Flow-mediated dilatation and its role in chronic rheumatic diseases

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Abstract

Flow-mediated dilatation (FMD) is widely used as a non-invasive method to assess endothelial function. Vascular endothelium is a biological interface between blood and vessel wall and has a crucial role in vascular homeostasis. The endothelium is a large paracrine organ that secretes numerous factors regulating vaso-motor function, cell growth, platelet and leukocyte interactions, inflammatory responses and thrombosis. It responds to various internal and external stimuli, through cell membrane receptors and signal transduction mechanisms, with numerous vasoactive substances released, including prostacyclins, endothelins, endothelial cell growth factors, interleukins, plasminogen inhibitors and nitric oxide (NO). In particular, NO is one of the most important molecules for its role as a vasodilator factor; inhibitor of inflammatory activity, vascular smooth muscle cell proliferation and platelet adhesion and aggregation. Classic and non-classic atherosclerotic risk factors such as hypertension, diabetes mellitus, smoking habit, obesity, dyslipidemia and systemic inflammation could lead to endothelial dysfunction and accelerated atherosclerosis. Chronic inflammatory rheumatic diseases have been associated with decreased endothelial function and accelerated atherosclerosis. This paper briefly reviews the role of FMD as a surrogate marker of endothelial function in rheumatic diseases.

Conclusion

FMD is a useful marker of endothelial function in chronic rheumatoid disease, but many factors can affect FMD assessment, and so further studies are needed to increase our understanding.

Introduction

Vessel homeostasis is determined by a balance between vasoconstrictor, vasodilator, proaggregating and antiaggregating molecules. Stimuli that alter vessel homeostasis can induce an altered endothelial function. This pathophysiological condition is associated with activated phenotype of endothelial cells, leading to increased expression of adhesion molecules, proinflammatory cytokines such as tumour necrosis factor (TNF) alpha, interleukin (IL)-1, IL-6 and interferon (IFN) gamma and prothrombotic factors. This process results in oxidative stress up-regulation, loss of vasodilatory ability and promotion of thrombosis, inflammation and cellular proliferation. Several studies demonstrated that endothelial dysfunction plays a central role in the pathogenesis of atherosclerosis, promotes early atherosclerotic changes and is predictive for the development of cardiovascular events. Thus, assessment of endothelium function, in the preclinical stage of atherosclerosis with non-invasive approaches, may serve as a valuable measure to be counted in the follow-up of patients with cardiovascular disease (CVD) risk. Among different methods, the assessment of flow-mediated dilatation (FMD) is one of the most used. FMD depends on endothelium production of vasodilator molecules including nitric oxide (NO) and prostacyclin. Assessment of FMD is based on the reactive hyperaemia phenomenon that occurs when arterial blood flow is restored after a period of transient arterial occlusion. Increased blood flow determines an enhancement in shear stress on the vessel wall that stimulates the release of NO and prostacyclin. FMD response is characteristically presented as a change in arterial baseline diameter after hyperaemia induced by applying sphygmomanometer cuff inflated to a pressure 25–50 mmHg above systolic arterial pressure. Usually, brachial artery can be assessed for its accessibility (Figures 1–3).

Figure 1: FMD execution technique: US probe was applied on the patient’s forearm to detect brachial artery.

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Critical review

Differences in substances and physical stimuli can induce vasodilator or vasoconstrictor molecule production—pro-oxidant and antioxidant factors such as smoke, short- and long-term ingestion of cocoa/chocolate, caffeine, ambient temperature and drugs could alter FMD values in healthy population.

This critical review discusses FMD and its role in chronic rheumatic diseases.

Discussion

FMD and CVD risk factors
Impaired FMD is associated with CVD risk factors and provides prognostic information. All traditional CVD risk factors determine endothelial dysfunction through different mechanisms. In fact, it has been demonstrated that FMD decreases with increasing age and is impaired in subjects with hypertension, obesity, type 2 diabetes mellitus, hypercholesterolaemia and in chronic smokers. Furthermore, it has been demonstrated that FMD has an important prognostic role: impaired FMD predicts long-term cardiovascular events in healthy subjects; it is associated with an increased risk to develop cerebrovascular diseases, coronary stenosis and peripheral vascular disease; lower FMD values increase mortality risk in subjects with both ischaemic and non-ischaemic heart failure. Despite these evidences, there is not a univocal consensus about the normal values of FMD, and there is no agreement on a FMD cut point beyond which, CVD risk increases.

FMD in rheumatic diseases
Generally, in response to a variety of noxious stimuli, endothelium undergoes phenotypic modulation from the normal state to a non-adaptive state, known as endothelial dysfunction. This process may lead to functional manifestations including impaired endothelium-dependent vasodilation and accelerated atherosclerosis. Accelerated atherosclerosis has been reported to occur in patients with various autoimmune rheumatic diseases, suggesting an involvement of autoimmune mechanisms in atherogenesis. On the other hand, several mechanisms in inflammatory rheumatic disease such as high levels of C-reactive protein (CRP), increased amounts of pro-atherogenic hormones, decreased amounts of anti-atherogenic hormones, autoantibody production, smooth muscle cell proliferation, coagulation and fibrinolytic system dysfunction could lead to endothelial dysfunction and early vascular damage. Chronic inflammatory rheumatic diseases have been associated with traditional atherosclerosis risk factors including smoking, dyslipidemia, obesity and metabolic syndrome, but these factors alone do not fully explain the increase of CVD morbidity and mortality. Therefore, early cardiovascular screening using non-invasive imaging techniques such as FMD, as well as laboratory biomarkers, could be useful to prevent and treat vascular disease, but its prognostic value is not well established and its utility in clinical practice to stratified CVD risk is unknown.

Systemic lupus erythematosus
Systemic lupus erythematosus (SLE) is associated with an increased CVD risk compared with the general population. Age at the time of diagnosis, hypertension, diabetes, dyslipidemia, smoking and sedentary lifestyle have been associated with CVD in SLE. However, in SLE patients, traditional risk factors do not fully explain the increase of CVD morbidity and mortality, and it has been suggested that chronic inflammation and disease-specific and therapy-related factors are involved in a process of accelerated atherosclerosis. Several studies demonstrated an increased carotid intima media thickness (IMT) and pulse wave velocity in SLE patients compared with healthy controls, but ambiguous results were found for FMD. Cypiené et al. did not report...
find differences in FMD values in a cohort of 30 SLE women without evident CVD compared with 66 healthy women\textsuperscript{15}. This result was confirmed in a cohort of 31 SLE patients and 72 controls in which no differences in FMD values were found among groups\textsuperscript{16}. Recently, Valdivielso et al. showed that SLE patients had significantly impaired brachial artery FMD in a cohort of 26 SLE patients without CVD compared with 21 healthy controls\textsuperscript{15}. This difference remained after adjusting for age, smoking, body mass index, waist circumference, total cholesterol, triglycerides, apolipoproteins A-1 and B100 levels and postmenopausal status. A significant association was found in SLE patients between FMD and lupus activity index. Magadmi et al. showed impaired FMD in a cohort of 62 SLE woman compared with healthy subjects, but FMD did not correlate with disease activity index\textsuperscript{15}. These results agree with those shown by Lima et al. who demonstrated lower FMD in SLE patients without traditional CVD risk in respect to matched controls\textsuperscript{15}.

Antiphospholipid syndrome

It is generally accepted that vascular disease, such as coronary artery occlusions and strokes in antiphospholipid syndrome (APS), is mainly related to the occurrence of thrombosis. Whether the enhanced atherosclerotic process, besides the hypercoagulable state, is a feature of APS is less clear. There is strong evidence from both \textit{in vitro} and \textit{in vivo} experimental models that antiphospholipid antibodies (aPLs) may affect directly endothelial cells by inducing a perturbation that is eventually responsible for a proinflammatory and procoagulant phenotype. The proposed mechanism was oxidative modification of LDL/β2 glycoprotein I and other lipoprotein complexes, which interact with specific antibodies and increase athrombosis, independently of other predisposing factors. These pathogenetic mechanisms could explain the presence of endothelial dysfunction and impaired FMD in APS patients\textsuperscript{17,18}. Recently, Charakida et al. showed impaired FMD in a large population of APS patients versus controls, and more interestingly, in their study, the authors demonstrated that high-density lipoprotein (HDL) inhibits endothelial NO production in aortic endothelial cells of APS patients. These results suggest that HDL seems to have a pathogenetic role in endothelial dysfunction in APS patients\textsuperscript{19}. Despite these findings, the role of FMD in predicting cardiovascular thrombotic events or its association with aPL titres is less clear and need further investigations.

Undifferentiated connective tissue disease and mixed connective tissue disease

A small number of studies considered endothelial dysfunction in patients with undifferentiated connective tissue disease (UCTD). Kerekes et al. demonstrated impaired FMD in 22 UCTD patients. In this study, FMD correlated with anti-DNA antibodies, suggesting a role for these autoantibodies in endothelial dysfunction, but the pathogenetic mechanism is unclear\textsuperscript{20}. Mosca et al. studied endothelial dysfunction through the assessment of vascular reactivity in a cohort of 15 UCTD patients and 15 controls without CVD risk factors. In this study, there were no differences in FMD values between two groups, and UCTD patients had low microvascular reactivity, assessed by intraarterious acetylcholine, than controls. These findings suggest that endothelial dysfunction may be present only at microvascular level in patients with UCTD\textsuperscript{21}. There was very little information regarding vascular function in mixed connective tissue disease (MCTD). MCTD, similarly to scleroderma, has been associated with oblitative macrovascular disease and pulmonary hypertension. Recently, impaired FMD, as well as
increased IMT of carotid wall, was found in 50 MCTD patients compared with 38 matched healthy controls.22

**Systemic sclerosis**

Systemic sclerosis (SSc) is an autoimmune disease characterized by Raynaud’s phenomenon and endothelial injury, resulting in microvascular and macrovascular obliterative disease, severe tissue hypoxia and skin fibrosis. In SSc, the initiating injury is unknown, but endothelial cell damage leads to enhanced expression of adhesion molecules resulting in inflammatory cell recruitment, transmigration across vessel wall and infiltration of the extracellular matrix. Another important component of endothelial dysfunction in SSc is dearangement of vasoactive mediators, with an increase in vasoconstrictive and decrease in vasodilator molecules.23 Increasing evidence shows that accelerated atherosclerosis is also present in SSc. A recent meta-analysis described that the prevalence of subclinical atherosclerosis seems to be more prevalent in patients with SSc than in controls. In four studies, significantly lower brachial artery FMD was observed in SSc patients compared with healthy controls, while other studies found no difference.24 Surprisingly, in these studies, no correlations were found between FMD, SSc pattern, presence of autoantibodies, pulmonary hypertension or organ involvement. These findings suggest that in SSc, atherosclerosis and early dysfunction in macrovascular circulation is present.

**Inflammatory myopathies**

Polymyositis (PM) and dermatomyositis (DM) are two inflammatory rheumatic diseases characterized pathologically by the presence of inflammatory infiltrates in the striated muscle. PM immune process is mediated by CD8+ cytotoxic T cells that invade muscle fibres and lead to muscle damage and fibrosis. The hallmark of DM is systemic microvascular injury in arterioles and capillaries with the development of prominent cutaneous erythema, muscle damage and histologic evidence of intravascular and perivascular inflammation.25 PM and DM are associated with elevated risk of CVD, but the presence of endothelial dysfunction is poorly defined. One study reported alteration of FMD in young patients with a diagnosis of juvenile DM in respect to controls.26 Another study showed that patients with DM and PM had abnormal endothelial-dependent mediated vasodilation and assessed response to acetylcholine infusion but no information about FMD was available.27 In conclusion, further studies are necessary to define the role of subclinical atherosclerosis to promote CVD risk and predictive value of FMD in patients with inflammatory myopathies.

**Rheumatoid arthritis**

Rheumatoid arthritis (RA) is associated with increased mortality due to cardiovascular events and results in an accelerated atherosclerotic process.28 Higher prevalence and severity of classical CVD risk factors such as hypertension, dyslipidemia, obesity and physical inactivity, leading to metabolic abnormalities, are present in RA. There is also a complex interplay between systemic inflammation, which characterizes RA, CVD risk factors and vascular function.29 Moreover, in large prospective epidemiologic studies, CRP and serum amyloid A are related with endothelial dysfunction and are predictive of future cardiovascular events.30,31 It has been demonstrated, on a small sample of patients with arthritis, that endothelial dysfunction occurs early in course of disease as shown by Adhikari et al. who found impaired FMD in a cohort of early arthritis patients.32 A systematic review on vascular function in RA showed that eight out of eleven studies reported an impaired endothelium-dependent macrovascular function, assessed by FMD.33 No differences between RA patients and controls were reported in endothelial-independent function in the three studies that explored these aspects. The decreased endothelium-dependent function does not appear to be further influenced by disease duration and disease activity assessed with disease activity score (DAS-28) or inflammatory markers such as CRP and erythrocyte sedimentation rate (ESR).34 Treatment of arthritis with non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors and steroids could also play a role in altering endothelial function. These findings suggest that in RA, endothelial function is impaired.

**Spondyloarthritis**

Spondyloarthritis, including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), have increased morbidity and mortality compared with the general population. Moreover, CVD is one of the leading causes of death.35 Atherosclerosis could be due to an increased prevalence of dyslipidemia, hypertension, obesity, hyperuricemia and diabetes mellitus in PsA patients with respect to healthy controls, but also to a complex interplay that involves systemic inflammation.36 To support this hypothesis, subclinical atherosclerosis and morphological abnormalities of carotid district were present in patients with PsA even in the absence of CVD risk factors, as shown by some studies.37 Endothelial dysfunction is also present in PsA patients as demonstrated by impaired FMD with respect to controls. Gonzales-Juanatey et al. showed decreased FMD in patients with PsA without risk factors for CVD. Interestingly in this study, FMD correlates with acute-phase reactants (ESR and PCR), suggesting that inflammation could influence NO production and lead to endothelial dysfunction.38 Contessa et al. showed similar results in their cohort of...
41 PsA patients. In this study, however, authors showed no correlation between FMD and clinical and laboratory findings.\textsuperscript{37} Prevalence of increased subclinical atherosclerosis was studied in AS through the assessment of FMD, but the presence of positive or negative history for CVD risk factors, events or concomitant medications led to ambiguous results.\textsuperscript{38–41} Furthermore, the correlation between FMD as an early marker of subclinical atherosclerosis with the disease activity or disability index is not clearly defined. A pilot study was done by Sari et al. which showed decreased FMD response in AS patients, without history of cardiovascular events, compared with healthy controls, but no correlations were found between FMD with inflammation markers, disease activity indices, smoking habit or metabolic profile.\textsuperscript{38} These results are similar with those shown by Bodnar et al.\textsuperscript{31}

**Vasculitis**

Vasculitis refers to a group of inflammatory autoimmune systemic diseases that affect blood vessel walls, leading to vascular damage and tissue necrosis.

Endothelial dysfunction was found in large- but not in medium- or small-sized vessel vasculitis: studies on giant cell arteritis, Takayasu’s arteritis, Wegener’s granulomatosis, polyarteritis nodosa (PAN) and Churg–Strauss syndrome demonstrated impaired brachial artery FMD with respect to controls. Moreover, FMD values improved after steroid therapy that suppresses inflammation, suggesting that inflammatory burden plays a central role in endothelial dysfunction in systemic vasculitis.

Interestingly, authors showed no correlation between FMD acute-phase reactants, vasculitis activities or damage indices.\textsuperscript{42–43} Endothelial dysfunction in systemic vasculitis could be related to endothelial cell activation and damage secondary to autoimmune process: antineutrophil cytoplasmic antibody mediates polymorphonuclear leukocyte damage to the endothelium through proteinases, reactive oxygen species and toxic levels of NO, but \textit{in vivo} evidence and correlation with methods that assess endothelial function are lacking.\textsuperscript{43}

**Conclusion**

In chronic rheumatic diseases, FMD seems to be a useful tool to assess endothelial function, but many confounding factors are able to interfere with FMD assessment. Further studies are needed to evaluate the prognostic and predictive value of FMD in rheumatic diseases in order to stratify patients at high risk factors for CVD.

**Abbreviations list**

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; AS, ankylosing spondylitis; CRP, C-reactive protein; CVD, cardiovascular disease; DAS, disease activity score; DM, dermatomyositis; eNOS, endothelial nitric oxide synthase; ESR, erythrocyte sedimentation rate; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; IMT, intima media thickness; MCTD, mixed connective tissue disease; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PM, polymyositis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSC, systemic sclerosis; TNF, tumour necrosis factor; UCTD, undifferentiated connective tissue disease

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