.6%, SD 4.6% control 8.5%, SD 4.1% ($p=0.49$)	No statistically significant difference between RA and control group; reduced brachial artery compliance
	Vaudo et al. (2004)	32	Mean RA 3.2%, SD 1.3% control 5.7%, SD 2.0% ($p<0.001$)	Early onset patients
	Bilsborough et al. (2006)	14	Mean baseline 6.5%, SEM 1.4% After 36 weeks of anti-TNF-α 8.6%, SEM 1.5% ($p=0.009$)	Improvement after anti-TNF
	Arosio et al. (2007)	65	Mean RA 8.2%, SD 2.0% control 11.5%, SD 3% ($p<0.05$)	FMD correlated with CRP
	Gonzalez-Juanatey et al. (2008)	6	Mean baseline 3.35%, SD 1.58% After 2 week of RTX 7.02% SD 2.31% ($p=0.03$)	FMD improved after rituximab
	Veselinovic et al. (2012)	52	Mean RA 9.16%, SD 7.03% control 12.60%, SD 5.49% ($p=0.005$)	Better FMD with lower dose corticosteroids
	Chatterjee Adhikari et al. (2012)	35	Mean RA 5.26% (2.9–10.6%) control 10.34% (7.4–14.3%) ($p=0.004$)	Early arthritis. FMD correlates with RF
Psoriatic arthritis	Yilmazer et al. (2015)	20	Mean PsA 11.0%, range 8.0–15.0% control 13.2%, range (8.1, 17.6%) ($p=0.01$)	
	Garg et al. (2016)	16	Mean PsA 6.3%, SD 0.95% control 9.3%, SD 1.4% ($p=0.01$)	Inversely correlates with c-IMT
Systemic lupus erythematosus	El-Magadmi et al. (2004)	62	Median SLE 3.6%, range (−6.3, +13.7) control 6.9%, range (−6.6, +17.8%) ($p=0.001$)	FMD negatively correlates with carotid artery IMT
	Kiss et al. (2006)	61	Mean SLE, CV^+ 5.54%, SD 4.36% SLE, CV^- 8.81%, SD 5.28% ($p=0.01$)	Significant difference between SLE patients with and without cardiovascular complications
	Sincer et al. (2015)	34	Mean SLE 8.1%, SD 4.9% control 10.6%, SD 4.7% ($p=0.04$)	Correlated with total antioxidant status

Table 2 (continued)

Disease	References	*N*	FMD	Comments
Anti-phospholipid syndrome	Cugno et al. (2010)	40	Mean APS 5.59%, SD 2.46% control 8.19%, SD 2.58% ($p=0.0001$)	Correlated with soluble markers of endothelial dysfunction
Systemic sclerosis	Szucs et al. (2007)	29	Mean SSc 4.82%, SD 3.76% control 8.86%, SD 3.56% ($p<0.001$)	
	Frech et al. (2015)	38	Mean SSc 5.23%, SEM 0.22% control 8.69%, SEM 0.21% ($p<0.001$)	Correlated with development of digital ulcers
	Silva et al. (2015)	77	FMD (AUC 0.754, 95%CI 0.643–0.864)	Independently correlated with digital ulcer development and recurrence

CRP C-reactive protein, *C-IMT* carotid-intima-media thickness measurement, *CV* cardiovascular, *AUC* area under the curve, *RTX* rituximab

diseases for both predicting cardiovascular morbidity and to evaluate treatment efficacy.

The effect of old and new immune modulating therapies on atherosclerosis is a critical field of interest for rheumatologists and immunologists, and warrants further research, particularly in the wide-spreading era of the new biological agents.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in relation to the presented work.

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