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Anatomic configuration affects the flow rate and diameter of porcine arteriovenous fistulae

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Although arteriovenous fistulae are currently the preferred form of vascular access, early failure is a significant problem. Since wall shear stress is thought to play an important role in the pathogenesis of early failure, and this stress varies markedly in different fistula configurations, we assessed the influence of configuration (curved or straight) on longitudinal changes of flow rate and lumen diameter in a porcine fistula model. Fistulae were created in eight pigs between the femoral artery and vein, with each animal having a curved and a straight configuration on opposite sides. Velocity measurements were obtained by ultrasound at the time of surgery and at intermediate time points up to 28 days. Quantification of both the configuration and the internal diameter of the fistulae was determined by CT scans. The overall rate of increased flow during each time interval (0 to 2 days, 2 to 7 days, and 7 to 28 days) was more pronounced with the curved fistulae. Moreover, the luminal diameter of curved fistulae had dilated more from the time of surgery to 28 days as compared to the straight fistulae. Thus, anatomical configuration of fistulae plays a major role in flow-mediated dilatation. Identifying the optimal configuration may result in increased diameter and consequently blood flow, and perhaps reduce the incidence of early failure.

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Arteriovenous (AV) fistulae are currently the preferred form of vascular access and are associated with improved patient survival and reduced costs.[1–3] These data resulted in the initiation of the Fistula First initiative by the Centers for Medicaid and Medicare Services, which has resulted in a significant increase in the AV fistula prevalence rate (55% currently).[4–6] Despite the many advantages associated with AV fistulae, it has been recently demonstrated that over 50% of AV fistulae are unsuitable for dialysis between 4 and 5 months postsurgery.[7]

At a radiological level, AV fistula non-maturation is characterized by a peri-anastomotic venous segment stenosis.[8] At a mechanistic level, the exact reasons for either AV fistula success (maturation) or failure (non-maturation) are unclear, but it is likely that the magnitude of stenosis is influenced, both by the amount of neointimal hyperplasia[9,10] and also by the ability or inability of the venous segment to dilate following creation of the AV anastomosis.

A number of experimental and clinical studies have described significant increases in blood flow and also venous segment diameter following creation of an AV fistula.[11–14] Most importantly, in the specific context of AV fistula maturation failure, Wong *et al.*[14] were able to demonstrate that patients with lower blood flows following surgery had a greater rate of AV fistula failure. Though a number of experimental and clinical studies[15–20] have been performed to examine the change of flow rate and its influence on maturation, it is however still unclear as to the exact mechanistic pathways that result in flow-mediated vasodilatation in AV fistulae.

To date, there have been limited *in vivo* fistula studies and minimal data available from *in vivo* AV fistula models that have focused on the influence of flow-mediated dilatation[20–22] with respect to time. Therefore, this study was performed in pig AV fistulae to study the longitudinal change in flow rate and diameter and the linkages between them. While absolute flow parameters are evidently important, we have recently demonstrated that different surgical configurations of AV fistulae result in very different hemodynamic shear stress profiles, which could then influence the possibility of causing failure in AV fistula maturation. As AV fistulae are created in many different surgical configurations, we felt that it was important to assess the impact of AV fistula anatomy on the two primary end points (blood flow and diameter) associated with AV fistula maturation. In particular, we felt that the availability of such data could initiate further research into determining best possible surgical configuration for the creation of AV fistulae.

RESULTS

The mean flow rate computed from flow velocity measured using Doppler ultrasound and the internal diameter variations computed using computed tomography (CT) angiography for the curved (Figure 1a) and straight AV fistula (Figure 1b) configurations from time 0 (0d) to the time of killing will be discussed in this section. The results from the two-way mixed analysis of variance for the mean flow rates, calculated from the velocity measurements, and the internal diameter variations for both the configurations with time will also be explained below.

Flow rate variation with time

The mean flow rate values at the proximal vein (PV) and the variation with respect to time (0 day, 2 days, 7 days, and 28 days) for the curved and straight configurations are shown in Figure 2. In general, the flow rate increased with time for both curved and straight configurations. However, the net mean flow rate at 28 days for the curved configuration was 41% more than that of the straight configuration (3887 ml/min for curved vs. 2760 ml/min for straight).

Table 1a describes the rate of change of flow rate during each time interval (0 to 2 days, 2 to 7 days, and 7 to 28 days) in ml/min/day calculated for both configurations. For the curved configuration, the rate of increase in the value of flow rate from 0 day to 2 days was almost two times that of the straight configuration (53 ml/min/day for curved vs. 27 ml/min/day for straight configuration). The rate of increase in the flow rate or the slope of the line for the 2- to 7-day interval in the case of the curved configuration was 30% more than the increase in the case of the straight configuration (i.e., [148 ml/min/day–113 ml/min/day] × 100/113 ml/min/day). Similarly, there was also an increase in the values of the flow rate during the 7- to 28-day interval for both configurations, but it was not as significant as compared with the 2- to 7-day interval.

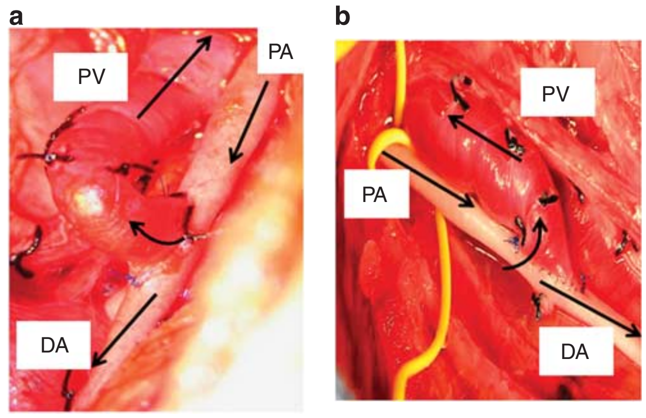

Figure 1 | Surgical creation of arteriovenous (AV) fistula in a pig model in two different configurations. Panel **a** describes the curved configuration, whereas panel **b** documents the straight configuration. DA, distal artery; PA, proximal artery; PV, proximal vein.

Diameter variation with time

The variation of average diameter with respect to time (0 day, 2 days, 7 days, and 28 days) was calculated for eight pigs for both curved and straight configurations. At 0 day, only one diameter measurement was recorded at an arbitrary distance from the anastomosis using the intraoperative ultrasound measurements. However, at 2-, 7-, and 28-day diameter from four cross-sections (8, 11, 19, and 25 mm; mm: distance from

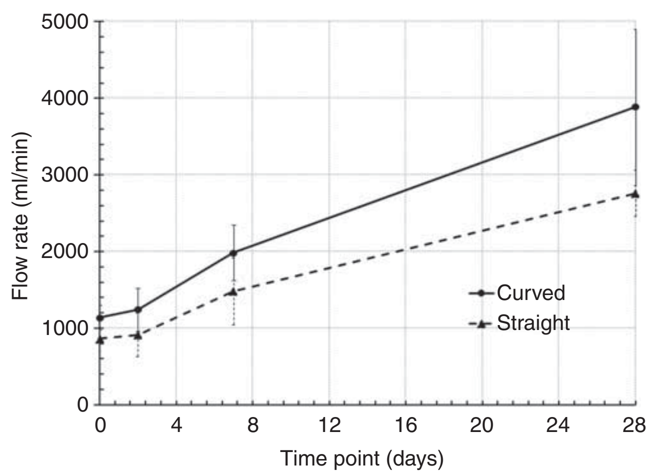

Figure 2 | Flow rate variation in the proximal vein region at different time points for curved and straight configurations. All values are represented as mean ± s.e.

Table 1a | Rate of change in the blood flow rate during time intervals: 0 to 2 days, 2 to 7 days, and 7 to 28 days for curved and straight configurations, respectively

Flow rate increase (ml/min/day)	0 to 2 Days	2 to 7 Days	7 to 28 Days
Curved	53	148	91
Straight	27	113	61

Table 1b | Percentage change in diameter at time intervals 0 to 2 days, 2 to 7 days, and 7 to 28 days for the curved and straight configurations, respectively

Change in diameter	0 to 2 Days	2 to 7 Days	7 to 28 Days
Curved	38%	38%	34%
Straight	38%	16%	−7%

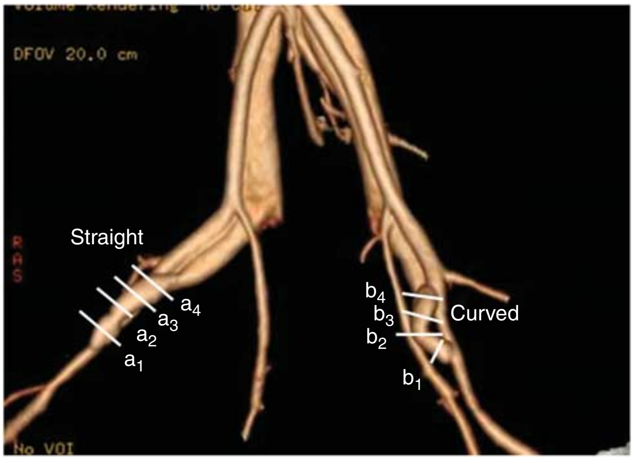

Figure 3 | Computed tomography angiogram reconstruction of an arteriovenous (AV) fistula showing curved (right side) and straight (left side) configurations. White lines denote the sections where diameters were computed at different time points for all pigs ($n = 8$). a_1, $b_1 = 8$ mm; a_2, $b_2 = 11$ mm; a_3, $b_3 = 19$ mm; a_4, $b_4 = 27$ mm from AV anastomosis.

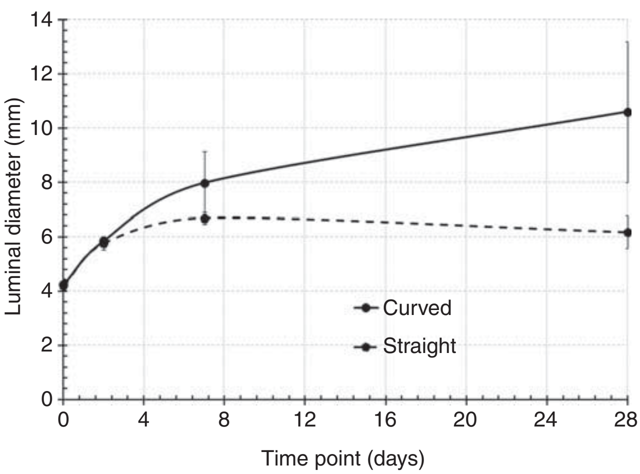

Figure 4 | Average luminal diameter variation of four cross-sections (8, 11, 19, 27 mm) in the proximal vein region at different time points for curved and straight configurations.

AV anastomosis as specified in Figure 3) were calculated using DICOM images from CT scans.

Figure 4 shows the change in diameter of curved and straight configurations at different times. Overall, both curved and straight configurations showed venous dilatation with respect to their baseline diameters. However, the rate of increase of the curved configuration was higher than that of the straight configuration with a continuing increase until 28 days (from 4.2 to 10.6 mm for curved vs. 4.2 to 6.2 mm for straight). In the case of the straight configuration, although the diameter increased consistently from 0 to 7 days, there was a relative reduction in the lumen diameter of the straight configuration during the 7- to 28-day time interval. The percentage change in diameter of the PV for each time interval has been listed in Table 1b. Both curved and straight configurations had a significant change in the luminal diameter during the initial time interval 0–2 days ($\sim$38% for both curved and straight: [5.8 mm–4.2 mm] $\times$ 100/ 4.2 mm). There was a relative decrease in the values of percentage change for the straight configuration during the time interval 2–7 days ($\sim$16% increase for straight vs. 38% increase for curved). During the 7- to 28-day time interval, the luminal diameter increased further in the curved configuration by another 34%. Conversely, there was a 7% decrease in the diameter of straight configuration during the 7- to 28-day time interval. Moreover, the luminal diameter of the curved fistulae had dilated more from 0 to 28 days as compared with the straight fistulae (150%—curved vs. 47%—straight).

Table 2 | Two-way analysis of variance showing the effect of configuration on grouped mean flow rate at all time points in the PA and PV regions and grouped mean luminal diameter at all time points in the PV region

	Curved	Straight	
Flow rate (ml/min)			
Proximal artery (PA)	2150 ± 206	1695 ± 206	$P < 0.05$
Proximal vein (PV)	1909 ± 204	1463 ± 204	
Diameter (mm)			
PV	6.7 ± 0.53	5.7 ± 0.54	$P < 0.05$

Grouped mean values of all time points for each configuration.
All values are represented as mean ± s.e.

Influence of configuration on flow rate and internal diameter

The group means of flow rate and diameter averaged over all time points for the curved and straight configurations were analyzed using the two-way mixed model analysis of variance and have been listed in Table 2. The first half of table shows the comparison of group means of the flow rate for curved and straight configurations (combined for all time points) in the proximal artery region. The statistical test achieved significance ($P < 0.05$), indicating that the group means (2150 ± 206 ml/min for curved vs. 1695 ± 206 ml/min for straight) differed significantly. Similarly, the difference in the group means of PV flow rates of curved and straight configurations also showed that they were significantly different from each other (1909 ± 204 ml/min for curved vs. 1463 ± 204 ml/min for straight; $P < 0.05$).

The impact of surgical configuration on the average venous luminal diameter calculated from four cross-sections in the PV region (as mentioned in Figure 3) for curved and straight configurations are listed in the bottom half of Table 2. The group means of luminal diameter for curved and straight configurations were 6.7 ± 0.53 mm and 5.7 ± 0.54 mm, respectively, signifying that the curved configuration had undergone significant dilatation as compared with the straight configuration ($P < 0.05$).

Influence of time on flow rate and internal diameter

The change in the group means of flow rate and diameter at different time points at the PV region when both the

Table 3 | Effect of time point on grouped mean flow rate and grouped mean diameter of all pigs for both of the configurations in the proximal vein region

	Time point				
	0 Day	2 Days	7 Days	28 Days	
Flow rate (ml/min)	950 ± 215	929 ± 244	1751 ± 227	3113 ± 307	$P<0.05$
Diameter (mm)	—	4.9 ± 0.53	6.4 ± 0.55	7.3 ± 0.58	$P<0.05$

All values are represented as mean ± s.e.
Grouped mean values of both configurations.

configurations were analyzed together is described in Table 3. The means of flow rate in PV increased consistently, by approximately 3 times from 950 ± 215 ml/min at 0 day to 3113 ± 307 ml/min at 28 days. Similarly, the mean diameters at different time points were statistically significant (4.9 ± 0.53 mm at 2 days vs. 7.3 ± 0.68 mm at 28 days), implying that time has a significant effect on luminal changes (dilatation or constriction) in PV.

DISCUSSION

The progression of AV fistula maturation for two different configurations of AV fistula was studied for the first time in a large animal model. In this study, repetitive anatomical and hemodynamic measurements were performed on the same animal at different time points, which helped in analyzing the effect of surgical configuration and time point on flow rate and diameter, respectively.

This study used Doppler ultrasound for all of the hemodynamic measurements. In clinical practice, Doppler ultrasound has been widely used to monitor changes in blood flow and also to perform routine access monitoring in patients undergoing dialysis.[17,18,23] Thus, ultrasound is not only a useful non-invasive tool for measuring the flow, but also allows for the assessment of fistula patency over time. At present, there are not many studies documenting the use of Doppler ultrasound on different configurations of pig AV fistula with data acquisition being performed at different time points. The present study has also tested out the use of CT angiography for obtaining the luminal diameters at different time points in the same pig. The better spatial resolution and the ability of the user to get the anatomic details of the curvature of the AV fistula resulted in our being able to determine the diameter with greater accuracy. This is particularly important in the context of complex AV fistula configurations, which would have resulted in less accurate measurements of internal diameter due to a lack of good control on the plane of data acquisition. CT angiography circumvented this problem and facilitated the gathering of internal diameter values, which in turn improved the accuracy of the flow rate recordings in the two AV fistula configurations.

An important limitation of this study is that the CT angiography and Doppler flow measurements were conducted in sequence and not simultaneously. Also, the hemodynamic data were obtained by sedating the animal, which could alter the flow rate when compared with non-anesthetized animals. However, to the best of our efforts, we have taken adequate measures to minimize the variability in the measured parameters by using a single operator for Doppler measurements, by monitoring the heart rate and also by avoiding any major fluctuations in systemic blood pressure measured with an external cuff. Owing to the invasive nature of pressure measurement, the transmural pressure inside the venous segment of AV fistula was not measured.

It should also be emphasized that while the goal of this study was to establish linkages between anatomical configuration and flow/diameter, we recognize that there are likely to be multiple mechanistic steps that are responsible for converting differences in anatomy into variations in flow and diameter. Potential mechanistic steps include changes in wall shear stress, differential endothelial recognition of changes in shear, endothelial cell and smooth muscle cell activation or quiescence, and the presence or absence of neointimal hyperplasia and flow-mediated dilation. Studies to address these and other mechanistic pathways that could determine AV fistula success or failure are currently ongoing in our laboratory.

Also the pigs that were used in this study were not uremic. However, we have previously demonstrated that the histology in our pig models of AV fistulae and AV grafts is similar to that seen in human tissue samples (with the exception of more medial hypertrophy in human as compared with pig specimens). This similarity in histology suggests to us that it is appropriate to use our pig model to study the pathogenesis of dialysis vascular access dysfunction and also to try and translate some of these findings into the human setting.

Besides the above factors that determine AV fistula success or failure, surgical manipulation and vessel trauma have a significant role in the development of peri-anastomotic stenosis in AV fistulae, which could alter the blood flow (and wall shear stress) and hence maturation. It is therefore important to avoid trauma caused by excessive mobilizations and manipulations of the vessel while placing fistulae of different configurations.

The surgical placement of the fistulae was mainly divided into two configurations with two extreme curvatures. Though we had a good control over placing the fistulae with two significantly different configurations, unfortunately it was not possible to minimize the small variations in the angle of each curved fistulae placed in our animals. During the surgery, the curvatures of the fistulae were mainly subjected to visual confirmation. However, the placements of the fistulae were performed by a single surgeon, thus eliminating the possibility of operator-dependent variations in the angle and curvature of the fistulae. To quantify this, the values of radius of curvature as well as the % change of this parameter from 2 days to the time of killing (28 days—pigs 1 and 2, 7 days—pig 3) for both the configurations are shown in Table 4a and b, respectively. Only three pigs are chosen for this analysis, as they were the only pigs with multiple measurements over time. Of note, there is a minimal variation in the curvatures for both the configurations between different time points. The maximum % change in the radius of curvature for any configuration is $\sim$12%, whereas the average changes in the radius of curvature for the curved and straight configurations are $\sim$7% and $\sim$8%, respectively. Moreover, the mean % difference between the radius of curvature of the curved and straight fistulae over all time points is $\sim$58%. Thus, it can be seen that the curvature is maintained from the time of surgery till killing for both the configurations and remained higher for the curved model.

In summary, our results show for the first time that differences in surgical configuration can result in significant differences in the two parameters that are key to AV fistula maturation; namely, blood flow and diameter.

We believe that these are critically important results in the current clinical scenario where the high rates of AV fistula maturation failure are a major impediment to the success of the Fistula First initiative. In particular, our results indicate that research into the identification of the 'ideal' AV fistula configuration, followed by the clinical placement of such fistulae, might improve AV fistula maturation rates.

We are cognizant of the fact that AV fistula maturation is a multifactorial process and also recognize that changing AV fistula configuration does not alter other basic parameters such as baseline vessel size and/or endothelial function. However, we do hypothesize that creation of an AV fistula with a near 'ideal' configuration will reduce maturation failure rates, especially when such fistulae are created in patients with marginal vessels, multiple comorbidities, and poor endothelial function.

Finally, while the descriptive nature of this study does not allow us dissect out the exact mechanisms responsible for the differences in flow and diameter between the curved and straight AV fistula configuration, we speculate that differences in the hemodynamic shear stress profiles between these two surgical configurations could have resulted in differential patterns of endothelial cell response and vascular remodeling. Further investigations into the mechanisms responsible for our results are currently in progress.

Table 4 | Radius of curvature (a) and percentage curvature change from 2 days to the time of killing for curved and straight configurations (b)

	Curved (mm)			Straight (mm)		
	2 Days	7 Days	28 Days	2 Days	7 Days	28 Days
(a)						
Pig 1	4.65	5.16	5.12	2.79	2.79	2.97
Pig 2	3.93	3.65	4.11	2.85	2.81	2.52
Pig 3	3.64	3.85		2.50	2.38	
(b)		Curved			Straight	
Pig 1		10%			6%	
Pig 2		4%			12%	
Pig 3		6%			5%	

MATERIALS AND METHODS

AV fistula creation

AV fistulae were created in two different configurations, namely, curved and straight, between the femoral artery and femoral vein in eight pigs, each weighing about 50 kg.[10] As surgical skills have been shown to be a determinant of AV fistula success or failure in the human setting, all the surgeries were performed by a single surgeon (YW).

Fistula geometry as shown in Figure 1 consisted of three main anatomical regions, namely, proximal artery, distal artery, and PV. Flow rate and internal diameter measurements were carried out immediately after the surgery (0 day) and at different time points

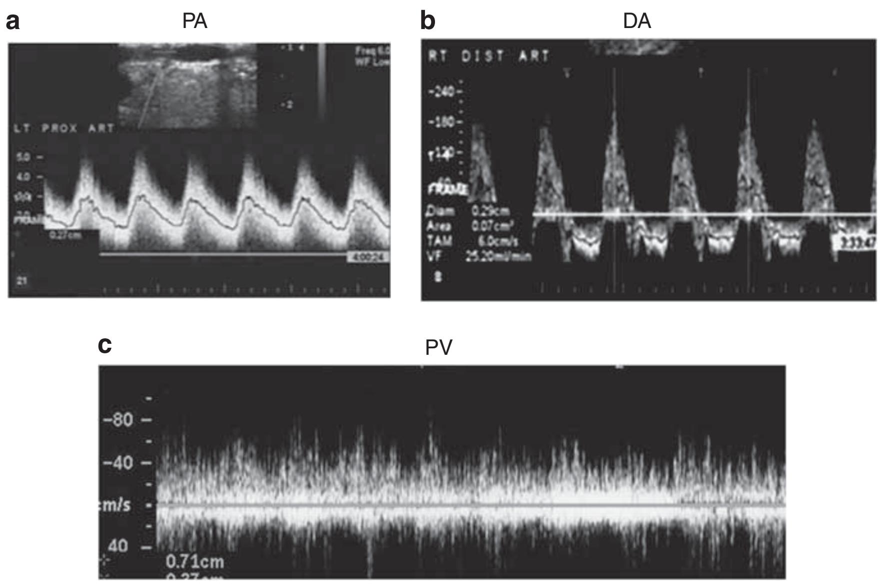

Figure 5 | Representative Doppler ultrasound measurements. Representative Doppler ultrasound recordings at the PA (**a**), DA (**b**), and PV locations (**c**). Note the expected flow reversal during diastole within the distal artery. PA, DA, and PV denote proximal artery, distal artery, and proximal vein locations, respectively.

(2 days, 7 days, and 28 days). Pigs were killed either at 2 days ($n=4$), 7 days ($n=2$), or at 28 days ($n=2$) time points after the surgery.

Anatomical measurements

Internal diameter measurements were obtained using two different methods. At 0 day, we used intraoperative ultrasound to obtain diameter recordings, which were then converted into area calculations (it was not possible to obtain CT scans immediately after surgery). However, at later time points (2 days, 7 days, and 28 days), DICOM images from 64 slice CT angiography was used to obtain measurements of internal diameter. In addition, the internal diameter was monitored at four locations: 8, 11, 19, and 27 mm from the AV anastomosis on both the configurations and at 2 days, 7 days, and 28 days, as indicated by the white lines in Figure 3.

Flow measurements

Color Doppler ultrasound (ATL HDI 5000 Ultrasound, ATL, Bothell, WA) was used to record the instantaneous velocity pulses at different time points (0 day intraoperative, 2 days, 7 days, and 28 days). A high-frequency intraoperative transducer was used to measure the velocity immediately after the surgery (0 day), at different locations on the proximal artery, distal artery, and PV. However, at intermediate and killing time points, a low-frequency transducer was used to obtain the velocity transcutaneously. The ultrasound velocity pulses were extracted from the recorded images and digitized for data analysis. Three repeated measurements were carried out at each anatomical location (proximal artery, distal artery, and PV) for both the configurations and at all time points. The time-averaged velocity was computed from the digitized velocity pulses for each measurement and multiplied by the area at the corresponding location of measurement to obtain the volume flow rate (see Figure 5, which describes representative Doppler velocity pulses at the three different locations). Blood pressure was monitored using the external pressure cuff to ensure that there were no major fluctuations in the Doppler measurements. The variation of average blood pressure measurements in our pigs during the procedures were between 68 and 72 mm Hg. As expected the heart rate varied between different pigs; however, it remained predominantly constant for a particular pig during any procedure. The typical range of heart rate variation in our pigs, from the time of CT scan to the time of performing Doppler ultrasound measurements was between 120 and 95 beats/min.

In our experiments, animals were sedated during all the procedures. During each procedure, blood pressure, body temperature, heart rate, and so on were carefully monitored. No major complications were observed during the procedures, and the time gap between the measurements (2 days, 7 days, and 28 days) helped the animal to fully recover from the previous procedure. Thus, to the best of our effort, the variability induced by subject state was minimized by following the same protocol for all measurements, by having a single operator to do all the measurements, and by performing appropriate measurements.

Statistical analysis

In this study, the two-way mixed model analysis of variance was used to compare the group means of flow rate in the venous and arterial portions of the AV fistula and to investigate the group means of diameter within the venous segment of the AV fistula. This approach allowed us to simultaneously evaluate the effects of two or more independent variables in a single analysis using the grouped means of the values. To implement the analysis of variance for flow rate and diameter, we focused on surgical configuration (curved, straight) and time point (0 day, 2 days, 7 days, and 28 days). A P-value <0.05 was considered to be statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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