

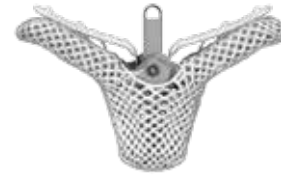
Clinical Insights

SUMMARY OF CLINICAL DATA

MITRACLIP™ TRANSCATHETER EDGE-TO-EDGE REPAIR

HEMODYNAMIC MONITORING DURING MITRACLIP™ PROCEDURES

Early Data, Future Promise



PERSPECTIVE

- MitraClip™ safely and effectively reduces mitral regurgitation (MR) with excellent clinical, functional, and quality of life outcomes, with worldwide usage of over 100,000 cases.
- Today, most MitraClip procedures are guided solely by echocardiography which is highly dependent on operator experience (transducer position, acoustic shadows, eccentric jets), and standardized MR quantification post-MitraClip is difficult due to split regurgitant jets.
- Adding intraprocedural objective assessments to echocardiography/color doppler would further optimize clip placement and future clinical benefits.

KEY HIGHLIGHTS

Hemodynamic monitoring of left atrial pressure (LAP) is an emerging area of interest. Its inclusion can potentially improve post-MitraClip outcomes. When used in combination with echocardiography/color doppler, LAP monitoring facilitates optimal MR reduction while minimizing the risk of iatrogenic stenosis. Importantly, preliminary data has shown continuous LAP monitoring to be:

- An important adjunct to echocardiography/color doppler for guiding clip placement
- Associated with clinically meaningful outcomes: improved heart failure rehospitalizations, symptom status, and exercise capacity
- Feasible in a clinical setting

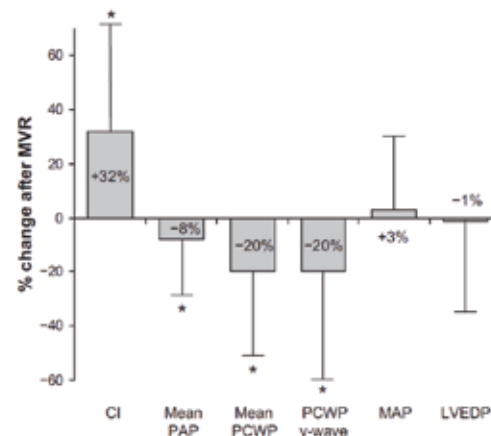
WHY INTRODUCE HEMODYNAMIC MONITORING WITH MITRACLIP?

Hemodynamic monitoring has a well-established role in Transcatheter Aortic Valve Replacement (TAVR) where transaortic pressure is a key index of procedural success. By contrast, reporting of hemodynamic parameters pre-, during, and post-MitraClip is a relatively new practice.

MitraClip placement is conventionally guided by transesophageal echocardiography (TEE) with color doppler imaging (CDI). While effective, both approaches do have limitations. MR defined by vena contracta, PISA, and other TEE measures are not always accurate. Regurgitant jet assessed by CDI is operator-dependent, transducer location-dependent, and lacks standardized quantitative metrics. Jet demarcation by color doppler reflects flow topography rather than the true regurgitant volume, presenting further challenges to interpretation¹.

Importantly, although clipping reduces MR, it also narrows the mitral valve orifice, inducing the risk of iatrogenic (treatment-related) mitral stenosis by elevating transmitral pressure gradients². Hence, continuous monitoring of LAP during a MitraClip procedure can supplement echocardiography to optimize MR reduction with minimal risk of stenosis².

FIGURE 1: PCWP AND HENCE LAP CHANGES ARE SENSITIVE TO MR CHANGES WITH MITRACLIP³

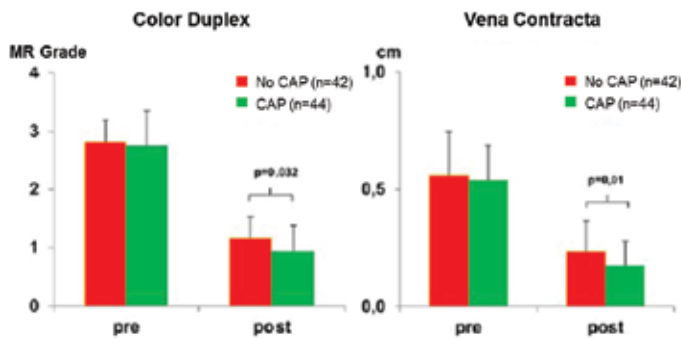


CI, cardiac index; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; MAP mean arterial pressure; LVEDP, left ventricular end diastolic pressure.

Source: Circulation 2013;127(9):1018–27.



FIGURE 2: CONTINUOUS LAP WITH ECHOCARDIOGRAPHY



Continuous LAP with echocardiography reduced MR grade and Vena Contracta after MitraClip compared to only echocardiography. Source: Catheterization and Cardiovascular Interventions 2016;88(7):1134–43.

DOES CONTINUOUS LAP MONITORING HAVE A CLINICALLY MEANINGFUL IMPACT?

Early observational studies showed improvement in multiple hemodynamic parameters following MitraClip, specifically pulmonary capillary wedge pressure, a surrogate of LAP [FIGURE 1]^{3,4}. Subsequent studies reported improved clinical outcomes with continuous LAP monitoring:

- **Lower post-procedural regurgitation, without a significant increase in procedural duration or complication rate** [FIGURE 2]⁵

In a study of 86 patients undergoing MitraClip, continuous LAP monitoring (CAP, n=44) was compared with intermittent measurement (n=42). A greater reduction in MR grade was observed in the group who underwent CAP compared to the intermittent measurement group (2.8→0.9 vs. 2.8→1.3, p=0.03) which persisted through discharge.

- **Improved exercise tolerance assessed by six minute walk distance (6MWD)** [FIGURES 3 AND 4]⁶

In a single center study of 50 patients, change in LAP v-wave was independently associated with longer 6MWD and improved New York Heart Association (NYHA) class at 30 days. Additionally, each 5 mmHg decrease in mean V-wave was associated with a 49% increase in the likelihood of improved 6MWD (OR=1.49, 95% CI: 1.01-2.18, p=0.04). Patients with V-wave drop of > 11 mmHg (median) were 3.8x more likely to improve their 6MWD (p=0.05)

- **Reduced heart failure rehospitalization (HFH) and NYHA III/IV** [FIGURE 5]⁷

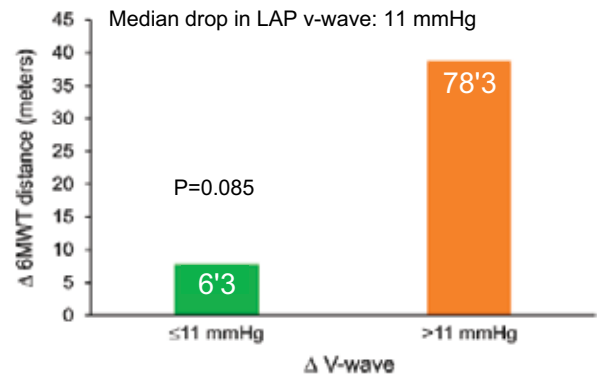
In a sub-study of 50 patients from the MitraSwiss registry, higher indexed mean LAP (LAMPi, mean LAP adjusted to LV systolic pressure) was associated with

- re-hospitalization for heart failure [FIGURE 5] (log rank p=0.001), and
- worsening NYHA III/IV (multivariate HR 1.5, 95%CI 1.01-2.10, p=0.005)

Residual MR by doppler echo failed to show these relationships, further supporting the adjunctive value of hemodynamics in deciding clip placement and/or repositioning.

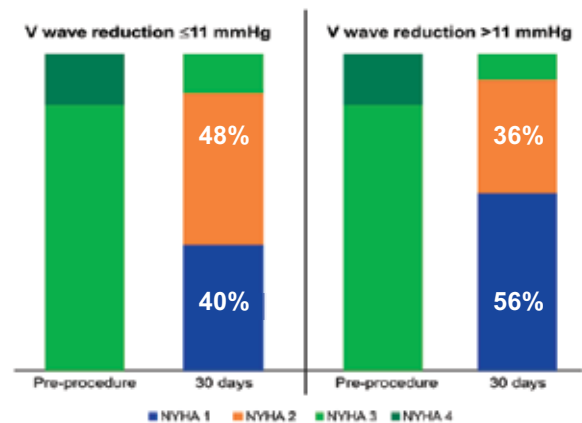
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FIGURE 3: 6MW TEST – PATIENTS WITH LAP V-WAVE DECREASE



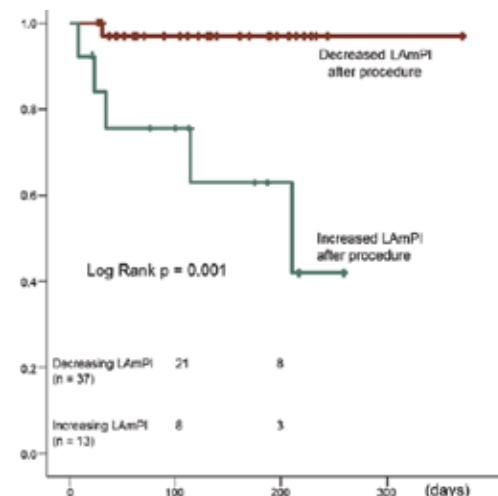
In the 6MW test, patients with a LAP v-wave decrease > 11 mmHg could walk substantially further after receiving a MitraClip than those with < 11 mmHg change. Source: Cardiovascular Interventions 2017;10(4):e004856.

FIGURE 4: PATIENTS WITH LAP V-WAVE DECREASE



Patients with a LAP v-wave decrease > 11 mmHg had a higher proportion of NYHA I/II after MitraClip compared to those with < 11 mmHg change. Source: Cardiovascular Interventions 2017;10(4):e004856.

FIGURE 5: HEART FAILURE REHOSPITALIZATION



Freedom from heart failure rehospitalization is statistically associated with a decrease in the indexed mean left atrial pressure (LAMPi). Source: JACC: Cardiovascular Interventions 2019;12(2):127–36.

HOW IS INTRAPROCEDURAL LAP MONITORING DONE AND IS IT FEASIBLE IN A CLINICAL SETTING?

Pulmonary capillary wedge pressure (PCWP) is frequently used as an indirect surrogate for LAP, and has a well-established prognostic role in mitral stenosis⁸, heart failure and mitral regurgitation⁹. In healthy states, the LAP and PCWP are well correlated ($r=0.95$)¹⁰. However in mitral regurgitation, the correlation is less evident ($r=0.79$)¹¹. Instead, direct LAP measurements are more accurate and is thus preferable to guide clip implantations.

LAP can be measured using a separate (buddy) catheter delivered transseptally to the left atrium but this approach increases complexity, risks, and procedural time¹². Instead, some users continuously transduced LAP through the steerable guide catheter (SGC) of the original MitraClip and the MitraClip NT and NTR/XTR systems. Flow inhibition within the SGC by the MitraClip delivery catheter (CDS) during clip placement can create problems.

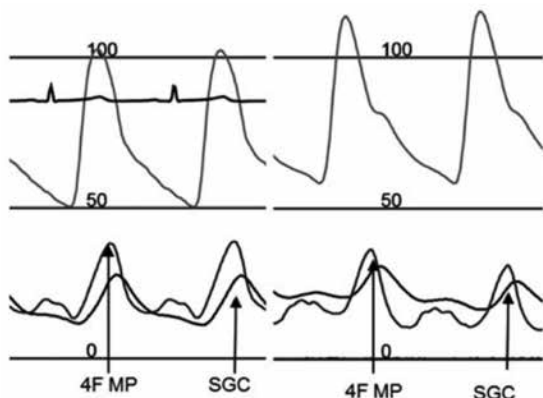
When blood flow in the SGC is unimpeded, continuous monitoring occurs [FIGURE 6]¹³ but the SGC waveforms are overdamped compared to those obtained with the buddy catheter [FIGURE 7]¹². When flow is insufficient, the signal is sporadic, overdamped, or drops off completely especially when the CDS rotates down to cross the mitral valve^{2,12}. A redesign of the SGC in the next generation MitraClip G4 will mitigate these issues and enable continuous tracking of the LAP with accuracy and consistency.

FIGURE 6: LEFT ATRIAL PRESSURE TRACINGS¹³



Consistency and reproducibility of left atrial pressure tracings transduced from the side-hole buddy catheter (red line) and via the SGC (yellow line) at key stages of the MitraClip procedure (5 cases). Mean and maximum observed difference in mean LA pressure between the SGC and side-hole catheter were 1.3 and 3.0 mm Hg, respectively. **Source: JACC: Cardiovascular Interventions 2017;10(14):1466-7**

FIGURE 7: THE SGC LAP WAVEFORM¹²



The SGC LAP waveform (SGC) is overdamped and slightly lagging that from a dedicated pigtail catheter (4F MP). **Source: Catheterization and Cardiovascular Interventions 2018;92(2):374-8.**

SUMMARY

- Adjunctive continuous LAP monitoring with standard color doppler imaging provides important objective data for proceduralists to optimize MR reduction while minimizing risks for iatrogenic mitral stenosis during MitraClip placement
- Continuous LAP monitoring has the potential to positively impact clinical outcomes by reducing heart failure rehospitalization, improving functional symptoms, and increasing exercise capacity.
- Continuous LAP monitoring is feasible clinically, though the promising early data will need to be confirmed in larger studies to establish optimal monitoring criteria.

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See Important Safety Information referenced within.

INDICATIONS FOR USE

- The MitraClip™ G4 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™ G4 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.

CONTRAINDICATIONS

The MitraClip G4 System is contraindicated in patients with the following conditions: Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or post procedural anti-platelet regime; Patients with known hypersensitivity to clip components (nickel / titanium, cobalt, chromium, polyester), or with contrast sensitivity; Active endocarditis of the mitral valve; Rheumatic mitral valve disease; Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

POTENTIAL COMPLICATIONS AND ADVERSE EVENTS

The following ANTICIPATED EVENTS have been identified as possible complications of the MitraClip G4 procedure: Allergic reactions or hypersensitivity to latex, contrast agent, anaesthesia, device materials (nickel / titanium, cobalt, chromium, polyester), and drug reactions to anticoagulation, or antiplatelet drugs, Vascular access complications which may require transfusion or vessel repair including: wound dehiscence, catheter site reactions, Bleeding (including ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage), Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture, vascular occlusion, Emboli (air thrombotic material, implant, device component); Peripheral Nerve Injury; Lymphatic complications; Pericardial complications which may require additional intervention, including: Pericardial effuse on, Cardiac tamponade, Pericarditis; Cardiac complications which may require additional interventions or emergency cardiac surgery, including: Cardiac perforation, Atrial septal defect; Mitral valve complications, which may complicate or prevent later surgical repair, including: Chordal entanglement / rupture, Single Leaflet Device Attachment (SLDA), Thrombosis, Dislodgement of previously implanted devices, Tissue damage, Mitral valve stenosis, Persistent or residual mitral regurgitation, Endocarditis; Cardiac arrhythmias (including conduction disorders, atrial arrhythmias, ventricular arrhythmias); Cardiac ischemic conditions (including myocardial infarction, myocardial ischemia, and unstable / stable angina); Venous thromboembolism (including deep vein thrombosis, pulmonary embolism, post procedure pulmonary embolism); Stroke / Cerebrovascular accident (CVA) and Transient Ischemic Attack (TIA); System organ failure: Cardio-respiratory arrest, Worsening heart failure, Pulmonary congestion, Respiratory dysfunction / failure / atelectasis, Renal insufficiency or failure, Shock (including cardiogenic and anaphylactic); Blood cell disorders (including coagulopathy, hemolysis, and Heparin Induced Thrombocytopenia (HIT)); Hypotension / hypertension; Infection including: Urinary Tract Infection (UTI), Pneumonia, Septicemia; Nausea / vomiting; Chest pain; Dyspnea; Edema; Fever or hyperthermia; Pain; Death; Fluoroscopy, Transesophageal echocardiogram (TEE) and Transthoracic echocardiogram (TTE) -related complications: Skin injury or tissue changes due to exposure to ionizing radiation, Esophageal irritation; Esophageal perforation, Gastrointestinal bleeding

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Abbott 3200 Lakeside Dr., Santa Clara, CA. 95054 USA, Tel: 1.800.227.9902

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