Percutaneous mitral valve repair using the edge-to-edge technique in a high-risk population

B.J.L. Van den Branden, M.C. Post, M.J. Swaans, B.J.W.M. Rensing, F.D. Eefting, H.W.M. Plokker, W. Jaarsma, J.A.S. Van der Heyden

Background. Percutaneous mitral valve (MV) repair using the edge-to-edge clip technique might be an alternative for patients with significant mitral regurgitation (MR) and an unacceptably high risk for operative repair or replacement. We report the short-term safety and efficacy of this new technique in a high-risk population.

Methods. All consecutive high-risk patients who underwent percutaneous MV repair with the Mitraclip® between January and August 2009 were included. All complications related to the procedure were reported. Transthoracic echocardiography for MR grading and right ventricular systolic pressure (RVSP) measurement were performed before, and at three and 30 days after the procedure. Differences in NYHA functional class and quality of life (QoL) index were reported.

Results. Nine patients were enrolled (78% male, age 75.9 ± 9.0 years, logistic EuroSCORE $33.8 \pm 9.0\%$). One patient developed inguinal bleeding. In one patient partial clip detachment occurred, a second clip was placed successfully. The MR grade before repair was ≥ 3 in 100%, one month after repair a reduction in MR grade to ≤ 2 was present in 78% ($p=0.001$). RVSP decreased from 43.9 ± 12.1 to 31.6 ± 11.7 mmHg ($p=0.009$), NYHA functional class improved

from median 3 (range 3 to 4) to 2 (range 1 to 4) ($p=0.04$), and QoL index improved from 62.9 ± 16.3 to 49.9 ± 30.7 ($p=0.12$).

Conclusion. In high-risk patients, transcatheter MV repair seems to be safe and a reduction in MR can be achieved in most patients, resulting in a short-term improvement of functional capacity and QoL. (Neth Heart J 2010;18:437-43.)

Keywords: Mitral Valve Repair; Mitral Valve Regurgitation; High Risk; Percutaneous

Mitral valve repair, rather than replacement, has become the preferred surgical treatment for severe mitral regurgitation (MR).¹ The mainstay of surgical repair is annuloplasty, which is associated with excellent outcome.² In 1991, a simple technique for mitral valve repair was introduced by Otavio Alfieri, involving the placement of a surgical suture in the mid portion of the anterior and posterior leaflets, creating a double-orifice mitral valve.³ This technique ensures a fixed area of coaptation during systole, without disturbing the subvalvular and annular function, preserving left ventricular function⁴ and seems to be associated with improved functional status and freedom from reoperation.⁵ However, most patients treated with the 'Alfieri stitch' also needed an annuloplasty. The surgical literature suggests that the absence of a ring is associated with suboptimal results and the frequent need for reoperation in patients with more severe MR.⁶ Therefore the technique was used in patients who are not candidates for conventional surgical repair.

Recently, a catheter-based, percutaneous method was introduced to accomplish the double-orifice repair. Using the transseptal approach, a clip device is delivered into the left atrium. The clip can grasp the free edges of the mitral valve simultaneously.

The first phase I clinical trial has shown safety and feasibility of this technique in non-high-risk patients.⁷ It might be an alternative strategy in patients with a high or prohibitive risk for standard surgery. We report the short-term results of percutaneous mitral valve repair in a high-risk population.

B.J.L. Van den Branden

M.C. Post

M.J. Swaans

B.J.W.M. Rensing

F.D. Eefting

H.W.M. Plokker

W. Jaarsma

J.A.S. Van der Heyden

Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands

Correspondence to: B.J.L. Van den Branden

Department of Cardiology, St. Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, the Netherlands

E-mail: b.van.den.branden@antoniusziekenhuis.nl

Methods

Patient selection

All patients with moderate to severe, highly symptomatic MR were discussed in our team of cardiac surgeons and cardiologists. Patients were considered to be eligible for the percutaneous approach when they were not candidates for mitral valve surgery because of a too high peri-operative risk, according to the logistic EuroSCORE (>20%), and they had a suitable valve anatomy as judged by the interdisciplinary team.

Pre-procedural work-up

All patients had a standard diagnostic work-up containing physical examination, quality of life/functional capacity assessment (New York Heart Association (NYHA) class, six-minute walk test, and Minnesota questionnaire), ECG, laboratory measurements (including NT-pro-BNP), transthoracic and transoesophageal echocardiography, coronary angiography and right heart catheterisation.

Procedure

All procedures were performed in the catheterisation laboratory under general anaesthesia and both fluoroscopic and transoesophageal echocardiographic (TEE, two-dimensional (2D) and three-dimensional (3D)) guiding. Venous access, using a 24 French sheath, was gained via the right femoral vein. A catheter was placed in the radial artery for continuous haemodynamic monitoring. Before the initial procedure, right heart catheterisation was performed with a 7 French multipurpose catheter via the left femoral vein. Prophylactic antibiotics were given before the procedure. All patients were pretreated with aspirin or coumadin.

Post-procedure

Post-procedure, repeat right heart catheterisation was performed. A figure eight suture was used to obtain haemostasis at the 24 French access site and removed 24 hours later. All patients were treated with aspirin 100 mg once a day for a period of six months if they had not received coumadin prior to the procedure. Endocarditis prophylaxis for six months was advised. Before discharge, all patients underwent TTE to assess the position of the clip and residual MR as described previously. ECG and laboratory testing were performed within 24 hours.

All peri-procedural and short-term complications were reported. Major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure-related surgical intervention, endocarditis, clip detachment, clip dislodgement/embolisation, stroke and death. Minor complications were defined as mitral valve injury, device thrombosis, bleeding not requiring blood transfusion, femoral arteriove-

nous fistula formation and femoral haematoma.

One month after the procedure, patients were seen at the outpatient clinic. An assessment of functional capacity and quality of life was made using the NYHA class and the Minnesota questionnaire. On the same day, ECG, laboratory testing and echocardiography were repeated.

Transthoracic echocardiography

Echocardiographic parameters included left ventricular ejection fraction (LVEF) using Simpson's method, left ventricular end-systolic and end-diastolic diameters (LVESD, LVEDD), left atrial (LA) dimension and volume, right ventricular systolic pressure (RVSP) using tricuspid regurgitation flow velocity and right atrial pressure using vena cava inferior dimensions. The severity of MR was assessed using a variety of parameters, according to recommendations published earlier.⁸⁻¹⁰ Severity scale of 1 to 4 using colour flow Doppler (colour flow mapping) and colour flow jet area (jet area/LA area) appeared to be the best reproducible parameters. Vena contracta and regurgitant orifice were recorded if possible but not included as parameters for MR assessment because they have not been validated for a double orifice valve. Two independent physicians performed the TTE endpoint analysis. The echocardiographic evaluation was performed before and three days after the ten procedures in nine patients. One-month follow-up data were available in nine patients, because one patient received two clips within one month.

Statistical analysis

Descriptive statistics were used to report patient characteristics. Continuous variables with normal distribution are reported by mean $\pm$ standard deviation. Median and range were used when normal distribution was absent. Percentages were used to report categorical variables. Patients' data before and after the procedure were compared with χ^2 or Fisher's exact test for nominal variables and independent Student's t-test for continuous variables. Paired samples t-test was used for within-patient comparison of continuous variables. All tests were two sided and $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., version 14.0 for Windows).

Results

Patient characteristics

A total of 22 patients were screened for percutaneous mitral valve repair in our centre.

In 11 patients the mitral valve itself was not amenable, due to severe calcification or rheumatic deformations. One patient was excluded because of a thrombus in the left ventricle.

Figure 1. The MitraClip device.

Figure 2. Three-dimensional TEE image showing a double orifice after successful clip placement.

Figure 3. Two-dimensional TEE image before (left side) and after (right side) mitral valve clipping showing a reduction in MR.

The MitraClip® repair device (Evalve Inc., Menlo Park, CA, USA) was used in all patients. The device consists of a metal clip, covered with polyester to stimulate leaflet-to-leaflet healing. The clip is 'V-shaped', has a diameter of 4 mm in closed position and a grasping span of about 2 cm when the two arms are opened. On the inner portion of the arms there are two grippers which 'capture' the leaflets and ensure stabilisation from the atrial aspect (figure 1). The clip is mounted on a tri-axial guiding and delivery catheter system which is steerable in medial-lateral and anterior-posterior direction. The clip delivery system was advanced into the left atrium after a standard transseptal puncture and intravenous heparin was administered to maintain an activated clotting time above 300 sec. The clip was centred over the mitral orifice, the arms were opened and rotated perpendicular to the line of leaflet coaptation, above the origin of the MR jet. Then the clip was advanced into the left ventricle and retracted during systole, grasping the mitral valve leaflets creating a double orifice (figure 2). The clip was partially closed and the quality of the grasp, the position of the clip and the reduction of MR was thoroughly assessed by TEE (figure 3). When the result was suboptimal, the clip arms were re-opened and a second attempt was undertaken. After adequate reduction of MR and adequate clip positioning, the clip was closed and detached from the delivery catheter.

Table 1. Baseline characteristics (n=9).

Sex, n (%)	
- Female	2 (22.2)
- Male	7 (77.8)
Age (years)	75.9±9.0
BMI (kg/m ²)	24.5±3.4
Blood pressure (mmHg)	
- Systolic	128.2±21.6
- Diastolic	74.7±11.1
NYHA class (1/2/3/4)	0/0/8/1
QoL index	62.9±16.3
6 MWT (m)	237.6±74.4
Medication, n (%)	
- Loop diuretics	9 (100)
- Spironolactone	6 (67)
- ACEI/ARB	6 (67)
- Beta-blocker	3 (33)
- Coumadin	6 (67)
- Aspirin	4 (44)
Laboratory	
- Hb (mmol/l)	7.8±1.3
- Creatinine (μmol/l)	155.8±50.5
- eGFR (ml/min)	41.1±12.6
- Log Pro-BNP (pg/ml)	8.3±1.0
ECG, n (%)	
- Rhythm (SR/AF/PM)	4 (44)/4 (44)/1 (11)
- QRS width (ms)	164.4±26.3
- LBBB	5 (56)
Haemodynamics (mmHg)	
- PAP systolic	43.6±14.0
- PAP diastolic	19.0±4.4
- PAP mean	25.0±8.1
EuroSCORE (%)	
- Standard	11.9±1.3
- Logistic	33.8±9.0
MR aetiology, n (%)	
- Functional	9 (100)
- Ischaemic	5 (56)
- Non-ischaemic	4 (44)
- Degenerative	0

BMI=body mass index, NYHA=New York Heart Association, QoL=quality of life, 6 MWT=six-minute walk test, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, Hb=haemoglobin, eGFR=estimated glomerular filtration rate, Log Pro-BNP=logarithmic pro-brain natriuretic peptide, ECG=electrocardiogram, SR=sinus rhythm, AF=atrial fibrillation, PM= pacemaker rhythm, LBBB=left bundle branch block, PAP=pulmonary artery pressure, MR=mitral regurgitation.

As a result, ten consecutive patients underwent percutaneous mitral valve repair between January and August 2009. One 66-year-old male with a dilated left ventricle and severe MR (grade 4) was in NYHA class II, had a low logistic EuroSCORE (8.4%) and a Minnesota quality of life index of 7. He refused cardiac surgery and preferred mitral valve clipping. One month after the uncomplicated procedure the MR grade was reduced to 3 and the NYHA functional class improved to I. Because of the low risk he was excluded from the main analysis. All other patients (78% male, mean age of 75.9±9.0 years) were in NYHA functional class III (89%) or IV (11%) before the procedure and four patients (44%) had atrial fibrillation. The aetiology of MR was functional (56% ischaemic, 44% non-ischaemic), with an MR grade of ≥3 in all patients. Mean LVEF was 28.0±13.5%, LVEDD 62.4±8.0 mm and the RVSP 43.9±12.1 mmHg. Mean logistic EuroSCORE was estimated at 33.8±9.0%. Baseline characteristics are shown in table 1. Echocardiographic characteristics at baseline are listed in table 2.

Procedural and in-hospital results

Overall procedure time, defined as the time from femoral vein access to sheath removal, was 207±63 minutes, with the last three procedures being performed within three hours. The clip was implanted successfully in all nine patients. Partial clip detachment from the anterior mitral leaflet occurred in one patient. This was recognised at the 24-hour post-procedure TTE and a second clip was placed five days later, with a good final result. The patient was discharged two days later without clinical events related to the clip detachment. One patient (the first enrolled) developed femoral bleeding which required blood transfusion (two units packed cells). No other complications occurred. Mean hospitalisation time was seven days, with a maximum of 15 days for the patient who received a second clip. Procedural and in-hospital characteristics are shown in table 3.

Follow-up results

Eight patients (89%) were discharged with a reduction in MR severity to ≤2 (p=0.002). MR versus LA area decreased significantly from 48.2±16.7% to 30.9±16.0% on day 3 (p=0.004) and to 23.4±8.5, 30 days after the procedure (p=0.007). At one-month follow-up, seven patients (78%) had MR ≤2 (p=0.001 vs. baseline) and one patient experienced a recurrence of MR grade 3. RVSP decreased significantly from 43.9±12.1 to 31.6±11.7 (p=0.009), without a change in left ventricular geometry and function. There was no difference in log NT-pro-BNP before and one month after the procedure (8.3±1.0 vs. 8.7±1.2, p=0.26).

Six patients (67%) improved to NYHA function-

Table 2. Echocardiographic and clinical follow-up characteristics.

	Baseline	Day 3	P (vs. baseline)	Day 30	P (vs. baseline)
Echocardiography					
- LVEDD (mm)	62.4±8.0	62.8±6.5	0.75	61.6±8.7	0.82
- LVESD (mm)	53.7±9.9	55.1±8.9	0.53	52.8±9.9	0.93
- LVEDV (ml)	193.0±63.1	214.8±85.0	0.21	194.9±93.2	0.03
- LVESV (ml)	146.8±66.3	165.4±85.6	0.29	139.8±76.4	0.11
- LVEF (%)	28.0±13.5	27.2±14.2	0.82	30.6±12.9	0.86
- LA volume index (ml/BSA)	40.7±13.6	35.5±11.4	0.42	51.1±7.9	0.12
- LA dimension (mm)	47.3±4.2	48.0±6.2	0.61	45.9±4.5	0.19
- MR grade (1/2/3/4), n	0/0/3/7	3/5/1/1	0.002	3/4/2/0	0.001
- MR/LA area (%)	48.2±16.7	30.9±16.0	0.004	23.4±8.5	0.007
- RVSP (mmHg)	43.9±12.1	35.5±13.4	0.01	31.6±11.7	0.009
- RA pressure (mmHg)	6.3±2.3	5.6±1.8	0.35	6.3±2.3	0.60
NYHA class (I/II/III/IV), n	0/0/8/1	-	-	3/3/1/2	0.04
QoL index	62.9±16.3	-	-	49.9±30.7	0.12
Laboratory					
- Log Pro-BNP (pg/ml)	8.3±1.0	-	-	8.7±1.2	0.26

LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, LVEDV=left ventricular end-diastolic volume, LVESV=left ventricular end-systolic volume, LVEF=left ventricular ejection fraction, LA=left atrium, MR=mitral regurgitation, RVSP=right ventricular systolic pressure, RA=right atrium, NYHA=New York Heart Association, QoL=quality of life, BNP=brain natriuretic peptide.

al class I or II, two patients (22%) had no change in NYHA class and one patient with refractory heart failure worsened to NYHA class IV (figure 4). Overall non-significant improvement of quality of life was seen after one month ($p=0.12$). As a result, the diuretic dose could be reduced in four patients, one month after the procedure. During short-term follow-up, no procedure-related complications occurred. Echocardiographic and clinical follow-up results are listed in table 2.

Discussion

We report the safety and efficacy of percutaneous MV repair using the edge-to-edge technique in a high-risk population who were not candidates for conventional surgery. Our results indicate that even in this specific population, a high procedural success rate, a low complication rate, and improvement in functional capacity can be obtained. Today, the different guidelines (ESC/ACC/AHA) do not recommend mitral valve surgery for patients with an ejection fraction of 30% or less and associated comorbidity (Class IIb, Level of evidence C).^{11,12} The treatment of MR in such patients is a common clinical dilemma. Operative mortality has been reported between 5 and 18% with two-year survival rates of 70% and five-year survival rates of 61%.¹³⁻¹⁶ However, recent studies have shown that valve surgery does not improve survival in patients with left

Table 3. Procedural and in-hospital characteristics.

Clips, n (%)	
- Total	10
- 1 per patient	9 (90)
- 2 per patient	1 (10)
Procedure time (min)	207±63
Radiation time (min)	50.2±12.7
Radiation dose (Gy/cm ²)	309±97
Hospitalisation (days)	
- Total	7 (4-15)
- ICU	1.5 (1-6)
Complications, n (%)	
- Major bleeding	1 (10)
- Partial clip detachment	1 (10)

Gy=Gray, ICU=intensive care unit.

ventricular dysfunction.^{17,18} Therefore, different percutaneous techniques were developed, offering an alternative treatment for MR in patients who are poor candidates for surgery.^{7,19,20}

One of the recent developments is the edge-to-edge technique using a clip. Goar and colleagues demonstrated for the first time that this technique

Figure 4. Change in NYHA class and MR grade at one month of follow-up.

can be performed successfully on the beating heart in a porcine model.^{21,22} Adequate tissue response and healing with complete encapsulation of the clip is demonstrated²³ and it has been hypothesised that the clip-initiated tissue bridge may help prevent future annular dilatation.²⁴ The six-month follow-up of the first phase I clinical trial, EVEREST I (Endovascular Valve Edge-to-Edge Repair Study) has been reported.⁷ In this study, the clip was successfully inserted in 24 of 27 non-high-risk patients and 22 patients were discharged with a clip in place. There were no procedural complications and four (18%) major adverse events occurred within 30 days: post-procedural stroke due to hypotension in one patient and partial clip detachment in three patients (11%). Finally, 82% (18/22) of the patients were discharged with MR $\leq 2+$. At one-month follow-up 63% (14/22) of the patients continued with MR $\leq 2+$. In our study group, partial clip detachment occurred in one patient one day after the procedure and one patient needed blood transfusion after femoral bleeding. Eight of our patients (89%) left the hospital with an improvement of MR to $\leq 2+$, which was maintained at one month in seven patients (78%). We also reported an improvement in functional capacity and quality of life, which was not studied in the EVEREST trial. In contrast to our study population, the patients included in the EVEREST study were all candidates for convention-

al surgery. Furthermore, LVEF $<30\%$ and LVESD >55 mm were exclusion criteria and only 59% of the patients had a history of congestive heart failure.

Recently, mid-term durability of the edge-to-edge technique in the EVEREST cohort was published.²⁵ A total of 107 patients were treated, 9% had a major adverse event, in another 9% partial clip detachment occurred. One year after clip placement, 66% of the patients were free from death, mitral valve surgery or MR $>2+$. However, the high-risk population was not included in this cohort (median LVEF 62%, 46% in NYHA class III or IV). Our results are in line with two recent reports which showed feasibility of MitraClip therapy in the high risk population.^{26,27}

Limitations of our study are the small number of patients and the short follow-up time, but we continue to select patients for this type of MV repair and will perform mid- and long-term follow-up regarding survival, functional capacity (including the 6-minute walk test) and MR reduction. Secondly, it is an observational study, not comparing the percutaneous technique to the conventional mitral valve repair. This is currently being investigated in a multicentre pivotal trial (EVEREST II). However, in this study high-risk patients were also excluded. Thirdly, the observational non-blinded design of the study might induce a placebo effect regarding the QoL questionnaire.

Conclusion

Percutaneous mitral valve repair using the edge-to-edge technique seems to be a safe and efficient alternative therapy for inoperable/high-risk patients with symptomatic MR. After one month, the majority of these patients experience an amelioration in functional class and a non-significant improvement in quality of life thanks to a sustained reduction in MR. ■

References

- 1 Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation*. 1995;91:1022-8.
- 2 David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. *J Thorac Cardiovasc Surg*. 2005;130:1242-9.
- 3 Alfieri O, Maisano F, De Bonis BM, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg*. 2001;122:674-81.
- 4 Umana JP, Salehizadeh B, DeRose JJ Jr, et al. 'Bow-tie' mitral valve repair: an adjuvant technique for ischemic mitral regurgitation. *Ann Thorac Surg*. 1998;66:1640-6.
- 5 Maisano F, Torracca L, Oppizzi M, et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. *Eur J Cardiothorac Surg*. 1998;13:240-5.
- 6 Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. *Ann Thorac Surg*. 2004;77:1598-606.
- 7 Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol*. 2005;46:2134-40.
- 8 Foster E, Wasserman HS, Gray W, et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. *Am J Cardiol*. 2007;100:1577-83.
- 9 Grayburn PA. How to measure severity of mitral regurgitation: valvular heart disease. *Heart*. 2008;94:376-83.
- 10 Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777-802.
- 11 Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists; endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114:e84-231.
- 12 Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J*. 2007;28:230-68.
- 13 Bax JJ, Braun J, Somer ST, et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation*. 2004;110:II103-II108.
- 14 Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg*. 1998;115:381-6.
- 15 Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001;122:1125-41.
- 16 Romano MA, Bolling SF. Update on mitral repair in dilated cardiomyopathy. *J Card Surg*. 2004;19:396-400.
- 17 Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2005;45:381-7.
- 18 Mehra MR, Griffith BP. Is mitral regurgitation a viable treatment target in heart failure? The plot just thickened. *J Am Coll Cardiol*. 2005;45:388-90.
- 19 Mack MJ. New techniques for percutaneous repair of the mitral valve. *Heart Fail Rev*. 2006;11:259-68.
- 20 Schofer J, Siminiak T, Haude M et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation*. 2009;120:326-33.
- 21 Fann JJ, St Goar FG, Komtebedde J et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation*. 2004;110:988-93.
- 22 St GF, Fann JJ, Komtebedde J et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation*. 2003;108:1990-3.
- 23 Luk A, Butany J, Ahn E, et al. Mitral repair with the Evalve MitraClip device: histopathologic findings in the porcine model. *Cardiovasc Pathol*. 2009;18:279-85.
- 24 De BM, Lapenna E, La CG et al. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy: role of the 'edge-to-edge' technique. *Circulation*. 2005;112:1402-8.
- 25 Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol*. 2009;54:686-94.
- 26 Franzen O, Baldus S, Rudolph V, et al. Acute outcomes of Mitraclip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J*. 2010;31:1373-81.
- 27 Tamburino C, Ussia GP, Maisano F, et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J*. 2010;31:1382-9.