Assessing the Hemodynamic Impact of Anterior Leaflet Laceration in Transcatheter Mitral Valve Replacement: An in silico Study

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Background: A clinical study comparing the hemodynamic outcomes of transcatheter mitral valve replacement (TMVR) with vs. without Laceration of the Anterior Mitral leaflet to Prevent Outflow Obstruction (LAMPOON) has never been designed nor conducted.

Aims: To quantify the hemodynamic impact of LAMPOON in TMVR using patient-specific computational (in silico) models.

Materials: Eight subjects from the LAMPOON investigational device exemption trial were included who had acceptable computed tomography (CT) data for analysis. All subjects were anticipated to be at prohibitive risk of left ventricular outflow tract (LVOT) obstruction from TMVR, and underwent successful LAMPOON immediately followed by TMVR. Using post-procedure CT scans, two 3D anatomical models were created for each subject: (1) TMVR with LAMPOON (performed procedure), and (2) TMVR without LAMPOON (virtual control). A validated computational fluid dynamics (CFD) paradigm was then used to simulate the hemodynamic outcomes for each condition.

Results: LAMPOON exposed on average $2 \pm 0.6$ transcatheter valve cells ($70 \pm 20 \text{mm}^2$ total increase in outflow area) which provided an additional pathway for flow into the LVOT. As compared to TMVR without LAMPOON, TMVR with LAMPOON resulted in lower peak LVOT velocity, lower peak LVOT gradient, and higher peak LVOT effective orifice area by $0.4 \pm 0.3 \text{m/s}$ ($14 \pm 7\%$ improvement, $p = 0.006$), $7.6 \pm 10.9 \text{mmHg}$ ($31 \pm 17\%$ improvement, $p = 0.01$), and $0.2 \pm 0.1 \text{cm}^2$ ($17 \pm 9\%$ improvement, $p = 0.002$), respectively.

Conclusion: This was the first study to permit a quantitative, patient-specific comparison of LVOT hemodynamics following TMVR with and without LAMPOON.
INTRODUCTION

Left ventricular outflow tract (LVOT) obstruction is a prevalent and potentially fatal complication of transcatheter mitral valve replacement (TMVR) caused by displacement of the anterior leaflet toward the ventricular septum (1). Laceration of the Anterior Mitral leaflet to Prevent Outflow Obstruction (LAMPOON) is a catheter-based technique designed to alleviate the risk of obstruction by mimicking surgical anterior leaflet resection. The optimal result of the LAMPOON procedure is a complete midline laceration of the anterior leaflet which, following TMVR, exposes open cells of the transcatheter valve. These exposed cells are thought to permit additional blood flow through the LVOT and decrease the risk of obstruction (2). LAMPOON is considered for patients who have a predicted residual LVOT neo-left ventricular outflow tract (neo-LVOT) area <200 mm² and are therefore anticipated to have significant LVOT obstruction from TMVR (3).

Despite the growing clinical experience with this technique, a controlled clinical trial comparing the outcomes of patients undergoing TMVR with vs. without LAMPOON has never been designed nor conducted. It would be impossible to conduct such a trial in which the control intervention (i.e., TMVR without LAMPOON) would be anticipated to cause immediate LVOT obstruction following valve implantation. Thus, while the LAMPOON technique has been shown to be safe and feasible, its impact on left ventricular outflow hemodynamics has never been investigated.

For this purpose, we conducted a computational (in silico) controlled study of TMVR with LAMPOON vs. TMVR without LAMPOON. We used a validated in silico approach using post-procedure computed tomography (CT) scans from subjects at prohibitive risk of LVOT obstruction who successfully underwent TMVR with LAMPOON (4). 3-D anatomical and flow information were extracted from the CT datasets and used as inputs into personalized computational fluid dynamics (CFD) models. For each subject, hemodynamics of TMVR with and without LAMPOON were simulated and compared. We hypothesized that LAMPOON improves flow dynamics through the LVOT in patients with a small neo-LVOT.

Abbreviations: CFD, computational fluid dynamics; CT, computed tomography; LAMPOON, intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction; LVOT, left ventricular outflow tract; TMVR, transcatheter mitral valve replacement.
FIGURE 1 | 3D anatomical models created for each subject. The left model represents the actual performed procedure (TMVR with LAMPOON). In this model, the left ventricular anatomy and implanted transcatheter valve geometry were segmented directly from the post-procedure CT dataset. The number and location of transcatheter valve cells exposed by LAMPOON were modeled based on visualization of the anterior leaflet splay in the post-procedure CT dataset. To simulate a “virtual control” procedure in which LAMPOON was not performed (TMVR without LAMPOON), we artificially closed the exposed cells of the transcatheter valve as shown in the right model. Ao, aorta; LV, left ventricle; THV, transcatheter heart valve.

Measurement of Neo-Left Ventricular Outflow Tract and Skirt Neo-Left Ventricular Outflow Tract Area
Computed tomography datasets were utilized to measure the neo-LVOT and skirt neo-LVOT area. The neo-LVOT area was measured in a plane perpendicular to the LVOT and located at the narrowest point along the residual LVOT after TMVR (Figure 1, right). Following LAMPOON, the transcatheter valve skirt still protrudes into the LVOT, creating a narrowing at the transcatheter valve skirt called the “skirt” neo-LVOT (8). Figure 1 illustrates differences between the neo-LVOT and skirt neo-LVOT. The skirt neo-LVOT area was measured in a plane perpendicular to the LVOT and located at the level of the transcatheter valve skirt (Figure 1, left). Both neo-LVOT and skirt neo-LVOT area measurements were first predicted on baseline CT, and then measured on post-procedure CT.

Computational Fluid Dynamics Simulations
Computational fluid dynamics (CFD) is a method used to simulate fluid flow with computer modeling. In this study, we utilized a validated CFD workflow for simulating patient-specific LVOT hemodynamics based on cardiac CT data (7). Patient-specific CFD simulations were performed for both modeled conditions (TMVR with and without LAMPOON) for each subject. The output of these simulations provided spatially varying velocity and pressure data across the entire left ventricle and aorta. The workflow used for performing the CFD simulations has been previously described and validated against clinical measurements from Doppler echocardiography (7). The average difference between CFD-derived and
echocardiography-derived peak LVOT velocity measurements was <10%, indicating a good agreement between the CFD simulations and clinical measurements. This CFD workflow is briefly summarized below.

All CFD simulations were performed for the peak-systolic phase of the cardiac cycle. The cardiac phase of the post-procedure CT scan which most closely coincided with the peak systolic flow rate was selected for creating a 3D model of the left heart anatomy and implanted transcatheter valve. For each 3D model, an inlet was placed at the left ventricular apex, and an outlet was placed at the sino-tubular junction. 3-Matic 12.0 (Materialize, Leuven, Belgium) computer aided design software was used to place a virtual wall at the level of the bioprosthetic valve leaflets to prevent regurgitant flow. A volumetric mesh was then generated using ANSYS Fluent Meshing (Ansys, Inc. Canonsburg, PA, United States). This mesh included polyhedral elements with an edge length of 0.5 mm, and a prismatic boundary layer mesh (10 layers with geometric growth of 1.05) which was applied on the left ventricular wall. The total number of mesh elements per patient model was on average ~1,800,000 elements. Transition-to-turbulence characteristics in the flow field were accounted for using the scale-adaptive simulation

### TABLE 1 | Baseline, procedural, and post-procedural characteristics.

| Subject | Age, years | Gender | Ejection fraction, % | LVEDV, ml from echo | Body surface area, m² | Mitral pathology | Aortic stenosis | Neo-LVOT area at end-systole (predicted), mm² | Skirt neo-LVOT area at end-systole (predicted), mm² |
|---------|------------|--------|---------------------|---------------------|----------------------|----------------|--------------|---------------------------------------------|---------------------------------------------|
| 1       | 85         | Female | 61                  | 75                  | 1.73                 | MR             | None         | 111                                         | 241                                         |
| 2       | 82         | Female | 65                  | 56                  | 1.81                 | MS             | Mild         | 57                                          | 278                                         |
| 3       | 50         | Female | 56                  | 48                  | 1.77                 | MS             | None         | 143                                         | 210                                         |
| 4       | 75         | Female | 53                  | 40                  | 1.68                 | MS             | None         | 81                                          | 247                                         |
| 5       | 84         | Female | 54                  | 36                  | 1.57                 | MS             | None         | 108                                         | 236                                         |
| 6       | 80         | Female | 67                  | 78                  | 1.99                 | MR             | None         | 168                                         | 333                                         |
| 7       | 83         | Female | 67                  | 65                  | 1.8                  | MR             | None         | 59                                          | 216                                         |
| 8       | 61         | Female | 70                  | 27                  | 1.43                 | MS             | Mild         | 55                                          | 189                                         |

### Procedural characteristics

| TMVR setting | Valve-in-Ring | Valve-in-MAC | Valve-in-Ring | Valve-in-MAC | Valve-in-MAC | Valve-in-MAC | Valve-in-MAC |
|--------------|---------------|--------------|---------------|--------------|--------------|--------------|--------------|
| Successful leaflet laceration | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Successful TMVR | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Implanted SAPIEN size, mm | 26 | 29 | 23 | 29 | 29 | 29 | 29 |
| No. of THV cells exposed by splayed leaflet | 1.5 | 2 | 2 | 1 | 2 | 2.5 | 2 |
| Combined area of THV cells exposed by splayed leaflet, mm² | 41 | 86 | 55 | 45 | 87 | 88 | 88 |
| Deployment depth, % in LV | 53 | 77 | 46 | 85 | 71 | 58 | 59 |
| Para-valvular regurgitation | None | Mild | None | Trace | Mild | None | Trace |

### Post-procedural characteristics

| Time of post-procedure CT scan | 30-day | 30-day | Pre-discharge | Pre-discharge | 30-day | 30-day | Pre-discharge | 30-day |
|-------------------------------|--------|--------|---------------|---------------|--------|--------|---------------|--------|
| Post-procedure peak flow rate, L/min | 13.3 | 18.8 | 21.3 | 15.3 | 20.3 | 37.8 | 24.8 | 30.5 |
| Neo-LVOT area at end-systole, mm² | 211 | 187 | 293 | 42 | 19 | 223 | 30 | 221 |
| Neo-LVOT area at peak-systole, mm² | 266 | 256 | 379 | 153 | 129 | 250 | 49 | 337 |
| Skirt neo-LVOT area at end-systole, mm² | 320 | 427 | 307 | 145 | 211 | 341 | 182 | 316 |
| Skirt neo-LVOT area at peak-systole, mm² | 344 | 418 | 351 | 176 | 231 | 313 | 162 | 358 |

Echocardiography was used to derive ejection fraction, left ventricular end-diastolic volume, aortic stenosis severity, and para-valvular regurgitation severity. The peak flow rate was obtained from the time-varying CT-derived left ventricular volumes. CT, computed tomography; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; MAC, mitral annular calcification; MR, mitral regurgitation; MS, mitral stenosis; THV, transcatheter heart valve; TMVR, transcatheter mitral valverplacement.
turbulence model. Turbulence boundary conditions included (1) hydraulic diameter (which is the inlet diameter, $D_H$) and (2) turbulence intensity (approximated using $0.16 \times Re_D^{-0.125}$, where $Re_D$ is the Reynolds number based on the patient-specific flow rate and the hydraulic diameter).

The time-varying left ventricular volume curve (obtained from the post-procedure CT scan) was used to calculate a peak systolic flow rate, which was then prescribed as the inlet boundary condition. The outlet boundary condition was set to a zero-reference pressure. All structures were assumed to be rigid and non-permeable, and a no-slip boundary condition was applied at the walls. Blood was modeled as a single-phase Newtonian fluid with a density of 1060 kg/m$^3$ and dynamic viscosity of 0.0034 poise. The 3-D Navier-Stokes equations were solved in ANSYS Fluent 19.0 using the SIMPLE scheme for pressure-velocity coupling. A bounded second-order implicit transient formulation was utilized with a time step of 0.001 s. The solution was considered converged when residuals in momentum and turbulence variables declined below $10^{-4}$. Three-thousand time steps were simulated, with the last time step being used for data analysis.

**Obtaining Simulated Hemodynamics**

Hemodynamic metrics were extracted from each CFD simulation, including the peak LVOT velocity ($V_{peak}$), peak LVOT pressure gradient ($\Delta P_{peak}$), and peak LVOT effective orifice area ($EOA_{peak}$). To calculate $\Delta P_{peak}$, the ventricular

![FIGURE 2](image-url)
pressure was derived from an average pressure across the model inlet (LV apical plane), and the aortic pressure was derived from an average pressure across the model outlet (sino-tubular junction plane). $\Delta P_{\text{peak}}$ was then calculated as the difference between the ventricular and aortic pressures. $E \Omega A_{\text{peak}}$ was calculated as the ratio of the peak volumetric flow rate ($Q_{\text{peak}}$) to the peak outflow velocity ($V_{\text{peak}}$) (9).

**Data Analysis**

All data analyses were performed with the MedCalc statistical software package (MedCalc, Ostend, Belgium). Simulated hemodynamics for each subject were compared between the two modeled conditions (TMVR with and without LAMPOON) using the paired samples $t$-test or Wilcoxon test for parametric and non-parametric data, respectively. Statistical significance was defined as $p < 0.05$.

**RESULTS**

**Subject Characteristics**

Baseline, procedural and post-procedural characteristics are shown in Table 1. All subjects were considered to be at prohibitive risk of LVOT obstruction based on small ventricular anatomy and small LVOT clearance (end-systolic neo-LVOT area <200 mm$^2$ as predicted on baseline CT), and therefore were considered candidates for the LAMPOON procedure. All subjects included were female, likely due to the selection of patients with small ventricular anatomy for LAMPOON. The indication for mitral valve replacement was mitral regurgitation in three subjects, and mitral stenosis in five subjects.

All subjects underwent successful midline anterior leaflet laceration (LAMPOON procedure) immediately followed by investigational use of the SAPIEN 3 transcatheter heart valve in

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**FIGURE 3** | Effect of LAMPOON on left ventricular pressure fields. Simulated pressure fields for a representative subject (Subject 5) are shown in color maps (red = highest pressure, blue = lowest pressure). The left column shows the simulated pressure drop at the LVOT for the virtual control procedure (TMVR without LAMPOON). The right column shows the simulated pressure drop at the LVOT for the actual performed procedure (TMVR with LAMPOON). The simulated LVOT gradient is substantially reduced following LAMPOON. In this subject, LAMPOON exposed three cells of the transcatheter valve, corresponding to a total increase in flow area of 87 mm$^2$. 

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FIGURE 4 | Comparison of simulated hemodynamics following TMVR with and without LAMPOON. Simulated hemodynamics following TMVR with LAMPOON were superior to those following TMVR without LAMPOON for all subjects. Following LAMPOON, the simulated peak outflow gradient ($\Delta P_{\text{peak}}$) and velocity ($v_{\text{peak}}$) decreased in all subjects ($p < 0.05$ for both comparisons) (A,B). Additionally, the simulated peak effective orifice area ($EOA_{\text{peak}}$) increased following LAMPOON in all subjects ($p < 0.05$) (C). LVOT, left ventricular outflow tract.

Effect of LAMPOON on Simulated Left Ventricular Flow Patterns

Simulations of left ventricular flow patterns are depicted by color maps (red = highest velocity, blue = lowest velocity) with streamlines for a representative subject (Subject 5) (Figure 2). For the condition of the virtual control procedure (TMVR without LAMPOON), flow acceleration occurred at the level of the neo-LVOT, resulting in a narrowed outflow jet (Figure 2, left panel). In this condition, the neo-LVOT was shown to be the predominant geometric narrowing for systolic flow. All forward flow was directed through the neo-LVOT, causing an increase in velocity at this location due to the reduced flow area. Additionally, there was a region of reduced flow adjacent to the transcatheater valve due to the narrowed outflow jet, as noted in the neo-LVOT short-axis view (Figure 2, upper left image).

For the condition of the performed interventional procedure (TMVR with LAMPOON), flow occurred both through the neo-LVOT and through exposed cells of the transcatheter valve (Figure 2, right panel). LAMPOON provided an additional source of flow into the LVOT, leading to a reduction in outflow velocity due to the increased flow area. The region of reduced flow adjacent to the valve in the case of TMVR without LAMPOON was decreased in the case of TMVR with LAMPOON, thus reflecting flow closer to normal flow physiology (Figure 2, upper right image). Following TMVR with LAMPOON, the main impediment to forward flow was observed to be the transcatheter valve skirt which still projected into the native LVOT.

Effect of LAMPOON on Simulated Left Ventricular Pressure Fields

Simulations of left ventricular pressure fields are depicted by color maps (red = highest pressure, blue = lowest pressure) for a representative subject (Subject 5) (Figure 3). For the condition of the virtual control procedure (TMVR without LAMPOON), there was a substantial pressure drop which occurred at the location of the neo-LVOT, corresponding to the location of geometric narrowing. For the condition of the performed interventional procedure (TMVR with LAMPOON), the simulated pressure drop was reduced at the neo-LVOT due to the increase in flow area from the splayed anterior leaflet. In this subject, the splayed anterior leaflet from LAMPOON exposed three cells of the transcatheter valve, corresponding to a total increase in flow area of 87 mm$^2$.

Comparison of Simulated Hemodynamics

As compared to TMVR without LAMPOON, TMVR with LAMPOON resulted in lower $V_{\text{peak}}$, lower $\Delta P_{\text{peak}}$, and higher $EOA_{\text{peak}}$ by 14 ± 7% ($p = 0.006$), 31 ± 17% ($p = 0.01$), and 17 ± 9% ($p = 0.002$), respectively (Figure 4). Following LAMPOON, $V_{\text{peak}}$ decreased from 2.6 ± 1.1 m/s to 2.2 ± 0.9 m/s, $\Delta P_{\text{peak}}$ decreased from 2.6 ± 1.1 mmHg to 2.2 ± 0.9 mmHg, $v_{\text{peak}}$ decreased from 4.5 ± 1.0 m/sec to 4.2 ± 0.8 m/sec, and $EOA_{\text{peak}}$ increased from 0.9 ± 0.3 cm$^2$ to 1.1 ± 0.4 cm$^2$.
FIGURE 5 | Relationship between post-procedure neo-LVOT area and hemodynamic improvement with LAMPOON. Subjects with a smaller post-procedure neo-LVOT area experienced a greater hemodynamic improvement with LAMPOON. The largest improvement in simulated LVOT gradient (32 mmHg reduction in gradient) was observed in the subject with the smallest post-procedure neo-LVOT area (49 mm$^2$). As neo-LVOT area increased beyond 250 mm$^2$, there was a smaller hemodynamic improvement with LAMPOON (<2 mmHg reduction in gradient). Neo-LVOT area = cross-sectional area at the narrowest point of the neo-left ventricular outflow tract. Skirt neo-LVOT area = cross-sectional area of the neo-left ventricular outflow tract measured at the level of the transcatheter valve skirt.

decompressed from 17.5 ± 19.6 mmHg to 10.0 ± 8.8 mmHg, and EOA$_{peak}$ increased from 1.6 ±0.6 cm$^2$ to 1.8 ±0.7 cm$^2$ ($p < 0.05$ for all comparisons). Subject 7 had a substantially larger simulated LVOT gradient than the other subjects and could be considered an outlier (Figure 4A). However, when we excluded this subject from the analysis, we observed the same significant trend for the effect of LAMPOON on simulated LVOT gradient ($p = 0.02$).

Relationship Between Neo-Left Ventricular Outflow Tract Area and LAMPOON Efficacy

LAMPOON was most effective in subjects who had a small post-procedure neo-LVOT area, as measured on post-procedure CT (Figure 5). The largest hemodynamic improvement with LAMPOON was observed in Subject 7 who had the smallest post-procedure neo-LVOT area across all subjects (49 mm$^2$). This subject experienced a 32 mmHg reduction in the simulated LVOT gradient following LAMPOON. 3D flow patterns in this subject were also shown to substantially improve following LAMPOON, as evidenced by more centrally directed flow along the LVOT (Supplementary Video 1).

As the post-procedure neo-LVOT area increased beyond 250 mm$^2$, LAMPOON began to demonstrate a smaller hemodynamic effect. For all subjects with a post-procedure neo-LVOT area greater than 250 mm$^2$, the simulated LVOT gradient reduced by less than 2 mmHg following LAMPOON. This finding is also illustrated in Figure 6 which shows simulations of flow patterns in two representative subjects with different neo-LVOT dimensions.

DISCUSSION

This study evaluated the hemodynamic impact of LAMPOON in TMVR using patient-specific in silico models. The main finding was that LAMPOON improved outflow hemodynamics in all subjects, with a larger hemodynamic effect in the setting of a smaller post-procedure neo-LVOT area. Because of the impossibility of performing a controlled clinical trial of TMVR with vs. without LAMPOON, the present in silico study is the first to provide quantitative insight into the hemodynamic effect of LAMPOON.

Left ventricular outflow tract obstruction is a significant problem for the broader adoption of TMVR as a therapy for
patients with mitral valve disease who are not otherwise surgical candidates. The risk of LVOT obstruction is a primary reason for screen failure in TMVR device trials (10). For patients at prohibitive risk of obstruction, LAMPOON is a potential option to mitigate the risk of obstruction. To date, all clinical studies of LAMPOON to have been single-arm studies to assess clinical safety and feasibility of the technique (4, 11, 12).

The hemodynamic impact of LAMPOON in TMVR has not previously been investigated since patients who are considered for LAMPOON are anticipated to be at prohibitive risk of LVOT obstruction and therefore are not considered anatomical candidates for the control procedure (TMVR without LAMPOON) which would be needed to compare hemodynamic outcomes. The only way to quantitatively assess the hemodynamic impact of the LAMPOON procedure would be to perform a controlled \textit{in vivo} (animal), \textit{in vitro} (bench), or \textit{in silico} (computational) study. \textit{In vivo} studies are not always feasible due to procedural and anatomical limitations of the animal model. \textit{In vitro} studies are more feasible but are also often very tedious to perform and can be costly. We chose to perform a controlled \textit{in silico} study, which allowed us to use each subject as their own virtual comparator.

\textit{In silico} modeling revealed that LAMPOON leads to a consistent improvement in hemodynamics following TMVR. Mechanistically, splaying the anterior mitral leaflet allows additional flow into the LVOT which decreases LVOT velocity and pressure gradient, while increasing the effective orifice area. The average number of transcatheter valve cells exposed by

\textbf{FIGURE 6} | Flow simulations demonstrating the relationship between neo-LVOT size and LAMPOON efficacy. Two representative subjects are shown, where the subject shown in the top panel (Subject 6) has a larger neo-LVOT area as compared to the subject shown in the bottom panel (Subject 7). 3D models and simulated flow patterns are shown for the conditions of TMVR with and without LAMPOON. As neo-LVOT area decreases, the hemodynamic effect of LAMPOON increases. The total area of the transcatheter valve cells exposed by the splayed anterior leaflet were identical in both subjects (88 mm$^2$). Ao, aorta; LV, left ventricle; neo-LVOT, neo-left ventricular outflow tract; THV, transcatheter heart valve.
LAMPOON was 2 ±0.6 cells which corresponded to a total increase in outflow area of 70 ±20 mm². On average, the area of a single exposed cell was 36 ±7 mm². This small increment in outflow area led to a critical improvement in simulated hemodynamics, particularly for subjects with a smaller post-procedure neo-LVOT area (Figure 5). In this study, TMVR without LAMPOON was modeled by artificially closing the exposed transcatheter valve cells to mimic an intact anterior leaflet. However, in the clinical setting, the anterior leaflet may not only drape the cells but also hang lower beyond the valve frame. Thus, the actual improvement in hemodynamics with LAMPOON may be even more dramatic than what was calculated in this study.

Flow simulations in this study also validated the importance of the skirt neo-LVOT concept when predicting the risk of LVOT obstruction following TMVR with LAMPOON. The skirt neo-LVOT area is measured at the level of the transcatheter valve skirt, and represents the main impediment to forward flow following TMVR with anterior leaflet resection or LAMPOON (8). In the subject with the smallest post-procedure neo-LVOT area (Subject 7), there was the largest hemodynamic improvement with LAMPOON (>30 mmHg decrease in simulated LVOT gradient). However, despite this improvement, this subject still had a 30 mmHg simulated LVOT gradient post-LAMPOON due to a small skirt neo-LVOT area (162 mm²). While initial clinical data suggested a skirt neo-LVOT area of <150 mm² should be avoided to prevent significant LVOT obstruction (catheterization gradient >30 mmHg), a more recent study from our group has shown that a skirt neo-LVOT area >180 mm² is ideal to ensure survival with measurable clinical benefit (e.g., improvement in Kansas City Cardiomyopathy Questionnaire Score) (9). Thus, flow simulations in this study corroborate the clinical observation that LVOT obstruction may still occur following LAMPOON in the case of a small skirt neo-LVOT, and confirm that the skirt neo-LVOT should be routinely and carefully evaluated prior to performing TMVR with LAMPOON.

This study also highlighted that there can be differences between the anticipated risk of LVOT obstruction and the actual risk of LVOT obstruction in patients undergoing TMVR. All subjects in this study were initially thought to be at prohibitive risk for obstruction based on a predicted end-systolic neo-LVOT area of <200 mm² measured on baseline CT. However, the neo-LVOT area measured on post-procedure CT was found to be substantially larger (>100 mm²) than the predicted neo-LVOT area at baseline in four subjects (Subjects 1, 2, 3, and 8) (Table 1), indicating that the actual risk of obstruction was substantially lower than the anticipated risk of obstruction. These four subjects experienced the least simulated hemodynamic benefit with LAMPOON. These data suggests that, in patients undergoing a valve-in-ring or valve-in-mitral annular calcification procedure, the anticipated risk of obstruction may in fact differ from the actual risk based on factors such as valve deployment depth (more atrial vs. more ventricular) or the valve deployment orientation (coaxial vs. canted with respect to the mitral valve). Personalized computational modeling may eventually help in better predicting the hemodynamic outcome of patients (13), and should account for a range of valve deployment scenarios. Recent interventional techniques have also enabled more predictable deployment of the transcatheter valve in the predicted landing zone, and may help improve future predictions of LVOT obstruction risk (14, 15).

In silico studies have the potential to provide key insights into the performance of novel interventional procedures such as LAMPOON which may be impossible to evaluate in a controlled clinical trial. The advantages of in silico studies are to (1) avoid the costs associated with conventional clinical trials, (2) avoid risk to patients, and (3) study unique metrics which may be difficult or impossible to attain in a clinical setting. Within the realm of structural heart disease interventions, prior in silico studies have evaluated para-valvular regurgitation in transcatheter aortic valve replacement (16, 17), device size selection for left atrial appendage occlusion (18), and LVOT hemodynamics in the setting of TMVR (7, 19, 20). In the future, in silico trials may also be used to supplement conventional clinical trial evidence and support the regulatory process of new devices and procedures (21). With appropriate validation, in silico data can represent a potentially valuable form of evidence which can be obtained at a reduced cost and without risk to patients (22).

Limitations

This was a retrospective study with a small sample size. As adoption of the LAMPOON technique expands, larger datasets will be needed to corroborate the findings of this study. The modeling of blood flow in this study using CFD may be limited given the assumptions of fixed left ventricular walls with zero wall velocity during peak systole, and steady flow boundary conditions. Since the pressure gradient across a normal aortic valve should be negligible relative to the gradient across an obstructed LVOT, we did not model an aortic valve in our simulations for simplicity. The anterior mitral leaflet was modeled depending on whether the leaflet could be reliably segmented on the post-procedure CT dataset. The posterior mitral leaflet was not modeled since the leaflet is not affected by the LAMPOON procedure and should not impact flow in the LVOT. The value of our CFD workflow is to provide a simplified, rapid approach to simulate LVOT hemodynamics. This method has been previously validated and has demonstrated good accuracy (<10% error) when compared to clinical hemodynamic measurements (7). Despite the discussed limitations, this study provides unique insight into the hemodynamic effect of LAMPOON which would have been impossible to study in a clinical setting.

CONCLUSION

A controlled in silico study was performed to investigate the hemodynamic impact of LAMPOON in TMVR. LAMPOON achieved a critical increment in outflow area which resulted in a consistent improvement in hemodynamic outcomes and 3D flow patterns following TMVR. Patients with a smaller post-procedure neo-LVOT area experienced a greater hemodynamic improvement with LAMPOON. This study demonstrates the
potential for in silico studies to evaluate procedures virtually which may improve cost-effectiveness and patient safety as compared to a conventional clinical trial.

DATA AVAILABILITY STATEMENT

Data can be made available upon reasonable request to NHLBI.

ETHICS STATEMENT

All subject data were acquired and analyzed under Institutional Review Board approvals at the National Institutes of Health (NCT03015194). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK, ZW, VS, RL, VB, AY, and JO: conception and design of the work. EP, AG, JK, RL, and VB: acquisition and compilation of clinical data. KK and ZW: development of methods for computer simulations. KK, ZW, AS, PB, and EP: initial drafting of manuscript. KK, ZW, VS, RL, VB, AY, and JO: final approval of manuscript. All authors analysis and interpretation of data, critical review of manuscript for important intellectual content, and final approval of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.869259/full#supplementary-material
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**Conflict of Interest:** KK has served as a consultant for Abbott Vascular. PB has served as a consultant for Edwards Lifesciences, Tendyne, Neovasc, and Circle Imaging. AG has served as a proctor for Edwards Lifesciences, Medtronic, and Abbott Vascular; and has served as a consultant for and is an equity holder in Transmural Systems. VB has served as a consultant for Edwards Lifesciences and Abbott Vascular; and has served as a consultant for and is an equity holder in Transmural Systems. JK and RL were co-inventors on patents, assigned to the NIH, on devices for leaflet laceration.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.