

EDITORIAL COMMENT

Capillary Blood Flow Abnormalities in the Skeletal Muscle and Microvascular Complications in Diabetes

Lessons That Cannot Be Learned From Larger Vessels*

Thomas R. Porter, MD

Omaha, Nebraska

The diagnosis of diabetes mellitus (DM) carries with it many serious consequences, the most serious of which is coronary artery disease (1). The outcome of diabetic patients with coronary artery disease is significantly worse than that of nondiabetic patients. In particular, it is the subset of diabetic patients that develop microvascular complications that is at greatest risk for myocardial infarction, left ventricular dysfunction, and death (2). In this issue of the *Journal*, Womack et al. (3) use high-resolution contrast-enhanced ultrasound (CEU) to examine capillary blood flow responses to handgrip exercise in diabetic patients. A defective capillary blood volume response was observed almost exclusively in the DM patients who had developed microvascular disease. Unlike microvascular complications, however, this defective capillary response was unrelated to the duration of disease.

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The study involved measurements of forearm contrast intensity during a continuous infusion of a commercially available ultrasound contrast agent. This group and others have already demonstrated that defective skeletal capillary blood flow responses to insulin occur in obese hyperinsulinemic subjects (4,5). In the present study, the authors discovered that the increase in skeletal muscle plateau contrast intensity (which reflects capillary blood volume) after mild or moderate isometric handgrip was significantly lower only in DM patients with microvascular complications. These abnormalities were observed despite no differences in brachial artery blood flow

responses in the diabetic and control subjects to the same degree of exercise. Their findings raise important questions as to whether defective capillary blood volume responses to exercise and insulin may play a role in the pathogenesis of microvascular complications.

Most of the data from this study, however, would appear to indicate that the defective skeletal muscle capillary responses were a consequence of microvascular disease and not a cause. For example, when a 2-cohort comparison was used, there did not even appear to be a trend in abnormal capillary responses in the DM patients without microvascular complications. If abnormal capillary blood volume responses were responsible for microvascular complications, one would have expected some of the DM patients without microvascular complications to exhibit defective blood volume responses to exercise. Second, the DM patients with microvascular complications also had greater levels of serum triglycerides, blood viscosity, and levels of inflammation. Although the differences in capillary blood volume responses between DM patients with and without microvascular complications remained significant after adjustment for each of these variables, it is possible that each of these variables play a role in causing the abnormal capillary blood flow responses.

Larger studies may be needed to further elucidate the role defective capillary blood volume responses have in the pathogenesis of microvascular disease. Individual responses were not reported in the study, and even if they were, the small number of patients in the microvascular disease group prevents us from defining a relationship between capillary blood volume reserve and microvascular complications. Nonetheless, CEU is a bedside technique that supplies high-resolution data on both capillary blood volume and flow response and, thus, it may permit us to quantify these measurements in larger patient cohorts.

In addition, CEU measurements of skeletal blood flow responses to exercise will allow us to assess the effects of interventions. The authors of this article have already demonstrated in small animal studies that DM is associated with defective capillary blood volume responses to hyperinsulinemia and that these defective responses in animal models can be partially reversed with the administration of angiotensin-converting enzyme inhibitors (6). The role of exercise therapy and various hypoglycemic agents also can potentially be evaluated with CEU to determine whether improvements in capillary blood volume responses occur in response to any of these therapies and if such improvements are associated with stabilization or even prevention of microvascular complications. The work of Womack et al. (3) demonstrates that examining larger vessel responses will not be sufficient in detecting and monitoring these pathologic vascular responses that occur in DM. Rather, CEU will be the preferred method by which defective skeletal muscle blood flow responses to exercise can be elucidated,

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From the University of Nebraska Medical Center, Omaha, Nebraska.

and subsequently used, to investigate and quantify responses to therapy.

Reprint requests and correspondence: Dr. Thomas R. Porter, University of Nebraska Medical Center, 981165 Nebraska Medical Center, Omaha, Nebraska 68198-1165. E-mail: trporter@unmc.edu.

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Key Words: diabetes mellitus ■ contrast ultrasound ■ microvascular dysfunction ■ muscle perfusion ■ microbubbles.