

## Use of patient-specific computational models for optimization of aortic insufficiency after implantation of left ventricular assist device

Patpilai Kasinpila, MD,<sup>a</sup> Sandra Kong,<sup>a</sup> Robyn Fong, BS,<sup>a</sup> Rohan Shad, MD,<sup>a</sup> Alexander D. Kaiser, PhD,<sup>b,c</sup> Alison L. Marsden, PhD,<sup>c,d</sup> Y. Joseph Woo, MD,<sup>a</sup> and William Hiesinger, MD<sup>a</sup>

### ABSTRACT

**Objective:** Aortic incompetence (AI) is observed to be accelerated in the continuous-flow left ventricular assist device (LVAD) population and is related to increased mortality. Using computational fluid dynamics (CFD), we investigated the hemodynamic conditions related to the orientation of the LVAD outflow in these patients.

**Method:** We identified 10 patients with new aortic regurgitation, and 20 who did not, after LVAD implantation between 2009 and 2018. Three-dimensional models of patients' aortas were created from their computed tomography scans. The geometry of the LVAD outflow graft in relation to the aorta was quantified using azimuth angles (AA), polar angles (PAs), and distance from aortic root. The models were used to run CFD simulations, which calculated the pressures and wall shear stress (rWSS) exerted on the aortic root.

**Results:** The AA and PA were found to be similar. However, for combinations of high values of AA and low values of PA, there were no patients with AI. The distance from aortic root to the outflow graft was also smaller in patients who developed AI ( $3.39 \pm 0.7$  vs  $4.07 \pm 0.77$  cm,  $P = .04$ ). There was no significant difference in aortic root pressures in the 2 groups. The rWSS was greater in AI patients ( $4.60 \pm 5.70$  vs  $2.37 \pm 1.20$  dyne/cm<sup>2</sup>,  $P < .001$ ). Qualitatively, we observed a trend of greater perturbations, regions of high rWSS, and flow eddies in the AI group.

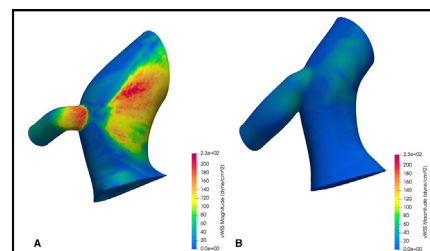
**Conclusions:** Using CFD simulations, we demonstrated that patients who developed de novo AI have greater rWSS at the aortic root, and their outflow grafts were placed closer to the aortic roots than those patients without de novo AI. (*J Thorac Cardiovasc Surg* 2020; ■:1-8)

The use of left ventricular assist devices (LVADs) for the treatment of advanced heart failure has steadily increased over the past decade, with more than 2500 implants per year.<sup>1</sup> Complications with long-term LVAD support arise from altered hemodynamics and structural changes. In

From the <sup>a</sup>Department of Cardiothoracic Surgery, Stanford University School of Medicine; and Departments of <sup>b</sup>Bioengineering and <sup>c</sup>Pediatrics (Cardiology), and <sup>d</sup>Institute for Computational and Mathematical Engineering, Stanford University, Stanford, Calif.

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Dr Kasinpila and Ms Kong contributed equally to this article.



Velocity and wall shear stress in patients without AI (A) and with AI (B).

### CENTRAL MESSAGE

LVAD outflow graft positioning has an effect on blood fluid dynamics at the aortic root. Optimized graft placement can potentially reduce development of new aortic insufficiency in LVAD patients.

### PERSPECTIVE

Aortic incompetence (AI) is a recognized phenomenon that occurs in a greater rate in LVAD patients. Here, computational fluid dynamics is used to simulate blood flow in LVAD patients. We found differences in flow patterns between patients who developed AI and those who did not, suggesting that graft positioning can be optimized to reduce the risk of AI development in LVAD patients.

See Commentary on page XXX.

particular, the development of aortic incompetence (AI) in patients with LVADs is well-documented, ranging from 15% to 25% after 1 year of support. AI leads to several downstream effects, such as recurrent heart failure symptoms, reduced cardiac output, end-organ malperfusion,

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Address for reprints: William Hiesinger, MD, Falk Cardiovascular Research Center, 870 Quarry Rd, Palo Alto, CA 94304 (E-mail: [Willhies@stanford.edu](mailto:Willhies@stanford.edu)). 0022-5223/\$36.00

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**Abbreviations and Acronyms**

3D	= 3-dimensional
AA	= azimuth angle
AI	= aortic incompetence
cf	= continuous flow
CFD	= computational fluid dynamics
CT	= computed tomography
LVAD	= left ventricular assist device
PA	= polar angle
rP	= pressure at aortic root
rWSS	= wall shear stress at aortic root
WSS	= wall shear stress

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and elevated left ventricle filling pressures.<sup>2</sup> Moreover, patients with LVADs and moderate-to-severe AI were found to be at greater risk of rehospitalizations and mortality.<sup>3</sup> Device adjustments, particularly increasing flow to compensate for reduced forward flow, only provide temporary solutions and increase device load.

Computational fluid dynamics (CFD) has been used to study complications associated with LVADs as case studies or in small cohorts.<sup>4</sup> These have indicated that the development and progression of AI can be attributed to the geometric positioning of the LVAD inflow graft and changes in the resulting hemodynamic parameters (wall shear stress [WSS], pressure, and velocity) at the aortic root region.<sup>4,5</sup> However, most studies of this nature are limited by small sample sizes, simplified boundary conditions, and the lack of patient-specific models.<sup>4,6,7</sup> In addition, only recently have comprehensive pipelines for modeling and simulating patient-specific geometries become accessible.<sup>8</sup>

In this study, 3-dimensional (3D) CFD simulations were performed on our cohort of 30 patients (10 with AI, 20 without AI) to determine the effect of the geometric positioning of the outflow graft on hemodynamic conditions and the development of AI. We tested the hypothesis that certain anastomotic angles between the LVAD outflow tract and the aortic wall modulate the development of AI due to changes in flow characteristics in the ascending aorta. We also hypothesized that outflow tracts anastomosed closer to the aortic root will increase WSS and pressure values in the region, ultimately contributing to aortic leaflet degradation and aortic insufficiency.

**METHODS****Patient Population**

With approval from the Stanford University institutional review board (IRB-40972; date approved: May 11, 2017), we retrospectively reviewed 309 patients between the period of 2009 and 2018. Study data were collected and managed using the REDCap electronic data capture tool.<sup>9</sup> The data were deidentified using the Health Insurance Portability and Accountability Act Safe Harbor method. We identified 27 patients who developed new or worsening AI post-LVAD implantation. Severity of AI was determined by echocardiographic guidelines. Of the 27 patients who met the AI inclusion criteria, 17 did not have thoracic computed tomography (CT) scans of sufficient resolution for 3D reconstruction, measurements of angles, and fluid dynamics simulations. The 10 remaining patients had no aortic valve interventions nor bicuspid valves. Random sampling of 20 control patients was performed based on the following criteria: no preoperative AI, no de novo AI development, and an average duration of LVAD support similar to or more than that of the AI cohort. Clinical images in the form of 1-week postoperative noncontrast and contrast CT images were then retrospectively collected from the 10 patients with AI and the 20 patients without AI following LVAD implantation from 2013 to 2018. There were no significant differences in the severity of preoperative AI between the 2 groups ( $P = .06$ ; confidence interval,  $-0.02$  to  $0.7$ ). Data on systolic and diastolic blood pressures, measured via a standard blood pressure cuff at the level of the brachial artery, were collected from 1-month, 6-month, and 1-year follow-up visits. In the AI population, 6 patients received the HeartMate II (Abbott, Abbott Park, Ill), and 4 patients received the HeartWare (Medtronic, Minneapolis, Minn) device. In the non-AI population, 15 patients receive HeartMate II, and 5 patients received HeartWare. Mean LVAD flow was  $4.54 \pm 0.91$  L/min.

**CFD Simulation Pipeline**

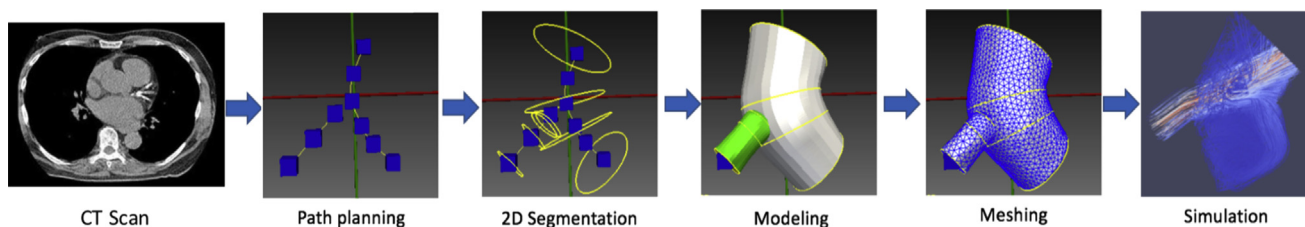
The CFD studies were performed on SimVascular, an open-source cardiovascular simulation package (Figure 1).<sup>8</sup> The collected CT images were used to first create path lines of the aortic root, proximal aortic arch, and distal LVAD outflow tract in a 3D space. The vessel boundaries were manually defined at each horizontal cross-section along the path lines to create 2-dimensional vascular outlines called “segmentations,” and a 3D model was generated from these segmentations. No flow was assumed at the aortic valve, as most patients did not have native valve ejection, and there was no statistically significant difference of native valve opening between the AI group and the non-AI group. Laplacian smoothing methods were applied to the walls of the generated model to eliminate sharp transition zones between vessels.

Each 3D model was subdivided into a 3D grid of 100,000 subunits, where each subunit of the grid is the domain within which the flow solver calculates velocities and pressures based on the patient-specific measurements and resistance parameters we input. The results from each subunit of this grid are then integrated over the entire geometry for the duration of the simulation, ensuring the basic principles of conservation of mass and momentum are not violated.

The simulations were run on the Sherlock high-performance computing cluster provided by the Stanford Research Computing Center under the following conditions: incompressible Newtonian fluid, rigid wall, no-slip condition, patient-specific nonphasic steady flow at the inlet, and constant resistance ( $1333.2$  dyne/cm<sup>2</sup>) at the outlet. Flow was governed by the time-dependent incompressible Navier–Stokes equations, and calculated pressures were validated with clinically measured mean arterial pressures.

**Geometric Characterization**

A computer-aided design modeling program, Fusion 360, was used to measure the polar angle (PA), azimuth angle (AA), and the distance between the outflow graft and the sinotubular junction of the aortic root for each model. The AA or “horizontal angle” is defined as the angle made



**FIGURE 1.** SimVascular pipeline to generate 3D computational fluid dynamics simulations. Computed tomography images were used to create path lines. 3D models were generated using manually defined vessel boundaries created at horizontal cross-sections. Simulations of the models discretized into an unstructured mesh were ran on the Sherlock cluster and postprocessed in ParaView. *CT*, Computed tomography.

between the vertical plane passing through the midpoints of both the ascending and descending aorta, and the axis through the center of the outflow graft at the anastomosis site (Figure 2). The polar angle, or “vertical inclination,” is defined as the angle between the vertical axis through the lumen of the ascending aorta, and the axis through the center of the outflow graft at the anastomosis site (Figure 2).

### Qualitative Analysis

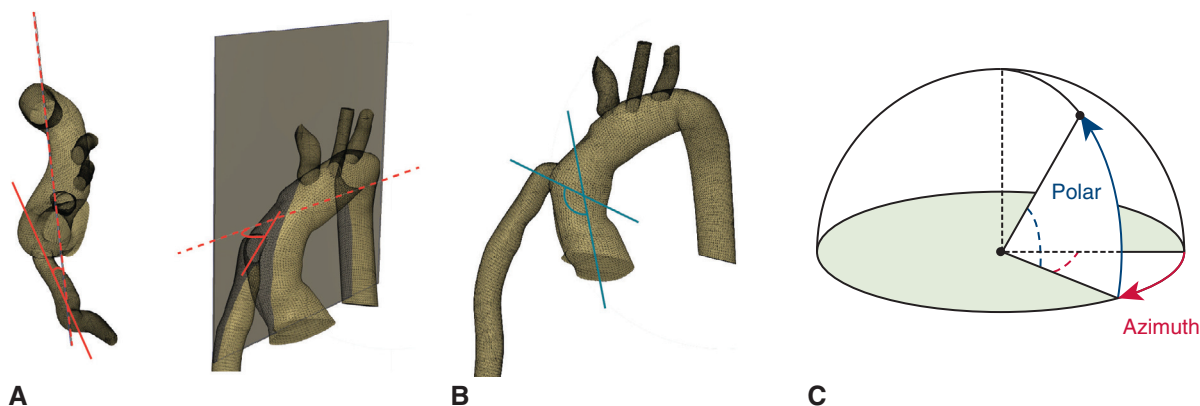
Data were postprocessed using the open-source visualization toolkit ParaView (Kitware, Inc, Clifton Park, NY). Time-averaged WSS from the aortic wall as well as pressure and velocity data from the aortic root was mapped and exported for analyses for both cohorts. The exported data were analyzed using R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Measured pressures were validated against an average of 1-month, 6-month, and 1-year clinical blood pressure measurements taken at the level of the brachial artery. Categorical variables (sex, age, and LVAD) were compared using the Fisher exact test, and continuous variables (time-averaged WSS, pressure, and outflow implant distance) were compared using the Welch 2 sample *t* test.

### RESULTS

The age, sex, preoperative body mass index, and LVAD indication were similar between the AI and control patient cohorts (Table 1). No statistically significant difference of pump speed (rpm) between the AI and non-AI cohorts was found for both HeartMate II and HeartWare devices ( $P = .43$  and  $P = -.49$ , respectively).

The orientation and conformation of the outflow graft were defined in 3D space by combination of AA, PA, and measured distance between the outflow tract and the sinotubular junction. Azimuth and polar angles were found to be similar between the 2 patient groups; however, for a combination of high values of AA and values of PA up to  $80^\circ$ , there were fewer patients with AI (Figure 3). This effect was not statistically significant after we adjusted for distance of the graft from the root. The mean distance of the outflow graft from the root was found to be significantly larger in the AI group when compared with the control group ( $3.39 \pm 0.7$  vs  $4.07 \pm 0.77$  cm,  $P = .04$ ) (Figure 4).

Qualitatively, larger recirculation zones were present in the aortic roots of the AI group (Figure 5). In addition, in patients with LVADs who developed AI, focal areas of elevated pressure and WSS (wall shear stress at aortic root [rWSS]) were observed at the aortic root and at the region of the aortic wall contralateral to the outflow graft. Within the AI cohort ( $n = 10$ ), the mean pressure at the aortic root (rP) and rWSS at the aortic root were  $68.77 \pm 19.05$  mm Hg and  $4.60 \pm 5.70$  dyne/cm<sup>2</sup> respectively. Within the control cohort ( $n = 20$ ), the mean rP and rWSS were  $67.48 \pm 26.34$  mm Hg and  $2.37 \pm 1.20$  dyne/cm<sup>2</sup>, respectively. The distributions for rWSS were compared between the AI and control groups



**FIGURE 2.** A, Two panels showing the azimuth or “horizontal” angle on a 3-dimensional reconstructed aorta, along with the plane that intersects the ascending and descending aorta. B, Panel showing the polar angle, or “vertical inclination,” on the same geometry. C, A schematic diagram showing the relationship between the polar and azimuth angles.

TABLE 1. Baseline characteristics for the AI and non-AI groups

	AI		Control		P value
	Mean ± SD	Frequency	Mean ± SD	Frequency	
Age, y	63.28 ± 10.3		55.17 ± 13.97		.12
Sex					.77
Female		3 (30%)		5 (25%)	
Male		7 (70%)		15 (75%)	
Preoperative BMI, kg/m <sup>2</sup>	25.51 ± 6.88		26.93 ± 4.20		.59
LVAD type					.58
Heartmate II		6 (60%)		14 (70%)	
HeartWare		4 (40%)		6 (30%)	
Pump flow, L/min	4.37 ± 0.82		4.62 ± 0.95		.46
Pump speed, rpm					
Heartmate II	8955 ± 273		8839 ± 318		.43
HeartWare	2495 ± 52		2560 ± 207		.49
Duration of LVAD support, d	487 ± 281		795 ± 682		.09

Continuous variables were compared with Welch 2-sample *t* test, and categorical variables were analyzed with  $\chi^2$  tests. AI, Aortic incompetence; SD, standard deviation; BMI, body mass index; LVAD, left ventricular assist device.

( $4.60 \pm 5.70$  vs  $2.37 \pm 1.20$  dyne/cm<sup>2</sup>,  $P < .001$ ). Overall, we observed a trend of greater perturbations in flow at the aortic root in the AI cohort as compared with their non-AI counterparts, especially with regards to the rWSS. We studied the role of geometric parameters of the outflow graft on rWSS and found that the distance from the sinotubular junction was well correlated with rWSS ( $P = .005$ ; Spearman rho  $-0.49$ ); however, polar and azimuth angles were not.

## DISCUSSION

The natural history of AI on continuous-flow (cf) LVAD support is well studied: a recent retrospective analysis of 1399 patients revealed a progressive course of AI, with

more than 50% of patients on LVAD support developing mild AI at 2 years and 15% developing moderate-to-severe disease in 2 years.<sup>3</sup> Research has shown that patients on long-term cf-LVAD support with minimal native valve ejection are at greater risk of developing AI.<sup>10</sup> Multiple mechanisms have been proposed for the worsening of AI following LVAD support: commissural fusion and leaflet deterioration, aortic sinus dilatation, valvular remodeling and mal-coaptation, and increased transvalvular gradients.<sup>11-13</sup> A recent meta-analysis also demonstrated that duration of cf-LVAD support was significantly associated with de novo AI.<sup>10</sup> Thrombus deposition in the aortic root is also a known and potentially underdiagnosed phenomenon with cf-LVADs: prolonged mechanical unloading may result in aortic root stasis that favors clot formation.<sup>14</sup> At a cellular level, an increase in wall shear stresses may contribute to endothelial dysfunction, which, when coupled with long-term thrombus deposition over the commissures, may accelerate the development of AI.<sup>11,15,16</sup>

Although we did not find a statistically significant difference in velocity and pressure between the AI and control groups, WSS in the AI cohort was greater than that in the control group. Pathologic changes in WSS have been shown to increase endothelial dysfunction and may partially contribute to both thrombus deposition and aortic valvular fusion.<sup>16</sup> Our data also show that WSS alone cannot explain the role of the azimuth and polar angles in the development of AI. On qualitative assessment of flow patterns in our simulations, we observed regions of flow recirculation and large eddies in the region of the aortic root in patients who eventually developed AI. These are phenomenon known to promote platelet aggregation and eventual thrombosis.<sup>17,18</sup>

Although AI has been shown to be an independent predictor of mortality in patients with LVADs, attempts to

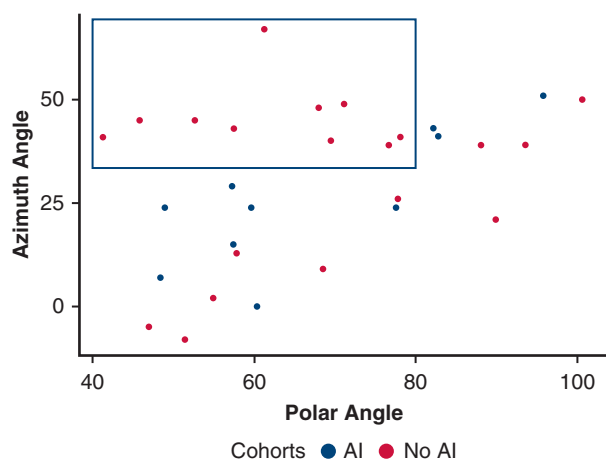
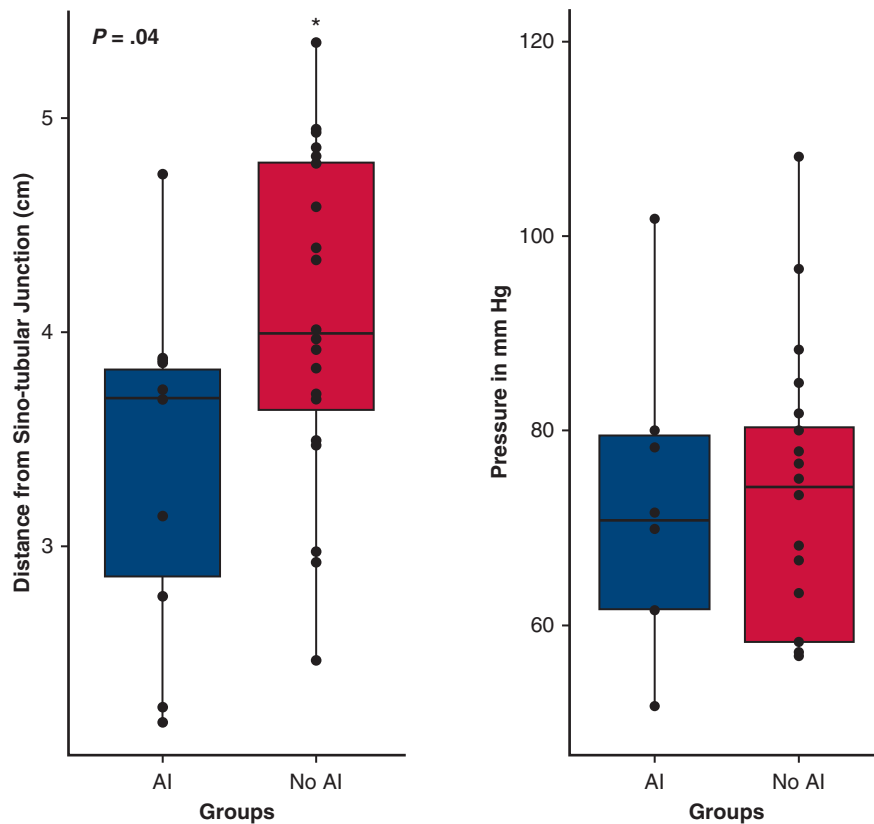


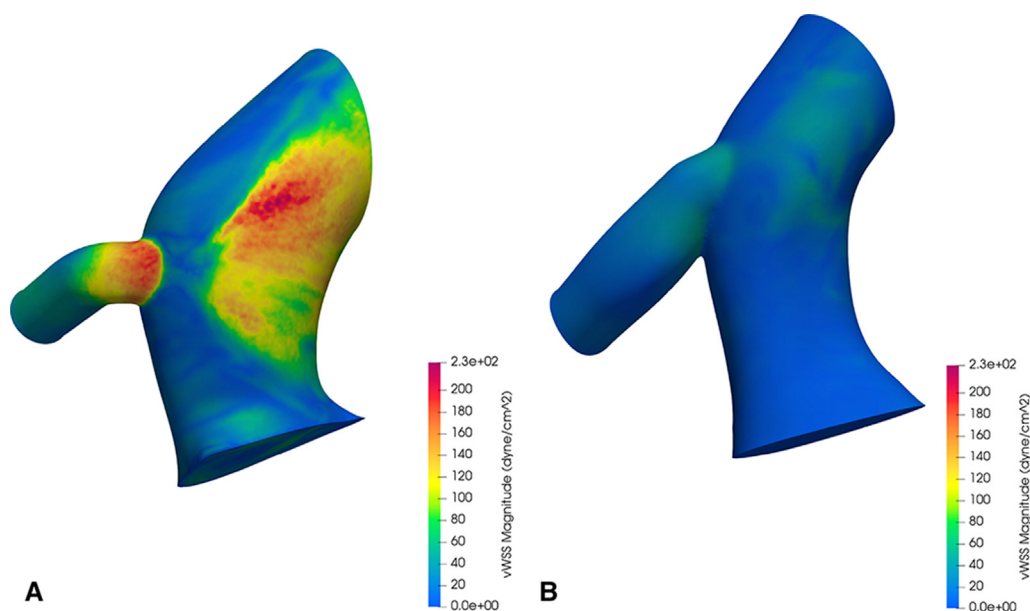
FIGURE 3. A plot depicting the 3-dimensional conformation of the outflow graft in relation to the aorta: polar angle is on the *x*-axis, and azimuth angle on the *y*-axis. For the 3-dimensional configuration of low polar angles coupled with a high azimuth angle, almost none of the patients had aortic incompetence.



**FIGURE 4.** Box plots showing the differences in distance from the aortic root to the entry point of the left ventricular assist device outflow graft (*left*). Measured pressures were found to not be significantly different between the 2 groups. \* $P < .05$ . AI, Aortic incompetence.

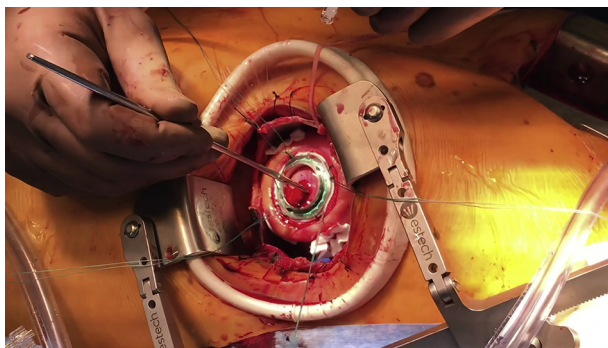
surgically prevent the progression of pre-existing moderate-to-severe AI by either replacing the aortic valve with a bio-prosthetic valve or by placing a closure stitch have both led

to mixed outcomes.<sup>19</sup> Moreover, these studies looked at patients with pre-existing AI rather than those who developed de novo AI.<sup>3,19</sup> Our data show that the initial positioning of



**FIGURE 5.** Postprocessed WSS renders of a patient with (A) AI and (B) no AI. Red color-mapped regions indicate high values whereas blue regions indicate low values of velocity and WSS. WSS, Wall shear stress.





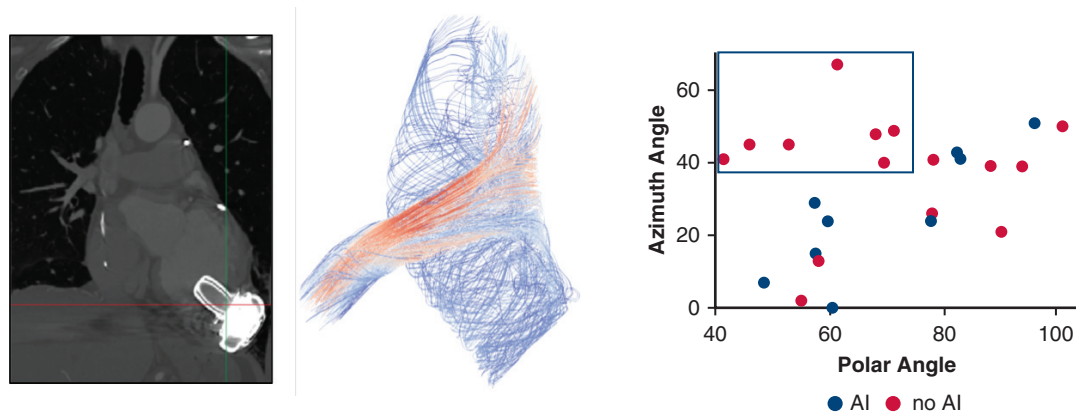
**VIDEO 1.** The video provides an overview of the paper and highlights its relevance. Narration is accompanied by relevant clips from an LVAD implantation procedure and from the SimVascular pipeline. Video available at: [https://www.jtcvs.org/article/S0022-5223\(20\)31173-9/fulltext](https://www.jtcvs.org/article/S0022-5223(20)31173-9/fulltext).

the outflow tract at the aortic anastomosis site may help optimize flow characteristics in the aortic root, reducing the likelihood of patients developing AI and obviating the need to perform traditional surgical methods to prevent AI. It was seen that a shorter distance of the outflow graft from the aortic root seems to have a protective effect against the development of AI. Optimization of the LVAD outflow tract such that the polar angle is maximized may reduce WSS, velocity, and turbulent eddies at the aortic root (Video 1).

The limitations of our study include the lack of rotational component to simulate LVAD flow through the outflow graft and native ejection, although it has been shown that by the time the blood enters the aortic root, the rotational component of flow does not qualitatively change flow patterns, and approximately less than 5% of flow occurs through the valve via the aortic valve even in patients with native valve opening.<sup>4,20</sup> The varying diameter of outflow grafts between different LVAD devices (14 mm for HeartMate II and 10 mm for HeartWare) may further

contribute to differences in flow patterns, although this is something our models do capture. We did not see any difference in flow patterns in patients with axial flow versus centrifugal flow devices, as the total sample size of our study may have been too small for this type of analysis. The inability of our study to comment on WSS distribution on the aortic leaflets is another limitation, as we were unable to reconstruct patient-specific aortic valve leaflets due to the poor quality of CT scans. However, one of the proposed mechanisms by which aortic valve incompetence progresses is the fusion of the aortic leaflets, not at the free edges but near the commissures.<sup>11</sup> It is therefore expected that aortic valves at the commissural ends (in close approximation to the root) would experience WSS similar to that experienced at the aortic root walls. The boundary conditions applied in these simulations may alter the calculated results. Although physiological boundary conditions that model the elastic properties of large arteries and distal peripheral resistances exist, these are difficult to quantify in patients with LVADs due to the myriad of downstream changes in circulatory autoregulation that occur place in patients on prolonged cf-LVAD support.<sup>21,22</sup> Finally, our simulations do not account for turbulent effects, and thus quantifying turbulence and drawing inferences were not possible. The development and integration of a validated low Reynolds number turbulence model for aortic and LVAD flow would be required to measure and simulate turbulent kinetic energy.

Mature methods now exist to perform simulations in vascular systems within clinical decision-making timeframes. Based on the theories surrounding the pathogenesis of AI in patients with LVADs, it may be prudent to simulate native valve ejection and pulsatile LVAD flow profiles arising from residual left ventricle contractility. The implementation of a validated turbulence model may help us understand the genesis of thrombosis mediated valvular



**FIGURE 6.** Computed tomography images were used to create 3-dimensional models for computation fluid dynamics simulations in 30 patients who underwent LVAD placement. Certain geometric positions of the LVAD outflow grafts predict the risk of development of AI in LVAD patients. AI, Aortic incompetence.

remodeling, in addition to providing insights about the distribution of ischemic events in patients on cf-LVAD support. The development of methods that allow for simulating the progression of cardiovascular disease rather than “snapshots” of the diseased state may also yield novel insights. In addition, studying long-term changes in the microstructure and transcriptomic profiles of the aortic valve using either chronic LVAD animal models or explanted human tissue is needed to fully understand the mechanistic aspects of aortic valvular fusion and resultant AI.

## CONCLUSIONS

Aortic insufficiency and its downstream effects on patients with LVAD support has been well studied; however, recent CFD studies have been limited by small patient cohort sizes and lack of patient-specific simulations. In our study, we created CFD simulations on a cohort of 10 patients with de novo AI and 20 patients with no AI using patient-specific flow rates. We demonstrate that the development of AI is associated with increased flow recirculation and turbulent eddies at the aortic root region. These findings correlate with increased distances between the outflow graft and the aortic root as well as minimized polar angles (Figure 6).

One of the limitations of this present study is that the parameters used to model vascular resistances were adapted from literature.<sup>23</sup> Refining the simulations using patient-specific resistances and capacitance parameters tuned to achieve clinically measured target pressures are critical for realistic and clinically translatable results. Despite this, this study is the largest of its kind and marks an important transition to drawing population level inferences from CFD analyses on patient-specific models.

## Webcast

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## Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or

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**Key Words:** aortic incompetence, left ventricular assist device, heart failure, computational fluid dynamics, SimVascular

## Discussion

### Presenter: Dr Patpilai Kasinpila



**Dr Edwin C. McGee, Jr** (*Maywood, Ill*). Thanks for the opportunity to discuss this paper, and thank you for giving me the abstract in a very prompt manner. This is a very elegant study and very compelling data. I think it emphasizes the whole idea behind this session—that as surgeons, we need to look

for ways to lessen ventricular assist device morbidity and not just blame the device when there's a problem. There's certainly things we can do to impact that.

Aortic incompetence (AI) certainly can be a problem, but as you mentioned, it's pretty infrequent that you have to deal with it. More problematic are thromboembolic events and issues related to inlet cannula placement. My main question is: Is there any way to look at inlet cannulas with this, or does the artifact from the pump just completely distort everything? Can you get some more data from that? In addition, what does pump speed do? You mentioned flow, but does having pulsatility—how does that impact—or having the heart completely unloaded, we certainly think that AI is improved if we allow the heart to eject somewhat. Is there a way to study that in terms of actual pump speed settings and doing these analyses with the heart ejecting every other beat or so?



**Dr Patpilai Kasinpila** (*Stanford, Calif*). Thank you for your thoughtful questions. To address the question of the inflow or the inlet, we've been in touch with the bioengineering department, and is our next step in looking at this. The tricky part is that when you want to look at anything associated

with the left ventricle, it requires a different type of computation where you have to look at fluid and surface interface, which is a different algorithm altogether. However, we are in the works with coming up with a model for that.

We did look at the pump speed with the model and the simulations. The nice thing with our model is that we are actually able to adjust the pump speed for every single simulation that we run. For all these patients who did not develop AI, we wondered, too, if it is due to a lower pump speed, or something like that that's kind of causing us to see the difference. We actually ran all of them at the same, uniform pump speed. These iterations did not show a significant difference. All that we saw was higher flow perturbations in the outflow graft, but this was limited to blood in the outflow graft only. Once the blood was ejected out of the outflow graft, there is no significant difference in terms of perceived or measured turbulence. So, the pattern is conserved. To your comment on pulsatility: We are working on adding on pulsatility and valve opening into these models as well.

**Dr McGee.** Nice job; thanks.

**Unidentified speaker.** Terrific presentation. Do you incorporate the vascular compliance—or are you assuming that the aortic compliance on all these patients is the same? Because it's clear that there is very different vascular compliance in different patients, and interestingly, in patients with dilated cardiomyopathies, there is an aortopathy associated with heart failure. So how do you incorporate that in your modeling? And again, a really terrific presentation.

**Dr Kasinpila.** We used the aortic compliance and resistance data that are published—so these are known values for general population of patients. However, you bring up a good point that different patients have different vascular resistance and compliances. We were able to validate our models by running these generalized values to generate peripheral pressures. These pressures were comparable to the patients' blood pressure measurements.



**000 Use of patient-specific computational models for optimization of aortic insufficiency after implantation of left ventricular assist device**

*Patpilai Kasinpila, MD, Sandra Kong, Robyn Fong, BS, Rohan Shad, MD, Alexander D. Kaiser, PhD, Alison L. Marsden, PhD, Y. Joseph Woo, MD, and William Hiesinger, MD, Stanford, Calif*

LVAD outflow graft positioning has an effect on blood fluid dynamics at the aortic root. Optimized graft placement can potentially reduce development of new aortic insufficiency in LVAD patients.