Chronic ischaemic mitral regurgitation.
Current treatment results and new mechanism-based surgical approaches

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Summary

Chronic ischaemic mitral regurgitation (CIMR) remains one of the most complex and unresolved aspects in the management of ischaemic heart disease. This review provides an overview of the present knowledge about the different aspects of CIMR with an emphasis on mechanisms, current surgical treatment results and new mechanism-based surgical approaches. CIMR occurs in approximately 20–25% of patients followed up after myocardial infarction (MI) and in 50% of those with post-infarct congestive heart failure (CHF). The presence of CIMR adversely affects prognosis, increasing mortality and the risk of CHF in a graded fashion according to CIMR severity. The primary mechanism of CIMR is ischaemia-induced left ventricular (LV) remodelling with papillary muscle displacement and apical tenting of the mitral valve leaflets. CIMR is often clinically silent, and colour-Doppler echocardiography remains the most reliable diagnostic tool. The most commonly performed surgical procedure for CIMR (restrictive annuloplasty combined with coronary artery bypass grafting (CABG)) can provide good results in selected patients with minimal LV dilatation and minimal tenting. However, in general the persistence and recurrence rate (at least MR grade 3+) for restrictive annuloplasty remains high (up to 30% at 6 months postoperatively), and after a 10-year follow-up there does not appear to be a survival benefit of a combined procedure compared to CABG alone (10-year survival rate for both is approximately 50%). Patients at risk of annuloplasty failure based on preoperative echocardiographic and clinical parameters may benefit from mitral valve replacement with preservation of the subvalvular apparatus or from new alternative procedures targeting the subvalvular apparatus including the LV. These new procedures include second-order chordal cutting, papillary muscle repositioning by a variety of techniques and ventricular approaches using external ventricular restraint devices or the Coapsys device. In addition, percutaneous transvenous repair techniques are being developed. Although promising, at this point these new procedures still lack investigation in large patient cohorts with long-term follow-up. They will, however, be the subject of much anticipated and necessary ongoing and future research.

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1. Introduction

Chronic ischaemic mitral regurgitation (CIMR) remains one of the most complex and unresolved aspects in the management of ischaemic heart disease. CIMR is not only common, but it also significantly affects prognosis. CIMR occurs in approximately 20–25% of patients followed up after myocardial infarction (MI) [1–5] and in 50% of those with post-infarct congestive heart failure (CHF) [6]. In patients with CHF, even a mild degree of mitral regurgitation (MR) adversely affects survival. Increasing MR severity is associated with a progressively worse 5-year survival rate [2].

Restrictive annuloplasty, combined with coronary artery bypass grafting (CABG), is currently the most commonly performed surgical procedure to treat CIMR; however,
subvalvular and ventricular approaches are under investigation. The sobering results of the current strategies [7,8] create the need for a better understanding and preoperative assessment of mitral valve and left ventricular (LV) geometry and function. This will help to improve risk stratification and the identification of patient subgroups that are likely to benefit from different surgical strategies.

Although our knowledge about ischaemic mitral valve disease has increased dramatically over the past 15 years, a great amount of uncertainty concerning this subject remains. This review provides an overview of the present knowledge about the different aspects of CIMR with an emphasis on mechanisms, current surgical treatment results and new mechanism-based surgical approaches.

2. Definition

CIMR can be defined as MR occurring as a consequence of MI or chronic myocardial ischaemia in the absence of any inherent structural damage to the leaflets, chordae or papillary muscles (PMs) [9]. According to Borger et al., CIMR should be defined as MR occurring more than 1 week after MI, with one or more LV segmental wall motion abnormalities, significant coronary artery disease (CAD) in the territory supplying the wall motion abnormality and structurally normal leaflets and chordae [10]. Myocardial ischaemia can induce both LV remodelling and mitral annular remodelling [11,12]. As a consequence, remodelling can lead to significant changes in the geometry of the mitral valve apparatus leading to MR. Thus, CIMR is primarily caused by a disease of the LV and not by a disease of the valve itself [9,10]. CIMR is also often defined as functional MR or secondary MR (as opposed to structural, primary or organic MR), which indicates that MR occurs in the absence of any inherent structural damage to the leaflets, chordae or papillary muscles. In our opinion, functional MR is a term that should be used for non-ischaemic MR resulting from dilated cardiomyopathy. It is important to verify that the aetiology of MR is in fact ischaemic. Some patients with concomitant MR and CAD do not have ischaemic MR, but instead have a primary mitral valve condition and co-existing CAD. Ischaemic MR can also have an organic substrate in the case of papillary muscle rupture resulting from acute MI. This review, however, focusses on chronic ischaemic MR.

3. Prevalence and risk factors

The prevalence of CIMR is difficult to assess because of the heterogeneity of the MR patients presented in different studies. In addition to the impact of the modality used to identify MR, discrepancies are also related to the timing of imaging [13]. CIMR occurs in approximately 20–25% of patients followed up after MI [1–5], in 50% of patients with post-infarct CHF [6], in 11–19% of patients undergoing cardiac catheterisation for symptomatic CAD [5,14] and in 28% of patients undergoing CABG [15]. CIMR is more common after inferior MI (38%) than after anterior MI (10%) at echocardiographic follow-up after 24 months [16]. CIMR may appear up to 6 weeks after MI [17]. The delay is attributed to remodelling of the LV [17]. CIMR is a widespread problem and is likely to increase in the next few decades as survival rates for acute MI improve.

Risk factors for development of CIMR after MI include advanced age, female gender, prior acute MI, large infarct size, recurrent myocardial ischaemia, multi-vessel CAD and CHF on admission [1].

4. Impact of CIMR on prognosis

Patients with CAD and CIMR have a worse prognosis than patients with CAD and no CIMR. After analysing the left ventriculograms of 11,748 cardiac catheterisation patients, Hickey et al. revealed that 1-year mortality for severe CIMR was 40%, for moderate CIMR 17%, for mild CIMR 10% and for patients without CIMR 6% [14].

The SAVE (Survival and Ventricular Enlargement) study demonstrated that mild CIMR increases the risk of cardiovascular mortality, even in patients without CHF [4]. Patients with CIMR had a higher incidence of cardiovascular mortality (29% vs 12%, p < 0.001) and CHF (24% vs 16%, p < 0.001) than patients without CIMR at a mean of 3.5 years after MI [4]. Grigioni et al., in a case-control study, demonstrated that patients with MR detected in the chronic phase (more than 16 days) after Q-wave MI have lower 5-year survival than patients without MR (38 ± 5% vs 61 ± 6%, p < 0.001) (Fig. 1A) [2]. Mortality increases even when CIMR is mild, and there is a graded relationship between CIMR severity and mortality.
(Fig. 1B) independent of LV function [2]. Grigioni et al., more recently, showed that CIMR is independently related to a 3.6-fold increase in the risk of CHF in patients with no or minimal symptoms [15]. These studies may differ in design, setting and technique, but they consistently indicate that CIMR has an adverse prognosis with increased risk of death and CHF.

5. Mechanisms

CIMR is a complex and multifactorial disease, which starts primarily in the LV wall and leads to secondary valvular changes. The main pathophysiological mechanisms include ischaemia-induced LV remodelling with papillary muscle (PM) displacement and leaflet tethering, a reduced leaflet closing force, PM dysfunction and dyssynchrony and annular enlargement.

5.1. Leaflet tethering

Systolic tethering of mitral leaflets secondary to LV dilatation is the main causative mechanism of CIMR (Carpentier type IIIb; restricted leaflet motion during systole) [19–21]. It provides a mechanistic and geometric explanation of CIMR.

MI leads to LV remodelling. In this process the LV becomes less elliptical and more spherical [11]. This causes apical and lateral displacement of the papillary muscles and tethering of the leaflets [11]. Restricted systolic leaflet motion displaces the coaptation point apically relative to the annular plane, which results in mitral valve tenting and 'incomplete mitral leaflet closure' (Fig. 2) [11].

Mitral valve chordae can be divided in primary and secondary chordae. Secondary chordae are the most responsible chordae for leaflet restriction in CIMR, but are not required to prevent leaflet prolapse. Apical tenting of the mitral valve leaflets is regionally augmented in the middle portion of the anterior leaflet with basal (second-order) chordal insertion, which produces a typical anterior leaflet concavity or anterior leaflet bend (the so-called 'seagull sign' or 'hockey stick configuration') (Fig. 2B) [22].

The systolic position of the leaflets is determined by two opposing forces. Transmitial pressure force (or closing force) pushes the leaflets towards the left atrium, while tethering force of the chordae pulls the leaflets towards the PMs [12,23]. Apical displacement of the leaflets results from a greater tethering force, caused by a reduced closing force and/or an increased tethering force [12,23]. Displacement of the PMs directly increases tethering force [12,23]. The position of the anterior annulus is fixed at the aortic root. Therefore, the distance between the anterior annulus and the PM tips can be used as a measure of PM displacement [12]. These distances can be measured in the apical two- and four-chamber views during routine two-dimensional transthoracic echocardiography [24].

PM tethering is not always proportional to LV dilatation. In anterocephal MI, there may be significant global LV remodelling without outward PM displacement and without MR [25]. In inferoposterior MI, however, there may be less global LV remodelling, but more local LV remodelling with significant PM displacement and significant MR [16,25]. Thus, CIMR is proportional to the outward displacement of the PMs rather than to global LV dilatation [23]. Consequently, two types of leaflet tethering occur in CIMR. Symmetric tethering results from global LV remodelling with apical displacement of both PMs [26]. This generally produces a central MR jet. Asymmetric tethering results from regional LV remodelling with displacement of the posteromedian PM and systolic posterior leaflet restriction [26]. This generally produces an eccentric MR jet directed towards the posterior left atrial wall. However, it is controversial whether asymmetric PM displacement leads to asymmetric tethering. Approximately symmetric leaflet tethering can occur in inferior MI with potential asymmetric PM displacement [27].

5.2. The additional influence of closing force

Reduced closing force due to LV dysfunction can increase CIMR in the presence of increased tethering force due to PM displacement [12,20]. LV dysfunction without LV dilatation and mitral valve tethering fails to produce significant MR [12,28]. Interestingly, Schwammenthal et al. showed that the severity of CIMR dynamically changes within a cardiac cycle, with the severity maximal in early and late systole and minimal in mid-systole with maximal LV pressure (also known as the 'loitering pattern') [29].

5.3. Papillary muscle dysfunction

PM dysfunction (syndrome) was first described as the main cause of CIMR [30,31]; however, this could not be confirmed [20]. In the leaflet tethering theory, the effect of PM dysfunction can be twofold. LV remodelling in the wall close to the PM may result in increased tethering [32]. In this case, PM dysfunction increases tethering [32]. On the other hand, when LV remodelling occurs in the wall close to the PM and
extends to include the PM, PM dysfunction may decrease longitudinal PM shortening and tethering [32, 33]. This may even cause leaflet prolapse [34]. In addition, PM dysynchrony can potentially worsen CIMR [35, 36].

5.4. Annular dilatation

Much debate remains about the exact contribution of annular dilatation (Carpentier type I dysfunction) to CIMR. Although annular dilatation is often associated with LV dilatation in CIMR, it is at this point unclear whether annular dilatation is a major determinant of CIMR in the absence of leaflet tethering due to LV dilatation. Annular dilatation as an isolated lesion is suggested to be insufficient to cause significant MR [37]. Annular dilatation may, however, as a modulating factor, influence CIMR in the presence of leaflet tethering [12].

In addition, flattening of the physiological annular saddle shape in dilated ventricles can lead to increased tethering and development of CIMR [38, 39]. A reduced systolic contraction of the annulus can also contribute to the development of CIMR [24].

5.5. CIMR as a dynamic lesion

CIMR is a dynamic lesion and, depending on the haemodynamic conditions, its severity may vary over time [40]. Anaesthetic induction and inotropic agents change the loading conditions and can substantially reduce CIMR, confounding intra-operative assessment of CIMR and intra-operative decisions regarding repair [41]. CIMR also responds dynamically to exercise [42].

5.6. Haemodynamic consequences of CIMR

The increase in preload caused by CIMR after MI is not accompanied by a parallel increase in contractility [43]. The chronic volume overload in a ventricle that has decreased compliance causes an increase in wall stress and left atrial (LA), ventricular end-diastolic and wedge pressures. The left atrium (LA) and ventricle enlarge, resulting in pulmonary hypertension and congestion, leading ultimately to heart failure and death [44, 45]. Ventricular dilatation increases tethering, which worsens MR severity, creating a cycle whereby MR begets MR in a self-perpetuating manner [46].

6. Diagnosis

6.1. Clinical examination

Patients with CIMR are often asymptomatic. Symptoms are mainly related to the underlying LV dysfunction and may include dyspnoea, fatigue and a reduced exercise tolerance. CIMR is often unrecognised clinically and its severity is often underestimated [13]. A murmur is heard only in a small percentage of patients, estimates ranging from 4% to 50% [4, 5, 47]. Compared to structural MR, CIMR produces a softer murmur and its intensity correlates poorly with the actual degree of MR due to decreased LV systolic function and LA compliance [48]. To conclude, cardiac auscultation is not a reliable tool to diagnose CIMR or to assess its severity.

6.2. Echocardiography

CIMR can be reliably diagnosed with colour-Doppler echocardiography. Two-dimensional trans-thoracic echocardiography (TTE) and trans-oesophageal echocardiography (TEE) are the preferred diagnostic imaging tools. Echocardiography provides accurate information about LV dimensions and function, regional wall motion abnormalities, MR aetiology, MR severity and mitral valve geometry, including annular dilatation and mitral valve tenting.

An important issue is the optimal timing for imaging after MI. At this point there are no data that suggest the optimal timing. This will require further research.

6.2.1. MR severity

Measurement of the regurgitant colour jet area has been widely used as a semi-quantitative method to assess the degree of CIMR (Fig. 3A) [49]. However, measurement of the colour jet area can lead to a misquantification of MR severity when an eccentric jet is present in CIMR [50, 51]. In addition, the vena contracta, defined as the smallest width of the colour jet that occurs at or just downstream from the regurgitant orifice [52], is a semi-quantitative method to assess CIMR severity (Fig. 3B) [53, 54]. A particular strength of the vena contracta is that it works equally well for central and eccentric jets [52]. However, colour-Doppler measurement of the vena contracta is significantly affected by flow rate and can overestimate the true regurgitant orifice [55]. Accurate quantification of CIMR severity can be achieved by measuring the effective regurgitant orifice area (ERO) and the regurgitant volume (RV) using the PISA method (proximal isovelocity surface area) (Fig. 3C) [52, 56]. The RV depends on the haemodynamic conditions and loading, whereas the ERO does not [52]. Current echocardiography guidelines recommend the following criteria to define severe MR: an ERO >40 mm², a RV ≥60 ml and a vena contracta width ≥7 mm [52]. However, for CIMR, adverse outcomes are associated with lower values, suggesting the following criteria to define severe CIMR: an ERO >20 mm², a RV ≥30 ml and a vena contracta width ≥4 mm [2, 52].

6.2.2. Mitral valve geometry

A method to assess annular dilatation and mitral valve tethering severity in CIMR during routine two-dimensional TTE is presented in Fig. 3D–F. As shown in Fig. 3D–F, several parameters can be measured to evaluate the severity and pattern of mitral valve tethering. Tenting area (TA) (the area between the tented leaflets and the annular plane in systole) and tenting height (TH) (distance between the point of leaflet coaptation and the mitral annular plane in systole) show a strong and positive correlation with the ERO [24].

Apart from providing additional information on tethering severity and pattern, measurement of parameters such as TA, TH, posterior and anterior leaflet tethering angles (PTA and ATA) and interpapillary muscle distance (IPMD) has been shown to provide prognostic information about the surgical treatment results of CIMR (Table 1) [57–60].
### Table 1
Independent preoperative echocardiographic predictors of restrictive mitral annuloplasty failure.

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>View</th>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trans-thoracic echocardiography (TTE)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Tenting area (TA)</td>
<td>AP4CH</td>
<td>≥2.5 cm²</td>
<td>64</td>
<td>95</td>
<td>[57]</td>
</tr>
<tr>
<td>Tenting height (TH)</td>
<td>AP4CH</td>
<td>≥10 mm</td>
<td>64</td>
<td>90</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>PLAX</td>
<td>≥11 mm</td>
<td>81</td>
<td>84</td>
<td>[59]</td>
</tr>
<tr>
<td>Posterior tethering angle (PTA)</td>
<td>AP4CH</td>
<td>≥45°</td>
<td>100</td>
<td>95</td>
<td>[57]</td>
</tr>
<tr>
<td>Anterior tethering angle (ATA)</td>
<td>PLAX</td>
<td>≥39.5°</td>
<td>98</td>
<td>97</td>
<td>[59]</td>
</tr>
<tr>
<td>Anterior/posterior tethering angle ratio (APTAR)</td>
<td>PLAX</td>
<td>0.76</td>
<td>87</td>
<td>86</td>
<td>[59]</td>
</tr>
<tr>
<td>MR jet direction</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>[110]</td>
</tr>
<tr>
<td>Interpapillary muscle distance (IPMD)</td>
<td>PSAX</td>
<td>&gt;20 mm</td>
<td>96</td>
<td>97</td>
<td>[60]</td>
</tr>
<tr>
<td>Left ventricular end-systolic volume (LVESV)</td>
<td>—</td>
<td>≥145 ml</td>
<td>90</td>
<td>90</td>
<td>[122]</td>
</tr>
<tr>
<td>Systolic sphericity index (SSI)</td>
<td>—</td>
<td>≥0.7</td>
<td>100</td>
<td>100</td>
<td>[122]</td>
</tr>
<tr>
<td>Myocardial performance index (MPI)</td>
<td>—</td>
<td>≥0.9</td>
<td>85</td>
<td>84</td>
<td>[122]</td>
</tr>
<tr>
<td>Wall motion score index (WMSI)</td>
<td>—</td>
<td>≥1.5</td>
<td>80</td>
<td>82</td>
<td>[122]</td>
</tr>
<tr>
<td>Diastolic LV function</td>
<td>—</td>
<td>Restrictive filling</td>
<td>—</td>
<td>—</td>
<td>[123]</td>
</tr>
<tr>
<td><strong>Trans-oesophageal echocardiography (TEE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral annular diameter (AD)</td>
<td>4CH</td>
<td>≥37 mm</td>
<td>84</td>
<td>76</td>
<td>[124]</td>
</tr>
<tr>
<td>Tenting area (TA)</td>
<td>LAX</td>
<td>≥1.6 cm²</td>
<td>80</td>
<td>54</td>
<td>[124]</td>
</tr>
<tr>
<td>MR grade</td>
<td>—</td>
<td>≥3.5</td>
<td>42</td>
<td>81</td>
<td>[124]</td>
</tr>
</tbody>
</table>


* Defined as postoperative persistence or recurrence (within 1-5 years) of grade ≥2+ CIMR.

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**Fig. 3.** Two-dimensional TTE assessment of CIMR severity (A–C) and mitral valve tethering (D–F). (A) Apical four-chamber view: severe ischaemic mitral regurgitation as determined by jet surface area (9.5 cm²) divided by the left atrial surface area (25.2 cm²) (38%). (B) Apical four-chamber view: severe ischaemic mitral regurgitation as determined by vena contracta (VC = 6 mm). (C) Apical four-chamber view: severe ischaemic mitral regurgitation as determined by proximal isovelocity surface area (PISA); effective regurgitant orifice area (ERO = 25 mm²) and regurgitant volume (RV = 65 ml). (D) Parasternal long-axis view, mid-systolic. (E) Apical four-chamber view, mid-systolic. (F) Parasternal short-axis view, end-systolic. The schematic overlays in views D–F show several important echocardiographic parameters (italic font) used in the assessment of mitral valve tethering severity. AD: annular diameter, ALPM: anterolateral papillary muscle, Ao: aorta, ATA: anterior tethering angle, ERO: effective regurgitant orifice area, IPMD: interpapillary muscle distance, LA: left atrium, LV: left ventricle, MR: mitral regurgitation, PISA: proximal isovelocity surface area, PMPM: posteromedian papillary muscle, PTA: posterior tethering angle, RV: regurgitant volume, RV: right ventricle, TA: tenting area, TH: tenting height and VC: vena contracta.
6.3. Exercise echocardiography

Semi-supine bicycle exercise echocardiography can provide additional useful information about the dynamic component of CIMR, because it may unmask higher degrees of MR [42,61]. The degree of MR at rest is unrelated to exercise-induced changes in MR [42]. Therefore, resting evaluation of CIMR may underestimate the full severity of the lesion and its impact [42]. Increased MR with exercise is associated with greater tethering at both the annular and PM ends of the leaflets [42]. Exercise echocardiography can be helpful in clinical decision making and in predicting clinical outcome [61], especially in certain patient subgroups, including (1) in patients with LV dysfunction who present exertional dyspnoea out of proportion to the severity of acute pulmonary oedema occurs without an obvious cause; (2) in patients in whom acute pulmonary oedema occurs with an obvious cause; (3) for stratifying the risk of mortality and heart failure decomposition, including (1) in patients with LV dysfunction who present exertional dyspnoea out of proportion to the severity of resting dysfunction or MR; (2) in patients in whom acute pulmonary oedema occurs without an obvious cause; (3) for stratifying the risk of mortality and heart failure decomposition in the individual patient; and (4) before surgical revascularisation in patients with moderate MR [62]. An increase in ERO \( \geq 13 \) mm\(^2\) during exercise is associated with an increased mortality and increased CHF hospital admission rate [61,63]. A decrease in ERO because of recruitable contraction of the basal LV segments is associated with a good long-term prognosis [61,63].

According to Piérard and Lancellotti, dobutamine stress testing for CIMR is not as useful, because dobutamine itself reduces preload, afterload and MR [62].

6.4. New imaging modalities

In addition to TTE and TEE, new imaging modalities for the assessment of CIMR, such as three-dimensional echocardiography and cardiac magnetic resonance imaging (CMRI), are subject of ongoing investigation [64—67]. They may provide superior-quality images and measurements compared to echocardiography [64—67]. However, their incremental value over TTE and TEE in clinical and surgical decision making remain to be determined.

7. Treatment and outcome

7.1. Non-surgical treatment

There are only a few studies that focus on the impact of medical treatment on CIMR. Medical treatment of CIMR may lead to a reduction in MR severity, and/or it may lead to attenuation or reversion of post-MI LV remodelling. Several studies suggest that angiotensin-converting enzyme inhibitors (ACEi), nitrates and diuretics can lead to a partial or long-term reduction in MR by increasing the transmural valve pressure gradient through either afterload or preload reduction [68—71]. In addition, inotropic vasopressors, such as dobutamine, can decrease CIMR [72]. As shown by the SAVED (Survival And Ventricular Enlargement) and SOLVD (Studies of Left Ventricular Dysfunction) studies, ACE inhibition can attenuate [73,74], arrest [75] or reverse [76] post-MI LV remodelling. In addition, the CAPRICOR (Carvedilol Post-Infarct Survival Controlled Evaluation) and CARMEN (Carvedilol and ACE Inhibitor Remodelling Mild Heart Failure Evaluation Trial) studies showed that the combination of ACE inhibition and \( \beta \)-blockade inhibits [77] or synergistically reverses [78] LV negative remodelling. There are, however, no data from large trials that show a decrease in the incidence of CIMR after attenuation or reversal of LV remodelling with ACE inhibition and \( \beta \)-blockade [79]. Despite the use of these drugs CIMR remains common.

Cardiac resynchronisation therapy (CRT) significantly and immediately reduces functional MR and CIMR due to improved co-ordinated timing of the PM insertion sites [35] and increased closing force [80]. Long-term CRT (up to 12 months) results in progressive structural and functional LV reverse remodelling, improved LV systolic and diastolic function and decreased MR severity in patients with moderate-to-severe heart failure and dyssynchronous ventricular contraction [81—83]. This effect is also evident during exercise, preventing the increase of MR during exercise [84]. However, approximately 30% of CHF patients treated with CRT do not respond to treatment [81,85]. Independent predictors of lack of response to CRT are ischaemic heart disease, severe MR and LV end-diastolic dimension \( \geq 75 \) mm [86]. This indicates that patients with CIMR are less likely to benefit from CRT, especially in advanced stages of LV dilatation and tenting [83].

Early reperfusion, that is, prompt thrombolysis within 3 hours after the onset of symptoms during a first (inferior) MI, may help reduce the incidence of CIMR [87,88]. Percutaneous coronary intervention (PCI) may also result in CIMR improvement, especially in the setting of acute MI [89,90]. Increasing CIMR severity at the time of PCI is associated with a significantly worse 3-year [91] and 5-year survival rate (57.5% for moderate-to-severe MR, 83.3% for mild MR and 97% for patients without MR after 5 years, \( p < 0.0001 \)) [92]. CIMR is an independent predictor of survival 5 years after PCI [92]. Despite prompt thrombolysis and PCI CIMR remains common.

7.2. Surgical treatment

7.2.1. Indications for surgery in CIMR

The indications for surgery in CIMR are not strictly defined. The general consensus is that patients who have an indication for CABG with moderate-to-severe or severe CIMR (grade 3+ or 4+) should also undergo concomitant mitral valve surgery [17,93—95].

It is controversial whether patients who have an indication for CABG with mild or moderate CIMR (grade 1+ or 2+) should also undergo concomitant mitral valve surgery. Different studies show that CIMR persists in 40—60% of patients early after CABG alone [96—98]. Multiple studies have also shown progression of CIMR after isolated CABG in patients with mild or moderate CIMR, which is associated with decreased long-term survival [96,98]. These data suggest that mitral valve surgery should be performed as a concomitant procedure at the time of CABG in patients with mild or moderate CIMR. However, subsequent retrospective studies to confirm a survival benefit of a combined procedure in mild or moderate CIMR showed conflicting evidence [99—101]. A definite advantage on survival could not be established. When choosing for a combined procedure, the risk of long-term CIMR and CHF progression must be balanced against the
increased perioperative risk of mitral valve surgery. Perioperative mortality for a combined procedure in CIMR is approximately 6–15% vs 3–5% for CABG alone [93, 94, 98, 102–104].

7.2.2. Mitral valve replacement (MVR)

Before the introduction of mitral valve annuloplasty (MVA), mitral valve replacement with a mechanical or bioprosthesis was the preferred surgical treatment for severe CIMR. It involved complete excision of the subvalvular apparatus. As a consequence, LV function deteriorated quickly, and initial mortality rates were high [105]. David et al. showed that the subvalvular apparatus can be preserved and that it results in improved preservation of LV function and improved survival [106].

Although restrictive MVA is currently the preferred treatment option in severe CIMR, we believe MVR with preservation of the subvalvular apparatus is still a good surgical alternative in severe CIMR, especially in patients with advanced tethering and a high risk of CIMR persistence or recurrence (Table 1) [93, 102]. In addition, severely ill patients who require emergency surgery and patients with a complex MR jet or a lateral wall motion abnormality should be considered for MVR [107]. In these patients with a short life expectancy a bioprosthesis may be indicated [93, 95].

7.2.3. Mitral valve annuloplasty (MVA)

Suboptimal results of MVR initiated development of MVA for CIMR. Restrictive MVA to reduce the septal—lateral mitral valve dimension combined with CABG is the most frequently used technique in the surgical treatment of severe CIMR. The concept of restrictive MVA by implanting undersized rings was introduced in 1995 by Bolling and Bach [108, 109].

7.2.3.1. CABG with or without MVA. Data showing a definite advantage of CABG and restrictive MVA over CABG alone are comparatively sparse. To date, there have been no randomised trials. Instead, propensity score matching is used as a statistical tool to help neutralise the inherent patient selection bias. Two retrospective studies using propensity score-matched cohorts recently showed that CABG and restrictive MVA are superior to CABG alone in reducing CIMR and in improving the early postoperative symptomatic status in patients with grade 3+ or 4+ CIMR [7, 8]. However, after a long-term follow-up of 10 years, there did not appear to be any difference in the functional status or survival (Fig. 4A) [7, 8].

7.2.3.2. MVA versus MVR. Although there have been no randomised trials comparing MVA to MVR for CIMR, two major retrospective studies show that both mitral valve repair (predominately MVA) and replacement are effective in eliminating CIMR immediately postoperatively [93, 94]. Although mitral valve repair (predominately MVA) is associated with a lower perioperative mortality [93, 94], high-risk patients with severe CIMR did just as well, and maybe even better, with replacement [93]. In a propensity score-matched study, Gillinov et al. showed that in the most complex, high-risk settings, 5-year survival rates for both repair (predominately MVA) and replacement did not differ significantly and were approximately 50% (Fig. 4B) [93]. The majority of patients have a lower risk profile, however, and will derive a survival benefit from mitral valve repair (predominately MVA). Reproduced with permission from Gillinov et al. Copyright 2006, Springer Science and Business Media LLC. Original copyright 2001, the American Association for Thoracic Surgery.
7.2.3.3. MVA recommendations. Annular downsizing does not relieve leaflet tethering, but it does shift the posterior annulus and leaflet anteriorly, which leads to restored coaptation [110]. Although it targets only the consequence and not the (ventricular) cause of the disease, restrictive MVA is able to improve outcomes in selected patients [111—113]. In addition, MVA is simple to perform, reproducible and effective in eliminating CIMR [111—113]. Careful downsizing is warranted, because restrictive MVA may create some degree of functional mitral stenosis [114]. Different types of annuloplasty rings can be used, including rigid versus flexible and complete versus incomplete rings. There do not appear to be definite advantages for any specific type of ring [10,110]. It has been suggested that a complete remodelling annuloplasty should be used rather than a posterior band because the anterior mitral annulus dilates as well [115] and that MVA should include a prosthetic device rather than simple suture or suture supported by pericardium [110,116]. Although both flexible and rigid annuloplasty rings provide good results in CIMR repair, there are some differences in favour of using rigid (or semi-rigid) rings, the most prominent being a more stable repair with less late failure [111,117,118]. Although a flexible ring allows for a more physiological annular area, shape and orifice area change during the cardiac cycle, a rigid or semi-rigid ring seems to provide better support of the posterior mitral annulus over time in CIMR with ongoing LV wall changes, which lowers the rate of CIMR recurrence [117,118].

7.2.3.4. Persistence and recurrence of CIMR after restrictive MVA. Different studies report a high rate of persistent and recurrent CIMR after restrictive MVA. In the early postoperative phase (<6 months), 15—30% of patients experience return of CIMR, which is grade 3+ or 4+ (Fig. 5) [110,119,120]. On the other hand, 70—85% of patients receive durable repair using current techniques. However, according to some investigators, the prevalence of CIMR grade 3+ or 4+ can increase up to 70% after 5 years [119].

Because restrictive MVA does not address tethering, advanced tethering may result in persistent or recurrent CIMR [110,119]. Restrictive MVA displaces the posterior annulus anteriorly and can lead to a significant increase in the posterior leaflet angle. Consequently, augmented asymmetric tethering with predominant posterior leaflet tethering occurs. This phenomenon is associated with persistent or recurrent CIMR after surgery [51,58,121]. In addition, even mild residual CIMR contributes to continued LV negative remodelling and increased tethering, leading to a vicious circle whereby MR begets more MR [119]. The presence of persistent or recurrent CIMR results in a significantly lower 3-year event-free survival (26 ± 20%) compared to non-persistent CIMR (75 ± 12%, p = 0.01) [57].

The suboptimal results of restrictive MVA for CIMR have led different investigators to identify preoperative echocardiographic predictors of restrictive MVA failure (defined as persistent or recurrent grade ≥2+ CIMR) (Table 1).

Interestingly, Bax and Braun et al. showed that stringent use of rigid or semi-rigid, complete annuloplasty rings that are one to two sizes smaller than the measured inter-trigonal length provide excellent freedom from CIMR recurrence up to 2 years [111]. They also demonstrated that preoperative LV dimensions predict LV reverse remodelling [112], which is unlikely if preoperative LV end-diastolic diameter exceeds 65 mm and/or end-systolic diameter exceeds 51 mm [112].

To conclude, restrictive MVA and CABG can provide good results in selected patients with minimal LV dilatation and minimal tenting. However, in general the persistence and recurrence rate for restrictive MVA remains high, and there does not appear to be a survival benefit of a combined procedure after a 10-year follow-up compared to CABG alone. Patients at risk of MVA failure based on preoperative echocardiographic and clinical parameters may benefit from mitral valve replacement with preservation of the subvalvular apparatus or from new alternative procedures targeting the subvalvular apparatus including the LV.

7.2.4. Evolving annular and valvular surgical techniques 7.2.4.1. Geometrically shaped annuloplasty rings. New annuloplasty rings are geometrically shaped to address the specific needs of patients with CIMR.

The GeoForm ring (Edwards Lifesciences, Irvine, CA, USA) was specifically designed to treat ischaemic and functional MR. It’s unique 3D shape pulls the PMs together by a geometric reshaping of the mitral annulus [125]. The initial results in five patients with CIMR and in five patients with functional MR were promising and showed a reduction of MR grade 3.5 ± 0.3 to 0.1 ± 0.1 (p < 0.05) 3 months after surgery, with significant tenting area reduction and LV reverse remodelling (Table 2) [125].

CIMR is associated with asymmetric changes in annular and ventricular geometry [126]. The new asymmetrical Carpentier—McCarthy—Adams (CMA) IMR ETlogix annuloplasty ring (Edwards Lifesciences, Irvine, CA, USA) is the first remodelling ring specifically designed to treat asymmetric leaflet tethering and annular dilatation [127]. The initial early results in a series of 59 patients with grade ≥2+ CIMR and relatively mild tenting were promising (Table 2). A total of 57 patients had grade ≤1+ CIMR early after surgery with a significant reduction in mean annular diameter, TA and TH [127].
It has become clear that the mitral valve annulus has a physiological saddle shape [128,129], which reduces force distribution on the annulus, leaflets and chordae [130–133]. Annuloplasty ring shape appears to affect leaflet curvature [132]. Increased leaflet curvature has been shown to reduce leaflet strain [130–133]. An improved stress distribution on the annulus, leaflets and chordae may ultimately improve repair durability. The St. Jude Medical rigid saddle ring (St. Jude Medical Inc., St. Paul, MN, USA) showed promising early results in patients with CIMR [134]. Preoperative grade ≥2+ MR was reduced to grade ≤1+ MR 3 months after surgery (Table 2) [134]. Saddle-shaped ring annuloplasty is now undergoing clinical trials in a series of 150 patients.

7.2.4.3. **Anterior leaflet augmentation.** Kincaid et al. introduced the technique of anterior leaflet augmentation to address the tethered leaflets in CIMR [138]. The technique consists of pericardial patch enlargement of the anterior mitral leaflet combined with a flexible annuloplasty band and CABG. This technique was used in 25 patients with grade ≥3+ CIMR. At 2 years actuarial freedom from grade ≥3+ CIMR was 81% (Table 2) [138]. Patch enlargement of the restricted posterior mitral leaflet has been described by Dobre et al. in only two patients [139].
7.2.4.4. Percutaneous annuloplasty and edge-to-edge repair. Percutaneous transvenous mitral annuloplasty (PTMA) (Viacor Inc., Wilmington, MS, USA) has recently been described in large animal models [140,141]. PTMA is based on the close proximity of the coronary sinus to the posterior mitral annulus. PTMA involves delivery of an annuloplasty device into the coronary sinus to shrink the mitral annulus. Initial experience with PTMA in five patients showed that the procedure is feasible and may reduce CIMR (Table 2) [142]. Percutaneous annuloplasty offers the advantage of avoiding an operation, but carries potential risks including coronary sinus perforation or thrombosis or injury to the adjacent circumflex coronary artery [143]. Lack of a fibrous connection between the coronary sinus and the mitral annulus may compromise the effectiveness and durability of the procedure [144,145].

Alferi edge-to-edge repair has been applied percutaneously with a newly designed clip device (MitraClip; Evalve Inc., Menlo Park, CA, USA) in a large porcine model [146] and is now undergoing clinical trials in patients [147]. Initial results from the phase I clinical trial with the MitraClip (EVEREST I) have demonstrated the safety and feasibility of the device in 55 patients [147]. However, only one patient had CIMR (Table 2). Because this procedure does not involve MVA, recurrence rates may be high [136].

Both percutaneous procedures were not specifically designed to treat CIMR and did not address tethering, which may also compromise durability.

8. New and evolving mechanism-based subvalvular and ventricular surgical techniques

The relatively high CIMR recurrence rate of restrictive MVA has led to the development of new alternative surgical procedures targeting the subvalvular apparatus including the LV. The objective is to tailor the ideal combination of annular, valvular, chordal, PM and ventricular approaches based on preoperative clinical and echocardiographic characteristics to achieve the best result in each patient. This will lead to a ‘continuum of therapies’ that can be customised to the individual patient’s needs [79]. An overview of selected new and evolving subvalvular and ventricular surgical repair techniques for CIMR is presented in Table 2. These new strategies designed to improve repair durability at this point still lack large patient cohorts and long-term follow-up, but will be the subject of future research.

8.1. Second-order chordal cutting

Messas et al. proposed to reduce leaflet tethering by cutting critically positioned second-order chordae tendineae, initially those attached to the anterior leaflet (Fig. 6A) [148,149].

In animal models of CIMR, this approach eliminated MR by restoration of the convex configuration and improved leaflet coaptation, without leaflet prolapse or a decline in LV ejection fraction [148,149]. Consequently, chordal cutting in combination with MVA has also been successfully applied to 43 clinical patients, and, when compared to MVA alone, this leads to improved coaptation and a reduction in the prevalence of recurrent CIMR (prevalence of grade ≥2+ CIMR 2 years after chordal cutting and MVA is 15% vs 37% for MVA alone, p = 0.03) (Table 2) [150]. Although concern has been raised regarding the effect of chordal cutting on regional and global LV function [151], both Messas and Borger showed that chordal cutting did not adversely affect LV function [150,152].

8.2. Surgical relocation of the posteromedian PM

Kron et al. described a new technique to treat CIMR with severe restriction of the P3 segment of the posterior mitral valve leaflet [153]. In addition to implanting an annuloplasty ring, a suture is used to connect the posteromedian PM to the mitral annulus, adjacent to the right fibrous trigone [153]. Subsequently, the suture can be shortened to decrease tethering and improve coaptation. In 18 patients with grade 2+ or 3+ CIMR, this procedure reduced CIMR to grade 0 2 months postoperatively (Table 2) [153].

Based on this ‘ring and string technique’, Langer and Schäfers introduced a valuable variation on this concept (‘the transventricular suture technique’) [154]. After a horizontal aortotomy, a suture is anchored to the head of the posteromedian PM. The suture is then passed through the fibrosa (mid-septal annular saddle horn) under direct vision and exteriorised through the aortic wall underneath the commissure between the non-coronary and left coronary aortic cusps. Subsequently, the suture is tied under echocardiographic guidance in the loaded beating heart to reposition the posteromedian PM. This technique, combined with MVA and CABG, effectively reduced grade ≥3+ CIMR to grade ≤1+ CIMR at a mean follow-up of 12 months (Table 2) [154].

8.3. Papillary muscle sling

Hvass et al. introduced another new experimental approach to treat CIMR [155]. It involves correcting abnormal PM displacement with an intraventricular Gore-Tex sling, encircling the trabecular base of both PMs. In addition, a moderately undersized mitral annuloplasty ring is inserted. In 10 patients, this ‘double ring’ or ‘ring and sling’ approach re-established a more normal annular-to-PM alignment and reduced grade 2+ or 3+ CIMR to grade 0 (nine patients) or grade 1 CIMR (one patient) (Table 2) [155].

8.4. Papillary muscle approximation

PM approximation was introduced by Rama et al. and involves repositioning of both PMs to the midline as a supplementary procedure to MVA and CABG [156]. A single U-shaped stitch reinforced by two patches of autologous pericardium is passed through both PMs and tightened (Fig. 6B). In eight patients with grade 2+ or 3+ CIMR, this procedure reduced CIMR to grade ≤1+ at a mean follow-up of 11.4 months (Table 2) [156].

8.5. PM repositioning by infarct plication

Plication of the infarcted region of the LV with mattress sutures reduces myocardial bulging and can result in
repositioning of the displaced PM tips towards the anterior mitral annulus with additional LV reverse remodelling in sheep (Fig. 6C) [157]. This procedure was effective in reducing moderate CIMR to mild or trace CIMR, without changing LV ejection fraction and with the additional advantage of preventing opening of the left side of the heart [157]. Recently, infarct plication for CIMR was described in humans [158]. CABG without MVA was combined with infarct plication of the posterolateral infarcted myocardial region in three patients with grade 3+ CIMR. After a mean follow-up of 7 months, all three patients had grade 0 CIMR (Table 2) [158].

8.6. PM repositioning and LV restoration

The Dor procedure (endoventricular circular patch plasty repair through a left ventriculotomy) is a surgical technique that was first developed to exclude LV aneurysms [159]. Subsequently, it is now also used for excluding the dilated dys- or akinetic area of the LV in severe dilated ischaemic cardiomyopathy. Placing an endoventricular patch restores LV wall geometry. In addition to improving LV ejection fraction, the Dor procedure can reduce MR in dilated ischaemic cardiomyopathy by reducing LV size and improving PM orientation [160,161]. However, tethering and CIMR may recur [162].

Menicanti et al. used a combined procedure of CABG, Dor’s excision and patching, and imbrication of the PMS without annuloplasty [163]. In 46 patients with grade ≥2+ CIMR, this combined approach was effective in reducing CIMR to grade ≤2+ immediately postoperatively in 38 patients (seven patients died during or immediately after surgery) (Table 2) [163]. Ventricular restoration and CABG can also be combined with MVA, by performing mitral valve repair through the left ventriculotomy [164]. In 108 patients with CIMR grade 2.9 ± 1.2, this combined approach reduced CIMR to grade 0.7 ± 0.7 (p = 0.0001) immediately postoperatively in 90 patients (18 patients died during or immediately after surgery) (Table 2) [164].

8.7. External ventricular restraint devices

Hung et al. have devised a localised patch that contains an epicardial balloon, and which is applied over inferior infarcts in the beating heart [165]. The patch is also positioned over the area of insertion of the PM, and the volume of the balloon
is adjusted under echocardiographic guidance to optimise the reduction of tethering and CIMR. Initial results are promising. In 10 sheep with CIMR, this approach effectively reduced MR (Table 2) without any constriction or negative side effects on left ventricular end-diastolic pressure or LV function [165].

Moanie et al. used a Marlex mesh patch to restrain infarct expansion after posterolateral MI in six sheep. This attenuated remodelling and reduced CIMR [166]. However, patch placement occurred before MI.

The Corcap Cardiac Support Device (CSD; Acorn Cardiovascular Inc., St. Paul, MN, USA) has a long-term beneficial impact on LV reverse remodelling in patients with CHF [167] and has been shown to provide an additional improvement in LV structure and function compared to mitral valve surgery alone for ischaemic and functional MR in humans [168]. This combined approach may ultimately improve repair durability.

8.8. The Coapsys device

The Coapsys device (Myocor Inc., Maple Grove, MN, USA) was designed to treat mitral annular dilatation and PM displacement (Fig. 6D) [169,170]. It has the advantage that it can be placed on a beating heart without cardiopulmonary bypass.

Grossi et al. compared restrictive MVA to implantation of the Coapsys device [171]. Both techniques were effective in reducing mitral annular diameter and CIMR [171]. However, the Coapsys device provided significantly greater LV reshaping than annuloplasty [171]. One-year follow-up of the first 11 patients with a Coapsys device and off-pump CABG showed effective CIMR and NYHA (New York Heart Association) class improvement [172]. Preoperative CIMR grade 2.9 ± 0.5 was reduced to CIMR grade 1.1 ± 0.8 at 1-year follow-up (p < 0.05) (Table 2) [172]. Recently, a novel trans-catheter system was developed for percutaneous implantation of the so-called iCoapsys device (Myocor Inc., Maple Grove, MN, USA) in animals [173].

9. Conclusion

The primary mechanism of CIMR is ischaemia-induced LV remodelling with PM displacement and apical tenting of the mitral valve leaflets. Restrictive MVA combined with CABG can provide good results in selected patients with minimal LV dilatation and minimal tenting. However, in general the persistence and recurrence rate for restrictive MVA remains high (up to 30% at 6 months postoperatively), and there does not appear to be a survival benefit of a combined procedure after a 10-year follow-up compared to CABG alone (10-year survival rate for both is approximately 50%). Patients at risk of MVA failure based on preoperative echocardiographic and clinical parameters may benefit from mitral valve replacement with preservation of the subvalvular apparatus or from new alternative procedures targeting the subvalvular apparatus including the LV. Although promising, studies concerning these new techniques at this point still lack large patient cohorts and long-term follow-up. Subvalvular and ventricular approaches will, however, be the subject of much anticipated and necessary ongoing and future research.

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References


