Measurement of hemodynamic and anatomic parameters in a swine arteriovenous fistula model

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Abstract: Purpose: Although arteriovenous fistulae (AVFs) are currently the preferred mode of permanent hemodialysis access they do have significant problems due to initial non-maturation and a later venous stenosis. These problems appear to have been exacerbated following a push to increase AVF prevalence in the US. The reasons for both AVF non-maturation and the later venous stenoses are unclear but are thought to be related to abnormal hemodynamic wall shear stress (WSS) profiles. This technical note aims to describe the successful development of measurement techniques that can be used to establish a complete hemodynamic profile in a pig model with two different configurations of AVF.

Methods and results: The curved and straight AVF configurations were created in an in vivo pig model. Flow and pressure in the AVFs were measured using the perivascular flow probes and Doppler flow wires while the pressure was recorded using a pressure transducer. The anatomical configuration was obtained using two different approaches: a) combination of intravascular ultrasound (IVUS) and angiograms, (b) 64 slice CT angiography. 3D models were reconstructed using image processing and computer modeling techniques. Numerical calculations were then performed by applying the measured flow and pressure data into the configurations to obtain the hemodynamic WSS profiles.

Conclusion: The described methodologies will allow the calculation and optimization of WSS profiles in animal models. This information could then be translated to the clinical setting where it would have a positive impact on improving the early maturation rates of AVFs as well as reducing the late venous stenoses. (J Vasc Access 2008; 9: 28-34)

Key words: Arteriovenous fistula, Hemodynamics, Measurement techniques, Computer modeling

INTRODUCTION

There are currently two main forms of permanent hemodialysis (HD) access, the polytetrafluoroethylene (PTFE) dialysis access graft and the native arteriovenous fistula (AVF) (1). Of these two forms of access, AVFs have a far lower infection and thrombosis/stenosis rate and are the preferred mode of access for HD. Despite these advantages, AVFs have two major problems which are (a) primary non-function or a “failure to mature” and (b) later venous stenoses (2). In particular, the push to increase fistula prevalence rates in the US has resulted in “failure to mature” rates of between 23-46% (3-5) as a result of fistula placement in patients with inadequate veins or demographic risk factors. Although the exact reasons for these two complications are unclear, it is likely that hemodynamic factors (especially the wall shear stress (WSS) profile) play an important role in determining AVF success or failure. Thus in order to be able to place successful AVFs in the vast majority of our patients (particularly those with inadequate veins or other risk factors), it is essential to be able to measure hemodynamic parameters. In addition clinically, AVFs are created in a number of different configurations which influence the pattern of WSS profiles. Thus it is necessary to develop methodologies for different case specific configurations of AVFs in in vivo models. The current study aims to describe the successful development of techniques that can be used to establish a
complete hemodynamic profile in the *in vivo* AVF setting. This technology could be used to identify clinically relevant linkages between anatomical configuration, WSS profiles and vascular stenosis, allowing us to optimize AVF configurations.

**METHODS AND RESULTS**

(a) **Surgical technique:** Yorkshire Cross pigs weighing 50 kg were used for the creation of AVFs. Animals were acclimatized for at least 3 days before surgery. All animals were treated with aspirin from the day prior to surgery until the day of sacrifice. Pigs were anesthetized and intubated with a combination of xylazine, telazol and atropine. Isoflurane was used for maintenance anesthesia. An AV anastomosis was created between the femoral artery and vein just below the inguinal ligament using continuous 6/0 polypropylene sutures (6). Two different surgical configurations: curved and straight were created (Fig. 1a, b). The fascia and skin were then closed in layers using 3/0 Dexon and silk. Buprenex was used for post-operative analgesia as needed. Fistula patency was confirmed immediately after surgery and then every 3 days by auscultation. Flow, pressure and internal diameter measurements (at the time of placement and sacrifice) were carried out (see below).

(b) **Flow measurements**
1. **Flow measurements at the time of surgery using perivascular probes:** Perivascular flow probes (Transonic systems Inc, Ithaca, NY) were used to measure blood flow in the different anatomical regions: proximal artery, distal artery and proximal vein. These comprise plastic probes that are placed snugly around the vessel followed by the liberal application of an acoustic coupling agent (Fig. 2). The mean and pulsatile volume flow rates of blood were recorded by a Transonic Flow meter (Transonic systems Inc, Ithaca, NY) on to a computer, using a data acquisition system (National Instruments, TX). Figure 3 shows representative flow values from the proximal artery (mean: 780 mL/min - as shown by arrow #1), distal artery (mean: 110 mL/min, as shown by arrow #3) and the proximal vein (mean: 650 mL/min, as shown by arrow #2). In particular, it may be noted that the reversal of diastolic flow occurs in the distal artery following AVF creation. The fact that we were able to achieve a flow balance within the AVF circuit demonstrates the strength of this technique. Interestingly, the blood flow in the proximal vein increased by about seven-fold, to approximately 700 mL/min within 30 min of the anastomosis being created, from a pre-surgery venous flow of 100 mL/min.

2. **Flow measurements at the time of surgery using intravascular flow wires:** Although it is easy to measure flow with the Transonics probes at the time of surgery,
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this is almost impossible after 5-7 days because of the aggressive fibrosis that occurs around the AVF. Thus, in order to measure blood flow within different parts of the AVF at the time of sacrifice (between 2 and 42 days), we placed sheaths in both the carotid and internal jugular veins, using an open cut down approach (Fig. 4). It is also possible to place such sheaths percutaneously. A multipurpose catheter was then advanced over a 0.035” wire (Boston Scientific Corp, MA) into the proximal artery of the AVF. The position of the catheter was confirmed on an angiogram (Fig. 5). A Doppler flow wire of 0.014” diameter (Volcano Corp, CA) was then introduced through the sheath and positioned in the proximal artery. Average peak velocity (APV) of the blood was then measured over a period of 12-14 cycles based on ultrasound technique (Fig. 6a). The process was then repeated following advancement of the catheter into the distal artery. An identical technique was used to advance a multipurpose catheter through the internal jugular sheath down into the proximal vein of the AVF (with angiography confirmation). A flow wire was then positioned in the proximal vein region of the AVF for flow measurements (see Figure 1 for a description of proximal artery, distal artery and proximal vein).

(c) Intravascular pressure measurements: These were measured at the time of surgery and sacrifice by positioning a catheter at the sites of measurement - either proximal artery (Fig. 6b) or proximal vein (Fig. 6c). The end of the catheter was then connected to an external pressure transducer which measured the prox-

Fig. 3 - Perivascular flow measurements: representative flow values from the PA, DA and PV using flow probes immediately after AVF creation.

Fig. 4 - Post surgery flow and pressure measurements: this can be done through the placement of percutaneous sheaths through which flow and pressure wires can be directed into the AVF.

Fig. 5 - Angiography: angiogram showing straight (a) and curved (b) AVF.
imal artery and venous pressures through the fluid filled sensors connected to the ComboMap system (Volcano Corp, CA).

A complete hemodynamic profile requires knowledge not only of the flow velocity within different regions of the fistula, but also knowledge of the internal diameter and the anatomical configuration of the AVF. We obtained this information in two ways: (a) angiography for anatomical configuration and intravascular ultrasound (IVUS) for internal diameter, (b) 64 slice CT angiography for both anatomical configuration and internal diameter.

(d) Intravascular ultrasound analysis and angiography for the creation of a 3D anatomical picture of the AVF: We used an Atlantis 40 MHz 2.3 F, Intravascular ultrasound catheter (Boston Scientific Corp, MA), which was connected to a Clearview Ultra IVUS machine (Boston Scientific Corp, MA), which displayed real time images. IVUS measurements were performed at the time of fistula placement by advancing the ultrasound probe under direct vision into the proximal artery (via the distal artery) about 3 cm proximal to the anastomosis. The probe was then pulled slowly into the distal artery, approximately 2 cm distal to the arteriovenous anastomosis. Digital pictures were saved every 3 mm (1 mm across the anastomosis). Figure 7a and b shows the IVUS images of the proximal artery and the AV anastomosis. Further, the ultrasound probe was then directed from the distal artery, across the AV
anastomosis and into proximal vein up to about 3 cm beyond the AV anastomosis. The probe was then drawn back into the distal artery, across the anastomosis, with digital pictures being saved every 3 mm (1 mm at the AV anastomosis). These IVUS images can be used for obtaining information about the internal diameter and also can be used to construct a geometric model of the AVF.

(e) Generation of the curved AVF CFD model: The IVUS images for the proximal artery, proximal vein and the AV anastomosis can used to build the 3D models. Since the IVUS images contained only 2D information, the images are stacked so that the centroids of all the images are aligned on a straight line for the arterial side. On the venous side of the AVF, the centroids of the images are oriented based on angiographic images of the AVF, in order to recreate the curved venous segment. The 3D model can be reconstructed using the surface fit to the polyline cross-sections. A CFD solution can be obtained using the finite volume method as described in the next section.

(f) Internal diameter and anatomical configuration data using a 64 slice CT scanner: In order to obtain animal specific geometries of AVFs simultaneously with flow, we have pioneered the use of 64 slice CT angiography in our pig models. The images have been acquired using a 64 slice CT scanner (Siemens Medical Systems, Florsheim, Germany) at a 512 × 512 resolution (Kvp: 120, effective mAs:190, 0.6 mm collimation, 0.37 sec rotation time and 0.8 pitch), in order to obtain the 3D geometries of the curved and straight fistulae. Images were obtained with a slice thickness of 2 mm and an interval of 1 mm (50% overlap). Figure 8a shows a coronal view of a 2D gray scale image of the straight and curved AVFs, respectively, which was obtained using the parameters mentioned above. The stack of these 2D DICOM images from the CT angiography was used to reconstruct the 3D geometries using image processing techniques (MIMICS 10.1, Materialise Inc, USA) (Fig. 8b). The images were segmented using appropriate threshold values to identify only those pixels of the image with a value higher than or equal to the threshold values. Finally, the segmented values were processed further to select only the domain containing the AVF. This image was further processed by segmenting the left (straight) and right (curved) sides to obtain the separate set of images for straight and curved sides. The edges of the 2D axial images for the straight and curved configurations were isolated using the edge detection algorithm. The edge information in the form of polylines were exported to GAMBIT software (ANSYS INC, USA) and were smoothened by fitting a cubic spline to remove the sharp corners. The smoothened crosssections were then used to fit a multisection surface spline in order to generate 3D geometries. Figure 8c and d shows the reconstructed models of the straight and curved AVFs geometries, respectively.
These geometries were meshed using GAMBIT software with tetrahedral cells. The meshed geometries were exported to FLUENT software to perform flow simulations on these specific anatomical configurations of AVFs.

(g) Finite volume method
(1) Governing equations: The flow simulations were carried out by numerically solving the following mass conservation (continuity) and momentum equations for pulsatile blood flow (7) using a finite volume method.

Mass conservation equation:
\[ \rho \nabla \cdot (\mathbf{V}) = 0 \] [1]

where \( \rho \) is the density of blood and \( \mathbf{V} \) is the velocity vector.

Momentum conservation equation:
\[ \rho \frac{\partial}{\partial t} (\mathbf{V}) + \rho \nabla \cdot (\mathbf{VV}) = -\nabla \mathbf{p} + \nabla \cdot (\sigma) \] [2]

where \( \mathbf{p} \) is the static pressure and \( (\sigma) \) is the stress tensor. The stress tensor \( (\sigma) \) is given by \( (\sigma) = \mu \left( (\nabla \mathbf{V} + \nabla \mathbf{V}^T) \right) \) [3]

where \( \mu \) is the molecular or laminar viscosity of the fluid defined by the ratio of shear stress to shear rate.

(2) Boundary conditions: The measured pulsatile flow and pressure data was fitted using a fourier series and averaged over one cycle to get a single volume flow rate and pressure pulse with a cycle time of 0.7 sec. These flow and pressure pulses were then applied at the proximal artery inlet and at two outlets: distal artery and proximal vein locations. Specifically, at the PA and DA locations, velocity inlet boundary conditions were applied by dividing the measured flow values at these locations with their respective cross-sectional areas. At the outlet of the PV, a pressure outlet boundary condition is specified. At the vessel wall, no-slip boundary condition was applied.

Equations [1]-[3] were solved using finite volume method (8). The governing equations were discretized using a second order time implicit scheme along with a 3D double precision, segregated and laminar solver. In addition, the pressure terms were discretized using a second order scheme. A second order upwind scheme was adapted for discretization of momentum. These were used to derive the hemodynamic wall shear stress contours.

(h) Hemodynamic wall shear stress profiles obtained using 64 slice CT angiography: WSS profiles for curved and straight AVFs were then calculated using finite volume method (7) using flow and pressure inputs and the reconstructed vascular 3D geometry. The measured velocity profiles for the proximal and distal artery were applied as an input along with a pressure outlet boundary condition at the outlet of proximal vein in order to calculate the WSS profiles for the AVFs. WSS profiles for the straight and the curved configuration are shown in Figure 9a and b, respectively, where red indicates regions of high WSS and blue indicating regions of low WSS. It can be noted that there are significant differences in the pattern of WSS between the two configurations. Our results document that WSS profiles can be de-
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DISCUSSION

In this brief technical report, we have described in detail the methodology used by our group to obtain flow, pressure, internal diameter (IVUS) and the anatomical configuration (angiograms) of individual fistulae; which can then be used to establish a shear stress profile for the AVF, either at the time of placement or at the time of sacrifice (9). We have also demonstrated the procedure for developing patient specific 3D geometries of the AVF from the CT images. We believe that this report is scientifically important and clinically relevant, because hemodynamic parameters such as flow and shear stress are likely to be important determinants, which determine both short- and long-term AVF success and failure. Specifically, experimental data suggests that higher blood flow with increased WSS results in patent lumens with minimal neointimal hyperplasia, while low flow with low WSS results in small lumens and the presence of neointimal hyperplasia (10-13). However, it is also possible that extremely high flow velocities and WSS values could cause endothelial and smooth muscle cell injury with subsequent neointimal hyperplasia and vascular stenosis.

We propose that the future measurements of detailed hemodynamic parameters using the techniques and technologies described in this report will allow for the optimization of hemodynamic stress profiles in animal models such as the one described. This information could then be translated to the clinical setting where it would hopefully have a positive impact both on primary non function and on later stenoses in the venous limb.

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Conflict of interest statement: I confirm that the results presented in this paper have not been published previously in whole or part, except in abstract format.

None of the authors has any proprietary interest.

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