

An in vitro study on the hemodynamics of transcatheter edge-to-edge mitral valve repair

Yunfan Yang^{1, 2}, Xinyi He^{1, 2}, Shuyi Feng^{3, 4, 5, 6}, Fan Wu^{1, 2}, Junqi Shen^{7*}, Hongping Wang^{1, 2}

¹The State Key Laboratory of Nonlinear Mechanics, Institute of Mechanics, Chinese Academy of Sciences, Beijing 100190, China

²School of Engineering Science, University of Chinese Academy of Sciences, Beijing 100049, China

³Department of Structural Heart Disease, National Center for Cardiovascular Disease, China & Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.

⁴National Health Commission Key Laboratory of Cardiovascular Regeneration Medicine.

⁵Key Laboratory of Innovative Cardiovascular Devices, Chinese Academy of Medical Sciences.

⁶National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences.

⁷China Aerodynamics Research and Development Center, Mianyang, 621000 Sichuan, China

*Corresponding author: Junqi Shen, China Aerodynamics Research and Development Center, Mianyang, 621000 Sichuan, China, e-mail address: shenjunqi27@126.com

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Abstract

Purpose: Transcatheter edge-to-edge mitral valve (MV) repair has been widely used to treat mitral valve regurgitation. In this catheter-based intervention, the edges of the two leaflets of MV are clipped together to generate a double-orifice MV. This intervention can directly reduce mitral regurgitation, but long-term outcomes for patients with residual mitral regurgitation and elevated MV pressure gradients remain somewhat controversial.

Methods: To identify who may benefit from transcatheter edge-to-edge MV repair, the hemodynamics of edge-to-edge repair are explored by measuring the flow rate, MV pressure gradient, and flow fields using particle image velocimetry (PIV) in an *in vitro* left heart simulator.

Results: The residual mitral regurgitation fraction (MRF) shows a linear dependence on the baseline MRF, and the effective orifice area (EOA) decreases to approximately half the value without intervention. These experimental results indicate that the models with $MRF < 60\%$ and $EOA > 4.8 \text{ cm}^2$ show excellent hemodynamic results. The alteration of the flow fields is also evaluated using vorticity, Reynolds shear stress, and viscous energy dissipation. The elevation of Reynolds shear stress and energy dissipation may be responsible for the risk of heart failure due to the increased burden on the heart.

Conclusions: Under the present *in vitro* conditions, model cases with baseline $MRF < 60\%$ and $EOA > 4.8 \text{ cm}^2$ exhibited favorable hemodynamic metrics after TEER. The associated elevation in Reynolds shear stress and energy dissipation, however, may increase cardiac burden and potentially contribute to heart failure risk.

Keywords: Mitral valve repair; Mitral regurgitation fraction; Effective orifice area; Heart failure risk

I. INTRODUCTION

The mitral valve (MV), one of the four cardiac valves, plays an essential role in allowing the unidirectional blood flow from the left ventricle (LV) to the left atrium (LA). The MV consists of four components, including the mitral annulus, the anterior and posterior leaflets, the chordae tendineae, and the papillary muscles. Under normal conditions, the MV opens to fill the ventricle during diastole and then closes to prevent blood from flowing back to the atrium during systole. However, chordae rupture, chordae elongation, restricted leaflet motion, and annular dilatation can lead to impaired leaflet coaptation [1], which further induces backward blood flow from the LV to the LA during systole. This clinical symptom is called mitral regurgitation (MR). It is further classified as degenerative MR or functional MR based on the pathophysiology [2], [3]. MR is a common valvular heart disease and contributes to significant morbidity and mortality [1], [4]. A population-based study shows that approximately 9.3% of people aged 75 and older suffer from MR, an estimate that is much higher than that for aortic regurgitation (2.0%) [5]. MR at baseline was graded as mild (MR1⁺), moderate (MR2⁺), moderate to severe (MR3⁺), and severe (MR4⁺) for clinical application [6]. The mitral regurgitation fraction (MRF) for MR1⁺, MR2⁺, MR3⁺, and MR4⁺ is < 30%, 30~39%, 40~49%, and ≥ 50%, respectively [1]. Severe MR can result in atrial fibrillation and heart failure; therefore, an intervention to treat MR is indispensable [7].

Surgical edge-to-edge repair offers a simple solution for treating MR, in which the edges of the two leaflets are sutured to create a double-orifice valve [8], [9]. For patients who are not suitable for open-heart surgery, the minimally invasive transcatheter edge-to-edge MV repair (TEER) technique provides a feasible and safe alternative to medical and surgical treatment [7], [10]. TEER is the only guideline-recommended catheter-based method to treat MR, and its recommendation has been upgraded based on evaluation against optimal medical therapy [11]. TEER with the MitraClip system (Abbott, Illinois, USA) treats MR by clipping together the anterior and posterior MV leaflets using a small and special clip. The Food and Drug Administration (FDA) has approved MitraClip to treat degenerative MR and functional MR [12]. Similar to surgical intervention, MitraClip also creates a double-orifice mitral valve with a smaller orifice area. TEER is the only transcatheter mitral valve repair therapy that is effective for both degenerative and functional MR [10].

MitraClip implantation has become the standard TEER procedure to treat patients with MR. However, approximately one third of patients have recurrent severe MR at 1-

year follow-up [13]. Therefore, its effectiveness is still somewhat controversial. First, apparently discordant results on the effect of MitraClip in patients with functional MR are obtained from two recent randomized controlled trials of MV repair [3]. The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial found no significant difference between the intervention and control groups in terms of the risk of death and the risk of hospitalization for heart failure [3]. However, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial found that patients assigned to MV clip repair had a lower risk of death and hospitalization [3]. Understanding the hemodynamics of TEER would help explain the discordant results between these trials and identify patients who could benefit from TEER [3]. Second, as mentioned previously, TEER significantly modifies the flow patterns in MV inflow to pulsatile twin jets due to the double-orifice valve [14]. Under normal conditions, a three-dimensional vortex ring is generated in the LV chamber by the interaction of the complex flow with the cardiac anatomy [14], [16]. Faludi et al. [18] found that the vortex in a healthy heart filling the entire ventricle stores the kinetic energy of the blood and smoothly redirects the blood to the outflow tract. However, after MitraClip implantation, significant potentially harmful changes in flow dynamics, including increased energy loss and flow force angle, were detected. These alterations may result in adverse LV remodeling [6], [19]. Recently, Gooden et al. [20] used particle image velocimetry (PIV) to quantitatively assess the flow fields associated with MitraClip. They found that the elevated shear stress generated by MitraClip may contribute to thrombus formation [19], [21].

It is of great significance to comprehensively understand the fluid dynamics of TEER. On the one hand, hemodynamics helps maximize the benefit of TEER by optimizing patient selection. On the other hand, statistical analyses of clinical data indicate that residual mitral regurgitation fraction (MRF) and an elevated mitral valve pressure gradient after TEER can lead to worse follow-up outcomes [22]-[26]. Therefore, it is essential to explore the relationship between the long-term outcomes and the nonphysiological flow induced by TEER. In the present work, we conducted in vitro experiments to measure hemodynamic parameters and flow fields before and after TEER, and used a series of 3D-printed silicone models to mimic the MV.

The rest of the paper is organized as follows. The experimental setup and measurement methods are introduced in the Materials and Methods section. The results

with and without TEER in terms of MRF, effective orifice area (EOA), and some characteristics of flow fields are presented in the Results section. Finally, we discuss and conclude on TEER.

II. MATERIALS AND METHODS

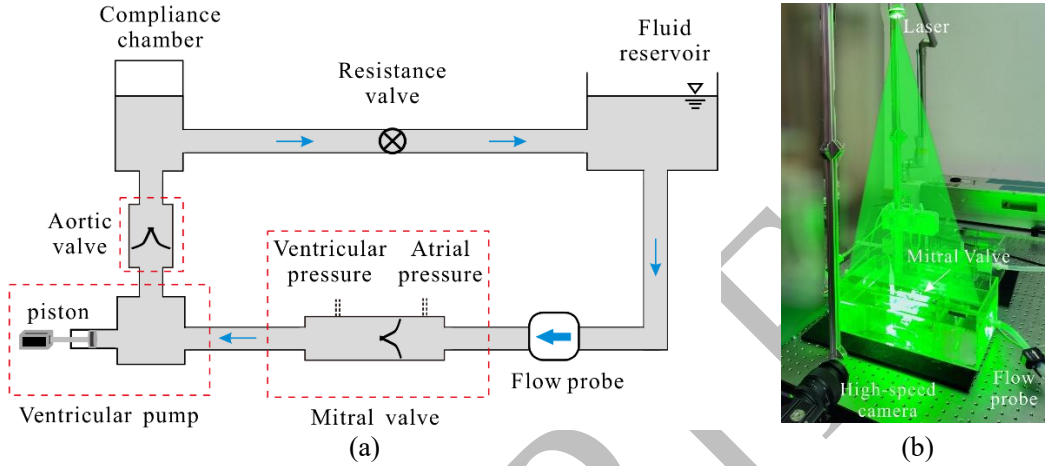


FIG. 1. (a) Schematic diagram of the left heart simulator. (b) Experimental setup of the PIV system.

In the present work, in vitro experiments were conducted to measure hemodynamic parameters and flow fields before and after TEER, and a series of 3D-printed silicone models were used to mimic MV. Figure 1 presents a schematic diagram of the left heart simulator used in the present work. Similar to the platform used in Gooden et al. [7], [20], the simulator contains a ventricular pump, aortic valve, compliance chamber, resistance valve, fluid reservoir, and MV. The piston drives the flow media and is directly connected to a linear motor. The piston displacement is controlled by a user-defined signal, which converts the time evolution of left ventricular volume extracted from Pedrizzetti and Perktold [28]. The aortic valve is a tilting disc valve with an inner diameter of 23 mm. The compliance chamber downstream of the aortic valve is used to mimic arterial compliance. The resistance valve is used to adjust the systemic resistance. The atrial pressure transducer and the ventricular pressure transducer are installed at 1D upstream of the MV and 3D downstream of the MV, respectively, where the parameter D denotes the MV diameter. The pressure transducers were placed according to ISO 5840-1:2021, avoiding upstream disturbance caused by the valve and ensuring the downstream pressure was measured out of the vena contracta zone. The pressure

uncertainty is ~ 0.6 mmHg at a 95% confidence level. An ultrasonic flow transducer (XY-TEK, China) with an accuracy of ± 0.2 L/min is placed upstream of the MV to measure the flow rate. The systole of the left ventricle is imitated with the contraction of the piston; the aortic valve is opened, and the mitral valve is closed. In contrast, the aortic valve is closed, and the mitral valve is opened during the period of relaxation of the piston.

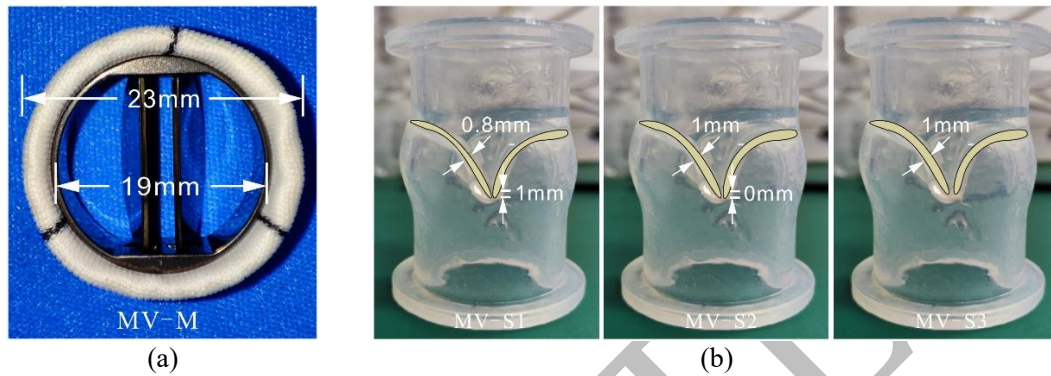


FIG. 2. MVs used in the present work. (a) MV-M, a bileaflet mechanical valve with a size of 23 mm (CORCYM, United Kingdom). (b) Three different 3D-printed silicone MVs, named MV-S1, MV-S2 and MV-S3. From left to right, the degree of MR increases by changing the leaflet thickness and coaptation height.

Four different MVs are used in the present work. One is a bileaflet valve with a size of 23 mm (CORCYM, United Kingdom), and the rest are 3D-printed silicone valves, as shown in Fig. 2. The mechanical valve is named MV-M, and the silicone MVs are named MV-S1, MV-S2, and MV-S3, respectively. Different from the experiment by Gooden et al. [20], where MR is induced by cutting the chordae tendineae of the porcine MV, we induced various degrees of MR by changing the coaptation height, the heart rate (HR), and cardiac output (CO) (please see Appendix A). The diameter of silicone MVs is 30 mm, which was designed in accordance with the annular diameter at the commissure of a natural MV [29]. Each silicone MV is clipped by a custom edge-to-edge clip, as shown in Fig. 3, to simulate TEER operation. In this experiment, we use pure water as the fluid medium. To replicate pulsatile blood flow in the heart, two relevant dimensionless numbers, the Reynolds number Re and the Womersley number Wo as defined in Eq. 1, should match those of a healthy heart [17].

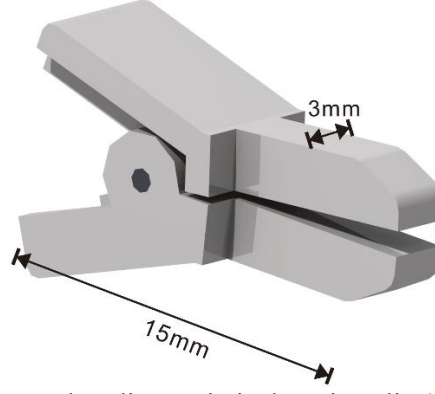


FIG. 3. Custom edge-to-edge clip to mimic the MitraClip (Abbott, Illinois, USA).

$$\begin{aligned} Re &= \frac{UD}{\nu}, \\ Wo &= \frac{D}{2} \sqrt{\frac{2\pi}{Tv}}. \end{aligned} \quad (1)$$

Here, U , D , T and ν are the velocity, diameter of MV, the time of a cardiac cycle and the kinematic viscosity of fluid media, respectively. Temperature was measured for each case, and the average water temperature was approximately 24°C. The kinematic viscosity of water is $\sim 0.91 \times 10^{-6} \text{ m}^2/\text{s}$, which is about 3.6 times smaller than the blood kinematic viscosity of $\sim 3.3 \times 10^{-6} \text{ m}^2/\text{s}$ [29]. We scaled HR and CO by the same ratio to ensure the Re and Wo numbers match in vivo conditions. Therefore, we set in vitro CO from 0.6 to 1.8 with an interval of 0.3 L/min to simulate the in vivo CO from 2.2 to 6.5 L/min, and set in vitro HR from 15 to 27 with an interval of 3 beats/min to simulate the in vivo HR from 54 to 97 beats/min. If we set the diameter D to 30 mm, the Re and Wo in the present study are 466-1399 and 19.7-26.4. Each silicone MV ran 50 tests with and without the custom clip.

A time-resolved two-dimensional two-component PIV system was used to measure the flow fields around the MV with and without the clip. As shown in Fig. 1(b), a double-pulse laser with a wavelength of 527 nm was used to illuminate the commissural plane. The thickness of the laser sheet was approximately 1 mm. To reduce refraction caused by the acrylic wall, fluorescent rhodamine-B-coated particles with a diameter of 7 μm were seeded in water. A high-speed camera (Imager HS, LaVision, Germany) placed $\sim 0.3 \text{ m}$ laterally was used to record the particle images at a sampling frequency of 200 Hz. Limited by the camera's memory, the image size was reduced to 2016×1172 pixels to guarantee a long-time acquisition. This configuration yielded a measurement domain of $62 \text{ mm} \times 36 \text{ mm}$ with a digital resolution of 0.03 mm/pixel. The velocity fields were

calculated using in-house PIV software with a three-pass window deformation iterative multigrid scheme [31]. The final interrogation window was set to 32×32 pixels with an overlap of 75%. Finally, outliers were rejected via the normalized median test proposed by Westerweel and Scarano [32], and the velocity fields were smoothed using Gaussian filtering. Twenty cardiac cycles were acquired for each case, and the velocity fields were further phase-averaged to reduce the measurement error. Note that the PIV experiments were only conducted under healthy heart conditions (HR = 76 beats/min, CO = 5.4 L/min).

III. RESULTS

A. Silicone valve and mechanical valve

As introduced in the Introduction section, TEER primarily changes the hemodynamics of MV by clipping together the anterior and posterior leaflets. This procedure was simulated by using a silicone valve in the present work. Therefore, the hemodynamics of the silicone valve are first compared with those of the mechanical valve. Figure 4(a) shows the variation of the left ventricular volume imposed by the piston at HR = 76 beats/min, CO = 5.4 L/min. The cardiac cycle was divided into two phases: systole and diastole. The volume decreases from 73 ml to 0 ml within 0.35T in systole, and then increases within 0.65T in diastole.

TABLE I. Comparison of MRF and EOA for mechanical valve (MV-M) and silicone valve (MV-S1) at HR= 76 beats/min, CO = 5.4 L/min.

MV	MRF (%)	EOA (cm ²)
MV-M	4.9	1.7
MV-S1	24.5	0.38

Figure 4 (b) shows the corresponding flow rate Q and mitral pressure gradient (atrial pressure – ventricular pressure) of the mechanical valve. During systole, ventricular pressure is higher than atrial pressure because the MV is closed; therefore, the pressure gradient is less than zero. Then, the MV opens during diastole and ΔP is close to zero. For the flow rate, it is reasonable to observe regurgitant flow (negative flow rate) in the bileaflet mechanical valve due to closing and leakage [33]. Compared with the results of the silicone valve (MV-S1) as shown in Fig. 4(c), the regurgitant flow of MV-S1 is

evidently larger than that of the mechanical valve. To quantitatively evaluate the effect of TEER, the hemodynamic parameters MRF and EOA are estimated as follows [7], [33]:

$$\text{MRF} = \frac{\int Q_-(t)dt}{\int Q_+(t)dt}, \quad (2)$$

$$\text{EOA} = \frac{Q_{rms}}{51.6\sqrt{\Delta p}}.$$

Here, $Q_+(t)$ and $Q_-(t)$ represent the forward and backward flow, respectively. Q_{rms} is the root mean square diastole flow rate (ml/s) during MV opening, and Δp is the corresponding mean pressure gradient (mmHg). MRF is used to assess the level of MR, and EOA is used to assess valve stenosis by estimating the orifice opening area. Note that EOA should be considered as a flow-dependent index rather than a precise measurement of actual orifice area [34], [35]. Table I presents the MRF and EOA computed from the data shown in Fig. 4 for the mechanical valve (MV-M) and silicone valve (MV-S1). The EOA of MV-M is consistent with the design value ($1.4 \pm 0.4 \text{ cm}^2$), and the EOA of MV-S1 is 0.38 cm^2 . Although the EOA of silicone valves is smaller than that of mechanical valves because of differences in material properties, the statistical results show good agreement with clinical data, as presented in the next section.

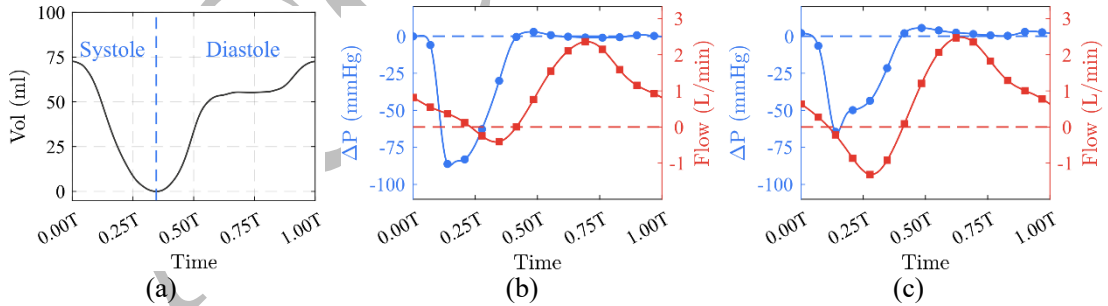


FIG. 4. (a) Time course of the left ventricular volume imposed by the piston. (b) Flow rate (red curve with solid square symbols) and mitral pressure gradient (blue curve with solid circle symbols) for the mechanical valve over a period of the cardiac cycle. (c) Flow rate (red curve) and mitral pressure gradient (blue curve) for the silicone valve (MV-S1) in a period of the cardiac cycle. All the curves are plotted at HR = 76 beats/min, CO = 5.4 L/min.

B. Impact of TEER on MRF and EOA

All silicone valves were tested with and without a custom clip to mimic TEER under different HR and CO conditions. The hemodynamic parameters MRF and EOA were

estimated for each case. The effects of TEER on MRF (a) and EOA (b) are presented as bar graphs in Fig. 5 at different grades of MR. The color bars represent the mean value, and the error bars represent the standard deviation. For mild, moderate, moderate-to-severe, and severe MR, one central placement clip statistically reduces MRF from 26.5% to 6.5%, 35.1% to 15.1%, 44.8% to 27.0%, and 54.2% to 36.3%, respectively. These values statistically show that TEER can reduce MR by two grades, consistent with clinical application. However, it is worth noting that the residual MRF (MRF after intervention by a clip) increases with increasing MR grade. For EOA, TEER can statistically reduce EOA from $\sim 0.3 \text{ cm}^2$ to $\sim 0.15 \text{ cm}^2$, with limited influence from MR grade.

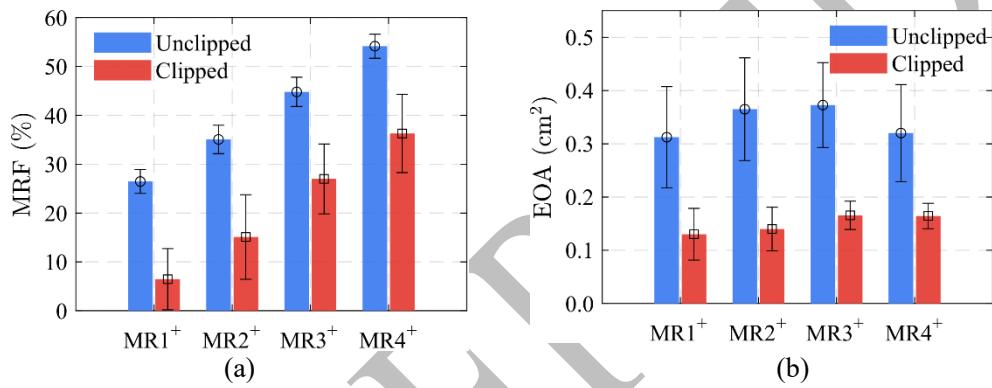


FIG. 5. Bar graphs of MRF (a) and EOA (b) at different MR grades. The color bars and the error bars represent the mean value and standard deviation, respectively.

TEER can reduce EOA and may cause mitral stenosis, which should be avoided in clinical application [25], [36]. The variation in MRF and EOA before and after TEER is shown in Fig. 6, and the location of the data points is determined by the hemodynamic parameters with and without clipping. The solid circles represent the results obtained in the present experiments and are colored by MR grade. The blue cross symbols represent data extracted from the numerical simulation by Caballero et al [37] and the in vitro experiment by Gooden et al [7]. Our results are qualitatively consistent with those data. All data points lie in the shaded region, indicating that TEER can reduce the MRF. However, the MRF after clipping shows a clear increasing trend as the unclipped MRF increases. The EOA also presents a similar trend. The relationships can be simply fit using a linear model as follows:

$$\begin{aligned} \text{MRF}_{\text{post}} &= 1.12 \cdot \text{MRF}_{\text{pre}} - 0.24 \left(\text{MRF}_{\text{pre}} > 22\%, R^2 = 0.64 \right), \\ \text{EOA}_{\text{post}} &= 0.42 \cdot \text{EOA}_{\text{pre}} \left(R^2 = 0.49 \right). \end{aligned} \quad (3)$$

Here, the subscripts ‘pre’ and ‘post’ represent the parameters obtained before and after intervention, respectively. The parameter R^2 denotes the coefficient of determination for regression. The MR should be reduced to below moderate grade ($\text{MRF}_{\text{post}} < 40\%$) in clinical application; therefore, the MRF of patients without intervention should be statistically less than 57%. If we consider the blue cross symbols when fitting the relationship, the MRF should be less than 61%. TEER can reduce the MR by two grades, consistent with clinical application; however, the residual MRF is still very high for severe MR. From our experiment, TEER is not suitable for those patients with an MRF larger than 60%.

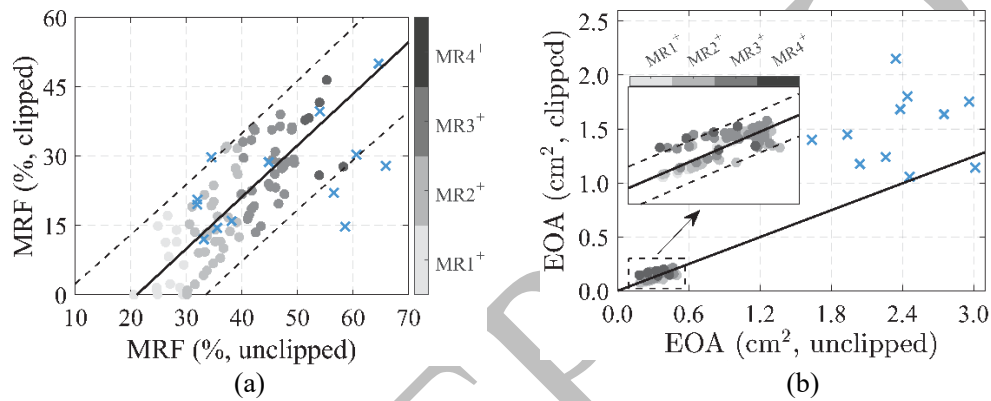


FIG. 6. Scatter plot of MRF (a) and EOA (b) after intervention by TEER with respect to values before intervention. The solid circles represent the results obtained in the present experiments and are colored according to the MR grades. The number of data points for MR1+, MR2+, MR3+ and MR4+ is 14, 33, 32 and 6, respectively, representing measurements under various HR and CO conditions. The blue cross symbols represent the data extracted from the numerical simulation by Caballero et al [37], and an in vitro experiment by Gooden et al [7]. The black dashed lines represent the results of linear regression, and the black solid lines represent the 95% confidence interval.

Another major concern with TEER is iatrogenic mitral stenosis with an increase in the mitral pressure gradient. It is evident from Fig. 6 (b) that the EOA after intervention is smaller than that without TEER, and the relationship is given in Eq. 3 as $\text{EOA}_{\text{post}} = 0.42 \cdot \text{EOA}_{\text{pre}}$ ($R^2 = 0.49$). This relationship can be qualitatively extrapolated to the region of the prosthetic valve indicated by the blue cross symbols. Moreover, the degree of MR has little influence on EOA. To explain the effect of TEER on EOA, Fig. 7 presents the schematic of the flow through a normal valve (a) and a clipped valve (b). In this figure, we use A_0 and A_1 to denote the geometrical orifice area and orifice area at the vena contracta, respectively. The value of A_1 is smaller than A_0 due to the contraction of the jets [30]. Note that EOA measured by Doppler using the continuity

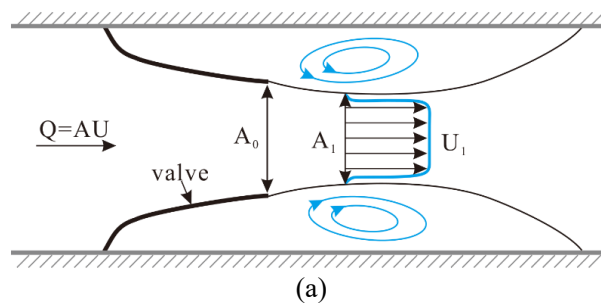
equation is theoretically in close agreement with EOA measured by catheter at the vena contracta [35]. For brevity, a contraction coefficient C_c is defined as $C_c = A_1 / A_0$. We need to make two assumptions. First, the variation in the flow rate caused by the clip is neglected. Second, the Bernoulli equation is simplified as $\Delta p = \frac{\rho}{2} U_1^2$ by ignoring the upstream velocity ($U_1 \ll U$) [30], [38], [39]. Therefore, the pressure gradient Δp is

$$\frac{\rho}{2} \left(\frac{Q}{C_c^{\text{pre}} A_0^{\text{pre}}} \right)^2 \text{ and } \frac{\rho}{2} \left(\frac{0.5Q}{C_c^{\text{post}} A_0^{\text{post}}} \right)^2 \text{ for a single orifice and double orifices, respectively.}$$

The parameter Q represents the flow rate. The geometrical area A_0^{post} is a quarter of the area A_0^{pre} . The ratio between Δp_{pre} and Δp_{post} , EOA_{pre} and EOA_{post} can be written as:

$$\begin{aligned} \frac{\Delta p_{\text{post}}}{\Delta p_{\text{pre}}} &= 4.0 \cdot \left(\frac{C_c^{\text{pre}}}{C_c^{\text{post}}} \right)^2, \\ \frac{\text{EOA}_{\text{post}}}{\text{EOA}_{\text{pre}}} &= 0.5 \cdot \frac{C_c^{\text{post}}}{C_c^{\text{pre}}}. \end{aligned} \quad (4)$$

The contraction coefficient C_c^{post} is smaller than C_c^{pre} for a sudden contraction pipe. Therefore, EOA_{post} is smaller than $0.5\text{EOA}_{\text{pre}}$ and Δp_{post} is larger than $4.0\Delta p_{\text{pre}}$, which is consistent with the relationship given in Eq. 3. Two remarks can be offered if we accept $C_c^{\text{post}} / C_c^{\text{pre}} = 0.42 / 0.5 = 0.84$. First, mitral stenosis is defined as an EOA reduces to below 2 cm^2 , thus, TEER should choose patients with an EOA larger than 4.8 cm^2 to avoid mitral stenosis. Second, the mitral valve pressure gradient can be elevated to $\sim 5.7 \text{ mmHg}$ if the normal pressure gradient is 1 mmHg . Neuss et al. [25] also reported that 25% of patients have an increased mitral pressure gradient $>5 \text{ mmHg}$ after mitral clip implantation. They also concluded that the elevated mitral valve pressure gradient deteriorates the long-term outcome and is a significant predictor for poorer prognosis and increased all-cause mortality.



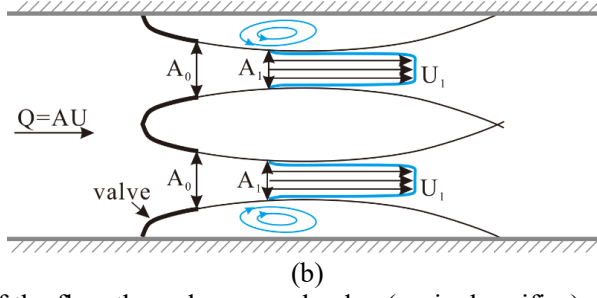


FIG. 7. Schematic of the flow through a normal valve (a, single orifice) and a clipped valve (b, double orifices).

C. Impact of TEER on flow fields

The PIV experiment was performed for MV-S3 at HR = 76 beats/min and CO = 5.4 L/min to explore the effect of TEER on the flow motions. Under this condition, the MRF decreases from 40% to 21% after clipping one custom clip at the central placement. Snapshots of the streamwise velocity u with vectors in the commissural plane are displayed in Fig. 8. It is obvious that two jets are generated after the clip is introduced [14], [20], [40], [41]. These two jets merge downstream of the clip to generate one combined jet due to the small spacing ratio between the distance of the center of each jet and the width of the jets [42]. The vorticity ω , kinetic energy (KE), Reynolds shear stress (RSS), and viscous energy dissipation ε were also estimated from the PIV fields. KE is the kinetic energy per unit volume in the instantaneous velocity field [42]. RSS stems from the momentum transfer by the fluctuating velocity field [43]. The dissipation ε represents the transformation from kinetic energy to internal energy due to viscous stress [43], and it always reduces kinetic energy. Formulations for two-dimensional PIV are given as follows:

$$\begin{aligned}
 \omega &= \frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \\
 \text{KE} &= \frac{\rho}{2} (u^2 + v^2) \\
 \text{RSS} &= -\rho u'v' \\
 \varepsilon &= \mu \left(2 \left(\frac{\partial u}{\partial x} \right)^2 + 2 \left(\frac{\partial v}{\partial y} \right)^2 + \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right)^2 \right)
 \end{aligned} \tag{5}$$

Here, the streamwise and wall-normal velocities are denoted by u and v , respectively. The velocity fluctuations are indicated with primes as $u' = u - U$, and the capital letter U denotes the time-averaged velocity. The parameters μ and ρ are the dynamic viscosity and density, respectively. We applied central differences for interior data

points, while using one-sided differences along the edges of the data matrix. The snapshots of ω , KE, RSS and ϵ are also displayed from top to bottom in Fig. 8. Using colour contours, we found that the intensity of vorticity, RSS, and dissipation increased after intervention by a clip at this time instant. The maximum RSS increases from ~ 100 Pa to ~ 125 Pa, and the maximum energy dissipation increases from ~ 400 J/(s $\cdot$ m ^{3}) to ~ 600 J/(s $\cdot$ m ^{3}).

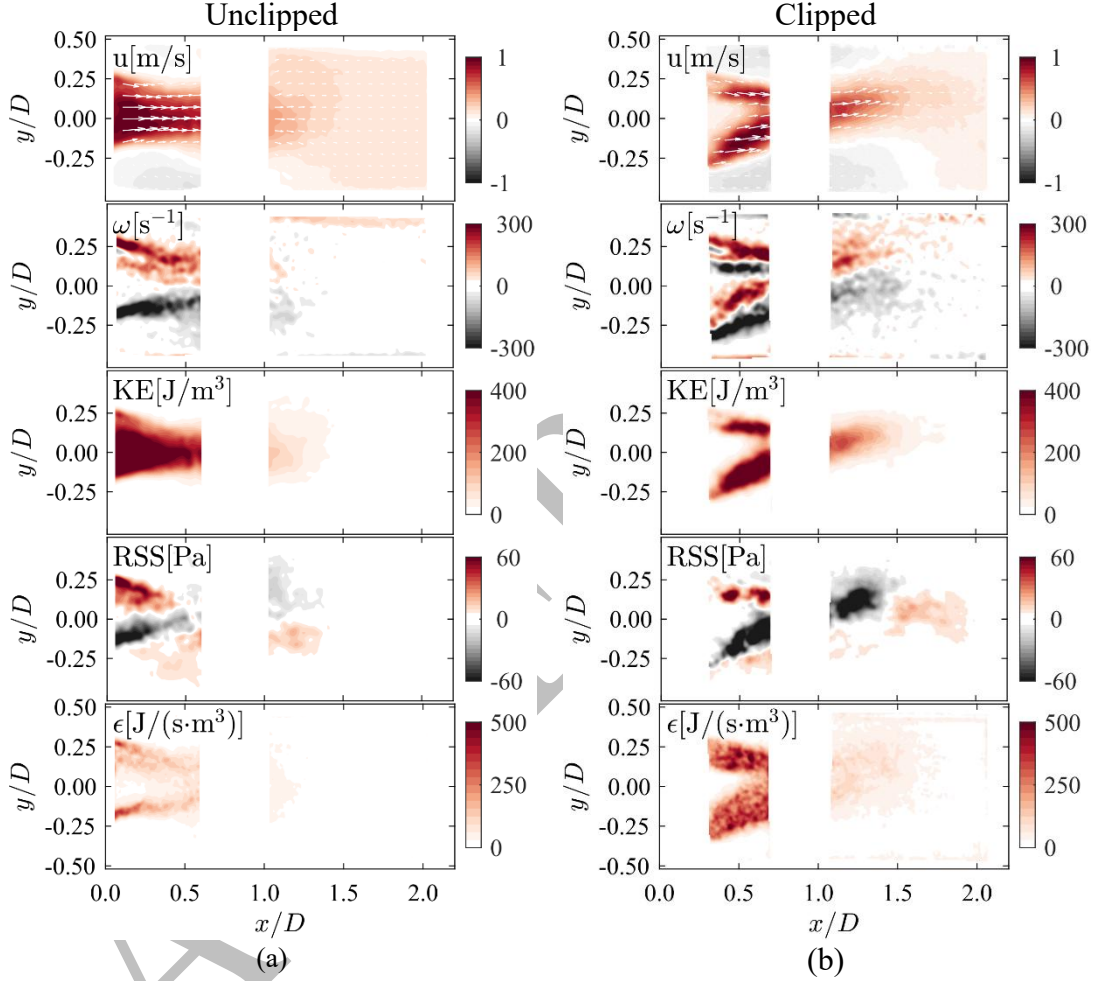


FIG. 8. Flow fields at the acceleration phase (before reaching the E-wave peak) with and without the custom clip. The velocity fields were obtained by averaging the PIV fields at the same phase. The results of streamwise velocity u , vorticity ω , KE, RSS and energy dissipation ϵ are displayed from top to bottom.

Following recent studies by Pedrizzetti and Domenichini [16]; Stugaard et al [45]. and Sargordi et al. [14], we also present the temporal evolution of the spatially averaged vorticity, RSS, and the in-plane viscous energy dissipation ϵ over one cardiac cycle in Fig. 9 (a), (b), and (c), respectively. From Fig. 9, it is evident that TEER increases the ω , RSS and ϵ during diastole. Especially for ϵ , its peak value increases

from $72 \text{ J}/(\text{s}\cdot\text{m}^3)$ to $165 \text{ J}/(\text{s}\cdot\text{m}^3)$ at $t \approx 0.14T$, and from $10 \text{ J}/(\text{s}\cdot\text{m}^3)$ to $55 \text{ J}/(\text{s}\cdot\text{m}^3)$ at $t \approx 0.57T$. A higher ε indicates higher energy consumption of the heart and higher risks of heart failure [14]. Additionally, vorticity, RSS and dissipation of the unclipped flow fields at $t \approx 0.8T$ are much higher than those of the flow fields with one clip due to regurgitant flow, which is consistent with the fact that flow parameters can be used to predict cardiovascular diseases [45]. All the curves reach a maximum at early diastole. Then, the vortical structures decay to a low level during isovolumic contraction until the beginning of atrial contraction.

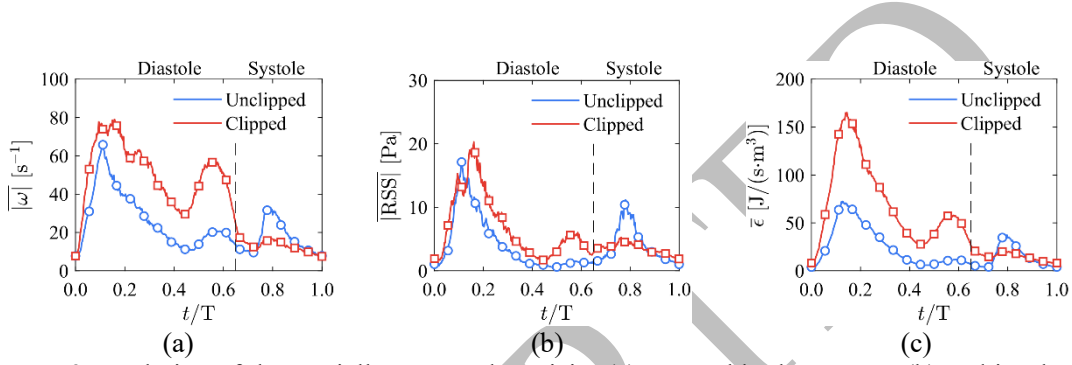


FIG. 9. Evolution of the spatially averaged vorticity (a), Reynolds shear stress (b) and in-plane viscous energy dissipation (c) over one cardiac cycle. All the curves are calculated over the domains of $0D \leq x \leq 2D$ and $-0.4D \leq y \leq 0.4D$ to exclude the boundary points. $\bar{(\cdot)}$ represents spatial averaging.

IV. DISCUSSION

Mitral valve repair by TEER has been adopted to treat patients with degenerative MR and functional MR. Here, there are still some fundamental controversies regarding its effect and fluid mechanism. Therefore, we performed an experimental study to assess TEER hemodynamics in terms of MRF, EOA, and flow structures. Several 3D-printed silicone models were used to mimic the MV, and a custom clip, which was designed to replicate the dimensions and functions of MitraClip, was used to reduce the MR by simulating the TEER intervention. The degree of MR was induced by changing the coaptation height of MV, the HR, and the CO of the left heart simulator. Our analyses yield two key findings. First, TEER statistically reduces the MRF by two grades; however, the residual MRF shows a remarkable linear correlation with the baseline MRF. This implies that TEER may not be suitable for patients with an MRF larger than 60%, according to our prediction formula: $\text{MRF}_{\text{post}} = 1.12\text{MRF}_{\text{pre}} - 0.24$. Second, experimental and theoretical analyses show that TEER reduces the EOA by

more than half, which may further induce mitral stenosis. Patients with an EOA smaller than 4.8 cm^2 are more likely to have mitral stenosis after the TEER procedure. The relevant discussions are presented next.

A. Residual MRF

TEER can statistically reduce the degree of MR by two grades, which is consistent with the clinical requirement. However, we found that residual MRF increases linearly as baseline MRF increases. This implies that for those patients with extremely severe MR (MRF > 60%), the residual MRF will still remain at a high level after the TEER procedure. Residual MRF is a key determinant of long-term outcomes after TEER [22-26]. The degree of residual MR after TEER has been shown to increase the risk of mortality, recurrent severe MR, and heart failure hospitalization [26]. Therefore, minimizing residual MRF is highly significant for the TEER procedure. From a fluid mechanics perspective, TEER performance may be suboptimal because residual MRF depends on baseline MRF, underscoring the importance of patient selection. Further improvement of device design (such as MitraClip G4 [46], PASCAL [47]) or combination with other intervention equipment, such as annuloplasty devices, may help minimize residual MRF.

B. Elevated mitral pressure gradient

Reducing MRF may conversely increase the risk of iatrogenic mitral stenosis, with an elevated mitral pressure gradient and reduced effective orifice area. Experimental and theoretical analyses show that EOA after TEER decreases to approximately half the value without clipping, as predicted by the formula $EOA_{post} = 0.42EOA_{pre}$, and the pressure gradient increases by approximately 5.7 times. The clinical data indicate that the mean pressure gradient significantly increases from 1.6 mmHg preintervention to 3.1 mmHg postintervention and to 3.8 mmHg at follow-up, and the mitral valve area decreases from 3.8 cm^2 preintervention to 2.6 cm^2 both postintervention and follow-up [26]. This deviation between the present experiments and the clinical data could be explained by two reasons: 1) the contraction coefficients between the silicone valve and the natural valve are different; 2) the location of the clip in clinical practice is not always in the center of the MV. The elevated pressure gradient deteriorates long-term outcomes in patients undergoing TEER and can be used as an independent predictor of adverse outcomes in patients with degenerative MR, not in those with functional MR [24]-[26].

The formula we derived may help predict the pressure gradient after TEER, which would help exclude unsuitable patients before intervention.

C. Flow structures in LV

Another negative effect of TEER is variation in the LV flow pattern. Two jets are generated from the resulting double orifices and then merge to form a single combined jet. We also computed the spatially averaged energy dissipation over one cardiac cycle. We found that energy dissipation increases to a high level compared with the value without intervention. This indicates that the heart would require more energy to maintain blood circulation, increasing the risk of heart failure [14], [45]. Pedrizzetti and Domenichini [16] found that the healthy intraventricular flow pattern has a natural structure that is optimal for minimizing energy dissipation. Therefore, energy dissipation $\mathcal{E}$ may be a useful indicator for determining the severity of cardiovascular diseases from the perspective of cardiac load [45]. In our results, we observed that TEER indeed increases these quantities during diastole (Fig. 9), with the peak energy dissipation rising from 72 to 165 J/(s·m³) at early diastole. This indicates that the heart requires more energy to maintain circulation after TEER, consistent with the finding that energy dissipation may serve as an indicator of cardiac load [45]. It is worth noting that the absolute values of energy dissipation depend on the specific flow domain and boundary conditions of the physiological LV, where jets interact with the ventricular walls, papillary muscles, and septum. Therefore, the absolute values in the present study should not be interpreted as clinical reference thresholds; rather, the key finding is that the relative increase (clipped versus unclipped under identical conditions) may indicate elevated cardiac burden. A long-term investigation of the effect of TEER on the LV is needed because it is still unclear whether the variation in the flow pattern results in a reverse remodeling of the LV.

D. Limitations

The present study has three main limitations. First, this study uses a series of 3D-printed silicone models to simulate natural MVs in the human body. The 3D-printed silicone MV does not contain chordae tendineae and has different material properties. These differences lead to a much smaller EOA for the silicone MV than for the natural MV. However, the statistical results are consistent with the clinical data and other in

vitro experiments using porcine MVs [7]. Second, the MV is mounted in a straight pipe without considering LV geometry. Thus, the vortex structures and velocities may present a different distribution due to the lack of interaction with the LV wall and interventricular septum. In the future, we will update and optimize the experimental conditions and devices to provide a more comprehensive investigation of TEER. **Third, all hemodynamic thresholds and conclusions in this manuscript are based solely on the present in vitro simulator with simplified silicone valve phantoms. These findings cannot be directly used as patient-selection criteria. Native mitral valves have substantial inter-individual variations in annular size, leaflet mechanics, and subvalvular structures. Dimensionless hemodynamic indices would be more appropriate for developing generalizable evaluation criteria for TEER in future investigations.**

V. CONCLUSIONS

The hemodynamic performance of TEER was investigated in vitro in terms of mitral pressure gradient, flow rate, and flow fields. The degree of MR was induced by changing the coaptation height, HR, and CO of the left heart simulator. The vorticity, Reynolds shear stress, and viscous energy dissipation were estimated from the velocity fields measured using PIV. **Our key finding is that under the experimental conditions and parameters of the present study,** patients with an MRF smaller than 60% and an EOA larger than 4.8 cm² could benefit from TEER intervention without concern of mitral stenosis. This finding is helpful for patient selection of TEER. Another qualitative finding is that energy dissipation increases to a high level after TEER intervention. Despite the fact that TEER can reduce the degree of MR by two grades, the negative impacts, including the residual MRF, elevated mitral pressure gradient, and changed flow pattern in the LV, could not be ignored and need to be further studied under more realistic experimental conditions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Appendix A: Mitral Regurgitation Induction

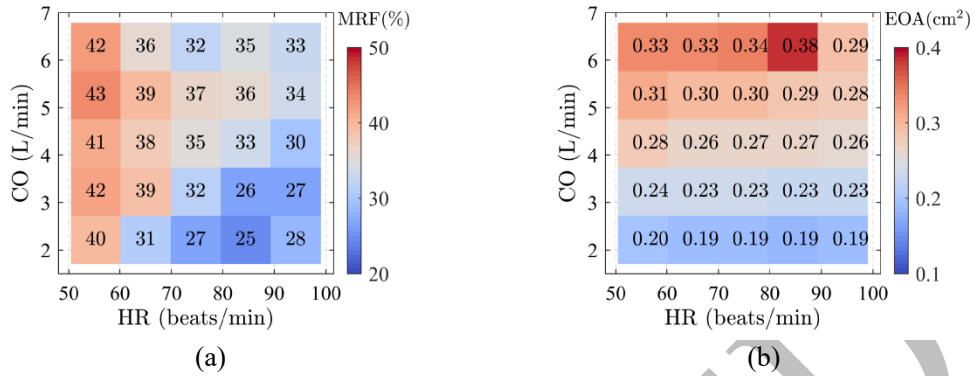


FIG. 10. MRF (a) and EOA (b) as a function of the CO and HR for silicone valve MV-S2.

The pathophysiology of MR is divided into primary regurgitation and secondary regurgitation [3], [48]. The former is caused by structural lesions of the valvular apparatus (valve leaflets or chordae tendineae). The latter refers to insufficient coaptation of a structurally normal valve caused by cardiac chamber remodeling. It is impossible to reproduce the pathophysiology of MR using silicone MV. However, we found that the degree of MR can be induced by changing the HR and CO of our left heart simulator. Figure 10 displays the MRF (a) and EOA (b) as functions of CO and HR for silicone valve MV-S2. The minimum and maximum of the MRF are 25% and 43%, respectively. The increase in MRF with reduced HR implies that reducing HR may aggravate MR severity. A clinical study by Supino et al. [49] confirmed that beta-blockade, which can decrease HR, appears to confer an increased risk of sudden cardiac death or indications for mitral valve surgery. However, the present experiment was conducted with silicone valves, and we will use fresh porcine mitral valves to further investigate the effect of HR and CO on MR.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

REFERENCES

- [1] Del Forno, B., De Bonis, M., Agricola, E., Melillo, F., Schiavi, D., Castiglioni, A., Montorfano, M., and Alfieri, O., Mitral valve regurgitation: a disease with a wide

spectrum of therapeutic options, *Nature Reviews Cardiology*, 2020, **17**(12), 807–827

- [2] Carabello, B. A., The Current Therapy for Mitral Regurgitation, *Journal of the American College of Cardiology*, 2008, **52**(5), 319–326
- [3] Grayburn, P. A., Sannino, A., and Packer, M., Proportionate and Disproportionate Functional Mitral Regurgitation: A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials, *JACC: Cardiovascular Imaging*, 2019, **12**(2), 353–362
- [4] Dziadzko, V., Dziadzko, M., Medina-Inojosa, J. R., Benfari, G., Michelena, H. I., Crestanello, J. A., Maalouf, J., Thapa, P., and Enriquez-Sarano, M., Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome, *European Heart Journal*, 2019, **40**(27), 2194–2202
- [5] Nkomo, V. T., Gardin, J. M., Skelton, T. N., Gottdiener, J. S., Scott, C. G., and Enriquez-Sarano, M., Burden of valvular heart diseases: a population-based study, *The Lancet*, 2006, **368**(9540), 1005–1011
- [6] Filomena, D., Cimino, S., Maestrini, V., Cantisani, D., Petronilli, V., Mancone, M., Tonti, G., Pedrizzetti, G., and Agati, L., Changes in Intraventricular Flow Patterns after MitraClip Implant in Patients with Functional Severe Mitral Regurgitation, *Journal of the American Society of Echocardiography*, 2019, **32**(9), 1250-1253.e1
- [7] Gooden, S. C. M., Hatoum, H., Zhang, W., Boudoulas, K. D., and Dasi, L. P., Multiple MitraClips: The balancing act between pressure gradient and regurgitation, *The Journal of Thoracic and Cardiovascular Surgery*, 2022, **163**(4), 1319-1327.e1
- [8] Maisano, F., Torracca, L., Oppizzi, M., Stefano, P. L., D’Addario, G., La Canna, G., Zogno, M., and Alfieri, O., The edge-to-edge technique: a simplified method to correct mitral insufficiency, *European Journal of Cardio-Thoracic Surgery*, 1998, **13**(3), 240–246
- [9] Alfieri, O., Maisano, F., De Bonis, M., Stefano, P. L., Torracca, L., Oppizzi, M., and La Canna, G., The double-orifice technique in mitral valve repair: A simple

- solution for complex problems, *The Journal of Thoracic and Cardiovascular Surgery*, 2001, 122(4), 674–681
- [10] De Backer, O., Wong, I., Taramasso, M., Maisano, F., Franzen, O., and Sondergaard, L., Transcatheter mitral valve repair: An overview of current and future devices, *Open Heart*, 2021, 8, e001564
- [11] Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S., Bauersachs, J., Capodanno, D., Conradi, L., De Bonis, M., De Paulis, R., Delgado, V., Freemantle, N., Gilard, M., Haugaa, K. H., Jeppsson, A., Jüni, P., Pierard, L., Prendergast, B. D., Sádaba, J. R., Tribouilloy, C., Wojakowski, W., and Esc/Eacts Scientific Document, G., 2021 ESC/EACTS Guidelines for the management of valvular heart disease, *European Heart Journal*, 2022, 43(7), 561
- [12] Shah, M., and Jorde, U. P., Percutaneous Mitral Valve Interventions (Repair): Current Indications and Future Perspectives, *Frontiers in Cardiovascular Medicine*, 2019, 6, 88
- [13] Buck, T., Eiswirth, N., Farah, A., Kahlert, H., Patsalis, P. C., Kahlert, P., and Plicht, B., Recurrence of Functional Versus Organic Mitral Regurgitation After Transcatheter Mitral Valve Repair: Implications from Three-Dimensional Echocardiographic Analysis of Mitral Valve Geometry and Left Ventricular Dilation for a Point of No Return, *Journal of the American Society of Echocardiography*, 2021, 34(7), 744–756
- [14] Sargordi, M., Chtchetinina, A., Labbio, G. D., Ng, H. D., and Kadem, L., Pulsatile twin parallel jets through a flexible orifice with application to edge-to-edge mitral valve repair, *Physics of Fluids*, 2020, 32(12), 121702
- [15] Gharib, M., Rambod, E., Kheradvar, A., Sahn, D. J., and Dabiri, J. O., Optimal vortex formation as an index of cardiac health, *Proceedings of the National Academy of Sciences*, 2006, 103(16), 6305–6308
- [16] Pedrizzetti, G., and Domenichini, F., Left Ventricular Fluid Mechanics: The Long Way from Theoretical Models to Clinical Applications, *Annals of Biomedical Engineering*, 2015, 43(1), 26–40

- [17] Sotiropoulos, F., Le, T. B., and Gilmanov, A., Fluid Mechanics of Heart Valves and Their Replacements, *Annual Review of Fluid Mechanics*, 2016, 48(1), 259–283
- [18] Faludi, R., Szulik, M., D’Hooge, J., Herijgers, P., Rademakers, F., Pedrizzetti, G., and Voigt, J.-U., Left ventricular flow patterns in healthy subjects and patients with prosthetic mitral valves: An in vivo study using echocardiographic particle image velocimetry, *The Journal of Thoracic and Cardiovascular Surgery*, 2010, 139(6), 1501–1510
- [19] Pedrizzetti, G., La Canna, G., Alfieri, O., and Tonti, G., The vortex-an early predictor of cardiovascular outcome?, *Nature Reviews Cardiology*, 2014, 11(9), 545–553
- [20] Gooden, S. C. M., Hatoum, H., Boudoulas, K. D., Vannan, M. A., and Dasi, L. P., Effects of MitraClip Therapy on Mitral Flow Patterns and Vortex Formation: An In Vitro Study, *Annals of Biomedical Engineering*, 2022, 50(6), 680–690
- [21] Suter, S. P., Flow-induced trauma to blood cells, *Circulation Research*, 1977, 41(1), 2–8
- [22] Orban, M., Lesevic, H., Massberg, S., and Hausleiter, J., Left ventricular thrombus formation after successful percutaneous edge-to-edge mitral valve repair, *European Heart Journal*, 2012, 34(12), 942
- [23] Toggweiler, S., Zuber, M., Sürder, D., Biaggi, P., Gstrein, C., Moccetti, T., Pasotti, E., Gaemperli, O., Faletra, F., Petrova-Slater, I., Grünenfelder, J., Jamshidi, P., Corti, R., Pedrazzini, G., Lüscher, T. F., and Erne, P., Two-year outcomes after percutaneous mitral valve repair with the MitraClip system: durability of the procedure and predictors of outcome, *Open Heart*, 2014, 1(1), e000056
- [24] Buzzatti, N., De Bonis, M., Denti, P., Barili, F., Schiavi, D., Di Giannuario, G., La Canna, G., and Alfieri, O., What is a “good” result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation, *The Journal of Thoracic and Cardiovascular Surgery*, 2016, 151(1), 88–96
- [25] Neuss, M., Schau, T., Isotani, A., Pilz, M., Schöpp, M., and Butter, C., Elevated Mitral Valve Pressure Gradient After MitraClip Implantation Deteriorates Long-

- Term Outcome in Patients With Severe Mitral Regurgitation and Severe Heart Failure, *JACC: Cardiovascular Interventions*, 2017, 10(9), 931–939
- [26] Patzelt, J., Zhang, W. Z., Sauter, R., Mezger, M., Nording, H., Ulrich, M., Becker, A., Patzelt, T., Rudolph, V., Eitel, I., Saad, M., Bamberg, F., Schlensak, C., Gawaz, M., Boekstegers, P., Schrieck, J., Seizer, P., and Langer, H. F., Elevated Mitral Valve Pressure Gradient Is Predictive of Long-Term Outcome After Percutaneous Edge-to-Edge Mitral Valve Repair in Patients With Degenerative Mitral Regurgitation (MR), But Not in Functional MR, *Journal of the American Heart Association*, 2019, 8(13), e011366
- [27] Koell, B., Ludwig, S., Weimann, J., Waldschmidt, L., Hildebrandt, A., Schofer, N., Schirmer, J., Westermann, D., Reichenspurner, H., Blankenberg, S., Conradi, L., Lubos, E., and Kalbacher, D., Long-Term Outcomes of Patients With Elevated Mitral Valve Pressure Gradient After Mitral Valve Edge-to-Edge Repair, *JACC: Cardiovascular Interventions*, 2022, 15(9), 922–934
- [28] Pedrizzetti, G., and Perktold, K., *Cardiovascular Fluid Mechanics*, Vienna, Springer Vienna, 2003
- [29] Oliveira, D., Srinivasan, J., Espino, D., Buchan, K., Dawson, D., and Shepherd, D., Geometric description for the anatomy of the mitral valve: A review, *Journal of Anatomy*, 2020, 237(2), 209–224
- [30] Chandran, K. B., Rittgers, S. E., and Yoganathan, A. P., *Biofluid mechanics: the human circulation*, CRC Press, 2012
- [31] Scarano, F., Iterative image deformation methods in PIV, *Measurement Science and Technology*, 2002, 13(1), R1–R19
- [32] Westerweel, J., and Scarano, F., Universal outlier detection for PIV data, *Experiments in Fluids*, 2005, 39(6), 1096–1100
- [33] Yoganathan, A. P., He, Z., and Jones, S. C., Fluid Mechanics of Heart Valves, *Annual Review of Biomedical Engineering*, 2004, 6(1), 331–362
- [34] Chambers, J. B., Spriggs, D. C., Cochrane, T., Allen, J., Morris, R., Black, M. M., and Jackson, G., Continuity equation and Gorlin formula compared with

- directly observed orifice area in native and prosthetic aortic valves, *British Heart Journal*, 1992, 67(2), 193–199
- [35] Garcia, D., Dumesnil, J. G., Durand, L. G., Kadem, L., and Pibarot, P., Discrepancies between catheter and Doppler estimates of valve effective orifice area can be predicted from the pressure recovery phenomenon: practical implications with regard to quantification of aortic stenosis severity, *Journal of the American College of Cardiology*, 2003, 41(3), 435–442
- [36] Bloodworth IV, C. H., Pierce, E. L., Kohli, K., Deaton, N. J., Jones, K. J., Duvvuri, R., Kamioka, N., Babaliaros, V. C., and Yoganathan, A. P., Impact of simulated MitraClip on forward flow obstruction in the setting of mitral leaflet tethering: An in vitro investigation, *Catheterization and Cardiovascular Interventions*, 2018, 92(4), 797–807
- [37] Caballero, A., Mao, W., McKay, R., Hahn, R. T., and Sun, W., A Comprehensive Engineering Analysis of Left Heart Dynamics After MitraClip in a Functional Mitral Regurgitation Patient, *Frontiers in Physiology*, 2020, 11, 432
- [38] Thomas, J. D., and Weyman, A. E., Doppler mitral pressure half-time: A clinical tool in search of theoretical justification, *Journal of the American College of Cardiology*, 1987, 10(4), 923–929
- [39] Dumesnil, J. G., and Yoganathan, A. P., Theoretical and practical differences between the Gorlin formula and the continuity equation for calculating aortic and mitral valve areas, *The American Journal of Cardiology*, 1991, 67(15), 1268–1272
- [40] Shi, L., and He, Z., Hemodynamics of the Mitral Valve Under Edge-to-Edge Repair: An In Vitro Steady Flow Study, *Journal of Biomechanical Engineering*, 2009, 131(5), 051010
- [41] Jeyhani, M., Shahriari, S., and Labrosse, M., Experimental Investigation of Left Ventricular Flow Patterns After Percutaneous Edge-to-Edge Mitral Valve Repair, *Artificial Organs*, 2018, 42(5), 516–524
- [42] Lee, S., and Hassan, Y. A., Experimental study of flow structures near the merging point of two parallel plane jets using PIV and POD, *International Journal of Heat and Mass Transfer*, 2018, 116, 871–888

- [43] Pope, S. B., *Turbulent Flows*, Cambridge University Press, 2000
- [44] Pedrizzetti, G., and Domenichini, F., Nature Optimizes the Swirling Flow in the Human Left Ventricle, *Physical Review Letters*, 2005, 95(10), 108101
- [45] Stugaard, M., Koriyama, H., Katsuki, K., Masuda, K., Asanuma, T., Takeda, Y., Sakata, Y., Itatani, K., and Nakatani, S., Energy loss in the left ventricle obtained by vector flow mapping as a new quantitative measure of severity of aortic regurgitation: a combined experimental and clinical study, *European Heart Journal - Cardiovascular Imaging*, 2015, 16(7), 723–730
- [46] Chakravarty, T., Makar, M., Patel, D., Oakley, L., Yoon, S. H., Stegic, J., Singh, S., Skaf, S., Nakamura, M., and Makkar, R. R., Transcatheter Edge-to-Edge Mitral Valve Repair With the MitraClip G4 System, *JACC: Cardiovascular Interventions*, 2020, 13(20), 2402–2414
- [47] Gerçek, M., Roder, F., Rudolph, T. K., Fortmeier, V., Zittermann, A., Rudolph, V., and Friedrichs, K. P., PASCAL mitral valve repair system versus MitraClip: comparison of transcatheter edge-to-edge strategies in complex primary mitral regurgitation, *Clinical Research in Cardiology*, 2021, 110(12), 1890–1899
- [48] Zoghbi, W. A., Adams, D., Bonow, R. O., Enriquez-Sarano, M., Foster, E., Grayburn, P. A., Hahn, R. T., Han, Y., Hung, J., Lang, R. M., Little, S. H., Shah, D. J., Sherman, S., Thavendiranathan, P., Thomas, J. D., and Weissman, N. J., Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance, *Journal of the American Society of Echocardiography*, 2017, 30(4), 303–371
- [49] Supino, P. G., Hai, O. Y., Sharma, A., Lampert, J., Hochreiter, C., Herrold, E. M., and Borer, J. S., Impact of Beta-Blockade on Cardiac Events in Patients with Chronic Severe Nonischemic Mitral Regurgitation, *Cardiology*, 2018, 139(1), 1–