Circulation: Heart Failure

ORIGINAL ARTICLE

Left Ventricular Assist Device Inflow Cannula Angle and Thrombosis Risk

Venkat Keshav Chivukula, PhD
Jennifer A. Beckman, MSN, ARNP
Anthony R. Prisco, MD, PhD
Todd Dardas, MD
Shin Lin, MD, PhD
Jason W. Smith, MD
Nahush A. Mokadam, MD
Alberto Aliseda, PhD
Claudius Mahr, DO

BACKGROUND: As heart failure prevalence continues to increase in the setting of a static donor supply, left ventricular assist device (LVAD) therapy for end-stage heart failure continues to grow. Anecdotal evidence suggests that malalignment of the LVAD inflow cannula may increase thrombosis risk, but this effect has not been explored mechanistically or quantified statistically. Our objective is to elucidate the impact of surgical angulation of the inflow cannula on thrombogenicity.

METHODS AND RESULTS: Unsteady computational fluid dynamics is used in conjunction with computational modeling and virtual surgery to model flow through the left ventricle for 5 different inflow cannula angulations. We use a holistic approach to evaluate thrombogenicity: platelet-based (Lagrangian) metrics to evaluate the platelet mechanical environment, combined with flow-based (Eulerian) metrics to investigate intraventricular hemodynamics. The thrombogenic potential of each LVAD inflow cannula angulation is quantitatively evaluated based on platelet shear stress history and residence time. Intraventricular hemodynamics are strongly influenced by LVAD inflow cannula angulation. Platelet behavior indicates elevated thrombogenic potential for certain inflow cannula angles, potentially leading to platelet activation. Our analysis demonstrates that the optimal range of inflow angulation is within 0±7° of the left ventricular apical axis.

CONCLUSIONS: Angulation of the inflow cannula >7° from the apical axis (axis connecting mitral valve and ventricular apex) leads to markedly unfavorable hemodynamics as determined by computational fluid dynamics. Computational hemodynamic simulations incorporating Lagrangian and Eulerian metrics are a powerful tool for studying optimization of LVAD implantation strategies, with the long-term potential of improving outcomes.

Key Words: cannula ■ heart assist devices ■ heart ventricles ■ stroke ■ thrombosis

http://circheartfailure.ahajournals.org

WHAT IS NEW?

- With the increasing prevalence of long-term VAD therapy for medical therapy refractory advanced heart failure, issues surrounding biocompatibility continue to emerge.
- Left ventricular assist device thrombogenicity is influenced by implantation configuration and patient management, making it imperative to elucidate the pathogenesis of complications to attain optimal outcomes.
- This study uses a novel approach to holistically evaluate risk of thrombosis conferred by inflow cannula angulation.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Blood exposed to unfavorable hemodynamic environments in the left ventricle is at risk of aggregation because of high shear and areas of stasis.
- This increases the risk of thrombosis and stroke for patients with malaligned inflow cannulae in a quantitative fashion.
- This study adds to the body of evidence for optimizing device implantation technique to reduce overall thrombogenicity and improve long-term biocompatibility of left ventricular assist device therapy.

Over 5 million people experience heart failure in the United States alone, with ≈1 million new cases annually.[1] Medical-therapy refractory advanced heart failure (stage D heart failure) represents ≤10% of the heart failure population in the United States,[2] and its prevalence is rapidly increasing, which coupled with limited donor heart availability, makes left ventricular assist devices (LVADs) a leading treatment option.[3,4] Recent advances in LVAD design have significantly improved 1-year survival rates, now approaching ≈90%,[2,5–9] but patients with LVAD remain at high risk for devastating complications, such as neurological events and thrombosis.[10–13] Optimization of LVAD implantation technique to reduce thrombogenic potential (TP) and improve long-term outcomes remains an area of active research.

Specific surgical configuration has not been studied in depth, and its influence on biocompatibility of LVAD therapy remains poorly understood.[2] Thrombogenesis in patients with LVAD is at least, in part, attributable to nonphysiological blood flow characteristics: oscillating shear environments (extreme values of high and low shear), as well as high spatial gradients and high-frequency temporal fluctuations, which lead to platelet activation.[10,11,14] This adverse hemodynamic environment is exacerbated by malangulation of the LVAD inflow cannula. Anecdotal evidence suggests that surgical implantation of the inflow cannula at different angles with respect to the apical ventricular axis influences LVAD thrombosis.[15–17] However, the impact of biomechanical stresses resulting from nonphysiological flow on thrombogenicity has not been established, specifically in the frame of reference of circulating platelets.

Investigations of inflow cannula positioning are limited,[18–20] with the impact of the inflow cannula angle still unexplored. Previously published hemodynamic simulations have assumed steady-state flow conditions and historically focused on single Eulerian parameters, such as wall shear stress, which are more applicable to understanding endothelial cell response than blood-suspended platelet activation, transport, and platelet aggregation. Blood flow in the left ventricle (LV) before entering the LVAD inflow cannula is inherently unstable, owing to residual native contractility, high Reynolds numbers, and a complex geometry, therefore, a fully unsteady simulation capturing intrinsic fluctuations of flow dynamics for many cardiac cycles is necessary to quantify complex LV hemodynamics and thrombogenic potential. Additionally, quantifying shear stress exposure and residence times (RTs) along the trajectories of circulating platelets, via a Lagrangian approach, is a novel method to understand platelet activation and thrombus initiation in patients with LVAD.

We hypothesize that deviations of LVAD inflow cannula alignment away from the apical LV axis induce unfavorable hemodynamics. The potential for sustained high shear, which promotes platelet activation, and stagnation and recirculation regions, which influence platelet–platelet signaling and agglomeration, is likely to vary, thus increasing risk of thrombosis. Shear stress history (SH) and RT computed along platelet trajectories inside the LV are evaluated with an emphasis on statistical outliers to rank the thrombogenicity of the flow induced by different inflow cannula angles.

This study focuses on rigorously quantifying LVAD TP by computing stress-time variables on particles flowing inside the LV for various LVAD inflow cannula configurations. The methodology developed in this work is general and uses a device-neutral strategy, laying the groundwork for incorporating inflow cannula alignment optimization into patient-specific computational simulation tools.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results on request via e-mail to the corresponding author. Institutional review board approval was obtained using institutional guidelines, and all subjects gave informed consent. To evaluate the TP of inflow cannula angulation, blood flow in the LV is simulated within a patient-derived 3-dimensional model of the LV with an LVAD inflow cannula implanted via virtual surgery.[18–20]

Virtual Surgery

An anatomic LV model was obtained by image segmentation of computed tomographic images of a patient (70-kg man with nonischemic cardiomyopathy and LV end-diastolic diameter of 7 cm), after necessary permissions and consent. Using virtual surgery, a generic inflow cannula 15 mm in diameter and 25 mm in length with a rounded (chamfered) tip that is representative of those used in all currently commercially available devices was implanted in the LV apex to an insertion depth of 26 mm inside the LV. The inflow cannula angulation was modified in subsequent models to span 5 different angles with respect to the apical axis of the LV, ranging from +14°, +7°, 0°, −7°, and −14°, with 0° representing the LV apical axis, negative angles representing septal angulation, and positive angles representing anterolateral angulation (Figure 1). Models with a greater degree of misalignment (>±14°) were also created but were not included owing to similar adverse hemodynamic performances as the ±14° configurations (see discussion below).

Computational Model

Blood was modeled as a homogeneous Newtonian fluid using Navier–Stokes equations to simulate intraventricular hemodynamics using high temporal and spatial resolution to capture chaotic flow and development of instabilities.

We simulated the motion of platelet-surrogate particles to obtain information about the platelet microenvironment. On achieving statistical periodicity, platelet-surrogate particles, 3 μm in diameter, were released every 1/10 s at the mitral valve (MV) inlet for 6 cardiac cycles. Over 100 000 particles are individually tracked for 10 cardiac cycles for each case, and particle trajectories were constructed as they traverse the LV. Platelets were modeled as inertialess tracers whose positions are updated at each time step assuming that they adopt the local fluid velocity surrounding it. To preserve the platelets within the computational domain, they were allowed to collide elastically with the walls via a collision model. The particle RT was calculated by tracking the time each particle remained in the vascular domain:

$$\boldsymbol{RT_i} = T_i^{entrance} - T_i^{exit} \tag{1}$$

In Equation 1, i is an index for each particle, $T_i^{entrance}$ represents the time the particle is injected into the domain, and T_i^{exit} represents the time the particle trajectory ends as a particle exits the domain or the simulation is terminated. Although many factors influence platelet activation, one of the most widely accepted theories is shear-induced platelet activation.[21–23] Lagrangian tracking allows for determination of accumulated shear stress on each platelet, as a function of time in the flow, to evaluate the level of shear-induced platelet activation associated with each LV size studied (Equation 2):

$$\boldsymbol{SH} = \int_{t_0}^{t} \tau\left(\boldsymbol{X}\left(t'\right), t'\right) dt' \tag{2}$$

Where τ is the instantaneous shear stress magnitude at a time t' and $X(t')$ is the platelet's location at that time. For more details about the numeric models, please refer to our previous work.[24]

Global hemodynamic parameters (wall shear stress) and pressure differential between the LV walls and inflow cannula were measured and added to cell-based RT and SH in assessing the influence of different inflow cannula angles on hemodynamics and potential for thrombus formation.

Quantifying TP

TP of each LVAD inflow cannula angulation was quantitatively evaluated based on ensemble platelet SH and RT,[18–20,25] adversely influencing thrombogenicity.

RESULTS

Blood Flow Patterns

Velocity contours and instantaneous blood flow patterns for the 0° and −14° cases at various times during LV filling are shown in Figure 2. The flow in the −14° case presents lower velocity and a higher rotational component, so blood spirals slowly around the inflow cannula before exiting the ventricle. For the 0° case, blood takes a more direct route through the LV. In the instants preceding MV closure (point T onward), flow decelerates and becomes more chaotic, with recircu-

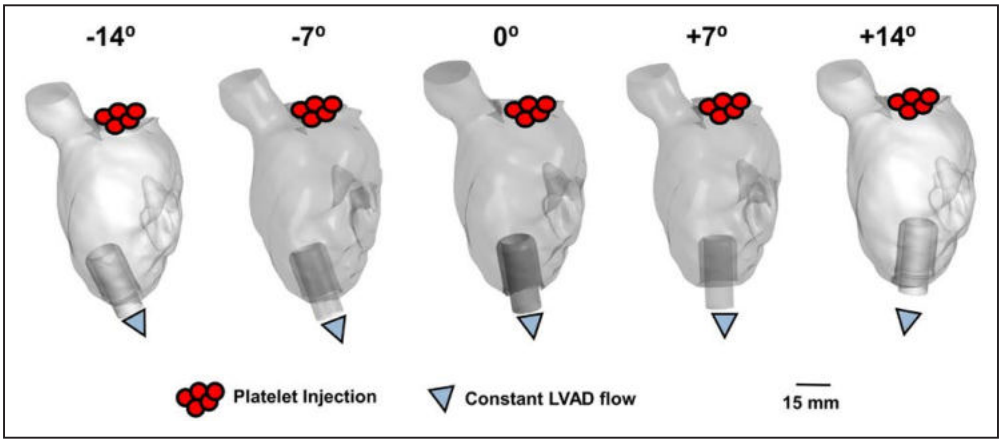

Figure 1. Five different inflow cannula angulations investigated.
LVAD indicates left ventricular assist device.

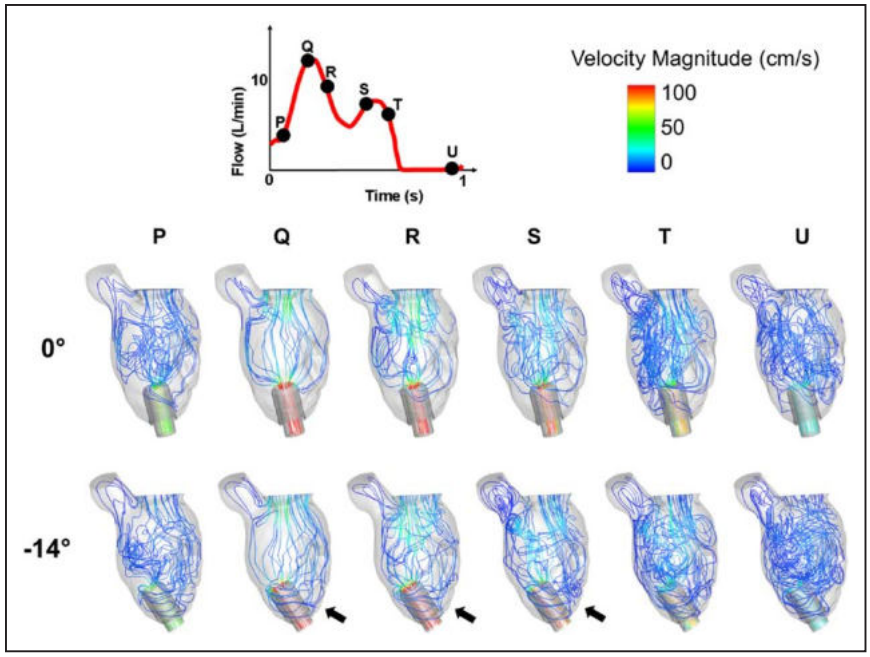

Figure 2. Instantaneous blood flow patterns (streamlines) colored by velocity magnitude for the 0° and –14° cases at various times in the cardiac cycle.

lation regions throughout the ventricle, most notably near the LV apex.

Suspended Platelet Metrics

For each configuration studied, >100 000 platelet-surrogate particles were injected into the LV via the MV every 0.1 s for 6 cardiac cycles and tracked for 10 cardiac cycles. Platelet metrics are computed to characterize hemodynamics and quantify thrombotic potential of each inflow angulation.

As seen in Figure 3, a large number of particles continue to recirculate beyond 5 s, and specific platelet accumulation areas begin to emerge. Platelets in the fringe configurations (–14° and +14°) circulate for longer times through the LV, compounding the contribution of stasis toward platelet activation. Platelets undergoing high shear through the MV remain trapped in the LV in a region of stasis for extended periods of time and serve as potential initiators of the coagulation cascade.

Figure 4 shows representative trajectories for 30 randomly chosen platelets for each inflow angle configuration. The trajectories are different for each configuration: qualitatively, the –14°, +7°, and +14° configurations present more convoluted patterns, with the platelets following more circuitous paths from the MV as they disperse through the LV. These trajectories lead to platelets entering the myocardial wall regions more often and potentially becoming trapped in zones of stasis between the LV wall and inflow cannula, precipitating aggregation. The –7° and 0° configurations, on the contrary, demonstrate more streamlined trajectories from the MV to the inflow cannula, consistent with more uniform LV emptying. As a result, platelets are much less likely to become trapped in a recirculation zone in these configurations. From both Figures 3 and 4, it is evident that intraventricular hemodynamics is a complex process and qualitative comparisons alone are insufficient in performing a detailed hemodynamic analysis.

Figure 5 shows box plots of RT and SH distributions for all platelets injected. Overall, platelets circulated for longer times in the 2 most misaligned configurations (–14° and +14°). The lowest median RT (1.64 s) is found for the +7° configuration, whereas the longest

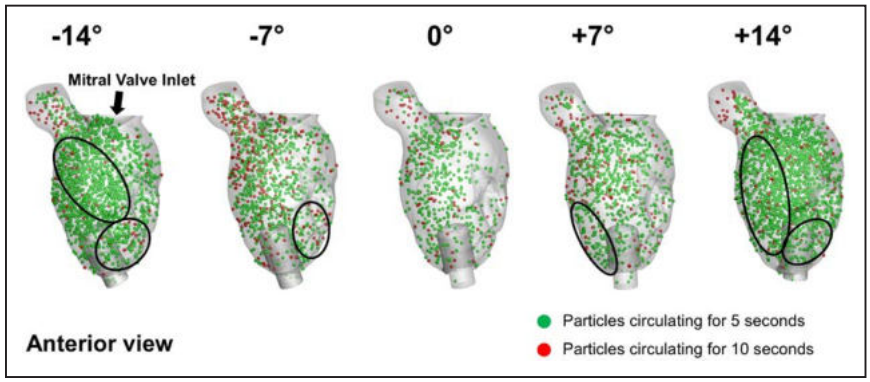

Figure 3. Distribution and clustering of particles circulating within the left ventricle at 5 and 10 s after injection for all inflow angulations.

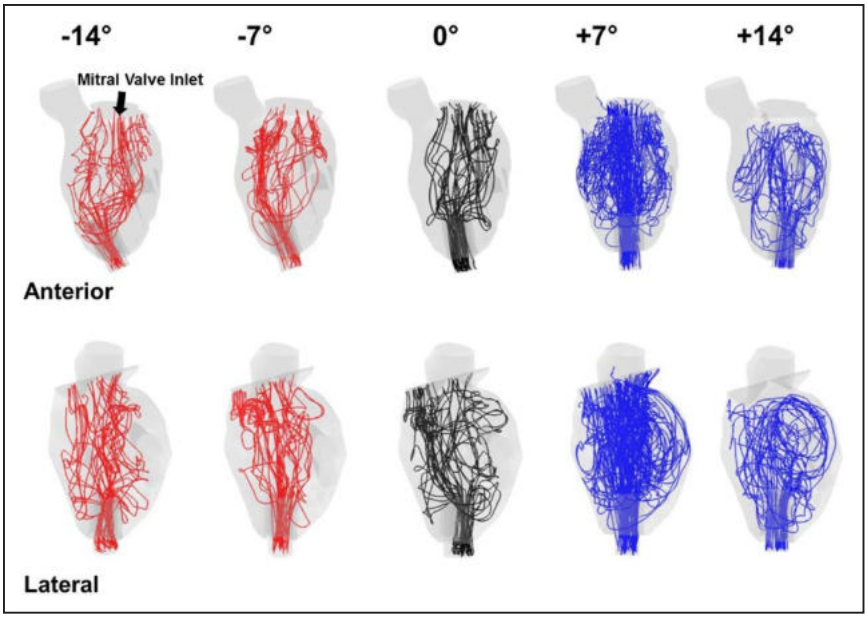

Figure 4. Particle trajectories characterizing the intraventricular transit of platelets for all inflow cannula angles.

RT (2.1 s) in the LV is for the −14° configuration, which represents the inflow cannula closest to the interventricular septum.

Median SH was the highest for particles in the +14° configuration (0.3 Pa.s), whereas it was the lowest for the −7°configuration (0.23 Pa.s). The 2 most misaligned configurations (−14° and +14°) demonstrated the highest SH platelets in this study (15.17 and 17.46 Pa.s, respectively), an increase of 73% over the configuration with the lowest maximum SH (10.1 Pa.s for the 0° configuration). All median and outlier platelet RT and SH data are shown in the Table.

Evaluation of TP

TP was evaluated for all configurations to evaluate their overall thrombogenic performance.[24] Overall, the configurations closest to the apical–mitral axis (0±7°) were the least thrombogenic, whereas the more misaligned orientations (−14° and +14°) were the most thrombogenic. The relationship of thrombogenicity and implantation angle is shown graphically in Figure 6, indicating low thrombogenicity zones for the 0±7° configurations. The scores for the various configurations, based on their platelet trajectory statistics for RT and shear history, are shown in the Table.

DISCUSSION

Stroke and device thrombosis are some of the most devastating complications of mechanical circulatory support.[4,26–28] It is clinically appreciated that proper inflow cannula alignment contributes to device performance[29–31] and multiple case studies have associated surgical angulation at extreme inflow cannula angles with

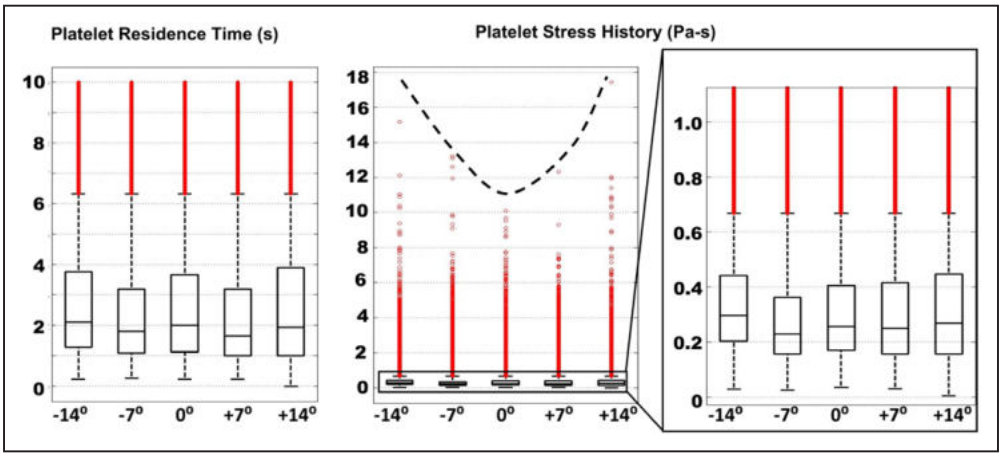

Figure 5. Box plots of platelet residence time and shear stress history (SH), displaying the lowest maximum SH for 0° angulation in a U-shaped distribution.
Red circles indicate outlier data.

Table. Median and Outlier Information of RT and SH for All Particles and TP Scores for All Inflow Angulations

Case	RT, s		SH, Pa.s		TP Scores
	Median	Outliers (Max, %)	Median	Outliers (Max, %)	
−14°	2.10*†‡§	9.99–7.61	0.3*†‡§	15.17–9.98	0.98
−7°	1.79‡§‖	9.99–6.87	0.23†‡§‖	13.23–7.19	0.0
0°	2.00‡§‖	9.99–8.67	0.26*§‖	10.10–8.95	0.43
+7°	1.64*†§‖	9.99–7.97	0.25*§‖	12.32–10.53	0.19
+14°	1.93*†‡‖	9.99–9.47	0.27*†‡‖	17.46–10.73	1.0

RT indicates residence time; SH, shear stress history; and TP, thrombogenic potential.

*Statistically significant (P<0.05) result in comparison with −7° configuration.

†Statistically significant (P<0.05) result in comparison with 0° configuration.

‡Statistically significant (P<0.05) result in comparison with +7° configuration.

§Statistically significant (P<0.05) result in comparison with +14° configuration.

‖Statistically significant (P<0.05) result in comparison with −14° configuration.

risk of thrombosis..[16,17] However, up until this time, the underlying mechanisms have not been clearly identified. Interdependencies of LV flow, inflow cannula angulation, and LVAD-operating conditions complicate assessment of LVAD thrombogenicity, requiring novel tools for quantitative evaluation of outcomes. We use a holistic strategy to globally assess device compatibility, including Lagrangian analysis of platelet trajectories inside the LV to assess thrombogenicity throughout the LV.

The intraventricular hemodynamic patterns demonstrated in this study reveal several differences for the various inflow cannula angles investigated. Inflow cannula angles closer to the apical axis result in more linear blood flow from the MV to the inflow cannula. Even with a modest misalignment of 7°, significant changes are detectable. At 14°, this effect becomes markedly abnormal. The most misaligned configurations of ≥14° result in strikingly more convoluted platelet trajectories, with higher potential of becoming trapped inside the LV, in particular, the space between the LV wall and inflow cannula near the apex. Clustering of blood in this space is seen in snapshots of particle trajectories at different times (Figures 2 and 3). Particles trapped in these recirculation/stagnation zones linger significantly longer and in the process, accumulate higher SH during their transit from MV to inflow cannula. This markedly increased TP remains at similar elevated levels for misalignments beyond 14° (not included in the study), clearly indicating a zone beyond 0±7° that subjects platelets to detrimental hemodynamic environments.

Outliers for both RT and SH (platelets that are subject to both high shear stress for at least a portion of their trajectory and long RTs) may be the critical link in thrombus initiation. Outlier behavior for RT showed that the +14° configuration resulted in the largest percentage of particles lingering in the LV for extended periods of time. Long RTs are one of the pathophysiologic mechanisms

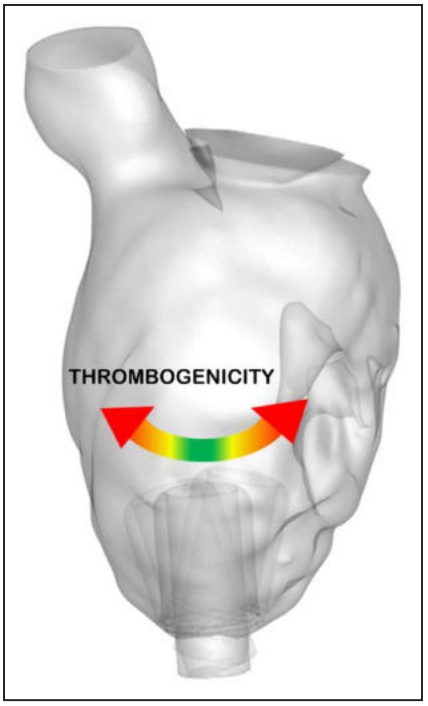

Figure 6. Range of thrombogenicity of inflow cannula angulation, indicating optimal angle in green.

of flow-induced platelet aggregation.[21–23] SH statistics also showed major differences between configurations: particles in inflow cannula angles of >−14° and +14° are subjected to the highest maximum values of SH—an increase of ≈73%. Our data further demonstrate that those configurations with high maximum values of SH also present high percentage of outliers. Platelets continue to circulate within the LV for well over 10 s, after having been activated by high values of SH.

All the platelet-based metrics studied, including outlier RT and SH values and percentages, are incorporated into the TP. The −14° and +14° configurations have the highest TP score, indicating that these configurations present a higher risk of platelet activation and thrombus formation. An inflow angulation of 0±7° from the LV apical axis presented the lowest overall TP score (Figure 6), representing the configurations that subject platelets to the lowest combined values of RTs and accumulated shear: the ideal balance of avoiding excess shear that activates platelets, while simultaneously avoiding prolonged RTs and stasis.

It is important to note that the TP score denotes a near-exponential probability of thrombosis, as a measure of the disturbance to the homeostasis of the clotting cascade. The −14 and +14 cases are surgically relevant as measurable in the operating room. The TP values for these cases represent a high increase in the thrombogenic risk, compared with the other 3 cases studied, consistent with our previous results.[24,32] The TP scores are computed from a statistically significant difference in platelet populations and analyzed for each cannula angulation.

In many ventricular assist device patients, the LV end-diastolic diameter decreases with reverse remodeling, which may further contribute to malangulation during long-term support. Suboptimal inflow cannula angulation also negatively influences the ability to effectively unload the LV,[15] affecting ventricular hemodynamics and potentially exacerbating hemodynamic conditions inside the LV contributing to thrombosis or cerebrovascular accident. Improper inflow cannula positioning can predispose platelet clusters to enter the LVAD with high thrombogenic indices (state of activation and interplatelet aggregation signaling). Consequently, this further increases the risk of pump thrombosis and microthrombi formation into systemic and cerebral circulation. Thus, overall LVAD hemodynamics beyond the device itself exacerbate stroke risk and need to be included in the investigation of LVAD thrombosis. Future inflow cannula and sewing ring designs that allow for modification of insertion depth and 3-dimensional echo-guided adaptive angulation may mitigate some of these issues.

Limitations

The current study evaluates the influence of LVAD inflow cannula angulation on thrombogenicity, introducing novel cell-based metrics to estimate platelet activation; nevertheless, there are several limitations. The subaortic region is a potential area of stagnation as we assumed a closed aortic valve. The rationale for this is (1) the focus of our simulations is near the ventricular apex and inflow cannula angulation and (2) aortic valve opening dynamics and its influence on ventricular and aortic hemodynamics are out of the scope of the current article but will be analyzed in a separate study that further builds on our recent publication of the benefits of intermittent aortic valve opening.[24] The LV was considered rigid, simplifying flow dynamics. Analyses of ventricular wall motion confirm minimal changes in typical patients with ventricular assist device with severe systolic dysfunction and markedly impaired contractile reserve. The platelets were assumed to have purely elastic collisions with each other and the LV walls. Future models could incorporate interplatelet signaling and adhesion models to further reflect coagulation.

Conclusions

The use of Lagrangian metrics provides a novel characterization of flow patterns and mechanical stresses experienced by blood-suspended cells in the LV. By focusing on the hemodynamic environment experienced by platelets in the LV, notably their RT and accumulated shear stress, our study supports clinical evidence that inflow cannula malalignment is detrimental to the efficacy of LVAD therapy. Integrating these methodologies holistically, our study demonstrates that malangulation of the inflow cannula away from the LV apical axis leads to markedly unfavorable hemodynamics within the LV, impairs effective unloading, and thus significantly diminishes the overall benefit of device support. Moreover, this strongly impacts platelet activation and increases risk of thrombosis. Our study provides quantitative evidence linking the degree of inflow cannula angulation to risk of thrombosis—an angle of 0±7° from the LV apical axis is most biocompatible and significantly reduces thrombogenic flow patterns. As the failing LV reverse remodels in response to mechanical unloading, any angle >±7° brings the inflow cannula even closer to the LV wall, further compounding the risk of high RT and high shear stress. Whenever possible, surgeons should aim to align the inflow cannula along the true LV apical axis to minimize the risk of cerebrovascular accident and device thrombosis.

ARTICLE INFORMATION

Received June 15, 2017; accepted February 26, 2018.

Correspondence

Claudius Mahr, DO, Division of Cardiology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195. E-mail cmahr@uw.edu

Affiliations

Department of Mechanical Engineering (V.K.C., A.A.), Division of Cardiology (J.A.B., T.D., S.L., C.M.), and Division of Cardiothoracic Surgery (J.W.S., N.A.M.), University of Washington, Seattle. Department of Medicine, University of Minnesota, Minneapolis (A.R.P.).

Acknowledgments

We would like to thank the High Performance Computing group for providing the High Performance Computing facility (Hyak) at the University of Washington to conduct the simulations described in this study. Thanks to Pablo Martinez-Legazpi and Juan Carlos del Alamo for the mitral valve flow rate waveform and the quantification of restricted ventricular volume change during the cardiac cycle.

Sources of Funding

This work was funded, in part, by an American Heart Association postdoctoral fellowship (16POST30520004).

Disclosures

C. Mahr has consulting relationships with Abbott (Thoratec), Medtronic (HeartWare), and Abiomed and is an investigator for Abbott (Thoratec), Medtronic (HeartWare), and SynCardia. Dr Mokadam has a consulting relationship with Abbott (Thoratec) and Medtronic (HeartWare) and is an investigator for Abbott (Thoratec), Medtronic (HeartWare), and SynCardia. Dr Smith has consulting relationships with Abbott (Thoratec) and Medtronic (HeartWare) and research support from Transmedics. J.A. Beckman has consulting relationships with Abiomed, Abbott (Thoratec), and Medtronic (HeartWare). The other authors report no conflicts.

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Commit-

tee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. doi: 10.1161/CIR.0000000000000485.
2. Mancini D, Colombo PC. Left ventricular assist devices: a rapidly evolving alternative to transplant. *J Am Coll Cardiol*. 2015;65:2542–2555. doi: 10.1016/j.jacc.2015.04.039.
3. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med*. 2007;357:885–896. doi: 10.1056/NEJMoa067758.
4. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM III, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361:2241–2251. doi: 10.1056/NEJMoa0909938.
5. Slaughter MS, Pagani FD, McGee EC, Birks EJ, Cotts WG, Gregoric I, Howard Frazier O, Icenogle T, Najjar SS, Boyce SW, Acker MA, John R, Hathaway DR, Najarian KB, Aaronson KD; HeartWare Bridge to Transplant ADVANCE Trial Investigators. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. *J Heart Lung Transplant*. 2013;32:675–683. doi: 10.1016/j.healun.2013.04.004.
6. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, Horstmanshof DA, Kormos RL, Teuteberg JJ, Slaughter MS, Birks EJ, Farrar DJ, Park SJ; HeartMate II Clinical Investigators. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol*. 2014;63:1751–1757. doi: 10.1016/j.jacc.2014.01.053.
7. Netuka I, Sood P, Pya Y, Zimpfer D, Krabatsch T, Garbade J, Rao V, Morshuis M, Marasco S, Beyersdorf F, Damme L, Schmitto JD. Fully magnetically levitated left ventricular assist system for treating advanced HF: a multicenter study. *J Am Coll Cardiol*. 2015;66:2579–2589. doi: 10.1016/j.jacc.2015.09.083.
8. Heatley G, Sood P, Goldstein D, Uriel N, Cleveland J, Middlebrook D, Mehra MR; MOMENTUM 3 Investigators. Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. *J Heart Lung Transplant*. 2016;35:528–536. doi: 10.1016/j.healun.2016.01.021.
9. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC, Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, Pagani FD, Aaronson KD, Dean DA, McCants K, Itoh A, Ewald GA, Horstmanshof D, Long JW, Salerno C. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med*. 2017;376:440–450. doi:10.1056/NEJMoa1610426.
10. Najjar SS, Slaughter MS, Pagani FD, Starling RC, McGee EC, Eckman P, Tatooles AJ, Moazami N, Kormos RL, Hathaway DR, Najarian KB, Bhat G, Aaronson KD, Boyce SW; HVAD Bridge to Transplant ADVANCE Trial Investigators. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. *J Heart Lung Transplant*. 2014;33:23–34. doi: 10.1016/j.healun.2013.12.001.
11. Mehra MR, Stewart GC, Uber PA. The vexing problem of thrombosis in long-term mechanical circulatory support. *J Heart Lung Transplant*. 2014;33:1–11. doi: 10.1016/j.healun.2013.12.002.
12. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Miller MA, Baldwin JT, Young JB. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant*. 2014;33:555–564. doi:10.1016/j.healun.2014.04.010.
13. Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, Rame JE, Acker MA, Blackstone EH, Ehrlinger J, Thuita L, Mountis MM, Soltesz EG, Lytle BW, Smedira NG. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med*. 2014;370:33–40. doi:10.1056/NEJMoa1313385.
14. Bluestein D, Chandran KB, Manning KB. Towards non-thrombogenic performance of blood recirculating devices. *Ann Biomed Eng*. 2010;38:1236–1256. doi: 10.1007/s10439-010-9905-9.
15. Taghavi S, Ward C, Jayarajan SN, Gaughan J, Wilson LM, Mangi AA. Surgical technique influences HeartMate II left ventricular assist device thrombosis. *Ann Thorac Surg*. 2013;96:1259–1265. doi: 10.1016/j.athoracsur.2013.05.081.
16. Atkins BZ, Hashmi ZA, Ganapathi AM, Harrison JK, Hughes GC, Rogers JG, Milano CA. Surgical correction of aortic valve insufficiency after left ventricular assist device implantation. *J Thorac Cardiovasc Surg*. 2013;146:1247–1252. doi: 10.1016/j.jtcvs.2013.05.019.
17. Bhama J, Eckert C, Lockard K, Shiose A, Bermudez C, Teuteberg J, Ramani R, Simon M, Badhwar V, Kormos R. Does LVAD inflow cannula position contribute to the development of pump thrombosis requiring device exchange? *J Am Coll Cardiol*. 2013;61:E719. doi:10.1016/S0735-1097(13)60719-6.
18. Fraser KH, Taskin ME, Griffith BP, Wu ZJ. The use of computational fluid dynamics in the development of ventricular assist devices. *Med Eng Phys*. 2011;33:263–280. doi: 10.1016/j.medengphy.2010.10.014.
19. Ong C, Dokos S, Chan B, Lim E, Al Abed A, Bin Abu Osman NA, Kadiman S, Lovell NH. Numerical investigation of the effect of cannula placement on thrombosis. *Theor Biol Med Model*. 2013;10:35. doi: 10.1186/1742-4682-10-35.
20. Laumen M, Kaufmann T, Timms D, Schlanstein P, Jansen S, Gregory S, Wong KC, Schmitz-Rode T, Steinseifer U. Flow analysis of ventricular assist device inflow and outflow cannula positioning using a naturally shaped ventricle and aortic branch. *Artif Organs*. 2010;34:798–806. doi: 10.1111/j.1525-1594.2010.01098.x.
21. Para A, Bark D, Lin A, Ku D. Rapid platelet accumulation leading to thrombotic occlusion. *Ann Biomed Eng*. 2011;39:1961–1971. doi: 10.1007/s10439-011-0296-3.
22. Ramstack JM, Zuckerman L, Mockros LF. Shear-induced activation of platelets. *J Biomech*. 1979;12:113–125.
23. Einav S, Bluestein D. Dynamics of blood flow and platelet transport in pathological vessels. *Ann N Y Acad Sci*. 2004;1015:351–366. doi: 10.1196/annals.1302.031.
24. Mahr C, Chivukula VK, McGah P, Prisco AR, Beckman JA, Mokadam NA, Aliseda A. Intermittent aortic valve opening and risk of thrombosis in ventricular assist device patients. *ASAIO J*. 2017;63:425–432. doi: 10.1097/MAT.0000000000000512.
25. Prisco AR, Aliseda A, Beckman JA, Mokadam NA, Mahr C, Garcia GJM. Impact of LVAD implantation site on ventricular blood stagnation. *ASAIO J*. 2017;63:392–400. doi: 10.1097/MAT.0000000000000503.
26. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, Jessup ML, Gregoric ID, Loyalka P, Frazier OH, Jeevanandam V, Anderson AS, Kormos RL, Teuteberg JJ, Levy WC, Naftel DC, Bittman RM, Pagani FD, Hathaway DR, Boyce SW; HeartWare Ventricular Assist Device (HVAD) Bridge to Transplant ADVANCE Trial Investigators. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation*. 2012;125:3191–3200. doi: 10.1161/CIRCULATIONAHA.111.058412.
27. Bartoli CR, Ailawadi G, Kern JA. Diagnosis, nonsurgical management, and prevention of LVAD thrombosis. *J Card Surg*. 2014;29:83–94. doi: 10.1111/jocs.12238.
28. Upshaw JN, Kiernan MS, Morine KJ, Kapur NK, DeNofrio D. Incidence, management, and outcome of suspected continuous-flow left ventricular assist device thrombosis. *ASAIO J*. 2016;62:33–39. doi: 10.1097/MAT.0000000000000294.
29. Milano CA, Simeone AA, Blue LJ, Rogers JG. Presentation and management of left ventricular assist device inflow cannula malposition. *J Heart Lung Transplant*. 2011;30:838–840. doi: 10.1016/j.healun.2011.03.003.
30. Crumpstone T, Martin TD, Yang JJ, Peng YG. Misplacement of LVAD inflow cannula leads to insufficient output and tissue hypoperfusion. *J Artif Organs*. 2010;13:225–227. doi: 10.1007/s10047-010-0516-x.
31. Sacks J, Gonzalez-Stawinski GV, Hall S, Lima B, MacHannaford J, Dockery W, Cura M, Chamogeorgakis T. Utility of cardiac computed tomography for inflow cannula patency assessment and prediction of clinical outcome in patients with the HeartMate II left ventricular assist device. *Interact Cardiovasc Thorac Surg*. 2015;21:590–593. doi: 10.1093/icvts/ivv205.
32. Aliseda A, Chivukula VK, Mcgah P, Prisco AR, Beckman JA, Garcia GJ, Mokadam NA, Mahr C. LVAD outflow graft angle and thrombosis risk. *ASAIO J*. 2017;63:14–23. doi: 10.1097/MAT.0000000000000443.

Left Ventricular Assist Device Inflow Cannula Angle and Thrombosis Risk

Venkat Keshav Chivukula, Jennifer A. Beckman, Anthony R. Prisco, Todd Dardas, Shin Lin, Jason W. Smith, Nahush A. Mokadam, Alberto Aliseda and Claudius Mahr

Circ Heart Fail. 2018;11:
doi: 10.1161/CIRCHEARTFAILURE.117.004325
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297