Endothelial function and myocardial infarction

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Received 15 January 1998; accepted 17 April 1998

1. Introduction

Several standard risk factors are now recognised for the development of coronary disease and a modulation of some of these factors has been shown to decrease the incidence and recurrence of coronary events [1–3]. Mortality in coronary disease is directly related to the number of diseased vessels, the presence of left ventricular dysfunction, and an ischaemic response on treadmill exercise testing. However, our ability to prognosticate based on an understanding of ischaemia or angiography still remains very poor. Furthermore, it is recognised that traditional antianginal therapy does not significantly alter prognosis; angioplasty does not prevent myocardial infarction or death on follow up and although by-pass surgery may decrease subsequent mortality in certain sub-groups, it has not been shown to decrease the future incidence of myocardial infarction [4,5].

At least one important reason for this unpredictability is that acute ischaemic events, particularly myocardial infarction, are unrelated to stenosis severity [6–8]. Acute coronary events, which include a diagnosis of unstable angina, acute myocardial infarction and some cases of sudden cardiac death, are usually related to a sudden disruption or fissure of an atherosclerotic plaque with the formation of thrombus that partially occludes (unstable angina) or completely occludes (myocardial infarction or sudden death) the coronary vessel. Serial angiographic studies performed prior to and following an acute event, or angiographic studies performed early after myocardial infarction, indicate that the underlying plaque responsible for unstable angina and myocardial infarction was usually less than 50% narrowed prior to the acute event [6,9]. Moreover, these lesions would be unlikely to cause ischaemia if looked for using ambulatory monitoring (a means to establish the total ischaemic burden). A recent angiographic study suggests that the positive correlation between the number of severely diseased arteries and coronary mortality may not just be related to the number of arteries with 70% or greater stenosis, but may be also tied in with the amount of minor plaque disease in other vessels [10]. Indeed, it is possible that patients with multivessel disease perhaps have a higher mortality than those with single vessel disease because they have more non-stenotic or mildly stenotic plaques that are sites for future coronary events.

These observations and the finding that the progression to an acute infarction is not proportionate related to the prior severity of the coronary stenosis [6,8,9] has been driving the search for other mechanisms of acute myocardial ischaemia/infarction. An increasing body of evidence is now highlighting a potentially important player in the acute coronary syndromes, the endothelium.

Until relatively recently, the endothelium was regarded simply as an inert nonthrombogenic diffusional barrier separating the blood from the vascular smooth muscle, and vascular control was considered primarily the domain of the sympathetic nervous system and circulating vasoactive hormones. The discoveries that the endothelium synthesises the important vasodilators nitric oxide (NO) [11] and prostacyclin [12] ignited enormous interest in endothelial function and its role in vascular control in health and disease. The endothelium influences not only vascular tone but also vascular remodelling, through production of growth-promoting and -inhibiting substances, and haemostasis and thrombosis through the antiplatelet, anticoagulant and fibrinolytic effects. Abnormalities in the function of the endothelium are therefore likely to play an important role in the pathogenesis of coronary disease.

There is significant in vitro evidence for demonstrating the presence of endothelial dysfunction in atherosclerotic vessels. Oxidised low density lipoprotein cholesterol induces the endothelium to express adhesion molecules (vascular cell adhesion molecules) and to produce monocyte chemotactic proteins that facilitate monocyte adhesion...
and migration through the vessel wall. It also stimulates the release of epidermal growth factor and platelet derived growth factors, which contribute to smooth muscle cell migration and proliferation in the intima [13]. All of these processes potentially serve to further predispose the vessel wall to plaque rupture and thrombosis. Moreover, a recent study has documented the risk of high circulating cell adhesion molecules with subsequent myocardial infarction [14]. However, what is the evidence for endothelial dysfunction in vivo in the acute coronary setting?

2. Endothelial dysfunction in myocardial infarction and unstable angina

Normal endothelial function can be defined as the functionally appropriate response of this cell layer when stimulated by physiological or pharmacological stimuli in vivo. Most studies have explored (and defined) endothelial function on the basis of the ability to respond appropriately to endothelium-dependent stimuli (sheer stress, ischaemia or pharmacological agents). Endothelium-dependent relaxation in man has been studied extensively in the epicardial coronary arteries, both in vitro and in vivo. In 1986, endothelial dysfunction (as defined by an impaired ability of the vessel to vasodilate when stimulated) was found in the coronary arteries of humans with advanced atherosclerosis [15] and, in 1994, Uren et al. [16] demonstrated reduced coronary vasodilator function in infarcted and normal myocardium following myocardial infarction. More recently, diffuse endothelial dysfunction has been demonstrated in patients with various acute coronary syndromes [17–19]. However, this dysfunction has been found to extend beyond the acute setting so that patients with chronic stable angina due to single vessel coronary artery disease have been shown to have reduced maximal myocardial blood flow, not only in territories perfused by the stenosed artery but also in regions supplied by angiographically “normal” coronaries [16,20–22]. Moreover, and equally fascinating are the recent studies that demonstrate endothelial dysfunction occurring in asymptomatic children and young adults with risk factors for atherosclerosis, such as hypercholesterolaemia and smoking [23–27]. These findings are highly suggestive of the presence of endothelial dysfunction significantly predate the acute myocardial event and lend further credence to the idea that the process of atherogenesis that ultimately leads to myocardial infarction is intimately related to the presence and severity of endothelial dysfunction.

How might endothelial dysfunction contribute to myocardial ischaemia? Obstructive coronary stenoses are usually thought to contribute to angina by providing a fixed limitation to coronary flow during periods of increased myocardial oxygen demand. However, several studies over the last ten years have shown that coronary stenoses are dynamic rather than fixed [28–30] and that impaired endothelium-dependent dilatation at the site of coronary plaques may result in paradoxical vasoconstriction during exercise or mental stress, just when vasodilatation is required [15,31–33]. Abnormal coronary responses to serotonin in the presence of endothelial dysfunction may be particularly important in the unstable coronary syndromes in vivo, given the involvement of platelets in the pathophysiology of these processes [34].

Similar endothelial dysfunction can also occur in the coronary microcirculation [17,18]. Because endothelial vasodilator function of the coronary microcirculation may be an important determinant of myocardial perfusion during periods of increased demand, microvascular endothelial dysfunction may play a significant role in the pathogenesis of myocardial ischaemia and infarction [19].

Most studies report the presence of impaired endothelium-dependent dilatation in atherosclerotic vessels and recent intervention trials [35–37] have confirmed the consistency of this dysfunction. The clinical correlate of impaired endothelial function in coronary arteries may be episodic myocardial ischaemia, either with or without chest pain, ultimately ending in vessel thrombosis and infarction.

However, it appears that, even after an acute infarction, the coronary vasodilator response in the infarcted myocardial region remains severely impaired, despite successful recanalisation of the infarct-artery by thrombolysis [38–40]. This impairment has been attributed to endothelial dysfunction of the resistance vessels in the infarcted tissue [40]. Uren et al. [16] showed that, in patients with acute myocardial infarction, the coronary vasodilator response is significantly impaired, even in areas that are not directly supplied by the infarct artery, compared with similar regions in patients with chronic stable disease. Furthermore, they showed that the marked reduction in response to endothelium-dependent dilators was still significantly impaired six months following the infarct, suggesting that impairment of endothelium-dependent dilatation persists for much longer than the acute insult (thrombosis), even in the myocardium remote from the site of infarction. However, impaired endothelium-dependent dilatation in response both to increased flow and acetylcholine is well documented in patients with chronic stable angina [17–19,41,42], which suggests that a generalised abnormal endothelial response is already present and that some other acute episode precipitates the coronary event.

3. Endothelial dysfunction precipitating acute myocardial infarction?

What events might predispose to an acute coronary event? Against the background of currently established risk factors for chronic atherogenesis, such as smoking, hypertension and diabetes, there has been also been considerable interest in the links between chronic infections and the
slow process of atherogenesis [43]. However, might acute infection impose a transient additional ischaemic burden that causes the shift in balance from stable angina to an acute coronary syndrome? Deaths from cardiovascular disease increase during and after epidemics of influenza [44]. This occurs not only in the frail elderly but also in previously well middle-aged men. Bacterial infections also seem to be associated with increased risk [45]. From case control studies, it has been estimated that about 4% of bacteraemic patients will develop acute myocardial infarction within one month of the onset of infection [45]. Abdominal surgery is often associated with transient bacteraemia or leakage of bacterial endotoxin into the circulation, and is accompanied by a systemic inflammatory response with cytokine production [46]. Again, there is an increase in the risk of cardiovascular disease, with the incidence of acute myocardial infarction remaining elevated for several weeks after surgery [47].

Together, these observations suggest that infection or acute systemic inflammation might temporarily increase the risk of an acute cardiovascular event. It seems unlikely that this increased risk is due to acute changes in the overall bulk of atheroma, but rather that the pre-existing atheroma becomes more likely to support thrombosis and vasoconstriction. Consistent with this idea, the transition from stable to unstable angina appears to be associated with a systemic inflammatory response [48], and markers of acute inflammation (including cytokines, C-reactive protein and white cell count) are all related to increased cardiovascular risk [48–50]. Interestingly, instability of atheroma is not always confined to one plaque, but can occur at multiple sites in different vascular beds, again suggesting that the underlying process may be systemic rather than local in origin [51].

How might inflammation or infection alter the risk associated with atheroma? One possibility is that a systemic inflammatory response increases risk by its effects on elevating the concentration of circulating clotting factors, such as fibrinogen [52]. Another is that endothelial function is altered. The normal metabolic activity of vascular endothelium exerts a basal thrombo-resistant and vasodilator influence upon the cardiovascular system [53,54]. Infection of endothelial cells [55,56], or exposure to certain pro-inflammatory cytokines, leads to expression of tissue factor, cell surface adhesion molecules and induction of procoagulant activity [49,53,54,56,57]. In addition, inflammation affects the process of endothelium-dependent relaxation [58,59].

Continuous generation of NO provides a basal dilator influence in the human cardiovascular system, inhibits adhesion of platelets and white cells to the vessel wall, prevents platelet aggregation and inhibits vascular smooth muscle cell growth [60]. An intact endothelial L-arginine: NO pathway is important to protect against the vasoconstrictor and pro-aggregatory effects of activated platelets. Recently, it has been demonstrated that bacterial endotoxin, or certain pro-inflammatory cytokines (particularly TNFα), may also inhibit the ability of endothelial cells to generate nitric oxide and/or certain vasodilator anti-aggregatory prostanoids [58,59,61,62]. These effects have been observed in whole animals [62] and in experimental models in healthy volunteers [58,59]. Initially, the infection or inflammation may lead to vasodilatation due to increased generation of NO or prostanoids from inducible isoforms of NO synthase (iNOS) [60] or cyclooxygenase (COX-II) [63] that are expressed in endothelial and smooth muscle cells in response to cytokines. However, co-incident with this process, and persisting for considerably longer, the physiological generation of NO and prostanoids by constitutive enzymes in the endothelial cell (eNOS) seems to be attenuated [58]. In healthy volunteers, even a very brief exposure to endotoxin or certain cytokines impairs endothelium-dependent relaxation for many days [58,59], and the degree of the impairment is considerably greater than that produced by chronic risk factors. This effect has been termed endothelial “stunning” [59]. The mechanisms underlying the temporary endothelial dysfunction that is produced by inflammation are not yet known. However, glucocorticoids, anti-inflammatory doses of aspirin and antioxidants all offer protection in experimental models [58,59,64], suggesting that prostanoids and/or local generation of superoxide may contribute to the effects.

After the acute vasodilator stage of the illness has resolved, the residual endothelial changes would tip the balance of mediators produced in favour of thrombosis and vasoconstriction, and this might be important in the pathogenesis of arterial thromboembolic disease [45]. The experimental and epidemiological data together suggest that endothelial dysfunction following acute infection or inflammation may indeed provide a transient risk factor for myocardial infarction and unstable angina, which might promote abnormal vascular behaviour and be amenable to pharmacological intervention. Indeed, several studies now report the potential benefit in treating patients with known ischaemic heart disease with antibiotics and report a significant reduction in the incidence of unstable angina and myocardial infarction [65,66].

Whatever the mechanism, if an abnormal vasomotor response (secondary to underlying endothelial dysfunction) were also present during the development of infarction, inappropriate constriction of resistance vessels distal to the site of coronary thrombosis could influence the development of myocardial necrosis. Mural thrombi can occur in unstable angina, and coronary occlusion may be intermittent in myocardial infarction [67]. In the vascular territory of the infarct-related artery, an enhanced response of resistance vessels (as a result of pre-existing endothelial dysfunction) to substances released by platelets (such as serotonin, ADP and thromboxane) can constrict the vascular smooth muscle surrounding the site of the thrombus when the artery is sufficiently compliant, but they can also
constrict distal vessels, as suggested by the intracoronary infusion of serotonin [34]. In the vascular bed of the non-infarct-related arteries in the presence of endothelial dysfunction, there is an enhanced response of resistance vessels to systemic and local neurohormonal constrictor stimuli, which could increase the extent of the ischaemia at the periphery of the infarcted area and reduce collateral flow to the infarct-related arterial bed, thus contributing to the acute impairment of ventricular function and to the extension of necrosis.

4. Therapeutic implications

What are the implications of these findings? Current research has raised the exciting prospect that endothelial dysfunction is potentially reversible (both experimentally and in clinical trials) [35–37,58,68–70]. Statins have already been identified as agents that improve endothelial function and significantly reduce the incidence of fatal and non-fatal myocardial infarction [71,72]. Agents such as L-arginine, vitamin C and other antioxidants, such as vitamin E [73], need to be studied in more detail with larger and longer trials with respect to defining the longevity of any beneficial effect with long-term therapy. More recently, two studies examined the effects of anti-biotic therapy on the incidence of cardiovascular events in patients admitted with evolving non-Q wave infarcts. Both studies reported a significant decrease in major ischaemic events in the antibiotic arm of the study [65,66]. These results now need to be re-affirmed by longer and larger randomised trials, to assess the benefit of antimicrobial prophylaxis in terms of cardiovascular mortality.

Treatment of endothelial dysfunction needs to be further refined, but may well become the cornerstone for effective management of unstable syndromes and in the control of important outcomes, such as myocardial infarction and coronary death. This can only occur with parallel efforts in furthering our basic physiological and clinical understanding of the role of the endothelium in health and disease.

Acknowledgements

Kiran Bhagat is supported by the British Heart Foundation

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