genetic factors with a defined genetic cause, and improved methodology for genotyping will enable rapid and (perhaps) inexpensive identification of individuals with deleterious (and protective) markers. The real challenge will be to:

- perform outcome studies to determine the relative importance of specific genes and alleles;
- identify means to modulate the risks of specific alleles; and
- perform intervention trials to prove the clinical utility of both the tests and the interventions.

**SUGGESTED READING**


**HEREDITARY RISK FACTORS FOR ANEURYSMAL DISEASE**

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Mutations in the gene for fibrillin-1 have been implicated as etiologic in aneurysms associated with Marfan syndrome, but the hereditary risk factors for more common aneurysmal conditions affecting the cerebral arteries and the aorta are uncertain. The present discussion will focus on the abdominal aortic aneurysm (AAA).

The stereotype of the AAA patient is an aging white male smoker with a positive family history for the disease. A recent ultrasound screening study of the siblings of AAA probands reaffirms this profile, with the three leading risk factors being male sex (12× increased risk), family history (4× increased risk), and age (2× increased risk). Another large scale screening study of 73,451 American veterans had similar confirmatory data. The three leading “positive” risk factors for AAs of 3.0 to 3.9 cm were smoking, family history, and age (with odds ratios of 2.72, 1.96, and 1.52, respectively); and the three leading “negative” risk factors were female sex, diabetes, and black race (with odds ratios of 0.62, 0.68, and 0.72, respectively). It is possible that additional associations of AAA (for example, with inguinal hernia3 and with elongation of the internal carotid artery)4 might also reflect hereditary risk factors.

Several candidate genes have been considered and rejected by our group and others. Mutation in the gene for procollagen III cosegregated with AAA disease in one family,5 but further studies revealed that mutation of this gene is an infrequent cause of AAA in a larger population.6 We reported a polymorphism of the gene for TIMP-1 in two of six AAA patients, but the transition was in the third position of the codon. The encoded amino acid was unchanged. The role, if any, for deficiency alleles of alpha-1 antitrypsin is unclear.7

Considering that much recent evidence points to a role for autoimmunity in AAA degeneration, our group reported MHC Class II DR typing on a small group of North Americans (26) of mixed descent. Eighty-one percent of these individuals had a DR allele with phenylalanine residues at positions 31 and 47 of the second hypervariable region; 35% had a double dose of a putative susceptibility allele.7 HLA DR-15 is one of the alleles7 with the above characteristics, and HLA DR-15 has been implicated in a North American population of patients with inflammatory AAA.8 In the more homogeneous population of Japan, DR-15 was detected in 59% of 46 AAA patients versus 28% of 50 control subjects.9 Further study of this population suggested that HLA-DQ3 had a protective effect.

If DR-15 positive and DQ-3 negative are the high-risk serotypes, then 89% of 36 AAA patients had one or both of these features, as compared with 41% of 39 control subjects.10 Although genes among structural matrix proteins, proteinases, and proteinase inhibitors have been the leading candidates to date, the possible role of HLA DR and DQ genes merits more study.

**REFERENCES**

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THE BIOLOGY OF TRANSLUMINAL ANGIOPLASTY
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The purpose of this presentation is to review the effects of transluminal angioplasty on the biology of the arterial wall. The review will first focus on the acute effects of angioplasty on arterial wall structure and function and then focus on the biologic responses that take place in the dilated artery.

Acute effects of balloon angioplasty on the arterial wall

The principle objective of balloon angioplasty is to increase the luminal diameter of the stenotic artery whose diameter was reduced by the presence of an atherosclerotic lesion. The mechanism(s) by which balloon angioplasty increase lumen diameter include (in order of magnitude)

• circumferential stretching of arterial wall producing longitudinal tears of the plaque and internal elastic lamina and irreversibly stretching the collagen fibers of arterial wall
• redistribution of plaque longitudinally
• plaque compression and extrusion of fluid
• embolization of plaque

The acute effects of balloon angioplasty on the arterial wall are summarized below.

Endothelial denudation. Injury/destruction of the endothelium results in a reduction/elimination of the endothelium-derived factors that normally inhibit platelet adhesion/aggregation and thrombus formation (prostacyclin, nitric oxide, plasminogen activators), inhibit recruitment of leukocytes (nitric oxide, low selectin and chemoattractant production), inhibit vascular smooth muscle contraction (nitric oxide, prostacyclin), and inhibit smooth muscle migration and proliferation (prostacyclin, nitric oxide, heparan sulfate).

Plaque disruption. Tearing of plaque exposes underlying thrombogenic surfaces resulting in platelet adhesion, aggregation, and degranulation, which releases factors including platelet-derived growth factor, a potent smooth muscle cell chemoattractant, and mitogen. Plaque disruption also releases tissue factor that activates the extrinsic coagulation pathway leading to the formation of thrombin that promotes both fibrin formation and smooth muscle proliferation.

Medial injury. Balloon dilation of the artery injures and lyses vascular smooth muscle cells and irreversibly stretches elastin and collagen. Depending on the magnitude of the injury, arterial contractility can increase (vasospasm) in response to the release of serotonin from platelets and/or endothelin from injured endothelial cells. Alternatively, contractility can decrease, even to the point of paralysis. Medial injury can increase fluid conductivity and decrease wall thickness, factors that affect arterial permeability to growth factors and cytokines.

Technical factors. A number of technical variables influence the effects of angioplasty on the arterial wall. For example, an increase in the balloon-artery ratio increases arterial stretch, which decreases the likelihood of elastic recoil but also increases the likelihood of arterial injury and cell death. Increasing the duration of balloon inflation, while not causing further changes in passive arterial mechanics, can increase vascular smooth muscle cell injury and decrease contractility.

Responses to angioplasty-induced arterial injury

Platelet deposition. Radiolabeled platelet studies have demonstrated that platelet recruitment begins immediately after angioplasty, peaks in about an hour, and subsides over the next several days. The magnitude of recruitment appears to be directly related to the severity of the injury.

Inflammation. After balloon angioplasty, polymorphonuclear leukocytes and monocytes are attracted to the injured arterial wall. Neutrophil accumulation begins within an hour after angioplasty and continues for days to weeks. Monocyte accumulation begins within a day and peaks 1 to 2 weeks after angioplasty. At least four mechanisms are potentially involved in the recruitment of leukocytes to the site of arterial injury. These include activation...