Computational fluid dynamics in patients with continuous-flow left ventricular assist device support show hemodynamic alterations in the ascending aorta

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Objective: Increased use of continuous-flow left ventricular assist devices for long-term mechanical support necessitates a better understanding of hemodynamic changes in the native heart and the ascending aorta. By using patient-specific computational models, correlations of potentially adverse hemodynamic conditions with the orientation of the left ventricular assist device outflow graft and their relationship with aortic insufficiency and ischemic events were investigated.

Methods: Computed hemodynamic parameters, including wall shear stress, pressure in the ascending aorta, and dissipation of turbulent energy, were correlated with the orientation of the left ventricular assist device graft outflow in 5 patients (4 with the HeartMate II device [Thoratec Corp, Pleasanton, Calif] and 1 with the HeartWare Ventricular Assist Device [HeartWare Inc, Framingham, Mass]; 3 patients experienced moderate aortic insufficiency, and 2 patients experienced ischemic events). Hemodynamic conditions for aortic insufficiency and ischemic events were differentiated by linear discriminant analysis.

Results: Positive correlations between left ventricular assist device outflow graft orientation and wall shear stress, pressure, and turbulent energy dissipation in the ascending aorta were found ($R^2 > 0.68$). Linear discriminant analysis indicated a relationship of the velocity magnitude of retrograde flow toward the aortic root with aortic insufficiency and of the turbulent energy and wall shear stress with ischemic events.

Conclusions: Computational fluid dynamic simulations using clinical image data indicate altered hemodynamic conditions after left ventricular assist device implantation. Consequently, the left ventricular assist device outflow graft should be placed so the jet of blood is aimed toward the lumen of the aortic arch to avoid turbulences that will increase wall shear stress and retrograde pressure of the aortic root. Further investigations are warranted to confirm these findings in a larger patient cohort. (J Thorac Cardiovasc Surg 2014;147:1326-33)

Supplemental material is available online.

Patients with end-stage heart failure who are not eligible or waiting for a heart transplant may undergo implantation of a left ventricular assist device (LVAD) to improve functional capacity and quality of life and prolong survival.¹⁻⁴ The

concept of long-term mechanical support is bridge to decision, bridge to transplantation, or destination therapy.⁵⁻⁷ In some cases, mechanical circulatory support may allow for the recovery of the native heart.^{8,9}

The long-term use of continuous-flow LVAD support requires a better understanding of the alterations in hemodynamics and their impact on the native heart and major vessels. One of these well-known architectural changes after LVAD implantation includes the development or progression of aortic valve diseases, mainly aortic insufficiency (AI).¹⁰⁻¹² In turn, AI may compromise LVAD function, eventually causing multiple organ malperfusion. Moreover, severe AI may prevent the recovery of the native heart after LVAD support and require aortic valve implantation.¹³

Patient-specific modeling of hemodynamic conditions using computational fluid dynamics (CFD) has been demonstrated in a variety of vascular diseases (ie, cerebral aneurysms, aortic dissections, aortic aneurysms, and carotid atherosclerosis).¹⁴⁻¹⁸ From these computational simulations, a variety of hemodynamic parameters, in

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Abbreviations and Acronyms

AI	= aortic insufficiency
CFD	= computational fluid dynamics
CT	= computed tomography
CTA	= computed tomography angiography
IE	= ischemic event
LDA	= linear discriminant analysis
LVAD	= left ventricular assist device
WSS	= wall shear stress

particular wall shear stress (WSS), are available that are not reliably accessible by clinical imaging methods.¹⁹⁻²¹ CFD is a clinical research tool that is gaining increasing popularity in a complementary approach to clinical imaging toward revealing distinct features of altered hemodynamics in the course of vascular diseases in individual patients.¹⁹

CFD was used in the current study to characterize potentially adverse hemodynamic conditions in 5 patients with continuous-flow LVAD devices and to explore the relationship of selected hemodynamic parameters with AI and ischemic events (IEs). The study was motivated by the increased incidence of AI and IEs in this patient group.^{13,22}

MATERIALS AND METHODS

Patients

The study was approved by the local ethics committee, and the patients gave written informed consent. Clinical computed tomography angiography (CTA) images were retrospectively collected from 5 patients (cases). The geometry of the LVAD graft inflow varied among patients with respect to the angle at which the LVAD outflow graft was inserted into the ascending aorta (azimuth angle), allowing for a systematic investigation of this angle on the hemodynamics at the aortic root. In the 5 patients, 4 HeartMate II devices (Thoratec Corp, Pleasanton, Calif) and 1 HeartWare Ventricular Assist Device (HeartWare Inc, Framingham, Mass) were implanted. The flow of the device in all patients was 4 to 5 L/min. The time of LVAD implantation to computed tomography (CT) investigation was on average 11.6 months (range, 5-30 months). At the time of the CT study, all patients were mobile. AI developed in patients 1, 2, and 5 after LVAD implantation (grade I-II). AI was measured noninvasively by trans-thoracic echocardiography according to the guidelines and standards of the American Society of Echocardiography. None of the patients had preoperative AI or developed AI postoperatively on echocardiography until discharge from the hospital. Patient 3 had an ischemic stroke 3 months after LVAD implantation, and patient 5 had an IE (colon ischemia) 12 months after LVAD implantation.

Geometric Characterization

For quantitative assessment, the position of the LVAD outflow graft was characterized by 2 angles (Figure 1). The first angle describes the lateral aspect of the LVAD graft orientation: First, the computational model was oriented to provide a view from the head down to the arch (Figure 1, A). Then, a line through the 2 midpoints of the ascending and descending aorta was drawn. Another line was drawn as the midline of the distal LVAD

outflow graft. The angle between these 2 lines was defined as the azimuth angle. The second angle describes the horizontal alignment of the LVAD graft relative to the ascending aorta: First, the midline of the ascending thoracic section of the aorta was drawn. Then, the midline of the distal LVAD outflow graft was drawn. The angle between these 2 lines was defined as the polar angle.

Computational Fluid Dynamics Simulations

CFD, as a branch of fluid dynamics, uses numeric methods to solve problems that involve fluid flows. Computational algorithms that approximate the real system and use boundary conditions define the geometry and the inflow and outflow parameters of the model, and calculate the velocity vector field and other derived hemodynamic parameters, such as pressures and WSS (ie, forces), which the fluid exerts onto the wall. In the first step of this process, the physical bounds of the computational model are defined.¹⁸ This defined volume is then divided into small elements (cells) that constitute the computational mesh. The governing physical equations, for this case, the Navier–Stokes equations, are then iteratively solved on the computational mesh taking into consideration the boundary conditions. Post-processing software is then used for further analysis and visualization.²³

The methodology for the CFD simulations for these kind of computational models of LVAD devices have been developed previously.²⁴ Technical details on how the computational models were created from the boundary conditions and the CFD simulations were carried out are provided in Appendix 1.

Qualitative analysis. For a qualitative overview, 3-dimensional surface reconstructions of the contours for the dynamic pressure, WSS, and streamlines were created for systolic flow.

Quantitative analysis. Pressure, velocity magnitude, turbulence dissipation, and turbulence energy were averaged over the cardiac cycle in a region of interest, which comprised the aortic lumen from the aortic root to a distance 3 cm distally. WSS was averaged over the cardiac cycle at the wall segment located contralaterally to the LVAD graft by extending a straight line across the aorta from the mid-point of the anastomotic opening. Potential relationships of these averaged hemodynamic parameters with the azimuth and the polar angle were evaluated with the Pearson correlation coefficient.

Exploratory linear discriminant analysis (LDA) (R-language, lda function of the “MASS” package) was used to investigate the relationships of the geometric parameters (azimuth and polar angle) and hemodynamic parameters (averaged velocity magnitude, WSS, pressure, turbulence dissipation, and turbulence energy) with the occurrence of AI (patients 1, 2, and 5) and IE (patients 3 and 5).

RESULTS

Geometric Characterization

The azimuth angle varied between 2 and 51 degrees because of the difference in location of the LVAD graft (anterior or lateral) and the difference in angle of the aortic arch relative to the LVAD graft (Figure 1, A). The polar angle varied between 29 and 78 degrees, with the largest value for patient 1.

Computational Fluid Dynamics Simulation Analysis

Qualitative analysis. No significant variation of the relative spatial distribution of the 3-dimensional velocity field and the streamlines derived from it was found during the cardiac cycle, motivating the use of averaged values for the hemodynamic parameters in the consequent

FIGURE 1. Visualization of geometry of the 5 computational models used in this study. A, View from the head looking down on the arch. On the *left* computational model (patient 1), the definition of the azimuth angle is shown: It was defined as the angle between the *line* (m) through the mid-points of the ascending (P1, *white dot*) and descending (P2, *white dot*) thoracic aorta and the midline of the distal LVAD outflow graft (g). B, Lateral view displaying geometric relationship between the wall of the ascending aorta and the LVAD graft anastomosis, which was quantified by the polar angle (values listed below models). On the computational model for patient 1 (*left*), the definition of the polar angle is shown: It was defined as the angle between the midline of the distal LVAD outflow tract (g) and the midline of the ascending aorta (a).

quantitative analysis. The contours of dynamic pressure projected at the wall of the computational model reveal

a region of elevated pressure in close proximity of the location of the LVAD graft anastomosis site (Figure 2, A). High pressures on the contralateral wall occurred in cases 1 and 3, whereas high pressures occurred on the ipsilateral wall distal to the anastomosis site in cases 2 and 5. No focal high pressure zones were found for case 4.

Visual inspection of the streamlines at systole revealed impingement zones corresponding to high pressure zones (Figure 1, B). For all cases, streamlines indicated unordered flow in the ascending aorta and the aortic arch of varying degree, most pronounced for cases 1, 3, and 4. In case 4, horizontally oriented vertices were noted extending into the descending aorta (Figure 2, B).

Contours of WSS followed qualitatively the pattern observed for the dynamic pressure (Figure 2, C). The LVAD graft itself was not the focus of this investigation; however, its high tortuosity for cases 3 and 4 resulted in focal high values for dynamic pressure and WSS. Table 1 shows the patients with AI and important causative factors.

Quantitative analysis

Correlation of hemodynamic and geometric parameters. Good correlations among pressure, WSS, and dissipation of turbulent energy and LVAD outflow graft orientation (as expressed by the azimuth and the polar angle) were found (Table 2 and Figure 3). Correlation for the remaining hemodynamic parameters (averaged velocity magnitude and turbulence energy) was weak.

FIGURE 2. A, Contours of dynamic pressure. B, Streamlines. C, WSS for systole. Focal regions of high pressure on the contralateral wall can be appreciated in cases with high azimuth angle (cases 1 and 3, *filled arrows*) where there is an impingement zone of the flow at the contralateral wall. In addition to these zones, focal regions of high pressures were found on the ipsilateral wall in cases with low azimuth angle (cases 2 and 5, *open arrows*) immediately at the anastomosis site. Disturbed flow in the ascending aorta can be appreciated for all cases as visualized by the unordered streamlines.

TABLE 1. Patients with aortic insufficiency along with important causative factors are listed

Patients with postoperative AI		Proximal position of the outflow graft: Blood jet collides with contralateral wall, causing turbulent flow in the ascending aorta	Distal position of the outflow graft: Blood jet flows into the aortic arch, avoiding “collision” with the contralateral wall and turbulences
Patient 1	x	x	
Patient 2	x	x	
Patient 3			x
Patient 4			x
Patient 5	x	x	

AI, Aortic insufficiency.

Liner discriminant analysis. In view of the small number of patients in whom AI developed (n = 3) and who experienced IE (n = 2), these LDA results should be considered exploratory and preliminary.

The velocity magnitude of the (retrograde) flow in the ascending aorta as a possible discriminating factor was found in the AI group (Figure 4). Single variation analysis (Student *t* test) revealed a *P* value of .048 when comparing the means for the velocity magnitude in the group of patients with AI versus the group of patients without AI.

A similar LDA analysis for IE did not identify a single hemodynamic parameter related to IEs. Turbulent energy in the ascending aorta and WSS exhibited highest values for the linear discriminant (Figure 4), with *P* values greater than .19 for single variance Student *t* test analyses.

DISCUSSION

These CFD results demonstrate altered hemodynamics in the ascending aorta and aortic root of LVAD-supported patients compared with the aorta of healthy subjects. This comes as no surprise because the jet flow of blood hits the contralateral aortic unless it is diverted into the lumen of the aortic arch without “collision” with the aortic wall, as can be observed in patient 4 (Figure 2).^{22,25} Retrograde flow of the outflow graft into the ascending aorta has been shown to induce an altered hemodynamics compared with the healthy aorta consisting of an early aortic valve closure and a shortened systole.^{25,26} Possible consequences may be blood stasis and thrombus formation in the aortic root area, as well as structural

TABLE 2. Squared correlation coefficient values (*R*²) indicating the strength of linear correlation with regard to geometric parameters (azimuth and polar angle of the left ventricular assist device graft inflow) with hemodynamic parameters (averaged over the cardiac cycle)

<i>R</i> ²	Azimuth angle	Polar angle
Pressure	0.96	0.76
WSS	0.70	0.95
Turbulence dissipation	0.87	0.68
Velocity magnitude	0.02	0.20
Turbulence energy	0.28	0.11

WSS, Wall shear stress.

remodeling of the aortic valve. This remodeling is accompanied by functional problems, such as aortic stenosis and AI due to pressure-induced valvular and aortic wall damage.¹³ In most cases, fibrous tissue is deposited at the commissures preventing complete opening. In addition, increased matrix metalloproteinases and activated endothelial cells have been identified during periods of high circumferential stretch in the leaflets that further upregulate growth factors and integrins as cell-signaling mediators.^{26,27} Before ventricular assist device support, a high left ventricular end-diastolic pressure can mask the severity of AI. However, we selected only patients who did not have AI after LVAD implantation.

The contribution of modified aortic flow patterns leading to clinically significant AI has not been described in detail in this patient cohort.^{10,28,29} The shear stress distribution on the wall of the aorta is known to be modified after LVAD implantation.³⁰ Large flow disturbances arise when the LVAD is functioning in series with proximal aortic outflow cannulation^{25,31,32} because blood velocity in the LVAD graft is unphysiologically elevated because of the relatively small conduit cross-section.²⁵ Various authors have demonstrated histologic changes in the aortic wall in response to high shear stress caused by this high-velocity LVAD outflow.^{25,31,32} Both patients with continuous-flow circulatory support showed histologic changes, such as thinning of the aortic medial layer, decreased smooth muscle cells, increased atrophic smooth muscle cells, and decreased elastin content of the aortic medial layer. Aortic valve pathology during LVAD support seems to be a remodeling process in response to high transvalvular pressures with resulting fusion of the leaflets.

Pathologic changes of the aortic valve have clinical implications in LVAD-supported patients. LVAD-supported patients who have aortic valve insufficiency have a limited exercise capacity because of decreased parallel flow and subendocardial ischemia. Aortic fusion seems to be responsible for a lower rate of myocardial recovery in patients with LVADs.^{13,22,25,31-35}

Our study demonstrated that the angle of the LVAD inflow graft has a direct influence on the flow patterns in the ascending aorta. In particular, we found increased focal WSS and dynamic pressure changes opposite of

FIGURE 3. Correlation plots illustrating the linear relationships between geometric (azimuth and polar angle) and hemodynamic (pressure, WSS, and turbulence dissipation) parameters. WSS, Wall shear stress.

the inflow graft in the aortic wall and retrograde flow to the aortic root.

According to our results, we recommend a more distal insertion of the LVAD outflow graft that enables direct jet blood flow into the lumen of the aortic arch and low LVAD flows early after the intervention, particularly in individuals with small body surface areas, to produce at least occasional parallel flow through the aortic valve and daily echocardiographic examinations to ensure intermittent aortic valve opening through adaptation of the LVAD flow. However, this approach requires more para-aortic preparation at the time of possible heart transplantation to have a proper crossclamp space close to the aortic arch. In addition, it is not clear whether less turbulence in the aortic root may cause stasis at the level of the aortic valve and create a risk factor for thromboembolic events, although we believe that the nonopening aortic valve is the main culprit for such a complication. After myocardial recovery, the LVAD output can then be gradually increased in the postoperative trajectory. This strategy reduces the transvalvular pressure gradient and shear stress on the aortic valve compared with the series-working mode of the LVAD. Adapting this regimen in LVAD-supported patients may prevent pressure-related changes in the aortic root.

The high statistical correlation of this velocity magnitude with the occurrence of (early) AI is remarkable but has to be

considered with caution because of the low number of cases in each group. Likewise, the lack of statistical correlation with the occurrence of IEs also awaits confirmation in a study with a larger number of cases.

Study Limitations

One of the limitations of this study is the low number of patients investigated. LVAD-supported patients who require CT with contrast material are rare, for example, CT is indicated in complicated procedures.^{36,37} Second, longitudinal follow-up was not performed in these options. Such follow-up studies are of interest to compare baseline hemodynamics (potentially before LVAD implantation) with alterations of the hemodynamics after LVAD implantation over time.³⁸ The CT datasets were acquired between 5 and 30 months after LVAD implantation. This is another clinical limitation. For comparison purposes, it would have been ideal to have CT datasets from the same time point after LVAD implantation. Once again, this patient population is rare, and it would have been unethical to perform a prospective CT contrast-enhanced study with potential harmful effects for the patients.

CONCLUSIONS

A growing number of patients undergo LVAD implantation for heart failure treatment.³⁹⁻⁴⁷ This study

FIGURE 4. Results of an exploratory linear discrimination analysis for 2 scenarios: A, Bar plots illustrate values of the linear discriminants for AI (left) and IE (right). B, Post hoc Student *t* test for the hemodynamic parameters with the highest discriminants for AI (left) and IE (right). A good separation between patients with and without AI can be appreciated corresponding to large value for the velocity magnitude as the dominating linear discriminant (filled arrows); a similar finding is absent for IE. AI, Aortic insufficiency; IE, ischemic event; WSS, wall shear stress.

demonstrates that angle and location of the LVAD outflow graft influence the aortic blood flow dynamics and kinetics in the ascending aorta. As we move toward a future of long-term cardiac support, further studies will be needed to determine the clinical significance of altered aortic flow patterns in LVAD-supported patients.

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APPENDIX 1. TECHNICAL DETAILS FOR COMPUTATIONAL FLUID DYNAMICS SIMULATIONS

From the CTA image data (axial or coronal images, in-plane resolution 0.53-0.75 mm, slice thickness 3 mm), 3-dimensional surface reconstructions of the thoracic aorta and LVAD outflow cannula were constructed and stored as stereolithographic files (Paraview; Kitware Inc, Canonsburg, Pa) (Figure 1, B). From these stereolithographic files, tetrahedral meshes for the CFD simulations were created (GAMBIT; Ansys Inc, Pittsburgh, Pa). Final mesh sizes were as follows: patient 1: 676,700; patient 2: 732,633; patient 3: 579,028; patient 4: 609,578; and patient 5: 679,775. To reduce computational bandwidth, tetrahedral elements were converted to polyhedral elements before the computations. Boundary conditions at the aortic valve were modeled as follows: during systole, the aortic valve was assumed to be open with a fraction of 5% cardiac output derived from the velocity waveform of a healthy volunteer (2-dimensional phase contrast, 2-dimensional phase contrast magnetic resonance imaging). At all other times during the cardiac cycle, the aortic valve was assumed to be closed (no AI). Because the exact contribution of the native heart was unknown, a sensitivity analysis was performed (Appendix 2). The total duration of the simulated cardiac cycle was 765 ms. CFD simulations comprised 3 cardiac cycles to

allow for the decay of initial transients, and the results are reported for the third cycle. The realizable k- ϵ model was used for the CFD simulations (Fluent; Ansys Inc) to account for potential turbulent effects due to the relatively high Reynolds number (2625 for a velocity of 1 m/s and a diameter of 1 cm for the LVAD cannula). Inflow from the LVAD device was kept constant at 1 m/s for the simulations. Zero pressure conditions were used at the outflows of the model. Computations were performed on a Dell workstation (Dell Inc, Round Rock, Tex) equipped with 2 dual-core 3.2 GHz processors using 4 parallel processes. The total time of computation for both geometries was approximately 4 hours. A mesh independence study for case 1 was performed, and final mesh size for the remaining cases was adapted from the results for this case. Values for hemodynamic parameters available at the nodes of the computational meshes were converted into CFD image data using the Shepard method (Visualization Tool Kit VTK, Kitware Inc), and conventional image analysis algorithms were used for subsequent quantitative analysis (ImageJ; National Institutes of Health, Bethesda, Md).

APPENDIX 2. INFLUENCE OF NATIVE CARDIAC OUTPUT ON COMPUTATIONAL FLUID DYNAMICS SIMULATION RESULTS

The contribution of the remnant native cardiac output to the aortic flow is in general unknown. Indications (as discussed in the text) exist that only a small fraction, if at all, is contributed by the heart itself. In the presented study, 5% of the cardiac output from the waveform of a healthy volunteer was therefore used. To gain insight into the dependence of the results on this remnant cardiac output, an additional CFD simulation was performed for case 1, in which the aortic valve was assumed to be closed during the entire cardiac cycle with constant inflow from the LVAD (1 m/s). Good qualitative, quantitative agreement was found for the distribution of the WSS and the pressure on the wall of the aortic model (Figure E1). As is the case with remnant cardiac outflow, retrograde flow toward the aortic root also was observed in this case. These results indicate a weak dependence on a (small) remnant cardiac output, indicating that its exact value to the aortic flow for the findings discussed in this article may result in only a second-order correction (if any).

FIGURE E1. Contours of dynamic pressure (A), stream lines (B), and WSS (C) in a CFD simulation for case 1, where the contribution from the native heart was removed (velocity at the aortic root set to zero). The results shown should be compared with the *left* column of Figure 2. Good qualitative, quantitative agreement of the main features in the distribution of the WSS, pressure, and stream lines is apparent.