Say NO to hypoperfusion!

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AUTOREGULATION is defined as the capacity of an organ or tissue to maintain a constant blood flow in the face of a change in perfusion pressure, while metabolism is unchanged. Under normal physiological conditions, large proximal arteries contribute little to the total resistance of a particular vascular bed. However, when atherosclerosis causes a conductance artery to narrow so that over ~70% of the luminal cross-sectional area becomes obliterated, such a stenosis results in a significant increase in proximal resistance and can cause a decrease in distal arterial perfusion pressure. Under these conditions, autoregulation will act to maintain flow distal to the stenosis.

The phenomenon of autoregulation within cardiac and skeletal muscle has been amply demonstrated in experimental animal studies (see Refs. 4 and 13 for further reading). In contrast, the ability to restore blood flow in response to hypoperfusion in contracting skeletal muscle of humans remains unclear. Thus studies using external pressure to reduce limb blood flow during rhythmic exercise have produced conflicting results (3, 9, 12). Moreover, an important limitation of studies into autoregulation in human skeletal muscle is that the external pressure cuff that is commonly used to create the stenosis, and which encompasses the entire arm under study, simultaneously compresses the venous system, thereby impeding venous outflow and hence increasing microcirculatory pressures. To overcome this limitation, Casey and Joyner in a recent study in the Journal of Applied Physiology (2) introduced an alternative and very elegant experimental approach to study autoregulation in the human forearm. For this purpose, the authors inserted a small balloon catheter into the brachial artery to reduce blood flow to contracting forearm muscles, which mimics the clinical situation of a proximal artery stenosis (without a venous obstruction) much closer than the earlier approach using a pressure cuff around the arm.

In the current issue of Journal of Applied Physiology, Casey and Joyner (1) employed this model to investigate the contribution of nitric oxide (NO) to the temporal changes in flow and conductance during forearm hypoperfusion by partial balloon inflation during handgrip exercise. Inflation of the balloon during exercise resulted in an initial decrease in brachial artery flow and conductance, which (despite maintained balloon volume and hence stenosis severity) both gradually recovered to preinflation levels within 40–50 s. Interestingly, forearm vascular conductance stayed slightly below baseline levels during steady-state conditions, suggesting that autoregulation may be less than perfect in human skeletal muscle under conditions of hypoperfusion (2, 3, 9).

One remarkable feature of the intravascular balloon model is that, following an initial decrease, brachial artery pressure gradually recovered toward preinflation levels. The partial restoration of poststenotic pressure was not due to loss of stenosis severity, as confirmed with echography, but was likely due to recruitment of collateral vessels in the elbow region. As a result the distal pressure stayed only ~10% below preinflation pressure level, which, through passive distension of the microvasculature, is likely to have contributed to the simultaneous increase in forearm vascular conductance and to the restoration of forearm blood flow. Another potential concern is that as flow through the collateral vessels is not captured in the flow measurements in the proximal brachial artery, this may have resulted in an underestimation of the actual forearm blood flow and vascular conductance. However, in their initial study (2), the authors validated the brachial artery flow measurements with plethysmography under resting conditions and found qualitatively similar responses to balloon inflations using both techniques. Nevertheless, in view of the rather modest steady-state changes in distal brachial pressure and forearm conductance, it would be of great interest to apply more severe degrees of stenosis and hence more severe brachial artery pressure reductions in future studies to interrogate the autoregulatory capacity of human skeletal muscle over a wider range of perfusion pressures.

The vasodilator mechanisms in the microcirculation that underlie autoregulation distal to a stenosis remain incompletely understood but likely include the myogenic response of the microcirculation and all the mechanisms that are involved in vasodilation in response to increased metabolic needs, including endothelial factors and metabolic messengers released from the muscle. The present study (1) shows for the first time that inhibition of NO synthase with N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA) blunted the magnitude of restoration of forearm blood flow and vascular conductance during exercise in the presence of a stenosis by 10–20%. Since L-NMMA was infused distal to the balloon it is unlikely that L-NMMA reached the collateral arteries and produced vasoconstriction in these vessels. Hence the changes in forearm vascular conductance responses to balloon inflation produced by NO synthase inhibition most likely represent changes in conductance of the forearm microvasculature. These observations are in good agreement with earlier observations in exercising dogs, in which inhibition of NO synthase aggravated myocardial hypoperfusion distal to a coronary artery stenosis as a result of vasoconstriction in the distal coronary microcirculation (5).

Unfortunately, the present study (1) assessed only the role of NO, without exploring the contribution of other endothelial factors (prostaglandins, endothelium-derived hyperpolarizing factors, or endothelin) or muscle metabolites (adenosine) to the recovery of forearm vascular conductance.
Interestingly, it has been shown that endothelin production is lower in the active muscles compared with inactive muscles of exercising humans (10). It therefore remains to be explored whether the vasodilator effects of NO are direct vasodilator effects or whether these are mediated in part through inhibition of endothelin production, similar to what has been described in the porcine coronary (11) as well as the systemic and pulmonary circulations (7). In the present study, L-NMMA blunted the fractional recovery of forearm vascular conductance by only 20%. These findings suggest that other (endothelium derived) vasodilators are still able to compensate the loss of NO in restoration of forearm blood flow during exercise, and therefore that forearm vascular control may follow a nonlinear redundancy design similar to what has been described for the canine coronary circulation (6, 8). Thus other factors involved in the vasodilator response to exercise in the hypoperfused forearm remain to be determined.

Notwithstanding these minor limitations, the present study (1) is important as it is the first to provide evidence for a role of NO in the autoregulatory blood flow responses of contracting human skeletal muscle. The observation that a loss of NO contributes to the vasodilator response in the microcirculation distal to a stenosis of a proximal artery may have important clinical implications as it suggests that patients with endothelial dysfunction are likely to be more susceptible to hypoperfusion and ischemia during exercise in vascular regions distal to a stenosis (figure 1).

REFERENCES
