While this study supports the role of PCI over tPA, it was not specifically designed to compare balloon angioplasty with stenting or the use of abciximab with its omission in the setting of acute myocardial infarction. The larger multicenter, randomized trial CADILLAC addressed these issues specifically, but the results are not yet published.[5] Preliminary data suggest an extremely low overall mortality rate of 1.5% at 30 days in this study, without any significant difference between balloon alone, stenting alone, and the use of balloon or stenting with abciximab. If the final trial results confirm these preliminary results, then the routine use of stents and abciximab may need to be questioned. Improved outcomes, in both Schömig and colleagues' study and the CADILLAC trial, are more likely due to the rapid reperfusion that was achieved at these centers (within 60 minutes in the Schömig study) and the very high TIMI 3 perfusion rate (96% in Schömig, 98% in CADILLAC). The key message from this report and previous studies is that optimal reperfusion is the central element in obtaining maximum myocardial salvage and a low 6-month event rate, no matter how achieved.

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Angiogenesis

The Role of Nitric Oxide in Atherogenesis

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Nitric oxide (NO) is known to be important in the control of vasomotor tone and as an inhibitor of atherogenesis. Not until recently, however, has the role NO plays in angiogenesis been defined. A number of angiogenic factors up-regulate the expression of endothelial NO synthase (eNOS) and stimulate the release of NO. Vascular endothelial growth factor (VEGF) stimulates the release of NO, and secretion is enhanced by NO's precursor, L-arginine.

NO seems to play a critical role in angiogenesis. Endothelial cells, when stimulated by VEGF or fibroblast growth factor (FGF), release NO and form 3-dimensional capillary-like structures. These effects are blocked by the NOS antagonist N-nitro-L-arginine methylester (L-NAME). An endogenous antagonist to NOS, called asymmetric dimethylarginine (ADMA), has been discovered recently and has been shown to compete with L-arginine for NOS. Hypercholesterolemia is associated with the elevation of ADMA. This paper explores the role of ADMA as an endogenous antiangiogenic factor.

The experiment was performed in normal (E+) and in apolipoprotein E–deficient hypercholesterolemic (E-) mice using a subcutaneous implantable disk angiogenesis system. Fibrovascular growth was assessed as an index of angiogenesis after 2 weeks. Basal and FGF-stimulated angiogenesis was impaired in E-mice, a finding associated with an elevation in plasma ADMA level. This inhibition was reversed by oral administration of L-arginine. Direct addition of ADMA to the disk also inhibited angiogenesis in a dose-dependent manner.

Angiogenesis Is Impaired by Hypercholesterolemia: Role of Asymmetric Dimethylarginine

Jang JJ, Ho H-KV, Kwan HH, et al.
Circulation. 2000;102:1414-1419.

This basic science report brings together several pieces of information that shed light on the pathogenesis of angiogenesis, showing that hypercholesterolemia inhibits angiogenesis and that ADMA plays a key role. This observation firmly ties together the NO pathway and the ability of the vascular system to regenerate itself at times of ischemia. Exactly how NO can lead to angiogenesis is still largely unknown. Whether angiogenesis supported by NO leads to collateral vessel formation or angiogenesis in the vasa vasorum is under active investigation.

Suggested Reading
1. Hood JD, Meninger CJ, Ziche M, et al. VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. *Am J Physiol*. 1998;274:H1054-H1058.
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