COMMENT

Inflammation and endothelial dysfunction: intimate companions in the pathogenesis of vascular disease?

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ABSTRACT

There is increasing evidence to implicate inflammation as an important precursor of endothelial dysfunction. This mechanistic link is apparent across the entire spectrum of inflammatory status, i.e. endothelial function is apparent following acute infection, and in subjects with chronic high-grade inflammation and, perhaps most importantly, persistent low-grade inflammation. The recognition of this relationship has present therapeutic ramifications, but also requires that future longitudinal studies determining the predictive ability of endothelial function measures for vascular events should incorporate markers of inflammation as potential confounders. In this issue of Clinical Science, Fichtlscherer and co-workers describe a link between endothelial function and sPLA₂ (secretory non-pancreatic type II phospholipase A₂) serum activity.

The concept of endothelial dysfunction has now been around for a number of years. Many researchers promote the notion that endothelial dysfunction is likely to be a critical early step in the process of atherogenesis, and, as such, they argue that endothelial dysfunction may represent an intermediate phenotype for vascular disease [1,2]. Its assessment has, therefore, assumed importance in clinical research and relevant methods, including both blood pressure measures and dynamic tests, are beginning to show promise in improving risk stratification. But what are the factors leading to endothelial dysfunction? Considerable early research was directed at traditional risk factors, including age, hyperlipidaemia, hypertension, diabetes and smoking, and all appear important. However, the observation in one excellent study [3] that traditional risk factors explain less than 20% of the variance in endothelial function [VOP (venous occlusion plethysmography)] intimates the importance of other ‘novel’ candidates.

Research in recent years indicates that nearly all candidate novel risk pathways may be detrimental to the endothelium. There is ample data linking obesity, insulin resistance, hyperhomocystinaemia, low birth weight and inflammation to endothelial dysfunction [4–7]. Of these, the inflammation–endothelial dysfunction link might be of particular clinical importance.

In a series of elegant studies [8–10] involving the application of direct or indirect inflammatory stimuli to specific areas of blood flow, Vallance and co-workers were among the first to demonstrate that acute inflammation is a potent initiator of endothelial dysfunction. Moreover, they were able to demonstrate that pretreatment with aspirin or steroids could attenuate inflammation-induced endothelial dysfunction [8,9]. As a result of their work, they suggested that “endothelial dysfunction after acute infection or inflammation may be a transient risk factor for cardiovascular disease that might promote abnormal vascular behaviour and might be amenable to pharmacological intervention” [11].

Others have now demonstrated that ‘chronic’ high-grade inflammation also promotes endothelial dysfunction [12], and such findings have been put forward as one explanation for the accelerated atherogenesis in patients with RA (rheumatoid arthritis) [13]. Indeed,

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endothelial function appears early in the course of RA and does so in proportion to the magnitude of the inflammatory response [12]. More significantly, a recent study employing FMD (flow-mediated vasodilation) in RA demonstrated improved endothelial function following anti-TNF-α (tumour necrosis factor-α) therapy, data directly implicating TNF-α as a mediator of endothelial dysfunction in RA [14]. TNF-α could mediate endothelial dysfunction via diminished expression of eNOS (endothelial nitric oxide synthase) and COX-I (cyclooxygenase I). TNF-α also impedes degradation of ADMA (asymmetric dimethylarginine), the endogenous inhibitor of NOS.

But does low-grade chronic inflammation also correlate with, and potentially mediate, endothelial dysfunction? Fichtlscherer and co-workers [15] were among the first to demonstrate such an association. In their study of 60 male patients with angiographically documented coronary artery disease, forearm blood flow responses to acetylcholine (by VOP) correlated inversely ($r = -0.46, P = 0.001$) with CRP (C-reactive protein) levels, most of which were <10 mg/l, i.e. within the low-grade inflammation range. This association was independent of other risk factors and, of note, normalization of elevated CRP levels over time was associated with a normalization of endothelium-mediated forearm blood flow responses after 3 months [15]. At about the same time, our group noted a strong correlation ($r = 0.85, P = 0.004$) between basal nitric oxide synthesis and CRP in a small study of healthy volunteers [16]. Additionally, a study in 79 healthy children (mean age, 10.5 years, thus atheroma less likely to be a confounder) confirmed an independent association of elevated CRP with impaired endothelial-dependent function (by FMD) [17].

In this issue of Clinical Science, Fichtlscherer and co-workers [18] confirm the association of endothelial function (by VOP) with elevated CRP in a group of patients with angiographically documented coronary artery disease, but, independent of this association, a link to sPLA2 (secretory non-pancreatic type II phospholipase A2) serum activity was established. Of course, correlations do not prove causality. Moreover, since both CRP and sPLA2 increase as part of the acute-phase response, their observations cannot exclude cytokines as ‘upstream’ mediators of vascular dysfunction.

That said, a number of other studies have recently indicated CRP may be directly damaging to the endothelium (reviewed in [7]). Serum PLA2 could also directly promote endothelial dysfunction, for example, by its ability to promote generation of lysophosphatidylcholine, a known inhibitor of eNOS. As indicated by Fichtlscherer et al. [18], to truly dissect out causality, intervention studies with specific sPLA2 blockers are required. There are no specific CRP blockers, however. Although many vascular and endothelial protective measures (e.g. statins, ACE (angiotensin-converting enzyme)-inhibitors and weight loss] also lower CRP, they all have effects on other pathways (e.g. lipids, blood pressure and insulin resistance) and so a direct link cannot be evoked. Alternatively, rather than CRP, IL-6 (interleukin-6) could be an upstream mediator of endothelial dysfunction [19]. It is of interest, therefore, that an antibody to the IL-6 receptor is in phase II and III trials in RA and in juvenile RA. There is also evidence for a role of other cytokines such as IL-18 (interleukin-18; reviewed in [7]).

Whatever the mechanisms linking low-grade inflammation to endothelial function, there is a clear ramification of this association for endothelial function research. Simply put, all ongoing or planned longitudinal studies examining endothelial function measures as predictors of vascular events should consider confounding by inflammatory measures. There are now several prospective studies demonstrating baseline measures of endothelial function to ‘independently’ predict subsequent coronary events (reviewed in [20]). However, few of these have considered CRP as a potential confounder. Moreover, in one such prospective study [21], where CRP was measured, it was decided to ‘omit’ it from the relevant multivariate Cox regression analysis due to its particularly strong inverse baseline association (up to $r = -0.78, P < 0.0001$) with endothelial-dependent dilation of epicardial coronary arteries. Given that CRP is easy to measure, whereas most direct endothelial function techniques are not, and that recent bodies propose the addition of CRP concentration to enhance risk factor stratification in specific circumstances [22], it would seem important to include CRP in future studies. Only by doing so can we truly examine whether endothelial function techniques give insight into risk beyond established and other emerging predictors of vascular events.

REFERENCES

Comment

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