Mitral Regurgitation (MR)

Background

1. Definition
    - Disorder in which mitral valve allows excessive return flow from the left ventricle (LV) to left atrium (LA).
    - Important distinctions:
        - Classification by cause
            - "Organic" MR: primary abnormalities in the mitral valve leaflets, annulus, or tensor apparatus. The majority of clinical data on MR management is based on organic MR.
            - "Functional" MR: secondary to LV dilatation, damage, or remodeling.
            - "Ischemic" MR: functional MR secondary to ischemic cardiomyopathy.
        - Classification by acuity
            - Acute MR
                - caused by rupture of chordae tendinae or papillary muscles, or by infective endocarditis.
                - severe surgical emergency requiring stabilization and hospitalization without delay.[1]
            - Chronic MR
                - many etiologies
                - time course of years to decades
                - may or may not ultimately necessitate surgical intervention
                - for prognostication, Chronic MR is classified as mild, moderate, or severe based on a combined clinical and ultrasound assessment.
2. General Information
    - 70% of normal population will have "physiologic" mitral regurgitation, i.e. detectable on transthoracic Doppler but not meeting criteria for even mild disease.
    - Second most common valvular pathology, behind aortic stenosis, and the most common valvular insufficiency.[2]

Pathophysiology

1. Pathology of disease
    - Chronic regurgitation of blood through the mitral valve causes LV overload.
    - LV overload initially causes compensatory remodeling and increased contractility maintaining cardiac output.
    - LA enlarges and becomes increasingly compliant in response to increased volume load, minimizing pressure in the pulmonary vasculature.
        - Causes LA dilatation, increasing risk of atrial fibrillation.
    - Over time, LV contractile dysfunction may develop, leading to decompensated MR, left-sided systolic heart failure, and pulmonary hypertension.
    - Acute MR may deteriorate rapidly.

- Chronic MR may be asymptomatic for many years with slower, progressive decompensation.
- Patients not necessarily symptomatic during the transition from compensated to decompensated MR.

2. Prevalence
   - In the Framingham Heart Study, mild MR had a prevalence of 19%
   - A 2006 Lancet analysis estimated the following prevalence for moderate to severe MR in US populations, by age:[3]
     - 18-44: 0.5% (0.3-0.8)
     - 45-54: 0.1% (0-0.8)
     - 55-64: 1.0% (0.5-1.8)
     - 65-74: 6.4% (5.7-7.3)
     - 75+: 9.3% (8.1-10.9)
     - Overall: 1.7% (1.5-1.9)
3. Risk factors
   - Age
   - Mitral Valve Prolapse: #1 risk factor for MR in developed world.
   - Rheumatic Fever: #1 risk factor worldwide.
   - History of disease associated with:
     - Abnormal leaflets
       - Rheumatic Fever
       - Mitral Valve Prolapse (MVP)
       - Infectious endocarditis
       - Libman-Sacks endocarditis, seen in Lupus and in the antiphospholipid syndrome.
       - Congenital unicuspid valve.
       - Endocardial cusion defect.
     - Abnormal or dilated annulus
       - Dilated or hypertrophic cardiomyopathy.
       - Calcification of annulus.
       - LV aneurysm.
     - Abnormal tensor apparatus
       - MI or ischemic cardiomyopathy
       - Traumatic rupture of papillary muscle or chordae tendinae.
     - Multifactorial or rare risk factors:
       - Complex congenital cardiac malformations
       - Acute myocarditis
       - Collagen vascular diseases
       - Myxoma or other intracardiac mass lesion
       - Vasculitis, esp. Takayasu's arteritis and Kawasaki's disease
       - Tertiary syphilis
       - Scleroderma and systemic fibrosis
       - Acromegaly
   - The ergot derivative dopamine agonists *pergolide* and *cabergoline* when used in high doses[4,5]

4. Morbidity/ mortality
    - Mild to moderate MR: no increased morbidity/mortality
    - Severe mitral regurgitation associated with progressive deterioration and increased morbidity/mortality.
        - 5 year mortality of 22%, 5 year cardiac morbidity/mortality of 33%.[1]
        - In MR secondary to MVP, 90% of initially asymptomatic patients die or receive surgical intervention within 10 years.[2]
        - Annual cardiac event rate up to 10-11%[6]
    - Increased risk of sudden cardiac death, up to 0.8% annually.[8]

Diagnostics

1. History and Symptoms
    - Acute MR
        - Recent MI, especially within the past 5 days.
        - Recent major chest trauma
        - Endocarditis risk, plus recent dental/GU/GI surgery or other potential bacteremia
        - IV drug use
        - Chest pain
        - Sudden onset of severe pulmonary edema symptoms (Sx)
            - Dyspnea/orthopnea, SOB, cough, foamy sputum
        - New, severe systolic heart failure symptoms
            - Fatigue, weakness, extreme exercise intolerance, shock
    - Chronic MR
        - Diseases associated with MR [See section: Risk Factors]
        - Often asymptomatic until advanced.
        - Presence of symptoms suggests decompensation.
            - Palpitations or irregular heartbeat, secondary to AFib
            - Chronic pulmonary edema Sx
                - Gradually increasing dypnea/orthopnea, SOB, foamy sputum
            - Chronic left heart failure Sx
                - Decreased exercise tolerance, peripheral edema, paroxysmal nocturnal dyspnea.
2. Physical Exam
    - Acute
        - Symptoms out of proportion to exam findings.
        - Murmur possibly absent or uncharacteristic.
        - Third heart sound and/or early diastolic rumble.[1]
    - Chronic
        - Characteristic murmur[7]
            - Holosystolic, “blowing” in character
            - Loudest over the apex and possibly radiating to the axilla, upper sternal borders, or subscapular region.
            - Louder with fist clench or squat.
            - Transiently quieter with valsalva.

- Murmur intensity of less than III/VI accurately predicts mild or moderate disease; murmur intensity of greater than III/VI accurately predicts severe disease; murmur intensity of III/VI is ambiguous.[8] (SOR:B)
- Soft first heart sound, widely split second heart sound.
- Third heart sound in severe disease.
- Prominent apical impulse
- Irregularly irregular heartbeat of atrial fibrillation
- In decompensated, severe disease, signs consistent with left-sided heart failure
  - Bilateral lung crackles or rales at the bases.
  - Lower extremity pitting edema.

3. Diagnostic Tests
   - Acute
     - All testing to be done at hospital capable of emergent open-heart surgery.
     - Diagnostic Imaging
       - Transthoracic echo (TTE) may underestimate severity in acute MR; hyperdynamic LV with acute heart failure is characteristic. [1,2]
       - Transesophageal echo (TEE) more accurate and is advised prior to surgery.[1]
   - Chronic
     - Diagnostic Imaging
       - TTE: initial modality of choice to diagnose and evaluate suspected MR. (American College of Cardiology (ACC) and American Heart Association (AHA), and European Society of Cardiology (ESC)[1,2]
         - Assess RV, LA, and LV size, LV function, pulmonary artery pressure, and severity of MR.
         - Determine the mechanism of the MR. [1,2]
       - TEE: appropriate if and only if unable to determine severity, mechanism, or LV function with TTE [1]
       - Chest X-ray: useful if decompensation and pulmonary congestion is suspected. [1]
     - Laboratory evaluation
       - Laboratory testing may be undertaken to identify cause of MR
         - Cardiac enzymes in the setting of suspected ischemia
         - Autoantibodies if a rheumatological cause is suspected
         - Blood cultures for endocarditis
       - Brain Natriuretic Peptide (BNP) is a biomarker of emerging significance.
         - Several studies demonstrate that high BNP (>105 pg/ml) independently predicts clinically significant increased morbidity/mortality in asymptomatic patients with chronic severe MR.[8,9,10]
         - Measurement of BNP may be considered if other workup fails to recommend definitively for or against surgery.
     - Other studies recommended by ACC/AHA practice guidelines:

- ECG to establish presence or absence of sinus rhythm. [1]
- Stress Echo to establish a baseline exercise tolerance, and unmask signs and symptoms of severe disease. [1]
- Cardiac catheterization if both TTE and TEE fail to identify severity, mechanism, and LV function. [1]

4. Diagnostic criteria
    - Acute:
        - No formal criteria for acute MR exist
        - Ultrasound imaging and cardiac catheterization will be used to define the lesion in preparation for emergency surgery.
    - Chronic
        - Diagnosis and grading of chronic MR is based on comprehensive analysis of qualitative and quantitative transthoracic ultrasound findings, correlated with clinical findings.
            - Quantitative criteria recommended by the ACC/AHA and the American Society of Echocardiography[11,12]:
                - Mild: regurgitant flow (RF) less than 30%, regurgitant volume (RVol) less than 30 ml/beat, and estimated regurgitant orifice (ERO) $<0.2 cm^2$
                - Moderate: RF 30-50%, RVol 31-59 ml, or ERO 0.2 to 0.39 cm^2
                - Severe: RF >50%, RVol >59 ml, or ERO > 0.39 cm^2
    - Severe MR should prompt assessment for signs of MR with LV contractile dysfunction:
        - End systolic LV diameter (ESD) >40 mm
        - Ejection fraction (EF) <60%
        - Pulmonary arterial pressure >50 mmHg at rest or >60 mmHg during exercise
        - Carries worse prognosis than Severe MR alone.

Differential Diagnosis

1. Holosystolic murmur
    - Tricuspid regurgitation
        - Murmur augmented by inhalation, MR murmur is not
    - Ventricular Septal Defect (VSD)
        - Murmur is generally harsher, unaffected by maneuvers, and loudest at the 3rd-4th intercostals space at the sternal borders.
2. Third heart sound
    - MI
    - Cardiomyopathy
    - Normal in athletic young adult
    - VSD
3. New onset atrial fibrillation [see: atrial fibrillation]
    - Other cardiac lesions causing atrial stretch
        - MI
        - Cardiomyopathy

        - Mitral stenosis
        - ASD
        - Hypertension
    - Hyperthyroidism
    - Pericarditis
    - Drugs
        - Caffeine, theophyline
        - EtOH
        - Digitalis
    - Sepsis
    - Idiopathic, age-related
4. Other symptoms of MR are the result of left-sided heart failure; see heart failure for further ddx
5. Exam may be nonspecific; have a low threshold of suspicion to send a patient with suspected chronic MR for a TTE, which is noninvasive and has exquisite sensitivity and specificity.

Therapeutics

1. Acute treatment
    - In acute severe MR
        - Resuscitation following ACLS guidelines.
        - Transfer to cardiac intensive care.
        - Afterload reduction, preferentially with Nitroprusside 0.3-10 mcg/kg/min
            - Reduces pressure gradient driving regurgitation and LV volume, improves MV competence. [1,2]
        - When hypotensive, give nitroprusside and augment with inotropic support. [1,2]
        - If infectious endocarditis is suspected, treat early and aggressively. [1]
    - In chronic MR, with new symptoms
        - Per ACC/AHA and ESC: Appearance of new symptoms in a patient with chronic MR should trigger:
            - Assessment with careful physical exam
            - TTE to check for changes in disease state. [1,2]
            - Urgent surgery referral. [1,2]
        - Heart failure with MR should be treated the same as decompensated heart failure due to other causes. [1,2]
            - Afterload reduction
            - ACEs/ARBs
            - See: Treatment of Acute CHF
        - New atrial fibrillation
            - Highly likely to recur if MR is unrepaired.
            - Cardioversion unlikely to be of benefit.
            - Anticoagulation and rate control preferable.[2]
2. Long Term Care
    - The only definitive treatment for MR is surgery.

        - Determining when surgery should best be undertaken significantly improves outcomes.[1,2,8]
    - Repair superior to replacement in long-term outcomes
        - MV repairs have significantly better outcomes at centers experienced in the procedure.
        - Working with the patient early to identify an acceptable medical center experienced in valve repair can help improve outcomes.[1,2]
    - Determining when surgery is appropriate:
        - Mild or moderate MR requires follow-up, NOT surgery[1,2]
        - Patients with severe organic MR and either signs of LV dysfunction or an easily repaired valve are surgical candidates.
            - Wide agreement that all *symptomatic* patients with severe MR with EF >30% and ESD >55 mm should receive prompt surgical referral. [1,2]
            - *Asymptomatic* patients with severe MR and EF >30% but <60%, or ESD >40 mm will benefit from surgery. [1,2]
            - Indications for surgery in an asymptomatic patient with severe MR and preserved LV function, (Endorsed by ACC/AHA and ESC , but expert opinion is not unanimous):
                - If the patient can receive a repair with a predicted success of better than 90%[2,13]
                - If afib develops[2,13]
                - If the patient has pulmonary arterial hypertension (systolic >50 mmHg at rest or >60 mmHg during exercise) [2,13]
        - Appropriate care is controversial for asymptomatic patients with severe chronic MR and preserved LV function, but whose certainty of successful repair is less than 90%
            - A review of several nonrandomized trials suggests that in severe MR, surgery is inevitable and "watchful waiting" carries a higher mortality than surgery.[8]
            - One nonrandomized trial, however, found that close, frequent follow up and medical management delayed surgery without excess risk.[13]
            - Additional tests of prognostic value in this situation.[8]
                - BNP levels – Brain Natriuretic Hormone levels above 105 pg/mL predict poor outcomes without surgery
                - Functional capacity – markedly reduced oxygen consumption during exercise predicts poor nonsurgical outcomes
            - In summary:
                - This group of patients should be followed very closely and very consistently if early valve repair is not chosen.
                - BNP levels and functional capacity may help identify patients for whom watchful waiting carries the greatest risk.

        - Patients with functional severe chronic MR, i.e. secondary to distorted LV geometry, have much higher operative morbidity and mortality.
            - ACC/AHA and ESC guidelines still recommend surgery to such patients if NYHA grade III or IV symptoms persist despite maximum medical therapy and biventricular pacing.[2,13]
    - Post-surgical care
        - Per ACC/AHA guidelines, early postoperative exam and TTE
            - Verify successful repair and establish a new baseline for follow-up[1]
        - Potential surgical complications
            - In patients with AFib prior to surgery, there is a post-operative stroke risk
            - Repair failure and persistent MR[1,2]
            - Prior LV dysfunction may persist with increased morbidity/mortality risk[1,2]
        - For patients with valve replacements
            - Bio-prostheses should be monitored long-term for eventual degradation. [1,2]
            - Mechanical valves require lifelong warfarin anticoagulation
                - Risk of bleeding or CVA [1,2]
    - Endocarditis Prophylaxis - <u>ACC/AHA recommendations updated in 2008</u>
        - MR is NOT an indication for endocarditis prophylaxis
            - Not even in the presence of complex MVP or congenital valvulopathy.[14]
        - Prior episode of infectious endocarditis IS an indication.[16]
        - Prosthetic valve IS an indication.[16]
        - Endocarditis prophylaxis is never indicated for non-dental procedures outside the setting of concurrent infection.[16]
    - No medications proven to be beneficial or disease modifying in isolated organic MR.
        - Co-morbidities should be treated appropriately.
            - MVP
                - consider aspirin 75-325 PO daily to reduce stroke risk.[13]
            - AFib
                - anticoagulation per CHADS2 score
                - rate control with beta blockers or cardioactive calcium channel blockers. [1,2]
            - Heart failure
                - afterload reduction and ACEs/ARBs.[1,2]
    - Physical Activity
        - Patients in sinus rhythm, with no pulmonary hypertension, and with normal LV and LA size may engage in sports and exercise without restriction.[1]
        - Patients with LV enlargement greater than 60mm, pulmonary hypertension, or reduced EF should not engage in competitive sports.[1]

Follow-Up

1. Office follow-up
    - All chronic MR requires close follow up.
    - In mild and moderate MR, focus on monitoring for increasing severity. In severe MR, focus on monitoring for new signs or symptoms that would prompt surgical referral.[1,2,10] (SOR:B)
        - Mild chronic MR should be followed by annual physical exam alone in the absence of changing signs or symptoms.
            - Changing signs/symptoms should trigger re-evaluation with TTE.[1,2]
        - Moderate to severe MR should be followed with assessments including both physical exam and TTE.
            - Ideal exam frequency has not been established, but every 6-12 months is commonly suggested.[1,2,10] (SOR:B)
2. Referrals
    - In severe chronic MR, many signs and symptoms should prompt surgical referral
        - New symptoms of heart failure
        - EF below 60%
        - End-systolic diameter at or above 40 mm
        - Pulmonary artery pressure exceeding 50 mmHg at rest or 60 mmHg during exercise.
    - Earlier referral is reasonable if the patient can go to a center experienced in mitral valve repair.[1,2]
3. Hospitalizations
    - A patient suspected of having acute MR should be hospitalized without delay.[1,2]

Prevention

1. Early detection and consistent follow-ups to prevent progression to decompensated MR and poor surgical outcomes.

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