ABSTRACT

Venous stenosis is one of the primary causes of the arteriovenous fistula (AVF) maturation-failure and is characterized by vasoconstriction and significant intima-media thickening (IMT). Although the hemodynamic endpoints are believed to play a crucial role in the pathogenesis of venous stenosis, the exact mechanism behind this is unclear. Our hypothesis is that the changes in the pressure drop over time ($\Delta p'$) can influence the remodeling factors in AVFs: changes in luminal diameter ($\Delta D_h$) and IMT. Curved (C-AVF; n = 3) and straight (S-AVF; n = 3) AVFs were created between the femoral arteries and veins of 3 pigs. CT-scan and ultrasound were utilized to numerically evaluate the flow field, and thus pressure drop in AVFs at 2D (D: days), 7D, and 28D post-surgery. For each AVF, IMT was also measured at 4 histological blocks along the vein. For the C-AVF, the pressure drop consistently decreased over time (from 18.32 mmHg at 2D to 4.58 mmHg at 28D), while opposite trend was found for the S-AVF (from 12.91 mmHg at 2D to 24.49 mmHg at 28D). The $\Delta p'$ was negative at all the histology blocks for C-AVF which showed the reduction in the resistance over time due to dilation (positive $\Delta D_h$) and outward hypertrophy of the venous segment (positive $\Delta D_h$/IMT). In contrast, $\Delta p'$ was mostly positive for the S-AVF which showed the increase in the resistance due to vasoconstriction (negative $\Delta D_h$) and inward hypertrophy (negative $\Delta D_h$/IMT). Thus, measuring $\Delta p'$ at the successive post-surgery time points can provide important information on the remodeling behavior of AVFs. Also, creating AVFs in a surgical configuration that can result in negative $\Delta p'$ and thus favorable remodeling could influence the life expectancy of the dialysis patients.

INTRODUCTION

Arteriovenous fistula (AVF) maturation-failure is mainly due to formation of venous stenosis characterized by vasoconstriction and significant amount of intima-media thickening (IMT) [1]. Hemodynamic parameters are believed to play a crucial role in AVF maturation or failure. Therefore, introducing an accessible hemodynamic measure that can predict the type of remodeling in AVFs is of great clinical importance. We have recently shown that variation of wall shear stress (WSS) over time can provide important information on the remodeling behavior of the AVFs [1]. However, complexities in the WSS measurements on regular basis are not trivial. In this study, variation in the pressure drop over time, which can be measured clinically, is assessed to predict the remodeling behavior in AVFs.
METHODS

As an extension to our previous study [1, 2], the data was re-assessed to explore the effect of pressure drop on the remodeling behavior of AVFs. A brief description of our previously published research is presented here [1, 2]. AVFs with curved (C-AVF; \( n = 3 \)) and straight (S-AVF; \( n = 3 \)) configurations (Figs 1A-B) were created between the femoral arteries and veins on the 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 [2]. The paraffin embedded AVFs were then divided into 4 histological blocks, namely as blocks A to D (Figs 1C-D). Blocks were cut into 4µm sections and stained with H&E (Figs 1E-F [1]). Intima-media thickening (IMT) at each section was evaluated by measuring the distance between intima (green line) and media (blue line) at four quadrants. These four values were then averaged for each section and considered as the average IMT of each block.

RESULTS

The longitudinal effects of pressure drop (\( \Delta p \)) on the remodeling behavior of the venous segment of the C-AVF and the S-AVF were studied. The Tukey’s test was performed to ascertain the significance of differences among the two configurations. A value of \( p < 0.05 \) was considered to be statistically significant. Results are presented as mean ± SE.

Parameter Definition. The \( \Delta p \) at each block was calculated based on the difference between the time-averaged pressure at the inlet of the proximal artery and the average pressure along the corresponding block. The \( \Delta p^\prime \) was defined as the slope of changes in the \( \Delta p \) between the 2D and the day of sacrifice \( \frac{\Delta p = (\Delta p_{2D} \text{ or } 7D - \Delta p_{2D})}{\text{time difference}} \). Moreover, the \( \Delta D_h \) at each block was defined as the difference between the hydraulic diameters \( (D_h = 4A/P; A: \text{cross-sectional area, } P: \text{wetted perimeter}) \) at the sacrifice day from the corresponding baseline value \( (\Delta D_h = (D_{h,2D} \text{ or } 7D) - (D_{h,2D})) \). In addition, \( \Delta D_h/\text{IMT} \) which is a non-dimensional parameter and represents both effects of \( \Delta D_h \) and IMT within each block was studied.

Variation of \( \Delta p \) over Time. Average changes in the \( \Delta p \) within the venous segments of the C-AVF and the S-AVF over time are shown in Fig 2. For C-AVF, the \( \Delta p \) decreased from 18.32 ± 6.43 mmHg at 2D to 14.87 ± 6.43 mmHg at 7D, and then to 4.58 ± 7.84 mmHg at 28D. In contrast, the \( \Delta p \) in the venous segment of the S-AVF consistently increased from 12.91 ± 6.40 mmHg at 2D to 19.42 ± 6.40 mmHg at 7D, and then to 24.49 ± 7.84 mmHg at 28D. The difference between the pressure drops of the C-AVF and S-AVF was not significant at 2D and 7D, while it achieved margin significance at 28D (\( p = 0.12 \)).

Longitudinal Effect of \( \Delta p \) on Remodeling. The variation of the \( \Delta D_h \) of each block within the venous segment of the C-AVF and the S-AVF with respect to the corresponding changes \( \Delta p^\prime \) are shown in Fig 3A. The \( \Delta p^\prime \) was negative for all the blocks of C-AVFs, while both positive and negative \( \Delta p^\prime \) were observed for S-AVFs. The \( \Delta D_h \) had a direct correlation with the \( \Delta p^\prime \) (\( R^2 = 0.48 \)) for C-AVF. The highest \( \Delta D_h \) occurred at the blocks with smaller magnitude of \( \Delta p^\prime \), whereas the lower \( \Delta D_h \) were associated with larger magnitude of \( \Delta p^\prime \).

In contrast, the \( \Delta D_h \) had a significant inverse correlation with the \( \Delta p^\prime \) (\( R^2 = 0.94 \)) for S-AVF. Relatively larger \( \Delta D_h \) occurred at the blocks with negative \( \Delta p^\prime \), while the blocks with smaller or negative \( \Delta D_h \) were associated with positive \( \Delta p^\prime \).

The correlation between the \( \Delta p^\prime \) and \( \Delta D_h/\text{IMT} \) for different blocks within the venous segments of C-AVFs and S-AVFs is shown in Fig 3B. The \( \Delta D_h/\text{IMT} \) is a parameter that specifies the direction of thickening in the vessels and also the relative growth of wall thickness as compared to the amount of vasodilation. The \( \Delta D_h/\text{IMT} \) had a strong direct correlation (\( R^2 = 0.5 \)) with \( \Delta p^\prime \) for C-AVF. For this configuration, the blocks with smaller magnitude of the \( \Delta p^\prime \) had the largest \( \Delta D_h/\text{IMT} \). In these blocks the \( \Delta D_h \) was also the largest, while the amount of IMT was relatively smaller as compared to the blocks with larger magnitude of \( \Delta p^\prime \). The latter blocks showed smaller amounts of the \( \Delta D_h/\text{IMT} \) for C-AVF. For S-AVF, \( \Delta D_h/\text{IMT} \) and \( \Delta p^\prime \) showed a strong inverse correlation (\( R^2 = 0.71 \)). The blocks with positive \( \Delta p^\prime \) had negative \( \Delta D_h/\text{IMT} \), while opposit was found for negative values of \( \Delta p^\prime \).

DISCUSSION

The reduction in the pressure drop within the venous segment of the C-AVF over time (negative \( \Delta p^\prime \)) was accompanied by vasodilatation (positive \( \Delta D_h \) and outward hypertrophy (positive \( \Delta D_h/\text{IMT} \)). This can be associated with the autoregulatory response of the C-AVF to reduce the resistance and therefore, increasing the blood flow to the vein. In contrast, the resistance to the blood flow, which was assessed by the \( \Delta p \), increased over time for S-AVF. This was translated into the vasocostriction (negative \( \Delta D_h \)) and inward hypertrophy (negative \( \Delta D_h/\text{IMT} \)), which are the two important factors that have adverse effect on the remodeling and can result in venous stenosis.

CONCLUSIONS

We showed that surgical configurations of AVF have a significant impact on their remodeling processes. Also, the temporal changes in the pressure drop within the venous segment of an AVF have a strong correlation with the remodeling factors such as alteration in the luminal diameter (\( \Delta D_h \)) and the direction of intima-media thickening (\( \Delta D_h/\text{IMT} \)). Thus, pressure drop at different time-points, which can be obtained under clinical setting, can be evaluated to assess the favorable or adverse remodeling in AVFs. Increase in pressure drop over time could be an indicative of venous stenosis (inward hypertrophic remodeling), while the decrease in pressure drop can be translated into an outward hypertrophic remodeling.

REFERENCES