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LETTERS TO THE EDITOR

Coronary Endothelial Dysfunction in the Early Months After Heart Transplantation

We read with interest the report by Aptecar et al. (1) that early after heart transplantation, coronary vasodilator effects of bradykinin are preserved despite abnormal response to intracoronary injection of acetylcholine. This absence of alterations to the vasodilator action of bradykinin is neither a new nor an unexpected finding. In cardiac transplant recipients with normal angiography, this preservation of the coronary response to endogenous vasodilator peptides has already been reported not only for substance P (2), as mentioned by Aptecar et al. (1), but also for bradykinin (3). In contrast to acetylcholine and serotonin, bradykinin and substance P are potent endothelium-dependent vasodilators. Their endothelial vasodilator effects are not counterbalanced by a direct constriction mediated by the stimulation of smooth muscle receptors.

As pointed out in our previous study (3) also performed in the early months following transplantation, the hypersensitivity to the vasoconstrictor effect of serotonin is not directly related to a decrease in endothelium-derived nitric oxide (NO) availability. Indeed, acute L-arginine supplementation in transplant recipients, as compared to hyperlipidemic patients, did not modify the hypersensitivity to serotonin (3).

Immune processes such as cytokines produced by activated macrophages and T cells play a major role in these abnormal responses, probably even in the absence of rejection episodes (4). First, this inflammatory response may promote the release of endothelin, an endothelium-derived contracting factor (EDCF) able to potentiate the vasoconstriction to various amines (5) and seems to play a major role in the development of the graft vasculopathy (6,7). Second, cytokines may also activate the inducible isoform of nitric oxide synthase (iNOS), promoting the release of potent oxidants such as superoxide anion and peroxynitrite (8). In line with this hypothesis, the coronary vasoconstriction to acetylcholine was enhanced in patients with rejection episodes cited in Aptecar et al. (1).

Hence, from available data, it is unlikely that the coronary endothelial NO synthase pathway is impaired early after heart transplantation. The abnormal responses to serotonin and acetylcholine are probably related to the presence of EDCF and/or changes in smooth muscle receptors. Therefore, a direct action on the endothelial NO synthase via an enhanced bradykinin availability by long-term angiotensin-converting enzyme (ACE) inhibition, as suggested by Aptecar et al. (1), should not markedly improve the endothelial function.

Furthermore, according to animal studies (9), NO formation is already enhanced by activation of iNOS in the early months after transplantation. This enhanced NO availability may explain the elevated resting coronary blood flow observed in the transplant recipients of Aptecar et al. (1), which is congruent with previous studies (10).

Therefore, therapeutical approaches, aiming at counteracting these abnormalities, with endothelin antagonists or/and antioxidants, seem more appealing than with ACE inhibitors, which may worsen cyclosporine-induced nephrotoxicity.

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Diurnal Rhythms and Hemostatic Factors in Atrial Fibrillation

In a recent publication, Li-Saw-Hee et al. (1) measured plasma concentrations of soluble p-selectin, von Willebrand factor, soluble thrombomodulin and fibrinogen at 6-h intervals in patients with atrial fibrillation and detected no variation in levels of these hemostatic factors over a 24-h period. On the basis of these results, it was concluded that atrial fibrillation was associated with a loss of diurnal variation in these hemostatic factors, and that this could contribute to the high risk of stroke and thromboembolic complications in this condition. However, we believe that there are a number of issues related to the experimental design and data interpretation of this study that cast doubt on the validity of these conclusions.

First, measurement of hemostatic factors was performed at 6-h intervals: 12 midnight, 6 AM, 12 noon, and 6 PM. While this may