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Similar degree of intimal hyperplasia in surgically detected stenotic and nonstenotic arteriovenous fistula segments: a preliminary report

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ABSTRACT

Background. Intimal hyperplasia has been historically associated with improper venous remodeling and stenosis after creation of an arteriovenous fistula. Recently, however, we showed that intimal hyperplasia by itself does not explain the failure of maturation of 2-stage arteriovenous fistulas. We seek to evaluate whether intimal hyperplasia plays a role in the development of focal stenosis of an arteriovenous fistula.
Methods. This study compares intimal hyperplasia lesions in stenotic and nearby nonstenotic segments collected from the same arteriovenous fistula. Focal areas of stenosis were detected in the operating room in patients ($n = 14$) undergoing the second-stage vein transposition procedure. The entire vein was inspected, and areas of stenosis were visually located with the aid of manual palpation and hemodynamic changes in the vein peripheral and central to the narrowing. Stenotic and nonstenotic segments were documented by photography before tissue collection (14 tissue pairs). Intimal area and thickness, intima-media thickness, and intima to media area ratio were measured in hematoxylin and eosin stained cross-sections followed by pairwise statistical comparisons.
Results. The intimal area in stenotic and nonstenotic segments ranged from 1.25 to 11.61 mm^2 and 1.29 to 5.81 mm^2, respectively. There was no significant difference between these 2 groups ($P = .26$). Maximal intimal thickness ($P = .22$), maximal intima-media thickness ($P = .13$), and intima to media area ratio ($P = .73$) were also similar between both types of segments.
Conclusion. This preliminary study indicates that postoperative intimal hyperplasia by itself is not associated with the development of focal venous stenosis in 2-stage fistulas. (Surgery 2017;160:XXX-XXX.)

Introduction

The arteriovenous fistula (AVF) is the preferred access for hemodialysis, because it has better outcomes and lesser incidence of complications than arteriovenous grafts and dialysis catheters.[1,2] The use of arteriovenous fistulas has increased considerably in the United States over the past 2 decades,[3] but the frequency of primary failure remains dramatically elevated.[4,5]

Intimal hyperplasia (IH) is one of the most frequently observed vascular pathologies in patients with failed AVFs,[6-9] but the notion that IH is the main cause of venous stenosis and AVF failure has been challenged by recent retrospective and prospective studies. Allon et al demonstrated that preexisting IH does not increase the risk of the development of stenosis after creation of an arteriovenous access.[10] In addition, a growing body of evidence indicates that neither preexisting nor postoperative IH by itself predisposes to primary failure of an AVF.[6,11]

To further understand the lack of association between the degree of IH and AVF maturation failure, in this study we evaluated whether postoperative IH plays any role in the development of focal stenosis.

Materials and Methods

Study design

This study included 14 patients with end-stage renal disease >21 years old with a planned, 2-stage AVF creation at Jackson Memorial Hospital or University of Miami Hospital. The aim was to compare the degree of IH in stenotic and nonstenotic segments obtained from

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the same AVF. The study design consisted in collecting a biopsy of the native vein during their first-stage operation and discarded juxta-anastomotic AVF tissues at the time of transposition, including stenotic and nearby nonstenotic segments. A single surgeon (M.T.) performed all operative procedures, using preoperative vascular mapping of the upper extremities to plan the AVF.[6] We followed the order of AVF preference recommended by the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative.[12] Veins that were not sclerotic visually and had a diameter ≥3.5 mm as determined by intraoperative measurement using a coronary dilator were used for AVF creation. Patients were followed for 3 months after transposition to assess primary failure. All sections of the study were performed according to the ethical principles of the Declaration of Helsinki and regulatory requirements at both institutions. The ethics committee and Institutional Review Board at the University of Miami approved the study.

Intraoperative assessment of AVF stenoses

At the time of AVF transposition (second-stage operation), the surgeon inspected the entire AVF for areas of stenosis with the aid of manual palpation and hemodynamic changes in the vein peripheral and central to the narrowing. Briefly, the AVF was dissected completely from the anastomosis to the upper arm. Proximal clamping of the AVF (central to the anastomosis) with the fingers resulted in engorgement of the AVF and helped differentiate a spasm from a real stenosis. On visual inspection using 3.5x magnification loupes, focal stenoses appeared typically as hourglass deformities. The AVF was inspected further for a pulse and a thrill. A clinically relevant stenosis was confirmed by the presence of a pulse peripheral to the narrowing followed by a thrill central to the narrowing. Tactile inspection also helped identify a focal stenosis by the presence of sclerosis or thickening in the area compared to the rest of the AVF. The above findings were confirmed using a coronary dilator to estimate the luminal diameter during sample collection. The luminal diameter of a focal stenosis was 3.5 to 4 mm compared to 6 to 9 mm in the rest of the AVF. All stenotic segments were located in the juxta-anastomotic region of the AVF (i.e., in the first 2 cm downstream from the arterial anastomosis).

Definitions

Macroscopic areas of stenosis were defined as the presence of vessel narrowing on intraoperative visual inspection and palpation compared to the normal AVF segment located adjacent to the stenosis (Fig 1).

Specimen collection and processing

Stenotic and nonstenotic segments were documented by photography before tissue collection (14 tissue pairs). The surgeon cut through the focal stenosis and removed a 2 to 3 mm ring where the narrowing looked the most severe. Another 2 to 3 mm ring was collected in the nonstenotic area, not >3 to 5 mm away from the focal narrowing. Tissue biopsies were submerged in neutral formalin immediately after collection, and deidentified and labeled with a numerical code once in the research laboratory. Tissues were processed, paraffin-embedded, and sectioned for histology.

Morphometric analysis

Tissue sections were stained with hematoxylin and eosin for gross histopathologic analysis. Full digital images were acquired with a Visiontek digital microscope (Sakura, Torrance, CA). Morphometric measurements were determined using ImageJ (National Institutes of Health, Bethesda, MD) by 2 independent observers (J.C.D., L.M.) blinded to the patient's clinical characteristics, AVF outcomes, and classification of the tissue sections. These included intimal area and thickness, intima-media thickness (IMT), and intima to media area ratio (I/M). Intimal thickness and IMT were determined as the linear distance from the endothelium to the internal and external elastic laminae, respectively.[13]

Statistical analyses

Pairwise statistical analyses were performed using XLSTAT (New York, NY).

Morphometric measurements were compared using Wilcoxon signed-rank tests and expressed as median and interquartile range.

Results

Demographic, clinical, and AVF characteristics of the study cohort

A total of 14 end-stage renal disease patients were included in the study. Ages ranged from 31 to 77 years (53 ± 12, mean ± SD); 10 patients were African American (71%), and 9 were females (64%). All 14 patients had a diagnosis of hypertension, 10 were diabetic (71%), 4 presented with coronary artery disease (29%), and 1 was diagnosed with congestive heart failure (7%). Brachiobasilic AVFs were created in 12 patients (86%) and brachial-brachial AVFs in the remaining 2 (14%). The median time interval between first-stage and second-stage operations was 92 days (interquartile range 70–126). In agreement with previous observations,[14] 10 AVFs matured successfully (71%) despite the presence of a focal juxta-anastomotic stenosis in all of them.

Comparison of IH between stenotic and nonstenotic segments

The intimal area in stenotic and nonstenotic segments ranged from 1.25 to 11.61 mm^2 and 1.29 to 5.81 mm^2, respectively. There was no significant difference between these 2 groups ($P = .26$; Table). Stenotic cross-sections had maximal intima thickness and IMT in the ranges of 0.36 to 2.29 mm and 0.53 to 2.84 mm, respectively; whereas the maximal intima thickness and IMT values for nonstenotic sections were 0.41 to 1.29 mm and 0.58 to 1.80 mm, respectively. There were no differences in any of these IH parameters between the 2 groups (Table).

Fig 2 demonstrates the degree of similarity in IH between stenotic and nonstenotic biopsies collected from 2 patients. In both

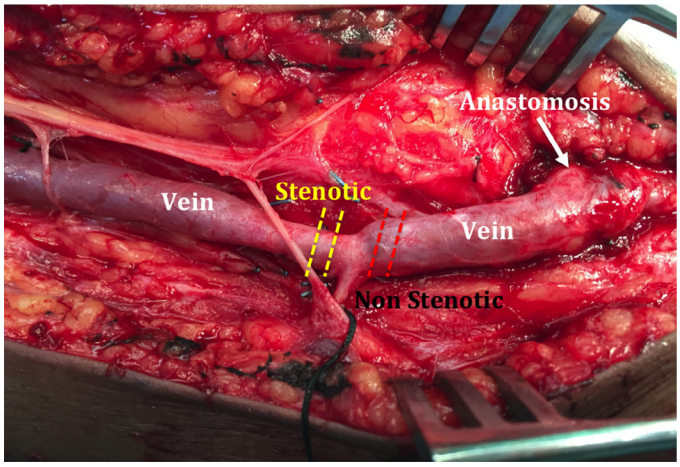

Fig. 1. Photograph of a first-stage brachiobasilic arteriovenous fistula demarcating the locations of the focal stenotic (yellow dashed lines) and nonstenotic segments (red dashed lines) in the outflow segment. (Color version of figure is available online.)

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