THE WOMEN'S INTERAGENCY HIV STUDY
SECTION 45: ECHO MANUAL OF OPERATIONS

INDEX

APPENDICES

A. BACKGROUND

Potent antiretroviral therapy (ART) has transformed HIV infection from an acute, rapidly fatal disease to a chronic infection with a life expectancy approaching that of the general population.[1] Despite improved survival, ART-treated HIV infection is associated with increased frequency of aging-related diseases,[2] including cardiovascular disease (CVD), which is a foremost cause of non-AIDS mortality in people living with HIV.[3] Apart from the well-documented HIV-related risk of atherosclerosis and coronary heart disease (CHD), cardiac imaging studies have highlighted an increased and premature occurrence of left ventricular (LV) systolic, and especially, diastolic dysfunction in individuals with HIV infection.[4, 5] Such structural and functional cardiac abnormalities are well recognized as precursors of major adverse clinical outcomes, including heart failure (HF)[6, 7] and cardiac dysrhythmias.[8] Indeed, clinical studies have reported an increased incidence of HF,[9] sudden cardiac death (SCD)[10] and atrial fibrillation (AF)[11] among patients with HIV infection. Available evidence of subclinical cardiac dysfunction in HIV-infected individuals, however, comes from studies that have been either uncontrolled or relied on healthy volunteers as controls, and had only limited characterization of HIV-related factors and medications.[5] Yet healthy volunteers do not share the psychosocial, behavioral and clinical risk factors enriched in HIV-infected populations. Accordingly, such studies do not permit distinctions between the roles of HIV infection and related factors, specific ART drugs, and behavioral and clinical risk factors, in the development of subclinical abnormalities. Moreover, existing studies have largely focused on white men; women and ethnic minority populations, who are especially susceptible to cardiac dysfunction and HF with preserved ejection fraction (HFpEF),[12, 13] remain largely unstudied. To fill these gaps, we propose to leverage the infrastructure and expertise of an ongoing study of cardiac dysfunction (R01 HL132794) which uses state of the art imaging including cardiac MRI and echocardiography on WIHS women at the Bronx and Brooklyn field centers (625 participants). The proposed study will perform echocardiography (echo) at the remaining 7 WIHS field centers on an additional 1,355 participants (80% of active participants therein). This will allow completion of echos in a targeted 1,980 women across the WIHS, enhancing our characterization of LV systolic and diastolic function, right ventricular (RV) function, pulmonary artery systolic pressure (PASP), and valvular disease. In so doing, the proposed project will: (1) provide the largest and most comprehensive assessment of cardiac structure and function in an ethnically and geographically diverse cohort of women with and without HIV infection who are followed prospectively, and (2) permit an unprecedented examination of the scope of HIV-related heart disease and its determinants in women.

B. REFERENCES

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C. SPECIFIC AIMS AND HYPOTHESES

Our overarching hypothesis is that HIV infection leads to abnormal cardiac structure and function in women, and that HIV-specific factors associated with poorer control or specific medications amplify such abnormalities. We will address the following specific aims:

Aim 1. To compare the burden of ECHO structural and functional abnormalities (increased LV mass and reduced LV ejection fraction; diminished global longitudinal strain; impaired LV diastolic function; elevated PASP; RV dysfunction; increased valvular disease) between HIV-infected and HIV-uninfected women in a national cohort after adjusting for behavioral and clinical risk factors.

Aim 2. To assess the relationship of HIV-specific factors (CD4+ T-cell count, antecedent persistent viral suppression) and medications (protease inhibitors, specific nucleoside reverse transcriptase inhibitors) with abnormal cardiac structure and function, as determined by echocardiography, in a national sample of women with HIV infection.

Impact: The stands to improve understanding of heart disease in HIV-infected, predominantly minority women, and to guide future efforts for identification, prevention, and treatment of this condition, with implications for the health not only of HIV-infected women, but potentially also for the general population.

D. RELEVANCE TO WIHS

The study addresses high-priority HIV/AIDS research areas, namely, the comorbidity of cardiovascular disease associated with long-term HIV disease and antiretroviral therapy, and the problem of health disparities in this regard. The project would supplement the ongoing echocardiography and cardiac magnetic resonance imaging in the Bronx and Brooklyn sites of the WIHS by extending echocardiography to remaining sites. It would also afford synergy with the WIHS ECG study, by allowing concurrent data on ECG-determined rhythm, waveforms, conduction, and heart rate variability on the one hand, and echocardiographic cardiac structure and function on the other. Such different modalities will afford complementary cardiac assessments in the WIHS cohort. In addition, the ECHO measures of cardiac structure and function may be linked to cardiovascular events in the future, allowing assessment of their implications for cardiovascular morbidity and mortality in the cohort.

E. OVERVIEW

The study plans to extend echocardiograms currently underway at the Bronx and Brooklyn sites of the WIHS (R01 HL132794) to the remaining 7 sites. It is estimated that 80% of active participants at these 7 sites (n=1,355) will provide consent and enroll into the study. This project will allow a larger and more fine-grained cross-sectional evaluation of the role of HIV and HIV-related factors as determinants of echocardiography-determined cardiac structure and function in this cohort.

The ***scientific objectives*** for this component are: (1) to compare the burden of cardiac structural and functional abnormalities between HIV-infected and HIV-uninfected women after adjustment for behavioral and clinical risk factors; and (2) to assess the relation of HIV-specific factors and medications with cardiac structural and functional abnormalities in HIV-infected women. For evaluation of cardiac structure and function, the ongoing Bronx-Brooklyn echocardiographic study will be expanded to the other 7 WIHS sites, with the addition of echocardiograms to the WIHS semiannual visits 47 and 48 at these sites. The WIHS ECHO Study will allow an unprecedented examination of the scope of HIV-related heart disease and its determinants in an ethnically and geographically diverse cohort of women. This will be accomplished by leveraging existing infrastructure and expertise at Echocardiography Laboratories in proximity to the WIHS sites. In addition, questionnaires to assess angina (ECHOROSE questionnaire) and New York Heart Association class (ECHONYHA questionnaire) will be administered.

The major steps in the WIHS ECHO Study research plan are as follows:

1) Establish expanded Echocardiography Reading Center (ERC)
2) Protocol development led by the PI, the ERC, site PIs, and WDMAC
3) Training of Sonographer-Readers at the ERC
4) Submission of IRB modifications
5) Purchase of licenses and installation of Vertex Routers/LifeImage at site ECHO Labs
6) Centralized training of site sonographers on performance of echocardiograms, procedures for alerts, and transmission of data
7) Certification of site sonographers following transmission of 2 qualifying studies
8) Teleconference with site cardiologists to review study procedures / alerts
9) Remote training of site staff on completion of Rose Angina (ECHOROSE) and NYHA Class (ECHONYHA) questionnaires
10) Provision of continual feedback to sonographer-readers and site sonographers
11) NHLBI staff will monitor project progress and research direction by attending:
    a) Biannual WIHS PI in-person meetings
    b) Monthly WIHS ECHO Study Group conference calls
    c) Bi-weekly WIHS Executive Committee teleconference calls
    d) Possible informal site visits to understand the site operations in conducting the WIHS ECHO Study
    e) Meeting with WIHS investigators at national conferences such as the annual American Heart Association Scientific Sessions and the Conference on Retroviruses and Opportunistic Infections.

F. TIMELINE

The ECHO study is planned for Visits 47 and 48 (October 1, 2017 through September 30, 2018). The ECHO should be performed at a visit separate from the core WIHS visit.

G. ROLES OF ERC, WIHS SITES, WDMAC

1. ECHOCARDIOGRAPHY READING CENTER (ERC)

Bronx-Brooklyn Study: As part of the ongoing Bronx-Brooklyn imaging study (R01 HL132794), procedures were developed for training and certification of 2 sonographers at each site; for identification of findings qualifying as critical alerts; for harmonization of echocardiogram reads between the co-leads of the ERC, Drs. Kizer and Lazar; for secure image transmission between Brooklyn and Bronx through purchase and installation of Vertex Router/LifeImage at the Brooklyn ECHO Lab; for secure remote access to Dr. Lazar to perform echocardiogram interpretations using the Montefiore's

Philips Xcelera Research System; and for mailing of reports back to participants. The echocardiographic component of the Bronx-Brooklyn imaging study has a targeted sample size of 625 women.

WIHS-Wide Expansion: To accommodate the 1,355 additional ECHOs proposed for the 7 remaining WIHS sites, the ERC will hire two new sonographer-readers to perform the ECHO interpretations, and add a third echocardiographer over-reader, Dr. Cynthia Taub, to join Drs. Kizer and Lazar in this effort. The ERC at Albert Einstein College of Medicine/Montefiore Medical Center will be expanded by acquisition of a dedicated computer terminal and work station, equipped with TomTec software for myocardial deformation imaging analysis. The Montefiore Imaging IT team responsible for setting up image transfer, processing, analysis, and storage capabilities, will provide increased storage capacity for the larger volume of echocardiograms to be transmitted to the ERC. During the start-up phase, the PI, Co-PI, and Co-I at the ERC will meet to review ECHO protocols, and to plan workflow and distribution of workload. Under the direction of Dr. Kizer, with contributions from Drs. Lazar and Taub, the two sonographer-readers will undergo training in theory, practice, and interpretation of echocardiograms, including myocardial deformation imaging. They will be certified in performance and interpretation of echocardiograms as per the WIHS ECHO Study protocol.

2. WIHS SITES

SITE ACTIVITIES: WIHS site staff will be in charge of submitting local IRB modifications, coordinating the recruitment and enrollment of participants into the ECHO Study, administering the study questionnaires (ECHOROSE and ECHONYHA), and scheduling the standardized echocardiograms. Each site has made arrangements to have ECHOs performed at nearby academic or high-volume ECHO Laboratories. WIHS site staff will interact closely with participating sonographers and cardiologists at the sites, and will ensure that recommendations from local cardiologists/echocardiographers regarding critical alerts are followed up. WIHS site staff will also store back-up CDs of completed ECHOs at each site, and will receive and relay completed ECHO reports from the ERC to participants and, if consented to by participants, their physician. WIHS site staff will be trained in aspects of the protocol, questionnaire administration, procedures for communicating with the ERC, and data entry into WDMAC’s Apollo database at teleconferences coordinated by the ERC and WDMAC. The ECHOROSE and ECHONYHA questionnaires will also be posted on the study website.

LOCAL ECHO LABS: Each ECHO Lab will vary as to their approach to the readings of echocardiograms. Some sites will undertake clinical reads of ECHOs on all participants. Others will have a cardiologist available to interface with sonographers, and perform reads and make triaging decisions only in the case of critical alerts identified by sonographers in the course of performing the ECHO scans. Regardless of the approach, all participating ECHO Labs will identify 1-2 sonographers for participation in the study. Such participation requires attending a centralized training session at the ERC, and subsequent transmission of two high-quality studies to the ERC in order to earn certification for participation in the WIHS ECHO Study. The WIHS ECHO protocol will be made available to sonographers on the study website, and sonographers will be provided with a laminated sheet containing the required image sequence. The sonographer-readers will not only participate in the centralized training session, but they will provide regular feedback to site sonographers regarding study quality, including formal grades, for the purpose of quality control and assurance. Local sonographers will also participate in monthly calls, also attended by WIHS site staff, to monitor progress and address quality and other issues across the study.

IMAGE TRANSFER AND DATA TRACKING: The proposed approach is to have local ECHO Labs identify a computer on-site for installation of the Vertex Router/LifeImage software, which will be performed by Montefiore Imaging IT specialists. Such software allows the secure transfer of images through a virtual private network, from where the images are directly routed to the ERC's Philips Xcelera Research System, and subsequently for myocardial deformation analysis using TomTec. The computer at the local ECHO Lab will also serve for the sonographer to upload information in Apollo, which will include date, WIHSID, current age, height, weight, systolic and diastolic blood pressure, and heart rate for each completed study. This will serve as a means of tracking study completion, and obtaining key information on each participant. The secure Apollo data entry screen will also contain a field for recording of critical alert findings, which will flag the study at the ERC for rapid interpretation. The ERC, including its IT specialists, and WDMAC, will coordinate the setup of Apollo stations for transfer of data between the sites, the ERC, and WDMAC.

CRITICAL ALERTS: Site sonographers will be instructed to identify ECHO findings of clinical importance, and to notify site staff and investigators with critical alerts when such findings are detected. Critical alerts include, but are not limited to: (1) cardiac tamponade; (2) obvious valvular vegetation or abscess; (3) thrombosed or overtly dysfunctional valvular prosthesis; (4) left ventricular pseudoaneurysm; (5) intracardiac thrombus; (6) aortic dissection. At sites conducting clinical ECHO reads in real time, such findings will be interpreted promptly, and a triage decision (e.g., emergency room, less acute clinical referral/follow-up) made by WIHS site staff in consultation with the interpreting echocardiographer. At sites with a cardiology investigator, the sonographer will contact such investigator for immediate review of the images, and a triage decision similarly made by the site cardiology investigator. In either case, the sonographer will mark the study as having a critical alert on the ECHOCA questionnaire, and describe the action taken. In addition, the WIHS site staff will compose an email containing the WIHSID of the participant, the finding of an alert, and the action taken locally, which will be sent to the ERC sonographer readers, research assistant, and the ERC investigators. In both instances, the ERC will undertake prompt interpretation of the echocardiogram, with a report faxed/mailed back to the site by the next business day. The report will be marked as a research study read, and site investigators will be advised to relay to participants and their providers that all clinical care decisions be based primarily on the local clinical read or initial interpretation by the site cardiologist.

3. WIHS DATA MANAGEMENT AND ANALYSIS CENTER (WDMAC)

WDMAC will assist with the development and dissemination of the ECHO performance, transfer, and data management protocols, including tracking echocardiogram completion and receipt of data, using an interactive data management system. All protocols will be placed on the WIHS study administrative website. WDMAC will also develop the codebooks for the ECHO data, and programs for quality assurance. WDMAC investigators will collaborate with site and reading center investigators in the analysis of the data and disseminating results according to concepts that are approved by the WIHS Executive Committee.

H. CERTIFICATION AND TRAINING

Each Lab will designate at least one sonographer and ideally two sonographers for certification for the research study. Sonographers will require RCS or RDCS credentials. Sonographer-technicians will attend an in-person training session organized by the ERC at Montefiore Medical Center. This session will provide an overview of the project aims and organization; detail the echocardiography protocol and pitfalls to be avoided, review planned workflow and remote transmission of echocardiograms, and discuss procedures for handling and reporting alerts. This will be followed by live demonstrations of the protocol, after which each sonographer will have the opportunity to complete a full scan on a volunteer. Supervised completion of the protocol will serve as the first step in sonographer certification. Thereafter, each sonographer will need independently to complete two full-protocol scans, and successfully transmit these to the ECHO Reading Center. To earn certification, the sonographer will be required to obtain all the requisite views, and achieve a passing grade (score ≥ 16) for each of the two scans. If the sonographer fails to meet these requirements for their two independent scans, there will be an opportunity for resubmission. Sonographer-technicians not participating in the centralized training session will need to be trained in person. The centralized training session will be videotaped and posted on the study website, such that sonographers can refer to its content for review after the training session is completed.

I. WORKFLOW AND IMAGE TRANSFER

1. RECRUITMENT

Current WIHS participants will be contacted by WIHS study staff and, if interested, will be scheduled for an appointment for the echocardiography component of the study.

2. STUDY VISIT

- The study will be explained to participants, and they will be given the opportunity to have all questions answered. If they are interested in participating, written informed consent will be obtained. Study consents will be stored in a locked cabinet in the WIHS office.
- Interested participants who sign consent for the echocardiogram will complete or have administered the Rose Angina Questionnaire (ECHOROSE) and the NYHA Questionnaire (ECHONYHA). The study coordinator will also obtain their current age, self-reported height and weight, and information on prior cardiac medical history, and complete Section 1 of the ECHO Technician Worksheet (ECHOTW). The participant will then proceed to the Echocardiography Lab to have the echocardiogram performed.
- The ECHO will be conducted by a trained sonographer according to the protocol. The sonographer will then complete the ECHO Technician Worksheet (ECHOTW) in Apollo by entering blood pressure measurements and information regarding completeness of imaging, and the presence of critical or urgent findings. In the presence of a critical alert or vital sign, the sonographer will also complete the ECHO Site Critical Alert or Vital Sign Documentation Form (ECHOCA).

- Data contained on the following forms will be entered into Apollo:
    - Rose Questionnaire (ECHOROSE)
    - NYHA Questionnaire (ECHONYHA)
    - ECHO Technician Worksheet (ECHOTW)
    - ECHO Site Critical Alert or Abnormal Vital Sign Documentation Form (ECHOCA)

3. ECHO TESTING

Site Procedure

- For patients in sinus rhythm, record at least 3 full cardiac cycles in each view (once images optimized)
- For patients in atrial fibrillation or frequent ectopy, record at least one 5 second acquisition for each view
- Maximize accuracy of 2D measurements
    - Optimize depth setting to achieve largest image size that fits within the imaging field – On-axis imaging, avoidance of apical-foreshortening is paramount
- Maximize accuracy of Doppler measurements
    - Spectral: Use 100 mm/s sweep speed; shift baseline and adjust Doppler scale to obtain spectral Doppler signals that occupy ⅔ to ¾ of the field – Color scale 50-60 cm/s

Pre-scanning Data

- Obtain height and weight.
- Brachial blood pressure obtained in duplicate with automated cuff (e.g., Omron) <30 minutes before start of echocardiogram, after participant has rested for 5 minutes.
- Obtain heart rate.

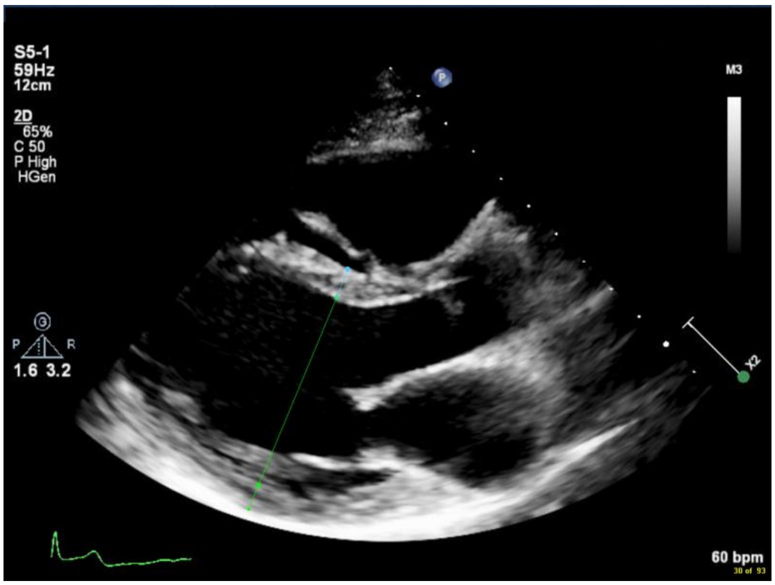
J. PRINCIPAL IMAGES AND MEASUREMENTS

All measurements will be made in accordance with the American Society of Echocardiography guidelines by the sonographer-readers and overseeing echocardiographers at the ECHO Reading Center.

QUANTIFICATION OF CHAMBER SIZE ***Measurements are made on acquired beats that are diagnostic quality ***

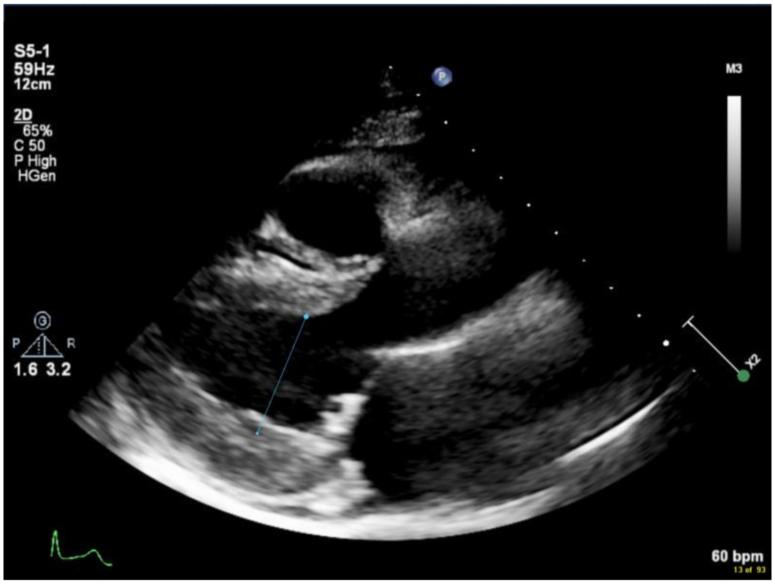
LINEAR MEASUREMENTS

PLAX VIEW: ***(From 2D, obtained at level of papillary muscle tip, perpendicular to the LV long axis)***



(End diastole = LV at maximal diameter, last frame with mitral leaflets extended)

- LV end-diastolic diameter
- Interventricular septal thickness
- Posterior wall thickness
- Aortic root diameter

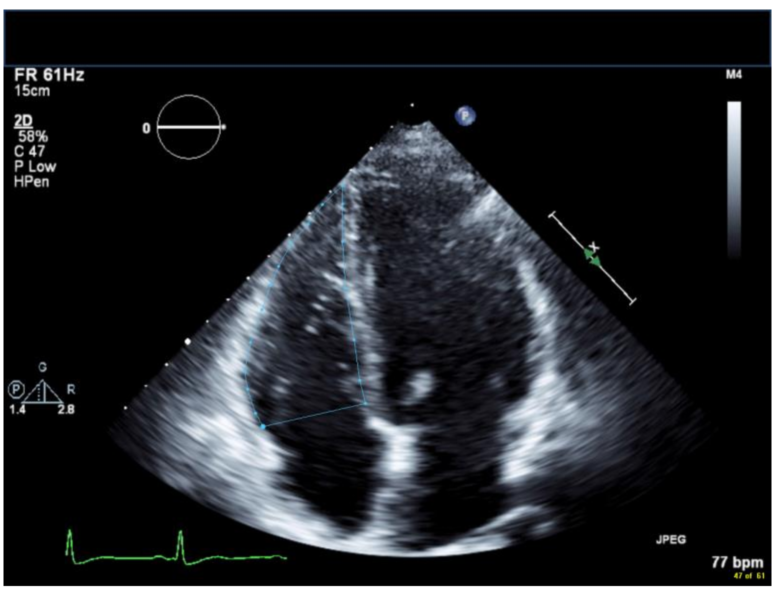


(End systole = LV at minimal diameter, mitral valve closed, aortic valve open)

- LV end-systolic diameter
- Left atrial end-systolic dimension

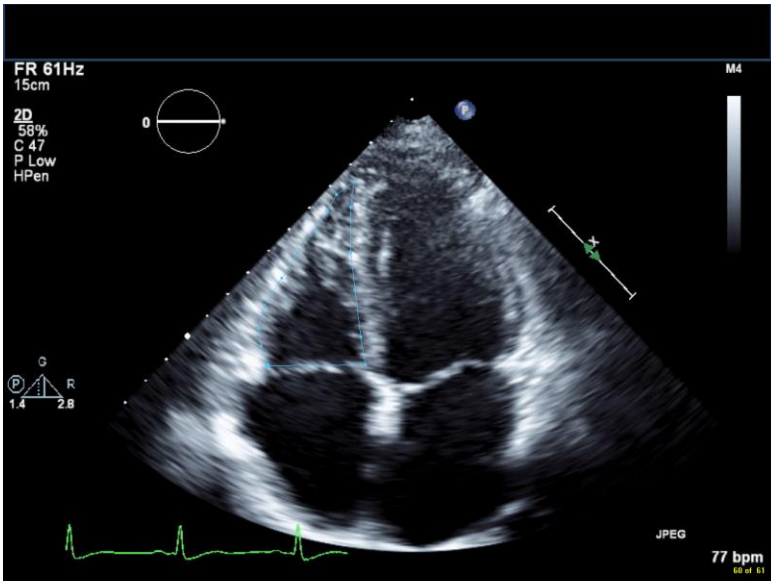
1. AREA MEASUREMENTS:

APICAL 4-CHAMBER VIEW *(Select RV zoom view, include trabeculations)*



(End Diastole = RV at maximal area)

- RV end-diastolic area

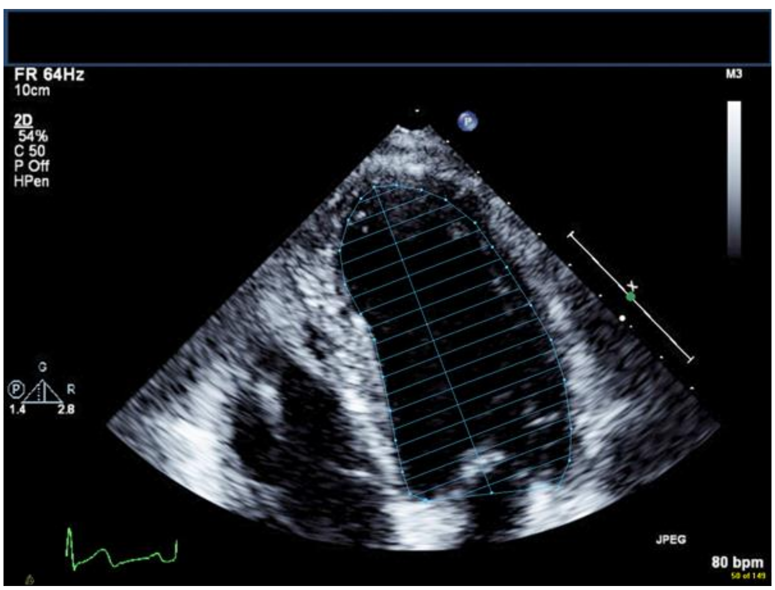


(End Systole = RV at minimal area)

- RV end-systolic area

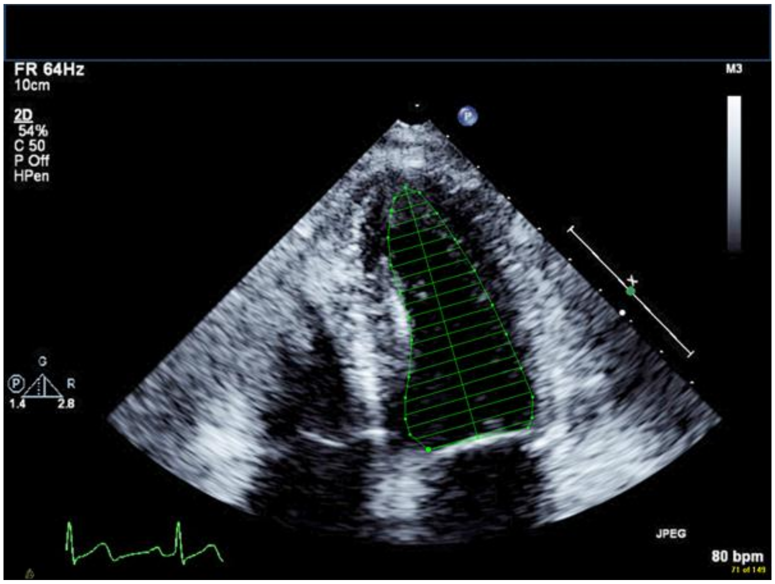
2. ESTIMATED VOLUME CALCULATIONS (SIMPSON'S METHOD OF DISCS): ***(Exclude trabeculations)***

APICAL 4-CHAMBER VIEW



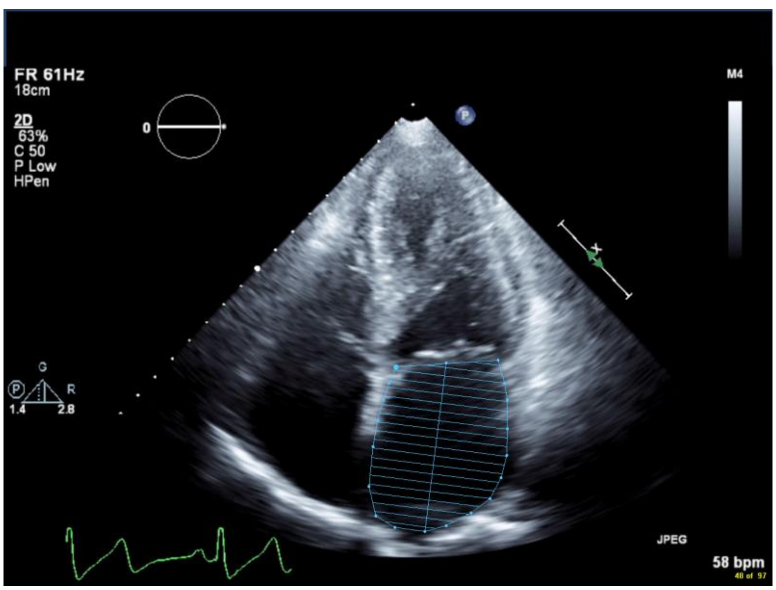
- LV end-diastolic volume

(End diastole = LV at maximal volume)



- LV end-systolic volume

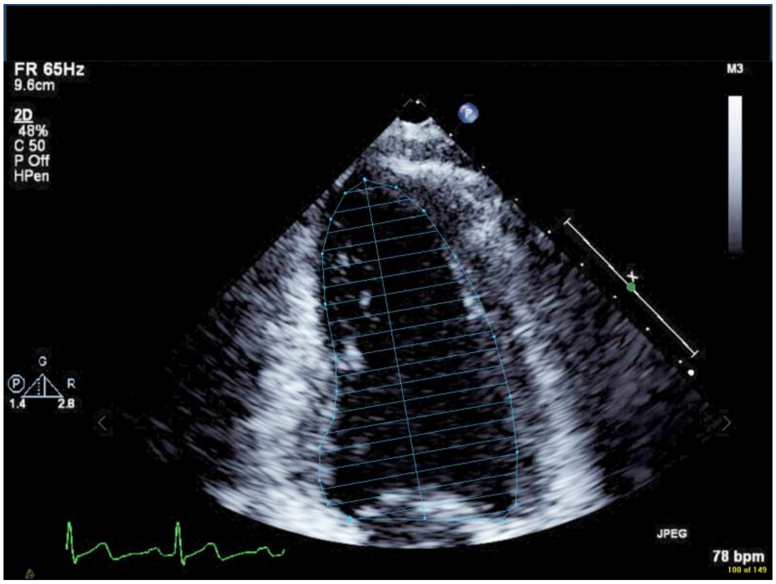
(End systole = LV at minimal volume)



- LA end-systolic volume (maximum volume)

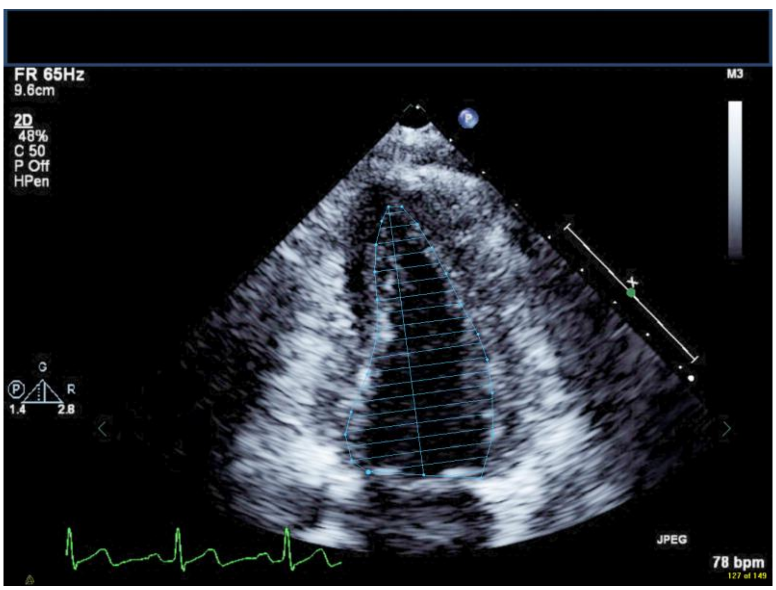
APICAL 2-CHAMBER VIEW

(End diastole = LV at maximal volume)

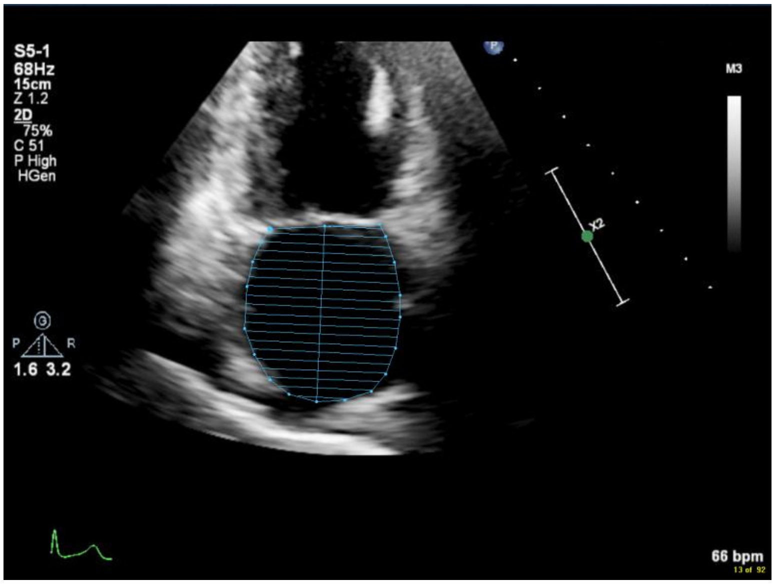


- LV end-diastolic volume

(End systole = LV at minimal volume)



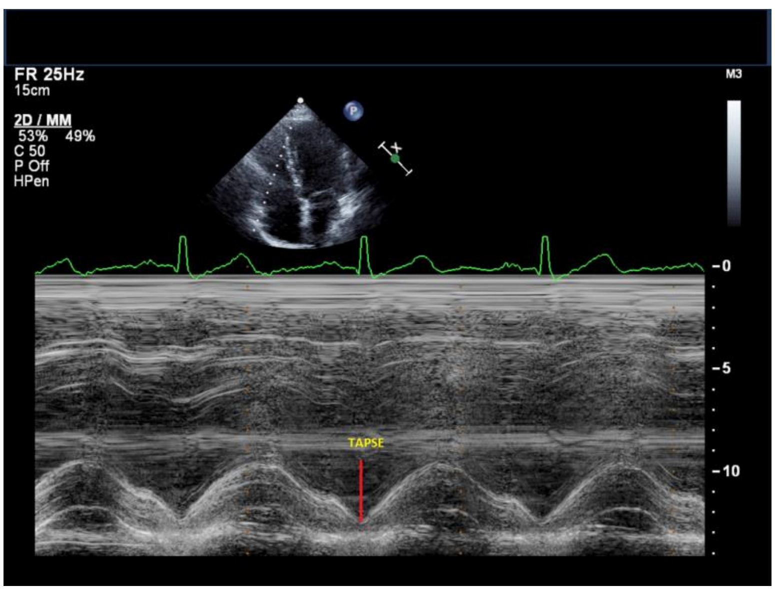
- LV end-systolic volume



- LA end-systolic volume (maximum volume)

M-MODE MEASUREMENTS

Right Ventricular Longitudinal Systolic Function measurement

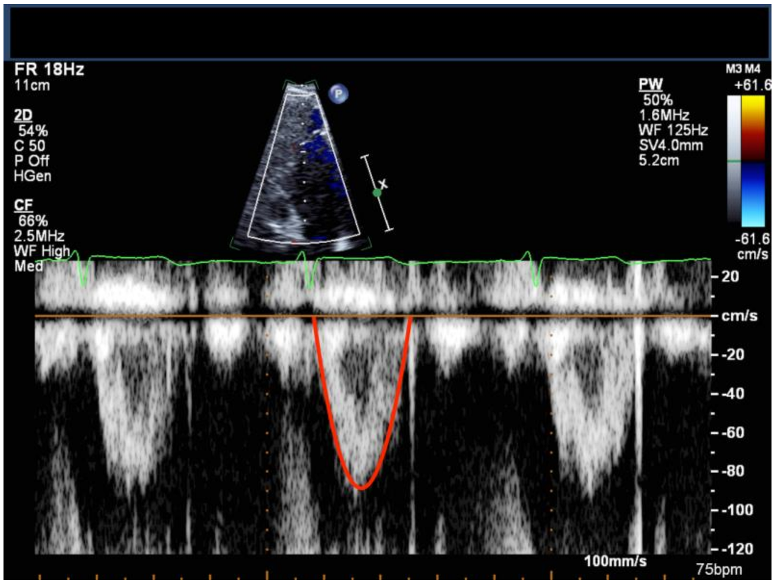


**Tricuspid Annular Plane Systolic Excursion (TAPSE)

1. M-mode cursor aligned along the direction of the tricuspid lateral annulus
2. Measurement between end-diastole and peak-systole

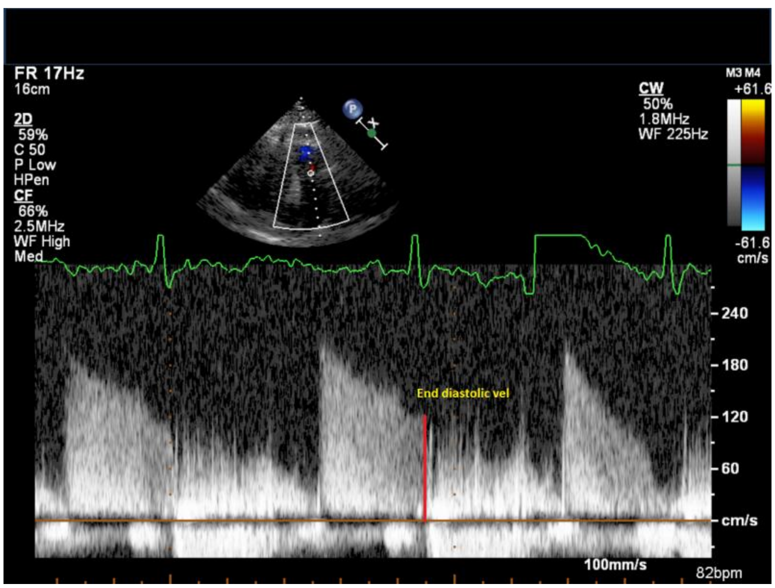
DOPPLER EVALUATION

RIGHT VENTRICULAR OUTFLOW TRACT



**Right ventricular outflow tract (PW-Doppler from 1. PLAX RV outflow view, 2. PSAX VIEW)

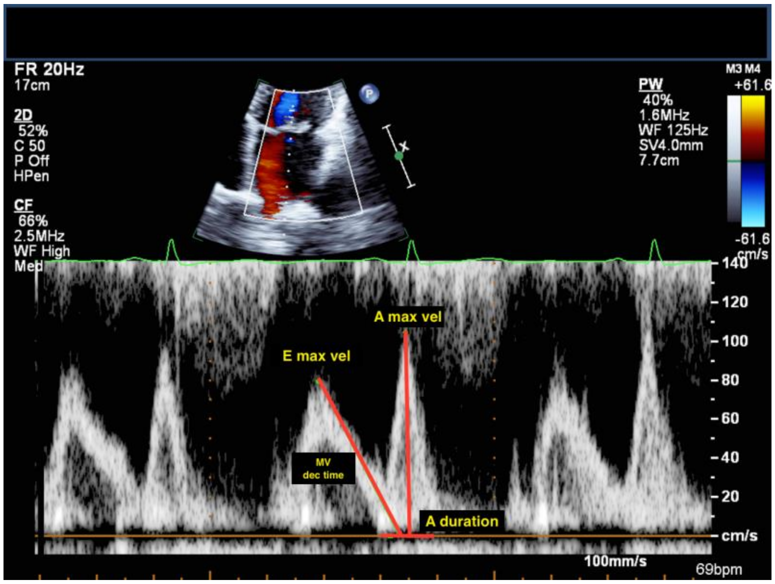
- RVOT VTI



**Pulmonic Regurgitation (CW Doppler aligned to PR from 1. PLAX RV outflow view, 2. PSAX view)

- Early pulmonic regurgitation velocity

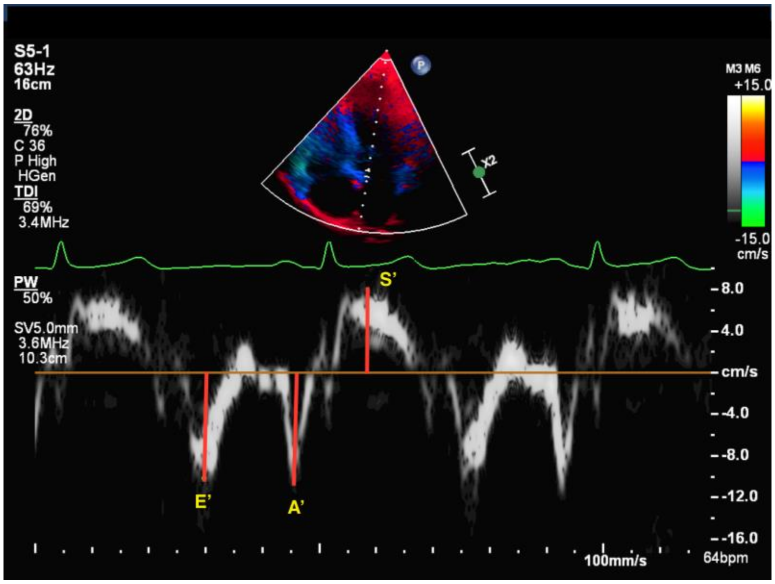
APICAL 4-CHAMBER VIEW



**Left ventricular inflow (PW Doppler at tips of mitral leaflets)[1]

- E-wave maximal velocity
- E-wave deceleration time
- A-wave maximal velocity
- A-wave duration

[1] ***** If rhythm regular measure once (tallest E-wave and corresponding A-wave generally end-expiration). If irregular, measure all acquired with diagnostic image quality. Only measure if distinct E-and A-waves *****



**Tissue Doppler at the septal mitral annulus (baseline centered)

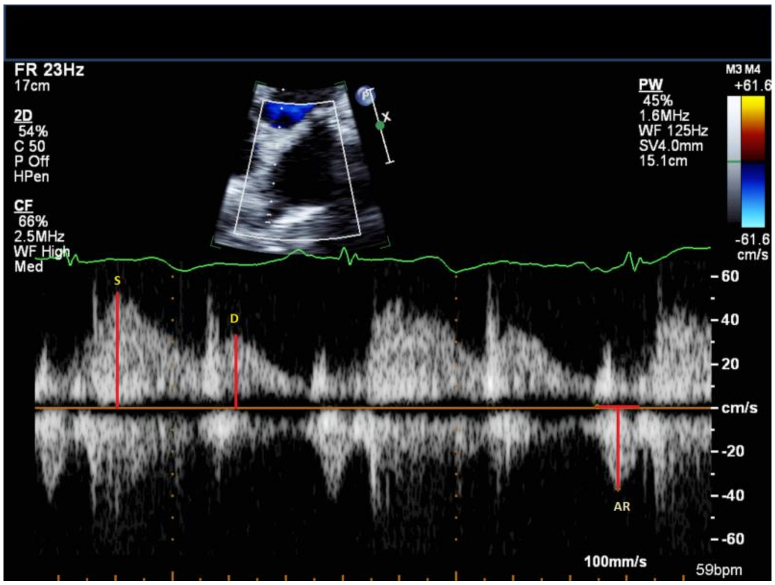
- S'-wave Max Velocity
- E'-wave Maximum Velocity
- A'-wave Maximum Velocity

(Repeat with sample volume at LATERAL mitral annulus)

- S’-wave Max Velocity
- E’-wave Maximum Velocity
- A’-wave Maximum Velocity

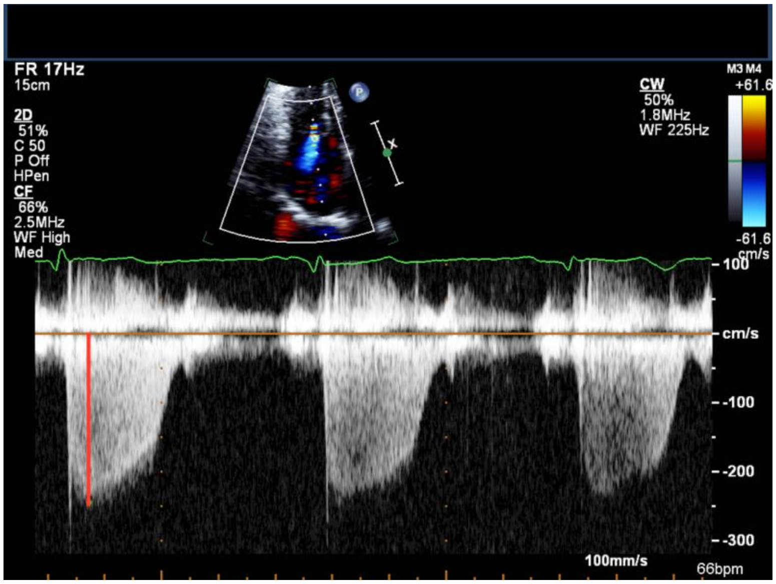
(Repeat with sample volume at LATERAL tricuspid annulus)

- S’-wave Max Velocity
- E’-wave Maximum Velocity
- A’-wave Maximum Velocity



**PW Doppler in right superior PV

- Pulmonary venous flow max S-wave velocity
- Pulmonary venous flow max D-wave velocity
- Pulmonary venous flow max A-wave reversal velocity
- Pulmonary venous flow max A-wave reversal duration



***Tricuspid Regurgitation[2] (CW-Doppler from 1. PSAX VIEW, 2. PLAX RV Inflow VIEW, 3. APICAL 4-CHAMBER VIEW, 4. SUBCOSTAL 4-CHAMBER VIEW)

- TR maximum velocity

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[2]***** If rhythm regular, use the highest maximal velocity seen in any of the views*****

K. SPECKLE-TRACKING EVALUATION

For speckle tracking evaluation, the following specific images will be acquired at 50-80 fps:
Parasternal short-axis view

- 2D imaging at mid-ventricular (papillary muscle) level at high depth (deep)
    - 2D imaging at mid-ventricular (papillary muscle) level at low depth (shallow)

Apical 4-chamber view

- 2D imaging
- 2D imaging, focused/zoomed on left ventricle
- 2D imaging, focused/zoomed on left atrium

Apical 2-chamber view

- 2D imaging
- 2D imaging, focused/zoomed on left ventricle
- 2D imaging, focused/zoomed on left atrium

Care must be taken to avoid foreshortening, while aiming to optimize endocardial definition of ventricular segments.

L. CONTINGENCY ECHO ASSESSMENTS

In the event that any of the following pathologies is present, the following assessments should be performed by site sonographers to permit interpretation at the Reading Center:

1. Aortic Stenosis: Ensure optimal LVOT and transaortic flow signals for determination of aortic valve area, mean transaortic gradient, and peak transaortic gradient.

2. Mitral Regurgitation: Proximal isovelocity surface area (PISA); CW Doppler of MR for determination of maximal velocity; ensure optimal assessment for vena contracta width

3. Aortic Regurgitation: CW of AR (A5C) for determination of pressure half time; ensure optimal assessment of VC width; assess for holodiastolic flow reversal by CW Doppler (suprasternal view).

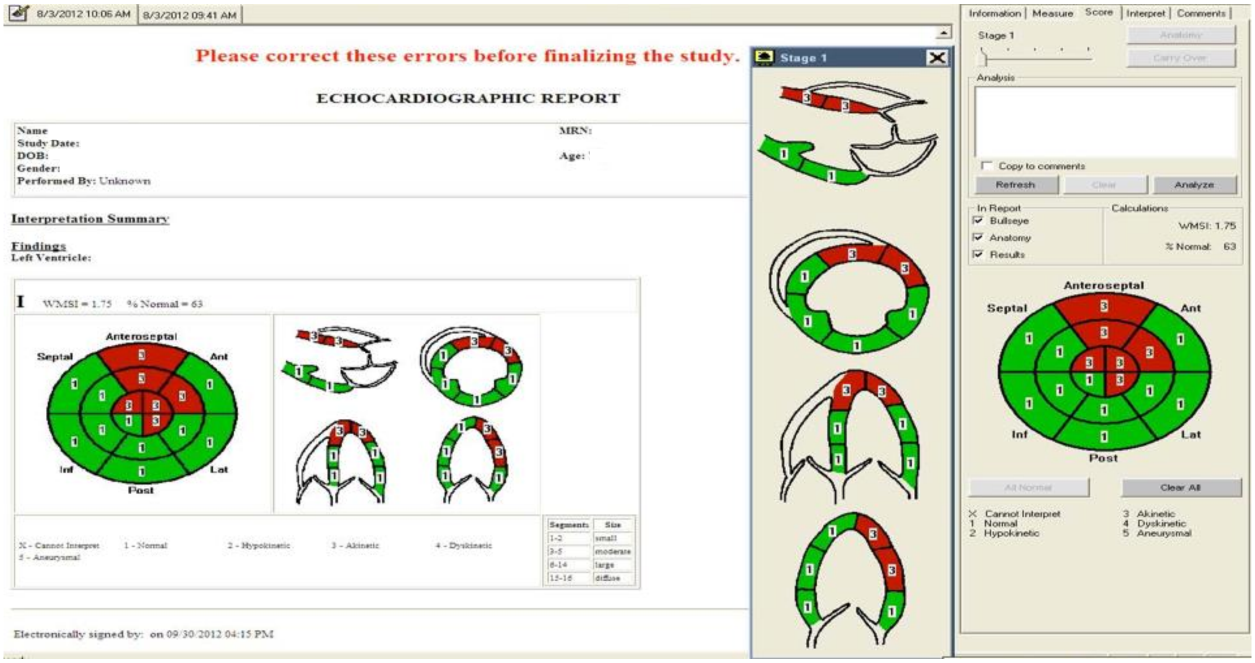
4. Mitral Stenosis: CW Doppler of mitral inflow for determination of MV mean gradient and pressure half time.

5. Hypertrophic Cardiomyopathy: LVOT peak gradient (with/without Valsalva)

6. Significant Pericardial Effusion: Respirophasic variability of mitral and tricuspid inflow at 25 mm/s sweep speed.

M. QUALITATIVE MEASUREMENTS

1. LV WALL MOTION:



LV wall motion must be assessed as follows for each segment as displayed above: 1. Normal; 2. Hypokinetic; 3. Akinetic; 4. Dyskinetic; 5. Aneurysmal

2. VALVE MORPHOLOGY AND REGURGITATION:

Each cardiac valve will assessed for morphology as follows:

1. Normal; 2. Thickened; 3. Calcificied; 3. Prolapse; 4. Rheumatic; 5. Congenital Abnormality; 6. Vegetation; 7. Prosthetic (Biologic or Mechanical).

Each cardiac valve will be graded for the severity of regurgitation as follows

1. None; 2. Mild; 3. Mild to Moderate; 4. Moderate; 5. Moderate to Severe; 6. Severe.

N. CONCLUSIONS/RECOMMENDATIONS

This field must be filled in. Participants will receive a copy of the report and an accompanying cover letter, which, for those who provide consent, will also be sent to their physicians. The salient features of the echocardiogram should be succinctly summarized.

O. QA PROCESS FOR ECHOCARDIOGRAPHY READING CENTER (ERC)

ERC Team

The echocardiography reading team at the ERC, composed of Drs. Kizer, Lazar and Taub, will hold regular sessions to harmonize reading styles. They will also participate in training of two sonographer-readers, who will undergo intensive image review and analysis not only for WIHS participant ECHOs currently under way for the WIHS Bronx-Brooklyn study, but also a range of clinical ECHOs. Both sonographer readers will be certified in performance of WIHS ECHOs by completing two full-protocol echocardiograms satisfying criteria for certification. Sonographer-readers will perform initial screens of incoming echocardiograms, alerting echocardiographers to previously unsuspected critical findings for timely review and interpretation. Sonographer-readers will also complete preliminary interpretations of all scans, which will be over-read by echocardiographer physicians.

Intra- and Inter-reader Reliability

Intra- and Inter-reader reliability of echocardiographer-physician interpretations will be assessed to promote consistency across readings. Measures of agreement will also be useful for assessment of generalizability of WIHS echocardiography data to other populations. The agreement between readings will be assessed by intra-class correlation, mean±SD of relative difference between readers and coefficients of variation.

Intra-reader reliability: Within the first 3 months of the echocardiogram acquisition period, a random sample of 20 echocardiographic examinations interpreted by each echocardiographer (Kizer, Lazar, Taub; 60 echocardiograms total) will be randomly selected by the research coordinator. The list of participant WIHSID and exam dates will be provided to the IT team at the ECHO Reading Center, who will proceed to replicate the indicated image set in the Reading Center PACS system with the participant's ID modified to indicate that it is a duplicate (or, in the case of inter-reader reliability determinations, triplicate or quadruplicate – see below). The previously reported values for the participants' echocardiographic measurements will not be attached, such that a new report can be generated and archived with the reader blinded to the original results. Each set of exams will be re-read by the same echocardiographer to evaluate his/her intra-reader reliability. The corrective actions required when intra-reader reliability and "temporal drift" exceed protocol criteria are discussed below.

Inter-reader reliability: The 20 echocardiograms that are chosen to be re-read by each echocardiographer for the intra-reader reliability assessment will also be suitable for analysis of inter-reader reliability, as all three readers will read the 60 duplicate scans (hence, the need for quadruplicates). The corrective actions required when inter-reader reliability exceeds protocol criteria are discussed below.

To maintain reproducibility standards, when mean relative difference between readings for intra-reader or inter-reader agreement exceeds 10% for linear measurements and calculations or 15% for traced measurements or calculations (i.e., volume), discrepancies (in either the intra-observer and intra-observer readings) will be reviewed by both readers jointly to identify errors and reconcile differences. This will enhance consistency both within and between readers.

P. FEEDBACK TO TECHNICIANS

The ERC staff will routinely provide feedback to the sonographer-technicians at each field center. Each received echocardiogram will be reviewed for completeness of the views as well as image quality for each acquired view as described above.

There are 68 required views specified in the protocol (see **Appendices A, B,** and **C**). Key image measurements are detailed in Section J of the Manual of Procedures. Of required views, the eight principal views or components of the examination will be graded for quality in the ECHO Score Card (ECHOSC), receiving a score as follows: 0=Not obtained 1=Poor image quality not adequate for measurements, 2=Suboptimal image quality but adequate for measurements, 3=High-quality image allowing accurate measurements. Accordingly, each exam will receive a total score between zero and 24.

- The eight key views/components included in the ECHO Score Card will be: (1) PLAx; (2) PSAx at mid-cavity level; (3) A4C LV; (4) A4C LA; (5) A2C LV; (6) A2C LA; (7) RV; (5) Doppler diastolic measures. ECHO Score Cards will be entered in Apollo.
- A score equal or greater to 16 is necessary to be considered passing.
- A standard of passing scores on each of two qualifying echocardiograms on volunteers will be required for initial technician certification prior to onset of research imaging; maintenance of technician certification will require 90% exams with passing scores per 6-month period.

Report cards will be automatically generated for each of the sonographer technicians at bimonthly intervals. The report card will contain data summarizing the technicians' total number of exams performed, the average image quality score as described above and also the percent of exams with a passing score. The report card will also give the scores received for every required view for exams that did not receive a passing grade. The summary data will be broken down into 6-month blocks to examine for trends over time. The report cards will be e-mailed to both the technician and each field center's echocardiographer(s).

Continual feedback will be provided to sonographer technicians by email or phone as issues with image quality are identified. Monthly QA teleconferences will be held by the physician echocardiographers, during which common or recurrent problems with image quality by one or more technicians are discussed. If interim reviews of technician scorecards reveal or confirm entrenched problems, tailored one-on-one or group review sessions may be scheduled as necessary. Counseling will be targeted to the type of task with which a particular technician has (or multiple technicians have) had difficulty complying. For example, if missing views is the deficiency, then the protocol will be reviewed again, and management strategies, such as routine filling out of a checklist will be employed. If the deficiency is improper alignment of 2D imaging, examples of the improper images will be provided along with adjacent to views that have been properly aligned. The purpose of these sessions will not only be to provide feedback, but also to illustrate proper technique. In cases where maintenance of passing scores and response to counseling is poor, Dr. Kizer and his team will hold discussions with the Echocardiography Lab Director/investigator at the corresponding site to discuss replacing the technician.

Q. CRITICAL AND URGENT FINDINGS

Critical Findings Participant report faxed to WIHS site by next business day	**Urgent Findings** Participant report faxed to WIHS site within 3 business days
Cardiac tamponade	LV wall motion abnormalities
Aortic dissection	Reduced LV or RV systolic function
Intracardiac thrombus, vegetation or tumor	More than moderate valve regurgitation
Severe prosthetic valve dysfunction	Moderate or greater LV outflow obstruction
LV pseudoaneurysm	More than moderate pulmonary hypertension
	More than moderate restrictive LV inflow
	Severe aortic root dilatation (≥5 cm)

The safety of the WIHS study participants is of the highest priority. Severe, life-threatening pathology can be found on echocardiography even in asymptomatic populations.

Site technicians will alert the local site echocardiographer about potential critical findings via phone. The echocardiographer will review the findings, and contact the research coordinator at each site. Since the cardiologist will not have any participant identifiers or any pertinent clinical information about the participant, the study coordinator will furnish information known about the participant's medical history as appropriate. The echocardiographer will then contact the participant and facilitate medical referral as deemed appropriate.

Each local echocardiographer will review echocardiograms for critical findings, and generate an alert by contacting the study coordinator at each field center according to the timeline specified in the Table above.

For each exam, the aim will be to complete interpretation within 4 weeks of study performance. Any critical or urgent findings that were not appreciated on initial review will be reported immediately. The ECHO Reading Center Critical or Urgent Finding Documentation Form (ECHOCARC) will be completed in Apollo. For local sites providing clinical reads, clinical echocardiographers will complete these ECHOCARC paper forms, and forward them to WIHS clinic staff along with final echocardiography report. At the ECHO Reading Center, echocardiography reports summarizing the main findings of each examination will be created for all performed echocardiographic examinations upon completion. For sites not obtaining local clinical interpretations of the echocardiograms, the central reports will faxed or mailed to the sites. The sites will in turn fax or mail these reports to study participants and, with their consent, their physicians. The central reports will be accompanied by a cover letter (see samples in **Appendix D** and **E**, which may be modified by each site as appropriate) indicating that the study is normal or that there are findings that are abnormal or require attention. In the case of sites that will be obtaining local clinical reads, these central research reports can also be provided, but this will be left to the discretion of each individual site.

Apart from critical and urgent ECHO findings, critical alerts will be generated by sonographers if the average blood pressure reading meets the following criteria: systolic blood pressure is ≥200 mm Hg or diastolic blood pressure is ≥110 mm Hg. A critical alert will also be triggered by a resting heart rate <40 bpm or ≥120 bpm. For critically high blood pressure, the sonographer will have the participant rest quietly for an additional 5 minutes, before repeating two blood pressure measurements. If the average of the two repeat measurements is again above critical limits – or if the initial heart rate is beyond the limits above – the sonographer will cancel the echocardiogram, and consult a clinician. The clinician may be the participating cardiologist at the ECHO Lab, the participant's own health provider, or the WIHS site clinician. The clinician will decide on appropriate disposition, such as referral to the emergency department or to a physician's office. The ECHO should be rescheduled at the discretion of the WIHS clinician once the vital signs are stabilized.

R. Comparability with MACS ECHO Reading Center

The WIHS ECHO Study is to be undertaken alongside a parallel effort in the Multicenter AIDS Cohort Study (MACS), in which Dr. Joao Lima of Johns Hopkins Medical Center will lead the Echocardiographic Reading Center. Drs. Kizer, Lazar, and Lima are multiple PI's on the Bronx-Brooklyn "Evaluation of HIV-associated Cardiac Dysfunction in Women project" (R01 HL132794), for which Dr. Lima directs the MRI Reading Center. To enhance comparability between the WIHS and MACS ECHO Studies, the ECHO Reading Center PI's and/or staff have exchanged protocols, which bear close similarities, and have been invited to attend their counterparts' centralized training session. There are differences, however, most notably the use of TomTec by the WIHS and Toshiba by the MACS for analysis of myocardial deformation, and the latter's plan to have a 3D imaging component. Previous data by Dr. Lima's group has shown high agreement between TomTec and Toshiba determined strain. However, we plan directly to determine agreement between the two studies by selecting a random subset of 100 studies from each cohort to be interpreted by the ECHO Reading Center of the other cohort.

APPENDIX A.
Women's Interagency HIV Study
Transthoracic Echocardiography Imaging Protocol

Machine Setup

- Change machine preset from "30 fps" to "Acquisition".

General Guidelines

- For patients in sinus rhythm, record at least 3 full cardiac cycles in each view (once images optimized)
- For patients in atrial fibrillation or frequent ectopy, record at least one 5 second acquisition for each view
- Maximize accuracy of 2D measurements
    - Optimize depth setting to achieve largest image size that fits within the imaging field
    - On-axis imaging, avoidance of apical-foreshortening is paramount
- Maximize accuracy of Doppler measurements
    - Spectral: Use 100 mm/s sweep speed; shift baseline and adjust Doppler scale to obtain spectral Doppler signals that occupy ⅔ to ¾ of the field
    - Color scale 50-60 cm/s (or greater)
    - For patients in sinus rhythm, record at least 3 full cardiac cycles in each view (once images optimized)
- For strain measurements, frame rate should be at least 50 to 80 fps

Protocol

- Obtain height and weight
- Brachial blood pressure obtained <30 minutes before start of echocardiogram, after resting for 5 minutes, using automated device (e.g., Omron)
- Obtain heart rate

Parasternal Windows

Parasternal Long Axis

- 2D imaging (deep – at high depth)
- 2D imaging (shallow – at low depth)
- Color Doppler of the aortic and mitral valves together (standard depth)
- 2D imaging of LV outflow tract/aortic valve and mitral valve separately (zoomed in)
- Color Doppler of the aortic and mitral valves separately (zoomed in)

Right Ventricular Inflow/Outflow

- 2D imaging (standard and zoomed in)
- Color Doppler of the tricuspid and pulmonic valves (standard depth)
- CW Doppler of the tricuspid valve to obtain peak TR velocity

- PW & CW Doppler of RV outflow tract (CW: transpulmonic flow & pulmonic regurgitation)

Parasternal Short Axis – Aortic Valve Level
- 2D imaging of aortic valve (standard and zoomed in)
- Color Doppler of aortic valve (standard and zoomed in)
- 2D imaging of tricuspid and pulmonic valves (standard)
- Color Doppler of the tricuspid and pulmonic valves (standard)
- CW Doppler of the tricuspid valve to obtain peak TR velocity
- PW & CW Doppler of RV outflow tract (CW: transpulmonic flow & pulmonic regurgitation)

Parasternal Short Axis – LV Base (Mitral Valve Level)
- 2D imaging
- M-mode

Parasternal Short Axis – LV Mid-cavity (Papillary Muscle Level)
- 2D imaging (Optimized at standard depth, and focused/zoomed on LV)

Parasternal Short Axis – LV Apex
- 2D imaging

Apical Windows
Apical 4-chamber
- 2D imaging
- 2D imaging, focused/zoomed on left ventricle
- 2D imaging, focused/zoomed on left atrium
- Color Doppler of the mitral valve/left atrium
- PW Doppler of mitral inflow
- PW Doppler of right upper pulmonary vein inflow
- TDI of septal and lateral mitral annulus (include s’, e’ and a’)
- 2D imaging focused on the right ventricle
- Color Doppler of the tricuspid valve/right atrium
- CW Doppler of tricuspid regurgitation
- TAPSE of lateral tricuspid annulus
- TDI of lateral tricuspid annulus (include s’, e’ and a’)

Apical 5-chamber
- 2D imaging
- CW Doppler near the aortomitral continuity
- Color Doppler of the left ventricular outflow tract
- PW Doppler of left ventricular outflow tract flow
- CW Doppler of transaortic flow

Apical 2-chamber

- 2D imaging
- 2D imaging focused/zoomed on left ventricle
- 2D imaging focused/zoomed on left atrium
- Color Doppler of mitral valve/left atrium

Apical 3-chamber

- 2D imaging
- Color Doppler of mitral valve/left atrium
- Color Doppler of left ventricular outflow tract
- PW Doppler of left ventricular outflow tract flow
- CW Doppler of transaortic flow

Subcostal Window

- 2D imaging of cardiac chambers (long axis) (standard)
- 2D imaging of cardiac chambers (short axis) – only if parasternal short-axis TDS
- Color Doppler of the interatrial septum
- 2D imaging of inferior vena cava (5-second acquisition) – at rest and after deep inspiration or sniff

Suprasternal Window

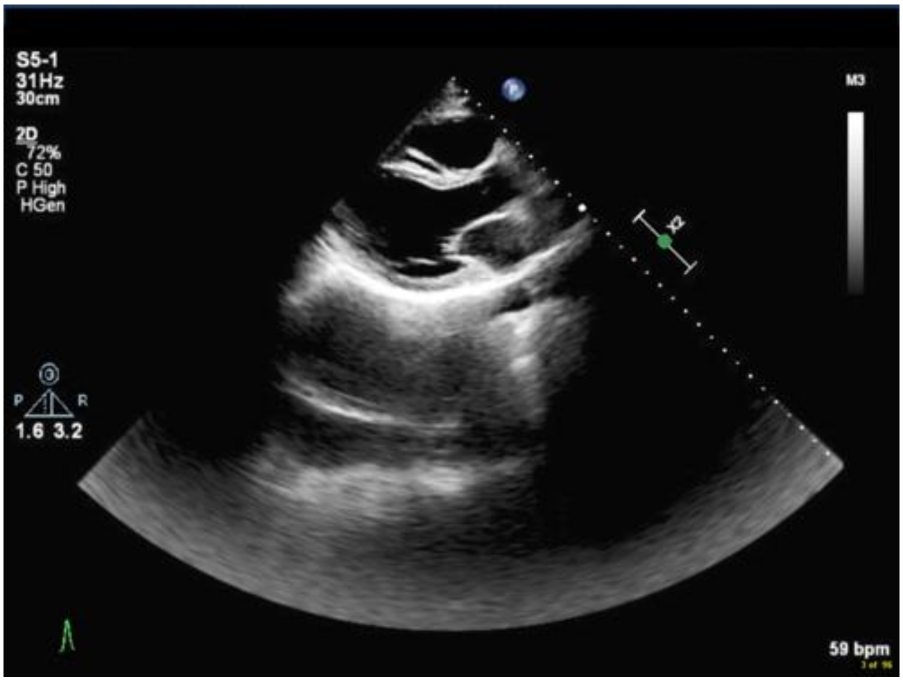
- 2D imaging at high depth (deep)
- 2D imaging at low depth (shallow)
- Color Doppler of aortic arch/descending aorta
- PW Doppler of proximal descending aorta
- CW Doppler of descending aorta

Upon conclusion of study, save images on CD and upload images using LifeImage.

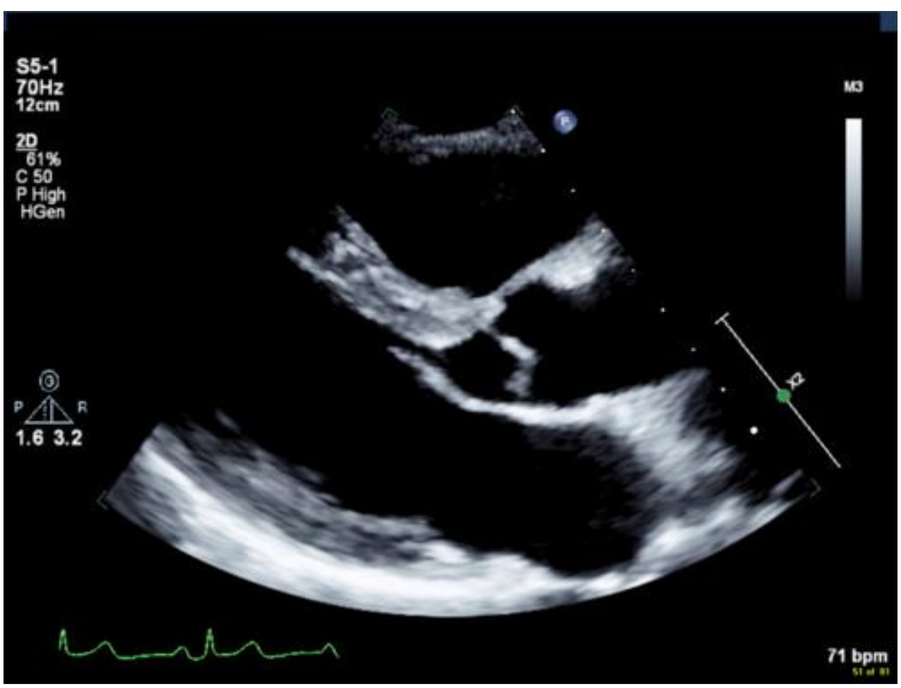
APPENDIX B.
Women's Interagency HIV Study
Example Scans

PARASTERNAL LONG AXIS

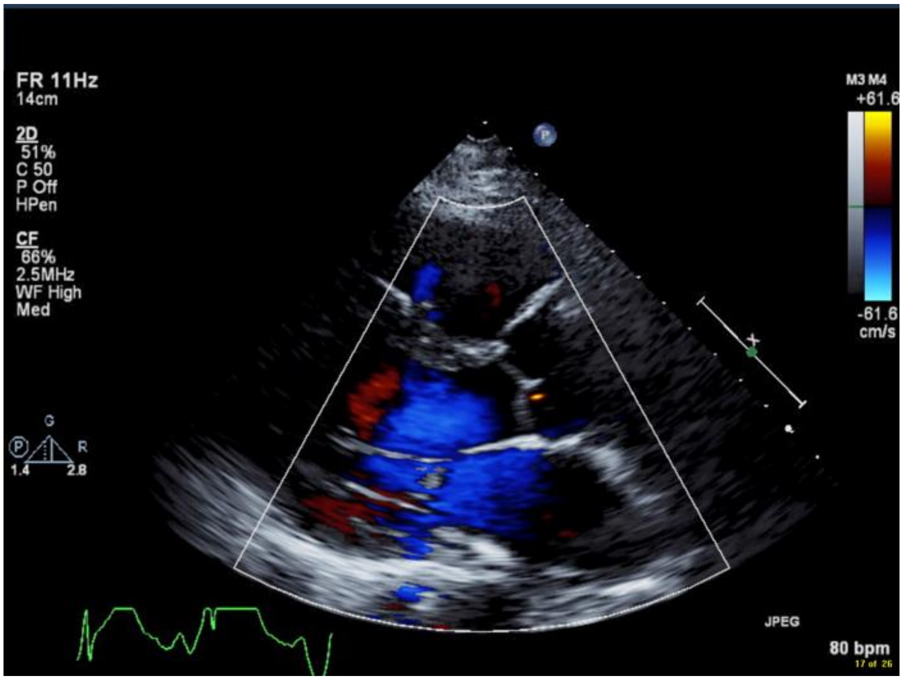
1. 2D Imaging – deep:



2. 2D imaging – shallow:

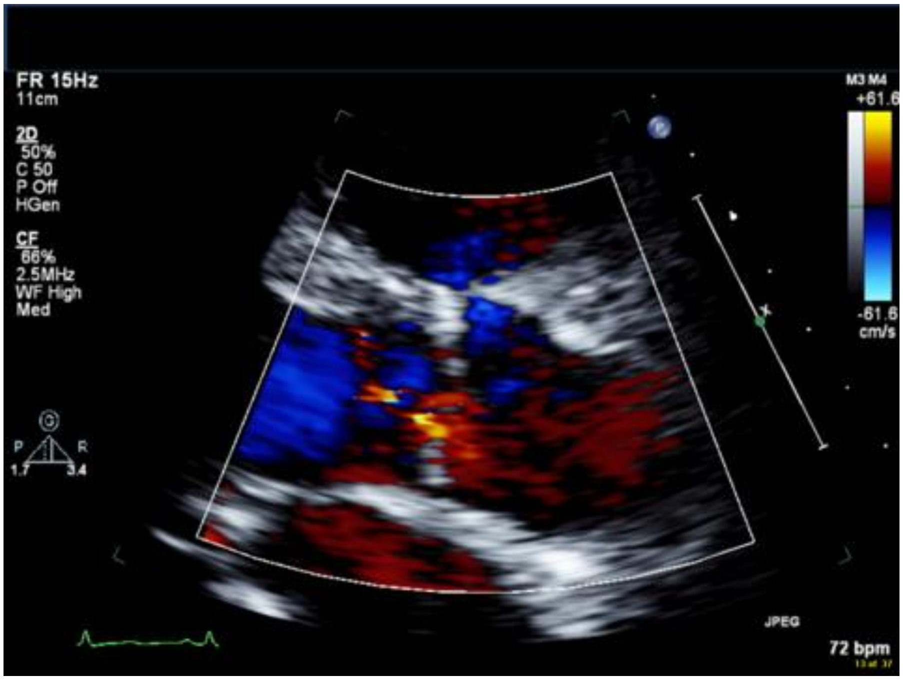


3. Color Doppler of the aortic and mitral valves together (standard depth):

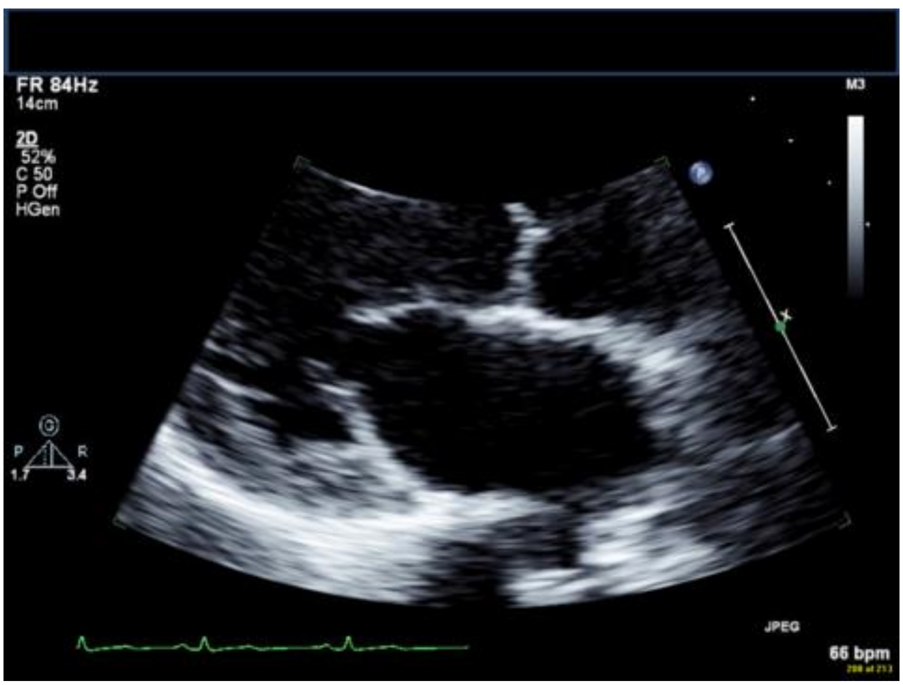


4. 2D imaging of LV outflow tract/aortic valve (zoomed in):

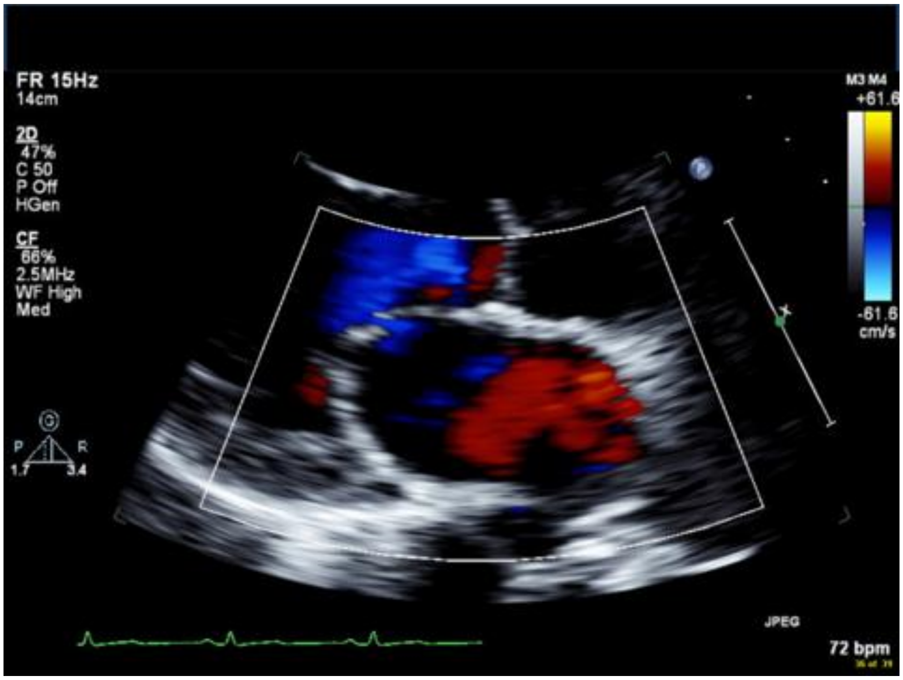
5. Color Doppler of LV outflow tract/aortic valve (zoomed in):



6. 2D imaging of mitral valve (zoomed in):

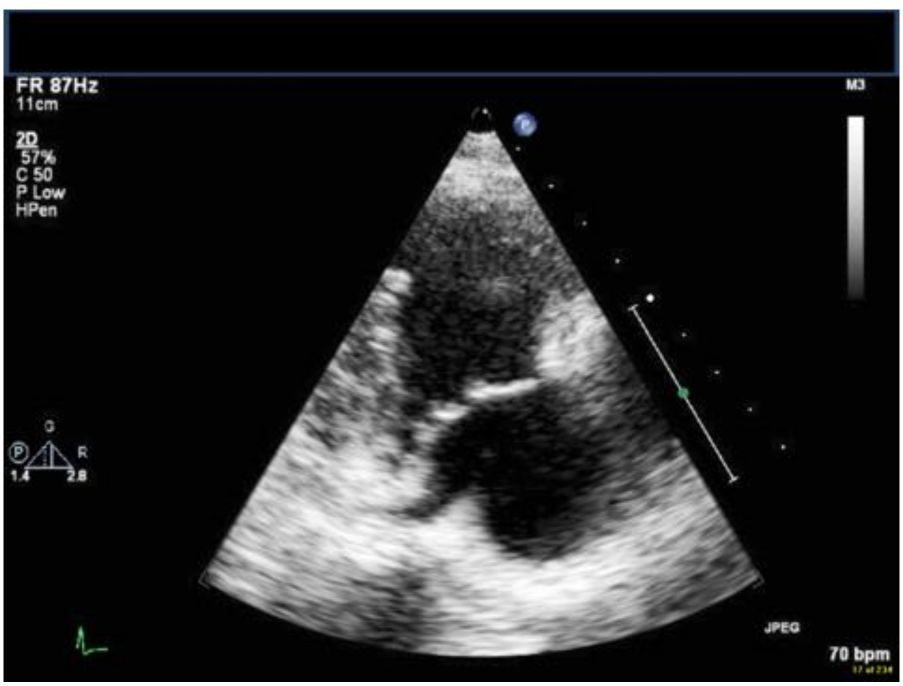


7. Color Doppler of mitral valve (zoomed in):

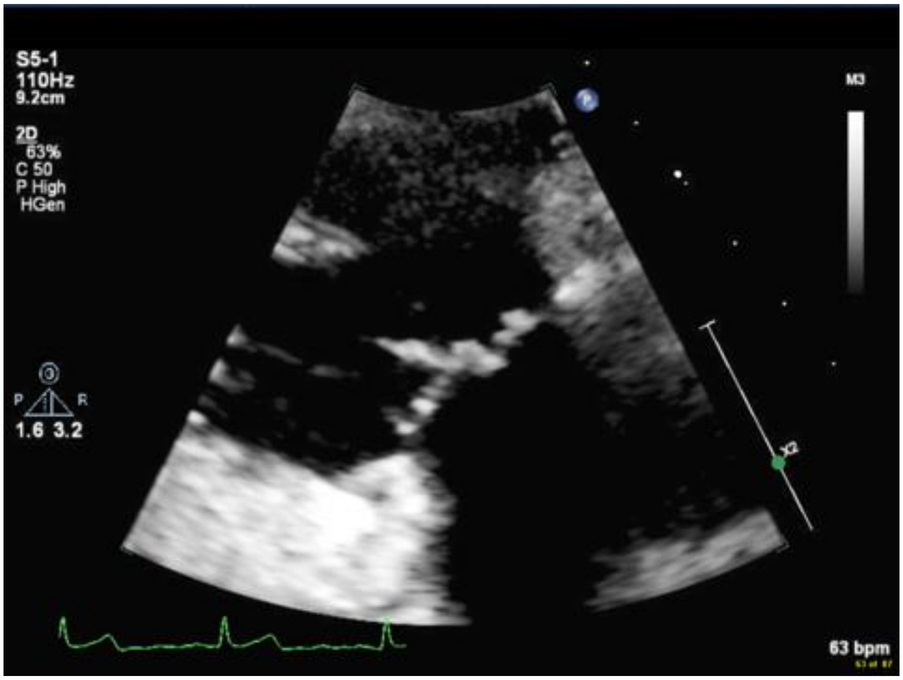


Right Ventricular Inflow

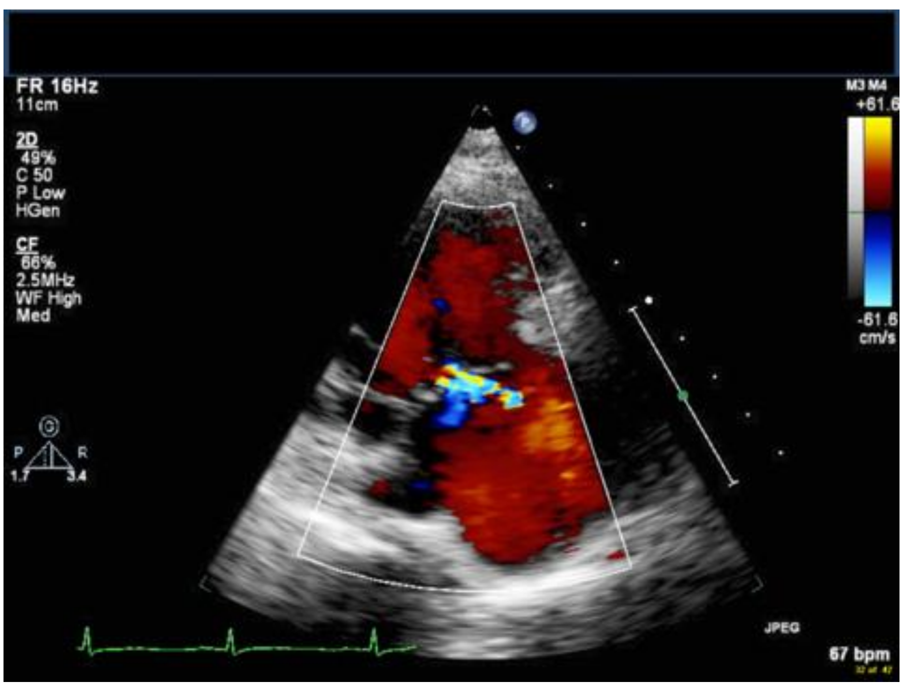
1. 2D imaging – RV inflow (standard):



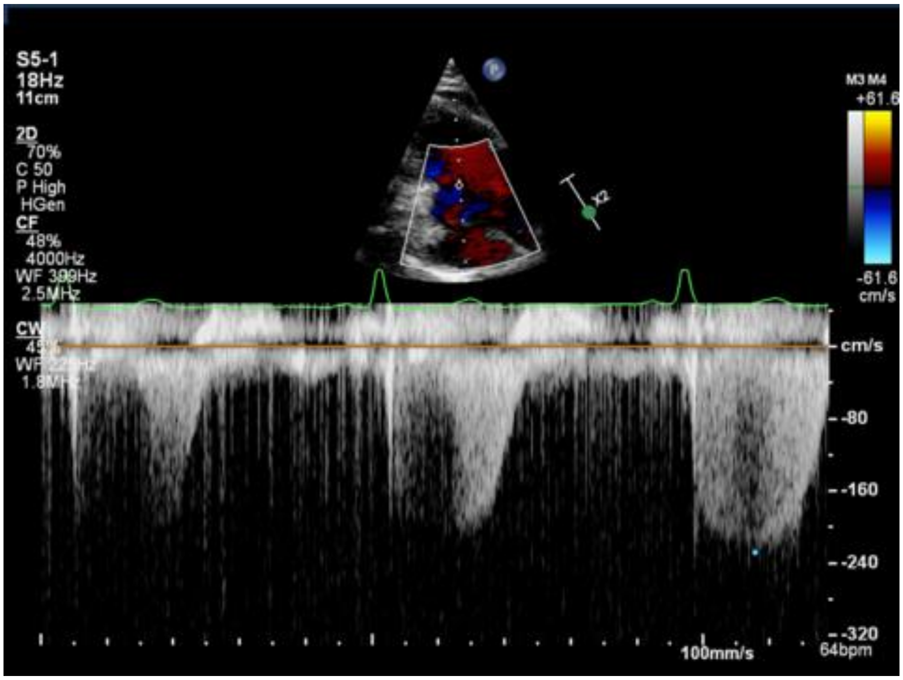
2. 2D imaging – RV inflow (zoomed in):



3. Color Doppler of the tricuspid valve (standard):

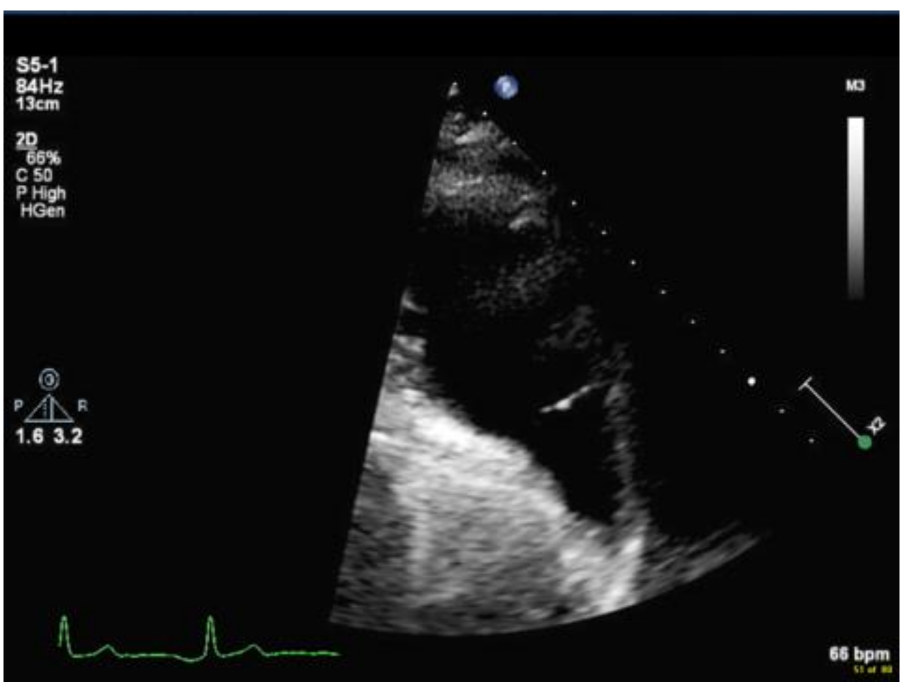


4. CW Doppler of the tricuspid valve for TR velocity:

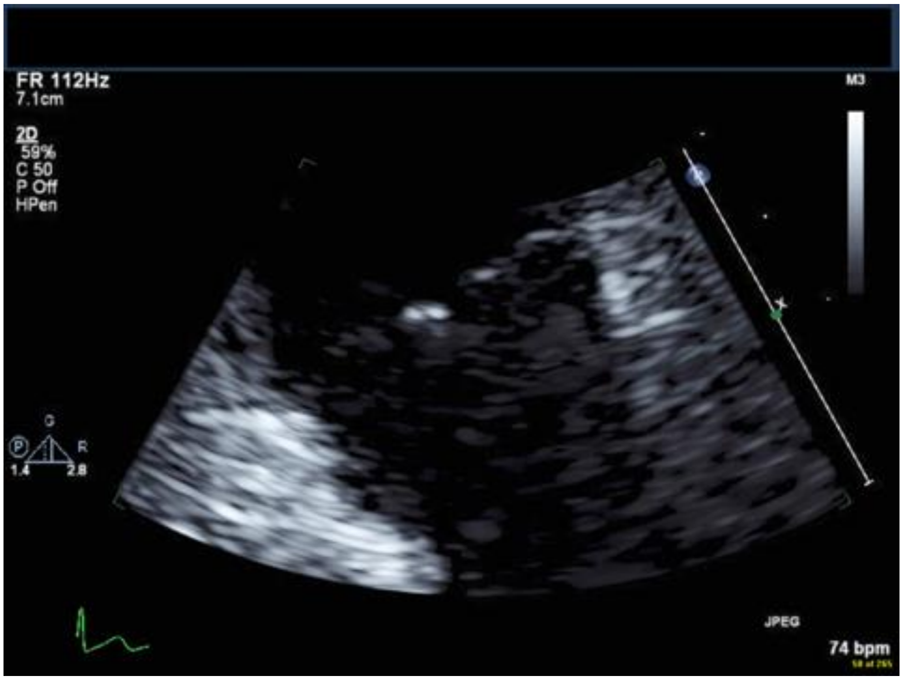


Right Ventricular Outflow

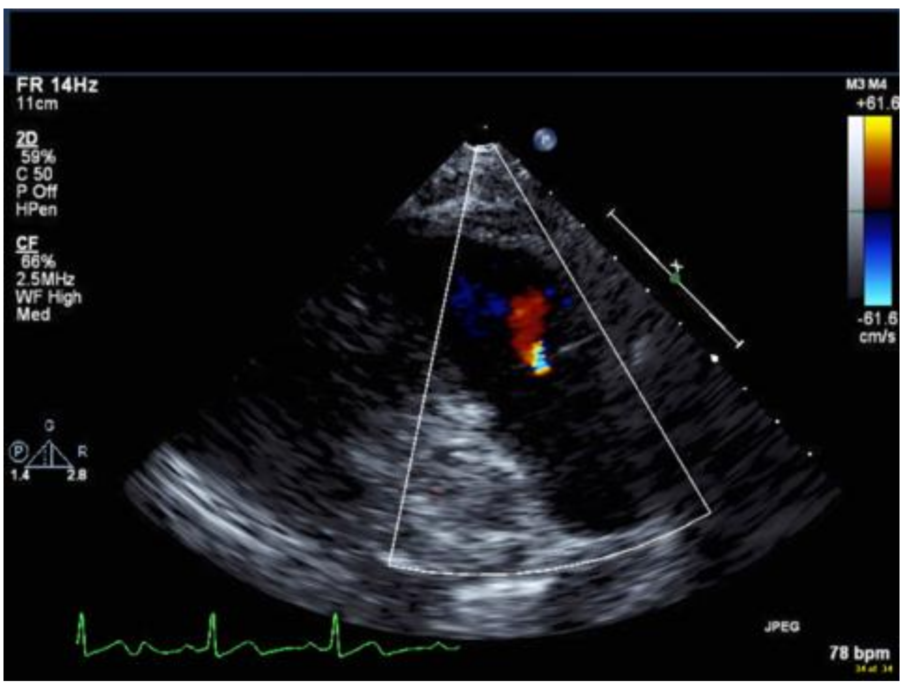
1. 2D imaging – RVOT (standard):



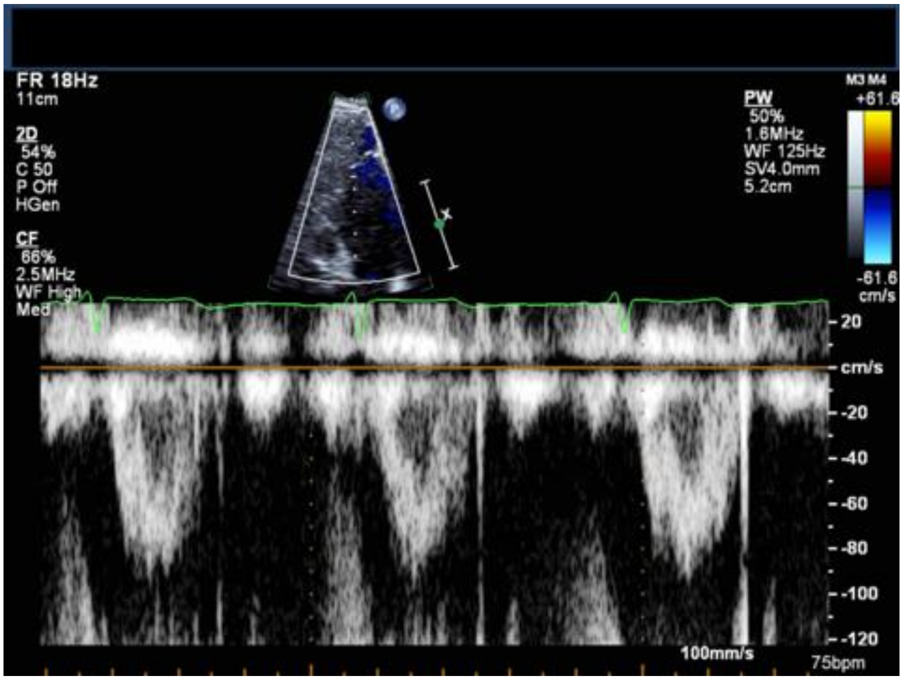
2. 2D imaging- RVOT (zoomed in):



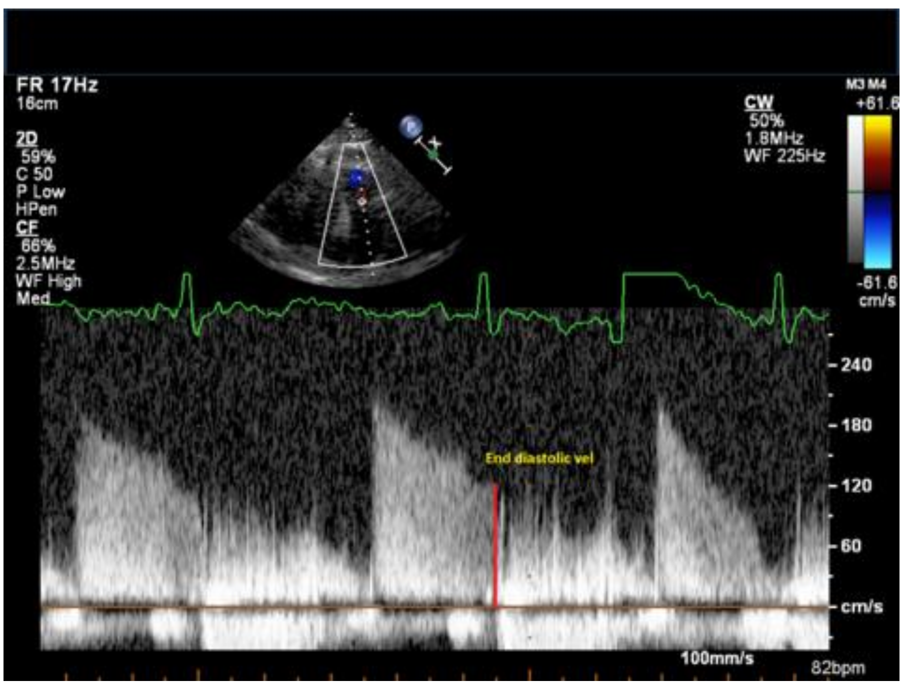
3. Color Doppler of the pulmonic valve (standard):



4. PW Doppler of RV outflow tract

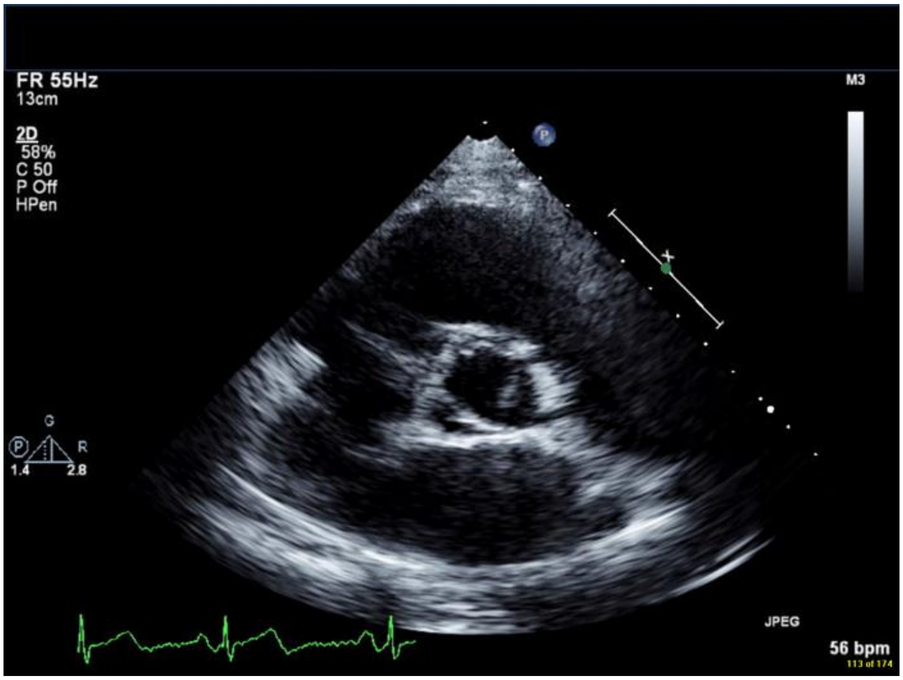


5. CW Doppler of RV outflow tract

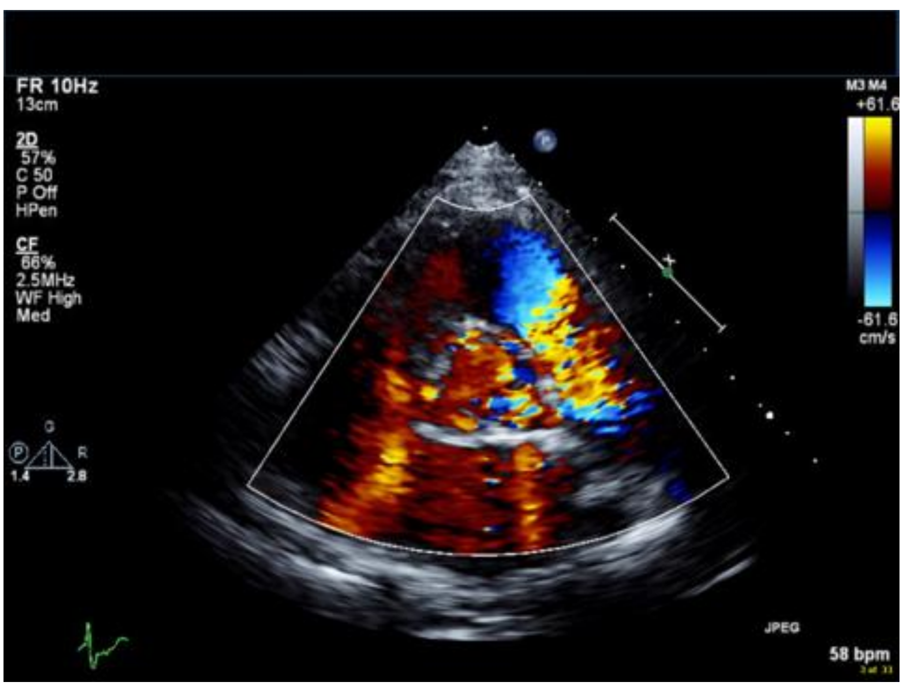


PARASTERNAL SHORT AXIS
Aortic Valve Level

1. 2D imaging of aortic valve (standard):

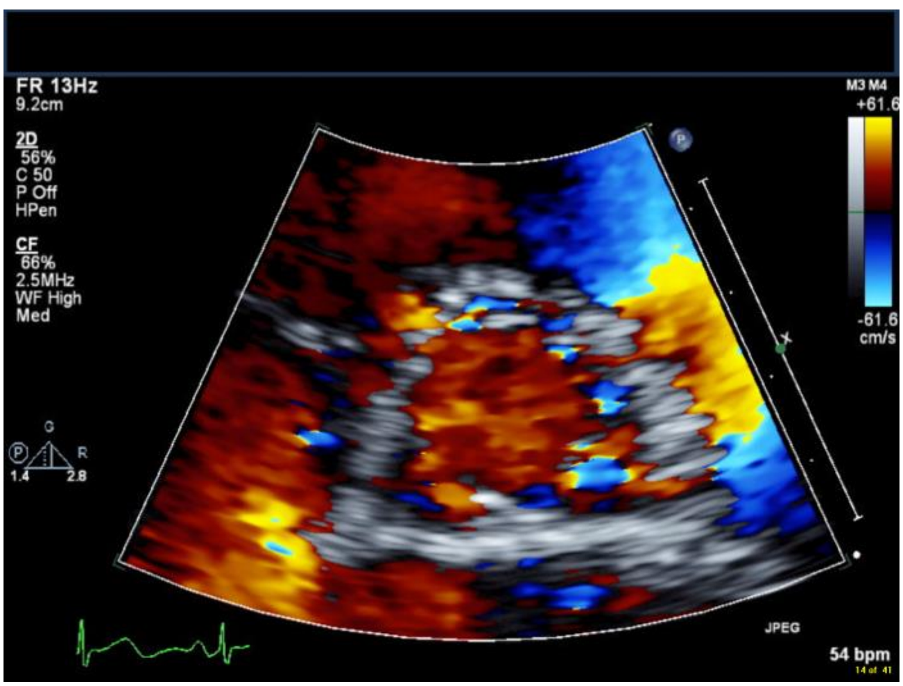


2. Color Doppler of aortic valve (standard):

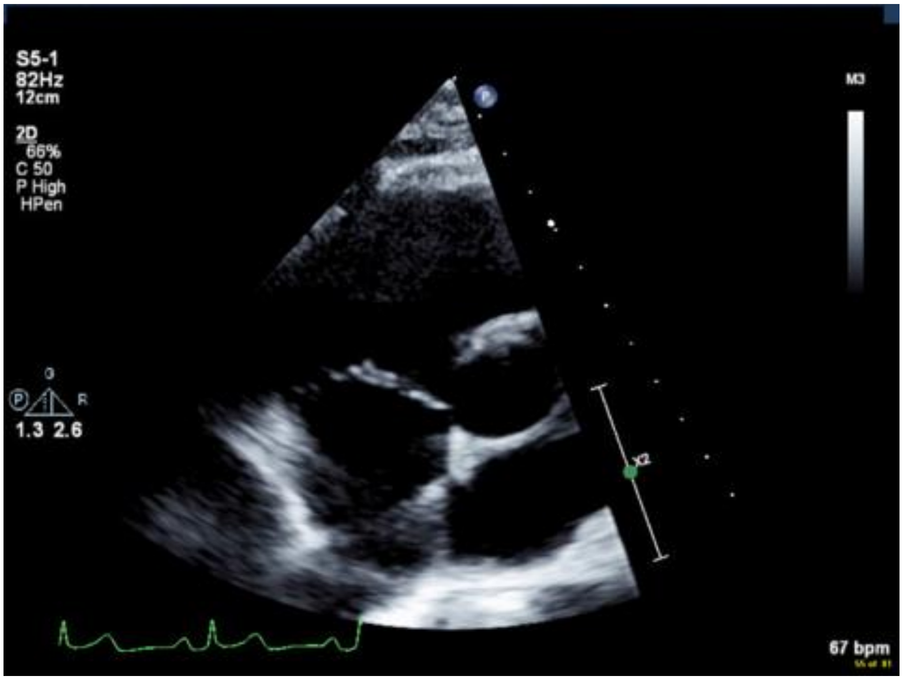


3. 2D imaging of aortic valve (zoomed in):

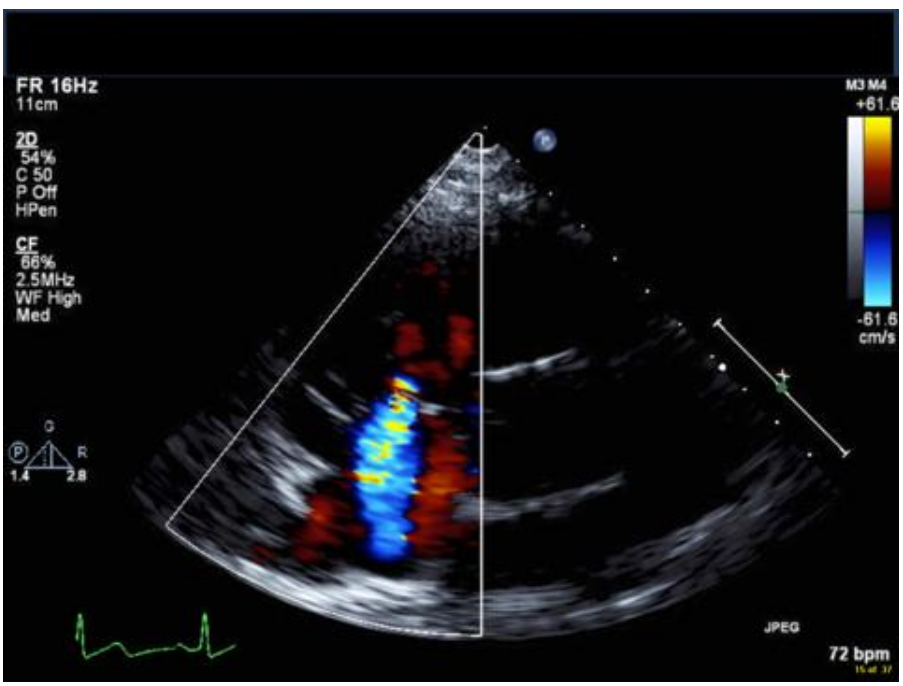
4. Color Doppler of aortic valve (zoomed in):



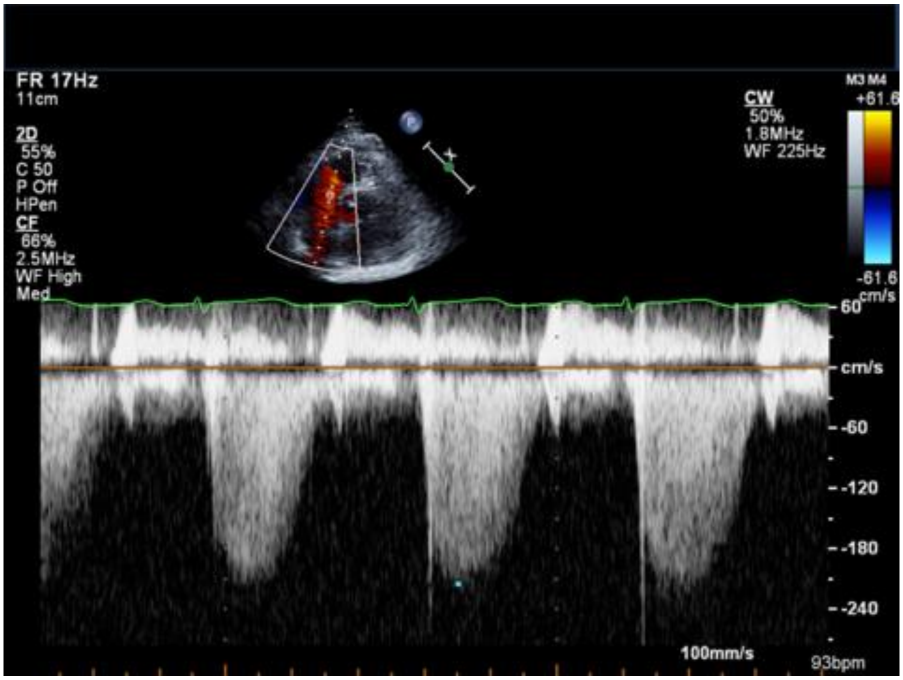
5. 2D imaging of tricuspid valve (standard):



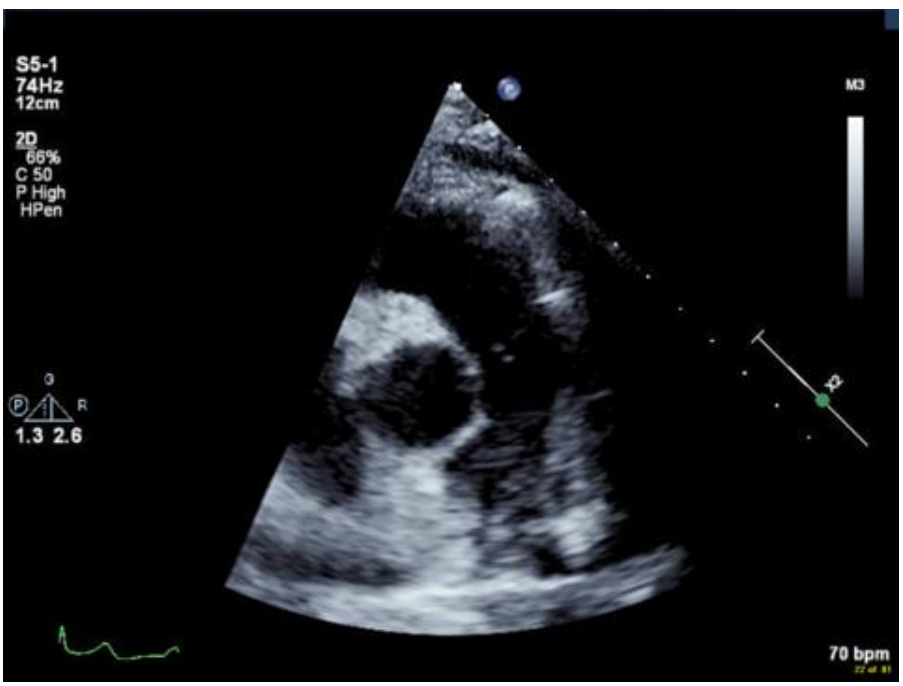
6. Color Doppler of tricuspid valve (standard):



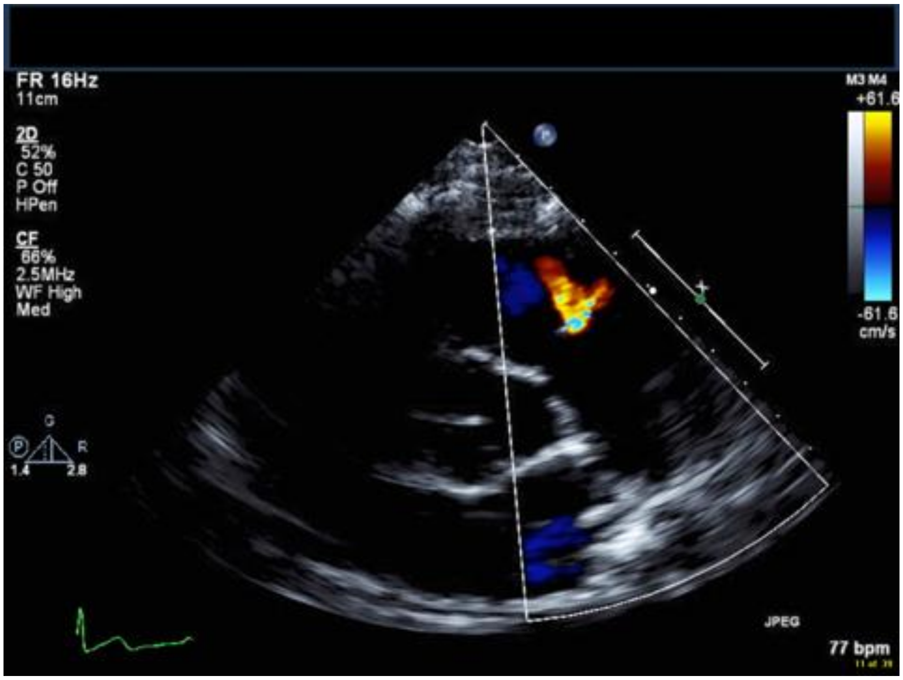
7. CW Doppler of tricuspid valve for TR velocity:



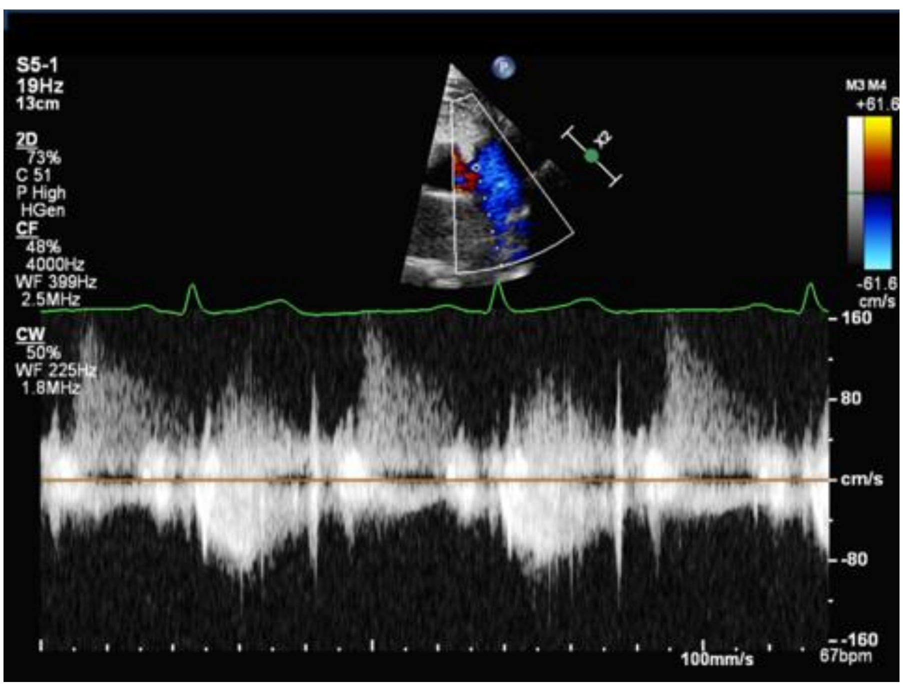
8. 2D imaging of pulmonic valve (standard):



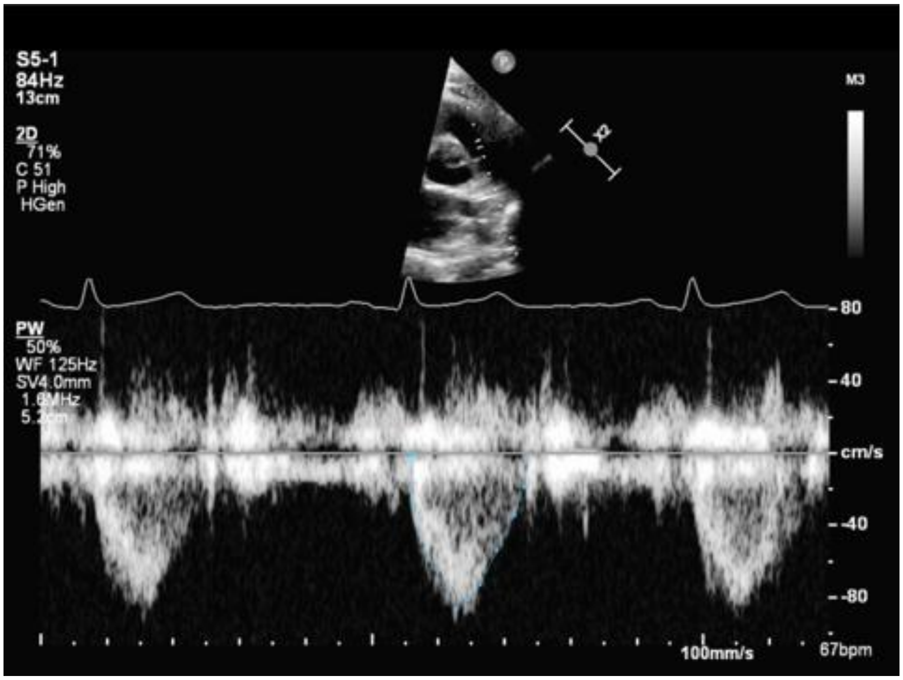
9. Color Doppler of pulmonic valves (standard):



10. CW Doppler of RV outflow tract:

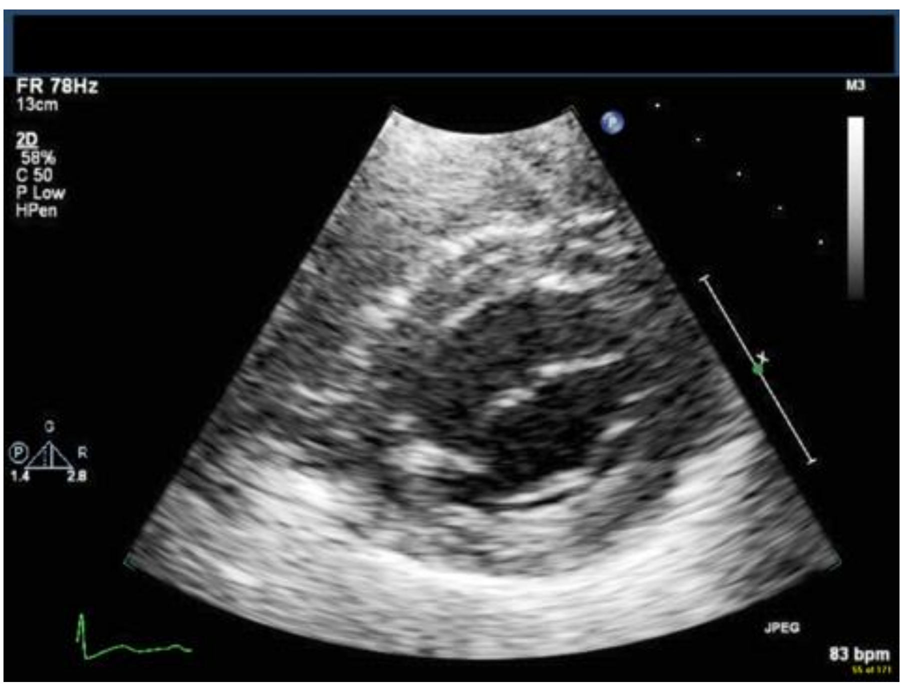


11. PW Doppler of RV outflow tract:

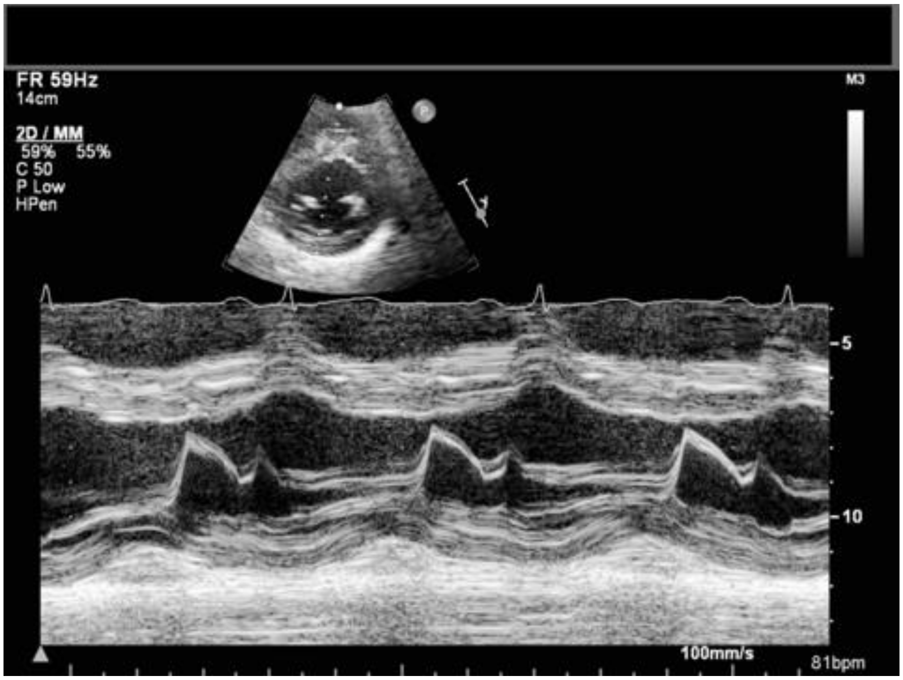


Left Ventricle Level

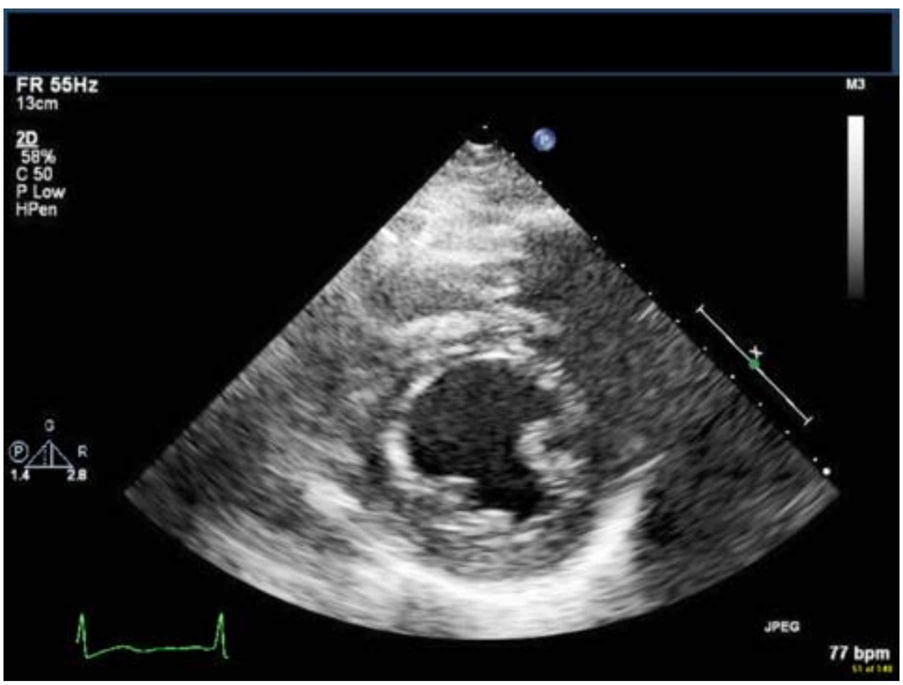
12. Base (mitral valve level)- 2D (standard depth):



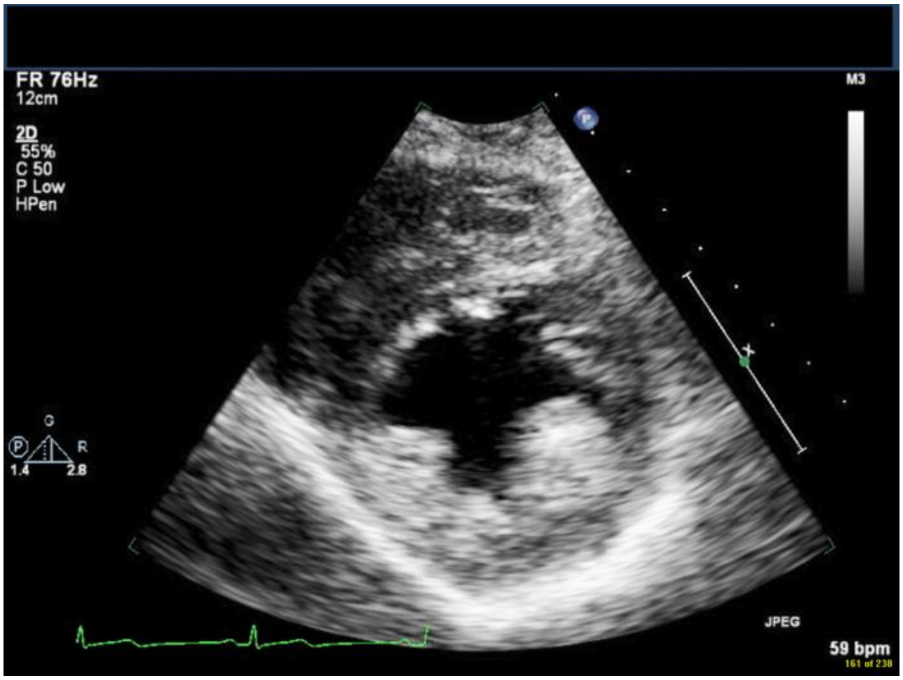
13. Base (mitral valve level): 2D and M-mode imaging (standard depth):



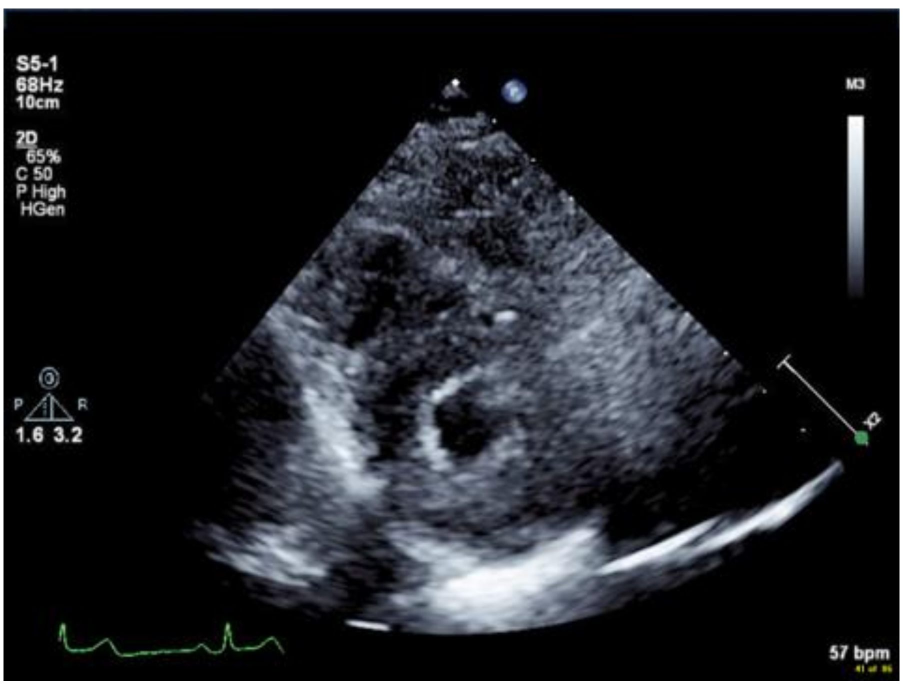
14. Mid (papillary muscle level) - 2D imaging (standard):



15. Mid (papillary muscle level) - 2D imaging (zoomed in):

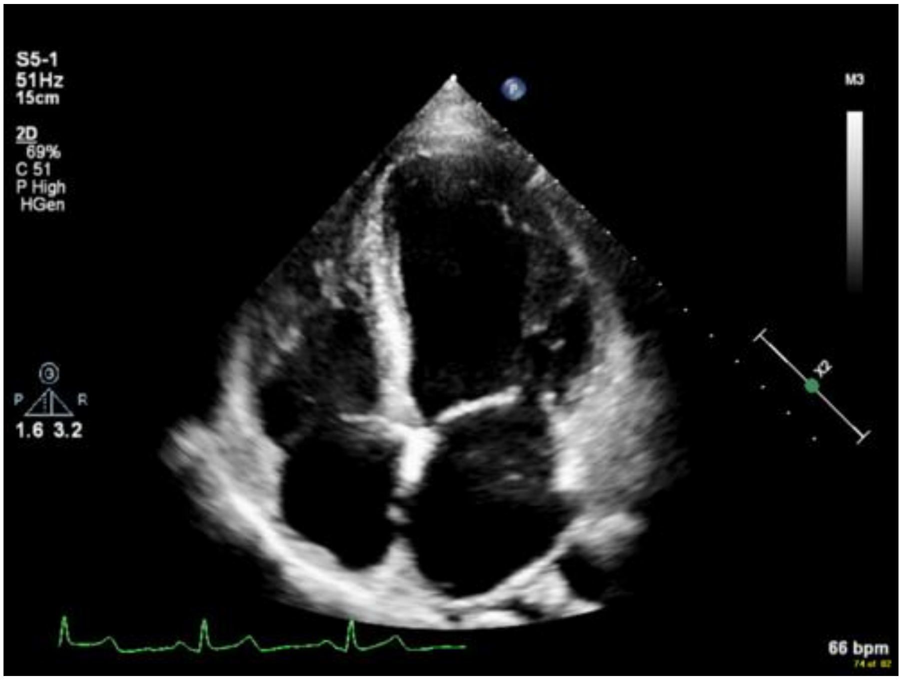


16. Apex: 2D imaging (standard depth):

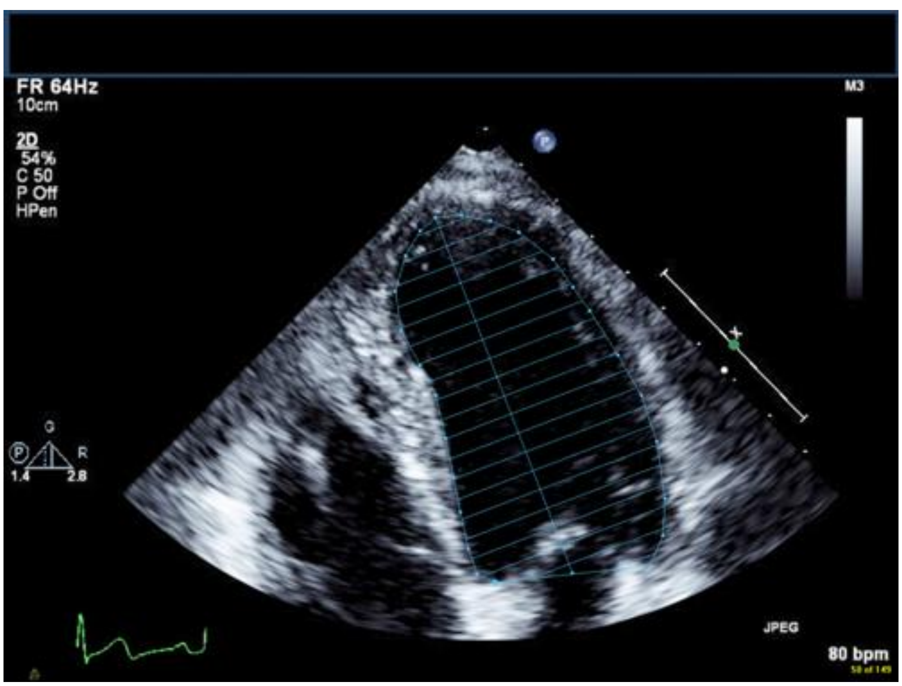


APICAL 4 CHAMBER

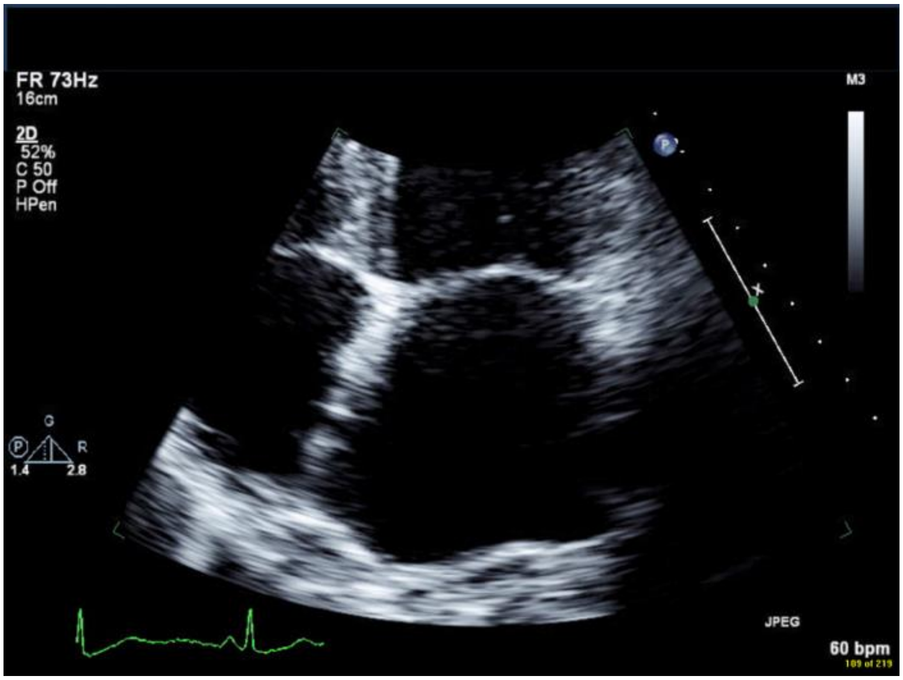
1. 2D imaging (standard depth):



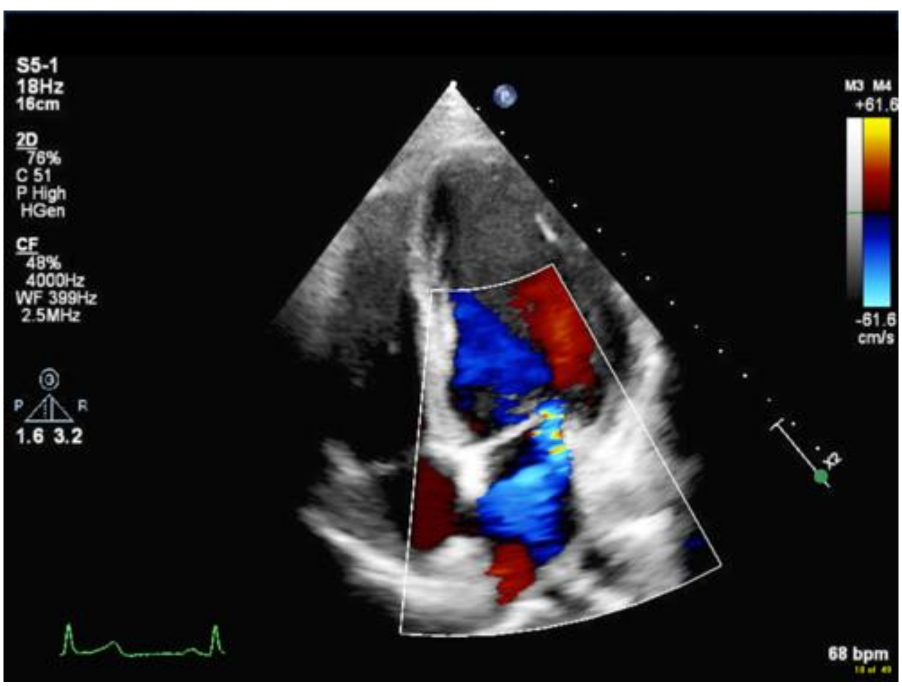
2. Focused/zoomed on LV:



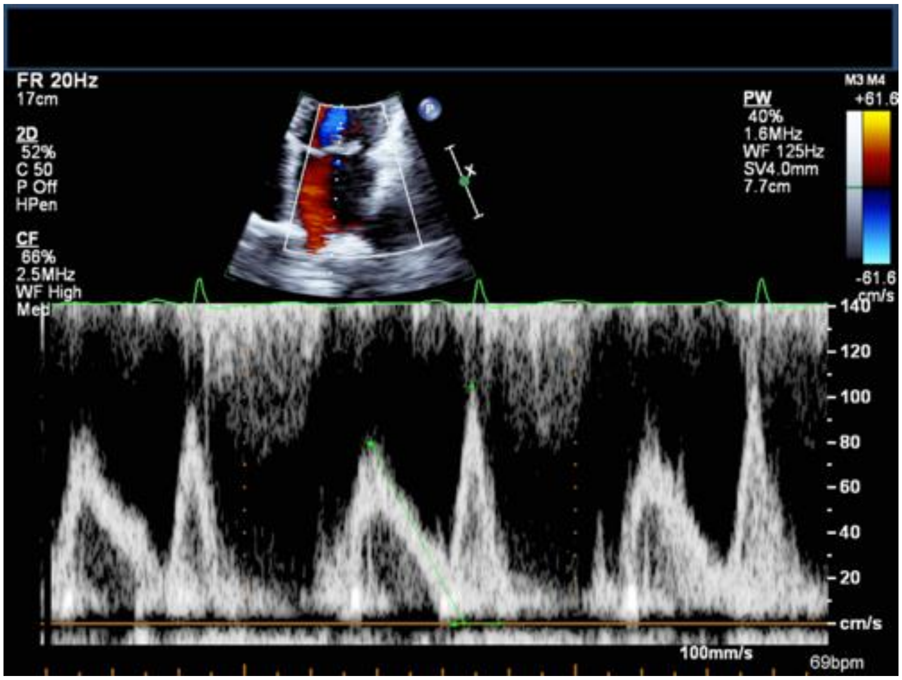
3. Focused/zoomed on LA:



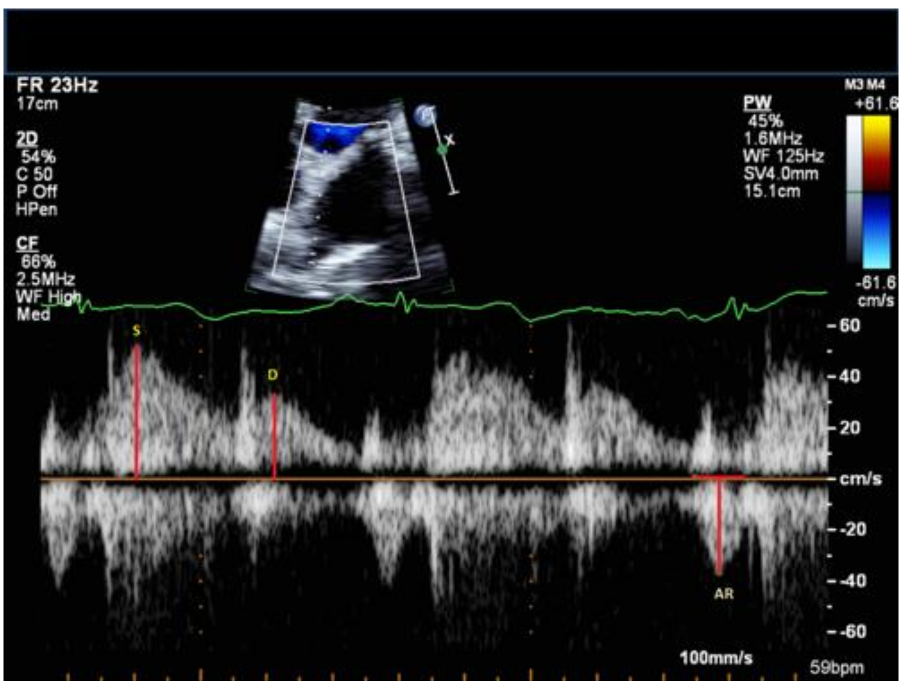
4. Color Doppler of the mitral valve/LA:



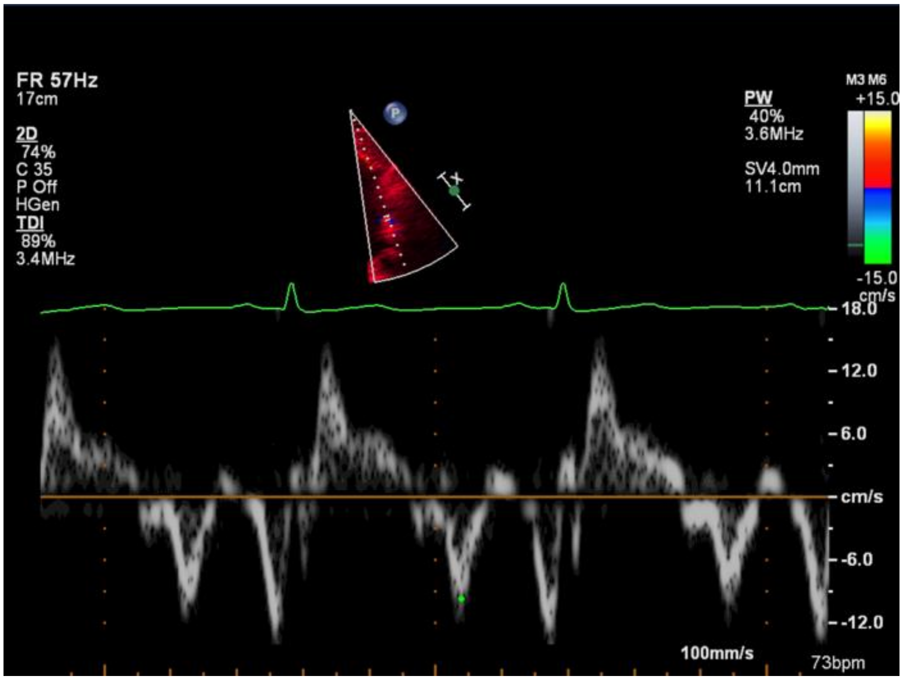
5. PW Doppler of mitral inflow:



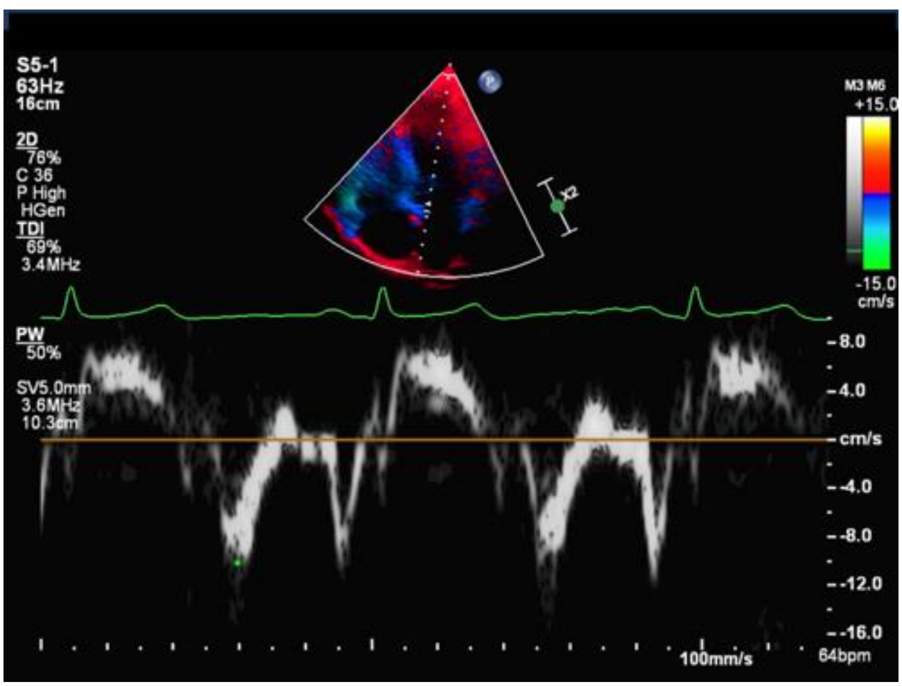
6. PW Doppler right upper pulmonary vein inflow:



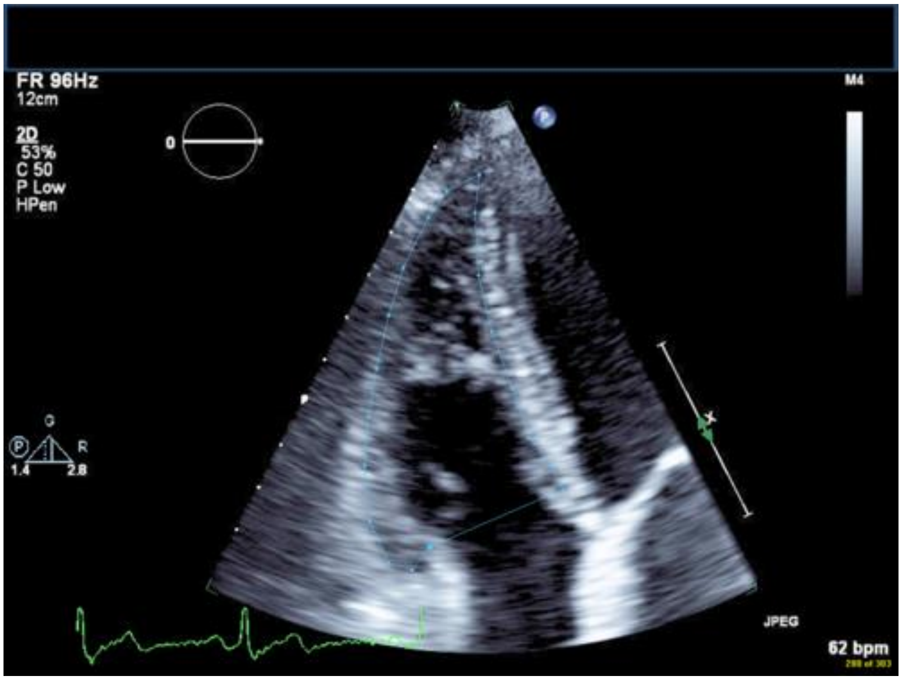
7. TDI of lateral mitral annulus:



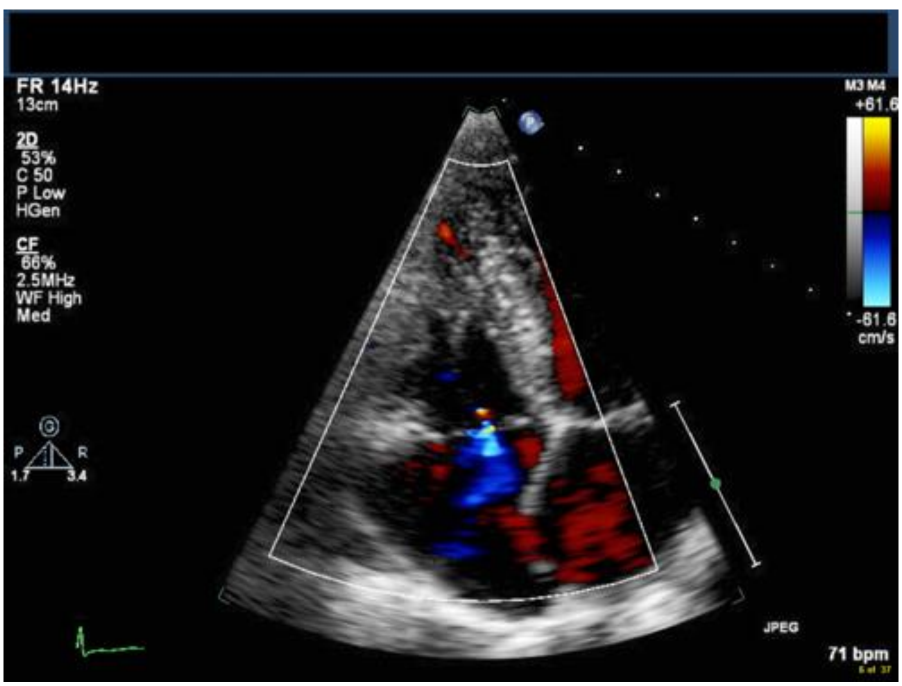
8. TDI of septal mitral annulus:



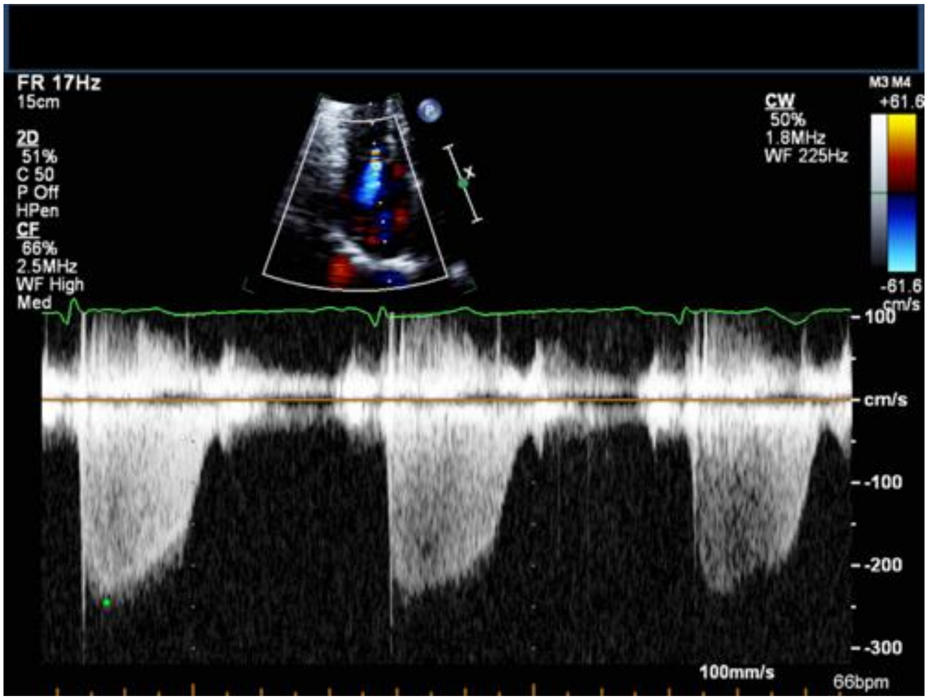
9. 2D imaging focused on the right ventricle:



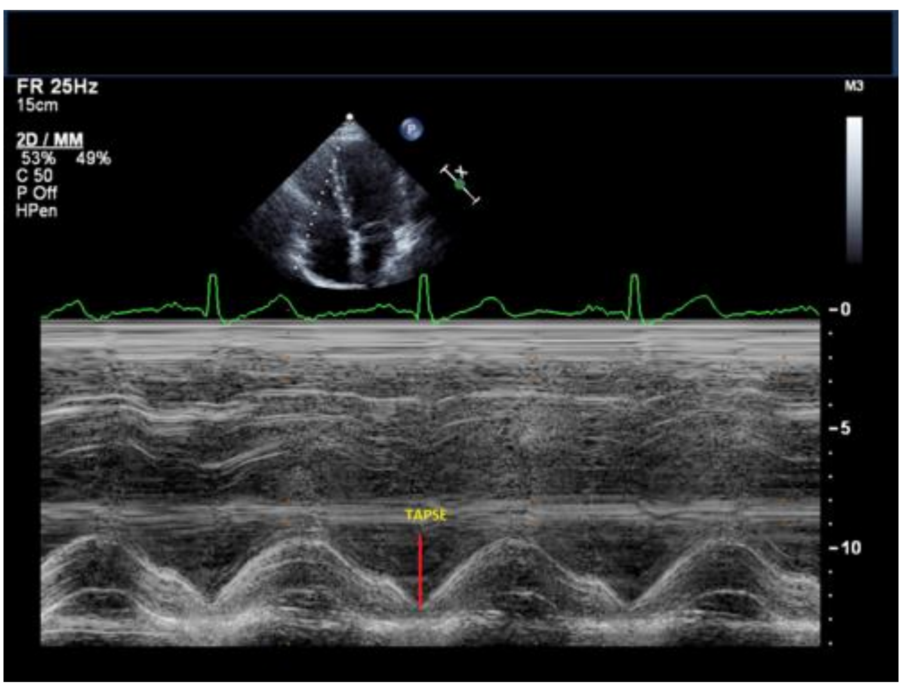
10. Color Doppler of the tricuspid valve/RA:



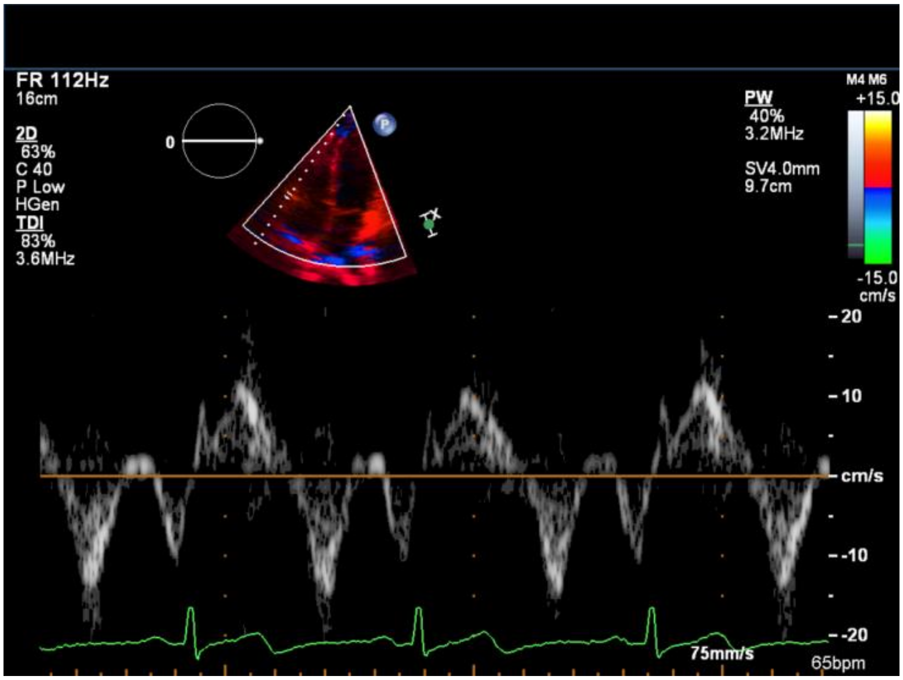
11. CW Doppler of tricuspid regurgitation:



12. TAPSE:

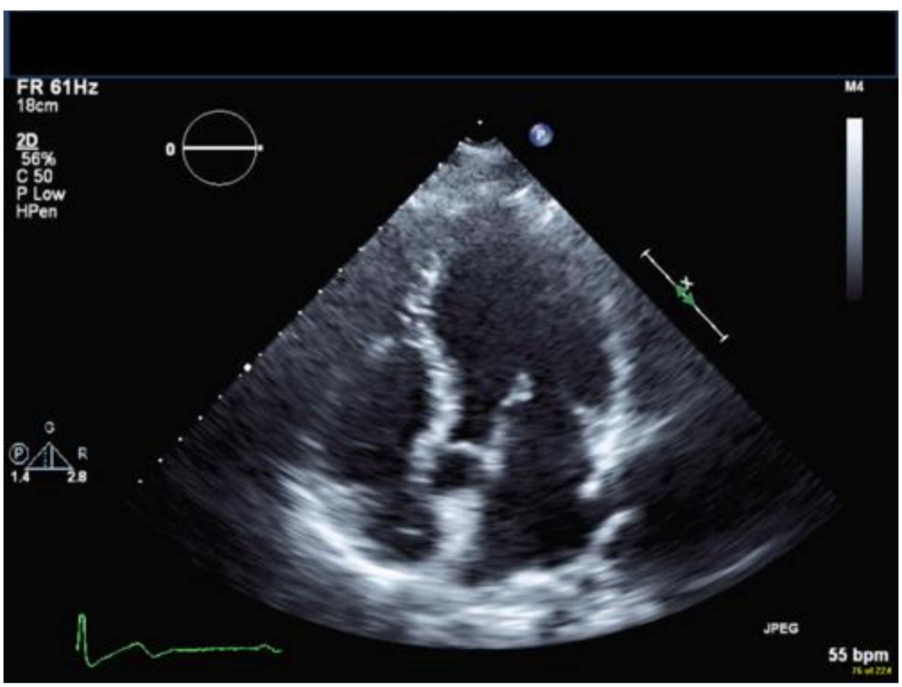


13. TDI of lateral tricuspid annulus:

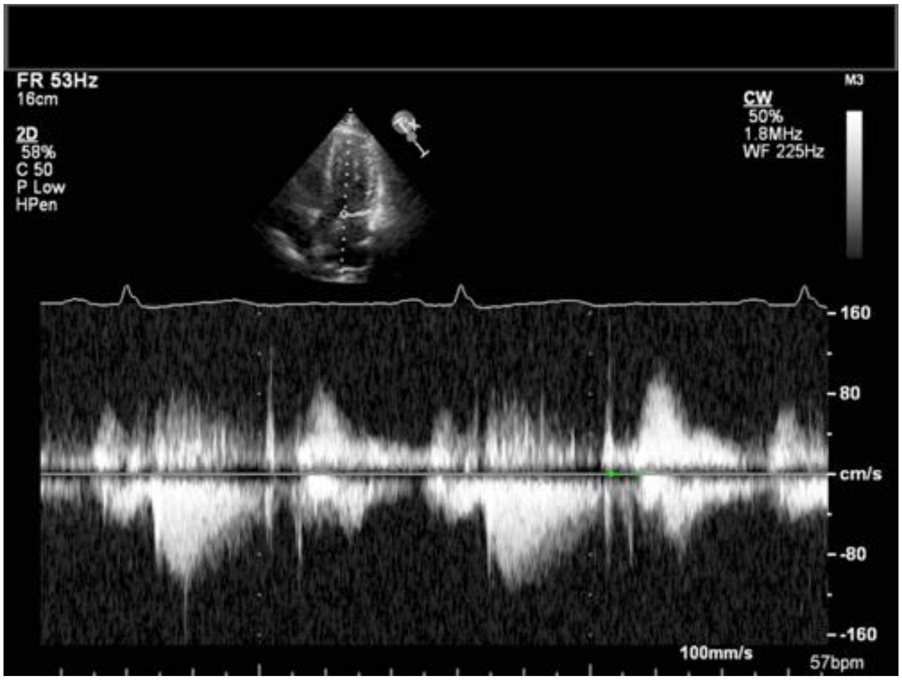


APICAL 5 CHAMBER

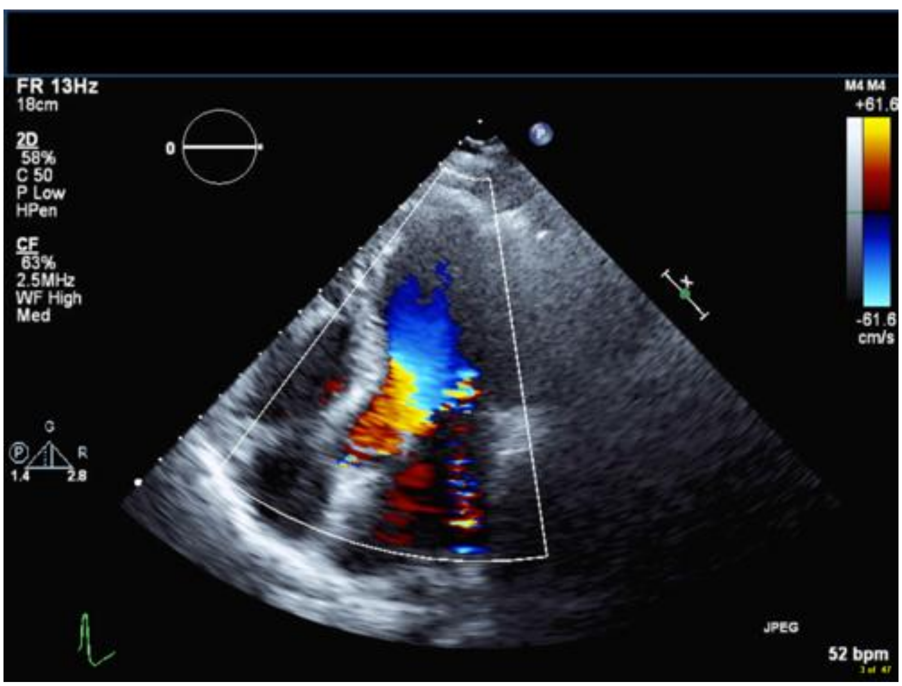
14. 2D imaging:



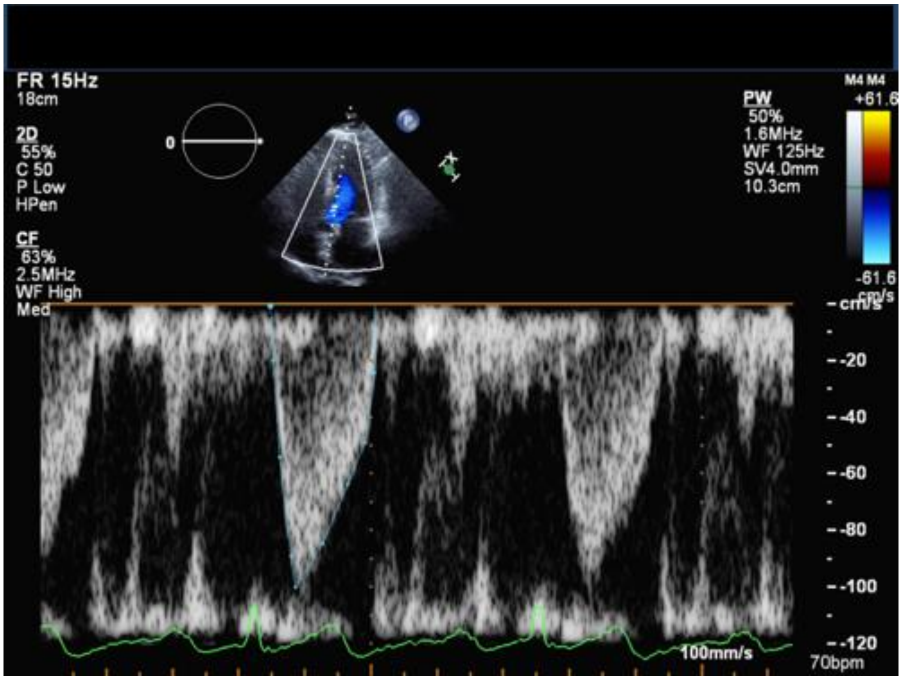
15. CW Doppler near the aortomitral continuity:



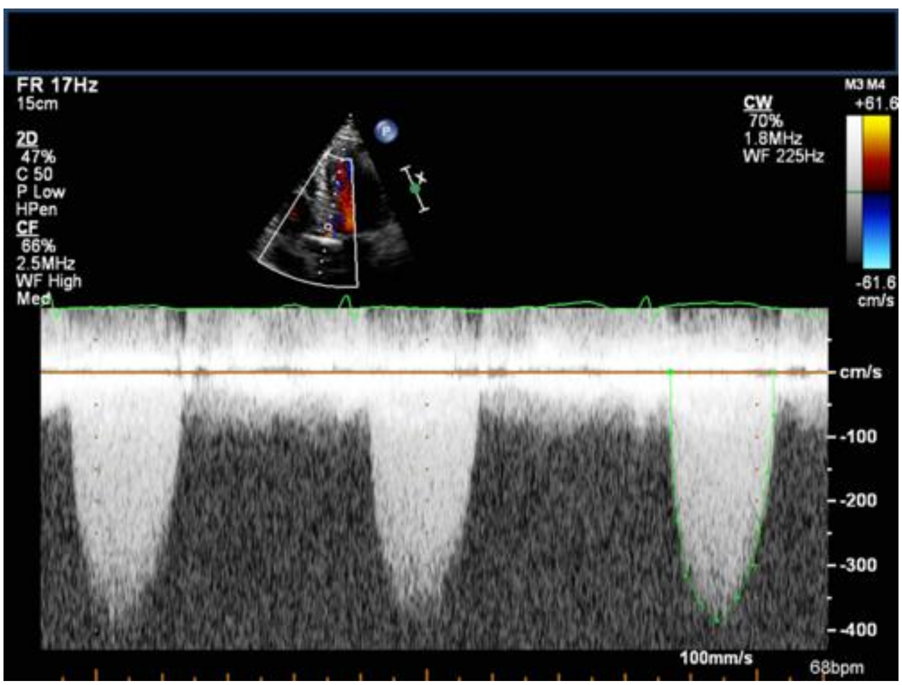
16. Color of the LV outflow tract:



17. PW of the LV outflow tract:

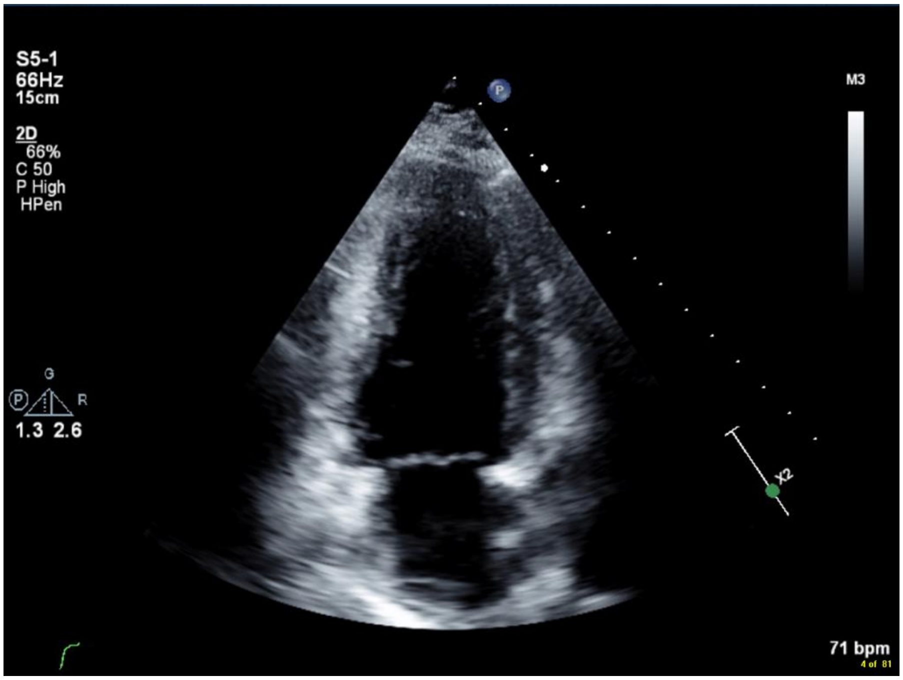


18. CW of the LV outflow tract:

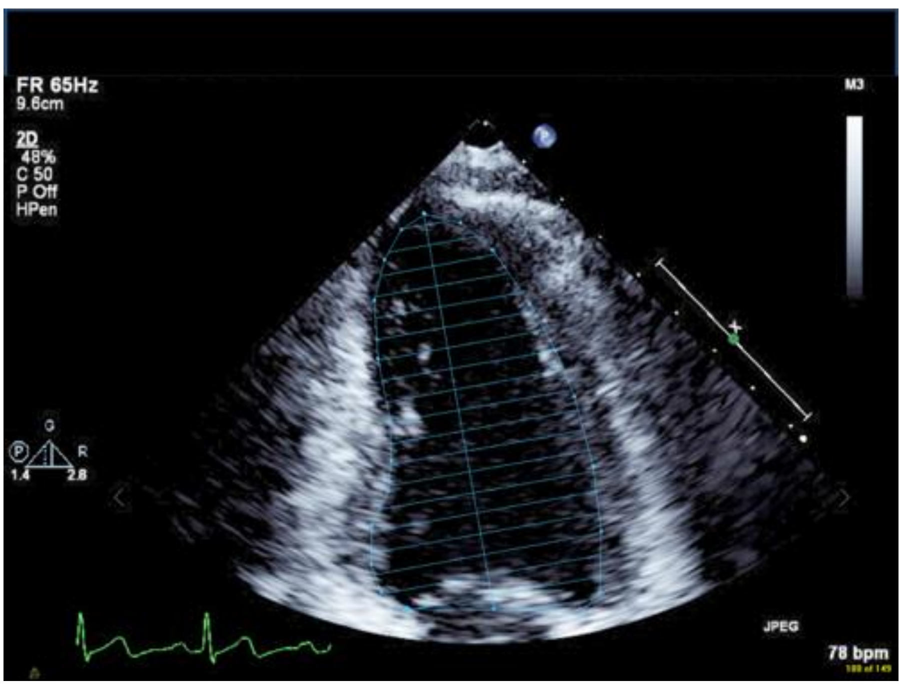


APICAL 2 CHAMBER

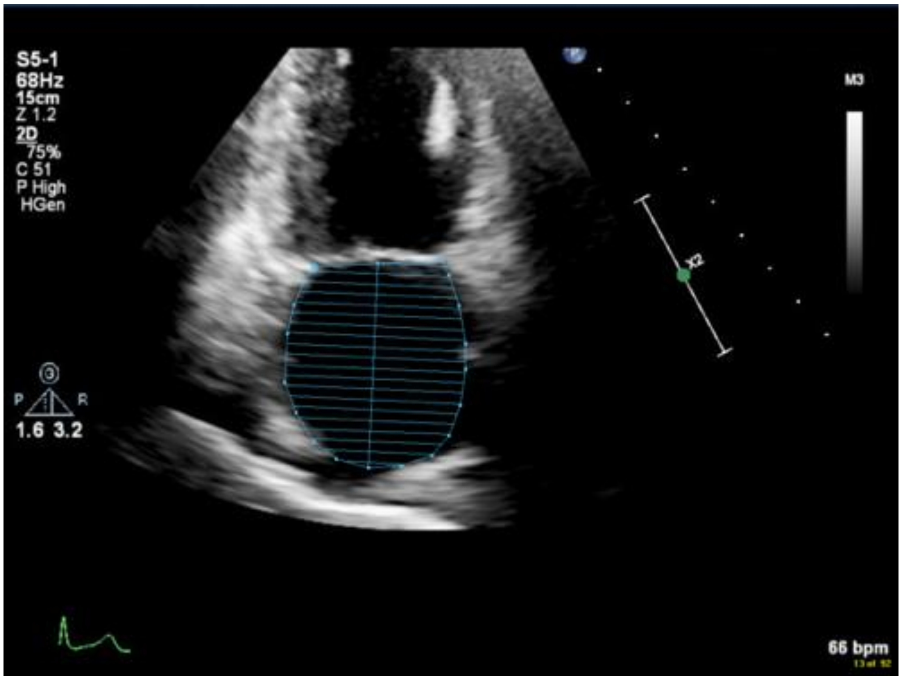
1. 2D imaging (standard):



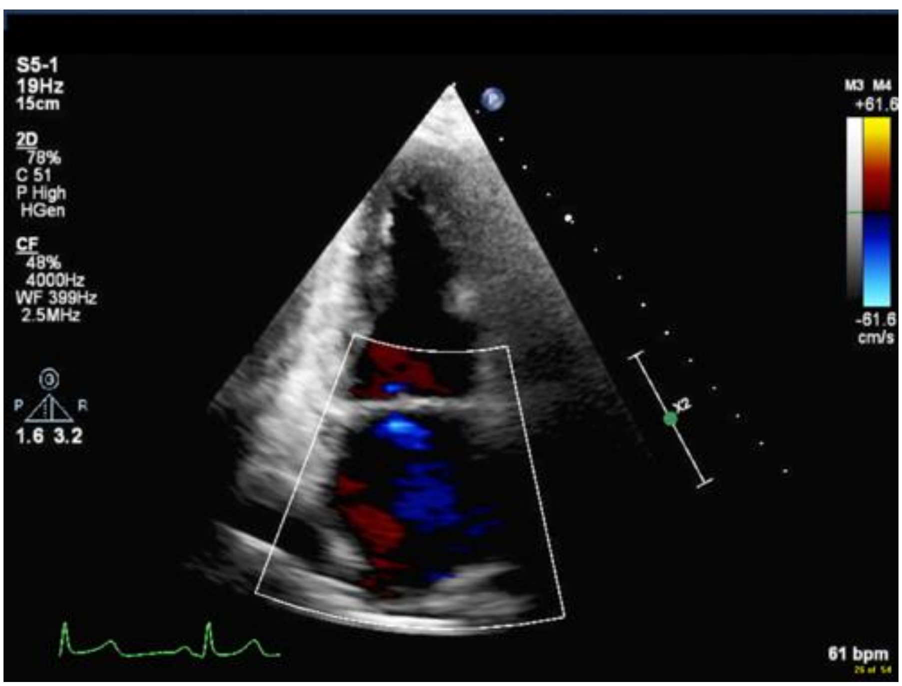
2. Focused/zoomed on LV:



3. Focused/zoomed on LA:

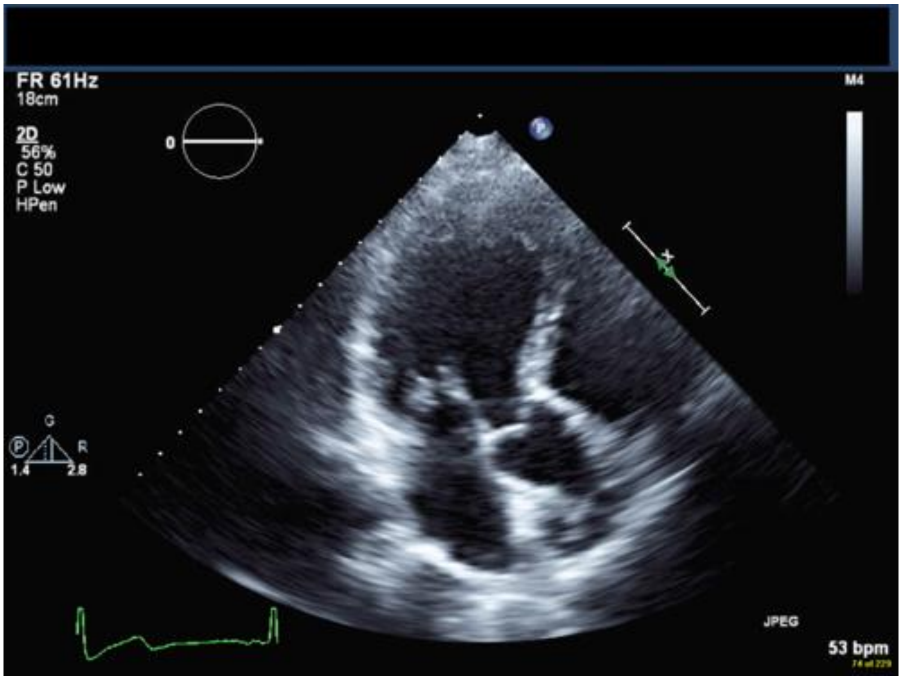


4. Color Doppler of mitral valve/LA:

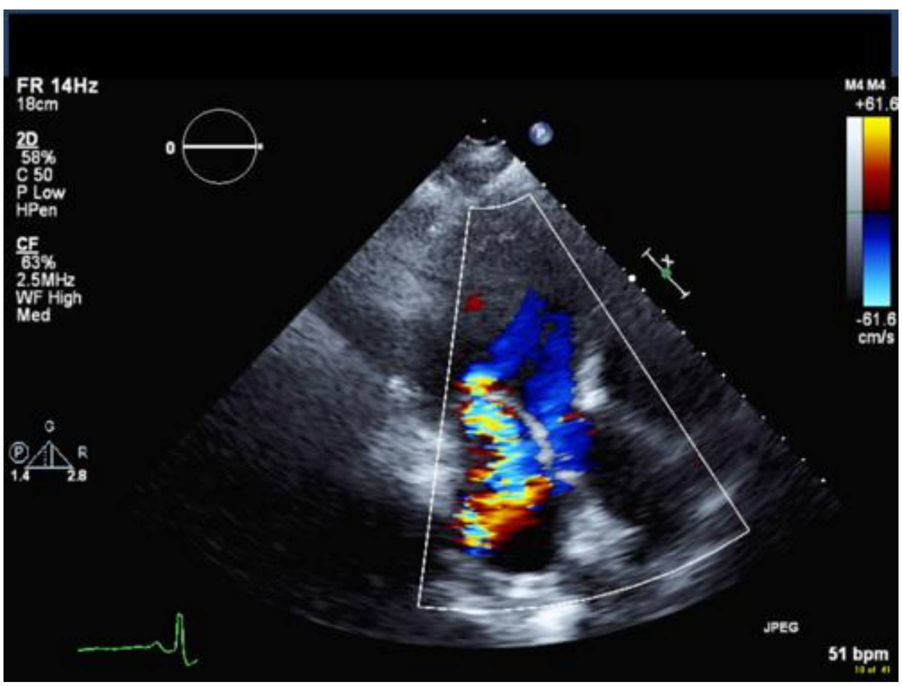


APICAL 3 CHAMBER

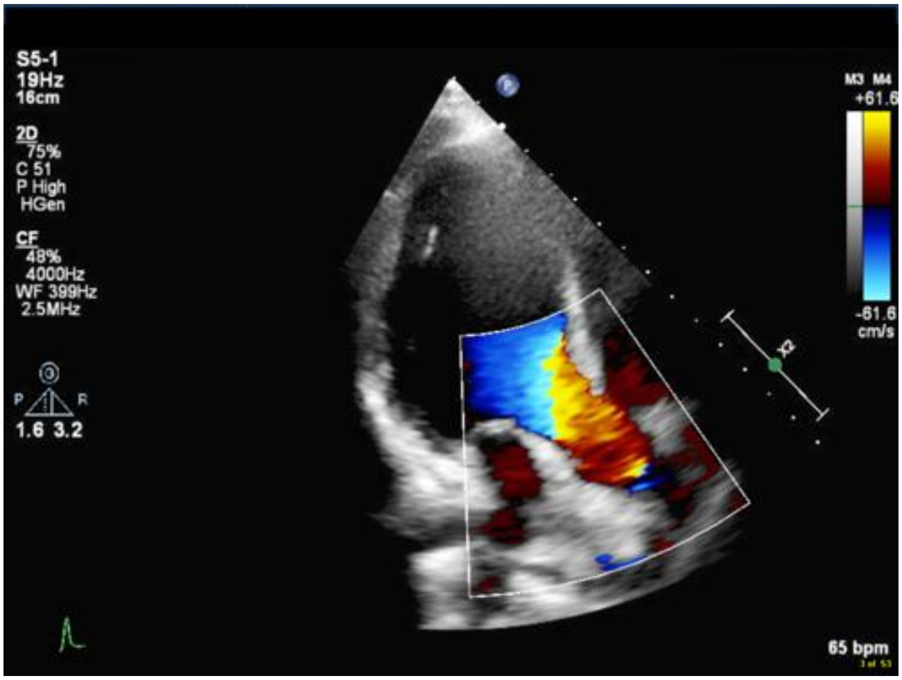
1. 2D imaging:



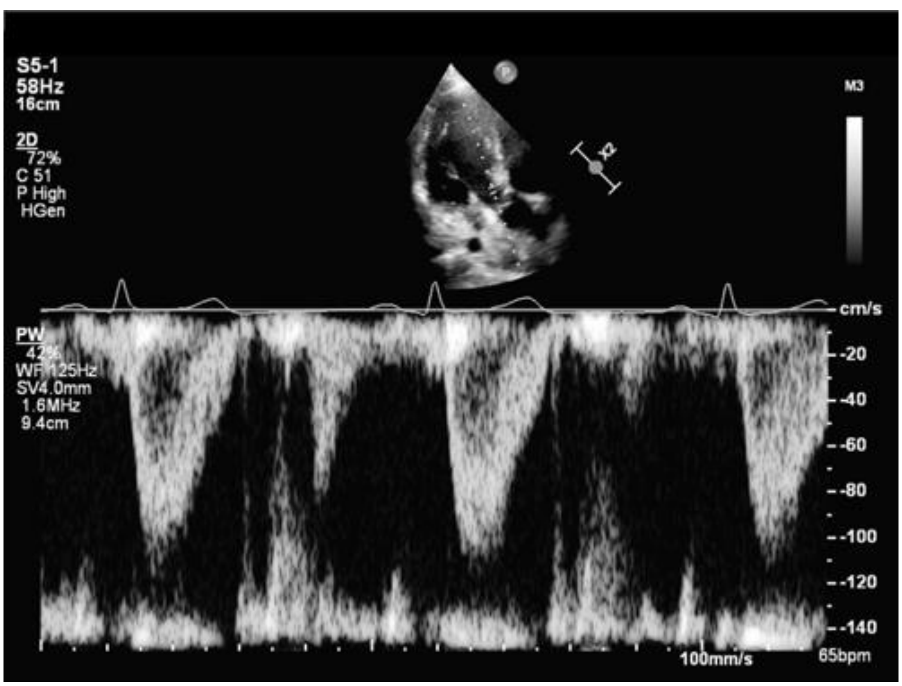
2. Color Doppler of mitral valve/LA:



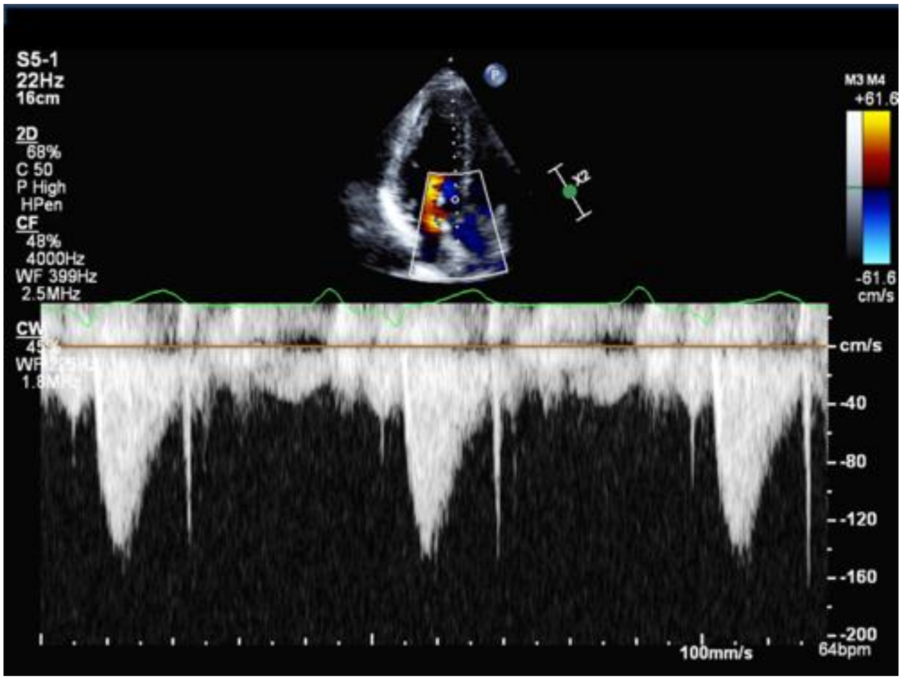
3. Color Doppler of LV outflow tract:



4. PW of LV outflow tract:

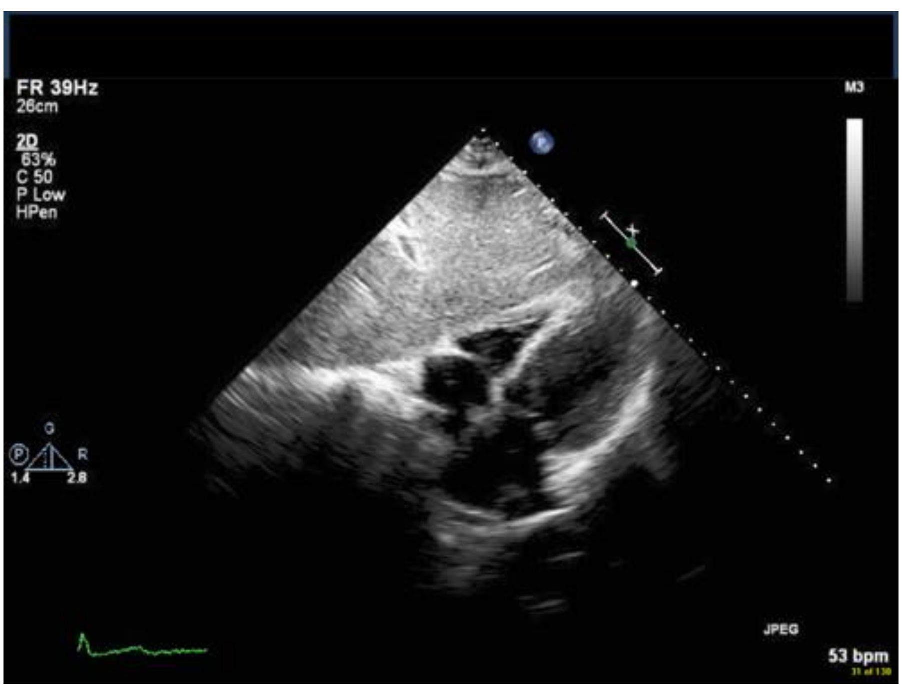


5. CW of LV outflow tract:

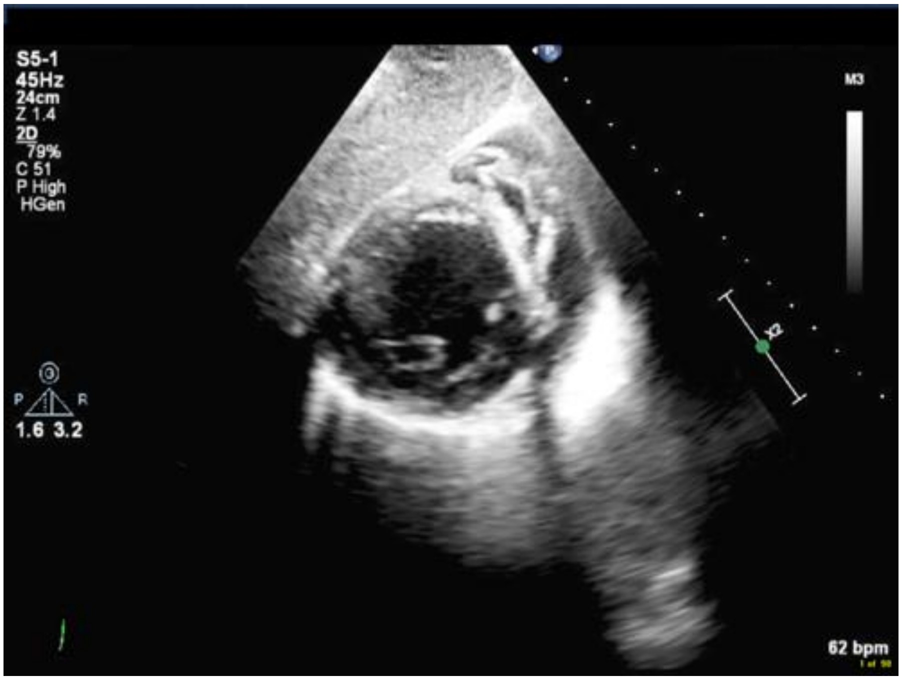


SUBCOSTAL WINDOW

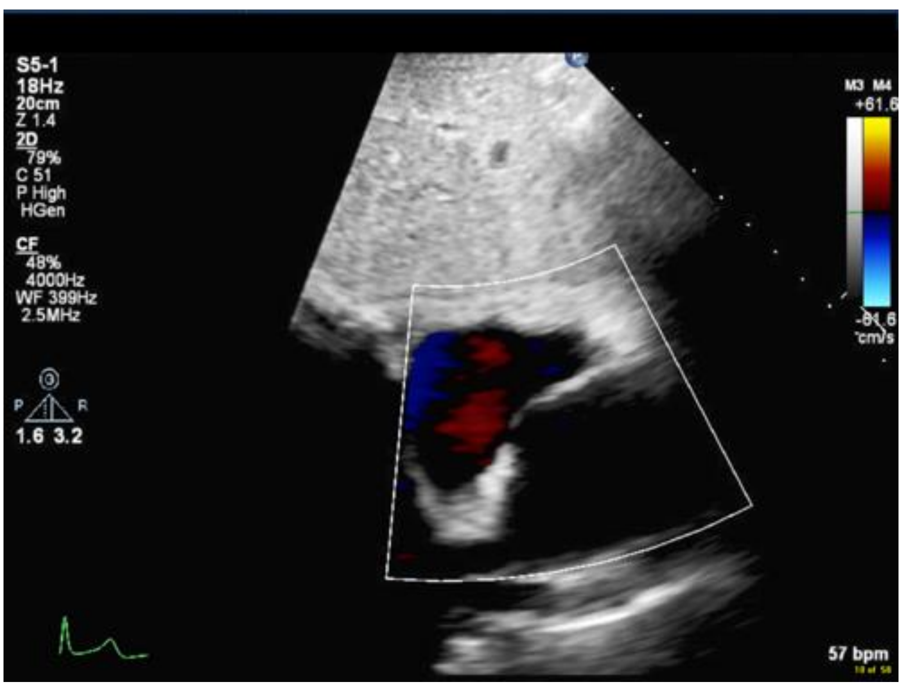
1. 2D long-axis imaging of cardiac chambers:



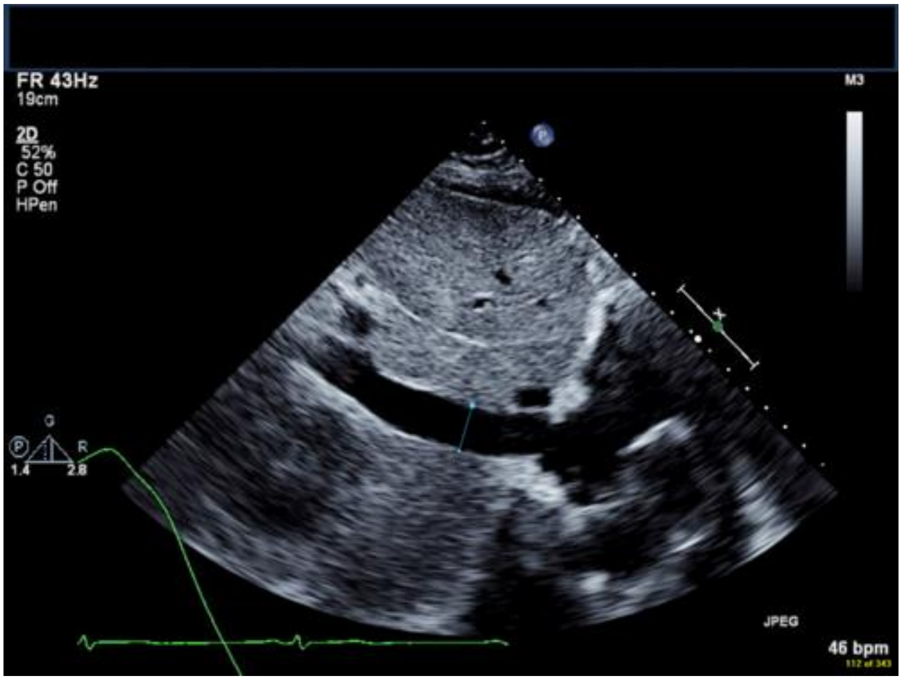
2. 2D long-axis imaging of short-axis (if parasternal TDS):



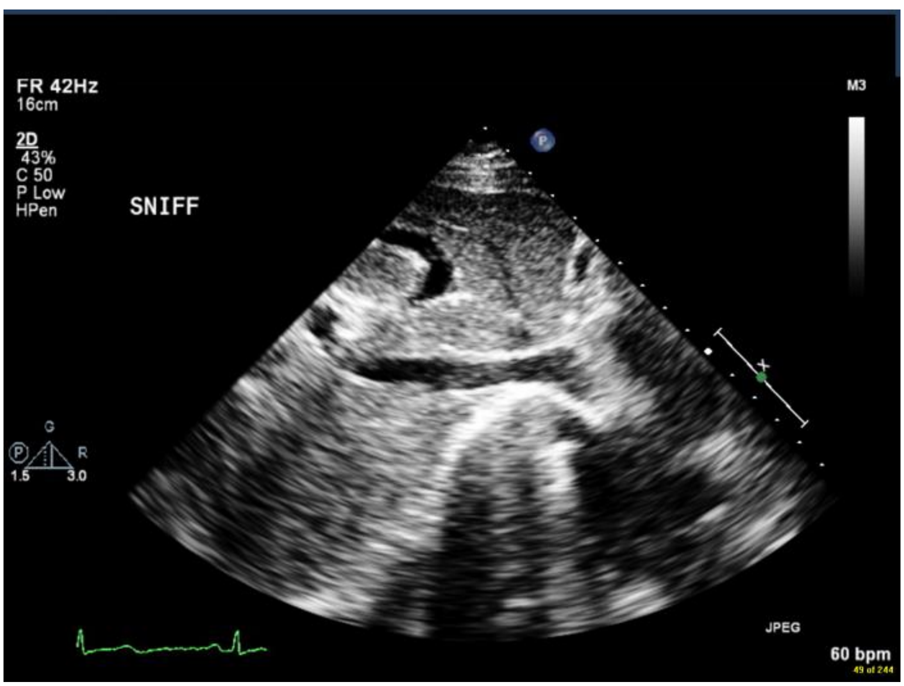
3. Color Doppler of the interatrial septum:



4. 2D imaging of IVC (5-second acquisition) – at rest and after sniff:

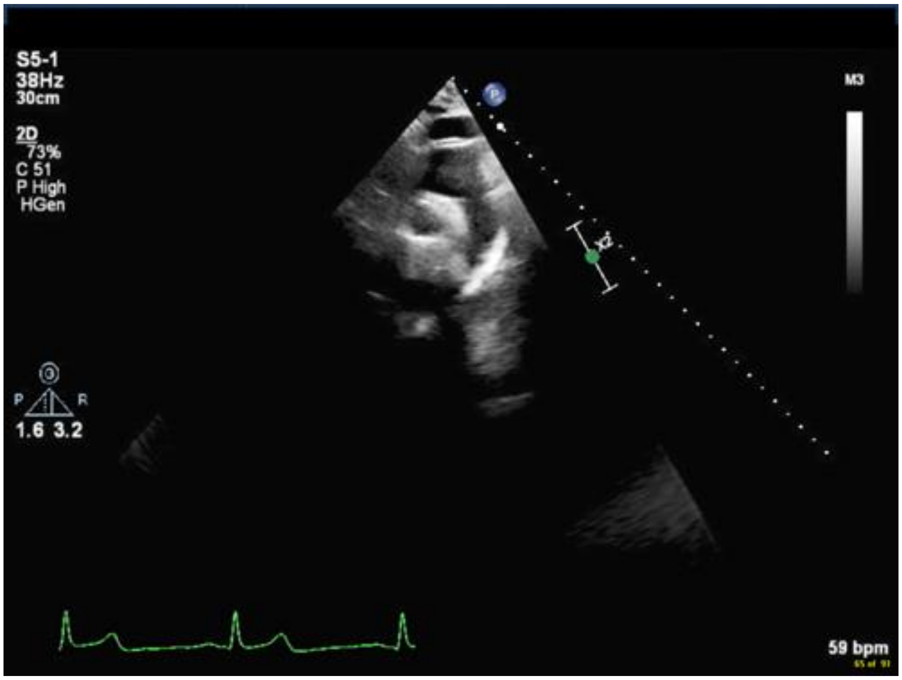


5. 2D imaging of IVC (5-second acquisition) – after sniff:

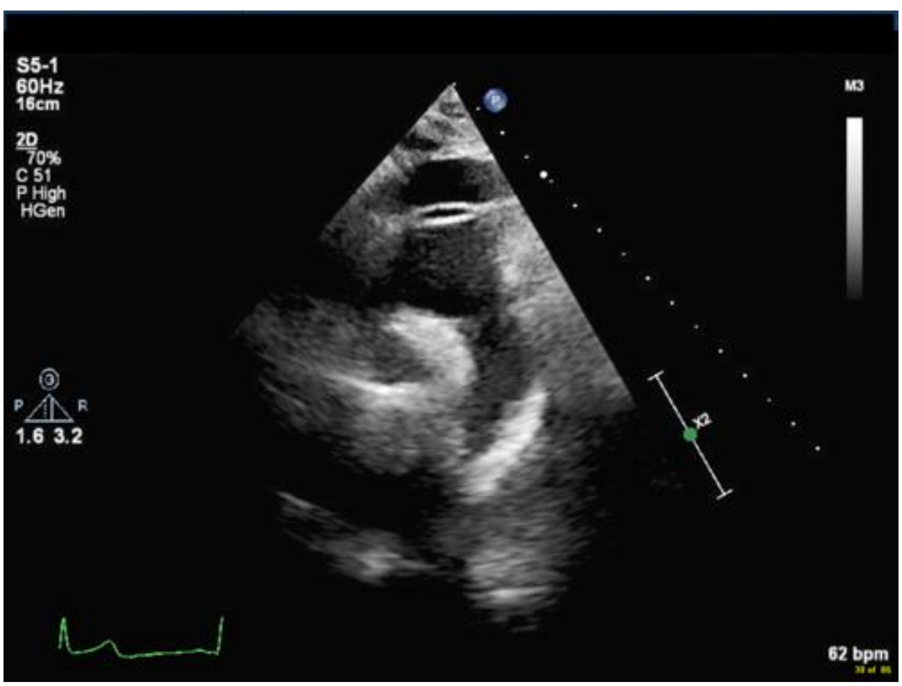


SUPRASTERNAL WINDOW

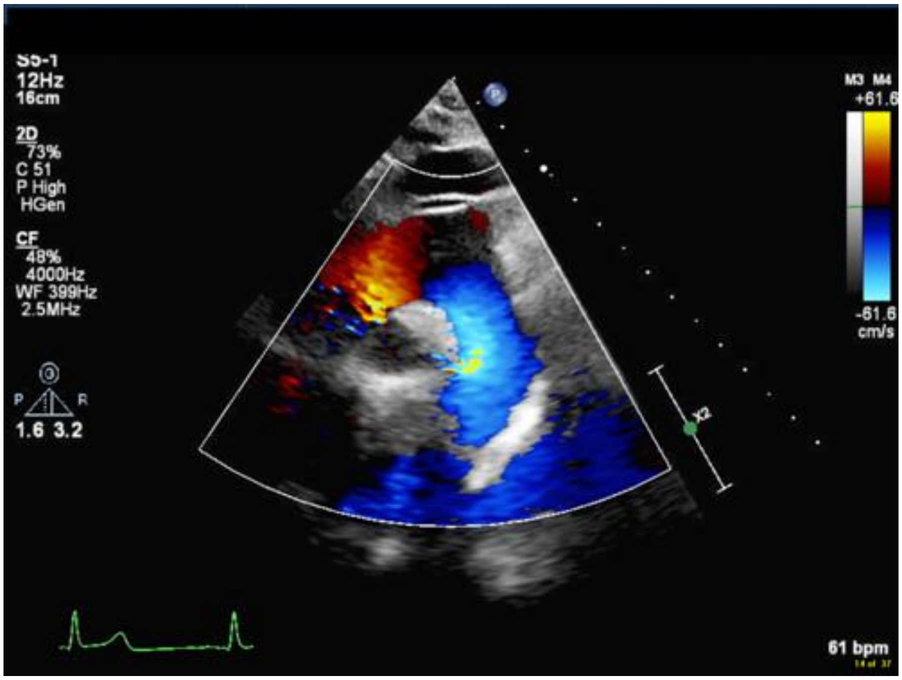
1. 2D imaging - Deep:



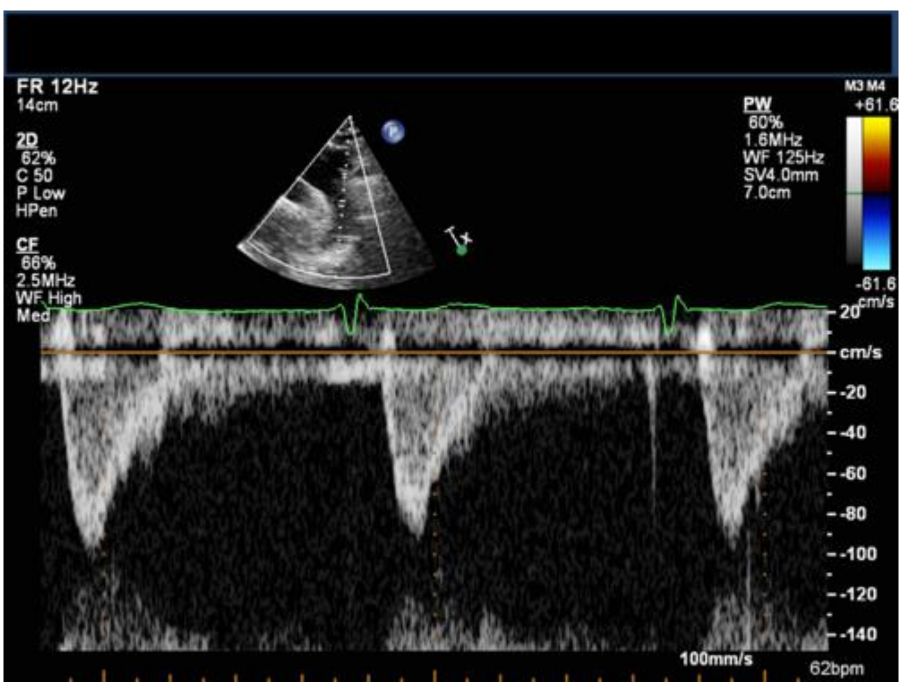
2. 2D imaging - Shallow:



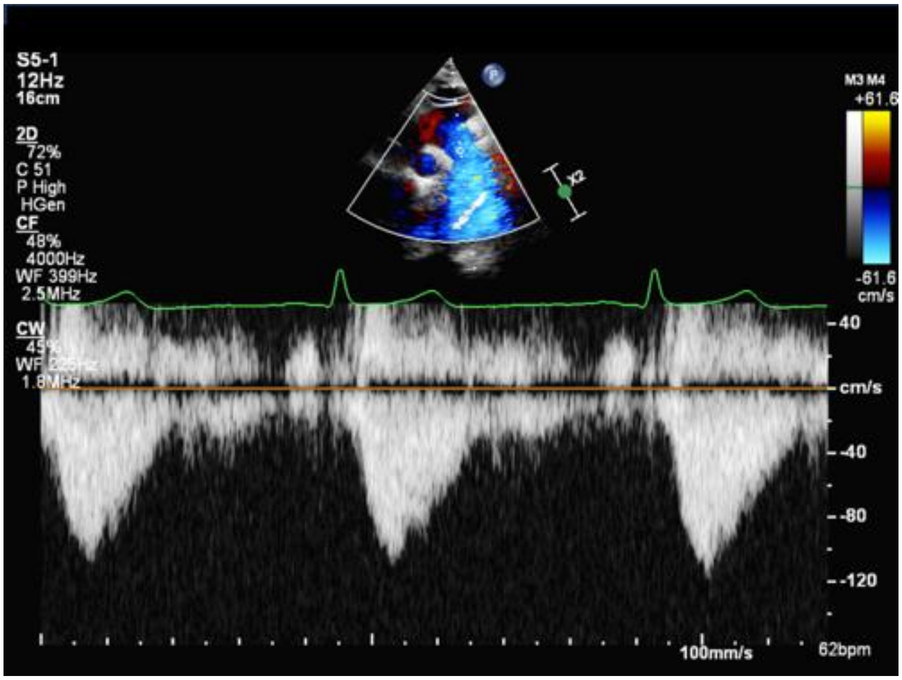
3. Color Doppler of aortic arch/descending aorta:



4. PW Doppler of (proximal) descending aorta:



5. CW Doppler of (proximal) descending aorta:



APPENDIX C. SUMMARY SHEET – WIHS ECHOCARDIOGRAPHY PROTOCOL

Set-Up	
Participant	• Obtain height and weight • Obtain 2 measurements of brachial blood pressure after ≥5 minute rest
Imaging	• Acquire 3 cycles in sinus rhythm; 5-second acquisition for atrial fibrillation • Spectral Doppler100 mm/s sweep speed; Color Doppler scale at least 50-60 cm/s • Frame rate 50-80 Hz for optimal strain determination
Parasternal Windows	
Parasternal Long Axis	• 2D imaging (deep and shallow) • Color Doppler of the aortic and mitral valves together (standard depth) • 2D imaging of LV outflow tract/aortic valve and mitral valve separately (zoomed in) • Color Doppler of the mitral and aortic valves separately (zoomed in)
Right Ventricular Inflow/Outflow	• 2D imaging (standard and zoomed in) • Color Doppler of the tricuspid and pulmonic valves (standard) • CW Doppler of the tricuspid valve for TR velocity; PW and CW Doppler of RV outflow tract
Parasternal Short Axis	• Aortic Valve Level - 2D imaging and color Doppler of aortic valve (standard and zoomed in) - 2D imaging and color Doppler of tricuspid and pulmonic valves (standard) - CW Doppler of tricuspid valve for TR velocity; PW and CW Doppler of RV outflow tract • LV Level - Base (mitral valve level): 2D and M-mode imaging (standard depth) - Mid (papillary muscle level): 2D imaging (standard and zoomed in) - Apex: 2D imaging (standard depth)
Apical Windows	
Apical 4 chamber	• 2D imaging (standard depth), then focused/zoomed on LV and LA • Color Doppler of the mitral valve/LA • PW Doppler of mitral inflow and right upper pulmonary vein inflow • TDI of septal and lateral mitral annulus • 2D imaging focused on the right ventricle • Color Doppler of the tricuspid valve/RA and CW Doppler of tricuspid regurgitation • TAPSE and TDI of lateral tricuspid annulus
Apical 5 chamber	• 2D imaging • CW Doppler near the aortomitral continuity • Color, PW, and CW of the LV outflow tract
Apical 2 chamber	• 2D imaging (standard), then focused/zoomed on LV and LA • Color Doppler of mitral valve/LA
Apical 3 chamber	• 2D imaging • Color Doppler of mitral valve/LA; color, PW, and CW of LV outflow tract
Subcostal Window	
	• 2D long-axis imaging of cardiac chambers – and, if parasternal TDS, also short-axis • Color Doppler of the interatrial septum • 2D imaging of IVC (5-second acquisition) – at rest and after sniff
Suprasternal Window	
	• 2D imaging (deep and shallow) • Color Doppler of aortic arch/descending aorta • PW and CW Doppler of (proximal) descending aorta

APPENDIX D. Sample Cover Letter – Normal Echo

Date

Dear Ms.________________,

Thank you again for participating in the WIHS Echo Study. Attached please find a copy of your research echocardiogram (echo) report for your records. The echocardiogram (ultrasound test of the heart) evaluates your heart size and function.

The echocardiogram shows that your heart is within normal limits. We have provided a copy of these results to your doctor if you previously indicated that we could do so. We suggest that you review your findings with your doctor.

Because this ultrasound test was performed for research purposes, this letter or the echo findings are not a substitute for medical care provided by a physician, clinic, or hospital. Please contact the study office at XXX XXX-XXXX if you, or your doctor, have any questions about this letter.

Yours sincerely,

XXXXXXXXXXX, MD

APPENDIX E. Sample Cover Letter – Abnormal Echo

Date

Dear Ms. _________,

Thank you again for participating in the WIHS Echo Study. Enclosed please find a copy of your research echocardiogram (echo) report for your records. The echocardiogram (ultrasound test of the heart) evaluates your heart size and function.

Please note that there are certain echo findings that are abnormal or require attention. We have provided a copy of this report to your doctor if you previously indicated that we could do so. If you have not requested this and would like your report sent to your doctor, please contact the [SITE NAME] office at XXX-XXX-XXXX. These findings may or may not be new. They may or may not cause any symptoms. Please review the detaisl with your doctor, particularly if you are having palpitations, fainting, light-headedness, chest discomfort, or shortness of breath.

Because this ultrasound study was performed for research purposes, this letter or echo findings are not a substitute for medical care provided by a physician, clinic, or hospital. Please contact our WIHS clinical staff at (XXX) XXX-XXXX If you or your doctor, have any questions about this letter.

Yours sincerely,

XXXXXXXXXXX, MD

APPENDIX F
WOMEN'S INTERAGENCY HIV STUDY
FORM ECHOCA: ECHO SITE CRITICAL ALERT OR VITAL SIGN DOCUMENTATION FORM

INSTRUCTIONS: THE PURPOSE OF THIS FORM IS TO TRACK THE OCCURRENCE OF CRITICAL ALERTS FOR PARTICIPANTS ENROLLED IN THE ECHO PROTOCOL.

A1. PARTICIPANT ID |___|-|___|___|-|___|___|___|___|-|___|

A2. WIHS CORE VISIT NUMBER DURING WHICH ECHO IS COMPLETED: |___|___|

A3. FORM VERSION: **1 2 / 0 7 / 1 7**

A4. FORM COMPLETED BY: |___|___|___|

A5. ECHO DATE: |___|___| / |___|___| / |___|___|
M D Y

A6. NATURE OF CRITICAL ALERT:
CARDIAC TAMPONADE 1
INTRACARDIAC THROMBUS, VEGETATION OR TUMOR 2
AORTIC DISSECTION 3
SEVERE PROSTHETIC VALVE DYSFUNCTION 4
LV PSEUDOANEURYSM 5
OTHER INDICATION 6
SPECIFY OTHER: ______________________________________

A7. NATURE OF CRITICAL VITAL SIGNS:
SEVERE HYPERTENSION 1
MARKED BRADYCARDIA OR TACHYCARDIA 2

A8. CLINICIAN ALERTED: ____

A9. CLINICIAN DECISION: ____

A10. PARTICIPANT ACTIONS: ____

A11. OTHER COMMENTS: ____

____

____

APPENDIX G
WOMEN'S INTERAGENCY HIV STUDY
FORM ECHOCARC: ECHO READING CENTER CRITICAL OR URGENT FINDING DOCUMENTATION FORM

INSTRUCTIONS: THE PURPOSE OF THIS FORM IS TO TRACK THE OCCURRENCE OF CRITICAL ALERTS FOR PARTICIPANTS ENROLLED IN THE ECHO PROTOCOL.

A1. PARTICIPANT ID |___|-|___|___|-|___|___|___|___|-|___|

A2. WIHS CORE VISIT NUMBER DURING WHICH ECHO IS COMPLETED: |___|___|

A3. FORM VERSION: **1 2 / 0 7 / 1 7**

A4. FORM COMPLETED BY: |___|___|___|

A5. ECHO DATE: |___|___| / |___|___| / |___|___|
M D Y

A6. WIHS ECHO SITE:
- WASHINGTON, DC........1
- SAN FRANCISCO........2
- CHICAGO........3
- UNC........4
- ATLANTA........5
- MIAMI........6
- UAB-MS (BIRMINGHAM)........7
- UAB-MS (JACKSON)........8

A7. ABNORMAL FINDINGS:
- CARDIAC TAMPONADE........1
- INTRACARDIAC THROMBUS, VEGETATION OR TUMOR........2
- AORTIC DISSECTION........3
- SEVERE PROSTHETIC VALVE DYSFUNCTION........4
- LV PSEUDOANEURYSM........5
- LV WALL MOTION ABNORMALITIES........6
- REDUCED LV OR RV SYSTOLIC FUNCTION........7
- MORE THAN MODERATE VALVE REGURGITATION........8
- MODERATE OR GREATER LV OUTFLOW OBSTRUCTION........9
- MODERATE OR GREATER PULMONARY HYPERTENSION........10
- MODERATE OR GREATER RESTRICTIVE LV INFLOW........11
- SEVERE AORTIC ROOT DILATATION........12
- OTHER........13

SPECIFY: ____

WIHSID

A8. COMMENTS: ____

____

____

A9. PHYSICIAN READER NAME: ____

A10. DATE OF SITE NOTIFICATION: |___|___| / |___|___| / |___|___|
M D Y

A11. NAME OF PERSON CONTACTED AT THE SITE: ____________________________________

APPENDIX H
WOMEN'S INTERAGENCY HIV STUDY
FORM ECHOSC: ECHO SCORE CARD

INSTRUCTIONS: THE PURPOSE OF THIS FORM IS TO TRACK THE OCCURRENCE OF CRITICAL ALERTS FOR PARTICIPANTS ENROLLED IN THE ECHO PROTOCOL.

A1. PARTICIPANT ID: |___|-|___|___|-|___|___|___|___|-|___|

A2. WIHS CORE VISIT NUMBER DURING WHICH ECHO IS COMPLETED: |___|___|

A3. FORM VERSION: **1 2 / 0 7 / 1 7**

A4. ECHO EXAM DATE: |___|___| / |___|___| / |___|___|
M D Y

A5. SONOGRAPHER ID: |___|___|___|

A6. ANALYST INITIALS: |___|___|___|

A7. WIHS ECHO SITE:
- WASHINGTON, DC....................1
- SAN FRANCISCO....................2
- CHICAGO....................3
- UNC....................4
- ATLANTA....................5
- MIAMI....................6
- UAB-MS (BIRMINGHAM)....................7
- UAB-MS (JACKSON)....................8

A8. PLAX:

a. SCORE:
- IMAGE NOT OBTAINED....................0
- POOR IMAGE, MEASUREMENT NOT OBTAINABLE....................1
- SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT....................2
- HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT....................3

b. COMMENTS:____

____

____

A9. PSAX:

a. SCORE:
- IMAGE NOT OBTAINED....................0
- POOR IMAGE, MEASUREMENT NOT OBTAINABLE....................1
- SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT....................2
- HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT....................3

WIHSID

b. COMMENTS:____

____

____

A10. A4C LEFT VENTRICLE:

a. SCORE:

IMAGE NOT OBTAINED 0
POOR IMAGE, MEASUREMENT NOT OBTAINABLE 1
SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT 2
HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT 3

b. COMMENTS:____

____

____

A11. A4C LEFT ATRIUM:

a. SCORE:

IMAGE NOT OBTAINED 0
POOR IMAGE, MEASUREMENT NOT OBTAINABLE 1
SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT 2
HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT 3

b. COMMENTS:____

____

____

A12. RIGHT VENTRICLE:

a. SCORE:

IMAGE NOT OBTAINED 0
POOR IMAGE, MEASUREMENT NOT OBTAINABLE 1
SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT 2
HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT 3

b. COMMENTS:____

____

____

WIHSID

A13. A2C LEFT VENTRICLE:

a. SCORE:

IMAGE NOT OBTAINED 0
POOR IMAGE, MEASUREMENT NOT OBTAINABLE 1
SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT 2
HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT 3

b. COMMENTS:____

____

____

A14. A2C LEFT ATRIUM:

a. SCORE:

IMAGE NOT OBTAINED 0
POOR IMAGE, MEASUREMENT NOT OBTAINABLE 1
SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT 2
HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT 3

b. COMMENTS:____

____

____

A15. DIASTOLOGY:

a. SCORE:

IMAGE NOT OBTAINED 0
POOR IMAGE, MEASUREMENT NOT OBTAINABLE 1
SUBOPTIMAL IMAGE, BUT ADEQUATE FOR MEASUREMENT 2
HIGH-QUALITY IMAGE ALLOWING ACCURATE MEASUREMENT 3

b. COMMENTS:____

____

____

A16. OVERALL SCORE / AVERAGE OF ABOVE PARAMETERS: __________________________

A17. COMMENTS (OTHER VIEWS):

____

____

____

____

APPENDIX I
WOMEN'S INTERAGENCY HIV STUDY
FORM ECHOTW: ECHO TECHNICIAN WORKSHEET

SECTION 1: TO BE FILLED OUT BY COORDINATOR OR SONOGRAPHER.

A1. PARTICIPANT ID: |___|-|___|___|-|___|___|___|___|-|___|

A2. WIHS CORE VISIT NUMBER DURING WHICH ECHO IS COMPLETED: |___|___|

A3. FORM VERSION: **1 2 / 0 7 / 1 7**

A4. FORM COMPLETED BY: |___|___|___|

A5. DATE: |___|___| / |___|___| / |___|___|
M D Y

A6. DOES PARTICIPANT AGREE TO PARTICIPATE IN THE ECHO STUDY?

YES ………………………………………………………………………… 1 **(A7)**
NO …………………………………………………………………………… 2 **(PROMPT)**

PROMPT: IF THE RESPONSE TO QUESTION A5 IS "2," THE REST OF THE FORM SHOULD BE LEFT BLANK.

A7. What is your current age? |___|___| YEARS

A8. What is your current height? |___|___| . |___|___| IN

A9. What is your current weight? |___|___|___| LBS

A10. Do you have previous cardiac (heart) history?

Yes ………………………………………………………………………….. 1
No …………………………………………………………………………… 2

SECTION 2: TO BE FILLED OUT BY SONOGRAPHER.

A11. FIRST BLOOD PRESSURE:

a. SYSTOLIC: |___|___|___|
b. DIASTOLIC: |___|___|___|

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A12. SECOND BLOOD PRESSURE:

a. SYSTOLIC: |___|___|___|

b. DIASTOLIC: |___|___|___|

A13. HEART RATE: |___|___|___|

PROMPT: IF AVERAGE SYSTOLIC BP ≥ 200 MM HG OR DIASTOLIC BP ≥ 110, ASK PARTICIPANT TO REST QUIETLY FOR 5 ADDITIONAL MINUTES AND REPEAT TWO BLOOD PRESSURE MEASUREMENTS. IF AVERAGE REMAINS ABOVE LIMIT, CANCEL ECHOCARDIOGRAM AND CONSULT WITH CLINICIAN (CARDIOLOGIST, PERSONAL PHYSICIAN, WIHS CLINICIAN) FOR DISPOSITION (E.G., EMERGENCY DEPARTMENT, PHYSICIAN'S OFFICE). DO THE SAME IF HEART RATE < 40 BPM OR ≥ 120 BPM.

WERE IMAGES OBTAINED FOR THE FOLLOWING COMPONENTS OF THE EXAM?

	YES	NO
A14. PLAX:		
a. 2D…………………………	1 **(b)**	2
IF NO, PLEASE EXPLAIN: ___________________________		
b. COLOR (MV, AV) …………………	1 **(A15)**	2
IF NO, PLEASE EXPLAIN: ___________________________		

	YES	NO
A15. PSAX:		
a. 2D (AV, TV, PV)…………………	1 **(b)**	2
IF NO, PLEASE EXPLAIN: _________________________		
b. COLOR (AV, PV, TV) …………………	1 **(c)**	2
IF NO, PLEASE EXPLAIN: _________________________		
c. DOPPLER (AV, TV, PV)…………………	1 **(d)**	2
IF NO, PLEASE EXPLAIN: _________________________		
d. 2D (LV BASE, MID, APEX) …………………	1 **(e)**	2
IF NO, PLEASE EXPLAIN: _________________________		
e. M-MODE (LV BASE) …………………	1 **(A16)**	2
IF NO, PLEASE EXPLAIN: _________________________		

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	YES	NO
A16. APICAL 4-CHAMBER:		
a. 2D (LV, LA)	1 **(b)**	2
IF NO, PLEASE EXPLAIN: ________________________		
b. COLOR (MV)	1 **(c)**	2
IF NO, PLEASE EXPLAIN: ________________________		
c. DOPPLER (MV, RUPV)	1 **(d)**	2
IF NO, PLEASE EXPLAIN: __________________________		
d. TDI (LATERAL, SEPTAL, RIGHT)........	1 **(e)**	2
IF NO, PLEASE EXPLAIN: __________________________		
e. 2D, TAPSE (RV)	1 **(f)**	2
IF NO, PLEASE EXPLAIN: __________________________		
f. COLOR , DOPPLER (TV)	1 **(A17)**	2
IF NO, PLEASE EXPLAIN: __________________________		

	YES	NO
A17. APICAL 5-CHAMBER:		
a. 2D	1 **(b)**	2
IF NO, PLEASE EXPLAIN: __________________________		
b. COLOR, DOPPLER (AORTO-MITRAL, LVOT, AV)........	1 **(A18)**	2
IF NO, PLEASE EXPLAIN: __________________________		

	YES	NO
A18. APICAL 2-CHAMBER:		
a. 2D (LV, LA)........	1 **(b)**	2
IF NO, PLEASE EXPLAIN: __________________________		
b. COLOR, DOPPLER (MV)	1 **(A19)**	2
IF NO, PLEASE EXPLAIN: __________________________		

	YES	NO
A19. APICAL 3-CHAMBER:		
a. 2D........	1 **(b)**	2
IF NO, PLEASE EXPLAIN: __________________________		
b. COLOR (MV, AV)	1 **(c)**	2
IF NO, PLEASE EXPLAIN: __________________________		

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	YES	NO
c. DOPPLER (AV)	1 **(A20)**	2

IF NO, PLEASE EXPLAIN: ___________________________

A20. SUBCOSTAL:

	YES	NO
a. 2D (LONG-AXIS, IVC)	1 **(b)**	2
IF NO, PLEASE EXPLAIN: ___________________________		
b. COLOR (INTERATRIAL SEPTUM)	1 **(A21)**	2
IF NO, PLEASE EXPLAIN: ___________________________		

A21. SUPRASTERNAL:

	YES	NO
a. 2D	1 **(b)**	2
IF NO, PLEASE EXPLAIN: ___________________________		
b. COLOR, DOPPLER	1 **(A22)**	2
IF NO, PLEASE EXPLAIN: ___________________________		

A22. ARE THERE ANY CRITICAL ALERT FINDINGS?

YES .... 1 **(A22a)**

NO .... 2 **(A23)**

a. WHAT ARE THE CRITICAL FINDINGS?

	YES	NO
i. CARDIAC TAMPONADE	1	2
ii. AORTIC DISSECTION	1	2
iii. THROMBUS	1	2
iv. VEGETATION	1	2
v. TUMOR	1	2
vi. SEVERE PROSTHETIC VALVE DYSFUNCTION........	1	2
vii. LV PSEUDOANEURYSM	1	2

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A23. ARE THERE ANY URGENT FINDINGS?

YES ....1 **(A22a)**

NO ....2 **(A23)**

		YES	NO
a. WHAT ARE THE URGENT FINDINGS?			
i.	LV WALL MOTION ABNORMALITIES	1	2
ii.	REDUCED LV OR RV FUNCTION	1	2
iii.	MORE THAN MODERATE REGURGITATION	1	2
iv.	MODERATE OR GREATER LVOT OBSTRUCTION	1	2
v.	MORE THAN MODERATE PULMONARY HTN	1	2
vi.	MORE THAN MODERATE RESTRICTIVE INFLOW	1	2
vii.	AORTIC ROOT DILATATION	1	2
viii.	OTHER	1	2

SPECIFY: _______________________

A24. COMMENTS FOR THE ECHO READING CENTER REGARDING PROBLEMS ENCOUNTERED WITH THE PARTICIPANT:

____

____

____

A25. COMMENTS FOR THE ECHO READING CENTER REGARDING IMAGE ACQUISITION:

____

____

____

A26. COMMENTS FOR THE ECHO READING CENTER REGARDING MACHINE FAILURE:

____

____

____

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A27. COMMENTS FOR THE ECHO READING CENTER REGARDING CARDIAC HISTORY:

____

____

____

A28. COMMENTS FOR THE ECHO READING CENTER REGARDING OTHER PROBLEMS:

____

____

____

A29. NUMBER OF FRAMES: _____________

A30. TECHNICIAN ID: _____________

APPENDIX J
WOMEN'S INTERAGENCY HIV STUDY
FORM ECHONYHA: NYHA QUESTIONNAIRE

A1. PARTICIPANT ID |___|-|___|___|-|___|___|___|___|-|___|

A2. FORM VERSION: **1 0 / 0 1 / 1 7**

A3. FORM COMPLETED BY: |___|___|___|

A4. DATE OF ECHO: |___|___| / |___|___| / |___|___|
M D Y

A5. WIHS CORE VISIT NUMBER DURING WHICH ECHO IS COMPLETED: |___|___|

A6. Which of the following types of activities bring on shortness of breath? ***(READ ALOUD EACH CLASS NUMBER FOLLOWED BY THE DESCRIPTION AND RECORD ONLY ONE)***	
Ordinary physical activity does not cause shortness of breath (dyspnea). You can carry 24 pounds (such as a toddler) up eight steps; do heavy lifting; do outdoor work (shovel snow, spade soil); do recreational activities (skiing, basketball, jog/walk 5 miles per hour). **CLASS 1**	1
You are comfortable at rest, but ordinary physical activity results in shortness of breath (dyspnea). You can do activities such as garden, rake, weed, dance, walk 4 miles per hour on level ground without stopping. **CLASS 2**	2
You are comfortable at rest, but less than ordinary physical activity causes shortness of breath (dyspnea). You can do activities such as shower without stopping, strip and make bed, play golf, dress without stopping, walk about 2.5 miles per hour. **CLASS 3**	3
You cannot carry on any physical activity without shortness of breath (dyspnea). Cannot carry out any activities listed above. **CLASS 4**	4

A7. Is there a known lung disease or other causes for dyspnea?
YES..1
NO 2

APPENDIX K
WOMEN'S INTERAGENCY HIV STUDY
FORM ECHOROSE: ROSE ANGINA QUESTIONNAIRE

A1. PARTICIPANT ID |___|-|___|___|-|___|___|___|___|-|___|

A2. FORM VERSION: **1 0 / 0 1 / 1 7**

A3. FORM COMPLETED BY: |___|___|___|

A4. DATE OF ECHO: |___|___| / |___|___| / |___|___|
M D Y

A5. WIHS CORE VISIT NUMBER DURING WHICH ECHO IS COMPLETED: |___|___|

SECTION B

		YES	NO
B1.	Have you ever had any pain or discomfort in your chest?	1	2 **(SECT. D)**
B2.	Do you get this pain or discomfort when you walk uphill or hurry?	1	2 **(SECT. C)**
B3.	Do you get it when you walk at an ordinary pace on the level?	1	2

B4. When you get any pain or discomfort in your chest what do you do?

Stop 1
Slow down..2
Continue at same pace 3

		YES	NO
B5.	Does it go away when you stand still?	1	2

B6. How soon?

10 minutes or less 1
More than 10 minutes 2

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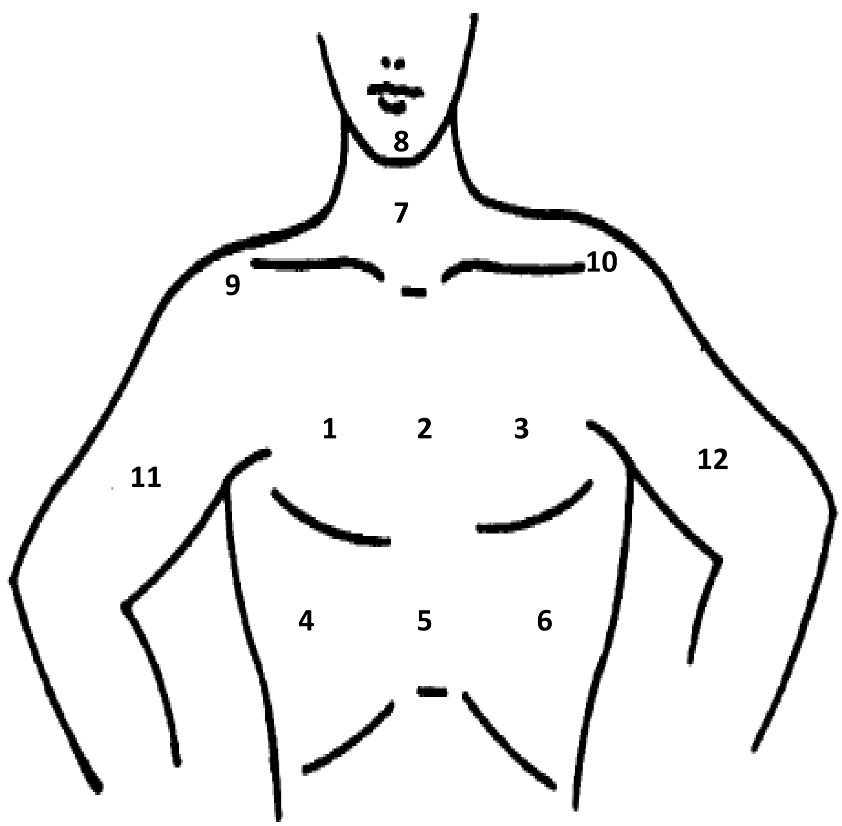
B7. Where do you get this pain or discomfort? Indicate "yes" or "no" for each location.
PROMPT: SHOW PARTICIPANT NUMBERED DIAGRAM OF CHEST.

	YES	NO
1. Right Chest	1	2
2. Sternum (mid-chest)	1	2
3. Left Chest	1	2
4. Right Upper Abdomen	1	2
5. Epigastrium	1	2
6. Left Upper Abdomen	1	2
7. Neck	1	2
8. Jaw	1	2
9. Right Shoulder	1	2
10. Left Shoulder	1	2
11. Right Arm	1	2
12. Left Arm	1	2



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SECTION C

		YES	NO
C1.	Have you ever had a severe pain across the front of your chest lasting for half an hour or more?	1	2

SECTION D

		YES	NO
D1.	Do you get a pain in either leg on walking?	1	2 **(END)**
D2.	Does this pain ever begin when you are standing still or sitting?	1	2
D3.	Do you get this pain in your calf (or calves)?	1	2
D4.	Do you get it when you walk uphill or hurry?	1	2
D5.	Do you get it when you walk at an ordinary pace on the level?	1	2
D6.	Does the pain ever disappear while you are still walking?	1	2

D7. What do you do if you get it when you are walking?

Stop 1
Slow down...2
Continue at same pace 3

D8. What happens to it if you stand still?

Usually continues more than 10 minutes......1
Usually disappears in 10 minutes or less.......2