PERSPECTIVES

Vasomotion and insulin-mediated capillary recruitment – part of the explanation?

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In the 1990s, Baron and colleagues were among the first to report that insulin dilated resistance vessels and increased skeletal muscle blood flow. They further suggested that a defect in insulin's action to increase blood flow to insulin-sensitive tissues contributed to insulin resistance (Baron *et al.* 2000). More recently it has been shown that insulin increases microvascular perfusion in skin and skeletal muscle, and that impairment of insulin-mediated microvascular dilator responses in skeletal muscle decreases glucose uptake. The functional increase in microvascular flow has been investigated extensively by Clark and colleagues (for review see Clark, 2008) who have argued that insulin-mediated recruitment of capillaries, in the absence of increases in bulk flow, is indicative of a redirection of blood flow from a non-nutritive to a nutritive route, an argument that has been hotly disputed in recent years (Poole *et al.* 2008).

In the most recent paper from this group in *The Journal of Physiology* (Newman *et al.* 2009), insulin-induced changes in muscle blood flux have been explored in an animal model of acute insulin resistance, using laser Doppler flowmetry (LDF), a widely used and generally non-invasive technique, to measure intramuscular blood flow. They go on to explore vasomotor activity in the microvascular bed by analysis of the component frequencies of the LDF signal using a Wavelet transform. These periodic oscillations in the LDF signal have been attributed to the influence of heart beat (spectral peaks at 0.6–2 Hz), respiration (0.15–0.6 Hz), myogenic activity in the vessel wall (∼0.05–0.15 Hz), sympathetic activity (∼0.02–0.05 Hz), and endothelial activity (∼0.008–0.02 Hz) (Kvandal *et al.* 2006). Using this analysis Newman *et al.* find that insulin acts to increase the ∼0.1 Hz, assumed myogenic component of vasomotor activity in muscle. They further show that both muscle microvascular flow and myogenic activity are depressed in the α-methylserotonin-induced acute insulin resistant state, and that this attenuation in insulin-induced microvascular flow is accompanied by reductions in glucose uptake in the muscle. From this, Newman *et al.* suggest that recruitment of microvascular flow by insulin may in part involve action on the vascular smooth muscle to increase vasomotion to thereby enhance perfusion and glucose uptake in skeletal muscle, and that this is impaired in acute insulin resistance. These new data are among the first to show a direct link with vasomotion and insulin, though others have drawn this conclusion from studies in insulin-resistant states such as obesity (e.g. O'Brien *et al.* 1999; de Jongh *et al.* 2008).

Vasomotion was originally defined as the rhythmic oscillations in vascular tone due to changes in smooth muscle constriction and dilatation. It has been commented upon since the earliest days of microscopical observation (Jones, 1852), and its assessment in muscle, indirectly using LDF, is well established (Oude Vrielink *et al.* 1987). In contrast to the recent work of Newman *et al.*, these authors, using a similar preparation but using intravital microscopy as well as LDF to identify red cell-perfused capillaries at rest and during reactive hyperaemia, showed no evidence for recruitment of arterioles or capillaries. To evaluate these findings we may need to return to the concept of recruitment and its definition – perfusion of a greater number of vessels (physical recruitment) or reduced periodicity of cyclic perfusion (temporal recruitment), both of which would lead to greater blood flow, substrate delivery, and effective capillary exchange surface area. It can be argued that with a minimal 10-fold range in red blood cell velocity among capillaries together with increased microvascular diameter during hyperaemia, changes in volume flow to explain substrate delivery/effective exchange surface may be accommodated by the existing capillary bed without the need to 'recruit' more vessels. The physical characteristics of the muscle in question may affect the extent of perfusion heterogeneity, e.g. being maximal in phasically active muscles with regional differences in intramuscular pressure. However, the mainstay of the argument for recruitment is the assumption of nutritive and non-nutritive vascular (capillary?) beds – an increasingly common assumption, for which there is little or no anatomical evidence (Grant & Wright 1970). In addition, to be functionally relevant this would require metabolic control to be located within vessels rather than mitochondria of the host tissue, in violation of most biochemical evidence.

Notwithstanding this, the association between insulin-mediated increases in muscle blood flow, by whatever means, and 'downstream' glucose uptake remains controversial. As described above, it is accepted by many that insulin at physiological levels acts to increase capillary exchange surface area. Whether this is a result of capillary 'recruitment' and/or alterations in flow pattern due to vasomotion has yet to be fully elucidated. The work by Newman *et al.* published recently in *The Journal of Physiology* provides a further insight into this phenomenon, and suggests a novel role for the myogenic response in an animal model of acute insulin resistance. However, the important question that remains to be answered is how, in insulin-resistant individuals, does impaired insulin action result in a decreased delivery of glucose, insulin and other metabolites to muscle fibres? Whether microvascular dysfunction contributes to and exacerbates insulin resistance, or whether microvascular dysfunction has an insulin sensitivity-independent action, to regulate glucose concentrations, is presently uncertain.

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Poole DC, Brown MD & Hudlická O (2008). *J Appl Physiol* **104**, 891–893 (and subsequent point-counter point discussion).