

Official study title: Utility of Three-dimensional Transesophageal Echocardiography in Right Ventricular Function Assessment in Surgical Aortic Valve Replacement, Mini-sternotomy Aortic Valve Replacement, and Transcatheter Aortic Valve Replacement

NCT05804240

Date: Dec 1, 2022

Jefferson Office of Human Research
Verbal Consent with Optional Use of Disclosure of PHI
OHR-8H
Version Date - FOR OHR USE: 1/20/20

Department: Anesthesiology
Principal Investigator: Yoshihisa Morita, MD

Study Title: Utility of three-dimensional transesophageal echocardiography in right ventricular function assessment in surgical aortic valve replacement, mini-sternotomy aortic valve replacement, and transcatheter aortic valve replacement

Lay Title: Right heart function assessment with 3D echocardiography in aortic valve surgery

Hello, my name is _____. I'm from Jefferson's Department of Anesthesiology Division of cardiac anesthesia.

I am calling to ask you to participate in our clinical research using echocardiographic assessments of your right heart function during your heart surgery.

I obtained your contact information from our electronic medical record system.

Transesophageal echocardiography (TEE) uses a narrow flexible tube containing a microscope which is inserted through your mouth into the esophagus and stomach to observe and evaluate your heart function. Insertion of this scope is standard of care during heart surgery. It is inserted after you are asleep, under general anesthesia, and allows us to observe your heart activity during the surgery. We are conducting a research study that consists of assessing the right side of the heart with TEE during your upcoming cardiac surgery. We estimate that this will take about 10 minutes of your time to complete.

The purpose of this research study is to compare right heart function during your surgery, before and after heart lung bypass, using TEE, which is part of the standard care. Using the same flexible tube and scope, we will be conducting 2-and 3-dimentional TEE in addition to standard TEE assessments.

The alternative to being in this study is to not take part. Your participation is voluntary. It is your choice whether or not you want to take part. If you choose

not to take part or choose to stop taking part at any time, there will be no penalty or loss of benefits if you do not participate.

Benefits include, not limited to, more detailed information regarding right heart function.

A risk of taking part in this study is that you may not feel comfortable answering some of the questions. If any question makes you feel uncomfortable, you do not have to answer the question.

The other possible risk is a loss of the confidentiality of your information. We will maintain your confidentiality by deidentifying your clinical information for data analysis, and restrict data sharing with Jefferson email. Information will be collected about you for this study. The information will be seen by the people involved with this research. Steps will be taken to protect your identity. But the information collected about you can never be 100% secure.

There is no additional research related risk anticipated.

You will not be paid for taking part in this study. If this research or the information or specimens you provide result in commercial profit, you will not receive any money.

New information may come out during this study. You will be given any new information that could change your decision to take part. You may ask to see the information collected about you, but not until the entire study is complete.

HIPAA (Health Insurance Portability and Accountability Act) – This is the law that protects your personal health information.

To do this study, we need to collect, use, and share your personal health information. I will explain why your information is being collected, what information will be collected, and who will have access to it. By agreeing, you are giving us permission to use your information as described in this form.

We are committed to respecting your privacy and to keeping your personal health information confidential. Your personal health information includes the information in your health care records and information that can identify you. For example, personal information may include your name, address, phone number, social security number, and medical information. The personal health information that may be collected, used, and shared for this research includes:

Information from your medical records, Demographic information such as name, gender, birth date, ethnicity, medical history, and health care providers, Physical examinations, procedures, tests, (including

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IRB NUMBER: iRISID-2022-0802
IRB APPROVAL DATE: 12/01/2022

echocardiography, X-ray), labs, your medical conditions, and medications you use, Information collected about any research related injury, Information about mental health, , drug and alcohol use, genetic test results, and other sensitive information

Your personal information will be used by and shared with the following:

- Personnel at Thomas Jefferson University and its affiliates for the purpose of this research
- Institutional Review Board (ethics committees that review research) of Thomas Jefferson University IRB.
- Health insurance providers
- Thomas Jefferson University, Department of Anesthesiology (sponsor), which is providing money to the researcher to carry out this research
- Others as required by law

When your personal information is provided to some of the people listed, it may no longer be protected under the HIPAA privacy law. You can see your health care records at any time. However, generally you will not be able to see your study records or the study results until the study is completed. A copy of this signed form, information about this study, and the results of any study test or procedure may be included in your health records which may be seen by your insurance company and your health care providers.

This authorization does not have an expiration date. If you want to end your permission to collect your information, please inform the investigator in writing. If you do this, no more information will be collected, but the information already collected will still be used. If you end your permission to use your personal information, you will not be able to continue in this study.

The information from this study may be published in scientific journals or presented at scientific meetings, but you will not be personally identified.

Your private information and specimens, with the identifiers removed, could be used for future research studies or distributed to other researchers for future research studies without your additional permission.

Do you agree to participate in this research study as it has been described to you?

If you have any questions about this research, you can contact:

Name: Yoshihisa Morita, MD

Phone Number: 215-503-6472
email: Yoshihisa.morita@jefferson.edu

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If you need to contact someone other than the study personnel about a concern or your rights as a research subject, please call the Jefferson IRB at: 215-503-0203, 215-503-8966, or 215-955-4239.

Investigator writes name of participant and signs to verify verbal response of subject:

Name _____ of _____ research _____ participant

☐ YES, the participant consented
consent

☐ NO, the participant did NOT

Name of Investigator
Date

Signature of Investigator

Please feel free to contact us, using the information below, if you have additional questions or concerns:

1. Yoshihisa Morita, MD – Principal Investigator
Department of Anesthesiology
111 S. 11th St., Suite8290 Gibbon Bldg, Philadelphia, PA 19107
215-955-6161 (P)/ 215-955-0677 (FAX)
2. If you need to contact someone other than the study personnel about a concern or your rights as a research subject, please call the Jefferson IRB at: 215-503-0203, 215-503-8966, or 215-955-4239.

RESEARCH PROTOCOL TEMPLATE INVESTIGATOR INITIATED TREATMENT TRIALS

Title of Project: Utility of three-dimensional transesophageal echocardiography in right ventricular function assessment in surgical aortic valve replacement, mini-sternotomy aortic valve replacement, and transcatheter aortic valve replacement

Principal Investigator: Yoshihisa Morita, MD; Department of Anesthesia

Co-Investigators: Marc Torjman, PhD; Department of Anesthesia
Jordan Goldhammer, MD; Department of Anesthesia
Jacob Rafael, MD; Department of Anesthesia
Luke Olson, DO; Department of Anesthesia
Michael Dougherty, DO; Department of Anesthesia
Praveen Mehrotra, MD; Department of Medicine
Yajnesh Vedanaparti; Medical Student

Abstract

Objective: Right ventricular (RV) function is known to be a critical factor to determine postoperative outcome in cardiac surgery, and echocardiography plays an important role in RV function assessment.¹⁻² In the previous studies, RV function was reported to be more reduced in surgical aortic valve replacement (SAVR) than transcatheter aortic valve replacement (TAVR), but its assessment was performed by 2-dimensional echocardiography.^{3,4} On the other hand, three-dimensional (3D) echocardiography has been the gold standard to assess RV systolic function (EF: ejection fraction), and its intraoperative use is getting more useful in cardiac surgery given recent technological advance in echocardiography machines.¹ However, reality is that we tend to determine RV function based on subjective information or traditional RV function indices, mostly due to unfamiliarity of 3D technique.

In this study, we plan to evaluate intraoperative RV function assessment by 3D transesophageal echocardiography (TEE). We will compare 3D RV EF with other traditional RV function indices ((RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE)) in SAVR, mini-sternotomy AVR (mini AVR), and TAVR.

A. Specific Aims

1. RV function assessment pre, post cardiopulmonary bypass (CPB), and post chest closure

In 3 arms (arm 1: surgical AVR, arm 2: mini AVR, arm 3: TAVR), baseline pre CPB RV function assessments done after induction of general anesthesia. Post CPB RV function assessment after weaning off CPB and after chest closure is done in the same way as baseline pre CPB RV function assessment. RV function assessment to include 3D RV EF, RV FAC, and TAPSE). In arm 3: TAVR, baseline RV function assessments done

after induction of general anesthesia. Post TAVR RV assessment is done in the same way as baseline RV function assessment.

2. **Compare 3D RV EF between SAVR, mini AVR, TAVR.**

See Table below for the timing of assessment

	SAVR	Mini AVR	TAVR
Baseline RV (T#1)	Post induction		
Post valve deployment RV (T#2)	Post CPB		Post valve deployment
Post chest closure RV (T#3)	Post chest closure or before extubation		

B. Background and Significance

The importance of postoperative RV function after cardiac surgery has been recognized for more than 30 years, but its assessment has been challenging due to the unique anatomy, physiology, and its position. The RV is pyramid shape, its contraction consists mostly of longitudinal movement, and is less accessible due to its retrosternal position. Thus, RV function assessment has been comprehensive utilizing RV size, RIMP, RV FAC, S', TAPSE, surgeons' "eyeball" impression. With emergence of 3D echocardiography technology, 3D-derived RV EF is the most accurate echocardiographic measure of global RV function¹ Previous study^{3,4} has shown that RV function is more reduced in SAVR than TAVR however their RV assessment was mostly with 2-dimensional echocardiography. This study will be the first study to utilize 3D echocardiography for RV function assessment for SAVR, mini AVR, and TAVR.

C. Preliminary Studies/Progress Report

N/A

D. Research Design and Methods

Design: Prospective clinical trial at single-center tertiary academic hospital.

Participants: Aortic valve surgery patients

Arm 1 (SAVR)

Arm 2 (mini AVR)

Arm 3: (TAVR)

Primary outcome: 3D RV EF

Secondary outcome: Traditional RV function indices (RVFAC and TAPSE)

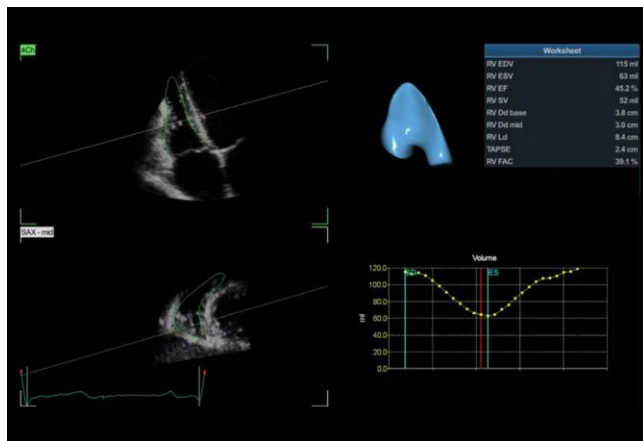
Anesthesia methods: general anesthesia with endotracheal intubation, arterial line, central venous line, pulmonary artery catheter (not for TAVR), TEE.

Anesthesia will be general anesthesia with endotracheal tube, pre-induction arterial line, central venous line, pulmonary arterial catheter (not for TAVR), and TEE; all of which are within standard care, and nothing specific to this study. Choice of the medication including inotropes and vasopressors, and intervention such as transfusion and fluid management will be at each anesthesiologist's discretion.

Measurements:

Training for acquisition of images will be provided by GE representatives to the Cardiac Anesthesiologists. All images will be saved in the operating room and transmitted to server for permanent catalogue. A single investigator will review all images and make the measurements described below.

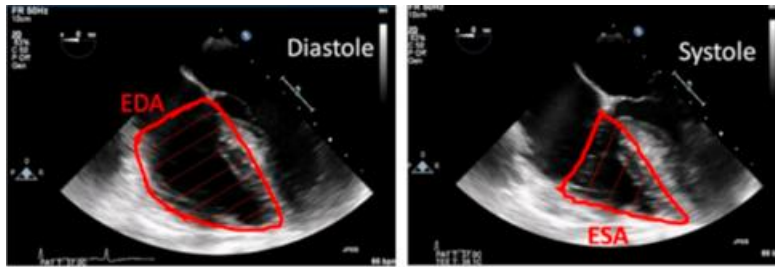
3D RV EF will be acquired using the GE software package on the GE vivid e95 TEE machine. Firstly, TEE midesophageal 4 chamber view (ME 4CV) with RV focus is acquired with 4D mode, then 4D RVQ software is activated on that image, align anatomical landmark as directed, and the software will calculate the 3D RV EF automatically.



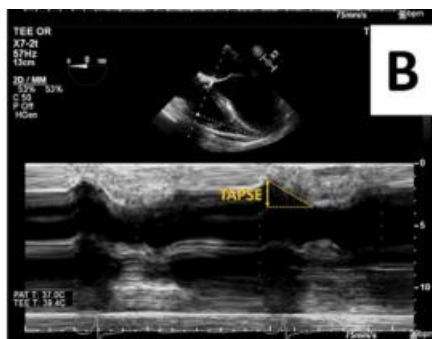
The following TEE measurements were then obtained over three consecutive beats using TEE 4CV with RV focus, and a single cardiac cycle from these image sets was then used to calculate post-hoc measures of RV function including TAPSE and RVFAC

RV FAC will be calculated from ME 4CV with RV focus.

FAC = $100 \times \frac{\text{end-diastolic area (Area ED)} - \text{end-systolic area (Area ES)}}{\text{end-diastolic area}}$. The endocardial border is traced in apical 4-chamber views from the tricuspid annulus along the free wall to the apex, then back to the annulus, along the interventricular septum at end-diastole (ED) and end-systole (ES). Trabeculation, tricuspid leaflets, and chords are included in the chamber.



TAPSE will be measured by TAPSE measurements obtained via the ME 4CV using anatomic M-mode (AMM TAPSE). The anatomic M-mode measurements were completed by placing the cursor on the lateral tricuspid annulus and the angle was adjusted such that the angle of measure was directed toward the apex.



E. Statistical Methods

Statistical analysis

Summary statistics will be reported for demographic and clinical data for each group. Similarly, variables are presented as mean \pm SD and median (IQR), when indicated. Categorical data are presented as frequencies and percentages according to the group. Demographic data will be analyzed using the independent t-test, and the Mann–Whitney U test will be used for nominal variables. RV echocardiographic indices will be analyzed using the Mann–Whitney U test (2 groups) or the analysis of covariance (ANCOVA) and pos-hoc pairwise comparisons with Bonferroni correction. For ANCOVA of % change (Timing #3 from #1) in RV indices, covariates included age, gender, norepinephrine equivalent (NE equiv) at Timing #3, CVP at Timing #1, and each RV index at the baseline (Timing #1). Univariate or multivariable logistic regression models were used to assess the association between each echocardiographic index and in-hospital MACCEs. Correlations between continuous variables will be assessed using Pearson's or Spearman's rank correlation tests. Statistical significance is set at $p < 0.05$. All statistical analyses are performed using R version 4.5.1 (The R Foundation for Statistical Computing).

Power analysis

Changes in RV echocardiographic measurements were used to calculate the required sample size, based on a study by Kempny et al.[4] Kempny et al. reported %change of right ventricular strain of - 25.2 (SAVR) and - 20.0 (TAVR) before and after the

procedure, respectively. With the criterion for significance (alpha) set at 0.05 and 80% power for a Mann–Whitney U test, we obtained a sample size of 22 patients per group. The rationale for using RV strain for power analysis is as follows; Sample size calculations for RV strain, RVFAC, and TAPSE provided 22, 7, and 15, respectively. Thus, we decided to use the strictest sample size calculation.

F. Gender/Minority/Pediatric Inclusion for Research

Adult patients over 18 years old are included. Any gender and race patients are included.

G. Human Subjects

1. Inclusion criteria: Adult patients over 18 years old who have mitral valve procedures
Exclusion criteria: patients' refusal, suboptimal echocardiography data
2. Sources of research material in the form of specimens, records or data.
Echocardiography data, medical information in EPIC
3. Plans for recruitment and consent procedures to be followed.
Phone consent will be done in preoperative or actual consent will be obtained in preoperative holding area.
4. Risks and assess likelihood and seriousness. No research related risks are anticipated because TEE measurements are standard care
5. Procedures for protecting against or minimizing potential risks. N/A
6. Potential benefits and importance to the subjects and others. Patients may benefit from more detailed clinical data than usual by joining this study. Especially, training cardiac anesthesiologists for 3D TEE will help for obtaining more clinical data which might be leading to necessary intervention.
7. Why risks are reasonable in relation to benefits. No research related risks are anticipated, and possible benefits are higher (described in 6)

H. Data and Safety Monitoring Plan

All protocols that pose greater than minimal risk must have a Data and Safety Monitoring Plan (see DHSP policy G 616 "Independent Monitoring of Investigator-Initiated Clinical Trials.")

1. Describe the Data and Safety Monitoring Plan (DSMP)
We will report to IRB if we should come across research related complications

2. If applicable, describe the Data and Safety Monitoring Board (DSMB) that will be responsible for monitoring the study. Indicate Chair, members, areas of expertise, frequency of meetings, distribution of reports.

N/A

I. Literature Cited

1. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L,

et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(January (1)). 1–39.e14.

2. Ternacle J, Berry M, Cognet T, Kloeckner M, Damy T, Monin JL, Couetil JP, Dubois-Rande JL, Gueret P, Lim P. Prognostic value of right ventricular twodimensional global strain in patients referred for cardiac surgery. J Am Soc Echocardiogr 2013;26:721–726.
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4. Kempny A, Diller GP, Kaleschke G, Orwat S, Funke A, Schmidt R, Kerckhoff G, Ghezelbash F, Rukosujew A, Reinecke H, Scheld HH, Baumgartner H. Impact of transcatheter aortic valve implantation or surgical aortic valve replacement on right ventricular function. Heart. 2012 Sep;98(17):1299-304.
5. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016 Jun;15(2):155-63.

Principal Investigator/ Date

Date _____

Version _____

Protocol Template, 11/15/2010