Can we use surrogate vascular beds for evaluating endothelial function of the coronary vasculature in patients with cardiac allografts?

Chelif Junor1 and Kevin C. Dellsperger1,2

Cardiology Division, Departments of Internal Medicine1 and Medical Pharmacology and Physiology,2 University of Missouri, Columbia, Missouri

A LANDMARK STUDY in vascular biology almost 30 years ago described the essential role of the endothelium as a mediator of vasodilator response to acetylcholine (4). Since then many studies have been performed in an effort to understand this complex organ. Endothelial function plays a pivotal role in the maintenance of vascular hemostasis. Endothelial dysfunction is now thought to play an integral role in the pathogenesis and clinical course of most cardiovascular disorders. Several investigators (5) showed that coronary endothelial dysfunction is associated with an increase in cardiovascular mortality. Furthermore, they found that these pathological states were associated with an overall increased level of oxidative stress. One of these conditions, acute hyperglycemia, is associated with increased oxidative stress and impaired endothelial function in the peripheral vasculature (7).

In a study presented in this issue of the American Journal of Physiology-Heart and Circulatory Physiology, McNulty et al. (8) sought to identify the coronary vascular response to “postprandial” hyperglycemia in patients that have received cardiac transplantation. Their study attempted to characterize coronary arterial response to acute hyperglycemia by observing changes following stimulation with endothelium-dependent and -independent agonists. This study was well performed by the investigators and had several strengths. First, the investigators carefully controlled hyperglycemia throughout the protocol. Second, the study evaluated both endothelium-dependent and -independent responses in the left anterior descending coronary artery. Third, state-of-the art methods were used to measure coronary vascular responses to the endothelium-dependent and -independent agonists. Fourth, correlation of oxidative stress with coronary vascular responses was performed by measurements of thiobarbituric acid reactive substances (TBARS), plasma free fatty acids, and malondialdehyde. Finally, the data were very consistent among the study patients as best illustrated by Fig. 1 of the study. Whereas the magnitude of effect was variable, the directional changes were quite consistent among those studied.

Despite these and other strengths, there were many important questions left unanswered. Was the response due to measurements in a single vessel? While carefully performed, the authors analyzed coronary dilation and blood flow in a single proximal segment of the left anterior descending artery. It is thought that endothelial dysfunction occurs in a time-dependent fashion and can be heterogeneous within the circulation of a single heart or allograft (2, 9, 10). The directional consistency of the McNulty et al. data suggested that this would not be the case.

Were the findings universally applicable to a “normal” population of patients? In one of the first studies evaluating the effects of acute hyperglycemia on the endothelium, Kawano et al. (7) showed suppression of flow-mediated endothelium-dependent vasodilation in brachial arteries of normal, impaired glucose tolerant, and diabetic patients. Importantly, during hyperglycemia, all patients, including normal patients in this study (7), had increase in a surrogate plasma marker ofvascular wall lipid peroxidation and oxidative stress TBARS. This study carefully measured indexes of oxidative stress as well as vascular responses. It should be emphasized that despite marked changes in the relative “oxidative” environment with hyperglycemia, there was not an effect on coronary vascular responses.

Did the investigators study the correct vessels within the coronary vascular bed? In the present study, coronary regional (macro- vs. microvascular) differences in endothelial function may have been present but were not systematically examined. Though this point may suggest the study represents an inadequate assessment of endothelial response, the consistent finding of acetylcholine-induced vasodilation in all of the patients contradicts that assertion.

Did the investigators miss the timing of potential abnormalities in patients with cardiac allografts? Fang et al. (3) showed that high baseline oxidative stress manifest in some form of early endothelial dysfunction in cardiac transplant patients. They showed that autoantibodies to oxidized LDL were more predictive of endothelial dysfunction within one year of cardiac transplant (3). It is possible that the early posttransplant period may represent a more vulnerable time frame where microvascular endothelial dysfunction is more easily affected by acute oxidative stress. The current study was performed an average of 3.3 yr posttransplant. If the timing of abnormalities were the issue, we would have anticipated more variability in the responses given that some patients were studied earlier posttransplantation than others in the population.

Could drug therapy have altered responses? It is also possible that the level of baseline oxidative stress may be blunted by statin therapy in the current patient population. Statins have been shown to have direct effects on NADPH oxidase regulation. The study cannot address this important possibility, and it will take additional carefully designed studies to evaluate the effects of statins in this patient population.

This study together with prior evaluations raises the question: Can we use a surrogate vascular bed to evaluate the coronary vasculature? For the last decade, investigators used a surrogate vascular bed, predominately the brachial vascular bed, to imply there was generalized endothelial impairment, and in particular, abnormalities in coronary vascular endothelial function (1). Despite a high systemic oxidative state resulting from acute hyperglycemia, the authors did not show a...
corresponding impairment of endothelium-dependent coronary vasodilation with acute hyperglycemia in the cardiac transplanted patient population. These unexpected and contrary findings call into question the relevance of using a peripheral vascular bed to suggest coronary vascular abnormalities. A definitive answer to this incongruence is not clearly apparent. However, possible explanations for the incongruence of coronary vascular responses with prior peripheral vascular studies are as follows. This study used cardiac transplant patients where their allografts are “deennervated” hearts. Whereas the autonomic nervous system contribution to coronary blood flow is minimal in comparison to local mediators, one cannot discount a small potential impact of the autonomic nervous system on coronary macro- and microvascular regulation that could have altered results. Additionally, most of the prior studies that showed abnormal responses were in diabetic patients. Thus the ability of diabetic subjects to compensate for increased oxidative stress may not have been as vigorous as in “normal” patients.

In summary, the study by McNulty and colleagues presents several interesting and provocative findings. First, the study raises many issues as to the comparability of responses of the coronary vascular bed in patients with cardiac transplantation compared with those without transplantation. Second, these studies raise important questions to the use of a surrogate vascular bed to predict coronary vascular responses. Third, additional studies evaluating current medical therapy (i.e., statins) on endothelium-dependent and -independent responses in this patient population is needed. Finally, investigations need to continue to identify the control mechanisms in the heart of cardiac transplant patients when exposed to environments of high oxidative stress.

REFERENCES