Study Title: **Use of Phenylephrine for Assessment of Mitral Regurgitation Severity**

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TITLE:

Evaluating the severity of mitral regurgitation using phenylephrine during transesophageal echocardiography.

BACKGROUND:

Mitral regurgitation (MR) is a major source of morbidity and mortality worldwide and is frequently associated with left ventricular dysfunction and congestive heart failure. In the Framingham Heart Study population-based cohort, mild MR was detected on transthoracic color flow doppler echocardiography in 19% of patients (1). MR may be due to a primary abnormality of one or more components of the valve apparatus, referred to as organic MR; or secondary to another cardiac disease such as coronary artery disease or cardiomyopathy, which is referred to as functional MR. The most common etiologies of MR are degenerative disease with mitral valve prolapse and coronary artery disease which causes ischemic MR. A high prevalence of MR in the range of 9 to 13% has been detected in cardiac catheterization following myocardial infarction (2). Patients have an annual death rate of 5% or more, without appropriate intervention (3).

Currently there are both open surgical and minimally invasive methods to repair MR. Surgery is recommended for moderate-to-severe (grade 3+) or severe (4+) MR in patients with symptoms or evidence of left ventricular dysfunction (4). It is therefore essential to determine the exact severity of MR in order to guide clinical decision making regarding mitral valve repair or replacement.

Transthoracic echocardiography (TTE) is the primary diagnostic modality to identify MR and determine its severity. Transesophageal echocardiogram (TEE) is indicated in the evaluation of patients with MR, in whom other noninvasive imaging is non-diagnostic in determining the MR severity and also to better understand the mechanism of the valvular disease. In some instances, however, these modalities can lead to underestimation of the true severity of MR as well as what was clinically suspected. MR is a dynamic condition and its severity varies with alteration in the hemodynamic conditions. Several factors including preload, afterload and heart rate can influence the severity of MR. Routine echocardiography quantifies the severity of MR at rest, thus underestimating the hemodynamic variation in the degree of MR that occurs with normal physical activity. Furthermore, alteration in hemodynamic conditions under sedation (afterload reduction) used to perform TEE can further cause changes in the grade of apparent MR, potentially resulting in underestimation of MR severity. For patients with symptoms that are greater than expected for the degree of MR at rest or with borderline echocardiographic findings, altering the hemodynamic profile to better represent a non-sedated state during TEE may be helpful. Since patients are sedated for comfort and tolerability, pharmacologic manipulation of the hemodynamic profile is the only feasible option.

Phenylephrine is a direct acting, selective α-adrenergic agonist, with no beta- adrenergic activity, that produces systemic arterial vasoconstriction. The increase in systemic vascular resistance causes dose-dependent increase in systolic and diastolic blood pressure and reduction in heart rate and cardiac output. The increase in the blood pressure is immediate after IV administration and duration of action lasts for 15-20 minutes. Phenylephrine is a vasopressor that is commonly used in the critical care setting. It has been utilized intraoperatively in prior studies to increase the systemic vascular resistance and afterload, subsequently offsetting the hemodynamic

variations and unloading effect caused by general anesthesia on the left ventricle, in order to have a more accurate assessment of MR severity during surgery (5,6). The study proposes to develop a phenylephrine protocol to be used during TEE, whereby intravenous phenylephrine would be used to increase afterload with the intent to mimic the awake hemodynamic profile and variation that occurs with normal physical activity. The investigators expect to see changes in severity of MR with increasing afterload, which in turn can provide more accurate quantification of MR severity to assist in clinical decision making. This would be particularly helpful in patients with inconclusive or discordant findings between echocardiography and clinical symptoms or between TTE and TEE severity.

OBJECTIVE:

The purpose of this study is to compare the echocardiographic parameters of MR before and after the use of phenylephrine during TEE. Our hypothesis is that compared to the baseline conditions, there will be a 25% increase in the MR severity, as demonstrated by an increase in MR grade, effective regurgitant orifice area (ERO), regurgitant volume (RVol) and 3D vena contracta width, following the administration of phenylephrine.

PRIMARY AIM:

To document an increase in echocardiographic parameters of MR after the use of phenylephrine in TEE.

OUTCOME MEASURES:

Visual MR grade, effective regurgitant orifice area (ERO), regurgitant volume (RVol) by PISA method and 3D vena contracta area before and after phenylephrine administration.

PATIENTS AND METHODS:

This is a single center prospective study that will be conducted at Montefiore medical center in Bronx, New York. Patients with any grade of MR on transthoracic echocardiographic evaluation who are scheduled to undergo transesophageal echocardiography for the clinical purpose of evaluating MR severity will be screened for eligibility. The transesophageal echocardiogram would be performed by the following cardiologists at Montefiore Medical Center: Dr. Mario Garcia, Dr Edwin Ho, Dr. Ythan Goldberg, Dr. Cynthia Taub. A detailed chart review of all the patients will be conducted using EPIC and clinical and laboratory parameters will be extracted from their charts.

Dr. Safeera Javed at Baylor College of Medicine will be involved in chart review of patients, updating data on clinical trials.gov, data analysis and writing the manuscript.

Inclusion criteria:

Patients 18 years or older with MR on baseline echocardiographic evaluation who are scheduled to undergo TEE for further evaluation of mitral regurgitation.

Exclusion criteria:

The following patients will be excluded from the study:

1. Patients who are not clinically eligible for TEE.
2. Patients with contraindications to esophageal intubation.
3. Patients with hemodynamic instability.
4. Patients with acute decompensated heart failure (HF).
5. Patients with un-revascularized severe coronary artery disease (triple vessel or left main disease).

6. Patients with ongoing unstable angina or ongoing myocardial infarction (MI)
7. Patients with significant arrhythmias including atrial fibrillation.
8. Patients with uncontrolled hypertension (BP ≥ 150/90).
9. Patients with preexisting bradycardia (HR < 50) and heart blocks.
10. Patients with severe symptomatic peripheral vascular disease.
11. Patients with severe pulmonary hypertension (estimated systolic pulmonary arterial pressure sPAP ≥ 60mm Hg).
12. Patients who are at high risk for intracranial bleeding such as patients with previous strokes, TIAs and vascular malformations.
13. Additionally, patients with mean arterial blood pressure MAP > 100 mmHg during TEE and those with severe MR (ERO > 39cm^2) on baseline TEE evaluation will not be given phenylephrine and excluded from the study.

The investigator will obtain further clinical information from each case including but not limited to:

1. Basic demographic information: age, gender, date of birth, race, SES status
2. Presenting clinical features and presence of heart failure symptoms.
3. Presence of clinical comorbidities such as hypertension, diabetes, hypercholesterolemia, smoking, emphysema/ COPD, rheumatic heart disease, heart failure, history of coronary artery disease CAD, prior myocardial infarction, prior CABG, prior valve surgery, arrythmias etc.
4. Etiology of MR: Organic vs functional MR
5. Transthoracic echocardiography findings such as left ventricular ejection fraction, wall motion abnormalities, left ventricular end-diastolic diameter, left ventricular end-systolic

diameter, left atrial diameter, MR grade, effective regurgitant orifice area (ERO), regurgitant volume, maximum regurgitant jet area, regurgitant jet area/left atrial area, regurgitant jet length, width of vena contracta, pulmonary venous spectral Doppler.

6. Hemodynamic measurements during LHC including pressures from the left ventricle, right atrium, right ventricle, pulmonary artery, pulmonary capillary wedge pressure.

Participant recruitment: Patients found to have mitral regurgitation on baseline transthoracic echocardiography, who are scheduled to undergo transesophageal echocardiography for further evaluation of MR severity, will be screened for eligibility and approached for the study. Study team members will then approach the interested patients to obtain consent for the research.

Procedure:

Patients will be kept NPO for at least 6 hours prior to the procedure. A focused TTE will be performed to assess the mitral valve using 2-dimensional echocardiography. BP and HR will be recorded at the time of TTE. Topical anesthesia with lidocaine spray or gel would then be applied to the pharynx, followed by mild-moderate sedation with intravenous versed and fentanyl. The transesophageal echocardiography will be performed as a standard of care in all these patients. TEE would be performed with a 3-dimensional multiplane probe using an ultrasound machine. A complete echocardiographic study would be performed using standard views and techniques. Mitral valve will then be assessed using 2 and 3-dimensional echocardiography from multiple views. Quantitative assessment of MR would be performed using the proximal isovelocity surface area (PISA) method as described below. Patients will be continuously monitored, and blood pressure will be measured at least every three minutes using a validated automatic cuff system. BP readings will be averaged to define the pre-phenylephrine

MAP. Thereafter phenylephrine will be administered through a peripheral intravenous line. Phenylephrine is available as phenylephrine hydrochloride HCl injection, 10 mg/mL in 1 mL vial. For intravascular bolus administration, we will prepare a solution containing 100 mcg/mL of phenylephrine hydrochloride, by withdrawing 10 mg (1ml of 10mg/mL) of phenylephrine HCl injection and diluting with 99 mL of 5% dextrose injection or 0.9% sodium chloride injection. A test dose of 20 mcg of phenylephrine will be given by the cardiologist performing the TEE. BP will be monitored after each bolus of phenylephrine. Subsequent phenylephrine injections will then be administered in 50 mcg aliquots every 10-15 mins, until the mean arterial blood pressure MAP increases by ≥ 20 mm Hg from the baseline MAP (which is an average of the last five blood pressure readings in the patient's medical chart), however making sure not to exceed a MAP of 100 mmHg. Once a desired blood pressure has been achieved and maintained (3 consecutive MAPs within ± 3 mm Hg of each other), TEE evaluation of MR would be repeated using the same imaging protocol. If, however, patient's MAP exceeds ≥ 120 mmHg and/or patient becomes symptomatic after phenylephrine injection, Labetalol will be given in 10 mg IV boluses in order to reverse the effect of phenylephrine. Phenylephrine will also not be injected in patients whose MAP exceeds 100 mmHg during baseline TEE and patients found to have severe MR (ERO > 0.39 cm^2) on baseline TEE assessment.

Quantitative evaluation of Regurgitation:

Doppler color jet area (CDJA) is the most commonly used method to evaluate the severity of MR, however this method is a semiquantitative method and is affected by a number of technical factors. We will use proximal isovelocity surface area (PISA) method which allows quantitative, objective and more precise analysis of MR (7,8). This method analyses the flow convergence region proximal to the regurgitant orifice during systole and calculates regurgitant flow using the

following formula: regurgitant flow=$2 \times \pi \times r^2 \times$ avel, where r is the radius of the measured shell at mid-S and avel is the aliasing velocity of the shell.

Grading MR severity: Quantitative grading will be done according to PISA results of ERO and RVol, and 3D vena contracta area.

BENEFITS: The potential benefit would be better estimation of the severity of MR in order to guide clinical decision making regarding mitral valve repair or replacement.

RISKS: Intravenous use of phenylephrine can cause hypertensive crises and increase pulmonary arterial hypertension. Our goal is to avoid use in patients with severe hypertension and severe pulmonary hypertension. It can cause severe reflex bradycardia and reduced cardiac output due to an increase afterload, especially in patients with preexisting LV dysfunction. Patients with bradycardia, heart blocks and decompensated heart failure will not be included in our study. Phenylephrine can also precipitate angina in patients with severe coronary artery disease and can cause severe peripheral and visceral vasoconstriction resulting in ischemia to vital organs, particularly in patients with peripheral vascular disease. Patients with severe coronary artery disease and severe symptomatic peripheral vascular disease will be excluded from the study. Extravasation of phenylephrine injection can cause skin and subcutaneous necrosis or sloughing of tissue. With carefully setting the exclusion criteria, excluding patients at high risk for the above risks, and careful administration of phenylephrine with continuous monitoring of heart rate, blood pressure, pulse oximetry and intravascular volume status during TEE, we intend to minimize these risks.

Antidote: In order to treat hypertension induced by phenylephrine, the following agents can be used:

1. **Labetalol:** Labetalol is both α and β blocker. It comes as 5 mg/ml injection and should be administered as 10 to 20 mg IV push over 2 minutes. The onset of action is within 5 minutes, with peak effect seen in 5 to 15 minutes Additional doses will be administered every 10 minutes interval until the target SBP is reached.

2. **Nitroprusside:** By causing peripheral vasodilation, it decreases preload and afterload; it would be preferable if the patient has also developed decompensated heart failure. It will be administered as continuous intravenous infusion at a rate of 0.3 to 0.5 μg/ kg/ min and titrated by 0.5 μg every few minutes with very close hemodynamic monitoring.

3. **Furosemide:** Furosemide can be used for the treatment of acute pulmonary edema, as IV push. It will be administered as 40 mg IV push; if response not adequate within 1 hour, may increase the dose to 80 mg, or start continuous infusion at a rate of 10 to 20 mg/ hour. Onset of action is within 5 minutes after IV administration with the peak effect seen in 0.5 hour.

DATA STORAGE AND CONFIDENTIALITY: Personal patient identifiers will be removed and replaced with a study number. Only persons involved in the study will review the patient records. All the images will be recorded on videotapes for subsequent analysis. Data will be stored in a secured storage device that will be password protected and access will be available for research team only. All data will be destroyed after finishing the study.

INFORMED CONSENT: Informed consent will be obtained by the cardiologist performing the transesophageal echocardiography, at the time of scheduling the patients for transesophageal echocardiography at Moses and Weiler. Patients who do not have capacity to consent will not be enrolled.

STATISTICAL CONSIDERATION:

Statistical Analysis

Descriptive statistics (mean, standard deviation, frequencies) will be used to characterize the demographic, clinical, angiographic and baseline transthoracic echocardiographic findings in the study population. Continuous variables will be summarized using, mean, median, standard deviation and inter-quartile range. Categorical / nominal variables will be summarized using frequencies and percentages. Continuous variables will be compared using the paired Student *t* test. Statistical analysis would be done with computer software (SAS). A p Value < 0.05 would be considered statistically significant.

Sample size justification

Assuming that in 50% of the cases there would be an increase of at least one grade of MR severity after phenylephrine injection during TEE, which represents a change of ERO of 0.10 cm^2, and assuming a SD of 0.15 cm^2 , it was estimated that 35 patients would be required to detect a significant difference with a bilateral alpha of 5% and a power of 80% (B =20%).

Hemodynamic and echocardiographic results

	Baseline TTE	TEE Pre-phenylephrine	TEE Post- phenylephrine
Systolic Blood Pressure, mmHg (mean± SD)			
Diastolic Blood Pressure, mmHg (mean± SD)			
Mean arterial blood pressure, mmHg (mean± SD)			
Heart rate, beats/ min (mean± SD)			
Central venous pressure, mmHg (mean± SD)			
Mean capillary wedge, mmHg (mean± SD)			
Vmax, cm/s (mean± SD)			
Color jet area, cm^2 (mean± SD)			
Vena contracta, cm (mean± SD)			
Effective regurgitant orifice area (ERO), cm^2 (mean± SD)			
Regurgitant volume (RVol), Ml (mean± SD)			
MR grade (1-4)			

DATA SAFETY MONITORING: Data safety monitoring will be conducted by the study investigators in accordance with IRB policies for reporting of internal and external adverse

events, monitoring the safety and performance of procedures and early termination of study in instance of safety concerns, or inadequate performance.

References:

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