examiner, and because laboratory screening may prove to be less expensive than repeated examination by medical specialists (particularly as less expensive PCR based screening assays are put to clinical use) (7), we believe that routine testing of this population can also be justified.

Testing in infancy can avoid the frustration that families often experience as they try to understand why the cardiac defect occurred, whether it will recur in subsequent pregnancies and whether other clinical problems, such as feeding disorders, relate to the cardiac disease. The 22q11 deletion syndrome provides parents with a unifying diagnosis and can preempt visits to different sub-specialists in search of new diagnoses. Most importantly, we hope that this discussion will heighten physicians’ awareness of the 22q11 deletion syndrome. Until more conclusive cost benefit analyses and clinical studies can better define appropriate screening guidelines, the decision to test for a 22q11 deletion in the cardiac patient must be considered by each physician according to the facilities and expertise available to them.

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REFERENCES


Role of Nitric Oxide in Venous and Arterial Graft Failure

We read with interest the paper from Chello et al. (1) reporting greater neutrophil adhesion in segments of human saphenous vein (SV) than internal mammary artery (IMA), which they ascribed to different endothelial nitric oxide (NO) formation in the two vessels. This, according to the authors, explains the superior early and long-term patency of the IMA as a conduit for coronary artery bypass surgery (CABG) when compared with the SV. Although we agree that the IMA is a preferable conduit, and that the SV produces less endothelial NO than arteries (2), we have a number of concerns over the methodology as well as the clinical implications of this study.

First, the authors presented no data as to the amount of endothelium present in the SV or IMA segments investigated. In our experience, this can be very variable and despite precautions taken at harvesting, there is always some degree of endothelial loss induced by buffers, constriction, dissection and mounting in culture plates. Because this could vary between artery and vein, quantitating endothelial loss should be essential. The evidence that the neutrophils adhered to endothelial cells (and not subendothelium) because less NO is released by SV compared with IMA was that vessels pretreated with sodium nitroprusside or L-arginine reversed the adhesion of neutrophils whereas L-NAME enhanced it. However, the concentrations of the agents used was very high (1–10 mM). Because these drugs are taken up into the interstitial space of vessel segments, they are probably released subsequently into the fluid containing the neutrophils and therefore affect the neutrophils directly. For example, nitroprusside stimulates cyclic GMP formation at 100 nM, which is 1/10,000th lower than the concentration used by Chello et al. One way around these above uncertainties would be to remove the endothelium by rubbing and then to assess neutrophil adhesion using the same treatments as for “intact” segments.

The overall question raised by this study is what role endothelial NO plays in early or late vein graft failure. In a study on porcine vein grafts, removal of the endothelium result in early thrombotic occlusion (3) but had no effect on neointima formation, supporting the idea that exposure of the subendothelium, per se, and not endothelial NO formation, is important in early thrombosis. In the same model, endothelial NO synthase (nNOS) in SV grafts, although initially low, is rapidly upregulated to similar levels of arterial nNOS within one month (2).

Finally, it follows from the study of Chello et al. (1) that the early administration of NO-donors may be beneficial in obviating graft failure in CABG. However, this should be approached with caution because NO elicits several potentially dangerous effects, including apoptosis of endothelial cells, promotion of VSMC proliferation and reactions with...
superoxide (generated by neutrophils) to produce peroxynitrite, a highly toxic free radical (4).

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REPLY

We thank Dr. Ascione et al. for their interest in our study (1), in which internal mammary arteries (IMA) and saphenous veins (SV) were obtained from patients undergoing coronary bypass surgery. Care was taken during harvesting of the blood vessels not to touch the inner surface of the blood vessels. The SV were harvested by using a no-touch technique, and the dilation procedure was avoided, whereas IMA were harvested as pedunculated graft. Each graft was sectioned carefully to minimize artifact induced by handling and cutting, particularly in the intimal surface. Presence of endothelium was evaluated by light microscopy in six nonadjacent sections of each graft, and endothelial cell confluence was observed over the entire examined surfaces. The concern that elevated concentrations of NO donors could affect directly neutrophil function is not justified for at least two reasons. First, after incubation with L-arginine and nипride, the vessel segments were repeatedly washed and transferred with fresh Krebs-Henseleit solution immediately before the neutrophil adherence assay. Second and most important, previous studies have clearly demonstrated, using an experimental model similar to that used in our study, that exogenous NO donors do not directly affect the ability of neutrophil to adhere.

Niu et al. (2) demonstrated that incubation of neutrophils with sodium nitroprusside (1.0 mmol/L) for 30 min did not modify the amount of their adhesion to endothelium. In a similar fashion, Ma et al. (3) demonstrated that incubation of PMNs, rather than vessel segments, with L-arginine (3 mM) for 20 min, did not significantly decrease PMN adhesion to coronary artery segments subject to 20 min of reperfusion, indicating that the inhibitory effect of L-arginine on PMN adherence occurs on the endothelium.

Many studies in the literature clearly show that, other than technical failures, acute thrombosis and delayed intimal hyperplasia are the two processes most closely linked with vein graft failure.

However, caution should be recommended in extending the result of animal studies (4,5) to the humans. Actually, although the differences between the porcine data and human vein data might be attributed to the different time periods that the veins are arterialized (7 to 12 years for humans, much less for pigs), it appears equally likely that heterogeneity of endothelium-dependent responses between different species have a significant role because the relevance of porcine vein graft data to human bypass is uncertain. It may be hypothesized that the short period of time (four weeks) involved in the animal vein graft study cited by Dr. Ascione (4), does not allow for the return of endothelial function seen in human vein grafts. Moreover, the anatomic position of the vein graft in the arterial circulation affects the phasic composition of flow. Grafts in the peripheral arteries, like the model used by Dr. Angelini (4), receive flow primarily in systole, whereas graft in the left coronary circulation receive flow principally in diastole. The different flow patterns and shear stress may significantly influence the results. A recent clinical study (6) has in fact revealed that, when compared with human saphenous veins studied before implantation, venous coronary bypass grafts develop somewhat more pronounced endothelium-dependent vasodilation to acetylcholine after implantation, although the potency of these responses is still markedly less than in arterial grafts.

Finally, we would like to point out that, as stated in the introduction of the report, the main purpose of our study was to evaluate the relation between the pattern of neutrophil-endothelial adhesion in SV and IMA and the endothelial production of NO. No therapeutic solutions have been proposed. We therefore agree with Dr. Ascione and coworkers by suggesting prudence in administering NO donors for the prevention of graft failure.

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REFERENCES