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VASCULAR REMODELING OF ARTERIOVENOUS FISTULA

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INTRODUCTION

Arteriovenous (AV) fistula failure is a major clinical problem for the 350,000 patients currently on hemodialysis in the United States. The reasons for this failure are mainly attributed to venous stenosis due to neointimal hyperplasia together with a possible failure of vascular dilatation [1]. Despite the magnitude of the clinical problem, there are currently no effective therapies for AV fistula failure. We believe that this is due to a lack of knowledge about the mechanisms involved in both neointimal hyperplasia and vascular dilatation in the specific context of AV fistulae.

Although it has been shown by several studies that the hemodynamic environment is primarily responsible for dilatation at early stages, the exact mechanism of flow mediated vascular dilatation in AV fistulae is still unclear [2]. In our preliminary studies we have documented the pattern of WSS in two different configurations at the time of surgery [3] and compared the results with the histology at 42 days when there was maximal stenosis [4]. In order to understand the factors responsible for vascular dilatation or constriction, it is important to study the progression of the remodeling phenomenon in the same animal in a temporal fashion.

Thus, this study *aims* to describe the methodology of measurement techniques that can be used to establish a complete hemodynamic data at different time points in a pig model with two different configurations of AV fistulae. We believe that such approach will facilitate the correlation of hemodynamic data with histological findings and thus help in identifying the best possible fistula configuration that will result in favorable remodeling and potentially a reduction in clinical AV fistula failure.

METHODS

The sequential steps that were adopted to evaluate hemodynamic and anatomic parameters in a single animal are shown in Fig 1. Two different anatomical configurations namely, curved and straight AV fistulae were created in the groin region between the femoral artery and femoral vein of a Yorkshire pig (Pig # CT-8), with left side having a curved configuration and the right side having a straight configuration. The hemodynamic end point: flow rate (Q) was obtained using Doppler ultrasound whereas the anatomic endpoint: 3-dim configurations and diameter were obtained using the CT angiography at different time points (2d, 7d, 14d and 28d; d: days). Repeated doppler ultrasound measurements were performed at the

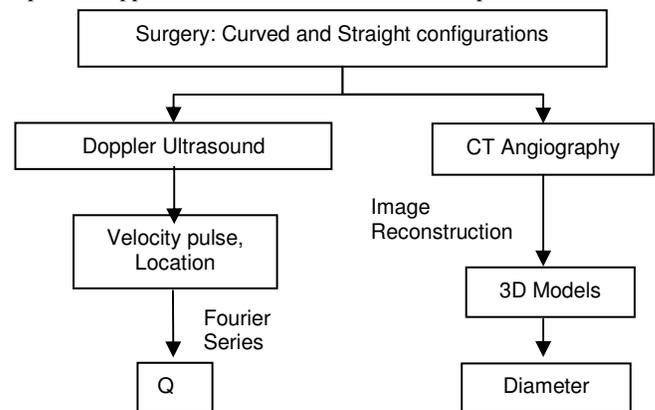


Fig 1: Flow chart for acquisition of hemodynamic and anatomical parameters

proximal artery (PA), distal artery (DA) and the proximal vein (PV) to obtain instantaneous velocities in the AV fistula circuit. The data was collected at the time of surgery (0d, d: days) and at 7d, 14d and 28d time-points, after which the animal was sacrificed. Representative doppler velocity pulses at the PA and DA locations in our AV fistula measurements for a single animal at the time of surgery are shown in Figs 2A and 2B, respectively. The *fourier series* (Fig 2C) was fitted to the averaged blood flow profiles at each time point for the PA and DA locations. Fourier constants that represent the flow at these locations were obtained for each time-point. Representative fourier flow pulse, with standard errors, from our measurements for PA and DA locations for one particular measurement is shown in Fig 2C.

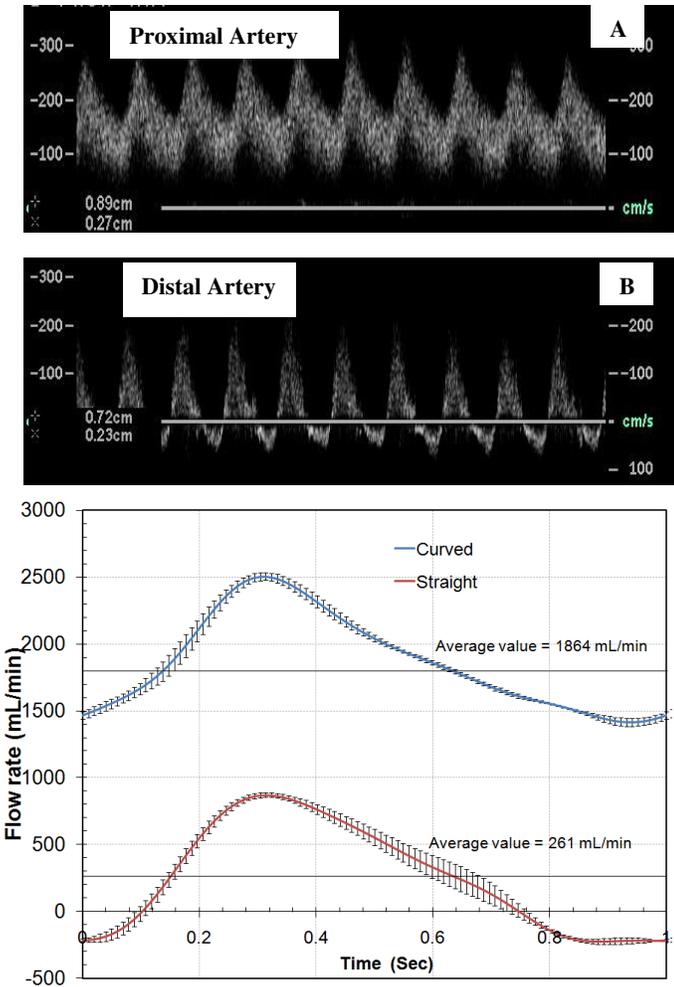


Fig 2: Experimental velocity measurements at PA (Fig 2A), DA (Fig 2B) and average flow rate pulse with standard errors (Fig 2C)

A 64 slice CT scanner (Siemens medical systems, USA) was used to scan the AV fistulae at 2d, 7d and 28d. The series of 2-Dim DICOM images from the CT scans were used to reconstruct the 3-Dim geometry of the two different configurations of AV fistulae at the different time points. The 3-Dim mesh geometries were created from the CT images using image processing algorithm and are described in Fig 3 for 2d and 28d for the curved and straight configurations respectively.

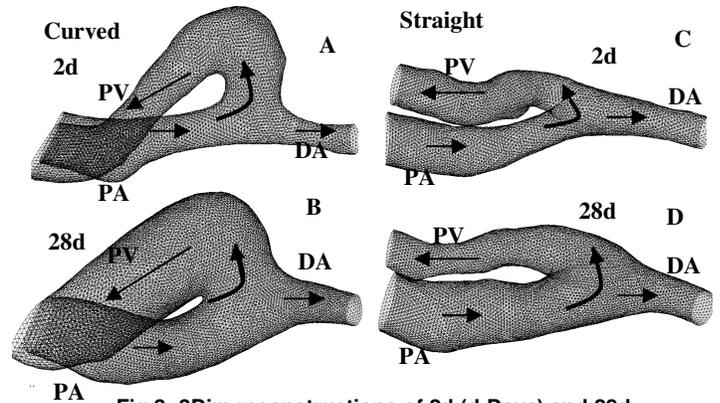


Fig 3: 3Dim reconstructions of 2d (d:Days) and 28d curved and straight AV fistulae

RESULTS AND DISCUSSION

The diameter variation at a cross-section, which is at 11 mm from the AV anastomosis, is shown in Fig 4 for both curved and straight configurations. Most importantly, there was a significant dilatation in curved configuration as compared to the straight configuration at 28d (overall increase of 140% for curved vs decrease of 2% for the straight). In addition, the flow measurements performed in a single pig AV fistula with two different anatomic configurations are reported in this study. The flow balance was checked in the AV fistula circuit at all time points (0d, 7d, 14d and 28d) for this single pig data. The difference in values (between PA and DA+PV) of the flow balance was within an average 13%. It is envisaged that with additional data points from more animals the flow balance will be improved. Hence, these hemodynamic end points will facilitate in the understanding of the remodeling phenomenon in AV fistula. We believe that these initial studies could be the first steps towards the scientific use of hemodynamic data for the reduction of clinical AV fistula dysfunction.

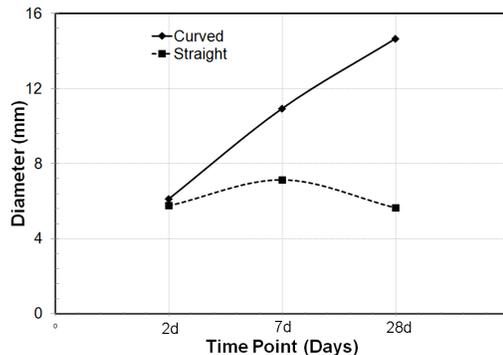


Fig 4: Diameter variation for the curved and straight configurations with time at 11mm from the anastomosis

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