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Review

Endothelial dysfunction in joint disease

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ABSTRACT

Inflammatory joint diseases and autoimmune diseases with joint manifestations are associated with premature and accelerated atherogenesis. Patients with rheumatoid arthritis (RA) have a 5- to 10-year decrease in life expectancy compared to the general population, and those exhibiting extraarticular manifestations have the greatest excess mortality. RA is now established as an independent cardiovascular risk factor. Complex interactions linking conventional cardiovascular risk factors, systemic inflammation, and vascular function may explain the increased cardiovascular risk among RA patients. Endothelial dysfunction is now recognized as both the key step in early atherogenesis and a contributor to atheroma plaque progression at later stages. Endothelial dysfunction is defined as impaired endothelium-dependent blood-vessel dilation in response to a stimulus. The underlying mechanisms remain speculative. Over the last decade, a role for endothelial dysfunction in the cardiovascular complications of inflammatory joint disease has been hypothesized and several maintenance drugs targeting this phenomenon have been tested, with promising results.

1. The vascular endothelium

Blood is circulated and distributed throughout the body via a closed network of vessels that carry blood from the heart to the body tissues then back to the heart. Blood vessels fall into three categories: arteries and arterioles carry blood from the heart to the peripheral tissues, capillaries allow gases and nutrients to travel between the blood and tissues, and veins and venules carry the blood from the peripheral tissues to the heart.

Despite differences in constitution, diameter, and wall thickness, arteries and veins share the same wall structure, with an outer adventitia composed chiefly of connective tissue; a media consisting mainly of smooth muscle cells; and an intima, which is a single layer of endothelial cells known as the vascular endothelium. The capillary wall is a single endothelial cell layer that lies on a basement membrane and receives support from a few collagen fibers.

The vascular endothelium is far more than an anatomic barrier between the bloodstream and the vascular smooth muscle cells. It plays a pivotal role in multiple physiological regulation systems of crucial importance. Under physiological conditions, endothelial biology is chiefly controlled by hemodynamic factors (blood pressure, blood flow rate) that exert either direct effects, mainly via variations in blood flow rate (mechanical stimuli), or indirect effects involving local changes in chemical factors (chemical stimuli).

The endothelium is well recognized as capable of producing and releasing a number of mediators, which, in turn, affect the circulating and vascular cells, thereby influencing vascular functions such as tone and proliferation, as well as interactions between circulating cells and vascular cells (adhesion, aggregation) [1]. Endothelial cells contribute to regulate vascular tone by producing both vasodilating and vasoconstricting substances. Vasodilators released by the endothelium include prostacyclin, endothelium-derived hyperpolarizing factor (EDHF), bradykinin, and nitric oxide (NO). NO is a key vasoactive factor that not only regulates vasodilation via effects on the smooth muscle cells, but also inhibits platelet aggregation and leukocyte adhesion to the vessel wall. The effects of endothelial vasodilators are counterbalanced by those of vasoconstrictors, also produced by the endothelium. Under physiological conditions, an appropriate balance exists between the productions of endothelial vasodilators and vasoconstrictors (Fig. 1).

Endothelial dysfunction manifests as an abnormality in the release of one or more of the above-listed factors. More generally, in most cardiovascular diseases, endothelial dysfunction is equated with abnormal endothelial NO availability and therefore impaired endothelium-dependent vasodilation, since

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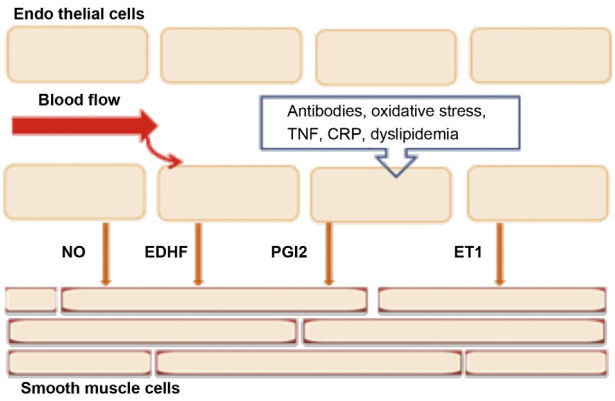

Fig. 1. The endothelium is a surface across which exchanges occur, notably with blood and smooth muscle cells. Depending on the stimuli received, the endothelial cells release numerous mediators including vasodilators (nitric oxide [NO], endothelium-derived hyperpolarizing factor [EDHF] and prostacyclin [PGI2]) and vasoconstrictors (endothelin-1 [ET1]), which act on the smooth muscle.

endothelium-independent vasodilation is effected by the smooth muscle cells in the vessel walls. Endothelial dysfunction is a functional abnormality, whereas atheroma consists of both functional and structural abnormalities.

2. Methods for evaluating endothelial dysfunction in humans

These methods involve the peripheral circulation and ultimately reflect endothelial NO release, which is considered a good marker for endothelial function. They consist in stimulating NO production then measuring the degree of NO-induced vasodilation. Table 1 briefly describes the three methods used to evaluate changes in large-artery diameter. The most widely used method is flow-mediated dilation (FMD), which measures the endothelial response to hypoxia induced by inflating a cuff around the forearm for 5 minutes. Distal peripheral arterial resistance decreases while the cuff is inflated, and releasing the cuff therefore results in a blood flow increase, which stimulates NO release. The excess NO induces relaxation of the arterial smooth muscle cells with an increase in arterial diameter (acetylcholine-dependent or endothelium-dependent relaxation). The effect is measured as the difference between the largest postocclusion diameter and the baseline diameter. In adults, FMD values lower than 7% are considered to indicate endothelial dysfunction.

Impaired vasodilation may indicate either inadequate NO production by the endothelial cells or an abnormal smooth-muscle-cell response to NO. Consequently, endothelium-independent vasodilation must be assessed by administering sublingual nitroglycerin to induce nitroglycerin-mediated vasodilation (NMD). Nitroglycerin directly relaxes the arterial smooth muscle cells, thereby inducing endothelium-independent vasodilation.

Forearm blood flow (FBF) measurement also assesses endothelial function in the large arteries. This is an invasive technique, since acetylcholine must be injected into the brachial artery. Plethysmography is then performed to measure the change in brachial artery blood flow related to acetylcholine-dependent vasodilation.

Finally, a more recent method evaluates arterial endothelium-dependent and endothelium-independent microvascular dilation using laser Doppler imaging with iontophoresis, at the skin. This method has been used to compare microvascular and macrovascular endothelial functions in patients with RA [2]. The results indicated that microvascular and macrovascular endothelial functions were independent of each other, supporting a role for different regulation mechanisms.

These three techniques evaluate endothelial function. In contrast, the assessment of subclinical atheroma relies on a structural parameter, namely, intima-media thickness (IMT).

Many biological markers for endothelial function have been identified (e.g., vascular cell adhesion molecule [VCAM], von Willebrand factor, and circulating endothelial cells), but none has been validated in RA. Asymmetric dimethylarginine (ADMA) is a potent endogenous NO-synthase (NOS) inhibitor. Plasma ADMA elevation, which may indicate endothelial dysfunction, has been evaluated in RA. Raised plasma ADMA levels may predict endothelial dysfunction in patients with recent-onset RA and no cardiovascular disease or cardiovascular risk factors [3].

3. Rheumatoid arthritis

3.1. Endothelial function in rheumatoid arthritis

A role for endothelial dysfunction in the genesis of the vascular complications of RA was suggested recently [4]. The seminal 2002 study showed impaired acetylcholine-dependent vasodilation of the brachial artery in RA patients compared to controls [5]. Since then, numerous clinical studies have produced additional evidence of endothelial dysfunction in RA, without, however, elucidating the underlying mechanisms.

Few methods are available for assessing endothelial function, and those used in humans usually focus on the brachial arteries to investigate the arterial macrocirculation. There are no methods for establishing a map of the lesions. Conflicting data have been reported regarding the links between the natural history of endothelial dysfunction and the course of RA. Although endothelial function seems to deteriorate as disease duration increases, the time at which endothelial dysfunction develops has not been determined. In a cross-sectional study in 35 patients with very recent-onset RA (less than 12 months; mean, 0.46 ± 0.28 years), the FMD values were impaired (5.26% vs. 10.34% in controls) [6]. In contrast, in 79 RA patients with symptoms for less than 12 months, FMD values were normal [7]. A recent observational study of 18 RA patients with a median symptom duration of only 2 months showed normal microvascular and macrovascular endothelial function contrasting with elevated values of molecular markers for endothelial damage [8]. Skin tests for microvascular dilation were not significantly different between patients with recent-onset RA and controls. Thus, no definite conclusions can be drawn regarding endothelial function during the first few years of RA. Conceivably,

Table 1
Techniques for evaluating macrovascular endothelial function in humans.

Technique	Type of vessel	Invasive	Method for measuring the arterial diameter change	Drug used	Function measured
FMD	MacrocirculationBrachial artery	No	B-mode ultrasound	–	Endothelium-dependent vasodilation
NMD	MacrocirculationBrachial artery	No	B-mode ultrasound	Sublingual nitroglycerin	Endothelium-independent vasodilation
FBF	MacrocirculationBrachial artery	Yes	Plethysmography	Acetylcholine in the brachial artery	Endothelium-dependent vasodilation

FMD: flow-mediated dilation; NMD: nitroglycerin-mediated vasodilation; FBF: forearm blood flow.