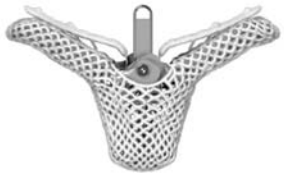
Clinical Insights

SUMMARY OF CLINICAL DATA

MITRACLIP™ TRANSCATHETER MITRAL VALVE REPAIR

CARDIOVASCULAR PHYSIOLOGY IN MITRAL REGURGITATION

What you need to know



ESSENTIAL HIGHLIGHTS

- The MitraClip™ can effectively perform valve leaflet coaptation to reduce MR under TEE and color doppler guidance. However, this approach provides, at best, semi-quantitative physiologic data
- When left uncorrected, chronic mitral valve regurgitation (MR) can lead to ventricular volume overload and increased risk of decompensated heart failure
- Left atrial pressure (LAP) is elevation is proportional to the severity of mitral regurgitation. Reduction in LAP and improved forward flow are key measures of successful MR repair
- Continuous LAP monitoring allows hemodynamic and functional feedback during MC placement to optimally reduce regurgitation severity and risk of inducing mitral stenosis

ACRONYMS

LAP	*Left atrial pressure*
LAmP	*left atrial mean pressure*
LAmPI	*Left atrial mean pressure index*
LAvP	*Left atrial v-wave pressure*
LAvPI	*Left atrial v-wave pressure index*
LAv height	*Left atrial v-wave height*
LVEDP	*Left ventricle end diastolic pressure*
LVSP	*Left ventricular systolic pressure*
MC	*MitraClip*
MR	*Mitral regurgitation*
PMR	*Primary mitral regurgitation*
SMR	*Secondary mitral regurgitation*
sBP	*Systemic blood pressure*
TEE	*Transesophageal echocardiography*
TMVR	*Transcatheter mitral valve repair*

BASIC CARDIOVASCULAR PHYSIOLOGY AND MITRAL REGURGITATION (MR)[2]

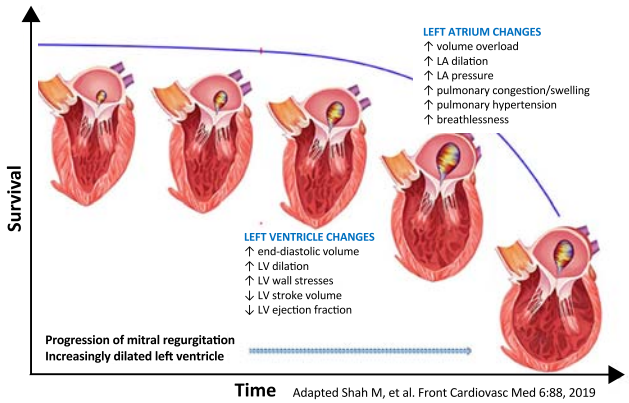
Mitral regurgitation (MR) refers to retrograde blood flow from the left ventricle back up to the left atrium during ventricular contraction, which can be a consequence of:

- Degenerative mitral valve abnormalities (**Primary MR**), or
- Ventricular dilatation and distortions from ischemic or idiopathic cardiomyopathy leading to displacement of the papillary muscles and leaflet tethering (**Secondary MR**)

Primary MR (PMR) begins with an abnormal mitral valve apparatus but mostly functional left ventricle.

1. During systole (contraction), higher regurgitant flow increases left atrial pressure (LAP)
2. During diastole (relaxation), regurgitant blood repeatedly flows back to the left ventricle, resulting in increasingly larger diastolic volumes and subsequently **higher left ventricular end diastolic pressures.** The heart initially compensates by pumping harder.
3. With chronic MR however, the left ventricle eventually becomes overloaded in diastole. Increased wall stress induces cardiac remodeling with dilation of the ventricle. The heart eventually decompensates into critical left ventricular dysfunction and clinical symptoms of heart failure [FIGURE 1].

FIGURE 1: PROGRESSION OF MR ON DETERIORATION OF LEFT HEART FUNCTION



Source: Front Cardiovasc Med. 6:88, 2019

INDICATION FOR USE: The MitraClip™ NTR/XTR Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

The MitraClip™ NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

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The goal of PMR repair is to avoid this process of decompensation early on in PMR.

Secondary (functional) MR begins with an already weak and dilated left ventricle, which alters mitral valve geometry, causing regurgitation. Chronic SMR quickly follows the pattern of decompensated MR described in step 3 of PMR. *The goal of SMR repair is to avoid further exacerbation of heart failure by improving cardiac output*

In both cases, clinical heart failure ensues because:

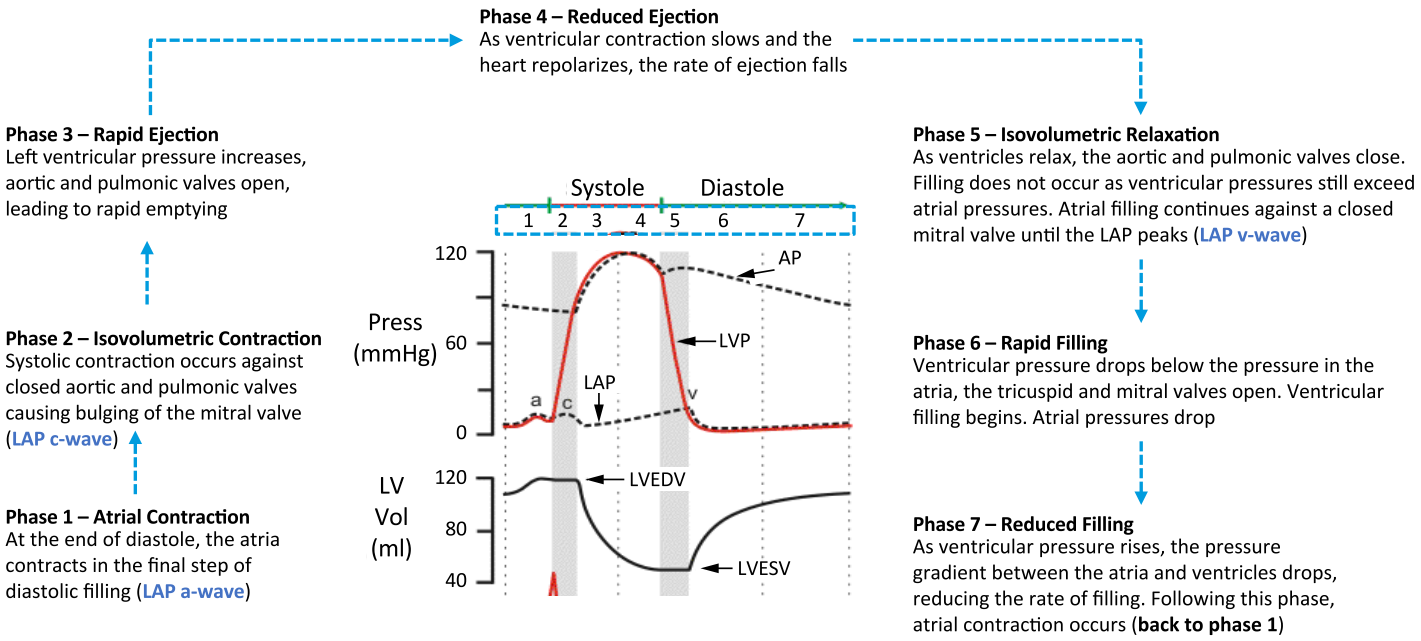
- Cardiac output is diminished, lowering renal blood flow. The kidneys interpret this as a low volume state and inappropriately stimulate water retention in an attempt to maintain blood volume and end organ perfusion.
- Abnormal water retention further stresses an already failing heart. Volume overload causes blood to back up into the pulmonary circuit, causing pulmonary edema (swelling) and dyspnea (breathlessness).
- Over time pulmonary pressures increase to compensate for volume overload, causing increased right ventricular stress and ultimately right-sided heart failure and peripheral volume overload

PHASES OF THE CARDIAC CYCLE

An understanding of the cardiac cycle underscores hemodynamic changes that occur in MR **[Figure 2].**

FIGURE 2: PHASES AND PRESSURES OF THE CARDIAC CYCLE IN THE LEFT HEART UNDER NORMAL CONDITIONS[3]

AP: aortic pressure; LAP: left atrial pressure; LV: left ventricle; LVEDV: left-ventricular end diastolic pressure; LVESV: left ventricular end systolic volume



Source: Klabunde R. Cardiovascular Physiology Concepts. https://www.cvphysiology.com/Heart%20Disease/HD005

LEFT ATRIAL PRESSURE AND MITRAL REGURGITATION[3]

Normal mean LAP is **6-12 mmHg**. In chronic MR, repetitive regurgitant flow increases atrial filling during phases 3-4 [Figure 2]. At the end of phase 5, the LAP can increase to as high as **25 mmHg** depending on MR etiology and severity, and patient state[3]. Visually, this is seen as a **tall v-wave**, the height of which [Figure 3], especially relative to the baseline, is an indicator of MR severity.

More sophisticated parameters can be used to quantify regurgitant flow in MR. These include:

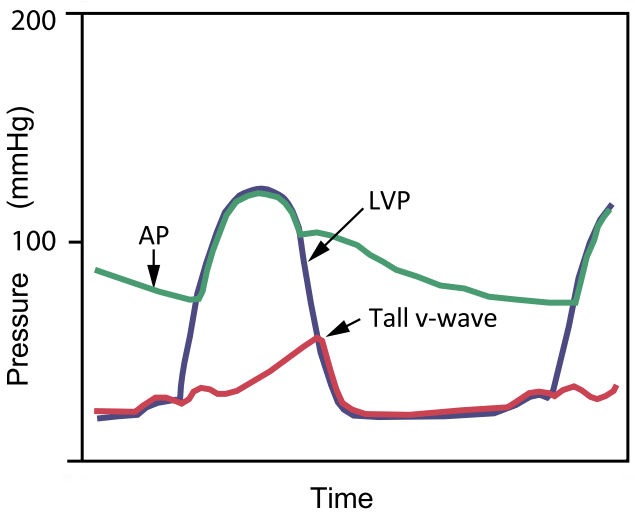
- **LAmP:** Mean pressure in the left atrium throughout the cardiac cycle
- **LAvP:** Peak LA v-wave pressure on the LAP tracing
- **LAv height:** Difference between the peak LA v-wave and the minimum LAP.

Ideally, LAmP, LAvP, and LAvheight would all decrease after mitral valve repair to alleviate MR. However, this is not always the case. Paradoxical Instances of reduction in v-wave height with LAmP increase can happen. Continuous LAP monitoring during mitral valve repair is thus important to track such subtle changes.

LAP is also influenced by systemic blood pressure (sBP). In two MR patients with identical hearts but different blood pressures, the patient with a higher sBP (hypertensive) will have an increased left ventricular systolic pressures (LVSP), more regurgitation (as blood will take the path of least resistance), and higher left atrial pressures, though the underlying valvular disorder is the same. Thus, changes in LVSP can affect LAP independent of underlying MR severity. To normalize for differences in LVSP, the LAP pressures can be "indexed" or normalized to the LVSP:

- **LAmPi:** LAmP indexed to (divided by) LVSP
- **LAvPI:** LAvP indexed to (divided by) LVSP

FIGURE 3: MR CONDITION: LEFT ATRIAL PRESSURE TRACING WITH TALL V-WAVE[3]



Source: Klabunde R. Cardiovascular Physiology Concepts. https://www.cvphysiology.com/Heart%20Disease/HD005

WHY PERFORM CONTINUOUS LAP MEASUREMENT DURING MITRACLIP PLACEMENT?

The MitraClip alleviates MR by coapting two leaflets, a procedure that currently relies on qualitative and semi-quantitative determination of residual MR based primarily on visualizing the regurgitant jets under color doppler echocardiography. While effective, it limits assessment of any potential iatrogenic mitral stenosis. Real time continuous LAP monitoring during MitraClip placement can provide adjunctive objective data to complement intraprocedural decision making, and establish optimal post-procedure MR reduction with minimal stenosis risks.

REFERENCES

1. Leonard, L. S. (2016). Pathophysiology of Heart Disease. A collaborative Project of Medical Students and Faculty. Wolters Kluwer, Philadelphia.
2. Shah M, Jorde UP. (2019) Percutaneous Mitral Valve Interventions (Repair): Current Indications and Future Perspectives. Front Cardiovasc Med. https://www.frontiersin.org/articles/10.3389/fcvm.2019.00088/full
3. Klabunde, R. (2011) Cardiovascular Physiology Concepts. Lippincott Williams & Wilkins, Philadelphia. https://www.cvphysiology.com/Heart%20Disease/HD005

IMPORTANT SAFETY INFORMATION

MITRACLIP CLIP DELIVERY SYSTEMS

Rx ONLY

INDICATION FOR USE

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- The MitraClip™ NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per AmericanSociety of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptomsand MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

CONTRAINDICATIONS

The MitraClip™ NTR/XTR Clip Delivery System is contraindicated in patients with the following conditions:

- Patients who cannot tolerate procedural anticoagulation or post procedural antiplatelet regimen
- Active endocarditis of the mitral valve
- Rheumatic mitral valve disease
- Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

WARNINGS

- **DO NOT use MitraClip™ outside of the labeled indication.**
- The MitraClip™ Implant should be implanted with sterile techniques using fluoroscopy and echocardiography (e.g., transesophageal [TEE] and transthoracic [TTE]) in a facility with on-site cardiac surgery and immediate access to a cardiac operating room.
- Read all instructions carefully. Failure to follow these instructions, warnings and precautions may lead to device damage, user injury or patient injury. Use universal precautions for biohazards and sharps while handling the MitraClip™ System to avoid user injury.
- Use of the MitraClip™ should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and those trained in the proper use of the system.
- The Clip Delivery System is provided sterile and designed for single use only. Cleaning, re-sterilization and / or reuse may result in infections, malfunction of the device or otherserious injury or death.
- Use caution when treating patients with hemodynamic instability requiring inotropic support or mechanical heart assistance due to the increased risk of mortality in this patient population. The safety and effectiveness of MitraClip™ in these patients has not been evaluated.

PRECAUTIONS

- Note the product "Use by" date specified on the package.
- Inspect all product prior to use. Do not use if the package is open or damaged, or if product is damaged.
- Prohibitive Risk Primary (or degenerative) Mitral Regurgitation
  - Prohibitive risk is determined by the clinical judgment of a heart team, including a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, due to the presence of one or more of the following documented surgical risk factors:
    - 30-day STS predicted operative mortality risk score of
      - ≥8% for patients deemed likely to undergo mitral valve replacement orr
      - ≥6% for patients deemed likely to undergo mitral valve repair
  - Porcelain aorta or extensively calcified ascending aorta.
  - Frailty (assessed by in-person cardiac surgeon consultation)
  - Hostile chest
  - Severe liver disease / cirrhosis (MELD Score > 12)
  - Severe pulmonary hypertension (systolic pulmonary artery pressure > 2/3 systemic pressure)
  - Unusual extenuating circumstance, such as right ventricular dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, immobility, AIDS, severe dementia, high risk of aspiration, internal mammary artery (IMA) at high risk of injury, etc.
  - Evaluable data regarding safety or effectiveness is not available for prohibitive risk DMR patients with an LVEF < 20% or an LVESD > 60 mm. MitraClip™ should be used only when criteria for clip suitability for DMR have been met.
  - The heart team should include a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease and may also include appropriate physicians to assess the adequacy of heart failure treatment and valvular anatomy.
- Secondary Mitral Regurgitation
  - Evaluable data regarding safety or effectiveness is not available for secondary MR patients with an LVEF < 20% or an LVESD > 70 mm.
  - The multidisciplinary heart team should be experienced in the evaluation and treatment of heart failure and mitral valve disease and determine that symptoms and MR severity persist despite maximally tolerated GDMT. rohibitive Risk Primary (or degenerative) Mitral Regurgitation

POTENTIAL COMPLICATIONS AND ADVERSE EVENTS

The following ANTICIPATED EVENTS have been identified as possible complications of the MitraClip™ procedure.

Death; Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex); Aneurysm or pseudo-aneurysm; Arrhythmias; Atrial fibrillation; Atrial septal defect requiring intervention; Arterio-venous fistula; Bleeding; Cardiac arrest; Cardiac perforation; Cardiac tamponade / Pericardial Effusion; Chordal entanglement / rupture; Coagulopathy; Conversion to standard valve surgery; Deep venous thrombus (DVT); Dislodgement of previously implanted devices; Dizziness; Drug reaction to anti-platelet / anticoagulation agents / contrast media; Dyskinesia; Dyspnea; Edema; Emboli (air, thrombus, MitraClip™ Implant); Emergency cardiac surgery; Endocarditis; Esophageal irritation; Esophageal perforation or stricture; Failure to deliver MitraClip™ to the intended site; Failure to retrieve MitraClip™ System components; Fever or hyperthermia; Gastrointestinal bleeding or infarct; Hematoma; Hemolysis; Hemorrhage requiring transfusion; Hypotension / hypertension; Infection; Injury to mitral valve complicating or preventing later surgical repair; Lymphatic complications; Mesenteric ischemia; MitraClip™ Implant erosion, migration or malposition; MitraClip™ Implant thrombosis; MitraClip™ System component(s) embolization; Mitral stenosis; Mitral valve injury; Multi-system organ failure; Myocardial infarction; Nausea / vomiting; Pain; Peripheral ischemia; Prolonged angina; Prolonged ventilation; Pulmonary congestion; Pulmonary thrombo-embolism; Renal insufficiency or failure; Respiratory failure / atelectasis / pneumonia; Septicemia; Shock, Anaphylactic or Cardiogenic; Single leaflet device attachment (SLDA); Skin injury or tissue changes due to exposure to ionizing radiation; Stroke or transient ischemic attack (TIA); Urinary tract infection; Vascular trauma, dissection or occlusion; Vessel spasm; Vessel perforation or laceration; Worsening heart failure; Worsening mitral regurgitation; Wound dehiscence

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See Important Safety Instructions referenced within.

CAUTION: This product is intended for use by or under the direction of a physician. Prior to use, reference the Instructions for Use, inside the product carton (when available) or at eifu.abbottvascular.com or at medical.abbott/manuals for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events.

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