Editorial

Microvessel haemodynamics: interesting news which is not NO news?

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Visceral obesity, a key factor of the metabolic syndrome and clinically to be recognized as an 'apple-shape' habitus and an increased waist circumference, is a strong predictor of cardiovascular events. There is a staggering increase in the prevalence of obesity in westernized societies in conjunction with an increase in type 2 diabetes and (sub)clinical atherosclerosis. From a clinical point of view, many regard type 2 diabetes as a vascular disease to express the seriousness of the ultimate atherosclerotic sequelae of the metabolic syndrome. From a pathophysiological point of view, there may be common mechanisms to explain both metabolic and vascular consequences of obesity.

It has been well established that both metabolic defects (insulin resistance—impairment of normal insulin-sensitive tissues to respond adequately to physiological concentrations of insulin) and haemodynamic defects (e.g. reduction in myocardial flow reserve or reduction in agonist-stimulated forearm blood flow) are present in subjects with visceral obesity and diabetes mellitus. Efforts trying to find a link between these modalities resulted in the concept of haemodynamic/metabolic coupling. The endothelium is an obvious candidate to provide this link.

Most research has focused on the endothelium as a first line of defence against atherosclerosis. Endothelium-derived nitric oxide plays a key role in vascular homeostasis and has been attributed many anti-atherogenic properties. NO is the most important vasodilator in conduit vessels such as the epicardial coronary arteries and the brachial artery. Reduced NO-dependent vasodilation in these conduit vessels is present in patients with obesity, type 2 diabetes and atherothrombosis, and predicts cardiovascular events. Many pharmacologic and non-pharmacologic interventions that reduce cardiovascular risk also improve NO-dependent vasodilation. Thus, restoration of NO bioavailability is a rational clinical target for therapeutic intervention.

Could NO be relevant for the concept of metabolic/haemodynamic coupling? In 1990 Baron and colleagues postulated that insulin increases blood flow to skeletal muscle in conjunction with augmented glucose disposal in this tissue and that this action of insulin was impaired in insulin resistant states such as obesity.1 They suggested that increased delivery of hormone and substrate enhances insulin’s overall effect. This proved to be a contentious issue. Although there is cumulating evidence that physiological insulin concentrations increase bulk flow to muscle tissue, it remains to be established that this haemodynamic effect leads to increased glucose disposal. Vasodilators such as nitroprusside and adenosine increase total blood flow but do not result in enhanced glucose uptake. In addition, it has been established that the contribution of NO to the vasodilative potential decreases as the vessels become smaller in size while the small arteriolar and capillary networks are vital for muscle metabolism. These lines of evidence suggest that NO-dependent vasodilation does not result in increased substrate oxidation.

Conceptually, microvessels are a more likely site to be involved in haemodynamic/metabolic coupling than large vessels. Endothelium-derived hyperpolarizing factor (EDHF) is a more important contributor to vasorelaxation in microvessels than NO. We showed that bradykinin is a endothelium-dependent activator of vascular smooth muscle relaxation in forearm resistance vessels independent of nitric oxide and prostacyclin.2 In conjunction with the assumption that haemodynamic/metabolic coupling partly underlies impairment of substrate metabolism in skeletal muscle in insulin resistant subjects, Vigili de Kreutzenberg et al. hypothesized that obese subjects with insulin resistance have EDHF-dependent rather than NO-dependent vascular...
dysfunction in forearm microvessels. In 10 obese subjects they showed impairment of forearm vessel vaso-relaxation to bradykinin during nitric oxide synthase and cyclooxygenase inhibition while the vasodilatory response to nitroprusside, an exogenous NO donor, was intact. Therefore, these new data strongly suggest that not NO but EDHF is primarily involved in abnormal microvessel vasorelaxation. The importance of these findings are related to the fact that EDHF-dependent vascular dysfunction is present in obesity, an early stage in the development of type 2 diabetes and vascular complications. In order to elucidate the relationship between EDHF-dependent vasodilation and haemodynamic/metabolic coupling further, future studies are needed to address whether EDHF-dependent vasodilation is related to the degree of insulin resistance and how EDHF-dependent vasodilation is affected by dietary habits before the onset of obesity.

The identity of EDHF remains enigmatic. Crucial events in EDHF-induced vasodilation are an increase of endothelial [Ca\(^{2+}\)] and opening of potassium channels leading to endothelial hyperpolarization. Although the term EDHF implies a factor released from the endothelium, such as potassium or products of the P450 monooxygenase pathway, leading to vascular smooth muscle hyperpolarization and vasorelaxation, signals from the endothelium to vascular smooth muscle cells via myo-endothelial gap junctions have also been proposed. Vigili de Kreutzenberg et al. addressed the question which steps in the EDHF-mediated signalling pathways could be involved. They showed that there is a defect in potassium conductance in obesity, and more specifically, this defect appears to involve the inwardly rectifying potassium channels.

It is tempting to extrapolate these new findings in non-cardiac muscular tissue to the heart. Patients with type 2 diabetes are also characterised by myocardial insulin resistance and subjects with obesity and type 2 diabetes have a reduced myocardial flow reserve. The microvasculature is the main determinant of myocardial flow reserve and therefore it is tempting to speculate that EDHF-dependent vasodilation plays an important role in microvascular function of the heart. Human studies focusing on this issue are scarce but if impaired EDHF-dependent vasodilation in the human heart is present in type 2 diabetes, this could have a profound adverse effect on post-ischaemic cardiac remodelling. Whether EDHF-dependent vasodilation also plays a role with regard to haemodynamic/metabolic coupling in the heart is an interesting but, as yet, unresolved issue.

References