Location matters: Offset in tissue-engineered vascular graft implantation location affects wall shear stress in porcine models

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ABSTRACT

Objective: Although surgical simulation using computational fluid dynamics has advanced, little is known about the accuracy of cardiac surgical procedures after patient-specific design. We evaluated the effects of discrepancies in location for patient-specific simulation and actual implantation on hemodynamic performance of patient-specific tissue-engineered vascular grafts (TEVGs) in porcine models.

Methods: Magnetic resonance angiography and 4-dimensional (4D) flow data were acquired in porcine models (n = 11) to create individualized TEVGs. Graft shapes were optimized and manufactured by electrospinning bioresorbable material onto a metal mandrel. TEVGs were implanted 1 or 3 months postimaging, and postoperative magnetic resonance angiography and 4D flow data were obtained and segmented. Displacement between intended and observed TEVG position was determined through center of mass analysis. Hemodynamic data were obtained from 4D flow analysis. Displacement and hemodynamic data were compared using linear regression.

Results: Patient-specific TEVGs were displaced between 1 and 8 mm during implantation compared with their surgically simulated, intended locations. Greater offset between intended and observed position correlated with greater wall shear stress (WSS) in postoperative vasculature (P < .01). Grafts that were implanted closer to their intended locations showed decreased WSS.

Conclusions: Patient-specific TEVGs are designed for precise locations to help optimize hemodynamic performance. However, if TEVGs were implanted far from their intended location, worse WSS was observed. This underscores the importance of not only patient-specific design but also precision-guided implantation to optimize hemodynamics in cardiac surgery and increase reproducibility of surgical simulation. (JTCVS Open 2022;12:355-63)

CENTRAL MESSAGE

Tissue-engineered vascular grafts have the potential to improve hemodynamics when implanted in their intended locations, emphasizing the importance of precision-guided implantation during surgery.

PERSPECTIVE

As the use of patient-specific tissue-engineered vascular grafts increases in patients with congenital heart disease, we must acknowledge how precise surgical implantation helps to further optimize their hemodynamic benefits by reducing wall shear stresses along vascular endothelial tissue.
Congenital heart disease (CHD) affects 1% of live births worldwide and is the leading cause of death in newborns. For children with severe CHD, surgeons implant commercially available grafts to correct narrowed blood vessels or bypass defective heart chambers. The current standard of care is using off-the-shelf grafts, but these can produce suboptimal hemodynamics and are subject to early failure. Additionally, grafts cannot grow with the patient and always require replacement. Patients with repaired CHD often face complications, such as exercise intolerance, ventricular dysfunction, arrhythmias, cyanosis, or major embolic events. Thus, there is a clinical need for patient-specific grafts designed to improve congenital vascular repair.

We developed patient-specific tissue-engineered vascular grafts (TEVGs) using magnetic resonance imaging (MRI) and subsequent 3D design to improve hemodynamics within unique patient anatomies. These customized biodegradable scaffolds promote cellular proliferation and maturation with potential for growth and anatomic reconstruction. Preclinical studies of patient-specific TEVGs in sheep models have shown favorable outcomes, such as decreased thrombogenicity, and TEVGs were also used to treat congenital pulmonary artery (PA) stenosis in 2 children, and exhibited safe histological and mechanical properties.

A patient-specific design approach requires image segmentation, computer-aided design modifications guided by computational fluid dynamics (CFD) simulations and electrospinning to create a customized conduit. CFD simulation explores various surgical solutions while predicting postoperative hemodynamics like wall shear stress (WSS) and energy loss. CFD results reveal that optimized grafts outperform standard grafts and improve hemodynamic parameters, demonstrating the potential to improve CHD surgery.

Higher levels of WSS (>10 Pa) have been shown to induce specific changes in endothelial cell behavior and exacerbate inflammation. Lower levels of WSS (<1 Pa) are typically associated with worse pulmonary vascular remodeling and pulmonary arterial hypertension. WSS has been implicated in repaired aortic coarctation patients, with high WSS correlated with reduced growth in the transverse arch. Research also suggests that abnormal WSS promotes the development and rupture of high-risk plaques, which might lead to atherosclerosis and myocardial infarction. From a histological standpoint, regions of low and high WSS correspond to medial thickening and degradation, respectively. Because of these clinical implications and profound effects on tissue biology, WSS is at the forefront of cardiovascular research and a key target in CFD optimization. Energy loss is also a consideration because of its correlation to abnormal arterial flow, evident in viscous energy losses in dilated aortas (>2 mW) and aortic stenosis (>10 mW).

Although CFD simulation is advanced in predicting surgical outcomes, little is known about the accuracy of surgical placement of patient-specific designed grafts. Our aim was to determine whether the location of TEVG implantation matters, and if so, the implications. Therefore, the primary objective of this study was to evaluate the offset in TEVG implantation location compared with its CFD simulated position. The secondary objective was to determine if the location of the implanted TEVG affects hemodynamic performance of the postoperative blood vessel in porcine models. We hypothesized that precise implantation of TEVGs in their intended positions would result in improved hemodynamic performance than TEVGs with greater offsets.

**METHODS**

**3D Model Design**

All procedures were performed at the University of Chicago Medical Center and approved by the Institutional Animal Care and Use Committee (72605; approved October 24, 2019). All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (Facility RRID:SCR_021806). Fourteen-week-old pigs weighing 20 to 30 kg underwent cardiac magnetic resonance angiography (MRA) with a 32-channel torso array on a 3.0 T magnet (Philips Ingenia) at approximately 1 month before implantation surgery (Figure 1, A). For the MRA acquisition we used a four-dimensional (4D)-TRAK sampling scheme over the cardiothoracic region using a sagittal view, with the following acquisition parameters: repetition time/time to echo/fractional anisotropy = 3.8/1.6 ms/25°, field of view = 410 × 410 × 240 to 250 mm³, spatial resolution = 0.9 × 0.9 × 6 mm³, and a compressed SENSE acceleration with reduction factor = 4. For the two 4D flow sequences, the velocity encoding gradients of 250 and 350 cm/s were matched to the following acquisition parameters: repetition time/time to echo/fractional anisotropy = 3.9/2.1 ms/14°, field of view = 284 × 284 × 120-160 mm³, spatial resolution = 0.85 × 0.85 × 1.7 mm³, reconstructed cardiac phases = 20 per heartbeat with automatic k-space view-sharing, and a compressed SENSE acceleration with reduction factor = 3.5 to 4.

### Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| AR           | augmented reality |
| CFD          | computational fluid dynamics |
| CHD          | congenital heart disease |
| 4D           | four-dimensional |
| LPA          | left pulmonary artery |
| MPA          | main pulmonary artery |
| MRA          | magnetic resonance angiography |
| MRI          | magnetic resonance imaging |
| PA           | pulmonary artery |
| RPA          | right pulmonary artery |
| SCA          | subclavian artery |
| αSMA         | α-smooth muscle actin |
| STL          | stereolithography |
| TEVG         | tissue-engineered vascular graft |
| WSS          | wall shear stress |
obtained (1-10 Pa 11 and processes continued until acceptable thresholds of WSS and energy loss were
converted into a 3D digital model and smoothed. To account for growth during the 1-month period between imaging and implantation, the vessel model was expanded by 5% uniformly using the scaling tool in 3-matic (Materialise). This percentage was determined on the basis of the growth curve of the mixed Yorkshire and Landrace porcine model and observed vessel diameter growth over a 1-month period in previous work.5 The resulting model was exported as a stereolithography (STL) file (Figure 1, B).

A graft was created on the basis of the exported vessel and optimized to enhance hemodynamic performance (Figure 1, C) by exploring graft geometries, performing high-fidelity CFD simulations, and using machine learning methods on the basis of preoperative 4D flow data and methods, consistent with our previous work in this area.9,20,21 Our iterative CFD processes continued until acceptable thresholds of WSS and energy loss were obtained (1-10 Pa11 and <2 mW18 in arterial flow, respectively). The optimized model was exported as an STL file for electrospinning.

Scaffold Fabrication

The STL file was modified for the electrospinning setup and removal of the electrospun polymer graft.22 Then, the modified graft was 3D-printed in stainless steel with direct metal laser sintering at an external printing house (Protolabs or Xometry; Figure 1, D). The steel mandrel was coated in a biodegradable nanofiber material composed of a 1:1 ratio of polycaprolactone and poly-L-lactide-co-D-caprolactone (Nanofiber Solutions). These polymer fibers were deposited on the mandrel during electrospinning while maintaining high voltage. When completed, the mandrel was disassembled, and the electrospun biodegradable graft was removed and placed in a standard Tyvek pouch (Figure 1, E). The graft was sterilized in low temperature with vaporized hydrogen peroxide and ozone (STERIZONE VP4; Getinge).23

In Vivo Graft Implantation

Eleven porcine models were subject to graft implantation cardiovascular surgery 1 month after preoperative imaging. Postoperative imaging was either acquired within 2 days after surgery for acute studies (n = 8) or 2 months for chronic studies (n = 3). Five of the animals received an aortic graft and 6 received PA bifurcated grafts. Each biodegradable graft included extensions, marked by ridges, to indicate where the graft should be sutured. The aortic grafts contained 3 ridges, located at the ascending aorta, descending aorta, and subclavian artery (SCA). The PA grafts also contained 3 ridges: 1 at the main PA (MPA), left PA (LPA), and right PA (RPA). Each graft was uniquely shaped and sized to their respective implantation sites using the TEVG manufacturing workflow detailed in Figure 1.

Graft implantation surgery was performed through a left thoracotomy with general anesthesia after removal of 1 rib to increase exposure (Figure 1, F). Aortic grafts were implanted in the descending aorta only (n = 2), or in the descending aorta and left SCA (n = 3). The inclusion of the SCA was predetermined in the design process. Aortic grafts including the SCA were anastomosed distal of the brachiocephalic trunk, whereas grafts without a branch were placed distal of the left SCA. This procedure was performed with partial bypass using 2 cannulas connected to the ascending aorta and distal of the descending aorta to provide the lower body perfusion while clamps were in place. The PA grafts were implanted from the MPA to the branch PA after removal of the central PA portion. This procedure was performed using cardiopulmonary bypass. All pigs woke up after the surgery and were extubated in the operating room. Grafts were explanted at acute (within 2 days; n = 8) or chronic (2 months; n = 3) phases after the surgery.

Center of Gravity Analysis

Postoperative MRA and 4D flow data were reacquired immediately before explantation using matched acquisition as the preoperative imaging, and the obtained volumetric data sets were segmented with identical methods as described previously. The preoperative and postoperative vasculature segmentations were aligned in space using the automatic global registration feature in 3-matic. To account for growth between pre- and postoperative imaging time points (1 month or 3 months), preoperative images were scaled to postoperative size according to species-specific estimated growth curves.23 Two copies of the designed graft on the basis of preoperative imaging were added to the workspace. One of the grafts was aligned using global registration to the preoperative image, what we referred to as the “ideal” graft position. Conversely, the other graft was aligned to the postoperative image, what we referred to as the “observed” graft position.

To quantify this offset in 3D space, an automated center of gravity analysis was performed using the proprietary 3-matic on the basis of previous methodologies.25,26 This software uses mesh fit programming to

FIGURE 1. Workflow of tissue engineering graft manufacturing for aortic (top) and pulmonary artery (bottom) grafts. A, Obtaining magnetic resonance angiography (MRA) images 1 month before implantation. B, Constructing 3D digital models using segmentation software. C, Optimizing graft design using computational fluid dynamics (CFD) techniques. D, 3D printing metal mandrels for scaffold fabrication. E, Electrospinning the biodegradable polymer graft. F, Implanting the graft into a porcine model.
determine the center of gravity of each model selected. Grafts were selected, instead of the vasculature, because they have the same mass and shape to allow for comparison. Finally, the measure distance tool in 3-matic was used to identify the offset between the 2 center of gravity points in 3D space (Figure 2).

Implanted Graft Hemodynamic Analysis

Postoperative 4D flow images of the implanted graft were exported for further analysis, similar to our previously published methods. In the aorta samples, measurements and average hemodynamics were calculated across the whole vessel, which includes the ascending aorta, the transverse arch, and the descending aorta. The ascending aorta was defined as the region from the top of the aortic root to the first head vessel. The transverse arch was the region from the first head vessel to the second head vessel. The descending aorta was defined as the region from the second head vessel continuing down to 1 cm below the starting plane of the ascending aorta. The aorta flow rates were measured at the beginning of the ascending aorta and at the end of the descending aorta.

The measurements and average hemodynamics of the PA samples were also calculated across the whole vessel, including the MPA, LPA, and RPA segments. The MPA was defined as the region from the end of the PA curve up to the junction of the LPA and RPA. The RPA was the region from the PA junction to the first branch on the RPA. The LPA was defined as the region of the LPA from the junction with the RPA equidistance as the RPA. The PA flow rates were measured at the beginning of the MPA, the beginning of the RPA, and the beginning of the LPA. All measurements were visualized in iTFlow for the identification of regions of interest (Figure 3).

Histological Analysis

Chronic phase grafts were explanted, fixed in 10% formalin for 24 hours, and then embedded in paraffin. Standard histology was completed using hematoxylin and eosin stains. Immunohistochemistry was performed using α-smooth muscle actin (αSMA; 1:1600 M0851 Dako). Detection of antibody binding was performed using biotinylated secondary antibodies (Vector Laboratories), followed by incubation with streptavidinated horseradish peroxidase (Vector Laboratories). A chromogenic reaction with 3,3-diaminobenzidine (Vector Laboratories) was performed for the development of immunohistochemistry. Counterstaining of the nuclei was performed with Gill’s hematoxylin (Vector Laboratories).

Statistical Analysis

Simple linear regression was performed to assess the associations between TEVG implantation offset and hemodynamic parameters. WSS, energy loss, helicity, and vorticity were presented as percent differences calculated using the following equation. $R^2$ and $P$ values were calculated using Prism Version 8 (GraphPad Software).

$$\text{%Difference} = \frac{\text{Postoperative} - \text{Preoperative}}{\sqrt{\frac{\text{Postoperative}^2 + \text{Preoperative}^2}}}/2$$
RESULTS

Anatomical Observations

Eleven (n = 11) pigs underwent graft implantation surgery and postoperative analysis. After MRI, the animals were euthanized, and grafts were explanted between 1 week and 2 months after the surgery. Growth periods are shown in Figure E1 (aorta: n = 5 at 1 month; PA: n = 3 at 1 month and n = 3 at 3 months). There were no stenosis or dilated grafts.

Our center of gravity results showed that patient-specific TEVGs were displaced by approximately 1 to 8 mm during implantation surgery compared with their intended locations used in CFD surgical simulations. On average, the aortic grafts exhibited greater displacement and wider variety within measurements (3.82 ± 2.77 mm) compared with the PA bifurcated grafts (2.30 ± 1.19 mm).

Effects of Displacement on Hemodynamics

Next, we analyzed the effects of the calculated offset on hemodynamic performance, including WSS, energy loss, helicity, and vorticity (Figure 4). Data for the 11 porcine models showed a positive correlation between displacement and average WSS ($R^2 = 0.79$). This trend was observed within the aortic and PA grafts. Thus, we concluded that greater offset between the intended and observed position led to a higher average WSS over postoperative vasculature ($P < .01$). Furthermore, less offset between intended and observed positions not only led to decreased average WSS but improvements in WSS between preoperative and postoperative vasculature (as indicated by negative values in Figure 4, A).

Conversely, there were no strong correlations between displacement and energy loss, helicity, and vorticity ($P = .18$, $P = .26$, and $P = .53$, respectively). Therefore, grafts that were implanted closer to their intended locations showed positive results on hemodynamic performance in terms of WSS, but not the other parameters. Displacement, WSS, energy loss, helicity, and vorticity data for all 11 porcine models are shown in Figure E1.

Effects of WSS on Histology

Histological analysis was performed on chronic cases only (n = 3). Porcine subject 4 was excluded from this
Histological analysis of the PA of porcine subject 5 showed neotissue formation of smooth muscle layers similar to native tissue. 4D flow MRI data showed a reduction in WSS between presurgical and 2-month postsurgical imaging (Figure 5, A and B).

For comparison, histological analysis was also performed on the PA of porcine subject 6, which showed higher WSS at 2 months postoperative than preoperative. In Figure 5, C and D, we see intimal hyperplasia due to vascular wall inflammation. Medial thinning occurred as a result, evident in the slight narrowing of the postoperative blood vessel shown in Figure E1, displacement figure of porcine subject 6.

**DISCUSSION**

Center of gravity analysis is a novel method for determining location. The 3-matic center of gravity analysis used in this study has been validated in other works but has yet to inform surgical procedures in the 3D space. This process allowed us to determine the intended location for the TEVG used in surgical simulation and CFD analysis, as well as the observed location of the implanted TEVG within the porcine model. Consequently, we calculated the difference between the intended and observed locations to determine the offset that occurs during cardiovascular surgery. We saw greater displacement in aortic grafts, which might be due to the more constrained operating space of PAs compared with aortas.

The results of this study validate the benefit of patient-specific TEVGs when implanted in vivo in porcine models. When the TEVG was implanted closer to the intended position that was used in surgical simulation and CFD analysis, results show improved WSS (decreased WSS in the postoperative case vs the preoperative). In other words, patient-specific TEVGs aim to reduce WSS when implanted correctly, revealing the importance of patient-specific design in optimizing hemodynamics. We found no correlations relating TEVG implantation location and the other hemodynamic parameters of energy loss, vorticity, and helicity.

However, it was also shown that greater TEVG displacement of the implanted TEVGs had negative effects on hemodynamics, increasing WSS in the postoperative cases. As shown in the histological analysis, high WSS produced intimal hyperplasia in a PA TEVG graft compared with its native tissue. Conversely, a PA sample with lower WSS showed similar formation of smooth muscle layer to its native tissue. In future work we will investigate additional histological analyses in other tissue samples, because our limited findings might not be representative for the whole cohort. Overall, the location of the TEVG matters, and precision-guided implantation must be improved for patient-specific design to be its most effective.

Considering that high WSS ranges are linked to thrombosis formation, our engineers focused on minimizing WSS in areas with the highest values when designing the TEVGs.
graft shape. Although helicity and vorticity have been studied extensively as markers of secondary flow formations and efficiency, there is no relationship established between a specific range of these values to any clinical parameter. The animals included in our study were healthy pigs with normal aorta and PA anatomies, whereas vortex and helix formations are commonly seen in abnormal valve, stenosis, and aneurysmal dilatation. Last, geometrical differences between the designed and native anatomies were not significant enough to create major changes in vorticity and helicity; thus, we did not consider optimizing these parameters when designing the TEVGs.

CFD surgical simulations show promising insights into improving cardiovascular surgery as a surgical planning tool. By simulating different models, CFD can reveal a TEVG configuration that can bypass surgical issues and optimize hemodynamic performance. However, the greatest challenge is for surgeons to reproduce the suggested operation with similar outcomes. For example, Trusty and colleagues showed that CFD-optimized Fontan conduits might still have deviations in predicted hepatic flow distribution, as a result of offset error during implantation. Such fidelity is only achieved by the surgeon’s involvement in preoperative modeling to create a surgically feasible configuration and commitment to precisely execute in the operating room. Methodological improvements are necessary to increase the overall accuracy and reproducibility of surgical planning; otherwise, the benefits of CFD will not be observed.

This study is limited because of its small sample size of 11 porcine models. The porcine animal model has an expedited growth curve compared with humans, whereas vortex and helix formations are commonly seen in abnormal valve, stenosis, and aneurysmal dilatation. Last, geometrical differences between the designed and native anatomies were not significant enough to create major changes in vorticity and helicity; thus, we did not consider optimizing these parameters when designing the TEVGs.

CONCLUSIONS

Patient-specific TEVGs are designed for precise locations to help optimize hemodynamics. The greater the difference between the intended versus actual implantation location of a TEVG, the worse the observed hemodynamic performance in terms of WSS. This underscores the importance of not only patient-specific design but also precision-guided implantation to optimize hemodynamics in cardiac surgery. There still presents a need for a precision tool to mimic implantation locations used in surgical simulations.

Conflict of Interest Statement

J. Johnson, A. Krieger, and N. Hibino are inventors listed on International Patent WO/2017/035500A1 (Patient-Specific Tissue Engineered Vascular Graft Utilizing Electrospinning). The patent filing has been disclosed for grant applications and to institutions. J. Johnson and N. Hibino are equity holders in Nanofiber Solutions. All other authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: tissue-engineered vascular grafts, displacement, wall shear stress, computational fluid dynamics, center of gravity, hemodynamics, surgical planning
FIGURE E1. Displacement, wall shear stress, energy loss, helicity, and vorticity for all 11 porcine models. Hemodynamic images reflect pre- (top) and postoperative (bottom) vasculature at systole. Note that images are 2-dimensional, which might not fully display the 3D data.