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Excessive vascular fibrosis predicts early failure of hemodialysis fistulas

Patients with end-stage renal disease require a functional vascular access to receive hemodialysis and prolong their lives. The arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. The AVF is surgically created by connecting a superficial vein to a nearby artery and allowing this vein to enlarge and increase in internal diameter under arterial circulation. Once ready, the enlarged vein (now a fistula) can be cannulated and connected to the dialysis machine to clean the patient's blood, remove water, and balance mineral concentrations. The transformation of the vein to a fistula that can be used for hemodialysis is known as maturation. Unfortunately, maturation fails in 20-40% of AVFs, which exposes the patient to additional surgical risks and life-threatening complications. At this moment, there is no effective treatment to prevent AVF maturation failure.

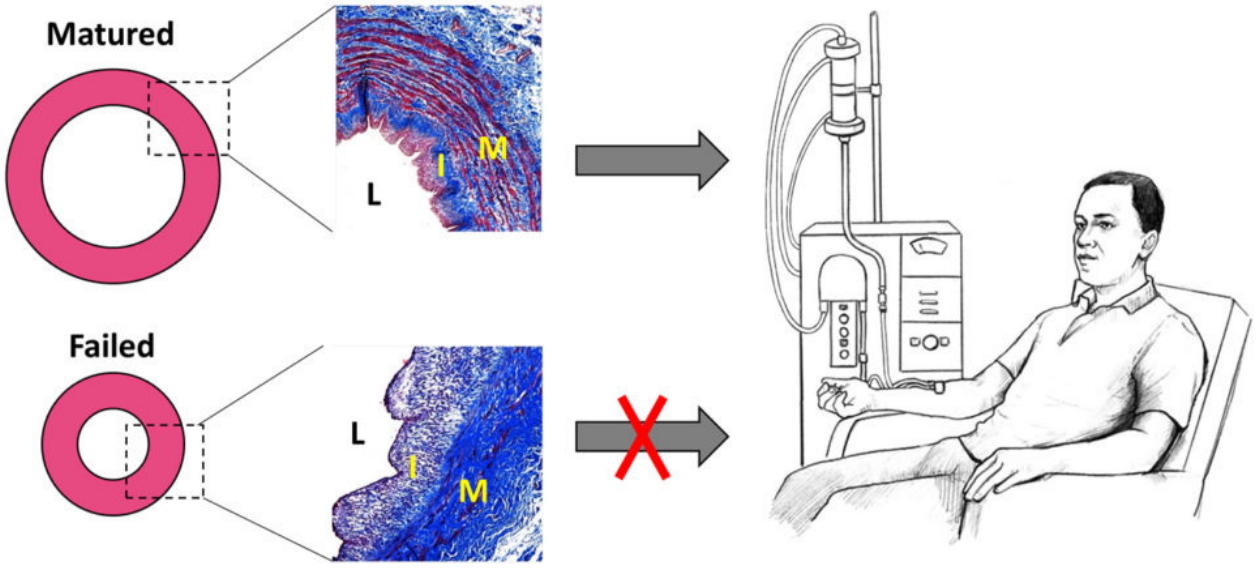

Fig. 1. Schematic illustration of arteriovenous fistulas (AVFs) with successful maturation or failure. The center panel shows representative cross-sections of AVFs that matured or failed after staining with Masson's trichrome for morphometric analysis. Cells stain in red/pink whereas the extracellular matrix stains in blue. Note the increased fibrosis in the media layer of AVFs that failed. L: lumen, I: intima, M: media. The drawing of a patient on hemodialysis was obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Image Library, image N01639.

The biological causes of maturation failure are still unknown. It is known that the wall of veins changes significantly in cellular and extracellular composition after AVF creation. The tunica intima (innermost layer of the vein) increases in thickness in a process known as intimal hyperplasia (IH). Concurrently, the tunica media (muscular layer of the vein) reorganizes as a result of smooth muscle cell (SMC) apoptosis, migration, and turnover of the extracellular matrix (ECM). The composition and organization of the ECM can influence

the ability of the vein to enlarge and mature after access creation. Accumulation of collagen in the fistula wall (fibrosis) may decrease vascular elasticity and distensibility, compromising the high blood flow required for maturation. Our main goal in this study was to determine the contribution of IH versus fibrosis to AVF maturation failure. We measured IH and fibrosis (ECM deposition) in fistulas samples obtained from 115 patients who underwent AVF creation surgery in the upper arm. Surprisingly, fistulas that failed to mature showed significant SMC loss in the media and accumulation of ECM. We found that the more medial fibrosis in fistula samples, the higher the risk of failure of the vascular access. A closer look at collagen organization in the media revealed that circumferential arrangement of collagen fibers around the wall was associated with maturation failure. In addition, while the degree of IH in the fistula was not associated with maturation failure by itself, it did represent an important exacerbating factor in the presence of high medial fibrosis. In other words, fistulas with high medial fibrosis and high IH were more likely to fail than those with high fibrosis but low IH.

Our study demonstrated the importance of a proper balance between remodeling of the media layer and growth of the intima for successful vein maturation after fistula creation. A better understanding of the molecular drivers of both IH and fibrosis will help pave the way toward preventive therapies for AVF maturation failure in the future.

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