

Treating Refractory Angina

What Is Refractory Angina?

Refractory angina (RA) is chest pain due to coronary artery disease (CAD) that keeps happening even after standard treatments like medications, stents, or bypass surgery. It occurs when the heart doesn't get enough oxygen because of blocked or narrowed coronary arteries, and typical treatments can't fully fix the problem. Patients with RA often have severe symptoms that limit their daily life, such as chest pain with minimal activity or even at rest. This guide provides a clear plan for diagnosing and treating RA in the hospital, with tables and real-life examples to help clinicians manage this challenging condition.

Why Does Refractory Angina Happen?

- RA happens because the heart muscle isn't getting enough blood flow (ischemia) despite treatment. Here's why:
- **Severe Coronary Artery Disease:** Multiple blockages in the coronary arteries that can't be fixed with stents or surgery (e.g., diffuse small vessel disease or chronic total occlusions).
- **Microvascular Dysfunction:** Tiny blood vessels in the heart don't work properly, even if the big arteries are open.
- **Incomplete Revascularization:** Stents or bypass surgery didn't fully restore blood flow (e.g., due to technical challenges or disease progression).
- **Comorbidities:** Conditions like diabetes, hypertension, or heart failure make it harder to control angina.
- **Collateral Circulation Failure:** The heart tries to grow new blood vessels to bypass blockages, but these may not provide enough flow.

How Do We Diagnose Refractory Angina?

Step 1: Confirm the Diagnosis

- Definition:
 - **Refractory Angina is diagnosed when a patient has:**
 - Chronic angina (chest pain) for >3 months.
 - Symptoms despite optimal medical therapy (OMT) with at least two anti-anginal drugs (e.g., beta-blockers, nitrates).
 - Evidence of ischemia (e.g., stress test showing reduced blood flow to the heart).

- No options for further revascularization (stents or bypass surgery) due to anatomy or prior procedures.
- Symptoms:
 - Chest pain or pressure, often triggered by activity, stress, or cold weather.
 - Pain may radiate to the jaw, arm, or back.
 - Shortness of breath, fatigue, or nausea (especially in women or elderly patients).
- Exam Findings:
 - Normal exam between episodes.
 - **During angina:** Tachycardia, hypertension, diaphoresis, S3/S4 gallop (if heart failure).

Step 2: Diagnostic Tests

- ECG:
 - Look for ST depression, T-wave inversion (ischemia), or prior Q waves (old MI).
- Stress Testing:
 - Treadmill or Pharmacologic Stress Test: Positive if ST changes or symptoms occur.
 - Stress Echocardiogram: Wall motion abnormalities indicate ischemia.
 - Myocardial Perfusion Imaging (MPI): Shows areas of reduced blood flow (reversible defects).
- Coronary Angiography:
 - Confirms severe CAD (e.g., diffuse disease, small vessel disease, or chronic total occlusions).
 - No targets for revascularization (e.g., vessels too small, prior stents/bypass).
- Labs:
 - **Troponin:** Usually normal in stable RA (elevated in acute coronary syndrome).
 - **BNP:** Elevated if heart failure is present.
 - **Lipid Panel, HbA1c:** Assess risk factors (dyslipidemia, diabetes).
- Other Tests:
 - **Echocardiogram:** Assess LV function (EF <40% indicates heart failure), wall motion abnormalities.
 - **Cardiac MRI:** Detects microvascular dysfunction or scar tissue (late gadolinium enhancement).

Treatment Options for Refractory Angina

Step 1: Optimize Medical Therapy (OMT)

- Even in RA, we start by making sure the patient is on the best possible medications:
 - **Beta-Blockers:** Metoprolol 25-100 mg PO daily (reduces heart rate, lowers oxygen demand).
 - **Nitrates:** Long-acting (isosorbide mononitrate 30-60 mg PO daily) or short-acting (nitroglycerin 0.4 mg SL prn) for symptom relief.
 - **Calcium Channel Blockers (CCBs):** Amlodipine 5-10 mg PO daily or diltiazem 120-360 mg PO daily (helps relax blood vessels).
 - **Ranolazine:** 500-1000 mg PO BID (improves oxygen use in the heart, reduces angina episodes).
 - **Ivabradine:** 5-7.5 mg PO BID (lowers heart rate, used if beta-blockers not tolerated).
 - **Statins:** High-intensity (atorvastatin 40-80 mg PO daily) to lower LDL and stabilize plaques.
 - **Antiplatelets:** Aspirin 81 mg PO daily or clopidogrel 75 mg PO daily (prevents clots).
- **Lifestyle Changes:** Smoking cessation, weight loss, low-fat diet, exercise (if tolerated).

Step 2: Add Advanced Medical Therapies

- If OMT doesn't control symptoms, consider these additional options:
 - Enhanced External Counterpulsation (EECP):
 - **How It Works:** Inflatable cuffs wrap around the legs and inflate during diastole (heart's resting phase), pushing blood back to the heart to improve coronary flow.
 - **When to Use:** RA patients with persistent symptoms (Canadian Cardiovascular Society [CCS] Class III-IV angina).
 - **Regimen:** 1-2 hours/day, 5 days/week for 7 weeks (35 sessions).
- Neurostimulation Therapies:
 - **Transcutaneous Electrical Nerve Stimulation (TENS):** Non-invasive, reduces pain perception.
 - **Spinal Cord Stimulation (SCS):** Implanted device, used for severe RA (CCS Class IV).
- Metabolic Modifiers:
 - **Trimetazidine:** 35 mg PO BID (improves heart energy use, not FDA-approved in the U.S.).

- **Perhexiline:** 100 mg PO BID (similar to trimetazidine, used in some countries).

Step 3: Consider Interventional and Surgical Options

- For patients who fail medical therapy, these procedures may help:
 - Coronary Sinus Reducer (CSR):
 - **Device implanted in the coronary sinus to increase pressure, redistributing blood flow to ischemic areas.**
 - **Indication:** RA with viable myocardium on imaging (e.g., MPI).
 - **Outcome:** Reduces angina (COSIRA trial: 71% improved CCS class).
 - Transmyocardial Laser Revascularization (TMR):
 - **Laser creates channels in the heart muscle to improve blood flow.**
 - **Indication:** RA with no revascularization options, viable myocardium.
 - **Outcome:** Improves angina but no survival benefit (used off-pump or with CABG).
 - Cell-Based Therapies:
 - **Stem Cell Therapy:** Injection of stem cells (e.g., CD34+) to promote angiogenesis.
 - **Status:** Experimental, under investigation in trials (e.g., RENEW trial).
 - Heart Transplant:
 - **Indication:** End-stage ischemic cardiomyopathy (EF <30%) with RA.
 - **Outcome:** Rarely used, reserved for severe cases with no other options.

Step 4: Manage Comorbidities and Risk Factors

- **Heart Failure:** Optimize diuretics (furosemide 20-40 mg IV/PO), ACEi (lisinopril 5-40 mg PO daily), beta-blockers.
- **Diabetes:** Tight glycemic control (HbA1c <7%) with metformin, insulin.
- **Hypertension:** Control BP (<130/80 mmHg) with amlodipine, lisinopril.
- **Anemia:** Transfuse PRBCs if Hgb <7 g/dL (increases oxygen delivery).

Complications of RA Treatment:

- Medication Side Effects:
 - **Nitrates:** Headache, hypotension (hold if SBP <90 mmHg).
 - **Ranolazine:** QT prolongation (check ECG), dizziness.
 - **Beta-Blockers:** Bradycardia, fatigue (monitor HR >50 bpm).
- EECF:
 - Leg discomfort, skin abrasions (use padding, monitor skin).

- CSR/TMR:
 - Bleeding, infection at implant site (antibiotics, monitor).
 - Arrhythmias (e.g., VT; amiodarone 150 mg IV bolus if needed).
 - Device migration (CSR): Rare, requires imaging/surgery.
- General Risks:
 - Worsening HF: Monitor BNP, daily weights, adjust diuretics.
 - Acute Coronary Syndrome (ACS): If new ST elevation or troponin rise, urgent cath.

Table: Common Medications for Refractory Angina

Medication	Dose	Mechanism	Side Effects	Monitoring
Metoprolol	25-100 mg PO daily	Reduces heart rate, oxygen demand	Bradycardia, fatigue	HR >50 bpm, BP
Isosorbide Mononitrate	30-60 mg PO daily	Vasodilation, reduces preload	Headache, hypotension	SBP >90 mmHg
Amlodipine	5-10 mg PO daily	Vasodilation, reduces afterload	Edema, dizziness	BP, ankle swelling
Ranolazine	500-1000 mg PO BID	Improves myocardial energy use	QT prolongation, nausea	ECG (QTc), renal function
Ivabradine	5-7.5 mg PO BID	Lowers heart rate	Bradycardia, visual changes	HR >50 bpm, vision

Table: Advanced Therapies for Refractory Angina

Therapy	Indication	Procedure	Benefits	Risks
EECP	CCS Class III-IV	35 sessions, 1-2 h/day	Reduces angina, improves QOL	Leg discomfort, skin abrasions
Coronary Sinus Reducer	RA, viable myocardium	Implanted in coronary sinus	Reduces angina (COSIRA trial)	Bleeding, device migration
Spinal Cord Stimulation	CCS Class IV	Implanted device	Pain relief, improved exercise	Infection, device failure
Transmyocardial Laser	No revascularization options	Laser channels in myocardium	Symptom relief	Arrhythmias, no survival benefit
Stem Cell Therapy	Experimental	CD34+ cell injection	Promotes angiogenesis	Still under investigation

Clinical Scenarios

Scenario 1: Elderly Male with RA and Failed Revascularization

- **Presentation:** A 68-year-old male with CAD (prior CABG, multiple stents) presents with daily chest pain (CCS Class III) despite metoprolol 50 mg PO daily, isosorbide mononitrate 60 mg PO daily, and aspirin 81 mg PO daily. Exam shows T 37°C, BP 130/80 mmHg, HR 70 bpm, RR 16/min, SpO2 96% on room air, no murmurs.
- **Diagnostic Workup:** **Stress MPI:** Reversible defect in LAD territory, EF 45%. Angiogram: Diffuse small vessel disease, no targets for further revascularization.
- **Diagnosis:** Refractory angina → Persistent symptoms, failed revascularization, ischemia on MPI.
- **Management:** Add ranolazine 500 mg PO BID (titrated to 1000 mg BID). Start EECP (35 sessions). Consult cardiology: Coronary sinus reducer considered if no improvement. Optimize risk factors: Atorvastatin 80 mg PO daily, HbA1c 6.5%. After 6 weeks, angina reduced to CCS Class II, patient resumes light activity.

Scenario 2: Middle-Aged Female with RA and Microvascular Dysfunction

- **Presentation:** A 55-year-old female with diabetes and hypertension presents with chest pain at rest (CCS Class IV) despite amlodipine 10 mg PO daily, nitroglycerin SL prn, and clopidogrel 75 mg PO daily. Exam shows T 37°C, BP 140/90 mmHg, HR 80 bpm, RR 18/min, SpO2 95% on room air.
- **Diagnostic Workup:** **ECG:** T-wave inversion in V1-V3, stress echo: No wall motion abnormalities, angiogram: Patent coronaries, cardiac MRI: Microvascular dysfunction.
- **Diagnosis:** Refractory angina with microvascular dysfunction → Symptoms despite OMT, normal coronaries, MRI findings.
- **Management:** Add ivabradine 5 mg PO BID (HR reduced to 60 bpm). Start SCS (implanted device, pain relief achieved). Control BP (lisinopril 10 mg PO daily added). Consult pain management: TENS as adjunct. Monitor ECG (QTc normal). After 4 weeks, angina reduced to CCS Class II, patient reports improved QOL.

Scenario 3: Elderly Male with RA and Acute Worsening

- Presentation: A 72-year-old male with RA (prior EECF, on ranolazine 1000 mg BID, metoprolol 100 mg daily) presents with sudden worsening chest pain and dyspnea. Exam shows T 37°C, BP 90/60 mmHg, HR 110 bpm, RR 24/min, SpO2 88% on room air, crackles, JVD.
- Diagnostic Workup: **ECG:** New ST elevation in V1-V4, troponin 1.5 ng/mL (baseline 0.1), ECHO: EF 30%, anterior wall akinesis.
- Diagnosis: Acute STEMI with cardiogenic shock → Worsening symptoms, new ST elevation, low EF.
- Management: **Admit to ICU (shock). Urgent cath:** LAD occlusion, not amenable to PCI (prior stents). Start dobutamine 5 µg/kg/min IV (BP improves to 110/70 mmHg). Furosemide 40 mg IV (crackles resolve). Consult cardiology: IABP placed, plan for TMR. Monitor troponin, EF. After 5 days, stabilizes, discharged with HF meds and TMR scheduled.

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