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REVIEW

Percutaneous interventional mitral regurgitation treatment using the Mitra-Clip system

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Abstract The interventional treatment of mitral valve regurgitation by the MitraClip procedure has grown rapidly in Germany and Europe during the past years. The MitraClip procedure has the potential to treat high-risk patients with secondary mitral valve regurgitation and poor left ventricular function. Furthermore, patients with primary mitral valve regurgitation may be treated successfully by the MitraClip procedure in case of high surgical risk or in very old patients. At the same time it has been emphasised that the MitraClip interventional treatment is still at an early stage of clinical development. The largest clinical experience with the MitraClip procedure so far is probably present in some German cardiovascular centers, which here summarise their recommendations on the current indications and procedural steps of the MitraClip treatment. These recommendations of the AGIK and ALKK may present a basis for future development.

Keywords Mitral valve regurgitation · Interventional treatment · MitraClip

Introduction

For patients with symptomatic, operable, severe mitral regurgitation, surgical intervention remains the gold standard treatment [8, 34]. Different techniques for the reconstruction of degenerated mitral valves are used, which are often combined with techniques for the reconstruction of the valve apparatus (e.g. artificial tendon fibres). The Carpentier Ring is considered the therapy of choice for primary—degenerative—and secondary—functional—mitral valve disease as a consequence of dilative or ischaemic cardiomyopathy [9].

For many patients with severe symptomatic mitral valve regurgitation, mitral valve surgery is not a realistic

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treatment option [23]. Overall every second patient with severe mitral valve disease is not operated on. For older patients and those with severe left ventricular failure or relevant co-morbidities, this percentage was even higher. In an attempt to reduce ventricular volumes and restore a more normal shape of the dilated ventricle, surgical ventricular reconstruction (SVR) was performed in combination with coronary artery bypass grafting [16]. In a subsequent analysis of the STICH trial, a survival benefit was suggested in patients undergoing coronary artery bypass grafting plussurgical ventricular reconstruction compared to bypass grafting alone, with the achievement of a postoperative endsystolic volume index of 70 ml/m^2 or less [24]. Extensive ventricular remodelling at baseline, however, might limit the ability of ventricular reconstruction to achieve a sufficient reduction in volume and clinical benefit [24].

Percutaneous catheter-based techniques can currently only partially replace the technically complex operative reconstruction. Different approaches are used that aim for narrowing of the mitral ring, similar to the operative implantation of a Carpentier Ring [33]. The only method that currently impacts on valve morphology and mitral ring configuration is the MitraClip Implant [11, 12]. Similar to the Alfieri-stich technique [1], a connection between the posterior and anterior mitral leaflets is created by placing a part of both leaflets on the MitraClip-arm, to then trap them and move them towards each other through closing of the clip.

Over 10,000 MitraClips have been implanted worldwide to date. Initially, these were exclusively carried out in the context of several clinical trials in the USA (EVEREST), which covered topics ranging from assessment of safety and applicability up to prospective randomised comparisons with the operative approaches [11, 12]. Following on from CE certification, there has been a high and rapidly increasing number of MitraClip procedures conducted in Germany over the last years.

The aim of this consensus paper is to summarise the currently available practical experience from 10 German hospitals which have carried out a significant number of Mitraclip interventions (in total approximately 2,000), in order to create recommendations regarding indication, application and after-care in patients undergoing the current procedure.

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Current data

The currently available evidence-base behind Mitraclip-treatment is limited to:

1. a first feasibility trial (EVEREST I),
2. a randomised-controlled trial (EVEREST II),
3. 3 industry-supported, multicentre registers (ACCESS Europe, Everest High-risk register, REALISM),
4. a German (TRAMI-Register) and a European register, both of which are performed in an industry-independent manner,
5. multiple single-centre cohorts, where, of more than 90 German centres that perform implantation, only few currently have high case numbers (>200).

The EVEREST II study is a prospective randomised trial in which the Mitraclip approach was compared with traditional mitral valve surgery [13]. 279 operable patients with a mean age of 67 were included in the study, for whom there is good evidence supporting the benefit of surgery according to the current guidelines: patients with degenerative mitral valve regurgitation, good left ventricular function and a low operative risk. When interpreting the data, it must be taken into account that the MitraClip procedure was predominantly conducted by interventionalists with an average experience of 3 MitraClip procedures before the randomisation phase. With respect to the primary combined end-point of the study [death, requirement for a second procedure or operation, or unchanged significant mitral regurgitation (regurgitation >II°)], the Mitraclip procedure was statistically significantly inferior to traditional mitral valve surgery.

A subgroup analysis performed on data from EVEREST II found that Mitraclip was not inferior to cardiac surgery in older patients and patients with functional regurgitation and reduced left ventricular function [13].

The German Mitral Valve register [4] and the ACCESS-Europe study [21], 2 multicentre registers with about 1400 and 567 patients, respectively, reported that in the daily clinical practice the patients receiving MitraClip treatment were significantly older (75 and 74 years, respectively) than in EVEREST II, had a significantly greater proportion of patients with relevant co-morbidities (log. EuroScore 23 % each) and functional mitral regurgitation (67 and 77 %, respectively), and a greater percentage with severe left ventricular dysfunction. Despite this, the results and clinical application were comparable with EVEREST II. The procedure-associated mortality, both in hospital (2.5 %) and at 30 days (3.4 %), and complication rate in the German Mitral Valve Register were relatively low however.

A subgroup analysis of the German Mitral Valve Register has shown that the older patients who received a MitraClip (>76 years, $n = 560$) had a comparably good

outcome to younger patients (<76 years, $n = 504$). The procedure-associated risks and the 30-day mortality in the older patients was similar to that in the younger (6.7 and 4.7 %, respectively, ns) [35].

A retrospective multicentre analysis of 50 patients with a left ventricular ejection fraction (LV-EF) of ≤25 % [15] and the prospective, multicentre register PERMIT-CARE with 51 heart failure-patients who did not sufficiently respond to biventricular pacing [3], showed clear clinical benefit of the MitraClip procedure on severe heart failure. The 30-day mortality, at 6 and 4.2 %, can be considered acceptable.

Diagnostic approach

The diagnosis and evaluation of the severity of mitral valve regurgitation as well as the treatment options are particularly based on transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE, see also chapter 'Echocardiography'). Stress-Echocardiography is usually not necessary, although in specific cases it can provide additional information on the severity of the regurgitation. Coronary angiography, where clinically indicated, is also recommended to rule out any significant coronary artery disease or to treat significant coronary stenoses before performing catheter-assisted valve reconstruction. Both left ventricular angiography and haemodynamic measurements using right heart catheterisation can provide additional relevant information for assessment of the severity of the valve disease. In patients with severe left ventricular failure and left bundle branch block, the indication for cardiac resynchronisation therapy should first be assessed as this intervention, in particular, can lead to reduced regurgitation in the context of functional valve disease [38].

Biochemical parameters, such as BNP/NT-pro-BNP, as well as classification using the NYHA-Score correlate with the severity and prognosis of the mitral regurgitation and can, therefore, also be used in the follow-up of patients. Moreover, standardised stress-tests, such as the 6-min walk-test or Spiroergometry, can help to objectify the exercise tolerance of the patient.

Echocardiography

Echocardiography is currently the method of choice for assessing valve morphology and function. The severity of symptomatic mitral regurgitation is established through the regurgitation volume, which depends on:

- the effective regurgitant oriface area (EROA),
- the flexibility of the leaflets and valve apparatus,
- the geometry and size of the mitral valve apparatus and aortomitral apparatus,
- a systolic time run-profile of the regurgitation,
- the size and pressure conditions in the left ventricle and the left atrium,
- the geometry and contraction of the left ventricle.

It must be remembered that echocardiographical assessment only provides a snapshot from a single time-point, which is affected by multiple factors including filling status, blood pressure, heart rate and arrhythmia (e.g. atrial fibrillation), but importantly also the use of sedatives,

Table 1 Echocardiographic quantification of mitral regurgitation

Parameter	Mild	Moderate	Severe
Qualitative			
Mitral valve morphology	Normal/abnormal	Normal/abnormal	Flail leaflet/PM rupture
Colour doppler MR jet	Narrow/central	Intermediate	Large central jet/eccentric jet to the posterior wall
Flow convergence zone	None/narrow	Intermediate	Large
CW-signal of the MR jet	Weak/parabolic	Dense/parabolic	Dense/triangular
Semi-quantitative			
VC-width (mm)	<3 mm	Intermediate	≥7 mm (>8 biplan)
Pulmonary vein flow	Systolic dominant	Systolic moderated	Systolic flow reversal
Mitral influx	A-waves dominant	Variable	E-waves dominant (>1.5 m/s)
VTI mitral to VTI aorta	<1	Intermediate	>1.4
Quantitative			
EROA (mm^2)	<20	20–29; 30–39	≥40 (PMR) ≥20 (SMR)
Regurgitation volume (ml)	<30	30–44; 45–59	≥60 (PMR) ≥ 30 (SMR)

narcotics and catecholamines. Consideration must, therefore, always be taken to ensure that the conditions under which the echo is performed remain identical before and after the procedure.

Common quantification methods of echocardiographic assessment of mitral regurgitation according to the guidelines are listed in Table 1. Although in earlier studies, including the EVEREST studies, a 4-level classification of mitral regurgitation was used, and a 3-level classification is now recommended by various specialist organisations (AHA, ACC, EAE, ESC) [6, 19].

LV and LA size as well as pulmonary systolic pressure in mild mitral regurgitation are usually normal. In acute, significant mitral regurgitation the systolic pulmonary pressure is normally increased while the LV size is normal. Chronic, severe mitral regurgitation usually causes LV and LA dilatation. Accepted cut-off values for a non-significant LA/LV enlargement are: LA-Volume <36 ml/m^2, LVEDD <56 mm. Primary (PMR) and secondary (SMR) mitral regurgitation. Left ventricular (LV). Left atrial (LA). Continuous wave (CW). Velocity time interval (VTI). Effective regurgitant oriface area (EROA), left ventricular end diastolic diameter (LVEDD). Papillary muscle (PM). Vena contracta (VA).

Despite the multiple options for quantification of mitral regurgitation, there is at present no single unambiguous method that has been used consistently in all studies and registers. The currently scientifically favoured methods of assessing mitral regurgitation are multidimensional measurements of the proximal jet-diameter, in particular, because of their high resolution in transoesophageal echocardiography. Therefore, determination of the resulting surface using the three dimensional volume-lead technique has been included in the current guidelines for 3D echocardiography [19]. A second technique is the determination of the effective regurgitant orifice area (EROA), which is calculated from Doppler measurement of the proximal flow convergence over the maximal regurgitant speed (V_{max} of MR) as a surrogate of the LV to LA-pressure difference, which reduces its dependence from haemodynamic pressure conditions [18].

Methods such as jet-assessment using Colour Doppler Echocardiography or CW-Doppler-Intensities (pulmonary vein flow reversal) are currently still widespread in clinical practice, the interpretation of which is more strongly operator-dependent, making quantification less reliable. In this case, it is strictly required that a very experienced operator determines the severity of the mitral regurgitation considering the limitations listed above. Additionally, it is desirable to increasingly include 3D-echocardiographical methods into the assessment.

Taking the severity of the mitral regurgitation into account, operation or catheter-based intervention is indicated in case of a regurgitant opening area of >40 mm^2 in PMR. For SMR, a cut-off of >20 mm^2 is appropriate. Accordingly operation or intervention is indicated for a regurgitation volume of >60 ml in PMR and >30 ml in SMR. Another critical step in choosing the most appropriate surgical, interventional or conservative treatment approach, is the determination of mitral valve morphology

Table 2 Morphology for a Mitraclip therapy

Optimal valve morphology	Conditionally suitable valve morphology	Unsuitable valve morphology
Central pathology in Segment 2	Pathology in Segment 1 oder 3	Perforated mitral valve leaflet or cleft
No leaflet calcification	Mild calcification outside of the grip-zone of the clip system; ring calcification, post annuloplasty	Severe calcification in the grip-zone
Mitral valve opening area >4 cm^2	Mitral valve opening area >3 cm^2 with good residual mobility	Haemodynamically significant mitral stenosis (valve opening area <3 cm^2, MPG ≥ 5 mmHg)
Mobile length of the posterior leaflet ≥10 mm	Mobile length of the posterior leaflet 7–<10 mm	Mobile length of the posterior leaflet <7 mm
Coaption depth <11 mm	Coaption depth ≥11 mm	
Normal leaflet strength and mobility	Leaflet restriction in systole (Carpentier IIIB)	Rheumatic leaflet thickening and restriction in systole and diastole(Carpentier IIIA)
Flail-width <15 mmFlail-Gap <10 mm	Flail-width >15 mm only with a large ring width and the option for multiple clips	Barlow's syndrome with multisegment flail leaflets

Morphological suitability criteria for the mitraclip intervention; modified according to the Everest criteria and the Crossroads training experiences on patient selection. 'Optimal morphology' is well-suited for implantation, 'conditionally suitable valve morphology' should be preferably treated in experienced centres and 'unsuitable valve morphology' is contraindicated to therapy. The PMR with flail leaflet is determined in the intercommissural 2-chamber view; the flail gap is determined in the long axis view as the distance of the end of the flail leaflets in the LA to the opposite-lying leaflet

MPG mean pressure gradient, *PMR* primary mitral regurgitation, *LA* left atrium

Table 3 Indications for the MitraClip therapy

Ideal for Mitralclip treatment	MitraClip to be considered	MitraClip not recommended or only in exceptional cases
Severe mitral regurgitation	Moderate to severe mitral regurgitation	Moderate to severe mitral regurgitation
and	**and**	**and**
Optimal valve morphology	Optimal valve morphology	Conditionally suitable valve morphology
and	**and**	**or**
SMR with LV-EF <30 %	SMR or PMR (with operation-indication following guidelines)	Life expectancy <12 months
or	**and**	**or**
PMR (with operation-indication following guidelines)	High operative risk, very high age or other risk-constellations	LV-EF < 15 % or cardiothoracic operation planned due to other indications
and		**or**
A high operative risk or other risk-constellations		previously operated mitral valve
		or
		as surgical/interventional hybrid procedure
		or
		at low operative risk

Interdisciplinary approach

which influences the mechanism of mitral regurgitation. The criteria characterising optimal, conditional and unsuitable mitral valve morphologies for mitral clip treatment are summarised in Table 2.

During the feasibility planning of MitraClip therapy, it is also important to rule out a co-existing relative mitral valve stenosis with a mean gradient of $\geq$5 mmHg as well as a rheumatic or a calcified, restrictive leaflet morphology, either of which leads to a clear rise in the mean mitral valve gradient after MitraClip implantation or can prevent secure attachment of the MitraClip.

Drawing from the current experience, the following recommendations have been developed: at the beginning of a MitralClip program, the first 50 patients should have an 'optimum valve morphology', in order to gain experience while ensuring maximum patient safety. With increasingly experienced operators, it is also possible to successfully treat mitral valves with more difficult morphology (see Table 3, Chapter Indication).

Indication

The indication to interventional treatment of mitral valve regurgitation should always be determined on an individual basis as currently there are no established guidelines for this therapy. During this decision making process, the following factors should be considered:

1. The recommendations from the current guidelines by the German and European societies for cardiology on the treatment of cardiac valve disease [26, 37].
2. The morphology of the mitral valve.
3. The cause and the severity of the mitral regurgitation.
4. The left ventricular function.
5. The operative risk.

Given the results of the EVEREST II study, it is currently not possible to recommend MitraClip therapy for those patients who are, based on the guidelines of the European Society for Cardiology for the Treatment of Cardiac Valve Disease, in a highly-recommended group for surgical treatment (class I or IIa indication). Mainly patients with PMR or with chronic-ischaemic SMR, for whom (operative) revascularisation is pursued, are grouped into those classes. However, the grade of evidence for most of the class I or class IIa indications for operation is based on 'expert-consensus'-level only (evidence grade C) [6, 37].

In the case of SMR without option for simultaneous revascularisation, there is little evidence for a benefit of surgery. According to the guidelines for such cases, the emphasis is on optimisation of the medical therapy and, in appropriate cases, on biventricular pacing. For certain patient groups, the MitraClip can be considered a new treatment option.

These include in particular:

- Patients with PMR, severe LV-failure (LV-EF < 30 %) and relevant co-morbidities.
- Symptomatic patients with severe SMR, severe LV-failure (EF < 30 %) and no option for revascularisation.
- Symptomatic patients with severe SMR, mild to moderate LV-failure (LV-EF > 30 %), no options for revascularisation and relevant co-morbidities.

It is for these patient groups, who often have also a high operative risk or are inoperable, that the MitraClip therapy

has turned out to be a safe treatment option with a low 30-day mortality (ACCESS, TRAMI-Register). Due to current lack of long term data, the decisions regarding therapy should be made by the interdisciplinary heart-team [26]. The definition of "high operative risk" and "very high age" (Table 3) should also be a heart-team decision based on clinical presentation of the individual patient, assessment of risk score (Euroscore II and STS score), left ventricular ejection fraction and morphology of the mitral valve (Table 2).

In our view indication to a MitralClip procedure for severe symptomatic (NYHA status III or IV) mitral regurgitation can be classified from 'optimal' to 'conditionally recommended' into three distinct groups (Table 3).

The use of MitraClip has also been shown to be successful in isolated cases of cardiogenic shock [40] with severe mitral regurgitation following papillary muscle rupture. The use of combined TAVI and MitraClip in patients with 2-valve disease has also been documented [27, 32]. A general indication-recommendation, however, currently cannot be given. MitraClip intervention is not recommended in patients with unsuitable valve morphology (see Table 2). Furthermore, relative or absolute contraindications include left atrial or ventricular thrombus or active mitral valve endocarditis.

As is the case with TAVI, the complexity of interventional treatment of mitral regurgitation and the high proportion of patients with co-morbidities make the creation of a defined treatment-team important. A mitral valve team ('Heart-team') should ideally consist of:

- Interventional cardiologist with experience in invasive and non-invasive diagnostics and treatment of valve-disease; a minimum experience of 25 interventional mitral valve procedures per year should be aimed for and expertise in transseptal puncture.
- Echocardiographer with experience in transthoracic and, in particular, transoesophageal echocardiographic diagnosis of valve disease, including the application of 3D approaches.
- Cardiothoracic surgeon with expertise in reconstructive operative methods.
- Anaesthesiologist with experience in cardiac anaesthetics.

A common decision from the cardiologists and cardiac surgeons in the Heart-team is necessary and should be documented [26]. In contrast to TAVI [14, 25], the presence or immediate availability of a cardiac surgeon is, however, not required due to the low risk of the MitraClip procedure.

Local set-up and radiation protection

The MitraClip procedure can, like the TAVI-procedure or the implantation of a pacemaker, be carried out in an appropriately equipped angiography suite. The procedure should be performed in rooms of hygiene class 1B (after DIN 1946-4) with all hygienic measures followed. The room size should be big enough so that there is additional space for:

- The echocardiographer with the echo-machine.
- The anesthesiologist and the ventilator (and medication trolley as appropriate).
- A large, sterile, preparation table for the MitraClip system.

The MitraClip procedure is predominantly controlled through transoesophageal echocardiography and can be supplemented by fluoroscopy for additional information during certain steps. It is, therefore, critically important that monitors are set up to allow the interventionalist straightforward and unobstructed view of the X-ray image, the transoesophagal echocardiography image and the haemodynamic readings. Ideally, the TEE image is displayed by the monitor arrangement of an angiography setup; this is, however, not mandatory. Figure 1 shows two possible options for arrangement of the angiography suite. This positioning allows the echocardiographer to simultaneously follow the fluoroscopy images on the monitor arrangement of the angiography setup.

The MitraClip is normally carried out under general anaesthesia, along with the accompanying monitoring (invasive arterial blood pressure, central venous line, pulse oximetry). As the procedure can take a long time, it is recommended to insert a urinary catheter to monitor urine output, and positioning of the patient on a warm-mat to avoid relevant periprocedural cooling. In patients with severely reduced left ventricular function, it can be considered to perform the intervention under intra aortic ballon pump support (IABP). Afterwards the patient should go to a suitable recovery room or to a cardiac intensive care unit for observation.

For radiation protection the general legal rules apply; however, the following specific points should additionally be followed:

- Usage of pulsed fluoroscopy with low image frequency (for example 3.5 images per second); referred to as 'electrophysiology' (EP) mode in some angiography suites.
- The use of very low intensity fluoroscopy. Both low image frequency and low fluoroscopy intensity are sufficient to monitor movement of the MitraClip system in the heart.
- Generous focusing (e.g. during the final arm angle check).
- Usage of mobile radiation protection walls for the echocardiographer, who must stay directly next to the

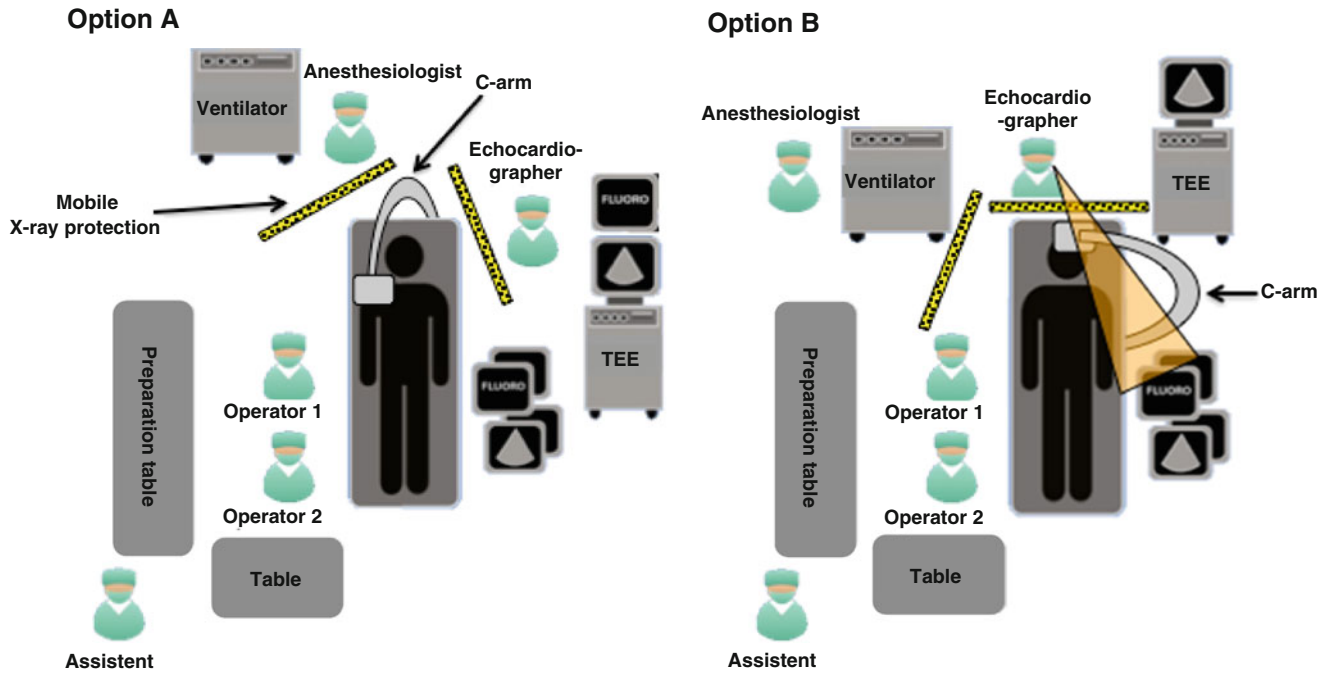

Fig. 1 The figure shows two possible arrangements in the angiography suite. In *A,* the C-Arm of the catheter display is cranial and the echocardiographer is positioned left lateral to the patient. The X-ray pictures are visible for the echocardiographer on a separate monitor (fluoro). The *yellow lines* represent mobile radiation protection walls. In *B,* the C-Arm is positioned left lateral to the patient; the anaesthetist and particularly the echocardiographer are found cranial to the patient and have better access to the head of the patient. The *orange cone* indicates the additional view angle onto the X-ray pictures on the angiography monitor arrangement

patient for the whole of the procedure, and, when appropriate, also for the anaesthesiologist.

Transseptal puncture

The actual MitraClip procedure starts with the transseptal puncture. Correct localisation of the puncture is a key to procedure success. In general, the puncture can be done very safely under TEE-control. The Fossa ovalis, which is to be punctured, is normally located caudal and posterior to the aortic arch, and posterior and cranial to the ostium of the coronary sinus and the tricuspid valve ring. This orientation can vary widely in cases of structural heart disease however. Left atrial enlargement also commonly causes clockwise rotation of the septum (more horizontal). Puncture of the cranial border of the muscular limbus must absolutely be avoided, as insertion of the MitraClip dilator can then only be achieved by applying significant pressure, which is an unnecessary risk.

The femoral vein should preferentially be used for venous puncture. To avoid apposition thrombosis at the wire or dilator, a small dose of intravenous heparin should be used (for example 2,500 U). The guide-wire and the Brokenbrough-catheter should then be inserted (Mullins sheath, SL0 or SL1-sheath) in the superior vein cava; the wire should be removed and the Brokenbrough-needle inserted. Additionally, air or small clots are removed and invasive pressure measurement can be connected. Eventually, the tube and the transseptal needle are pulled back from the superior vena cava towards the atrial septum. Anatomical orientation is facilitated by the TEE using bicaval view (100° setting of the TEE-probe) and by fluoroscopy using different planes where appropriate (‘right anterior oblique’RAO 30°/0°, ‘left anterior oblique’ LAO 45°/0°). The arrow (needle and sheath) is turned clockwise upon pull-back of the dilator into the atrium and the needle is positioned posterior-medial (4 o’clock to 7 o’clock). Upon passing of the limbus fossae ovalis usually medial movement of the dilator tip is visible. A clear posterior positioning relative to the aortic arch needs to be visible in the TEE in a short axis section view (30° rotation). In this position, clockwise rotation of sheath and needle allows posterior shifting of the sheath tip, while counter-clockwise rotation allows anterior shifting. The position of the tent-like stretching (‘tenting’) of the atrial septum should be confirmed in the TEE 4 chamber view (0°) (see Fig. 2). Depending on the position of the axis of the heart, the TEE can also be positioned at approximately 170°. The ‘tenting’ and with it the puncture height position should be approximately 4 cm above the mitral valve annulus. In cases of prolapse, a higher puncture position can be

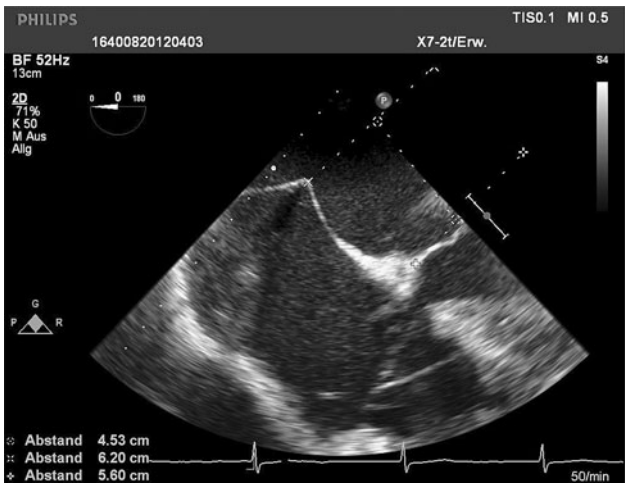

Fig. 2 Adoption of the optimal puncture position in the atrial septum in TOE. With the transseptal needle, a tent-like spreading of the atrial septum is achieved. The distance of the puncture height to the mitral valve annuals should be approximately 4.0 cm, in the case displayed the height is 4.5 cm

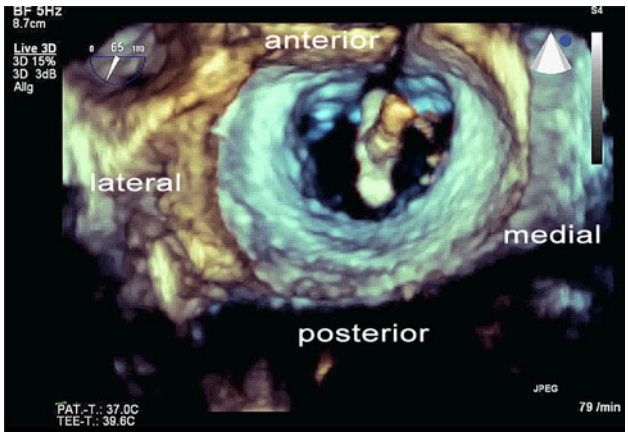

Fig. 3 Left atrial echocardiographic 3D alignment of the MitraClip system, surgical orientation with alignment of the aorta at 11–12 o'clock

considered (up to 5 cm), while for significant 'tethering' and secondary mitral regurgitation a lower puncture position is appropriate (approx. 3.5 cm above the mitral valve annulus, or 4–4.5 cm above the coaptation of both leaflets).

The stability of the needle position can be checked by carefully pushing the sheath against the septum. If the sheath cannot be pushed against the septum or if the sheath moves cranially, then no puncture must be performed. In general, the needle/sheath should be perpendicularly aligned relative to the septum. It is recommended to puncture when there is clear 'tenting' of the atrial septum. Accidental probing of a persistent foramen ovale (PFO) should be avoided as it results in an overly anterior passage through the septum. After successful puncture, immediate anticoagulation with heparin (ACT 250–300 s) is recommended.

MitraClip procedure

The details of the MitraClip procedure have already been comprehensively described elsewhere [12]. Changes to these come from the increasing use of 3D echocardiography [2], in particular, for the vertical positioning of the clip arms relative to the line of closure (Fig. 3, Video 1), as well as the so called x-plane echocardiography, used for directing the clip into the left ventricle and for validating the insertion of the leaflets into the clip (Video 2 and 3). To judge the position of the clip arm, transgastric images are being used increasingly less. This may be partially due to the risk of gastric lesions resulting from excessive use of this technique. In judging the position of the clip, attention is to be paid to medial and lateral shifting of the clip due to respiration when using the intercommissural TEE view. A reduction of this ventilation-dependent movement can be achieved through increased ventilation frequency with lower volumes [22]. Although the standard echo images used for control of the leaflet insertion still play an important role, it is additionally recommendable to record a longer echo loop of the closure procedure and to potentially re-assess the leaflet insertion. Repeated full closure of the MitraClip with multiple re-detachment of the Mitraclip should be avoided as this can lead to laceration of the mitral leaflets. It is, therefore, recommended that, after fastening of the mitral leaflets with the 'grip arms', the MitraClip is partially closed to a 60–90° position. Then, leaflet insertion and the effect on mitral regurgitation reduction are checked and the clip is only fully closed when a satisfactory result has been achieved. For the assessment of leaflet insertion, the use of the x-plane method during the phase of gripping of the mitral leaflets can be helpful. In particular cases, techniques such as rapid pacing or use of adenosine can make the grip procedure easier [7, 29, 30].

Also in contrast to previous descriptions, many interventionalists now dynamically adjust the anterior–posterior position of the clip during the retraction in the direction of the leaflets under X-ray guidance. There is currently no validated study result to suggest whether one or two clips should be implanted. Along with the goal of a further reduction in mitral regurgitation with a second clip, a second clip can also help stabilise the generated bridge between the posterior and anterior mitral valve leaflet. It has been documented that even more than two clips have been successfully implanted in selected cases [17, 29–31].

In case of introduction of a second or third clip into the left ventricle, the orientation of the clip arms should be checked in the left atrium and subsequently always guided through the mitral valve next to the first MitraClip in its

closed state to be only opened in the left ventricle. Subsequently strong movement or rotation of the MitraClip should be avoided in order to prevent the clip arm from getting entangled in the tendon fibres. It must be emphasised that a second or third MitraClip occasionally cannot, despite inversion, be pulled back into the left atrium thus making its removal impossible. Usually it should be aimed to place the second clip as parallel as possible to the first clip under fluoroscopic guidance to avoid artificial creasing of the leaflets in between the clips with consecutive, non-correctable mitral regurgitation.

During certain steps of the MitraClip procedure (for example the removal of the dilators after the introduction of the leading catheter into the left ventricle, retraction of the delivery system) aspiration of the wall of the left ventricle should be strictly avoided as it can mediate the occurrence of air emboli.

Assessment of the procedure outcome

The most common goal of MitraClip implantation is to maximise the reduction in mitral regurgitation. The severity of the mitral regurgitation, the degree of stenosis and the morphological result should be established before and after the implantation of the first, and, where appropriate, second or third, MitraClip. It is important to note that the final release of the MitraClip from the delivery system can significantly change the outcome of the procedure. The assessment of procedural success is usually made while the patient is still under anaesthetic and, therefore, the type and depth of anaesthetic, as well the use of catecholamines, can influence measurements via the pre- and after-load, as well as the filling pressure of the left atrium and ventricle. It is, therefore, important that all intraprocedural measurements are carried out under similar conditions, aiming for the characteristic everyday-life haemodynamic values of the respective patient. As with the assessment of native valves, it is also appropriate to carry out a multimode analysis of the residual regurgitation following MitraClip implantation. The following methods can be used during the procedure to assess the severity of MR:

- Reduction of the regurgitation as seen in echocardiography.
- Reduction in left atrial pressures (in particular, the V-wave).
- Increase in cardiac output using the thermodilution method or PICCO catheter system [36].
- Reduction in mitral regurgitation in left ventricular angiography.
- TOE-based calculation of the regurgitation current from ‘bubbles’ in the left atrium during left ventricular angiography.

Echocardiography plays a central role in the assessment of residual mitral regurgitation and a variety of methods can be used (see Table 1). In current clinical practice, the evaluation of the colour jet using colour doppler is commonly used. It should be noted that the total surface of the colour jets is larger for multiple jets than for single jets, which can lead to an overestimation of mitral regurgitation in cases with multiple jets [20, 28]. Artifacts caused by the clip can also interfere with the results. Small, persistent colour jets, which can also occur multiply, usually indicate mild mitral regurgitation.

In the absence of aortic regurgitation, the regurgitation volume can be calculated from the difference between the left ventricular total stroke volume (end diastolic volume - end systolic volume) and the forward flow (calculated from the product of the velocity time integral in the left ventricular outflow tract (LVOT) and the surface area of the LVOT) [5]. The left ventricular volumes should preferably be assessed using biplane 2D- or 3D- echocardiography [19].

A morphological assessment must establish if both leaflets are adequately held by the respective MitraClip. The clip gives rise to a section of tissue bridging of both leaflets that separates a medial and a lateral opening (loop). Left atrial and ventricular 3D view allow particularly straightforward assessment of this tissue section (loop). An isosceles triangle, as seen in 3D view, suggests even traction of the clip on the valve leaflets (Fig. 4). After positioning of each of the clips, the degree of mitral stenosis must also be determined. The transvalvular gradient is usually assessed using CW-Doppler (a mean gradient of $\leq$5 mmHg is considered to be acceptable; alternatively PW-Doppler can be used). Additionally, planimetric

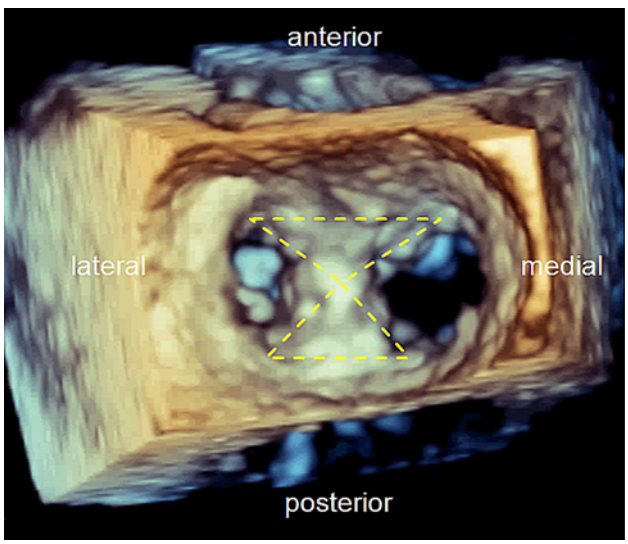

Fig. 4 Left atrial echocardiographic 3D view of the newly created tissue bridge and both mitral valve openings

measurements of both mitral valve openings can be made, ideally with 3D TOE or alternatively with 2D TOE in the transgastric short axis. In the EVEREST study, a planimetric mitral valve opening surface area of <1.5 cm^2 was considered significant [11, 12, 39]. The PISA method is validated neither for multiple regurgitant jets, which usually occur after MitraClip implantation, nor for the newly created geometry of the valve—with 2 or 3 openings. Valid summation of 2D measurements of the vena contracta of multiple jets is not possible either. By contrast, direct measurement of the surface of the vena contracta by 3D echocardiography is promising for the quantification of residual mitral regurgitation [10], although there is currently still no reference data. The extent to which 3D-based echocardiographical analyses, alone or in combination with other methods, will lead to improved quantification of residual mitral regurgitation following MitraClip therapy, must be assessed in future prospective studies.

Supportive therapy

In order to avoid thrombus buildup, patients should be anticoagulated with heparin during the peri-procedural period. It is recommended that heparinisation begins ready for transseptal puncture (see transseptal puncture). After transseptal puncture, the heparinisation should be continued with a target activated clotting time (ACT) between 250 and 300 s. In particular during long procedures, the ACT should be controlled every half an hour. In patients who are anticoagulated using Marcumar the heparin dose should be reduced according to the current clotting values in order to reduce the risk from bleeding. Although in some centres the action of heparin is reversed using Protamine at the end of the procedure, this cannot be universally recommended and should follow risk–benefit analysis.

The post procedural therapy is currently guided by recommendations from the EVEREST studies. Patients without other indication for therapeutic anticoagulation (for example atrial fibrillation) should receive anti-platelet therapy with acetylsalicylic acid (ASS) for at least 6 months. In contrast to the dosing from the EVEREST studies, a dose of 100 mg ASS per day has been found to be sufficient based on the current experience in Germany. Additionally, the patients should receive combination therapy with Clopidogrel (75 mg/day) in the first month. Pretreatment with antiplatelets is not recommended. In patients with an indication for therapeutic anticoagulation, triple therapy for the first month is not recommended. Instead they should receive combination treatment with an anticoagulant and an antiplatelet (ASS or Clopidogrel). Subsequently, the oral anticoagulation should be continued as appropriate.

Periprocedural endocarditis prophylaxis is recommended based on local guidelines. Endocarditis prophylaxis should be used for at least 6 months after the procedure.

Conclusions

As the first of the interventional approaches to treat mitral regurgitation, the MitraClip procedure has the potential to effectively treat high-risk patients with secondary—functional—mitral regurgitation and significantly reduced left ventricular function, who, in the past, would otherwise have frequently been refused conventional surgical approaches. Moreover, patients with primary—degenerative—mitral regurgitation and a high operative risk or of a very high age can be provided with, at least in the mid-term, a clinically sensible treatment. Up until this point, there has not been sufficient research performed to evaluate the benefit in patients with intermediate risk for the operative intervention.

It has to be emphasised that this interventional therapeutic approach is currently in an early stage of its clinical development. Most available results, including the published data of the EVEREST trials, are based on interventions performed during the early learning stage of the respective interventionalist. With increasing establishment of the method and continued self-critical use, further improvement in the treatment results can be expected. The most comprehensive clinical experience with the MitraClip therapy is currently established in a few german centres which have collaborated to provide the treatment recommendations presented here. These recommendations should provide a framework for less-experienced centres and help to estimate better the clinical value of the MitraClip therapy.

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