Percutaneous treatments of heart valve disease
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DIAGNOSTIC AND THERAPEUTIC STRATEGIES
FOR THE MANAGEMENT OF SEVERE MITRAL REGURGITATION

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ABSTRACT

Mitral regurgitation is the second most frequent valvular heart disease. Echocardiography is the principal examination to determine severity, mechanism and hemodynamic consequences of mitral regurgitation and consequently contributes to the assessment and accurate timing of the best treatment strategy. To clarify clinical decision making in severe mitral regurgitation, this review will discuss the diagnostic work-up and treatment options according to the most recent guidelines. Mitral valve surgery, preferably repair, is indicated in symptomatic patients with severe, organic mitral regurgitation. Chronic, severe functional mitral regurgitation is often medically treated (including cardiac resynchronization therapy if indicated), but surgery (preferably annuloplasty) can be recommended. Percutaneous MitraClip implantation may be considered as an alternative option in symptomatic patients with severe mitral regurgitation who are considered inoperable. At present, there is no consensus on the optimal care in asymptomatic patients with severe, organic mitral regurgitation and preserved left ventricular function. A prospective trial is highly needed to elucidate this best treatment strategy.
INTRODUCTION

In this manuscript we will discuss the current status concerning the diagnostic work-up and treatment options of chronic mitral regurgitation (MR). MR is, after aortic valve stenosis, the most common heart valve disease. The prevalence of heart valve abnormalities in Europe and North America is on average 2% (less than 1% at the age of 18-44 years, more than 13% at the age of 75 years and older and 32% of those abnormalities is MR). In the year 2000 about 2-2.5 million persons had MR in the United States; in Europe nowadays 3-3.5 million persons have MR and the prevalence will probably increase as a consequence of the aging of the population. The left ventricle can often overcome the hemodynamic consequences of the regurgitant heart valve in order to preserve the heart function, but in the long term this chronic volume overload will lead to compensatory enlargement of the left side of the heart and eventually to insufficient contractile function. At this stage symptoms of heart failure will occur. Of the patients of 50 years and older who use medication due to moderate to severe MR caused by an abnormality of the valve leaflet annually 3-6% die, the majority due to heart failure and sudden heart death. Mortality and morbidity rates do improve with adequate treatment started at the right time.

Organic or functional

According to etiology organic (primary) and functional (secondary) MR are distinguished. Organic MR is caused by an abnormality of the mitral valve apparatus. The mitral valve apparatus consists of valve leaflets, chordae tendineae, papillary muscles and the annulus (Figure 1a). A common abnormality is myxomatous degeneration, which results in protrusion of the valve leaflet (Figure 1b) or chordae tendineae rupture. Furthermore, volume overload of the left atrium and the left ventricle leads to compensatory dilatation, contractile dysfunction, atrial fibrillation and pulmonary hypertension. In functional MR the valve is normal: an abnormal mitral valve function is caused by dysfunction of the left ventricle, for example after ischemic remodeling or by a dilated cardiomyopathy due to hypertension. This can cause annulus dilatation or restriction of a valve leaflet, resulting in MR. Atrial fibrillation can also lead to annulus dilatation resulting in MR.

Medical history and physical examination

A careful medical history and physical examination are important elements in the diagnostics of MR. Possible complaints are shortness of breath, fatigue, reduced exercise tolerance, orthopnoea and palpitations. Some patients may have severe MR without any complaints. Whether a patient is either symptomatic or asymptomatic has serious consequences for the initial treatment.

At physical examination signs of left sided and eventually right sided heart failure can be found such as lung crepitations, increased central venous pressure,
Figure 1. The mitral valve viewed from above and in a longitudinal section. (a) Normal anatomy; (b) Central prolapse of the posterior valve; (c) Mechanic 'bileaflet'-prosthesis; (d) Repair according to the method of Carpentier (see figure 2); (e) MitraClip; a tool to reduce the orifice and thereby reducing regurgitation.
hepatomegaly and edema. A mid-to-high frequent holosystolic murmur at the apex is a classic sign during auscultation and could be best heard when the patient is laying on the left side. The intensity of the murmur and the presence of a third heart sound can give an indication about the severity of the regurgitation, but also a soft murmur can be an indication of severe MR. The murmur will be less loud when the systolic pressure difference between atrium and ventricle decreases, for example in case of acute severe MR, a small left atrium or severe left ventricular dysfunction. Both MR and aortic valve stenosis are characterized by a systolic murmur; they can be distinguished based on the following: the murmur of aortic valve stenosis is not linked to the first and second heart sound, can be heard best at the right second intercostal space and varies in loudness after an extra systole or during atrial fibrillation.

Additional examinations

Additional examinations that may be performed by the general practitioner includes an ECG and chest X-ray. Increased voltages of the left atrium (the terminal part of the P-wave) and increased voltages of the left and right ventricle in case of pulmonary hypertension may be noticeable on the ECG. An increase of the left atrium and ventricle and pulmonary edema with redistribution on the chest X-ray are an indication of left sided heart failure. If MR is actually diagnosed, further investigations should be performed by the cardiologist to determine the cause and severity. Keystone in the diagnostics of MR is transthoracic echocardiography (TTE). Several variables can be determined such as regurgitant volume, rate of early left ventricular filling and reversal of pulmonary venous flow. Based on cut off values from international guidelines, severity of MR can be expressed on a scale from grade 1 (trivial) to grade 4 (severe). The interpretation of the TTE parameters in relation to the effects of the regurgitation on the left atrium, left ventricle and pulmonary pressures makes accurate and reproducible quantification of MR a difficult process which requires quite some expertise.

TTE does not always provide sufficient insight in the underlying mechanism and hemodynamic consequences of MR. Often transoesophageal echocardiography (TEE) is necessary, but this is an unpleasant procedure which will only be performed when TTE does not provide a definite answer about the treatment strategy. To determine severity of the regurgitation and the stress on the left and right ventricle during hemodynamic changes, stress echocardiography may be of additional value, especially in patients with functional MR. If there still remains lack of clarity after above stated tests, MRI can supply information about severity of MR, ventricular volumes, heart function and possible myocardial fibrosis. Heart catheterization provides extra information about cardiac and pulmonary vascular pressures, cardiac output and pulmonary resistance. For the following patients who undergo a surgical treatment a pre-operative coronary angiogram is recommended: males older than 40 years, postmenopausal women, patients with at least one risk factor for coronary artery disease and patients with angina or a myocardial infarction in the medical history.
Heart valve team

If mitral valve replacement or repair is necessary, involvement of a specialized center with a so called ‘heart valve team’ is advisable. This team consists of cardiologists specialized in interventional cardiology and cardiac imaging and cardiac thoracic surgeons. They are best fitted to consider surgical risks and the expected results after the treatment, taking into account comorbidities, previous heart surgeries and the overall condition of the patient.

TREATMENT OPTIONS FOR SYMPTOMATIC MITRAL REGURGITATION

Mitral valve surgery

Mild to moderate MR with a preserved left ventricular function is often no indication for surgery. An annual check-up at the cardiologist including echocardiography once every two years is recommended. Surgery is indicated in case of symptoms due to severe, chronic, organic MR. Valve repair is preferred due to lower mortality and morbidity on long term compared to valve replacement. The mitral valve apparatus and geometry of the left ventricle are maintained and there are less thromboembolic and bleeding events after repair.

In case of valve replacement there are two options: a mechanical valve or a bioprosthesis of animal origin. There is no difference in survival between both valve types, but mechanical valves are preferred in younger patients due to the deterioration of the bioprosthesis over time. The disadvantage of mechanical valves is the need for lifelong use of anticoagulants. When a bioprosthesis is used, the use of anticoagulants can be discontinued after 3 months if there are no other indications.

Valve repair (Figure 2) is a more complex intervention than valve replacement and success depends on surgical expertise and morphology of the mitral valve. The morphology determines the repair strategy. The sliding plasty (Figure 2c) is the most applied approach in case of organic MR.

In case of functional MR choices are less clear. There is no ideal reconstruction technique and sometimes it is better to choose for medical treatment. According to the guidelines a surgical intervention -preferably valve repair- is indicated in patients with severe functional MR and a left ventricular ejection fraction of more than 30% who undergo bypass surgery. The MR can be treated by placement of a relatively small ring (restrictive annuloplasty). Coaptation of the valve leaflets will be restored and valve regurgitation is reduced which can lead to remodeling of the left ventricle, even in a severely disturbed left ventricular function. Randomized trials have shown alternating results after surgery in functional MR and surgery does not always have a beneficial influence on survival. The classic approach in valve repair or replacement is a median sternotomy, although currently a minimal invasive video guided intervention via a lateral mini-thoracotomy is possible. In both approaches extracorporeal circulation by a heart-lungmachine is necessary.
Despite an indication for surgery, almost half of the symptomatic patients with severe MR in Europe will not undergo surgery due to high age, poor left ventricular function or comorbidity. Percutaneous implantation of a MitraClip is sometimes possible in these patients. These are patients with mitral valve prolapse or functional MR in whom the valve leaflets are not severely affected and considered inoperable or with high surgical risk. Via the femoral vein, right atrium, intra-atrial septum and left atrium one or more clips are placed at the position of the most severe regurgitation (Figure 3). Consequently, a double orifice of the mitral valve is created (Figure 1E), resulting in a reduction of the MR. The procedure is performed in a cardiac catheterization laboratory under general anesthesia and is monitored by three-dimensional transoesophageal echocardiographic guidance. In several randomized trials and European registries the

**MitraClip**

Figure 2. Repair of the posterior leaflet of the mitral valve according to the method of Carpentier. (a) From the prolapsed part (often P2) a three- or four sided area will be excised. (b) Image of resection area after four sided (quadrangular) resection. (c) With a sliding plasty the remaining parts of the posterior valve leaflet- P1 or the left part of P2 and P3 or right part of P2- are stitched together and stitched back on the annulus. (d) The procedure will be completed by consolidating the annulus with a ring.
Figure 3. Percutaneous implantation of a MitraClip in severe symptomatic mitral regurgitation. (a) The clip is brought into the right atrium via the femoral vein and the inferior vena cava and through the septum into the left atrium. (b) In the left atrium the clip will be opened and positioned under the valve leaflets. (c-d) From this position the clip will be maneuvered to the location with the largest regurgitation. (e-f) At the position where regurgitation is reduced best, the clip will be attached permanently.
MitraClip was proved to be safe and regurgitation was effectively reduced, although this reduction was less compared to surgery. European guidelines consider this procedure possible for patients with above stated indications.

**Medical treatment**

Symptomatic patients with chronic organic MR in whom no other intervention is possible, receive medical treatment similar to heart failure patients: ACE-inhibitors, loopdiuretics, spironolactone and beta-blockers. Anticoagulants are indicated in case of a systemic embolus, thrombus in the left atrium and atrial fibrillation. In chronic functional MR, for example due to dilated cardiomyopathy, medical treatment is often the first choice treatment. In case of systolic left ventricular dysfunction, ACE-inhibitors and beta-blockers are effective, and in case of heart failure this is completed with loopdiuretics, aldosterone antagonists and nitrates. In acute, severe MR medical therapy can realize hemodynamic stabilization. Nitrates improve forward output due to reduction of the afterload and regurgitation, whereas diuretics reduce filling pressures and pulmonary resistance. In case of hypotension and signs of reduced organ perfusion, inotropes are indicated.

**Cardiac resynchronization therapy**

Many patients with heart failure have a functional MR due to dyssynchrony of the left ventricle. Sometimes dyssynchrony can recover with cardiac resynchronization therapy, when the right and left ventricle are stimulated simultaneously via the coronary sinus. This treatment may improve left ventricular function and symptoms of heart failure and can be complementary to medical therapy or valve surgery. The guidelines suggest cardiac resynchronization therapy in patients with severe functional MR, a left ventricular ejection fraction < 35% and a QRS duration > 120ms who maintain severely symptomatic despite optimal medical therapy.

**TREATMENT OPTIONS ASYMPHOMATIC MITRAL REGURGITATION**

‘Watchful waiting’ or surgery

Patients with severe organic MR and preserved left ventricular function can be asymptomatic. Opinions about the best treatment strategy for these patients vary. European guidelines prefer ‘watchful waiting’, with every 6 months a cardiac evaluation at the cardiologist and echocardiography every year to detect any potential dysfunction of the left ventricle at an early stage. ‘Watchful waiting’ seems safe and in case of dysfunction, surgery can still be performed with good post-operative results and recovery of the left ventricle afterwards. In contrast, the American guidelines suggest early valve surgery to prevent left ventricular dysfunction. The finding that 90% of the patients within 10 year of ‘watchful waiting’ have an indication for surgery.
is in favor for the American point of view.24 However, this percentage is debated: other research revealed 50%.23 Pleading also against the American point of view is the risk of complications in asymptomatic patients, although surgery has a very low mortality and morbidity rate.25,26 In case of severe functional MR, there is left ventricular dysfunction most of the time. These patients are usually not asymptomatic.

**Medical treatment**

There is no proven effective medical treatment for patients with asymptomatic chronic MR.6,27 Also vessel dilating drugs, including ACE-inhibitors, have no effect on the volume of the left ventricle or the severity of the regurgitation in these patients.6,27

**NEW DEVELOPMENTS IN DIAGNOSTICS**

In 2D-echocardiography – transthoracic or transoesophageal- there can be a discrepancy between the severity of symptoms and the observed severity of MR. In patients with many or atypical complaints, 2D-echo sometimes shows not more than mild MR, other patients are asymptomatic although echocardiography shows severe regurgitation. Often 2D-echocardiography does not supply sufficient information. Nevertheless, imaging techniques are becoming more accurate.

**3D-echocardiography**

With 3D-echocardiography, the morphology of the mitral valve and the volume and dimensions of the left atrium and left ventricle can provide very useful additional information on anatomy, severity and chronicity of the MR. Therefore it is a useful tool and it may lead to more insight into the right timing of a possible surgical procedure.6,7

**Stress echocardiography**

Stress echocardiography is of additional value when a patient has recognizable complaints during exercise, to determine the hemodynamic severity of the MR and the stress of the left and right ventricle. Also the exercise induced increase of the MR can be assessed and the left ventricular function and systolic pressure in the pulmonary artery can be measured during stress.28 Pulmonary hypertension is associated with a poor prognosis when left ventricular dysfunction is present.29

**BNP assessment**

Assessment of the brain natriuretic peptide (BNP) can provide information about the risk of left ventricular dysfunction, heart failure and mortality in asymptomatic severe MR. It may be useful in the decision making of valve surgery. It is not clear which cut-off value can be used for the indication of a surgical procedure and the prognostic value of the BNP-serum concentration on long term is unknown.30-32 Moreover, the BNP-value
can be influenced by pre-existent atrial fibrillation, hypertension and renal failure.\textsuperscript{31,32} There are no clear cut-off points for the BNP-concentration in severe, asymptomatic MR, although a BNP increase can be interpreted as a potential deterioration of the left ventricular function or the functional capacity.

New developments in treatment strategies

No prospective randomized trials have been performed to determine the best treatment strategy in asymptomatic patients with severe organic MR and preserved left ventricular function which prevents a clear opinion about this clinical challenge. Therefore a prospective randomized trial has been started in the Netherlands: the Dutch Asymptomatic Mitral Regurgitation trial (www.dutchamr.nl).\textsuperscript{33} For patients with severe functional MR and a revascularization option the optimal treatment strategy is debated: only revascularization, restrictive annuloplasty or mitral valve replacement? Also for this question randomized trials are needed.\textsuperscript{6,7}

CONCLUSION

Which treatment can be used in a patient with MR, will depend on the severity, cause and effects of MR. Echocardiography is the keystone in diagnostics and discussion in a ‘heart valve team’ is important to determine the best treatment strategy.

Appropriate treatment of symptomatic patients with severe organic MR is surgical valve repair. In an inoperable patient with severe functional MR medical treatment will be often used, possibly with cardiac resynchronization therapy. When surgery is indicated, restrictive annuloplasty can be a good option. In patients with severe MR who are considered inoperable or with high surgical risk, MitraClip implantation can be a treatment option.

Patients who are considered for one of the above mentioned interventions need to be referred to a center with verifiable expertise in the area of these treatment options. This is also true for asymptomatic patients.

REFERENCES


