United States Senate
COMMITTEE ON THE JUDICIARY
WASHINGTON, DC 20510-6275

March 4, 2014

VIA ELECTRONIC TRANSMISSION

Morton Schapiro
President
Northwestern University
633 Clark Street
Evanston, IL 60208

Richard J. Gannotta
President
Northwestern Memorial Hospital
251 East Huron Street
Chicago, IL 60611

Dear Mr. Schapiro and Mr. Gannotta:

On December 8, 2008, and September 30, 2009, I wrote to you about troubling allegations that the Myxo-ETlogix 5100 Ring (Myxo Ring), an annuloplasty ring used in heart valve repair, had not been cleared for marketing by the Food and Drug Administration (FDA) before it was implanted in patients as part of an outcomes study.[1] In April 2009, the device was cleared with a new name, dETlogix Annuloplasty Ring.

Since we last corresponded, several inadequacies in the responses I received from the Northwestern entities[2] have been brought to my attention. First, it appears that Dr. Patrick McCarthy made contradictory statements regarding the similarity of the Myxo Ring to preexisting devices. Second, it is not clear whether patients received sufficient notice of the safety questions that arose regarding the Mxyo Ring implanted at Northwestern Memorial Hospital (NMH).

Most alarmingly, however, I recently received a report from Dr. Nalini Rajamannan – a former professor and physician at Northwestern University's Feinberg School of Medicine and co-author of the protocol for the study – alleging that a series of documents that fall squarely within the scope of my December 8, 2008 letter was withheld by the University, without any notice that the documents were being withheld.

Specifically, the withheld documents pertain to IRB Project Number 1532-004 and consist of the following:

(1) A Protocol Application signed by Dr. Patrick McCarthy;

(2) An Echo Protocol entitled, "Mitral Valve Pathology: A Quantitative Assessment Pre- and Post- Repair," authored by Dr. McCarthy;

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[1] "Early and Late Outcomes Following Surgical Intervention for Atrial Fibrillation Database."
[2] Northwestern University (University); Northwestern Memorial Hospital (NMH); and Northwestern Memorial Faculty Foundation (NMFF).

(3) A Waiver of Consent Form signed by Dr. McCarthy;

(4) A cover letter dated June 29, 2006 and addressed to Dr. McCarthy from Eileen Yates of the University's IRB, which approved IRB Project Number 1532-004 for the period 6/29/2006-6/27/2007 under submission accession number 200606-0680; and

(5) A HIPAA Waiver of Authorization Form attached to a cover letter dated June 29, 2006 and addressed to Dr. McCarthy from Eileen Yates of the University's IRB.

Moreover, it is alleged that each of these documents were either signed or submitted by Dr. McCarthy in June 2006. If these allegations are true, each of these documents should have been produced in response to Question 2 of my December 8, 2008 letter, which requested:

> Please provide a copy of all internal communications and correspondence regarding the Myxo Ring and the use of the device as part of an outcomes study. This request covers the period of January 2006 through the date of this letter.

As part of its January 5, 2009 response, the University produced a number of documents pertaining to IRB Project Number 1532-003 which were held out as responsive – including a New Project Submission Form (NPSF),[6] a Waiver of Consent Form,[7] and a HIPPA Waiver of Authorization Form.[8] If other responsive documents were to be withheld, then notice and an explanation of the reasons for withholding them should have been provided.

To address this inadequacy in your previous document productions, please respond to the following requests for information:

(1) Please provide a copy of the following documents pertaining to IRB Project Number 1532-004:

a. A Protocol Application signed by Dr. Patrick McCarthy;

b. An Echo Protocol entitled, "Mitral Valve Pathology: A Quantitative Assessment Pre- and Post- Repair," authored by Dr. McCarthy;

c. A Waiver of Consent Form signed by Dr. McCarthy;

d. A cover letter dated June 29, 2006 and addressed to Dr. McCarthy from Eileen Yates of the University's IRB, which approved IRB Project Number 1532-004 for the period 6/29/2006-6/27/2007 under submission accession number 200606-0680; and

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[6] NWU 00042 – NWU 00058.
[7] NWU 00059 – NWU 00060.
[8] NWU 00061 – NWU 00065.

e. A HIPAA Waiver of Authorization Form attached to a cover letter dated June 29, 2006 and addressed to Dr. McCarthy from Eileen Yates of the University's IRB.

(2) Please provide a copy of any other documentation, form, report, email, or memorandum regarding IRB Project Number 1532-004, including a New Project Submission Form, that is in the possession of the University, NMH, or NMFF. This request covers the period of January 2005 through the date of this letter.

Thank you for your cooperation in this matter. I would appreciate a response by March 14, 2014. Should you have any questions, please contact Jay Lim of my Committee staff at (202) 224-5225.

Sincerely,

Chuck Grassley

Charles E. Grassley
Ranking Member
Committee on the Judiciary

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Office for the Protection of Research Subjects

Northwestern University
750 North Lake Shore Drive
Suite 700
Chicago, Illinois 60611

irb@northwestern.edu
Phone 312-503-9338
Fax 312-503-0555

NORTHWESTERN UNIVERSITY

June 29, 2006

Patrick McCarthy, M.D.
Cardiac Surgery
201 E. Huron Street
Galter 10-105
Chicago Campus

IRB Project Number: 1532-004
Review Date: 6/27/2006
Approval Period: 6/29/2006 - 6/27/2007
Study Sites: Northwestern University, Northwestern Memorial Hospital, Northwestern Medical Faculty Foundation

Project Title: Mitral Valve Pathology: A Quantitative Assessment Pre- and Post-Repair

Submission Accession Number: 200606-0680
Submission(s) Considered: New Project
Status: APPROVED **Project Expiration: 6/27/2007**

On a member of the Institutional Review Board considered and approved your submission referenced above for a one year period ending 6/27/2007. IRB approval includes approval of the protocol, HIPAA Compliance and waiver of written and verbal consent.

Version Date: 06/08/2006 Waiver of Consent
Version Date: 06/07/2006 Protocol

IRB approval is granted with the understanding that the investigator will:

- Change neither the procedures nor the consent form without prior IRB review and approval of those changes. Proposed changes must be submitted via the IRB Revisions Submission Form found on the OPRS website.
- Report any serious adverse events (SAEs) involving an NU subject to the IRB within 5 days.
- Report any unanticipated problems involving risks to subjects or adverse events (AEs) to the IRB within 30 days.
- Submit a periodic review (PR) to the IRB 6 weeks prior to the expiration of this approval. If renewal is not obtained by the expiration date indicated above, the project will be closed.
- Send a copy of the final approved consent form and a copy of this approval letter to the Office of Sponsored Research (OSR) if this is a sponsored project. Additionally, OSR must be contacted if any amendments are made to this project that may affect the award.
- **For research involving Jesse Brown Veteran's Affairs Medical Center (JBVAMC):** Research may not be initiated at JB until after JBVAMC Research and Development (R&D) Committee approval. Use only IRB-approved and stamped VA consent documents.

Sincerely,

Eileen Yates, BA, CIP
Senior IRB Coordinator

EXHIBIT
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NMH

For more information regarding OPRS submissions and guidelines, please consult http://www.northwestern.edu/research/OPRS/irb
This Institution has an approved Federalwide Assurance with the Department of Health and Human Services: Assurance ID# FWA00001549.

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irb@northwestern.edu
Phone 312-503-9338
Fax 312-503-0555

NORTHWESTERN UNIVERSITY

June 29, 2006

Patrick McCarthy, M.D.
Cardiac Surgery
201 E. Huron Street
Galter 10-105

IRB Project Number: 1532-004

Project Title: Mitral Valve Pathology: A Quantitative Assessment Pre- and Post-Repair

Review Procedure: Expedited
Attachments: Waiver of Authorization Form

Dear Dr. McCarthy:

The Institutional Review Board, in compliance with section 45 CFR 164 512 (i) 2(ii) of the HIPAA Privacy Rule and with Northwestern University's HIPAA Research Policy, has reviewed your request for Waiver of Authorization form dated 6/8/2006.

Based on the information provided, the IRB determined that:

- The use of disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
  a) An adequate plan to protect the identifiers from improper use and disclosure;
  b) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law: and
  c) Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by HIPAA.
- The research could not practicably be conducted without the waiver, and
- The research could not practicably be conducted without access to and use of the Protected Health Information;

and therefore **approved Waiver of Authorization for this research.**

Please note that this is a one-time approval and that you do not need to re-submit the HIPAA response form with your periodic review submission.

Sincerely,

Eileen Yates, BA, CIP
Senior IRB Coordinator

EXHIBIT
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For more information regarding OPRS submissions and guidelines, please consult http://www.northwestern.edu/research/OPRS/irb.
This Institution has an approved Federalwide Assurance with the Department of Health and Human Services' Assurance ID# FWA00001549.

NMH 000006

IRB Review - Office Use Only	IRB Date Stamp - Office Use Only	IRB Accession Number
Northwestern University Institutional Review Board EXPEDITED REVIEW Date/Initials [illegible]	RECEIVED JUN 2 0 2006 OPRS	2006060-0680 Office Use Only IRB Project Number: 1532-004

Northwestern University – Office for the Protection of Research Subjects

HIPAA Waiver of Authorization Form

Instruction:
Consult Northwestern University's HIPAA Research Policy for additional guidance
http://www.northwestern.edu/research/OPRS/irb/handbook/NU HIPAA policy doc
Waivers and exceptions (other than de-identified information) are not available if your research involves sensitive information including information related to AIDS/HIV, mental health or substance abuse or genetics.
Forward this submission OPRS, Rubloff, 7th Floor, 750 N. Lake Shore Drive, Chicago, IL 60611 or
Hogan, G100-6th Floor, 2205 Tech Drive, Evanston, IL 60208
HANDWRITTEN FORMS WILL NOT BE ACCEPTED.

1. Date of Preparation: 6/8/06 REVISED 6/20/06

2. Project Title:
Mitral Valve Pathology: A Quantitative Assessment Pre- and Post-Repair

3. Investigators:

Principal Investigator Name:	Patrick M. McCarthy	☒ Faculty ☐ Faculty Advisor	
School/Center:	Medical		
Department/Division:	Surgery/ Cardiothoracic Division		
Mailing Address:	201 E. Huron		
(Building/Room #/Campus):	Galter 10-105		
Telephone Number:	312-695--3114	Fax Number:	5-1903
Pager Number:	5-5420	E-Mail Address:	pmccart@nmh.org

Submission Preparer:	Anna Huskin, RN		
School/Center:	Medicine		
Department/Division	Cardiology		
Mailing Address:	201 E. Huron		
(Building/Room #)	Galter 11-215		
Telephone Number:	312-695--4067	Fax Number:	5-6854
E-Mail Address:	ahuskin@nmh.org		

4. Abstract Summary: (Please use the abstract summary that is included in the New Project Submission Form, if applicable) *Summarize the proposed research project. The summary should be written in non-technical language that can be understood by non-scientific members. The information must include: 1) a brief statement of the problem and related theory supporting the reason for the study. 2) a brief but specific description of the procedure(s) involving human subjects.*
(This summary should be 200 words or less [approximately ½ page].)

Mitral regurgitation (MR) is the most commonly encountered valve lesion in modern clinical practice. In fact, there about 500,000 discharge diagnoses of mitral valve disease annually in the United States. MR may be due to a primary abnormality of the valve apparatus or may be secondary to another cardiac disease. Patients with chronic severe MR may remain asymptomatic for years; however, as the disease progresses patients may experience dyspnea (shortness of breath), paroxysmal nocturnal dyspnea, and palpitations due to atrial fibrillation. Mitral regurgitation may eventually result in dilation of the left ventricle dilation and hypertrophy to accommodate for the increasing regurgitant volume.

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This increased volume leads to enlargement of the left atrium and in turn causes dilation of the mitral valve annulus and worsening of MR. If left untreated, mitral regurgitation can eventually lead to congestive heart failure and even death.

This is a single-center, retrospective study. No randomization will be used. There are no study interventions. Medical record reviews will be conducted on patients who underwent mitral valve repair between April 2004 and June 2006. Data collected for this study can be seen in the Protocol Appendix (pages 13-17). Race, gender, economic class, age, and mental ability will have no influence on study inclusion. The primary objectives of this project are 1) Quantify mitral valve pathology pre- and post-repair by echocardiographic examination and direct surgical analysis. 2) Assess the effects of the CMA IMR and Myxo ETlogix rings on mitral valve geometry and reduction in mitral regurgitation, as measured by 2D/3D echocardiography.

5. Project Funding:

5.1 Project initiated by: ☐ Sponsor ☒ Investigator ☐ Other (Explain)

5.2 Funding Source:
☐ Federal/State ☐ Foundation ☐ Industry Sponsored ☐ Voluntary Health Organization
☐ Northwestern University Sponsored ☐ Internal Sources ☐ Department ☐ Gift
☒ Other (Explain) **No funding- project supported by the Bluhm Cardiovascular Institute**

5.3 Sponsor/Company: Contract or Grant Number:
Contact Name: Contact Phone:

6. Project Site(s): *(Check all boxes indicating where the study is conducted.)*

☒ Northwestern University (NU)
☐ Northwestern Center for Clinical Research (NCCR)
☒ Northwestern Medical Faculty Foundation (NMFF)
☒ Northwestern Memorial (NM)
- ☒ Northwestern Memorial Hospital
- ☐ General Clinical Research Center (GCRC)
- ☐ Northwestern Memorial Home Health Care (NMHHCC)
- ☐ Northwestern Memorial Physician's Group (NMPG)

☐ Rehabilitation Institute of Chicago (RIC)
☐ VA - Lakeside Division (VALMC)
☐ Evanston Northwestern Hospital (ENH)
☐ Children's Memorial Hospital (CMH)
☐ Edward H. Kaplan & Associates
☐ Mercy Group
☐ Midwest Cancer Research Group
☐ Midwest Center Hematology/Oncology – Silver Cross
☐ Other (Specify and Explain)

7. Protected Health Information (PHI):

Describe the criteria you will use for selecting particular subject records:
All patients who underwent mitral valve repair from April 2004 through June 2006 will be reviewed retrospectively. Race, gender, economic class, age, and mental ability will have no influence on study inclusion.

The purpose of accessing these records is (please check below):
☒ to collect retrospective data for purpose of the study as described in the study protocol
☐ to recruit: Identification of potential participants.
☐ Other (please describe):

Please check below the PHI elements that you intend to use and to collect for your research:

☒ Names
☐ All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if according to the current publicly available data from the Bureau of the census: a) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and b) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, death date; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
☐ Telephone numbers
☐ Fax numbers
☐ Electronic mail addresses
☐ Social security numbers
☐ Medical record numbers
☐ Health plan identification numbers

- ☐ Account numbers
- ☐ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers, including license plate numbers
- ☐ Device identifiers and serial numbers
- ☐ Web Universal Resource Locators (URLs)
- ☐ Internet Protocol (IP) address numbers
- ☐ Biometric identifiers, including finger and voice prints
- ☐ Full-face photographic images and any comparable images
- ☐ Any other unique identifying number, characteristic or codes. If yes, explain:

8. Minimal Necessary Standard:
Describe how the information you are collecting (indicated above in #7) is the minimally necessary required information to conduct your research. **Collecting information about characteristics of the entire study population, determining outcomes (succ rate, complication rate, etc.) and avoidance of record duplication can only be accomplished through access to and us of the protected health information.**

9. Full Waiver = Waiver for Purposes other than Recruitment This section does not apply ☐

Please complete this section only if the purpose of your research study is to collect retrospective information from a medical chart review, and if your study qualifies for a waiver of consent form.

9.1 The proposed use of the protected health information presents no more than minimal risk to the privacy of individuals because:

- **Minimal risk has been defined as the amount of risk that an individual would encounter in their daily life. Using this definition, the study does not involve any physical risk to the patient. There are no prescribed interventions for this study. Any reports will have information analyzed in aggregate to make individual identification impossible.**

9.2 Describe the plan to protect identifiers or links to identifiers from improper use and disclosure:

- **For this study protected health information will be maintained in both paper and electronic formats. Access to protected health information maintained in a paper format will be secured in a locked document storage room when the information is not in use. Access to protected health information maintained in electronic format will be secured by limiting access to the information using password protection and operating system user permission.**
- **Data is only available to persons entering data (coordinator) and to the Investigator/Co-Investigators. Study data will be stored in a password-protected computer and only the authorized study personnel will have access to the data after it is entered. The coordinator will keep paper copies of the Data Collection Forms (DCF) in locked file cabinets, accessible to authorized personnel only, until later entry into the computer spreadsheet. No personally identifying information will ever be presented/published**

9.3 Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of research:

- **Study documentation, hard copies and electronic, will be retained for a period of five years following completion of data analysis and manuscript preparation. At this time the site will delete all computer files and all paper records will be shredded.**

9.4 The research could not practicably be conducted without the waiver of authorization because:

- **Due to the large number of patients (> 100) undergoing mitral valve repair it would be difficult to contact all patients, as contact information may not be current, and some of the patients may no longer be alive.**

9.5 The research could not practicably be conducted without access to and use of protected health information because:

- **This research could not practicably be conducted without access to and use of the protected health information because protected health information (i.e., patient name and DOB) is necessary to identify patients who satisfy the patient selection criteria. Collecting information about outcomes (complications, success rate, etc.) of mitral valve surgery treatment can only be accomplished through access to and use of protected health information**

10. Where will you obtain the protected health information (PHI) that you plan to use in this research study?
In order to collect the research data, you will need to access Patient Records of the following Institution: please check the appropriate site(s) below:

- ☒ Northwestern University (NU)
- ☐ Northwestern Center for Clinical Research (NCCR)
- ☒ Northwestern Medical Faculty Foundation (NMFF)
- ☒ Northwestern Memorial (NM)
  - ☒ Northwestern Memorial Hospital
  - ☐ General Clinical Research Center (GCRC)
  - ☐ Northwestern Memorial Home Health Care (NMHHCC)
  - ☐ Northwestern Memorial Physician's Group (NMPG)
- ☐ Rehabilitation Institute of Chicago (RIC)
- ☐ VA - Lakeside Division (VALMC)
- ☐ Evanston Northwestern Hospital (ENH)
- ☐ Children's Memorial Hospital (CMH)
- ☐ Edward H. Kaplan & Associates
- ☐ Mercy Group
- ☐ Midwest Cancer Research Group
- ☐ Midwest Center for Hematology/Oncology-Silver Cross
- ☐ Other (Specify and Explain)

11. List all the entities or individuals who may use or will have access to protected health information:
(Please note: The IRB Board Members and the OPRS staff have access to all research records as part of their compliance and quality control oversight responsibilities.)

- ☒ Principal investigator
- ☐ Data Coordinating Centers
- ☐ Contract Research Organizations Offices (Name:)
- ☐ Sponsors
- ☒ Research Data Management Offices (Name Offices: **Bluhm Cardiovascular Institute's Clinical Trials Unit**)
- ☐ Other (Specify and Explain:)
- ☒ Other NU staff working on the project
- ☐ Collaborating Centers (Name Centers.)
- ☐ Government Agencies

12. Waiver for Recruitment purposes only: **This section does not apply ☒**

As of December 13, 2005, a waiver for recruitment is not necessary if you are receiving patient information from NMH, NMFF and/or RIC for the purpose of contacting these patients to enroll them in a research study. If you are receiving potential subject information from any other healthcare provider, you are required to complete this section.

This waiver is considered a PARTIAL Waiver; you will need to obtain authorization from subjects who consent to participate in your study.

12.1 Any PHI used to identify individuals to enroll as study participants will not be removed form the source's site
Please check "Yes" or "No" below If "No", the waiver cannot be granted.
☐ Yes ☐ No

12.2. Describe the processes used for selecting subjects and the methods of recruitment?

12.3 Who will review the records to gather information?
(Note: this person(s) must be listed on the authorized personnel list of the IRB's NPSF and must be allowed to review the records under IRB regulations of the Common Rule (e.g., the treating physician or a study coordinator who is also a nurse in the practice are persons who would, under IRB rules, be allowed to review the records.)
Name of Person doing review of the records:

The IRB will require a letter from the relevant physician or authorized personnel of that physician evidencing their consent to permit the above named individual(s) to review the records. A template letter is attached to this application and should be revised to reflect the relevant physician or authorized personnel from whom you seek permission, as well as the individual(s) who will be reviewing the records. IRB will not grant the Waiver for Recruitment without this letter

12.4 The proposed use of the protected health information presents no more that minimal risk to the privacy of individuals because:

12.5 The research could not practicably be conducted without the waiver of authorization because:

12.6 The research could not practicably be conducted without access to and use of protected health information because:

13. Investigator/Faculty Advisor Assurance

Investigator's Assurance:

11. List all the entities or individuals who may use or will have access to protected health information:
(Please note: The IRB Board Members and the OPRS staff have access to all research records as part of their compliance and quality control oversight responsibilities)

- ☒ Principal investigator
- ☐ Data Coordinating Centers
- ☐ Contract Research Organizations Offices (Name:)
- ☐ Sponsors
- ☒ Research Data Management Offices (Name Offices: Bluhm Cardiovascular Institute's Clinical Trials Unit)
- ☐ Other (Specify and Explain:)
- ☒ Other NU staff working on the project
- ☐ Collaborating Centers (Name Centers:)
- ☐ Government Agencies

12. Waiver for Recruitment purposes only: This section does not apply ☒

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12.1 Any PHI used to identify individuals to enroll as study participants will not be removed form the source's site
Please check "Yes" or "No" below. If "No", the waiver cannot be granted.
☐ Yes ☐ No

12.2. Describe the processes used for selecting subjects and the methods of recruitment?

12.3 Who will review the records to gather information?
(Note: this person(s) must be listed on the authorized personnel list of the IRB's NPSF and must be allowed to review the records under IRB regulations of the Common Rule (e.g., the treating physician or a study coordinator who is also a nurse in the practice are persons who would, under IRB rules, be allowed to review the records.)
Name of Person doing review of the records:

The IRB will require a letter from the relevant physician or authorized personnel of that physician evidencing their consent to permit the above named individual(s) to review the records. A template letter is attached to this application and should be revised to reflect the relevant physician or authorized personnel from whom you seek permission, as well as the individual(s) who will be reviewing the records. IRB will not grant the Waiver for Recruitment without this letter

12.4 The proposed use of the protected health information presents no more that minimal risk to the privacy of individuals because

12.5 The research could not practicably be conducted without the waiver of authorization because:

12.6 The research could not practicably be conducted without access to and use of protected health information because:

13. Investigator/Faculty Advisor Assurance

Investigator's Assurance:

- I certify that the information provided in this application is complete and accurate, and that I will comply with the use and disclosure restrictions described above. Information about data will not be used or disclosed to any other person or entity.
- I agree to notify the NU IRB of any material change in the statements made on this application. I further certify that any and all protected health information obtained in the course of my research is that amount which is minimally necessary to conduct the research.

Patrick M. McCarthy, MD Principal Investigator's Name	PMcC Principal Investigator's Signature	6-12-06 Date
Student Investigator's Name	Student Investigator's Signature	Date
Faculty Advisor's Name	Faculty Advisor's Signature	Date

Mitral Valve Pathology:
A Quantitative Assessment Pre- and Post-Repair

Patrick M. McCarthy, MD; Principal Investigator

Thomas G. Gleason, MD; Co-Investigator
Edwin C. McGee, MD, Co-Investigator
Nalini Rajamannan, MD; Co-Investigator
Vera H. Rigolin, MD; Co-Investigator

Supported by: The Bluhm Cardiovascular Institute

Patrick M. McCarthy M.D.
Chief, Division of Cardiothoracic Surgery
Co-Director, Bluhm Cardiovascular Institute
Professor of Surgery, Feinberg School of Medicine
Northwestern University
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pmccart@nmh.org

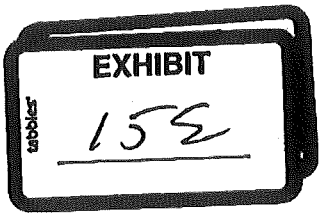


Table of Contents

I. BACKGROUND/RATIONALE

A. Mitral Valve Disease

Valvular heart disease is the fifth most common cardiovascular disorder affecting millions of people worldwide.[1] Fortunately, during the last three decades there have been remarkable advances in terms of understanding, diagnosing and managing valvular heart disease. These advances provide patients the promise of improved quality of life and the potential for a normal lifespan.[2,3] However, as a result of these advances the number of patients undergoing complex valve repairs has been dramatically increasing over the past few years. In fact, estimates show that valvular surgical cases will increase by about 14% from 2003 to 2008 (from 89,981 to 102,578), most of which will be for repairs of the mitral valve.[4]

The mitral valve (MV) is a complex structure composed of two valve leaflets (anterior and posterior), the mitral valve annulus (which forms a ring around the valve leaflets), the papillary muscles (which tether the valve leaflets to the left ventricle, preventing them from prolapsing into the left atrium), and the chordae tendineae (which connect the valve leaflets to the papillary muscles). The posterior leaflet is the widest around the annulus and divided into three scallops, P1, P2, and P3. P1 is adjacent to the antero-lateral commissure and is closest to the aorta (anterior). The opposing sections of the anterior leaflet are designated A1, A2 and A3. [5,6] The two leaflets are separated at the annulus by the posteromedial and anterolateral commissures. A dysfunction of any of these components of the mitral valve apparatus can cause mitral regurgitation.

B. Mitral Regurgitation

Mitral regurgitation (MR) is the most commonly encountered valve lesion in modern clinical practice. In fact, there about 500,000 discharge diagnoses of mitral valve disease annually in the United States.[7] MR may be due to a primary abnormality of the valve apparatus or may be secondary to another cardiac disease. Causes of primary MR include myxomatous mitral valve (also called degenerative disease, or MV prolapse), inflammatory (i.e., rheumatic heart disease), infective endocarditis, trauma (i.e., ruptured chordae) and congenital causes. The secondary (functional) causes of MR include ischemic heart disease, left ventricular systolic dysfunction and hypertrophic cardiomyopathy.

Patients with chronic severe MR may remain asymptomatic for years because the regurgitant volume load is well tolerated as a result of compensatory ventricular dilatation. However, as the disease progresses patients may experience dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and palpitations due to atrial fibrillation.[8] Mitral regurgitation may eventually result in left ventricle dilation and hypertrophy to accommodate for the increasing regurgitant volume.[8-10] This increased volume leads to enlargement of the left atrium and in turn causes dilation of the valve annulus and worsening of leaflet coaptation. As the severity of mitral regurgitation increases, the left ventricle (LV) continues to dilate leading to increases in systolic wall stress and end-systolic volume with left ventricle dysfunction. If left untreated, mitral regurgitation can eventually lead to congestive heart failure and even death.[8-11]

Today, the optimal surgical intervention for mitral regurgitation is valve repair. Surgical repair of a valve involves rebuilding the valve apparatus so that it functions properly. As compared with valve replacement, successful valve repair results in superior hemodynamics, lower operative risk, better

long-term survival, lower risk of thromboembolic complications, better preservation of ventricular function, and eliminates the need for long-term anticoagulation.[11]

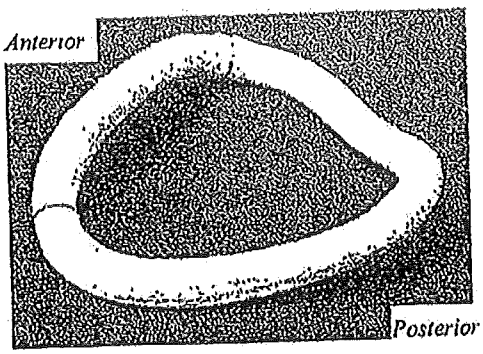
C. Myxomatous Mitral Regurgitation

The most common cause of mitral regurgitation in the United States is myxomatous (also known as degenerative , "floppy" or "billowing" valve) degeneration of the mitral valve.[6,12] Degeneration of the MV is caused by a genetic abnormality in the connective tissue resulting in thickened, elongated valve leaflet(s) and chordae tendineae and commonly involves thickening and dilation of the annulus.[12-14] The elongation of the leaflets and chordae tendineae prevent the mitral valve leaflets from fully coapting when closed, causing the free edge of the leaflets to over-ride the plane of the annulus resulting in a prolapse into the left atrium; thereby causing mitral regurgitation.

The gold standard for repair of myxomatous valves is performed via a quadrangular resection followed by either annulus placation or and/or sliding leaflet technique (sliding-plasty).[15] The quadrangular technique involves removal of a section of the valve leaflet, most commonly the posterior leaflet, cinching the remaining tissues together, and reinforcing the repair with an annuloplasty ring; sliding-plasty procedure reduces the height of the posterior leaflet, which ultimately moves the coaptation line posteriorly.[15,16] Using these techniques, up to 90% of patients can undergo repair of myxomatous valves[16,17]; however, these techniques are very time-consuming, quite difficult to perform and require numerous years of experience to perform successfully As a result, it is likely that a significant percentage of these cases are instead addressed via a valve replacement.

After quadrangular resection myxomatous valve repairs are most often accompanied by implantation of an annuloplasty ring. An annuloplasty ring reduces the size of the mitral orifice and allows for improved leaflet coaptation as well as to stabilize repairs done on the valve leaflets or support structures. Nevertheless, repair with current ring systems do not address the specific etiology of myxomatous MV (excessive leaflet tissue), which may lead to a serious complication known as systolic anterior motion (SAM). This increased risk of SAM after repair of myxomatous valves has been shown to be due to excess tissue or anterior displacement, or both, of the leaflet coaptation point. [18,19]

The Myxo ETlogix Annuloplasty Ring was specifically developed for patients with myxomatous mitral valves to help eliminate the need to perform the complex, time-consuming sliding-plasty procedure. The Myxo ETlogix is the first ring to address designed to reshape the annulus to accommodate the larger leaflets (increases AP distance by 29%) or as previously described by Carpentier - allows the door (leaflets) to fit the frame (annulus), but by reshaping the frame instead of cutting the door.[20] In addition, the 3-D design is elevated at the P2 segment; thereby, pulling the posterior leaflet away from the aortic outflow tract to reduce the risk of SAM. The design of the ring should result in a simplification of the complex repair and thus, will drive more widespread adoption of mitral valve repair.



Myxo ETlogix Ring

Previous findings suggest that preoperative measurements such as height of the anterior and posterior leaflets, septal thickness, left ventricular contractility, and distance of the coaptation point of the leaflets to the septum are useful in predicting those patients at higher risk for developing SAM.[21,22] In addition, studies have also shown that reducing excessive leaflet tissue and posterior leaflet height has been shown to reduce SAM following repair of the mitral valve.[23,24]

D. Ischemic mitral regurgitation

Ischemic mitral regurgitation (IMR) most often results from coronary heart disease, particularly in the setting of a prior MI.[25] IMR results from several anatomic and pathophysiological changes including 1) left ventricular wall remodeling [wall motion abnormalities, dilatation] 2) papillary muscle displacement 3) dilatation/distortion of mitral annulus, due to left ventricular enlargement.[25,26] The initiating insult in IMR is ventricular, specifically left ventricular remodeling following myocardial ischemia or infarction. This remodeling changes the shape of the LV, which ultimately leads to poor leaflet coaptation, particularly the posterior leaflet during systole.[12]

The outlook for the patient with ischemic MR is substantially worse than that for regurgitation from other causes.[3,9,27-29] A worse prognosis accrues from the fact that ischemic MR is usually caused by LV dysfunction due to myocardial infarction. Furthermore, the mitral valve itself is usually anatomically normal and MR is secondary alterations in the geometry of the left ventricle and to papillary muscle dysfunction and/or displacement making repair of the valve more difficult.[3,30]

Surgical repair of IMR is often accomplished by placement of an undersized annuloplasty ring. Nevertheless, using the standard, symmetric annuloplasty rings still leaves up to 30% of patients with residual or recurrent mitral regurgitation.[26,31-34] The Carpentier-McCarthy-Adams IMR ETlogix Annuloplasty Ring (CMA IMR ring) was specifically developed for patients with ischemic mitral regurgitation. It is the first asymmetric ring designed to treat asymmetric annular dilatation, especially in the anterior-posterior (A-P) direction, which is observed in patients with IMR.[35-37] This annuloplasty ring can be fitted strategically to the mitral valve to reduce the antero-posterior dimensions to improve function and reduce the amount of regurgitation in persons with IMR. The asymmetric 3-D design with reduced middle to medial (P2-P3) curvature and a slight dip at the P2-P3 segments increases coaptation of the tethered P2-P3 segments.

IMR ETlogix ring

The optimal treatment of IMR is a matter of controversy and there is still wide variation in practice among cardiovascular surgeons.[12,38] We aim to investigate the efficacy and safety of CMA IMR ring in surgical treatment of IMR.

E. Quantitative Assessment

Echocardiography is routinely used to assess the mechanisms of valve dysfunction and evaluate the results of valve repair. Intraoperative echocardiographic examination aides in determining predictors of SAM such as the location and severity of leaflet prolapse, leaflet mobility, point of leaflet coaptation and thickness of interventricular septum.[15] Currently, surgeons at NMH are directly measuring the height of mitral valve leaflets using specially designed calipers. Through these direct measurements it was identified that anterior leaflet height (A2) and width (commissure-to-commissure [C-C]) varied extensively in patients with myxomatous mitral valve disease. This information may explain the variability used for selection of ring sizing [e.g. tall A2, narrow C-C, or the opposite can occur]. Quantification of mitral valve pathology pre- and post-repair by echocardiographic examination and direct surgical analysis could potentially allow for tailoring of the valve repair techniques. Quantifying the precise leaflet(s) measurements (i.e. height of P2, P3, etc.) that result in successful valve repairs may allow for a more predictable repair and advance this surgical technique from an art to a science.

II. Study Objectives

Primary objectives

1. Quantify mitral valve pathology pre- and post-repair by echocardiographic examination and direct surgical analysis.
2. Assess the effects of the CMA IMR and Myxo ETlogix rings on mitral valve geometry, as measured by 2D/3D echocardiography.

Secondary objectives.

1. Evaluate early results of myxomatous mitral valve repair using the Myxo ETlogix Annuloplasty Ring in terms of reduction in mitral regurgitation.
2. Determine early results of surgical mitral valve repair with the CMA IMR ring in terms of the reduction of ischemic mitral regurgitation.
3. Compare outcomes of mitral valve repair using the Myxo ETlogix Annuloplasty ring and CMA IMR ring to other annuloplasty ring systems.
4. Disseminate research findings through, scientific conferences, peer-reviewed journals and other publications.

III. Study Design

This is a single-center, retrospective study. No randomization will be used. Medical record reviews will be conducted on patients who underwent mitral valve repair between April 2004 and June 2006. Race, gender, economic class, age, and mental ability will have no influence on study inclusion.

Data will be obtained from the Investigator's and Co-Investigator's patient records at Northwestern Memorial Hospital (NMH), Northwestern Medical Faculty Foundation (NMFF) and from our patient population in the Society of Thoracic Surgeons (STS) database (note: In accordance with STS guidelines, as a Participant in the database we are able to use our individual database-derived information for clinical research purposes[39]). All available inpatient (NMH) and outpatient (NMFF) echo studies (2D/m-mode, Doppler, stress echo, RT3DE, and TEE) will be reviewed. Echo and clinical parameters pre- and post-surgery will be compared. All data gathered during this study is

normal and customary clinical information recorded by treating physicians. Data collected for this study can be seen in Appendix A.

IV. Potential Risks/Confidentiality

Minimal risk has been defined as the amount of risk that an individual would encounter in their daily life. Using this definition, this study does not involve any physical risk to the patient. There are no prescribed interventions. All data that are collected are from pre-existing medical record reviews. The study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants.

In cases where study data is published or shared with other institutions, data will be de-identified. It will never include identifiable information, such as name, social security number, address or medical record number in order to maintain patient's identity In addition, in most cases the data will not include identifiers other than age, race, sex, and diagnosis since most reports are only concerned with descriptive summaries and statistical analyses of "grouped" data. (*Note*. Patients will not be informed of any study results, as data is analyzed and reported in aggregate.)

V. Ethics

All patients who underwent mitral valve repair from April 2004 through June 2006 will be reviewed retrospectively. Race, gender, economic class, age, and mental ability will have no influence on study inclusion.

We are requesting a waiver of verbal/written consent and Health Insurance Portability and Accountability Act (HIPAA) authorization for this retrospective analysis based on the following points:

- The use or disclosure of protected health information involves no more than minimal risk to the individuals (HIPAA Privacy; Title 45 CRF Part 46)
  - Minimal risk has been defined as the amount of risk that an individual would encounter in their daily life. Using this definition, this retrospective project does not involve any risk to the patients; it is a review of pre-existing data only. There are no prescribed interventions. All data that are collected are confidential and no patient identifiers will be transmitted outside the participating institution.
  - Any reports or publications will have information analyzed in aggregate to make individual identification impossible. No identifying information will ever be presented or published.

- The alteration or waiver will not adversely affect the privacy rights and the welfare of the individuals (Title 45 CFR Part 46)
  - Patient-identifying information will be protected and will not be released.
  - Data will be presented in aggregate and subject identifiers will not be used.
  - No personal identifying information will ever be presented or published.

- There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law (HIPAA Privacy Rule);
  - All paper records produced or collected in connection with this project (i.e , data collection forms, electronic files) will be destroyed 5 years following completion of data analysis. Paper documents will be destroyed by shredding and will be performed in a manner that ensures information cannot be reconstructed. Electronic records will be erased or destroyed in a manner that guarantees that the risk of disclosure of information is removed.

- There are adequate written assurances that PHI will not be used or disclosed to a third party except as required by law, for authorized oversight of the project, or for other uses and disclosures permitted by the Privacy Rule (HIPAA Privacy Rule);
  - Access to protected health information is limited to only those individuals who need to have access to the information to perform their responsibilities for the study.
  - For this study protected health information will be maintained in both paper and electronic formats. Access to protected health information maintained in a paper format will be secured in a locked document storage room when the information is not in use. Access to protected health information maintained in electronic format will be secured by limiting access to the information using password protection and operating system user permission.

- The project could not practicably be conducted without a waiver of individual informed consent:
  - Due to the large number of patients (> 125) undergoing mitral valve repair at Northwestern Memorial Hospital between April 2004 and June 2006 it is not practicable to obtain consent as contact information may longer be current, and some of the patients may no longer be alive.

- The project could not practicably be conducted without access to and use of the protected health information (HIPAA Privacy Rule);
  - Collecting information about outcomes (reduction in MR, complications, success rate, etc.) of mitral valve repair can only be accomplished through access to and use of protected health information.

VI. DATA MANAGEMENT/SECURITY

Study data will be stored by patient's name and date of birth in a Microsoft Excel spreadsheet for analysis on a secure, password protected computer. Only the study investigators and authorized research personnel will have access to this data. This data will be housed on a network that is separated from the internet through the use of a firewall. By design, this denies all external access to the database. To ensure integrity and confidentiality of the data, the system will not run without the entry of a valid username and password.

VII. RECORD KEEPING

The paper file for each subject will contain the corresponding Data Collection Forms. The participant's study folder will be identified by a numeric ID (MVR001, MVR002) and patient initials and will be kept in the investigators or study coordinator's office in a locked file cabinet. Access to safe and locked drawers will be granted only to the Investigator and study coordinator.

Study documentation, hard copies and electronic, will be retained for a period of five years following completion of data analysis and manuscript preparation. At this time the site will delete all computer files and all paper records will be shredded.

VIII. DATA ANALYSES

Descriptive statistics will be used to compare echocardiographic and surgical measurements before and after surgery for valvular regurgitation. Parametric tests will be employed to assess the significance of echocardiographic changes. Appropriate comparison will be made within and between patients The differences in other echocardiographic measurements between preoperative and postoperative values will be analyzed by paired *t*-test.

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APPENDIX A: DATA COLLECTION

Data collection is broken into four periods: Preoperative, Operative (MV Repair), Postoperative prior to discharge, and Follow-up (if available). The following data will be obtained for this retrospective study:

Preoperative Patient characteristics:

1) Patient Demographics:
   a) Age (at time of procedure)
   b) Gender
   c) Height (cm)
   d) Weight (kg)

2) Previous cardiac comorbidities
   a) Arrhythmia
   b) Cerebrovascular accident (yes/no)
   c) Number of coronary arteries with stenosis (>50%)
   d) Recent MI (<14 days) (yes or no)
   e) Previous cardiac operations (PCI, CABG, etc)
   f) Family history of coronary artery disease (yes/no)
   g) Re-operation (yes/no)
   h) Other significant valvular disease

3) Non-cardiac comorbidity
   a) Diabetes
   b) Hyperlipidemia
   c) Hypertension (DBP > 90 mmHg)
   d) Hyperlididemia (yes or no)
   e) Smoking
      i) Currently smoking (yes/no)
      ii) Previously smoke (yes/no)
   f) Chronic obstructive pulmonary disease (COPD)
   g) Renal insufficiency (creatinine ≥ 2.0 mg/dL)
   h) Other

4) Emergent operation (yes or no)

5) Echocardiographic evaluations- Refer to echo data collection

Mitral Valve Repair Procedure:

Pre-Repair:

1) Date of repair
2) Regurgitation: (None; +1;+2; +3; +4)
3) Etiology: (Myxomatous;Ischemic; Calcific; Rheumatic; Radiation; Cardiomyopathy; Other)
4) Leaflet (posterior): (normal; flail (prolapse); tethering)
5) Leaflet Height (mm): (P1; P2; P3; A2)
6) Lesion: (Posterior, Anterior, bi-leaflet)

Intra-Operative Repair

1) Commissure to Commissure (mm)
2) Trigone to Trigone (mm)
3) Quandragular Resection (yes/no)
   a) Width of Resection (mm)
   b) Width of Resection (mm) (after annuloplasty)
   c) Width of Resection (mm) (after compression)
4) Sliding Annuloplasty (yes/no)

Post-Repair

1) Valve Procedure
   a) Annuloplasty Only
   b) Reconstruction w Annuloplasty
   c) Reconstruction w/o Annuloplasty
   d) Repair w reconstruction
      i) Chordal Transfer (yes/no)
      ii) Quadrangular Resection (yes/no)
      iii) Alfieri Repair
      iv) Plication
      v) Compression
      vi) Patch
2) X-Clamp time (hh:mm)
3) CPB time (hh:mm)
4) Regurgitation: (None; +1; +2, +3; +4)
5) Leaflet Height (mm): (P1; P2; P3; A2; P-middle)
6) Coaptation Depth/ Overlap (mm): (P1; P2; P3; A1; A2; A3)
7) Annuloplasty Ring (mm)
8) Mitral Ring Type: Physio; Et-Logix; Myxo-logic
9) Inside of Ring to Coaptation Point (mm)
10) Concomitant procedures
   a) Coronary artery bypass graft (# of vessels)
   b) Left ventricular reconstruction
   c) Maze procedure
   d) Ligation of left atrial appendectomy
   e) Tricuspid repair
   f) Patent foramen ovale (PFO) closure

g) Aortic root /valve replacement
h) Other

5) Operative complications
   a) Atrial Fibrillation (yes or no)
   b) Arrhythmia
   c) Bleeding
   d) Pleural effusion
   e) Cardiac arrest
   f) Congestive heart failure
   g) Pericardial effusion
   h) Death
   i) Other

6) Transesophageal echocardiography (TEE)- Refer to echo data collection forms

Postoperative Prior to Discharge

1) Complications
   a) AF (yes or no)
   b) Arrhythmia
   c) Bleeding
   d) Pleural effusion
   e) Cardiac arrest
   f) Congestive heart failure
   g) Death
   h) Other
   i) NYHA class (I-V)
2. Echocardiography (2-10 days after surgery)- Refer to echo data collection forms

Follow-up (6 months after operation):

Collect, if available

1) Medical history for the follow-up period (e.g., hospitalizations)
2) NYHA Classification (I-V)
3) Echocardiography- Refer to echo data collection forms

Echocardiography Data Collection

Mitral Valve Repair
Echocardiography Data Collection

Demographics

Date of Echo __/__/____ (mm / yy) ☐ Preoperative ☐ Intraoperative ☐ Post op # days: _____

Patient Name _____ (last) _____ (first) _____ (middle)

Gender ☐ Female ☐ Male Race ☐ Caucasian ☐ Black ☐ Hispanic ☐ Asian ☐ Native American ☐ Other

*Date of Birth __/__/____ Age: _____

Location of Echo: ☐ NMH → ☐ 8th floor ☐ 19th floor ☐ Other, specify _____

*Type of Echo ☐ TEE (Transesophageal) ☐ TTE (Transthoracic) ☐ Dobutamine stress echo ☐ Exercise stress echo

Mitral Valve Data

Mitral Structure/Function

☐ 1 Normal
☐ 2. Rheumatic
☐ 3 Myxomatous (redundant)
☐ 4 Prolapse → ☐ Anterior leaflet ☐ Posterior leaflet ☐ Holosystolic ☐ Late systolic
☐ 5 Flail leaflets → ☐ Anterior leaflet (identify segment ↓) ☐ Posterior leaflet (identify scallop ↓)
☐ Medial ☐ Middle ☐ Lateral ☐ Multiple ☐ Medial ☐ Middle ☐ Lateral ☐ Multiple
☐ 6 Ruptured cordae → ☐ Anterior leaflet ☐ Posterior leaflet
☐ 7 Other chordal disease → ☐ Shortening ☐ Fusion ☐ Other
☐ 8 Leaflet elongation → ☐ Anterior leaflet ☐ Posterior leaflet
☐ 9 Leaflet thickening/calcification → ☐ Anterior leaflet ☐ Posterior leaflet
☐ 10. Leaflet mobility → ☐ Normal ☐ Abnormal (if abnormal →) ☐ Anterior leaflet ☐ Posterior leaflet
☐ 11. Annular calcification ☐ Mild ☐ Moderate ☐ Severe
☐ 12 Systolic anterior motion (SAM) → ☐ Anterior leaflet ☐ Posterior leaflet ☐ Chordal

Mitral Regurgitation

1 Severity ☐ None ☐ 1+ ☐ 2+ ☐ 3+ ☐ 4+ ☐ Not reported
2 Jet direction: ☐ Anteriorly-directed ☐ Posteriorly-directed ☐ Centrally-directed ☐ Wall impinging jet
3 Diastolic mitral regurgitation ☐ Present ☐ Absent
4. Quantitative Measurements (if MR present):
a Mitral regurgitant volume: _____ by pulsed Doppler echo method _____ by PISA color Doppler method
b Effective mitral regurgitant orifice area: _____ by pulsed Doppler echo method _____ by PISA color Doppler method

Mitral Valve Echo DCF
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Mitral Measurements

1. Anterior leaflet length (AL) to mitral valve contribution (annulus to coaptation). ____ (cm) ☐ Not reported
2. Posterior leaflet length (PL) to mitral valve contribution (annulus to coaptation). ____ (cm) ☐ Not reported
3. Residual leaf length (amount of leaflet beyond the mitral coaptation point) ____ (cm) ☐ Not reported
4. Distance of coaptation point to septum (C-Sept) ____ (cm) ☐ Not reported
5. Mitral Annular diameter ____ (cm) ☐ Not reported
6. Mitral Valve gradient ____ (mmHg) ☐ Not reported
7. Distance from coaptation point to annulus (Coapt Ann) ____ (cm) ☐ Not reported
8. Left ventricular internal diameter in systole (LVIDs) ____ (cm) ☐ Not reported
9. Mitral valve tethering area (MVTa) ____ ☐ Not reported
10. Mitral valve tethering heights (MVTh) ____ ☐ Not reported
11. Vena contracta width ____ ☐ Not reported
12. MR Grade. ____ ☐ Not reported
13. Ejection fraction (%) ____ ☐ Not reported

Mitral Valve Geometry

1. TA 4ch (cm^2) ____ ☐ Not reported
2. TA 2ch (cm^2) ____ ☐ Not reported
3. TA LAX (cm^2) ____ ☐ Not reported
4. MAD 4ch (cm): ____ ☐ Not reported
5. MAD 2ch (cm) ____ ☐ Not reported
6. MAD LAX (cm). ____ ☐ Not reported

Left Ventricle and Left Atrium

LVEDV (mL) ____ ☐ Not reported

LVESV (mL). ____ ☐ Not reported

Left Atrium area (cm^2). ____ ☐ Not reported

Anterior leaflet to Outflow Tract Distance: ____ ☐ Not reported

HCM = Hypertrophic cardiomyopathy

HOCM = hypertrophic obstructive cardiomyopathy