Assessment of Pulmonary Congestion During Cardiac Hemodynamic Stress Testing

NCT04019613

October 28, 2021

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Brandon M. Wiley, MD
Co-Principal Investigator:
Co-Investigators:
Hilal Kucuk Olgun, MD
Masaru Obokata, MD PHD
Yogesh N. Reddy, MD
Barry A. Borlaug, MD
Charles E. Luoma, RDCS
Bruce Johnson, PHD

Study Title:

Assessment of Pulmonary Congestion during Cardiac Hemodynamic Stress Testing
"Mayo Sonographic Cardiopulmonary Exam for Dyspnea"

Protocol version number and date:

Initial Version: Version 1.0 04/19/2019
Revised: Version 2.0 07/11/2019
Revised: Version 3.0 01/10/2020
Revised: Version 4.0 10/28/2021

MAYO CLINIC

Research Question and Aims

Hypothesis:

1. Patients with an exercise induced increase in extravascular lung water (EVLW), assessed using the gold standard of pulmonary thermodilution, will develop an increase in sonographic interstitial lung thickening (B-line artifacts) during exercise.
2. Patients developing B-lines will display more severe symptoms of dyspnea, altered ventilatory mechanics (higher V_E/VCO_2 slope), and reduced aerobic capacity (lower peak VO_2)
3. The severity of EVLW, assessed by number of B-lines, will correlate with LV filling pressures.

Aims:

1) Innovation:
   I. First study to correlate quantitative LUS with gold-standard invasive hemodynamics during exercise in a continuous fashion.
   II. First study to use pulmonary thermodilution for dynamic EVLW measurements to allow direct correlation with sonographic interstitial lung thickening (B-lines) both at rest and during maximal effort exercise.
   III. First study to examine how development of EVLW and B-lines relates to exercise capacity, symptoms and ventilatory control.
2) Clinical Significance:
   1. Incorporation of comprehensive LUS into hemodynamic stress testing (including pre-test imaging) creates the potential of a robust **"Mayo Sonographic Cardiopulmonary Exam for Dyspnea"** that would be generalizable to wide-spectrum of medical settings (including low-resource environments where catheterization labs and invasive hemodynamic diagnostics are unlikely to be present).

Background:

Echocardiography has evolved into the core non-invasive modality for evaluation of LV filling pressures during provocative stress testing. However, the feasibility of echocardiography is limited due to difficult acoustic windows or presence of confounding pathology (left bundle branch block,

paced rhythm, atrial fibrillation). Obokata et al demonstrated that echocardiographic parameters of LV filling pressures at peak stress were unattainable in 20% of patients (1). Ultimately, high LV filling pressures cause symptoms due to an increase in EVLW (pulmonary edema). Lung ultrasound (LUS) is a simple non-invasive procedure that is feasible in > 99% of patients (2) (3) and is more sensitive than chest radiography for detecting EVLW (4). LUS illustrates interstitial lung thickening caused by EVLW as reverberation artifacts (B-lines) (5). The detection of EVLW by LUS during stress testing has been shown to correlate with echocardiographic markers of elevated LV filling pressures in patients with both normal and reduced ejection fractions, and is predictive of outcomes (2,3). However, validation of LUS and echocardiographic correlation using invasively derived hemodynamics has not been well studied. Current knowledge is limited to a recent study from our group that demonstrated an association between exercise-provoked elevation in pulmonary capillary wedge pressure and non-quantitative assessment of sonographic EVLW in 15 patients with HFpEF (manuscript under review). The mechanism for the development of sonographic EVLW remains unclear, as these patients also demonstrated elevated right-sided cardiac filling pressures at rest and with stress suggesting an additive component of right ventricular dysfunction that could be contributing to the development of EVLW (subclinical pulmonary vascular congestion). Our research aim is to evaluate etiology of sonographic lung interstitial thickening (B-lines) using invasive hemodynamic catheterization while simultaneously utilizing transpulmonary thermodilution to measure the exact amount of EVLW present before and after provocative testing.

References

1. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation 2017;135:825-838.
2. Scali MC, Cortigiani L, Simionuc A, Gregori D, Marzilli M, Picano E. Exercise-induced B-lines identify worse functional and prognostic stage in heart failure patients with depressed left ventricular ejection fraction. Eur J Heart Fail 2017;19:1468-1478.
3. Simonovic D, Coiro S, Carluccio E et al. Exercise elicits dynamic changes in extravascular lung water and haemodynamic congestion in heart failure patients with preserved ejection fraction. Eur J Heart Fail 2018;20:1366-1369.
4. Pivetta E, Goffi A, Lupia E et al. Lung Ultrasound-Implemented Diagnosis of Acute Decompensated Heart Failure in the ED: A SIMEU Multicenter Study. Chest 2015;148:202-210.
5. Volpicelli G, Elbarbary M, Blaivas M et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38:577-91.
6. Volpicelli G, Skurzak S, Boero E et al. Lung ultrasound predicts well extravascular lung water but is of limited usefulness in the prediction of wedge pressure. Anesthesiology 2014;121:320-7.
7. Shyamsundar M, Attwood B, Keating L, Walden AP. Clinical review: the role of ultrasound in estimating extra-vascular lung water. Critical care (London, England) 2013;17:237.
8. Picano E, Pellikka PA. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. European heart journal 2016;37:2097-104.
9. Jambrik Z, Monti S, Coppola V et al. Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. The American journal of cardiology 2004;93:1265-70.
10. Baldi G, Gargani L, Abramo A et al. Lung water assessment by lung ultrasonography in intensive care: a pilot study. Intensive Care Med 2013;39:74-84.
11. Enghard P, Rademacher S, Nee J et al. Simplified lung ultrasound protocol shows excellent prediction of extravascular lung water in ventilated intensive care patients. Critical care (London, England) 2015;19:36.
12. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588-95.
13. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. Chest 2002;122:2080-6.
14. Jozwiak M, Silva S, Persichini R et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. Crit Care Med 2013;41:472-80.
15. Sakka SG, Ruhl CC, Pfeiffer UJ et al. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. Intensive Care Med 2000;26:180-7.

16. Tagami T, Kushimoto S, Yamamoto Y et al. Validation of extravascular lung water measurement by single transpulmonary thermodilution: human autopsy study. Crit Care 2010;14:R162.
17. Volpicelli G, Elbarbary M, Blaivas M et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38:577-91.
18. Sekiguchi H, Schenck LA, Horie R et al. Critical care ultrasonography differentiates ARDS, pulmonary edema, and other causes in the early course of acute hypoxemic respiratory failure. Chest 2015;148:912-918.

Study Design and Methods

Methods:

Lung ultrasound and calculations of extravascular lung water will be conducted for research purposes during clinically indicated invasive hemodynamic stress testing. The clinical protocol for invasive hemodynamic stress testing has been well developed at Mayo Clinic (12). Briefly, exercise testing is performed using supine cycle ergometry in the cardiac catheterization laboratory. Standard right heart catheterization (RHC) is conducted using a 9 Fr sheath via the internal jugular vein. If indicated, left heart catheterization is performed using a 5-6 Fr sheath in the radial or femoral artery. During the clinical invasive exercise stress test there is continuous monitoring of intra-cardiac pressures, cardiac output (pulmonary thermodilution and Fick method) as well as measures of ventilatory mechanics and focused echocardiography. In addition, blood is draw at different levels of exercise to assess for changes in biomarkers of cardiac output and oxygen delivery.

The research objectives of lung ultrasound and calculations of extravascular lung water will integrate seamlessly into the clinical protocol for invasive hemodynamic stress testing. The combination of ultrasound imaging and invasive hemodynamic supine ergometry has been well described in the Mayo catheterization laboratory (1). LUS is performed using a standard echocardiography machine which provides a synergistic method for noninvasive ultrasound assessment during exercise. Pulmonary thermodilution calculation of extravascular lung water will also seamlessly integrate into the hemodynamic stress test since the clinical standard-of-care for invasive hemodynamic stress testing already uses the thermodilution method for calculation of cardiac output. The PiCCO™ system uses the same central venous catheter that is used for the right heart catheterization and the PiCCO™ arterial catheter will be inserted through existing radial artery sheath. The PiCCO™ system (Maquet, Germany) is a FDA approved hemodynamic monitoring device that is simply a display monitor that connects to the PiCCO™ vascular catheters (Figure 1). The system will provide hemodynamic indices including pulse pressure variation, stroke volume variation, and cardiac output measurements using pulse contour analysis and transpulmonary thermodilution methods. This thermodilution process is the same process used during the clinical invasive hemodynamic stress

testing and is standard-of-care for determination of cardiac output. The only change is that the thermodilution measurements are calculated by the PiCCO™ system using the catheter in the radial artery. Using the transpulmonary thermodilution technique (Figure 2), the amount of extravascular lung water (EVLW) present can be determined. EVLW is fluid within the lungs but outside the vascular compartment. Pulmonary edema is the most common clinical manifestation of EVLW. Normal values of EVLW are suggested to be < 10 mL/kg with increased levels being correlated with worse outcomes including mortality (13) (14). The transpulmonary thermodilution measures EVLW using relationships of intrathoracic thermal volume (ITTV), intrathoracic blood volume (ITBV), pulmonary thermal volume and global end-diastolic volume (GEDV) (Figure 2). Studies have found this transpulmonary thermodilution dilution method to be accurate in the measurement of EVLW (15,16).

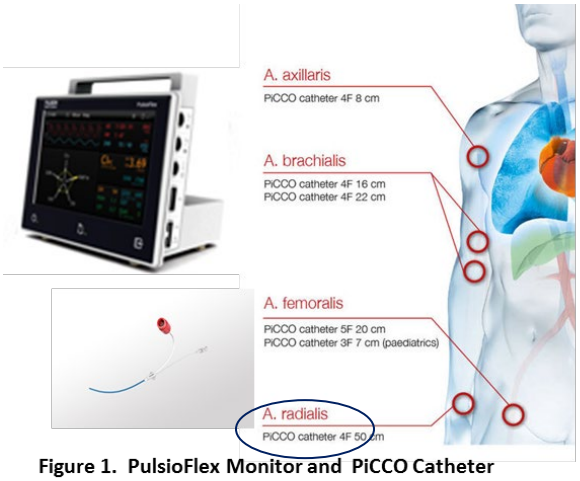

Figure 1. PulsioFlex Monitor and PiCCO Catheter
Transpulmonary thermodilution performed with PiCCO catheter in radial, axillary or brachial arteries

The PiCCO™ system consists of a monitoring unit that is connected to a venous and arterial catheter. The use of the PiCCO™ system during clinical invasive hemodynamic stress testing is possible because the clinical stress testing requires venous and arterial vascular access to measure hemodynamics.
The PiCCO™ system works with the standard venous catheter used during all clinical invasive hemodynamic stress testing. The arterial measurement catheter is a proprietary catheter that will be inserted in the radial artery.

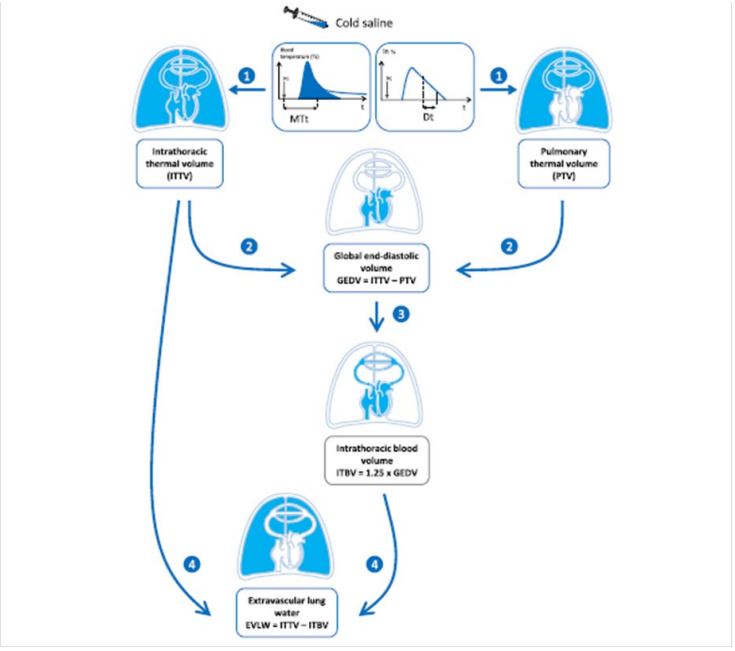

Figure 2. Transpulmonary Thermodilution
Intrathoracic thermal volume (ITTV) is calculated from the mean transit time of cold injectate (MTt). Pulmonary thermal volume (PTV) is calculated from the slope of the cold injectate time (Dt). The global end-diastolic volume is then derived from the difference of ITTV and PTV. Intrathoracic blood volume (ITBV) is calculated from GEDV. ELVW then equals the difference of ITTV and ITBV. (Figure from Monnet et al. Critical Care 2017)

Pulmonary function testing (PFTs) are often clinically indicated in patients with chronic dyspnea and as a result many patients may have recent PFT results prior to catheterization. PFTs will be performed following catheterization (within 7 days) or will be abstracted from the charts for those patients with recent PFTs (within 30 days) performed clinically.

Patients will be followed up at 1 year and 2 year intervals via 1- phone interviews (questioning heart failure hospitalization, ischemic events and death), 2- medical record reviews and 3- quality of life questionnaires.

Finally, we will draw two small samples of blood plasma at rest and stress that will be placed in frozen storage. These samples will prove valuable for future research in biomarkers for heart failure. Recent studies, including those evaluating adrenomedullin have demonstrated that certain biomarkers may be important as markers of congestion and pulmonary edema. However, there is scant data on the evaluation of these biomarkers during exercise. Therefore, we aim to utilize our stored samples as a resource for future studies of the validity of novel biomarkers during exercise in patients with heart failure and preserved left ventricular systolic function.

Brief Protocol

1. Baseline/Resting Evaluation
    a. Comprehensive ultrasound evaluation (lung and cardiac) performed with patient in the supine position on the catheterization table
        i. Time required for completion of LUS will be documented
    b. RHC hemodynamics (measured continuously during rest/stress/recovery)
    c. Transpulmonary thermodilution will be performed by injecting cold saline into the RHC catheter present in the right internal jugular vein. The process is analogous to the cardiac thermodilution method for calculation of cardiac output that is standard-of-care for RHC hemodynamics and clinical invasive stress testing. The only difference is that transpulmonary thermodilution measurements are calculated with the PiCCO™ system (a monitoring device with visual display) using a proprietary PICCO™ catheter that is placed in the radial artery.
    d. Biomarkers: BNP, total protein concentration, albumin
    e. ,hemoglobin, cystatin C and 5-8 ml of plasma will be collected for research purposes. Results of VBG and ABG blood test results which will be done as part of clinical assessment will be retrieved from medical records. Optional plasma will be collected and stored for future research
    f. Expired gas analysis for oxygen consumption will be performed as per standard-of-care for clinical invasive stress testing.
2. Exercise (supine cycle)
    a. RHC hemodynamics will be recorded during exercise and 1 minute recovery
    b. Comprehensive ultrasound (cardiac and LUS) during exercise and 1 minute recovery
        i. Time required for completion of LUS will be documented
    c. Transpulmonary thermodilution during exercise and 1 minute recovery
    d. Biomarkers and plasma (optional) sample 5-8ml will be collected for research purposes as noted below.
3. Prolonged Recovery

    Focused lung ultrasound imaging at 5, 10 and 15 min post-exercise to evaluate persistence and timing of resolution for B-line artifacts

Schedule of Events

	Visit 1 Procedure day			Visit 2
	Baseline/Rest	**Exercise**	**Recovery**	
Right Heart Catheterization[#,1] (RHC)	**X**	**X**	**X**	
Comprehensive Ultrasound[1,2] (lung and cardiac)	**X**	**X**	**X**	
Blood Draw[1,3]	**X**	**X**	**X**	
Pulmonary Thermodilution[4]	**X**	**X**	**X**	
Expired Gas Analysis [#,1]	**X**	**X**	**X**	
Kansas City Cardiomyopathy Questionnaire (KCCQ-12)[5]	**X**			
Pulmonary Function Test[6]				**X**
Optional Research Blood Draw[7]	**x**	**x**		

[#] RHC hemodynamics and expired gas analysis are performed continuously during baseline/exercise/recovery.
[1] Standard-of-care component of the clinical invasive hemodynamic stress test
[2] Cardiac ultrasound (echocardiography) is standard-of-care. Lung ultrasound (LUS) will be performed synchronously with cardiac ultrasound.
[3] Blood will be draw directly from the RHC catheter. In addition to the routine labs (venous/arterial blood gas), specific biomarkers will be collected a various time points for research purposes (Rest only: cystatin C; Rest/Peak –Stress: BNP, plasma; Rest/Low-Stress/Peak-Stress: hemoglobin, total protein concentration, albumin)
[4] Performed with PiCCO™ system and catheter
[5] In addition to baseline assessment, the KCCQ-12 will be completed 1 & 2 years post RHC during a follow-up phone call or in person if the patient comes to the clinic for a follow-up visit
[6] If performed within 30 days of procedure, the results can be extracted from the medical record, otherwise will be performed within 7 days of the procedure (visit 2).
[7] Blood plasma (5-8 ml) will be stored using Mayo Biospecimens Accessioning and Processing (BAP) for future studies.

MAYO CLINIC

H. Statistical Analysis and Power

The ability of B-lines to identify EVLW will be evaluated by measuring sensitivity and specificity. The table below demonstrates the width of the resulting confidence intervals for sensitivity and specificity (based on exact binomial methods) for a study sample of 60 patients:

If the observed sensitivity & specificity is…	**… then the respective 95% confidence intervals will be:**
60%	**(43, 75)**
70%	**(53, 83)**
80%	**(64, 91)**
90%	**(76, 97)**

Resources:

Lung ultrasound will be integrated into the clinical protocol for invasive hemodynamic stress testing. Lung ultrasound and the routine components of the clinical invasive hemodynamic stress to (echocardiography, invasive hemodynamic measurements, pulmonary thermodilution) will be performed during the clinical stress test by the experienced research staff. The PiCCO system will provide the standard measurements of thermodilution cardiac output in addition to calculations of extravascular lung water. Designated research staff will do the data analyses. Results of lung ultrasound and extravascular lung water measurements will not be placed in the medical records of the patients. All participants in the research may be informed of the overall results of the study but not of their individual results. If concerns will be raised on the research findings, the patient's referring cardiologist will be directly contacted and a plan will be developed for further clinical evaluation. Dissemination of results will take place by different methods, including presenting data at national and international congress and publishing papers in national and international journals.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

MAYO CLINIC

Subject Information

Target accrual: 60

Inclusion Criteria:

1. All adult patients (≥18 years) who are referred for invasive hemodynamic assessment of chronic dyspnea
2. Patients who have the capacity to understand and consent for the research study

Exclusion Criteria:

1. Patients with known interstitial lung disease or pulmonary fibrosis.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☒ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.
   > Blood is draw through a catheter that is already placed as standard-of-care.
3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☒ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: (total)

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _Blood draw will occur during invasive cardiac testing at rest and during exercise.

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: 25ml total (Including all research bloods and the optional blood draw)

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc) N/A

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective and prospective chart review and ask subjects to complete the Kansas City Cardiomyopathy questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.
- Two samples of plasma (5-8 ml) collected during the exercise stress test will be frozen in storage for potential assessment of future novel biomarkers. (optional)

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

MAYO CLINIC

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face		

photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	X None

Data Analysis

Data Analysis Plan:

The ability of B-lines to identify EVLW will be evaluated by measuring sensitivity and specificity. The table below demonstrates the width of the resulting confidence intervals for sensitivity and specificity (based on exact binomial methods) for a study sample of 60 patients:

If the observed sensitivity & specificity is…	**… then the respective 95% confidence intervals will be:**
60%	**(43, 75)**
70%	**(53, 83)**
80%	**(64, 91)**
90%	**(76, 97)**

Endpoints

Primary:

1. Completion clinically indicated invasive hemodynamic stress testing with adjunct lung ultrasound and pulmonary thermodilution measurements in the 60 patient cohort
2. Data analysis and correlation of LUS measurements with invasive derived hemodynamics
3. Data analysis and correlation of LUS measurements with thermodilution measurements of EVLW

Secondary:

1. Long-term follow-up at 1-year and 2-year intervals

a. CVD events (hospitalization, ischemic events, death)
b. Quality-of-life survey (Kansa city Cardiomyopathy Questionnaire)