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LONGITUDINAL EFFECT OF WALL SHEAR STRESS ON THE AMOUNT OF INTIMAL-MEDIAL THICKENING OF VENOUS WALL IN ARTERIOVENOUS FISTULA

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ABSTRACT

Arteriovenous fistula (AVF) maturation failure is mainly due to venous stenosis characterized by significant amount of intima-media thickening (IMT). Although hemodynamic endpoints are believed to play a crucial role in pathogenesis of venous stenosis, the exact mechanism behind this is unclear. Our *hypothesis* is that longitudinal (temporal) changes of hemodynamic parameters, specifically wall shear stress (WSS), influences amount of IMT in maturation process of AVF. AVFs were created in curved (C-AVF) and straight (S-AVF) configurations between femoral artery and vein of 3 pigs. CT-scans and ultrasound were utilized to calculate WSS at 2D (D: days), 7D, and 28D post-surgery. IMT was measured at 4 histological blocks along the vein of AVFs. It was found that C-AVF underwent outward remodeling characterized by consistent increase in venous diameter and larger IMT. This remodeling process was governed by negative temporal gradient of WSS ($\tau^{\cdot}$) [-0.99 ± 0.60 dyn/cm^2/day]. In contrast, S-AVF underwent inward remodeling characterized by temporal decrease in venous diameter and relatively smaller IMT. This remodeling process was governed by positive $\tau^{\cdot}$ (0.42 ± 0.6 dyn/cm^2/day). In summary, *temporal gradient of WSS influences IMT*. Temporal decrease of WSS in C-AVF resulted in vasodilation and outward growth of wall (favorable to maturation). However, temporal increase in WSS in S-AVF leaded to vasoconstriction and inward growth of wall (detrimental to maturation). Thus, clinically it can be of great importance to surgeons to create AVF in a configuration that can result in favorable hemodynamic parameters and histological end-points.

INTRODUCTION

Arteriovenous fistula (AVF) maturation failure is mainly due to formation of venous stenosis characterized by significant amount of intima-media thickening (IMT) [1]. Among all the factors that may contribute to venous stenosis, hemodynamic parameters of AVF are believed to play a crucial role. Placement of AVF is accompanied by significant increase in wall shear stress (WSS) caused by elevated venous flow rate [2]. Consequently, vessels undergo intensive remodeling processes to maintain WSS within its physiological range. Thus, remodeling is a dynamic process and an understanding of this phenomenon won't be achieved without studying the longitudinal changes of hemodynamic parameters, specifically WSS. In our recent studies [3], using a pig model, we showed that pattern of WSS changes over

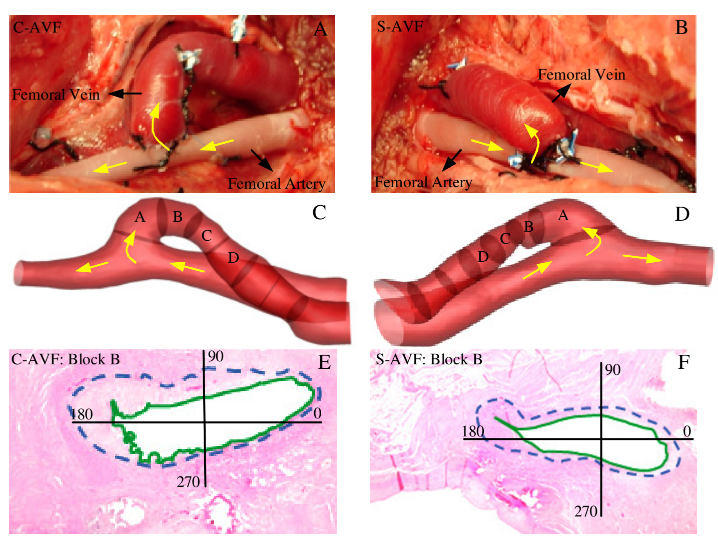

Figure 1. Actual and reconstructed geometry of C-AVF (A, C) and S-AVF (B, D). Arrows show the flow direction. Histology sections stained with H&E for block B of C-AVF (E) and S-AVF (F) of a 28D pig.

time (increase or decrease) have a significant effect on luminal area of AVF (vasodilation or vasoconstriction). Thus, our *hypothesis* in this study is that temporal gradient of WSS can influence the amount of IMT in AVFs with different configurations.

METHODS

AVFs with curved (C-AVF) [n = 3] and straight (S-AVF) [n = 3] configurations (Figs 1A and 1B) were created between the femoral artery and vein, on either limb of 3 pigs. Pigs were sacrificed either at 7D (n = 1) or 28D (n = 2) post-surgery. Details regarding the animal experiment, methods, and CFD analysis were explained in our previous studies [4]. Paraffin embedded AVFs were divided into 4 histological blocks, namely as blocks A to D (Figs 1C and 1D). Using the shrinkage factor of AVFs (ratio of AVF lengths before and after embedding process), in-*vivo* locations of histology blocks were found. Blocks were cut into 4μm sections and stained with H&E (Figs 1Eand 1F). Intima-media thickening (IMT) at each section was evaluated by measuring the distance between intima (green line) and media (blue line) at four quadrants and then averaged for each section.

Characteristics of remodeling process in AVFs were described based on two parameters: A) ΔD_h defined as variation in hydraulic diameter ($D_h = 4A/P$; A: cross-sectional area, P: wetted perimeter) of vein over time ($\Delta D_h = [D_{h\,(28D\text{ or }7D)} - D_{h\,(7D\text{ or }2D)}]$); and B) $\tau^{\cdot}$ defined as variation in WSS levels over time ($\tau^{\cdot} = \frac{WSS_{28D} - WSS_{2D}}{\Delta time}$ and $\tau^{\cdot} = \frac{WSS_{7D} - WSS_{2D}}{\Delta time}$). Positive (or negative) ΔD_h was interpreted as increase (or decrease) in venous diameter over time; thus, the corresponding remodeling process was considered to be outward (or inward) remodeling, respectively. Moreover, positive (or negative) $\tau^{\cdot}$ was interpreted as increase (or decrease) in WSS levels over time.

RESULTS

Effects of temporal gradient of WSS ($\tau^{\cdot}$) on the amount of intima-media thickness (IMT) of venous wall for C-AVF and S-AVF are discussed. Results are presented as mean ± SD.

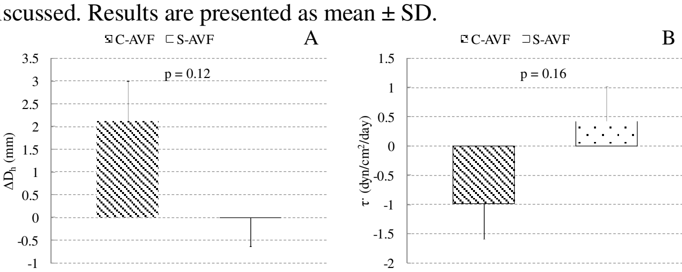

Figure 2. A) Changes in hydraulic diameter of venous segment and B) overall mean of temporal gradient of WSS ($\tau^{\cdot}$) for C-AVF and S-AVF.

Remodeling Characteristics of C-AVF and S-AVF. In order to assess the remodeling process in C-AVF and S-AVF, overall variation of ΔD_h was evaluated for these configurations (Fig 2A). ΔD_h was positive for C-AVF (2.11 ± 0.88 mm); and thus, C-AVF underwent outward remodeling (OR). In contrast, ΔD_h was negative for S-AVF (-0.0012 ± 0.63 mm); and thus, S-AVF underwent inward remodeling (IR). Difference in ΔD_h of two configurations was found to be moderately significant ($p = 0.12$). Also, in order to find the effect of WSS on these remodeling processes, $\tau^{\cdot}$ was measured for C-AVF and S-AVF (Fig 2B). For C-AVF, $\tau^{\cdot}$ was negative (-0.99 ± 0.60 dyn/cm^2/day) showing OR, while being positive (0.42 ± 0.6 dyn/cm^2/day) for S-AVF showing IR; being moderately significant ($p = 0.16$). Thus, OR in C-AVF was governed by decrease in WSS over time, while increase in WSS over time for S-AVF resulted in IR.

Effect of Local WSS Levels on Venous Wall Thickness. Variation of IMT with respect to local WSS levels at sacrifice day for C-AVF and S-AVF are shown in Fig 3A. For C-AVF, an inverse correlation ($p < 0.05$; $r = 0.53$) was found between IMT and WSS. For C-AVF showing OR, larger amount of IMT was found at regions with normal WSS (~ 5 dyn/cm^2). Thus, in these regions, IMT increased as WSS decreased to maintain the physiological conditions of vessel. In contrast, for S-AVF a direct correlation ($p < 0.03$; $r = 0.61$) was found between IMT and WSS. For S-AVF showing IR, larger amount of IMT was found in the regions of high WSS which can be associated with formation of stenosis at these sites.

Effect of AVF Configuration on Intima-Media Thickness. In order to assess the effect of AVF configuration on the amount of IMT, this parameter was plotted at each histology blocks for C-AVF and S-AVF (Fig 3B). It was found that IMT in C-AVF (32.42 ± 12.28, 43.80 ± 11.27, 61.24 ± 11.27, and 79.50 ± 11.27 units for blocks A to D, respectively) was larger in comparison to IMT in S-AVF (32.21 ± 17.37, 59.51 ± 12.65, 39.62 ± 12.65, and 46.20 ± 12.65 units for blocks A to D, respectively). Thus, C-AVF with OR gained larger amount of IMT in outward direction, while reversed pattern was found for S-AVF.

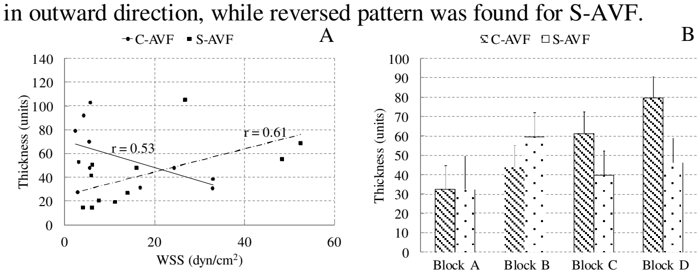

Figure 3. A) Variation of venous wall thickness with respect to local WSS levels at the sacrifice day for C-AVF and S-AVF. B) Average thickness of vessel wall at each histology block in C-AVF and S-AVF.

CONCLUSIONS

We showed that surgical configurations of AVF have a significant effect on the remodeling processes of AVF by inducing different longitudinal patterns of WSS. *C-AVF* underwent *outward remodeling* as its venous luminal diameter consistently increased over time, while achieving relatively larger amount of IMT. This remodeling pattern of C-AVF was characterized with *consistent decrease in WSS over time*. In contrast, *S-AVF* underwent *inward remodeling* as its luminal diameter decreased over time, while the amount of IMT was smaller in this configuration as compared to C-AVF. This remodeling pattern of S-AVF was characterized by *consistent increase in WSS levels over time*. Finally, from the clinical prospective, this study emphasizes the role of surgical configurations of AVF on its maturation process. It can be seen that creating AVF with larger radius of curvature (as in C-AVF as compared to S-AVF) can have a positive impact on maturation of AVF. Consequently, proper translation of these results under clinical settings may have a great impact on the life of hemodialysis patients.

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