Letter to the Editor

Lipid lowering and the assessment of endothelial function

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We read with interest the report by Malik et al. [1] that both atorvastatin and fenofibrate equally improved endothelium-dependent arterial vasoreactivity in patients with combined hyperlipidaemia. Interestingly, a recent study by Šebestjén et al. [2] reported similar observations using cerivastatin and fenofibrate, although the effects seemed to be greater in the patients receiving the statin. Indeed, most of us now recognise that the beneficial effects of statins on the early cardiovascular events reduction in major clinical trials may involve mechanisms that modify endothelial function, inflammatory responses, plaque stability, and thrombus formation which may be unrelated, or indirectly related, to their lipid-lowering abilities [3].

Endothelial dysfunction has been regarded as an early event in atherogenesis, preceding the formation of atherosclerotic plaques. An important functional consequence of endothelial damage/dysfunction is a reduced vasodilatory responses to a variety of pharmacological and physiological stimuli such as reactive hyperaemia. This is most commonly assessed by postischaemic dilation of forearm vessels, using plethysmography, or flow-mediated dilatation (FMD) of the brachial artery, using ultrasound.

However, the methods used by Malik et al. in assessing vascular reactivity (or ‘function’) seem particularly attractive. In their study, FMD of brachial artery measured by automatic border detection B-mode scans was compared directly with reactive hyperaemia measured by peak blood flow (PBF) and blood flow increase (BFI) using pulse-Doppler spectral scans. As pointed out by the authors, FMD has considerably higher inter- and intra-observer variability as well as intra-subject variability and thus worst reproducibility as compared to PBF, which reflects ‘mean’ vascular reactivity of a relatively large portion of arterial tree and (perhaps) more representative of endothelial function.

Nevertheless, the best way of assessing endothelial damage/dysfunction is uncertain. Blann and Lip [4] has suggested that a continuum probably exists between endothelial activation (from early exposure to risk factors, such as smoking), endothelial dysfunction (resulting in thrombogenesis and atherogenesis) and finally, endothelial damage (with overt vascular damage and atherosclerosis).

An alternative way to assess endothelial damage/dysfunction is perhaps by measurement of plasma markers that are related to the endothelium, such as von Willebrand factor (vWF), soluble thrombomodulin or E-selectin [5]. Indeed, vWF has been most widely used as an index of endothelial damage in experimental studies. This molecule is synthesised by and stored in endothelial cells and when released, it mediates platelet aggregation and adhesion to the vascular endothelium, which is the first step in thrombus formation. It is therefore plausible that levels of vWF are more representative of the extent of endothelial damage in the whole vascular system rather than segmental arterial dysfunction which might be the case for methods that rely on reactive local arterial vasodilatation. In fact, increased levels of vWF have been found in atherosclerotic vascular diseases and in the presence of several of its major risk factors (smoking, hypercholesterolaemia, hypertension, obesity and diabetes). Furthermore, treatment of these risk factors has been shown to lower plasma vWF levels [5], and high plasma vWF levels have been shown to be an independent prognostic marker of death and cardiovascular events. Moreover, plasma markers measurement is relatively cheaper, easier and more readily available, with good reproducibility and low inter- and intra-observer variability, when compared to observer-dependent techniques such as FMD, PBF or BFI measurements. Indeed, as a plasma marker with such advantageous properties, vWF would be ideal as a screening tool in large population-based epidemiological studies.

However, the next question is whether a significant relationship exits between plasma vWF level and FMD? Our recent pilot study on 89 hypertensive patients (78 men; mean age 64 years, S.D. 8.4; mean BP 167/91 mmHg) has suggested that such a relationship does exist (Spearman’s, \( r = -0.517, P<0.001 \)). Furthermore, using

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scanning electron microscopy, we have also shown a significant correlation between the severity of atrial endothelial/endocardial damage and increasing plasma vWF levels [6]. Accordingly, in a 4-month randomised double blind comparison study of pravastatin and placebo in patients with vascular disease and hypercholesterolaemia, plasma vWF, total cholesterol and LDL-C levels were significantly reduced in patients treated with pravastatin, when compared to baseline (untreated) levels [7]. Thus, plasma markers such as vWF would be an alternative assessment of endothelial damage/dysfunction in studying the ‘ancillary’ effects of lipid-lowering agents, and perhaps Malik et al. [1] may have such data to complement their study.

References


