

STRUCTURAL

Effects of Mechanical Ventilation on Heart Geometry and Mitral Valve Leaflet Coaptation During Percutaneous Edge-to-Edge Mitral Valve Repair



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ABSTRACT

OBJECTIVES This study sought to evaluate a ventilation maneuver to facilitate percutaneous edge-to-edge mitral valve repair (PMVR) and its effects on heart geometry.

BACKGROUND In patients with challenging anatomy, the application of PMVR is limited, potentially resulting in insufficient reduction of mitral regurgitation (MR) or clip detachment. Under general anesthesia, however, ventilation maneuvers can be used to facilitate PMVR.

METHODS A total of 50 consecutive patients undergoing PMVR were included. During mechanical ventilation, different levels of positive end-expiratory pressure (PEEP) were applied, and parameters of heart geometry were assessed using transesophageal echocardiography.

RESULTS We found that increased PEEP results in elevated central venous pressure. Specifically, central venous pressure increased from 14.0 ± 6.5 mm Hg (PEEP 3 mm Hg) to 19.3 ± 5.9 mm Hg (PEEP 20 mm Hg; $p < 0.001$). As a consequence, the reduced pre-load resulted in reduction of the left ventricular end-systolic diameter from 43.8 ± 10.7 mm (PEEP 3 mm Hg) to 39.9 ± 11.0 mm (PEEP 20 mm Hg; $p < 0.001$), mitral valve annulus anterior-posterior diameter from 32.4 ± 4.3 mm (PEEP 3 mm Hg) to 30.5 ± 4.4 mm (PEEP 20 mm Hg; $p < 0.001$), and the medio-lateral diameter from 35.4 ± 4.2 mm to 34.1 ± 3.9 mm ($p = 0.002$). In parallel, we observed a significant increase in leaflet coaptation length from 3.0 ± 0.8 mm (PEEP 3 mm Hg) to 5.4 ± 1.1 mm (PEEP 20 mm Hg; $p < 0.001$). The increase in coaptation length was more pronounced in MR with functional or mixed genesis. Importantly, a coaptation length >4.9 mm at PEEP of 10 mm Hg resulted in a significant reduction of PMVR procedure time (152 ± 49 min to 116 ± 26 min; $p = 0.05$).

CONCLUSIONS In this study, we describe a novel ventilation maneuver improving mitral valve coaptation length during the PMVR procedure, which facilitates clip positioning. Our observations could help to improve PMVR therapy and could make nonsurgical candidates accessible to PMVR therapy, particularly in challenging cases with functional MR. (J Am Coll Cardiol Intv 2016;9:151-9) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CVP = central venous pressure

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

MR = mitral regurgitation

PEEP = positive end-expiratory pressure

PMVR = percutaneous mitral valve repair

TEE = transesophageal echocardiography

Percutaneous mitral valve repair (PMVR) using the MitraClip system (Abbott Vascular, Santa Clara, California) is an innovative method for the treatment of mitral regurgitation (MR) in patients who are not accessible by conventional operation. Since the first randomized controlled trial, which included preferentially patients with MR caused by degeneration of the valve, the application of PMVR has tremendously increased over the last decade (1). A subgroup analysis of the EVEREST II (Endovascular Valve Edge-to-Edge Repair) trial suggested that

besides older patients, those with functional MR particularly profit from PMVR (2). A major advantage of the interventional approach over conventional operation is the avoidance of open-heart surgery with no major injuries and no need for extracorporeal circulation (3,4). Recent trials suggested a benefit of PMVR in high-risk patients (5,6), patients with severe left ventricular dysfunction (7), or nonresponders to cardiac resynchronization therapy (8).

Indication expansion for a procedure is usually paralleled by the appearance of novel pitfalls and obstacles, which become apparent when more challenging cases are treated. A major disadvantage of PMVR in comparison to conventional operation is that mitral valve reconstruction cannot be carried out by a direct approach providing complete direct vision of mitral valve pathology. Thus, clip delivery using an interventional PMVR device can be challenging and sometimes frustrating (9). Recent technical progress such as the application of 3-dimensional transesophageal echocardiography (TEE) has revolutionized the PMVR procedure, increased periprocedural comfort, and immensely improved success in MR reduction (10). Nevertheless, challenging anatomies still limit application of the procedure. For instance, mitral valve regurgitation due to degenerative disease with severe calcifications, reduced coaptation length and depth, or reduced leaflet mobility length may preclude PMVR, and may cause insufficient reduction of

MR, embolization of the device, or procedural failure (11).

Although recent reports (12) and our own experience indicate that interventional therapy of MR is feasible under deep sedation in some patients, the procedure is generally carried out under general anesthesia with its potential disadvantages, such as hypotensive episodes, aspiration, or post-interventional delirium in these frail patients. Mechanical ventilation is furthermore paralleled by hemodynamic changes. For instance, acute application of positive end-expiratory pressure (PEEP) results in reduction of transmural cardiac filling pressures, cardiac index, and stroke index (13). In another clinical setting, it has been reported that continuous positive airway pressure ventilation over a period of 3 months leads to reduction of mitral regurgitant fraction and an increase in left ventricular ejection fraction in patients with chronic heart failure (14). Moreover, an immediate reduction of MR and a significant increase in left ventricular ejection fraction (LVEF) after 30 min of continuous positive airway pressure ventilation or bilevel ventilation was observed (15). As mechanical ventilation under general anesthesia at present is the gold standard for PMVR, it is important not only to consider its previously mentioned drawbacks, but also to take advantage of hemodynamic alterations induced by mechanical ventilation.

Here, we report a novel concept of using a high PEEP to increase coaptation length of the anterior and posterior leaflet of the mitral valve to facilitate the PMVR procedure.

METHODS

STUDY POPULATION. Between May 2014 and August 2015, 81 patients with grade 3 or 4 MR underwent PMVR at the University Hospital, Department for Cardiology and Cardiovascular Medicine, University of Tuebingen. We measured echocardiographic changes at different PEEP levels in 50 patients. A total of 26 patients were not included, as they underwent the procedure in deep sedation

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without endotracheal intubation. In 5 patients, no measurements were obtained due to the critical state of the patient. The study was approved by the local ethics committee (260/2015R). In patients with high-grade MR and a high surgical risk, the indication for treatment of MR was assessed according to the current guidelines by an interdisciplinary team of interventional cardiologists and cardiac surgeons. The stratification of surgical risk was based on either the EuroSCORE (European System for Cardiac Operative Risk Evaluation) (16) or on the presence of specific surgical risk factors not covered in the EuroSCORE. Valve anatomy was also assessed by the interdisciplinary team as to the suitability for MitraClip treatment. Exclusion criteria for mitral clipping were a transmitral gradient >5 mm Hg (as evaluated by Doppler echocardiography), active endocarditis, severely degenerated valve morphology such as extensively prolapsed or flail leaflets (prolapse width >25 mm, flail gap >20 mm), heavy calcifications, or a retracted posterior leaflet shorter than 8 mm. All patients underwent trans-thoracic echocardiography (TTE), TEE, and clinical assessment before the intervention to assess MR severity, mitral valve morphology, and New York Heart Association functional class. Heart failure patients had to be on optimal medical treatment according to current guidelines for at least 3 months prior to MitraClip treatment.

ECHOCARDIOGRAPHIC ASSESSMENT. TTE and TEE were performed in all patients within 30 days prior to the procedure using a Philips CX 50 and iE 33 machine (Philips HealthCare, Hamburg, Germany). The severity of MR at baseline and the etiology of the mechanism of regurgitation were determined according to the current European Association of Echocardiography guidelines (17). Post-intervention, the severity of MR was assessed according to the technique described by Foster et al. (18). Post-interventional echocardiographic measurements were carried out immediately after clip implantation. All echocardiographic loops were recorded. A total of 6 additional investigators blinded to the PEEP maneuver repeated measurements using the Centricity Enterprise Web 3.0 software (GE Medical Systems, Barrington, Illinois). The mean of measurements was calculated and taken as a final value.

PMVR PROCEDURE. After induction of general anesthesia, the TEE probe was introduced into the esophagus. The intercommissural and septolateral views of the mitral valve were obtained in a mid-esophageal view at 50° to 70° and 140° to 160°, respectively. Coaptation length of the mitral valve

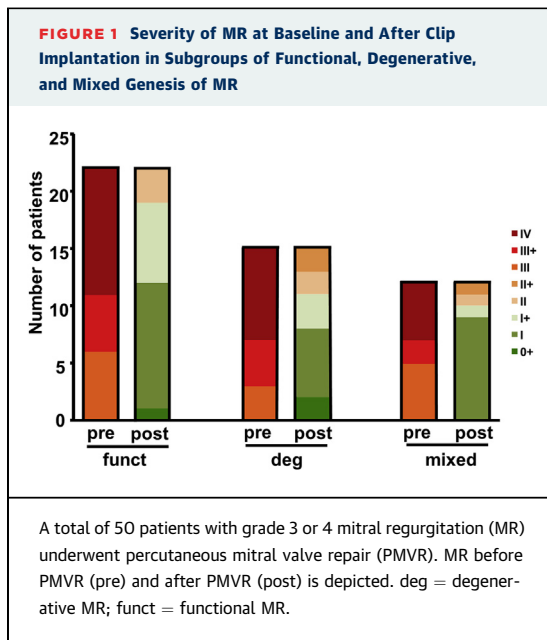
TABLE 1 Baseline Patient Characteristics (n = 50)

Age, yrs	74.8 (38-91)
Male	30 (60.0)
Coronary heart disease	39 (78.0)
Atrial fibrillation	35 (70.0)
Hypertension	40 (80.0)
Smoker	10 (20.0)
Hyperlipoproteinemia	28 (56.0)
Diabetes	21 (42.0)
NYHA functional class 3-4	44 (88.0)
Renal insufficiency	34 (68.0)
LVEDD	54.6 ± 8.3
LV function, %	
≤35	25 (50.0)
36-50	17 (30.0)
>50	10 (20.0)
Regurgitation etiology	
Functional	23 (46.0)
Degenerative	15 (30.0)
Mixed	12 (24.0)
Beta-blockers	48 (96.0)
Aldosterone antagonist	31 (62.0)
ACE inhibitors/sartans	47 (94.0)
Diuretic agents	46 (92.0)
Digitalis	4 (8.0)
Calcium antagonists	7 (14.3)
Anticoagulation	37 (74.0)

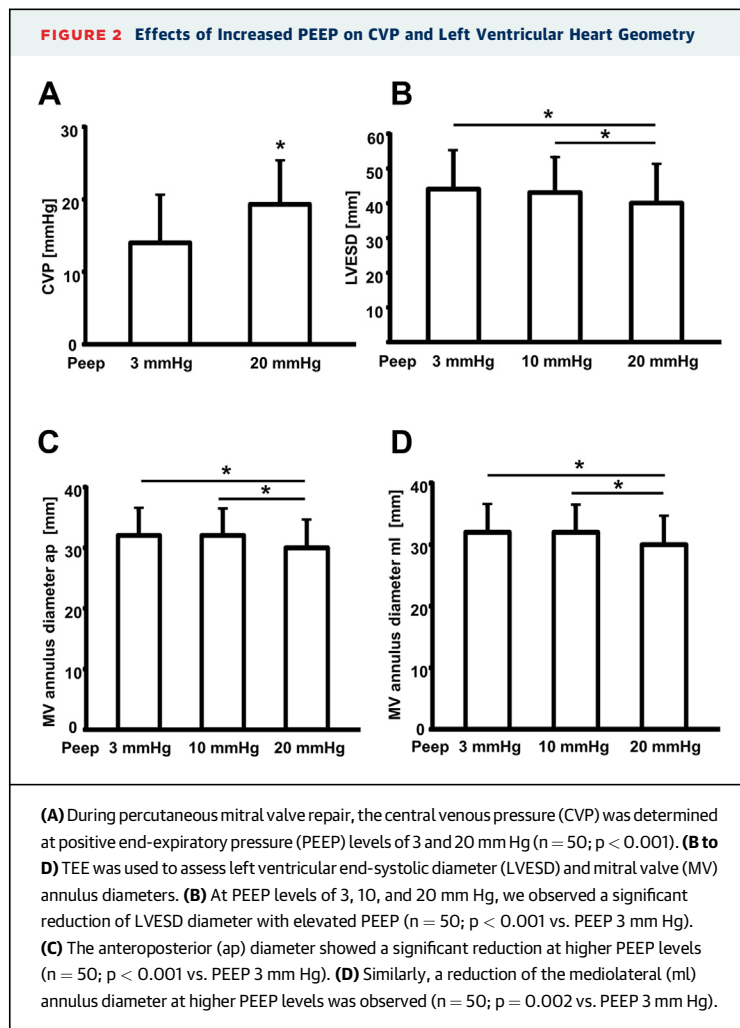
Values are mean (range), n (%), mean ± SD.
 ACE = angiotensin-converting enzyme; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association.

was measured in the septolateral view at different PEEP levels (3, 10, and 20 mm Hg). All echocardiographic parameters after PEEP modifications were assessed when the central venous pressure (CVP) had reached a steady state value. CVP was obtained via a jugular central venous line. PMVR procedure time was defined as the start time of the first venous puncture to the time of closure of the puncture wound. Using fluoroscopic and transesophageal 2- and 3-dimensional echocardiographic guidance, the MitraClip device was advanced via the trans-septal route across the mitral annulus into the left ventricle. With the 2 arms of the clip extended, the device was retracted to capture and subsequently closed to coapt the mitral leaflets, thereby emulating the surgical double-orifice technique introduced by Alfieri et al. (19). After clip deployment and right heart catheterization using a Swan-Ganz catheter, final TEE and TTE measurements were performed.

STATISTICAL ANALYSIS. Statistical analysis was performed with SPSS (version 22, IBM Deutschland GmbH, Ehningen, Germany). Categorical variables



are presented as absolute numbers or percentages and continuous variables as mean \pm SD. Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to examine for normal distribution of variables. All variables showed normal distribution, and parametric tests were used for statistical comparison. For patient analysis, the paired Student *t* test was used to compare means. Intergroup comparisons were performed by analysis of variance. The 2-tailed *p* values were calculated, and a value of *p* < 0.05 was considered statistically significant. Echocardiographic views were assessed by 7 independent investigators, 6 of whom were blinded to the results. The intraclass correlation coefficient for absolute agreement was used to assess reproducibility of echocardiographic measurements, with good agreement defined as >0.80. For the assessment of intraobserver reliability, 20 randomly chosen patients were analyzed by 1 investigator twice. Absolute agreement among the observations was calculated using intraclass correlation coefficient analysis.



RESULTS

PMVR is commonly carried out under general anesthesia. Mechanical ventilation causes hemodynamic changes, offering possibilities to modify heart geometry. Here, we evaluated the effects of different PEEP levels applied during PMVR on different hemodynamic and anatomical parameters influencing the interventional procedure.

In 50 patients undergoing PMVR in general anesthesia, we evaluated the influence of different PEEP levels on central venous pressure and on heart geometry. **Table 1** shows the baseline characteristics for all patients. The majority of patients had New York Heart Association functional class III to IV (88.0%), and there was a high percentage of patients with severely reduced (<35% ejection fraction) left ventricular function (i.e., 50.0%). Functional MR was present in 46.0% of the patients and degenerative MR in 30.0% of the patients. A total of 78.0% of the patients had previously diagnosed coronary artery disease, 70.0% atrial fibrillation, and 68.0% renal insufficiency. Before and after PMVR, MR and reduction of MR by the intervention was assessed using TEE. **Figure 1** depicts severity and genesis of MR. All patients had successful reduction of MR after PMVR. During PMVR, we monitored changes in CVP depending on different PEEP values (3 and 20 mm Hg). At a PEEP level of 3 mm Hg, mean CVP values were 14.0 ± 6.5 mm Hg, whereas PEEP levels of 20 mm Hg resulted in CVP of

19.3 ± 5.9 mm Hg (p < 0.001), indicating an increase of intrathoracic pressure (Figure 2A). End-systolic medio-lateral (intercommissural) and anterior-posterior diameters of the mitral valve annulus as well as the left ventricular end-systolic diameter (LVESD) in the septo-lateral view were measured at PEEP levels of 3, 10, and 20 mm Hg. Interestingly, we observed geometrical alterations of the LVESD (Figure 2B) and of the mitral valve annulus diameter (Figures 2C and 2D), respectively, with rising PEEP. The LVESD decreased from 43.8 ± 10.7 mm (PEEP 3 mm Hg) to 39.9 ± 11.0 mm (PEEP 20 mm Hg; p < 0.001) (Figure 2B). Accordingly, both the medio-lateral diameter (35.4 ± 4.2 mm at PEEP 3 mm Hg, 34.1 ± 3.9 mm at PEEP 20 mm Hg; p = 0.002) and the anterior-posterior diameter (32.4 ± 4.3 at PEEP 3 mm Hg, 30.5 ± 4.4 at PEEP 20 mm Hg; p < 0.001) of the mitral valve annulus showed a significant decrease (Figures 2C and 2D). Table 2 shows intraobserver and interobserver variability of echocardiographic measurements. In the following, coaptation length of the mitral valve leaflets was measured at the respective PEEP settings in end-systole. As illustrated in Figure 3A, mechanical ventilation offers the possibility to modify hemodynamics during the PMVR procedure. Applying an increased PEEP, the altered heart geometry results in a decrease of the mitral valve annulus size and subsequently an increase of mitral valve leaflet coaptation length. Figure 3B exemplifies how the leaflet coaptation length was measured and provides sample images of coaptation length increase upon PEEP elevation. In parallel to a reduction of LVESD and mitral valve annulus diameter, we observed a significant amplification of mitral valve leaflet coaptation length from 3.0 ± 0.8 mm to 4.2 ± 0.9 mm to 5.4 ± 1.1 mm at PEEP levels of 3, 10, and 20 mm Hg, respectively (p < 0.001) (Figure 3C). This increase in coaptation length provides more leaflet material for a potentially facilitated grip. To account for a possible difference regarding augmentation of leaflet coaptation in different mitral valve pathologies, we analyzed the subsets of MR genesis (i.e., functional MR vs. degenerative vs. mixed genesis) for differences in coaptation length-increase. In particular, we found that coaptation length increased in all 3 subgroups with elevated PEEP (Figure 4). Interestingly, in functional MR and in MR with a mixed genesis, the coaptation length increase was more pronounced than in degenerative MR (p = 0.02) (Figure 4). Importantly, increased coaptation length had an effect on procedure time. For instance, time to successful clip delivery defined by a reduction of MR by at least 2° was decreased significantly by ≈24% in patients with a mitral valve leaflet coaptation length ≥4.9 mm measured at an intermediate PEEP level of 10 mm Hg

TABLE 2 Intraclass Correlations for Interobserver and Intraobserver Agreement of Echocardiographic Measurements

	Interobserver Agreement	p Value	Intraobserver Agreement	p Value
Coaptation				
3 mm Hg	0.88	<0.001	0.91	<0.001
10 mm Hg	0.92	<0.001	0.94	<0.001
20 mm Hg	0.90	<0.001	0.98	<0.001
Annulus a.-p.				
3 mm Hg	0.95	<0.001	0.80	<0.001
10 mm Hg	0.96	<0.001	0.86	<0.001
20 mm Hg	0.94	<0.001	0.91	<0.001
Annulus m.-l.				
3 mm Hg	0.96	<0.001	0.95	<0.001
10 mm Hg	0.96	<0.001	0.86	<0.001
20 mm Hg	0.94	<0.001	0.95	<0.001
LVESD				
3 mm Hg	0.98	<0.001	1.00	<0.001
10 mm Hg	0.98	<0.001	0.99	<0.001
20 mm Hg	0.95	<0.001	0.98	<0.001

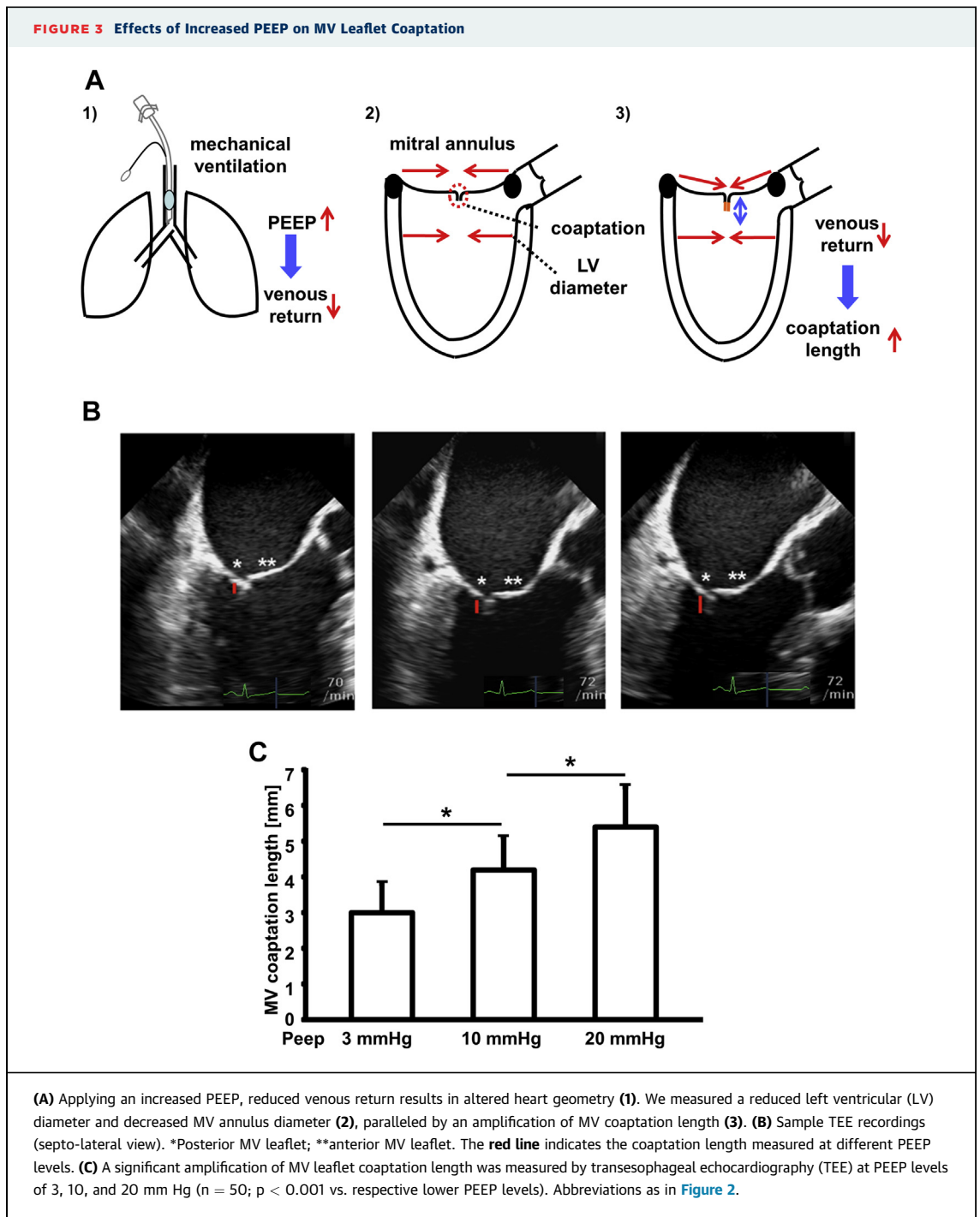
Interobserver and intraobserver agreement for echocardiographic measurements at different positive end-expiratory pressure levels.
 a.-p. = anteroposterior diameter; LVESD = left ventricular end-systolic diameter; m.-l. = medio-lateral diameter.

(Figure 5). Specifically, the procedure time in patients with a coaptation length <4.9 mm was 152 ± 49 min compared with 116 ± 26 min in patients with an increased leaflet coaptation length (p = 0.05) (Figure 5). There were no significant differences in atrial diameter between the 2 groups (data not shown) or any transeptal problems that might explain the differences in procedure times. Furthermore, the baseline characteristics were not significantly different between the 2 groups (data not shown). These observations indicate that an increase in mitral valve coaptation length could facilitate the PMVR procedure.

DISCUSSION

In this study, we describe application of PEEP as a novel maneuver improving mitral valve coaptation length during the PMVR procedure, which facilitates clip positioning. This conclusion is supported by the following data: 1) mitral valve coaptation length shows a robust amplification with increased PEEP levels; 2) modifications in heart geometry (such as reduction in mitral valve annulus diameter) can explain this observed effect; and 3) increased coaptation length resulted in a significant reduction of PMVR procedure time.

PMVR using the MitraClip system is an innovative method to treat MR in patients who are at high risk for surgical treatment (20). Positioning of the clip remains the most significant challenge in PMVR. Different

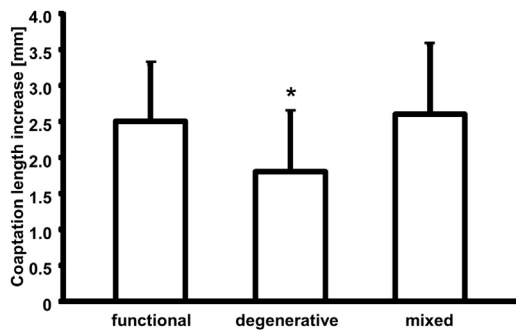


approaches have been suggested to improve the PMVR procedure such as the induction of asystole/bradycardia via an adenosine bolus injection or rapid pacing (21). We recently described a case in which clip positioning was facilitated after inducing temporary asystole, with resulting cardiac arrest due to a pause

>20 s preceding the ventricular escape rhythm in a pacemaker-dependent patient (22).

Interestingly, it is known that continuous positive airway pressure ventilation can reduce MR and enhance LVEF in acute (15,23,24) or chronic heart failure (14). However, acute application of PEEP is

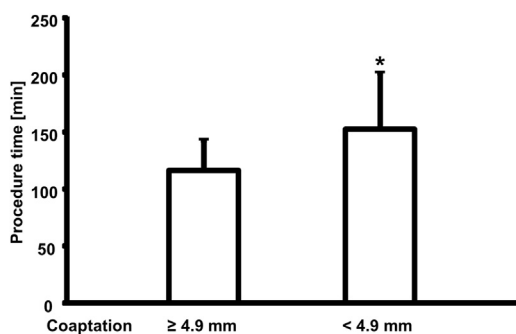
FIGURE 4 Increase in MV Leaflet Coaptation Length at Different PEEP Levels in Mitral Regurgitation of Functional, Degenerative, or Mixed Genesis



The coaptation length of the anterior and posterior mitral valve leaflet was measured by TEE at different PEEP levels after a steady state CVP level had been reached as described in Figure 3. The increase of coaptation length between PEEP levels of 3 and 20 mm Hg in functional, degenerative, and mixed genesis of mitral regurgitation is depicted. * $p = 0.02$ versus functional mitral regurgitation. Abbreviations as in Figures 2 and 3.

known to reduce cardiac index and stroke index (13). Although it is reasonable to assume that these hemodynamic changes have their correlation in an altered cardiac chamber size and geometry, to our knowledge no systematic imaging studies exist evaluating the effect of different PEEP levels on cardiac geometry. On the basis of the consideration that

FIGURE 5 Increased MV Leaflet Coaptation Length Is Associated With Reduced PMVR Procedure Time



The patient collective was divided in 2 groups according to coaptation length at an intermediate PEEP level of 10 mm Hg. In patients with an MV coaptation length of ≥ 4.9 mm, the PMVR procedure time was significantly reduced compared with patients with a coaptation length < 4.9 mm ($n = 42$ for coaptation length < 4.9 mm; * $p = 0.05$). Abbreviations as in Figures 1 and 2.

reduced cardiac output is paralleled by a decrease of cardiac chamber size and, as a consequence, by a reduced size of the mitral annulus, we hypothesized an amplification of mitral coaptation length given that leaflet length remains unchanged. Indeed, we observed a significant PEEP-dependent relationship between coaptation length and the degree of PEEP applied (PEEP 3 mm Hg: 3.0 ± 0.8 mm to PEEP 20 mm Hg: 5.4 ± 1.1 mm; $p < 0.001$).

STUDY LIMITATIONS. Certainly, we have to acknowledge a limited sample size. For example, a subgroup analysis of MR genesis (functional: $n = 23$, degenerative: $n = 15$, mixed: $n = 12$) will need further confirmation with larger groups. Given the novelty of the PMVR technique and its complexity, however, the sample size seems reasonable, particularly as the effect on increase in leaflet adaptation was very robust and “dose-dependent.” We cannot entirely rule out the possibility that reduced afterload upon PEEP increase mediates the observed changes in heart geometry, although arterial blood pressure was kept at a steady state by adjusting catecholamine doses. Furthermore, other parameters such as fluctuations in catheter position, blood viscosity, or body temperature may have altered the results, although parameters were kept as constant as possible for example by using an active self-warming blanket. As we selected our patients according to the EVEREST criteria, we had only 2 patients with a baseline coaptation length < 2 mm. Future trials will be needed to assess effects of the PEEP maneuver in patients with lesser leaflet coaptation.

POTENTIAL RISKS OF THE PEEP MANEUVER. The grasping maneuver takes only few seconds, but usually < 1 min. Accordingly, elevated PEEP levels were applied for only a short time. Nevertheless, potential risks have to be taken into consideration. If increased PEEP levels are kept over a longer period of time, adverse effects on hemodynamics, particularly in patients with severely reduced LVEF or who are hemodynamically unstable, can lead to drops in arterial blood pressure (13). In our patients, arterial blood pressure was monitored invasively, and the PEEP maneuver was stopped in case of hemodynamic instability; thus, we observed no relevant adverse effects. Furthermore, high PEEP levels have been associated with occurrence of a pneumothorax (25). Accordingly, an extensive PEEP maneuver should not be applied in patients with severe lung emphysema.

CLINICAL IMPLICATIONS. We measured the influence of different PEEP levels on various parameters. We found a significant correlation between PEEP

levels and coaptation length of the mitral valve. This finding points out a beneficial maneuver to facilitate the grasping of the leaflets in patients with difficult valve anatomies.

It is tempting to speculate that applying ventilation with an increased PEEP for the short time of grasping the leaflets could improve success rates for PMVR. This hypothesis is supported by our finding that the PMVR procedure time was substantially shorter in patients when the mitral valve coaptation length reached a certain value. Given the fact that PMVR is also possible in deep sedation (12), our findings may influence the choice of anesthesia, particularly in challenging cases of mitral valve morphology. It has to be considered, however, that after a successful grip, leaflet insertion has to be re-evaluated after reversing to normal PEEP levels, because our measurements indicate that changed hemodynamics alter heart and particularly valve morphology. Moreover, it has to be kept in mind that high PEEP levels are not tolerated for a long time, and it is helpful to test effects of temporarily elevated PEEP levels on hemodynamics, for instance, arterial blood pressure, in these fragile patients at the beginning of the procedure.

CONCLUSIONS

In this study, we describe the application of elevated PEEP as a novel maneuver improving mitral valve coaptation length during the PMVR procedure, which facilitates clip positioning. Our observations could help to improve PMVR therapy and could make nonsurgical candidates accessible to PMVR therapy, particularly in challenging cases with functional MR.

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PERSPECTIVES

WHAT IS KNOWN? Interventional therapy of MR is beneficial in patients not accessible by conventional surgery, however, positioning of the MitraClip can be challenging in certain valve anatomies precluding PMVR.

WHAT IS NEW? Using ventilation maneuvers during general anesthesia, this study describes a very robust increase in mitral valve leaflet coaptation length with increasing PEEP levels during PMVR paralleled by corresponding changes in heart geometry, for instance, reduced LVESD and reduced mitral valve annulus diameter. Above a threshold of a coaptation length >4.9 mm at PEEP of 10 mm Hg, PMVR procedure time was significantly decreased.

WHAT IS NEXT? Further studies are needed to evaluate procedure success applying the proposed ventilation maneuver in a prospective fashion and enrolling patients with a mitral valve leaflet coaptation length of ≤ 2 mm—an exclusion criterion according to the early EVEREST specifications.

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