Experimental Investigation of Left Ventricular Flow Patterns After Percutaneous Edge-to-Edge Mitral Valve Repair

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Abstract: Mitral valve percutaneous edge-to-edge repair (PVEER) is a viable solution in high-risk patients with severe symptomatic mitral regurgitation. However, the generated double-orifice configuration poses challenges for the evaluation of the hemodynamic performance of the mitral valve and may alter flow patterns in the left ventricle (LV) during diastole. This in vitro study aims to evaluate the hemodynamic modifications following a simulated PVEER. A custom-made mitral valve was developed, and two configurations were tested: (i) a single-orifice valve with mitral regurgitation and (ii) a double-orifice mitral valve configuration following PVEER. The hemodynamic performance of the valve was evaluated using Doppler echocardiography and catheterization, while the flow patterns in the LV were investigated using particle image velocimetry (PIV). The tests were run at a stroke volume of 65 mL and a heart rate of 70 bpm. PVEER was found to significantly reduce the regurgitant volume (15 vs. 34 mL). There was a good agreement between Doppler and catheter transmitral pressure gradients (peak gradient: 9 vs. 7 mm Hg; mean gradient: 4 vs. 3 mm Hg) as well as an excellent agreement between maximal velocity measured by Doppler and PIV (1.60 vs. 1.58 m/s). Vortex development in the LV during diastole was significantly different after repair. PVEER significantly increased the amplitude of Reynolds and viscous shear stresses, as well as the number of high shear regions in the LV, potentially promoting thromboembolism events. Key Words: Percutaneous edge-to-edge repair—Particle image velocimetry—Doppler echocardiography—Flow pattern—Hemodynamic performance—Mitral valve.
In this work, we experimentally studied the effect of simulated PEtER on Doppler and catheter pressure gradients and on turbulent flow patterns in the LV using an in vitro cardiac simulator and particle image velocimetry.

**MATERIALS AND METHODS**

**In vitro model**

For the purpose of this study, a ViVitro pulse duplicator (ViVitro Labs, Victoria, BC, Canada) was used (Fig. 1). This system is capable of reproducing physiological flow and pressure waveforms in left heart cavity models. The system is powered by a piston-cylinder pulsatile pump. The setup includes an atrium chamber that contains a custom-made bicuspid mitral valve, a silicone model of the LV, and a rigid glass model of the ascending aorta including a trileaflet biological aortic valve. The circulatory fluid is a mixture of water and glycerol with a density of 1080 kg/m$^3$ and a viscosity of 3.5 cP so as to simulate the physiological characteristics of blood under high shear rate conditions. Flow through the mitral valve was measured using an electromagnetic flow meter (Carolina Medical Electronics, King, NC, USA) with an accuracy of

**FIG. 1.** Sketch of the cardiac simulator used in this study. The distance between the orifices for the simulated percutaneous edge-to-edge repair is 4 mm to mimic the width of the MitraClip device. Camera and laser configurations for particle image velocimetry measurements are shown. Δt is the time between two laser pulses; GOA is the valve total geometrical orifice area. [Color figure can be viewed at wileyonlinelibrary.com]
Pressure measurements were performed using Millar MPR 500 transducers (Millar Instruments, Houston, TX, USA) with an accuracy of ±0.025% full scale.

**Mitral valve models**

Custom-made bicuspid mitral valves were developed for the purpose of this study. Two configurations were tested: (i) one single-orifice mitral valve with MR and (ii) one double-orifice mitral valve resulting from PEtER (Fig. 1). As a MitraClip system was not available to us, the double-orifice mitral valve was created by suturing a 4-mm width patch in the middle portion of the leaflets. The width of the patch was selected to mimic the cobalt-chromium clip used in transcatheter edge-to-edge mitral valve repair using a MitraClip system (Abbott Vascular). The geometrical orifice area of the valve before PEtER was 572 mm² while that of the generated double-orifice was 245 mm². As the valve model did not include chordae, three small strings of 0.3 mm in diameter were positioned at the level of the mitral annulus to avoid mitral valve prolapse. Following fluid mechanics principles, these strings are not expected to disturb the flow downstream of the mitral valve. In the aortic valve position, a St. Jude Medical porcine aortic heart valve (EL-23A) with a tissue annulus diameter of 23 mm was used.

**Test conditions**

The measurements were performed under physiological conditions; heart rate of 70 bpm, arterial systolic and diastolic pressures of 110 and 80 mm Hg, respectively, and a constant pump stroke volume of 65 mL.

**Doppler measurements**

Doppler echocardiography measurements were performed using an Acuson 128 XP/10 system (Universal Diagnostic Solutions, Oceanside, CA, USA) and a V219 (2.5 MHz) probe. The beam was carefully aligned with the main jet direction. For the double-orifice configuration, the beam was aligned with one of the orifices. For all measurements, continuous-wave Doppler was used, and the following parameters were determined: (i) peak E-wave velocity and (ii) peak and mean transvalvular pressure gradient using the simplified Bernoulli equation.

**Catheter measurements**

Peak and mean catheter pressure gradients were measured using a miniaturized multi-sensor pressure wire developed by HemoDynamix Medical Systems (Toronto, ON, Canada). This pressure wire is based on fiber-optic technology, and the distance between the sensors was 2 cm. The small diameter of the pressure wire (0.71 mm) ensures a minimal disturbance to the flow. One sensor was located upstream of the mitral valve model and a second one just at the level of the tip of the valve leaflets. For the double-orifice case, the probe was passed through one of the orifices.

**Digital particle image velocimetry measurements**

The velocity field inside the LV for both valve configurations (MR and PEtER) was investigated using digital particle image velocimetry (DPIV). Hollow glass spheres with a 10 μm diameter and density of 1.1 g/cm³ were used for seeding the flow. A LaVision system (LaVision GmbH, Goettingen, Germany) was used in combination with a dual cavity Nd: YLF laser (Litron Lasers, Warwickshire, UK) with a maximum pulse energy of 10 mJ at 527 nm. The laser sheet, with a thickness of approximately 1 mm, was positioned parallel to the mitral valve flow jet (Fig. 1). A high-speed digital camera (Phantom V9.1, Vision Research, Wayne, NJ, USA) with a maximal resolution of 1632 × 1200 pixels at 1000 fps was used for image capture. The DaVis 7.2 software was used for capturing and post-processing the PIV images (DaVis 7.2, LaVision GmbH). Phase-locked PIV measurements were performed at different instants during diastole (Fig. 1). To optimize the cross-correlation of the DPIV measurements, the time step between two consecutive laser pulses (Δt) was modified, for each phase, to satisfy the 1/4 law (Δt range: 100–700 μs) (13). A total of 200 images were recorded for each phase and averaged. Multi-pass cross-correlations were used with an initial interrogation region size of 32 × 32 pixels and a final size of 16 × 16 pixels with 50% overlapping. The final spatial resolution was 0.49 × 0.49 mm².

**Uncertainty analysis**

The effect of peak-locking was minimized in our experiments by having particle image diameters approximately 3 pixels (13). The density ratio of the particles was 0.96, leading to a ratio of settling velocity to smallest flow velocity of 6 × 10⁻⁴. An uncertainty analysis was performed taking into account the errors due to the magnification factor, image displacement, and image interval. The uncertainty in velocity measurements for the MR and the PEtER cases were 6.2 and 1.2%, respectively. Finally, a 3-by-3 Gaussian filter was used to reduce
the inherent uncertainties associated with the velocity measurements (14,15).

RESULTS

Figure 2 shows mitral flow waveform for the MR (panel A) and the PEtER cases (panel B). The simulated PEtER successfully reduced the regurgitant volume (area under the flow curve during systole) from 34 to 15 mL (56% reduction).

Figure 3 displays peak and mean transmitral pressure gradients (TMPG) as measured by the catheter and Doppler ultrasound. There was a good agreement between the results: for peak TMPG, Doppler: 9 mm Hg versus Catheter: 7 mm Hg; for mean TMPG, Doppler 4 mm Hg versus Catheter: 3 mm Hg.

Figure 4 shows the flow patterns inside the LV for the MR and PEtER cases at three different instants during diastole: peak E-wave, diastasis, and peak A-wave. PEtER significantly altered the flow in the LV by creating a double-jet configuration. The maximal velocity, during peak E-wave, was increased significantly from 0.4 to 1.6 m/s. Figure 5 shows the velocity profile at 15 mm downstream of the tip of the mitral valve leaflets. While for the MR case, the velocity profile was relatively flat throughout diastole, PEtER generated a double-jet configuration with low velocity in valve centerline. The ratio of orifice jet velocity to central velocity varied during diastole and ranged from 3.6 to 6.0.

Figure 6 shows the velocity streamlines corresponding to the flow patterns displayed in Fig. 4. Interestingly, this clearly demonstrates the formation of vortex structures in the LV with MR and following PEtER. In both cases, two vortices can be observed. The vortices in the MR case were larger than those created in the LV following PEtER. Furthermore, it can be noticed that the vortices were more rapidly convected toward the apex in the case of PEtER.

Figure 7 displays major Reynolds shear stresses (Panel A) and viscous shear stresses (Panel B) in the LV before and after PEtER at different instants during diastole (peak E-wave, diastasis, and peak A-wave). Significantly higher Reynolds and viscous shear stresses were generated in the LV following PEtER. Elevated shear stresses were mainly concentrated in the shear layer surrounding the mitral jet. The specific double-jet configuration resulting...
from PEtER also led to an increase in high shear regions in the LV.

**DISCUSSION**

**The key findings**

By carrying out this study, we were able to determine the following: (i) there was a good agreement between Doppler and catheter transvalvular pressure measurements in the case of the double-orifice mitral valve configuration; (ii) PEtER significantly modified flow patterns and vortex dynamics in the LV; and (iii) PEtER increased the number of regions within the LV with significantly high Reynolds and viscous shear stresses.

Recent studies have shown that about half of the patients with symptomatic severe MR are not referred to surgery mainly because of age or the presence of comorbidities (3,6). For such patients, PEtER using MitraClip appears to be a viable solution. EVEREST I (Endovascular Valve Edge-to-Edge Repair Study I) demonstrated the safety and feasibility of the MitraClip (16). However, the results from EVEREST II in 279 patients have shown that PEtER does not outperform surgery in symptomatic patients with MR (17). Although the number of the main adverse events was significantly lower in patients with a MitraClip, the rate of surgery/reoperation was significantly higher compared to the surgical group. As a consequence, the
recent guidelines from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery suggest that MitraClip is used in high surgical risk patients (18,19). The procedure also has to be considered by a multidisciplinary team.

**Comparison of Doppler-catheter pressure gradients**

In this study, we showed that there was a good agreement between the maximal velocity measured by Doppler and PIV (1.60 vs. 1.58 m/s). Furthermore, we found a good match between Doppler and catheter TMPG (Peak TMPG: 9 mm Hg vs. Catheter: 7 mm Hg; Mean TMPG: 4 mm Hg vs. 3 mm Hg). The values for TMPG obtained in this study are in good agreement with and reflective of in vivo data from the literature. In a study on 84 patients with EtER (5) a peak TMPG of 10.7 ± 0.5 mm Hg and a mean TMPG of 4.3 ± 0.2 mm Hg found, while Hermann et al. reported a mean TMPG of 4.1 ± 2.2, and Divchev et al. a mean TMPG of 3.6 ± 1.5 mm Hg (20,21).

**Location of Doppler measurements**

Maisano et al. showed numerically that up to 35% error could be obtained in the estimation of TMPG depending on the location of the measurements (22). In this study, we found even larger differences between the jet velocity and the central line velocity. At the peak of the E-wave, the jet velocity was around three times higher than the central line velocity, while at the peak of the A-wave, the jet velocity was about six times higher. Alignment of the Doppler probe is therefore essential to limit measurement errors. Another finding was that the maximal velocity remained constant for about two orifice diameters (around 20 mm). As a result, if pulsed Doppler is used to evaluate mitral valve function following EtER, the results

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**FIG. 5.** Velocity profiles measured by particle image velocimetry 15 mm downstream of the tip of the mitral valve leaflets at the peak of E-wave (Panel A), during diastasis (Panel B) and peak A-wave (Panel C). The measurements were performed before and after simulated percutaneous edge-to-edge mitral repair. The induced double jet configuration significantly increased the velocity magnitude. [Color figure can be viewed at wileyonlinelibrary.com]
are less sensitive to the longitudinal positioning of the probe inside the LV.

**Flow patterns in the LV following PEtER**

The results of this study showed significant modifications in flow patterns in the LV following PEtER. Except for the development of a double-jet configuration, also shown numerically by (22–24), the vortex structures in the LV were significantly different when compared to a normal LV filling. PEtER generated smaller vortex structures that were rapidly convected toward the apex and
significantly contributed in dissipating flow energy. This energy lost as heat is not available during LV systole to transport blood flow through the arterial system. This might contribute to a suboptimal LV filling efficiency (25).

**Shear stresses in the LV following PEtER**

The results of this study not only show that PEtER leads to significantly higher shear stresses compared to MR case, but most importantly, that the specific flow configuration in the LV, as induced by PEtER, increases the number of regions with elevated shear stresses. Knowing that blood component damage is correlated to both the intensity of shear stresses and to the residence time, such flow configuration might promote thromboembolism events. Interestingly, in a recent case study, Orban et al. reported thrombus formation in the LV following a successful PEtER (7).

**CONCLUSION**

In conclusion, the double-orifice configuration resulting from percutaneous edge-to-edge repair poses challenges regarding the evaluation of mitral valve function and the flow in the left ventricle. In this in vitro study, we showed that there was a good agreement between Doppler and catheter TMPG and that the flow patterns in the LV were significantly modified following PEtER. The abnormal flow patterns increased significantly the number of regions within the LV with significantly higher shear stresses. Further, in vivo studies have to evaluate to which extend this might contribute to thromboembolism events.
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REFERENCES

19. McMurray JJ, Adamopoulos VS, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur Heart J 2012;33:1787–847.