

Data Coordinating Center (DCC)
Cleveland Clinic
Department of Quantitative Health Sciences, JJN3
9500 Euclid Avenue
Cleveland, Ohio 44195

Document Title: **Longitudinal PVDOMICS Study
Chapter 260 - Echocardiography Manual of Procedures**

Trial Sponsor: Data Coordinating Center

Protocol Title: Pulmonary Vascular Disease Phenomics Program –
L-PVDOMICS

**Confidential: This document is confidential and is intended for use in the
above referenced study only.**

Note to sites:

The Imaging Core Lab analysis results are intended for research purposes only and should not be used for clinical patient management.

Each site must have a plan for ensuring that clinically relevant findings are observed and managed at the site level.

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2 Hours of Operation

2.1 Hours of Operation

The Imaging Core Lab is open Monday through Friday, 8:00 AM to 4:30 PM, Eastern Standard Time.

2.2 2016-2021 Holidays

The Imaging Core Lab is closed on the following dates for holidays:

2016

Memorial Day	May 30, 2016
Independence Day	July 4, 2016
Labor Day	September 5, 2016
Thanksgiving	November 24-25, 2016
Christmas	December 23-26, 2016

2017

New Year's Day	January 2, 2017
Memorial Day	May 29, 2017
Independence Day	July 4, 2017
Labor Day	September 4, 2017
Thanksgiving	November 23-24, 2017
Christmas	December 25-26, 2017

2018

New Year's Day	January 1, 2018
Memorial Day	May 28, 2018
Independence Day	July 4, 2018
Labor Day	September 3, 2018
Thanksgiving	November 22-23, 2018
Christmas	December 24-25, 2018

2019

New Year's Day	January 1, 2019
Memorial Day	May 27, 2019
Independence Day	July 4, 2019
Labor Day	September 2, 2019
Thanksgiving	November 28-29, 2019
Christmas	December 24-25, 2019

2020

New Year's Day	January 1, 2020
Memorial Day	May 25, 2020
Independence Day	July 6, 2020
Labor Day	September 7, 2020
Thanksgiving	November 26-27, 2020
Christmas	December 24-25, 2020

2021

New Year's Day	January 1, 2021
Memorial Day	May 31, 2021
Independence Day	July 5, 2021
Labor Day	September 6, 2021
Thanksgiving	November 25-26, 2021
Christmas	December 24-25, 2021

3 Abbreviations and Acronyms

2D	Two-dimensional
3D	Three-dimensional
4C	4-Chamber
A2C	Apical 2-Chamber
A4C	Apical 4-Chamber
A5C	Apical 5-Chamber
ADM	Administration
AO	Aorta or Aortic
AS	Aortic Stenosis
ASD	Atrial Septal Defect
ASE	American Society of Echocardiography
AV	Aortic Valve
CFD	Color Flow Doppler
CVP	Central Venous Pressure
CW	Continuous Wave
DCC	Data Coordinating Center
DCF	Data Clarification Form
DCM	Dilated Cardiomyopathy
DICOM	Digital Imaging and Communications in Medicine
DICOMDIR	DICOM Directory
DOB	Date of Birth
DTF	Data Transmittal Form
DVD	Digital Video Disc
EBD	Endocardial Border Definition
EKG / ECG	Electrocardiogram
ECHO	Echocardiogram
FOV	Field of View
FPS	Frames per Second

FR	Frame Rate
HIPAA	Health Insurance Portability and Accountability Act
HV	Hepatic Vein
IAS	Interatrial Septum
ICL	Imaging Core Lab
ICS	Intercostal Space
ID	Identification
IDCM	Ischemic Dilated Cardiomyopathy
IVC	Inferior Vena Cava
LA	Left Atrium
L-PVDOMICS	Longitudinal PVDOMICS
LV	Left Ventricle
LVOT	Left Ventricular Outflow Tract
M-Mode	Motion Mode
MV	Mitral Valve
NA	Not Applicable
NATIVE DICOM format	Philips Proprietary Format
NHLBI	National Heart, Lung, and Blood Institute
mm	millimeters
PA	Pulmonary Artery
PACS	Picture Archiving and Communication System
PAP	Pulmonary Artery Pressure
PFO	Patent Foramen Ovale
PH	Pulmonary Hypertension
PLAX	Parasternal Long Axis
PM	Preventative Maintenance
PSAX	Parasternal Short Axis
PV	Pulmonic Valve
PVC	Premature Ventricular Contraction
PW	Pulsed Wave

QC	Quality Control
Qp/Qs	Ratio of pulmonary to systemic blood flow
RA	Right Atrium
RAW DICOM format	GE Proprietary Format
RIMP	Right Index of Myocardial Performance
RR	R wave to R wave timing (ms)
RV	Right Ventricle
RVIF	Right Ventricular Inflow
RVOT	Right Ventricular Outflow Tract
RVSP	Right Ventricular Systolic Pressure
STJ	Sinotubular Junction
SV	Sample Volume
SVC	Superior Vena Cava
TAPSE	Tricuspid Annular Plane Systolic Excursion
TDI	Tissue Doppler Imaging
TR	Tricuspid Regurgitation
WHO	World Health Organization
WMA	Wall Motion Abnormality

4 Document Revision History

4.1 V5.0 14Sep2020

This document is the current approved version. Amended versions will be described in this section and include a history of changes.

Version	Changes Made	Effective Date
1.0	Original	09Sep2016
2.0	1. Section 6.4.18, page 30, Clarification provided for agitated saline contrast use for shunt detection. 2. Section 6.6, page 39, Clarification provided for agitated saline contrast use for peak TR velocity jet. 3. Section 7.5.2, page 60, 61, clarification of boxes to check to assure 3D data transfers in Native format.	25Jan2017
3.0	1. Section 6.2.4, page 11, Change in the number of cardiac cycles and clips collected. 2. Figure 9 page 21, Change in the number of cardiac cycles and clips collected. 3. Figure 10, page 22, Change in the number of cardiac cycles and clips collected. 4. Figure 12, page 24, Change in the number of cardiac cycles and clips collected. 5. Section 6.6, page 39, Change in the number of cardiac cycles and clips collected.	02Mar2017
4.0	1. Section 1.0, page 1-2, Core lab Contact list updated to reflect current personnel and credentials. 2. Section 2.2, page 3-4, 2020 Holiday calendar added.	11Oct2019

	3. Section 3, page 5, Abbreviations and Acronyms, added Longitudinal PVDOMICS. 4. Section 5.5, page 12, Echo Instrumentation, contrast section updated to include the use of a contrast enhancing agent on all follow-up echoes that had contrast at baseline. 5. Section 5.5, page 12, Table 1 Echo Imaging Schedule updated to include a follow-up visit (L-PVDOMICS) 6. Section 5.6.18, page 30, updated section on saline bubble study requirement to include Follow-up (L_PVDOMICS) exams. 7. Section 5.8, page 43, Table 1, Echo Protocol Imaging Acquisition updated to reflect the elimination of a bubble study during Follow –up exams (L-PVDOMICS). 8. Section 10, page 70, Forms, updated to reflect L-PVDOMICS electronic web page information.	
5.0	Section 5.3.6, page 11, Clinical sonographers are exempt from qualification when performing clinical exams. Section 5.4.2, page 11, Echo acquisition instructions for Clinical Sonographers performing L-PVDOMICS additional variables. Section 5.9, page 44-45, Longitudinal PVDOMICS (L-PVDOMICS), Clinical Echocardiography Sonographer Guide of Additional Variables to be captured. Section 6.1.4, page 47, Echo Scan Submission Procedure instructions for patient identifiers and Protected Health Information for clinically performed L-PVDOMICS exams. Section 2.2, page 3, Updated Holidays to include 2021 Updated TOC to reflect all previous and current changes.	

5 Study Overview

5.1 Purpose

The purpose of this C5Research (C5R) Imaging Manual is to instruct sites in: 1) protocol-specific image acquisition requirements; 2) necessary documentation, image data transfer instructions and data storage; and 3) the query resolution process for any clerical discrepancies and/or non-compliant data.

The goal of the Echocardiography Manual of Operations is to assist sites in obtaining high quality, reproducible, quantitative information about the structure, function and hemodynamics of the right and left heart. The hemodynamic (Doppler) and functional variables will be analyzed at the ICL to determine clinically useful parameters which may aide in early diagnosis, and re-classification of pulmonary hypertension. Advanced Echocardiographic measures of right ventricular performance will be compared to cardiac MRI.

5.2 Study Synopsis (from core PVDOMICS Protocol V1.0, April 29, 2016)

PVDOMICS is a novel NHLBI Research Initiative in Pulmonary Vascular Disease. It is recognized that patients with various forms of heart and lung disease exhibit varying degrees of pulmonary hypertension, pulmonary vascular remodeling, and right ventricular dysfunction. The genetic, molecular, and cellular processes driving these phenomena are not well understood. Rapid advances in high throughput omic methodology, combined with powerful bioinformatics and network biology capability, have created the opportunity to conduct studies that broadly search for homologies and differences across the spectrum of disease states associated with pulmonary hypertension and determinants of the spectrum of pulmonary vascular disease and RV compensation that accompanies these conditions.

The 2010 NHLBI Pulmonary Vascular Strategic Plan identified the development of a comprehensive cohort to define phenotypes integrating Omics technologies and systems approaches as a top priority. The current WHO PH classification, based solely on clinical/hemodynamic subsets, limits the ability to customize treatment for an individual patient, or to assign meaningful clinical phenotype designations, e.g., Long-term survivor or Maladaptive RV Hypertrophy. **The overall goal of the PVDOMICS network is to perform comprehensive phenotyping (demographic, physiologic, clinical chemistries, and imaging) and endophenotyping (genomic, proteomic, metabolomic, coagulomic, cell and/or tissue based) across the World Health Organization (WHO) classified PH clinical groups 1 through 5 as well as intermediate phenotypes (including those without overt PH) in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with PVD. The long-term goal is utilization of endophenotypes/biomarkers for early diagnosis, at-risk screening, and personalized approaches for interventions and/or preventions of PVD.**

The PVDOMICS protocol is designed to lead to new understanding of patients with PH and right heart dysfunction, based on molecular, clinical, hemodynamic, dynamic and imaging characteristics. Development of new classifications will be a product of association of these in depth phenotypic descriptions with specific molecular mechanisms of pathogenesis. The protocol will be implemented to lead to identification of both sub-phenotypes of lung vascular disease and to biomarkers of disease that may be useful for early diagnosis or for assessment of interventions to prevent or treat this condition.

The first aim will be a natural product of the protocol, to identify the molecular basis of pulmonary vascular disease regardless of WHO clinical classification, by comparison of current subsets of PH patients. The second aim is to discover biological measures of disease and therapeutic responses that may be useful not only in diagnosis but also as outcome measures in treatment and possibly prevention trials. ECHO Process

5.3 Echo Qualification Submission Process

- 5.3.1** Prior to qualification, a copy of the current Preventive Maintenance (PM) document for each ultrasound system planned for use in the trial must be submitted to the Imaging Core Lab (*including serial number*). A copy of the PM document should be maintained at the site with the trial regulatory files.
- 5.3.2** **The qualification process must be completed prior to sites submitting exams of enrolled subjects.** All sites will be required to submit a de-identified sample echocardiogram to the Imaging Core Lab, via AG MEDNET for *each sonographer* participating in the trial. A backup sonographer should be identified and follow the same qualification process.
- 5.3.3** The qualification study performed should follow the PVDOMICS or L-PVDOMICS imaging protocol. The purpose of the Echo Qualification Process is to ensure compatibility between site echo acquisition and Core

Lab analysis tools prior to subject recruitment and to ensure adherence to the imaging protocol.

- 5.3.4** The site and Data Coordinating Center (DCC) will be notified of the sonographer qualification status via email or fax.
- 5.3.5** If a sonographer does not qualify with the first submission, the Imaging Core Lab will use the critique to recommend changes for resubmission of another echo qualification study.
- 5.3.6** Clinical Sonographers performing additional images during the subject's clinically ordered echocardiogram for the PVDOMICS study are exempt from the qualification process.

5.4 Echo Acquisition

- 5.4.1** Acquire images according to the parameters described in this manual. Only *qualified sonographers* should perform PVDOMICS study echocardiograms.
- 5.4.2** As stated in section 5.3.6 for L-PVDOMICS **only** clinical sonographers are exempt from qualification. Clinical sonographers performing additional images during a clinically scheduled exam for L-PVDOMICS should follow the L-PVDOMICS Instructions for Clinical Sonographers (see Appendix 2) which will be provided to the Clinical Sonographer by the study coordinator or the study PI at the time of the exam.
- 5.4.3** **Images must be exported in RAW/NATIVE DICOM data format.**
- 5.4.4** Affix a 3-lead EKG, ensuring that a clean tracing is obtained with a tall R wave and free of muscle tremor.
- 5.4.5** For digital acquisition, obtain one capture of 4-5 *complete cardiac cycles* (normal sinus rhythm) for each required parameter. If a view is suboptimal, a new imaging plane should be attempted with controlled respiration. When possible, do not submit

sets of cardiac cycles that are preceded by or include cardiac arrhythmias.

- 5.4.6** Doppler and M-mode image acquisitions should be recorded at 50-100 mm/sec sweep speed (depending on heart rate) and the scale adjusted to ensure Doppler peaks are fully visualized.
- 5.4.7** All echo studies must be labeled on the ultrasound system monitor with the study name and subject ID. Be certain the *correct date* and time of image acquisition are displayed on the screen.

5.5 Echo Instrumentation

Echocardiographic equipment manufacturer and model varies from site to site. Each site will be required to record this information on the Data Transmittal Form. A description of this should include the brand and model of the echocardiography system used in the examination of each subject. In addition, the institution must provide documentation by a third party ensuring the equipment has been validated and calibrated. If more than one echo machine is to be used in this trial then the information above should be provided for all of the systems that will be utilized. Each machine must have the capability to record proper date, time and subject identification (ID).

Digital Capture - Typically the transthoracic images are obtained with the subject in the left lateral decubitus position during quiet respiration or end expiration. Due to the nature of the trial subjects, capturing images during end expiration (apnea) may provide the best quality images and help reduce image translation. A qualified physician or sonographer must perform all ultrasound exams. At least four to five sinus cardiac cycles of each view should be digitally captured during quiet respiration or at end expiration. *At least 10 cardiac cycles should be recorded if the subject is in atrial fibrillation.* For digital acquisition, obtain **one capture of 4-5** complete cardiac cycles (normal sinus rhythm) for each required parameter. For each view, the gain, compression, depth and image sector width should be optimized to ensure the best echocardiographic image. The selection of harmonics or fundamental frequency should depend upon which yields the best definition of structures.

Frame Rate - To ensure high frame rate image acquisition, that is, frame rates of 60 to 90 frames per second (FPS) narrow the sector width to include the entire left ventricular (LV) myocardium and reduce depth to include 1/3 of left atrium (LA) to ensure full visualization of basal LV. The same method will yield high frame rate imaging of the right ventricle (RV) from which 2D RV myocardial strain will be analyzed at the ICL.

ECG - All images should have a good quality ECG tracing maximizing the “R” wave.

Doppler and M-Mode - For spectral Doppler tracings, the sweep speed should be 50-100 mm/sec and the scale and baseline should be adjusted to make sure that the entire Doppler signal is visualized. Time and velocity calibration markers must be present on the Doppler tracing. For spectral and color Doppler, the appropriate gain level should be selected that detects flow without extraneous noise or extension of signal into adjoining tissue.

Contrast - If visualization of the left ventricular endocardial border is inadequate, then an approved contrast agent can be administered following institutional standards. ***However, the contrast enhanced imaging should only be performed after all other images and parameters are obtained.*** Doppler signals should be repeated after 2D contrast images are acquired. When Doppler signals are obtained during the contrast phase of the study, the gain must be reduced to optimize the velocity signal.

Please Note: If contrast was used to enhance the Baseline PVDOMICS ECHO visit then the Follow-up (L-PVDOMICS) ECHO visit should also include contrast to enhance the images.

Table 1: ECHO Imaging Schedule

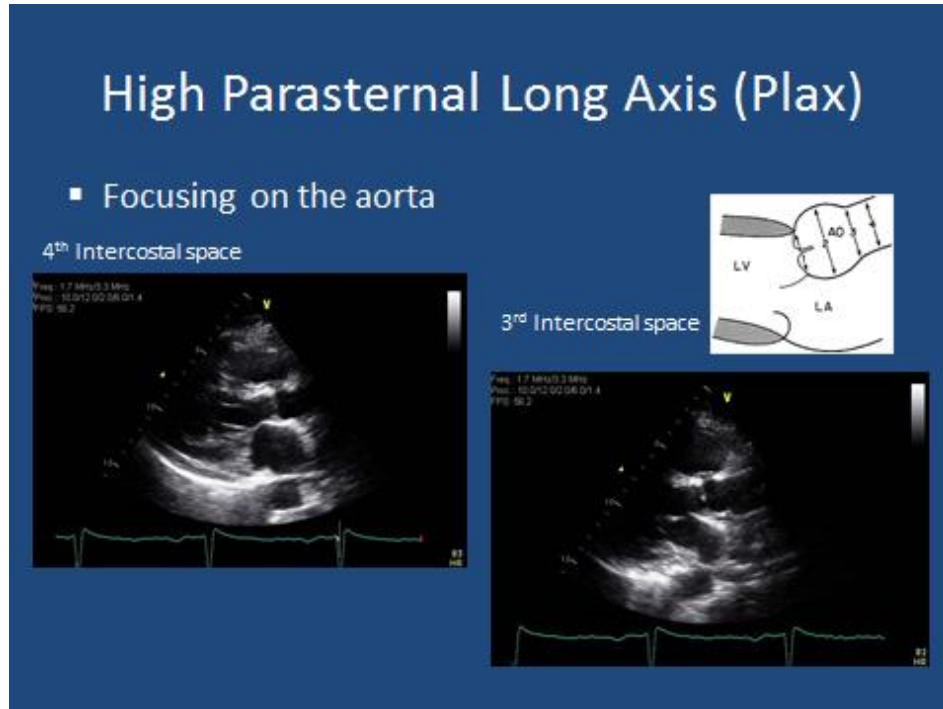
Imaging Visits	Description
Qualification	Submit a qualification echo to Core Lab before enrollment
Baseline Evaluation	Baseline Echo
Follow-up	L-PVDOMICS follow-up visit

5.6 Echo Protocol Parameters and Imaging Guidelines

The required images to obtain the measurements which will be performed at the ICL are detailed within the PVDOMICS **TRANSTHORACIC ECHO PROTOCOL** (Appendix 1)

- 5.6.1** Begin with subject in the left lateral decubitus position. Echo bed cutout should be utilized to optimize apical views.
- 5.6.2** Obtain a high PLAX view with transducer in second or third intercostal space to focus on the ascending aorta (See Figure 1)

Figure 1



- 5.6.3** Obtain views of the LVOT and Aortic valve in both the PLAX and PSAX to identify the LVOT, RVOT proximal and distal linear dimensions. (See Figure 2 and 3).

Figure 2

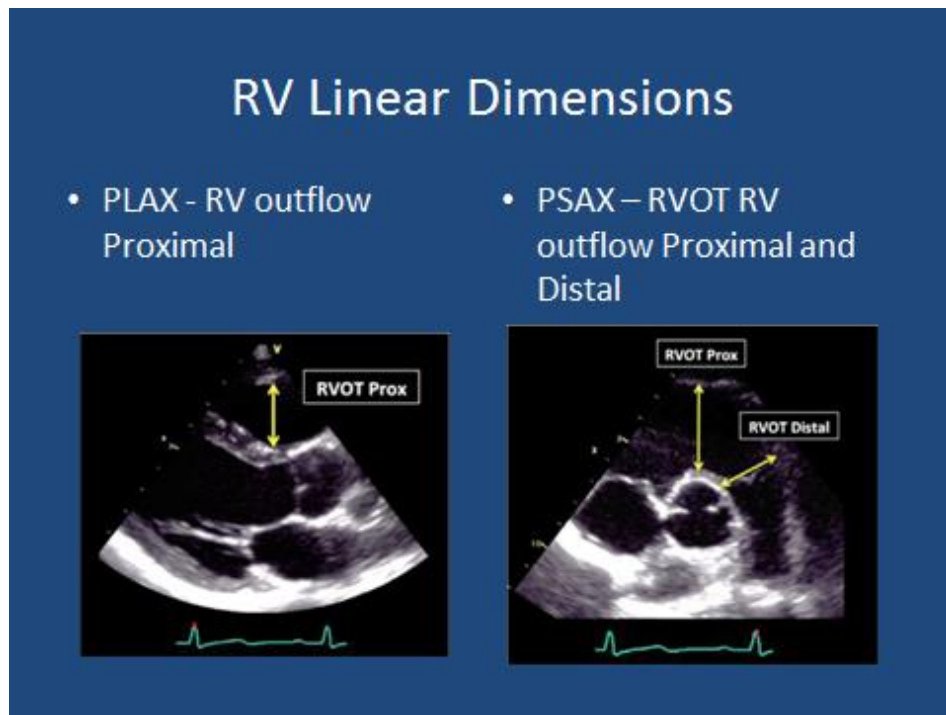
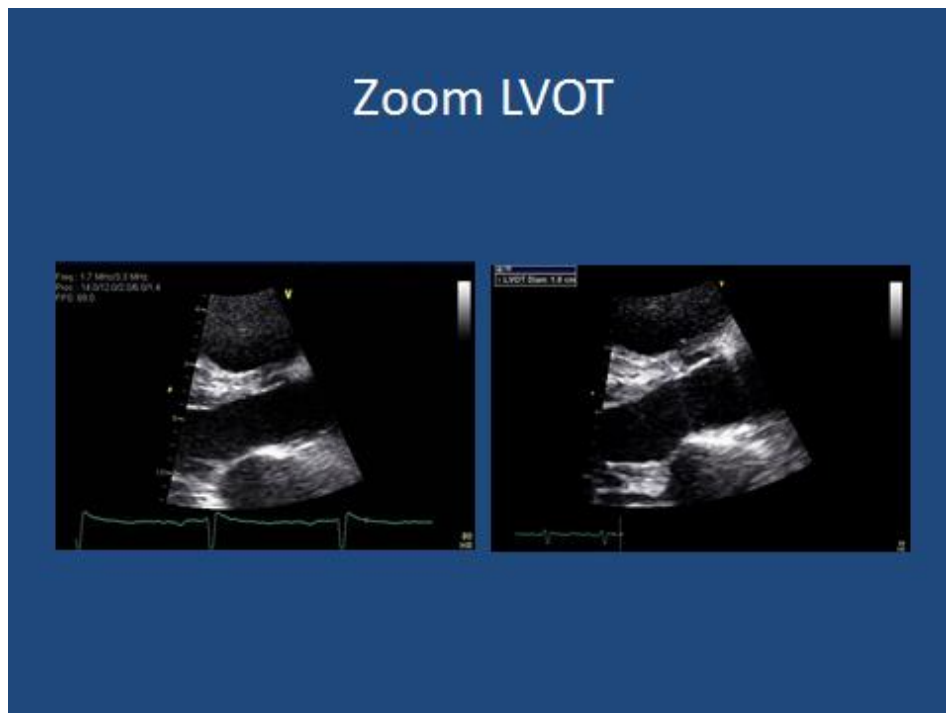
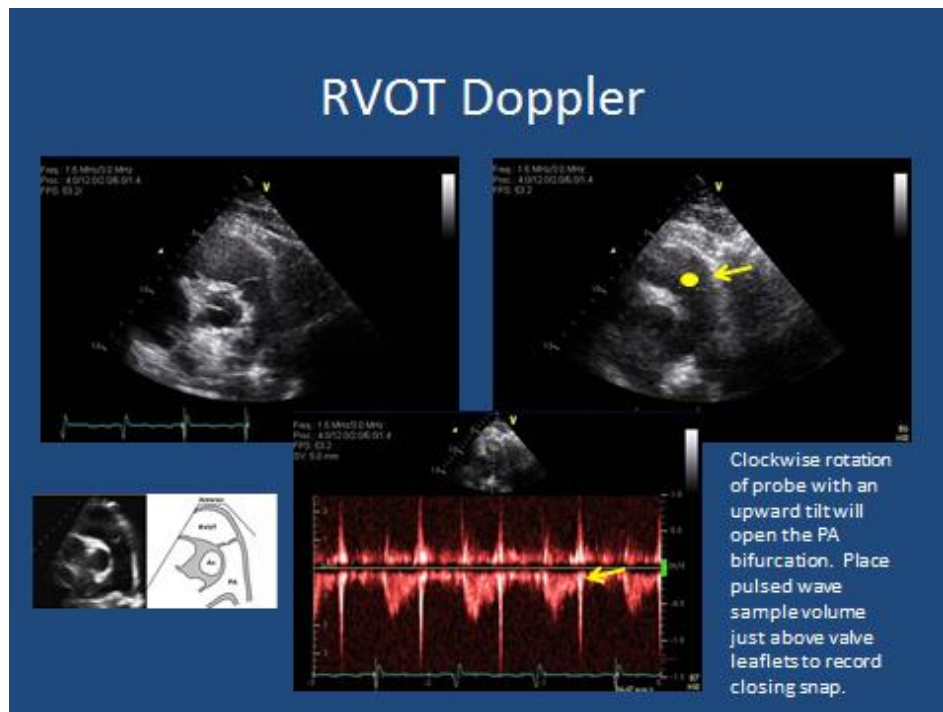


Figure 3



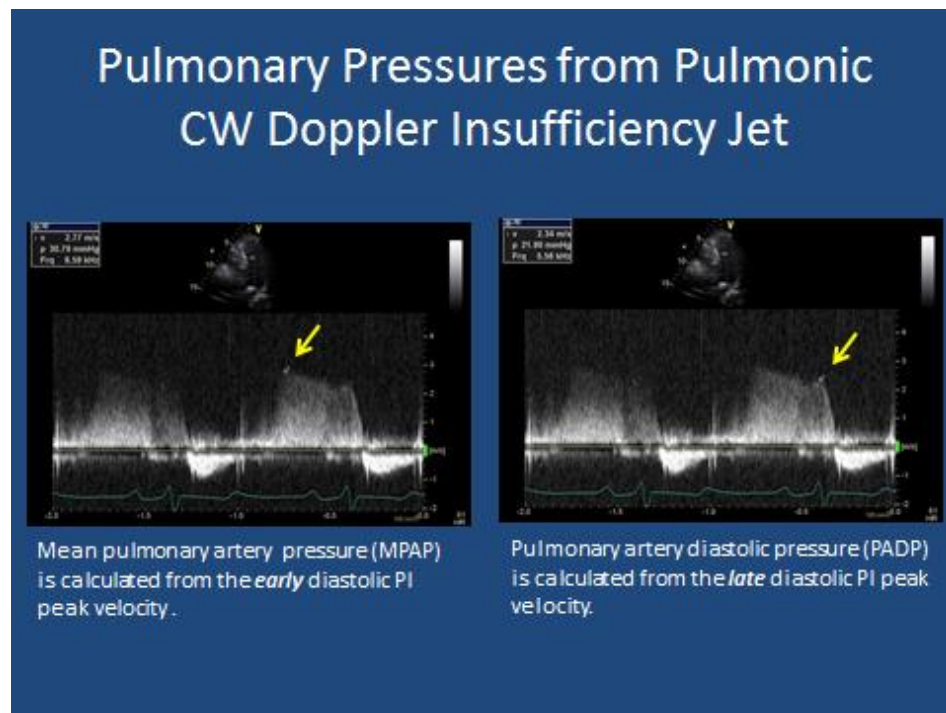
- 5.6.4** From the basal PSAX view, perform a clockwise rotation and slight anterior tilt to view the pulmonary artery and its branches. Record RVOT spectral pulsed wave (PW) Doppler with the closing snap identified. (See Figure 4)

Figure 4



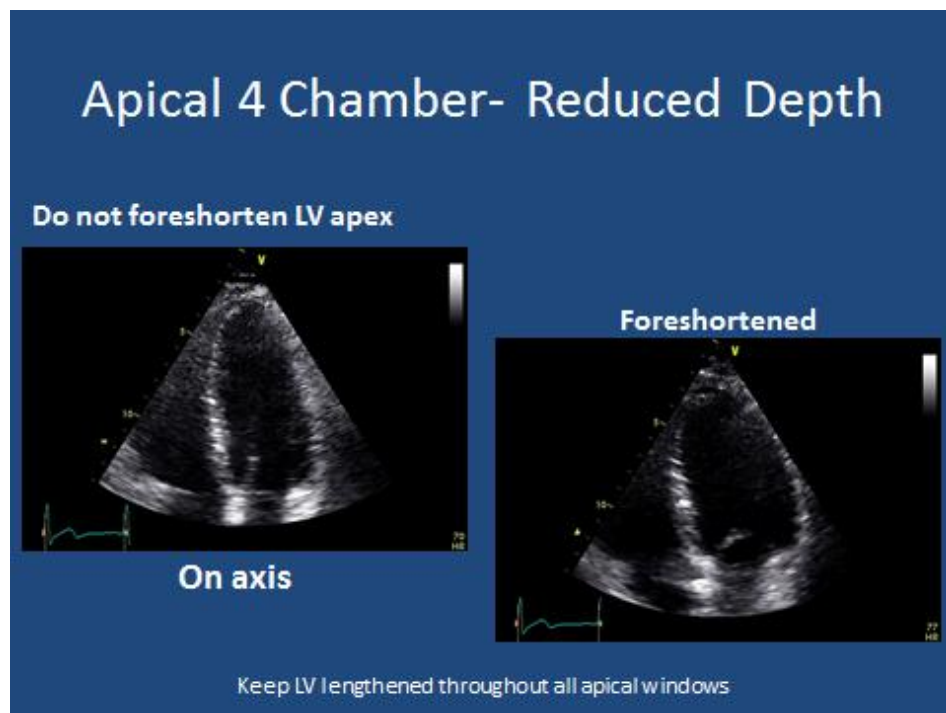
- 5.6.5** When pulmonary insufficiency is present collect Continuous Wave (CW) Doppler for additional estimation of pulmonary pressures. (See Figure 5)

Figure 5



- 5.6.6** Apical views should be acquired on axis. The apical myocardium should appear thin and pointed when in the correct plane. A foreshortened apex will appear rounded with thickened myocardium. When the image is foreshortened, apical contractility will thicken toward the mitral valve rather than toward the contralateral walls. (See Figure 6)

Figure 6



To ensure reduced depth high frame rate image acquisition (frame rate of 60 to 90 FPS), narrow the sector size to include entire LV myocardium. Remember to include 1/3 of left atrium to ensure full visualization of basal LV.

5.6.7 Right ventricular (RV) comprehensive imaging: includes the apical four-chamber, RV-focused apical four-chamber, modified apical four-chamber, left parasternal long and short-axis, left parasternal RV inflow, RV outflow and subcostal views.

5.6.8 Dedicated RV-focused apical four-chamber view: RV dimensions are best measured from an RV focused A4C view. The LV should remain long and in the center of the sector while showing the largest RV basal diameter. (See Figure 7A and 7B)

Figure 7A

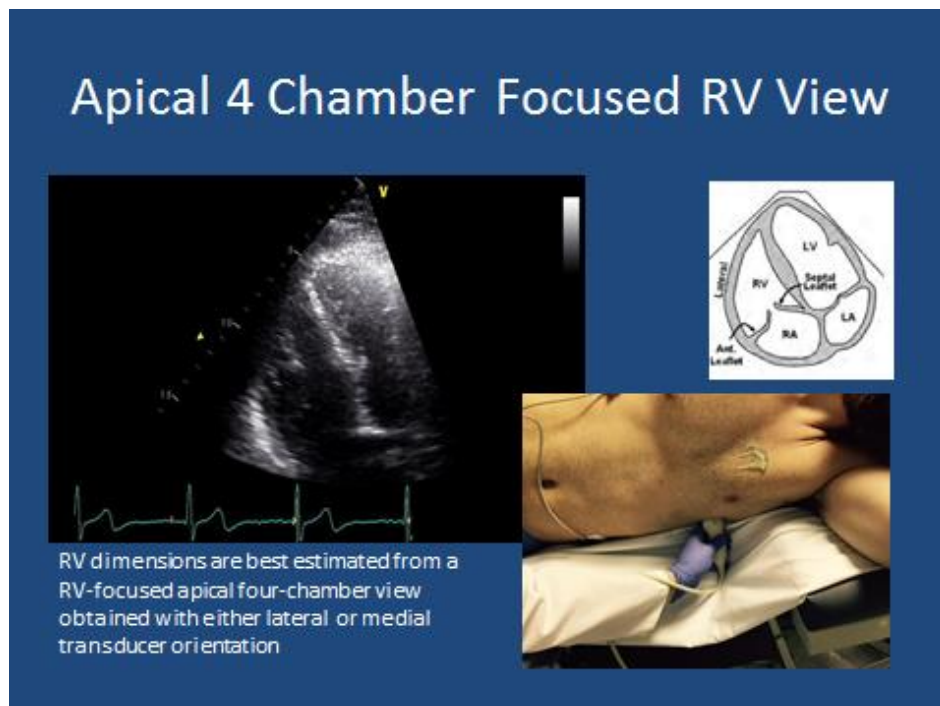
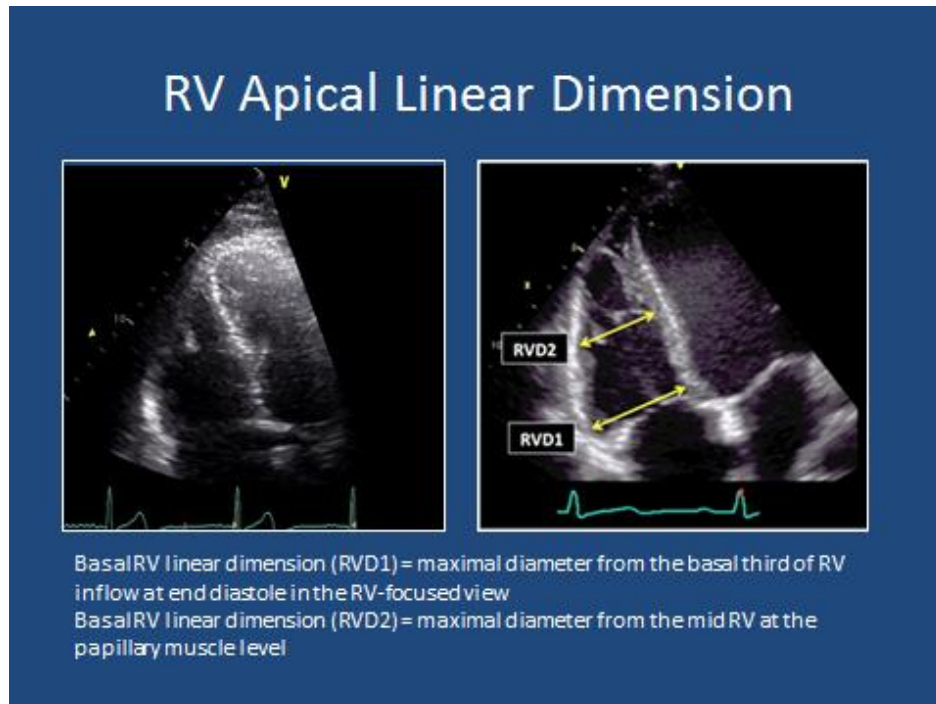


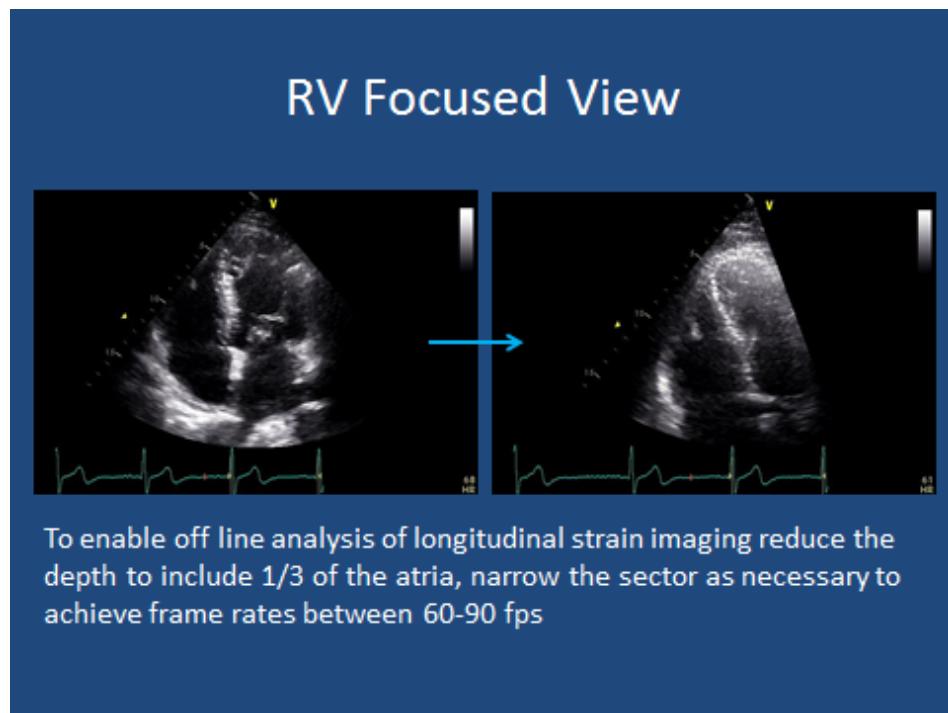
Figure 7B



5.6.9 Dedicated RV-focused apical four-chamber view:

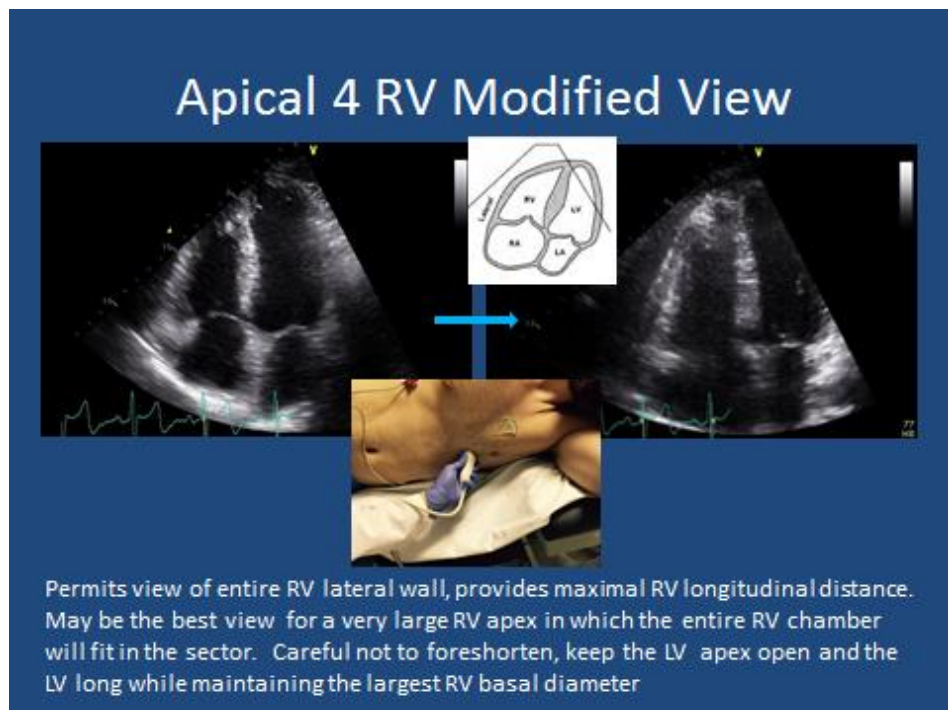
To ensure reduced depth high frame rate image acquisition (frame rate of 60 to 90 FPS) narrow the sector size to include the entire RV lateral wall myocardium. Remember to include 1/3 of right atrium to ensure full visualization of basal RV. (See figure 8)

Figure 8



5.6.10 Apical 4C RV Modified View: Permits view of the entire RV lateral wall, and provides maximal RV longitudinal distance. For a severely dilated RV this view may allow the entire RV chamber to fit within the sector. Use care not to foreshorten the RV, keeping the LV apex open and the LV elongated while maintaining the largest RV basal diameter. (See Figure 9)

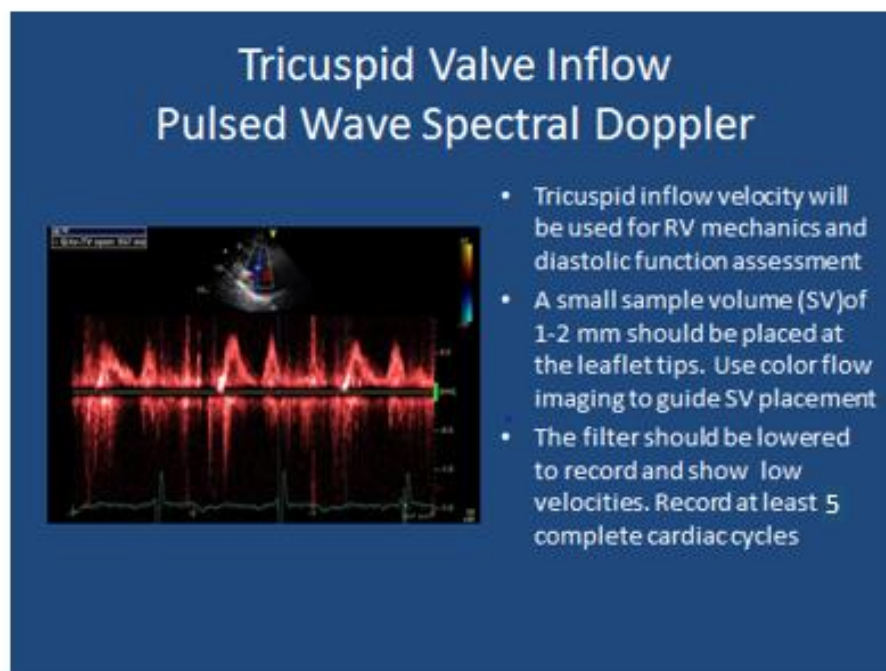
Figure 9



Note: During image acquisition maintain a clean ECG baseline free of baseline wandering and muscle tremor. Obtain a *minimum* of one capture with 4-5 complete cardiac cycles. Frame rates between 60-90 FPS.

5.6.11 Tricuspid Valve Inflow: PW Doppler will be used to evaluate RV performance. Spectral Doppler of RV inflow may be obtained from the PLAX RV inflow, PSAX at the aortic level, or apical views. Use color Doppler to guide SV placement in the center of flow close to the TV leaflet tips to achieve the best spectral waveform. Adjust filter to better identify valve opening and closing. (Figure 10)

Figure 10

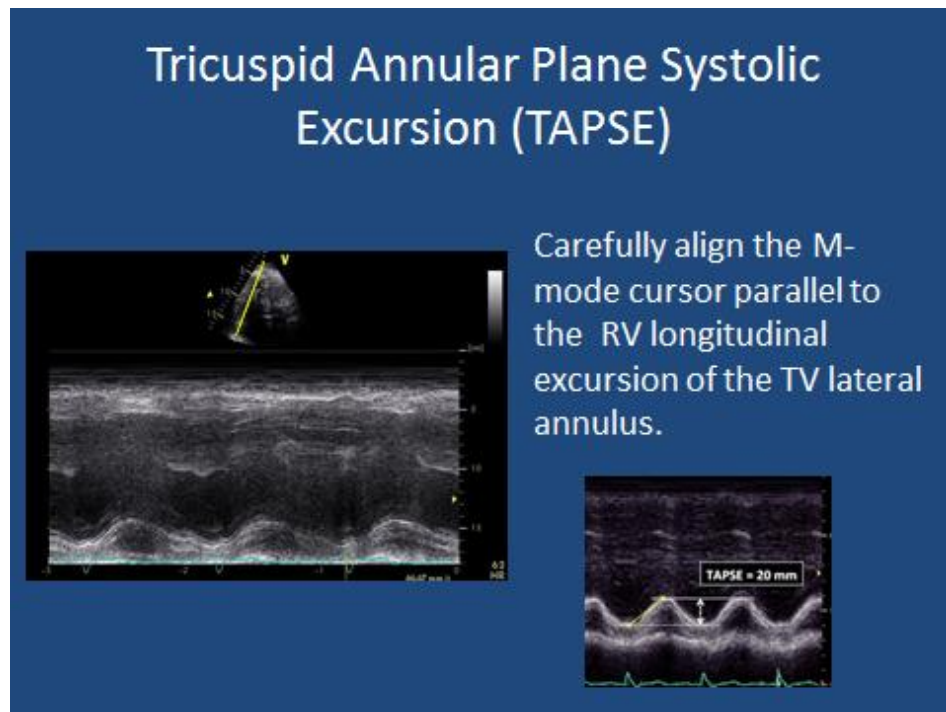


5.6.12 Tricuspid Annular Systolic Excursion (TAPSE):

Derive from M-mode analysis of the lateral tricuspid annular longitudinal movement towards the apex.

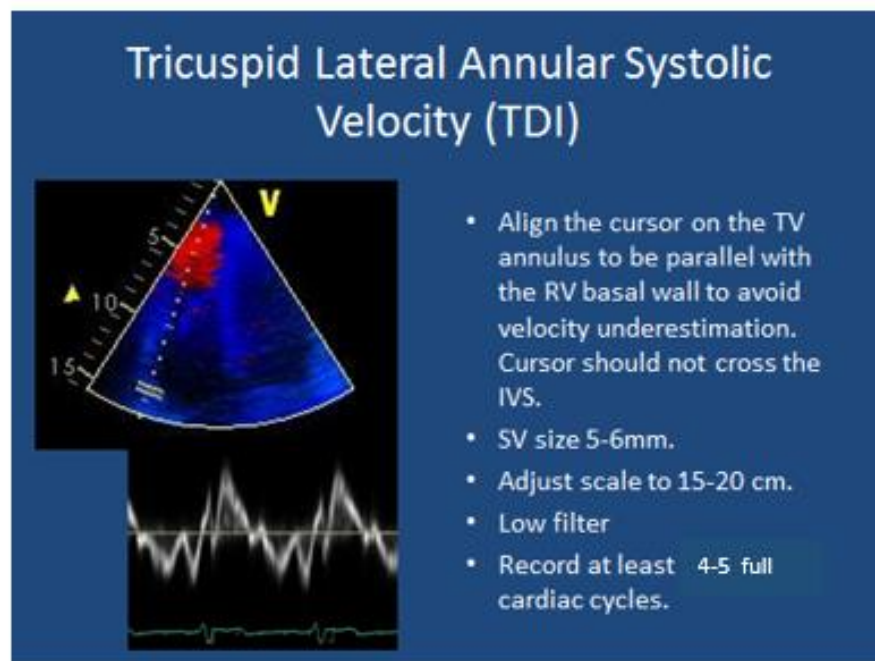
Take care to align the M-mode cursor parallel to the lateral wall. Record at 50 mm/s sweep speed. (See Figure 11)

Figure 11



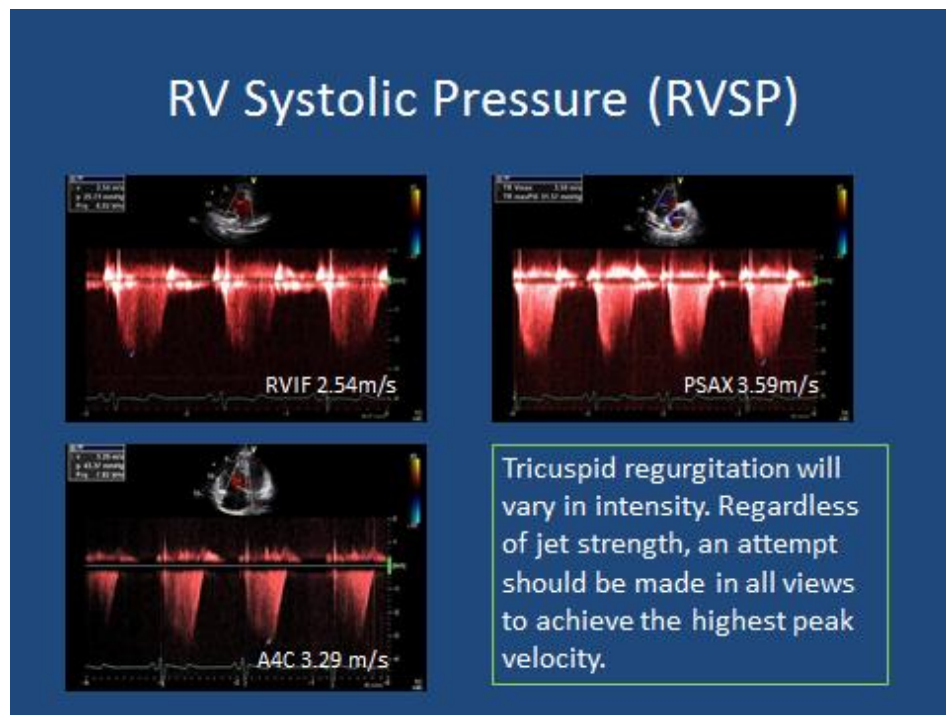
5.6.13 Tissue Doppler Imaging (TDI): TDI of the lateral TV annulus will be utilized to measure RV performance (RIMP, “s” wave and diastolic function). Align the cursor on the TV annulus to be parallel with the RV basal wall to avoid velocity underestimation. (See Figure 12)

Figure 12



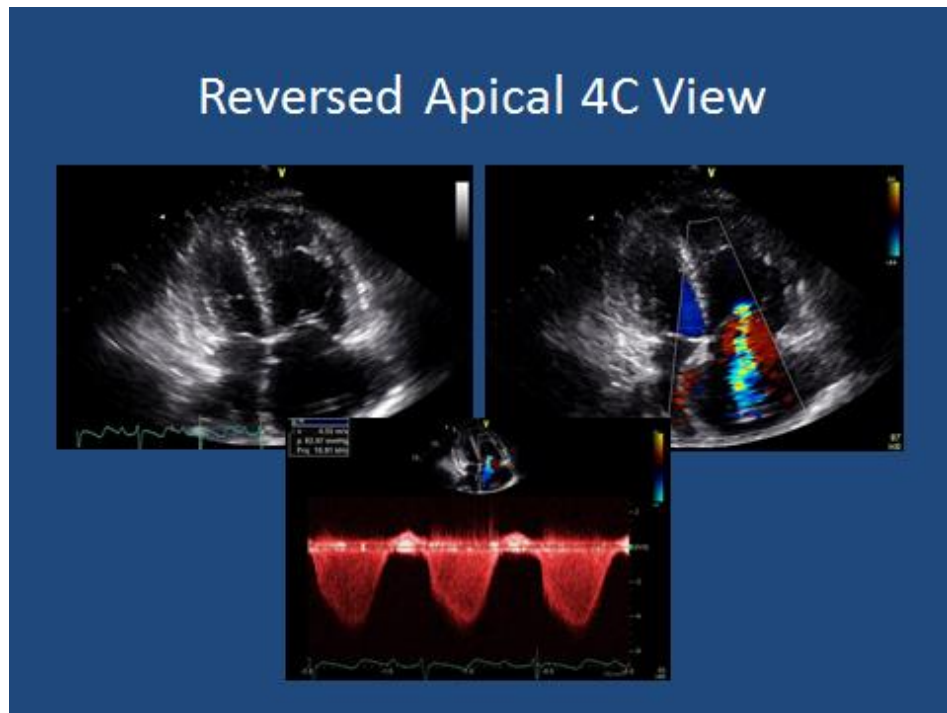
5.6.14 Continuous Wave Doppler (CW): CW Doppler of the TV regurgitation jet allows for estimation of RV systolic pulmonary artery pressures. CW Doppler may be obtained with the duplex imaging or non-imaging probe from the RV inflow, PSAX at the basal level, A4C, reversed A4C, and off axis imaging views to achieve the highest and cleanest signal. Respiratory variation may be alleviated when recorded at end expiration. (See Figure13)

Figure 13



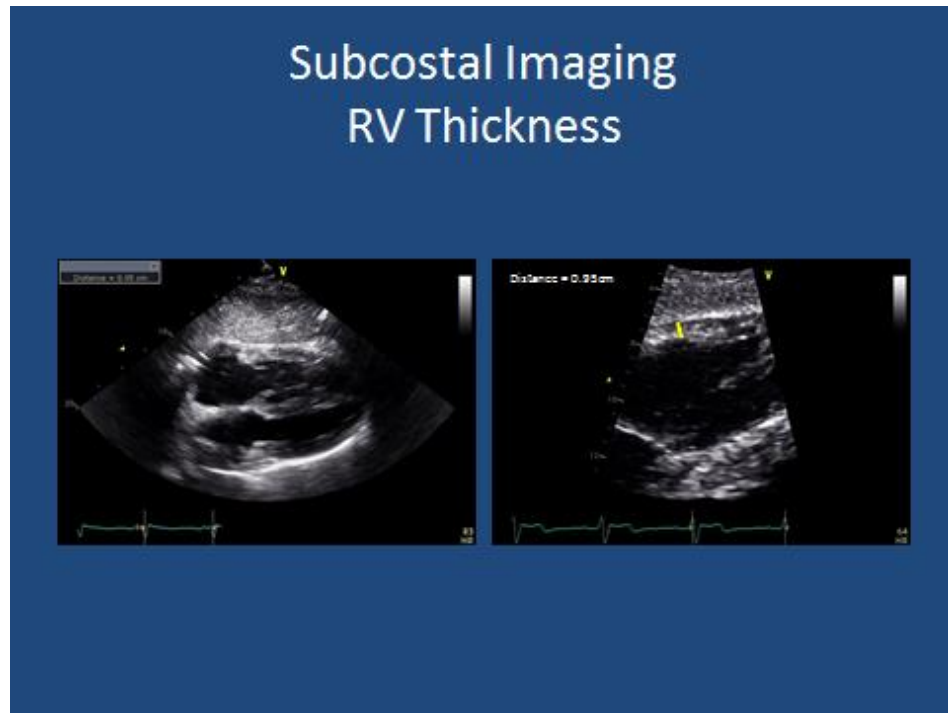
5.6.15 Reversed Apical 4C View: Optimize the image to best align the Doppler flow to achieve the highest velocities for RVSP estimation. This may be achieved with reversed imaging on select patients. (See Figure 14)

Figure 14



5.6.16 Subcostal View: Subcostal four chamber view (*frontal view*) allows for measurement of the RV free wall thickness. Zoomed imaging helps to define the true RV wall. (See Figure 15)

Figure 15



5.6.17 Subcostal View: Subcostal imaging of the four chamber view (frontal view) also allows for imaging of the atrial septum along its anterior –posterior axis from the SVC to the atrioventricular valves. Color Doppler interrogation of the IAS from the subcostal imaging windows should include the four chamber view (frontal view), with short axis clockwise rotation 90 degrees (sagittal view) (See Figure 16a, 16b and 17)

Figure 16a

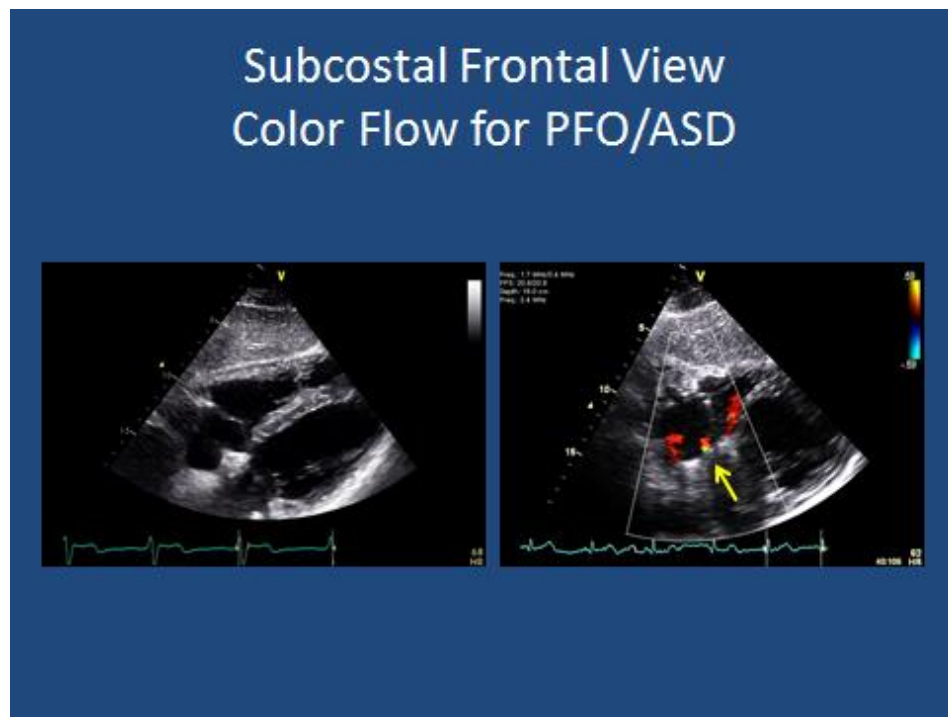


Figure 16b

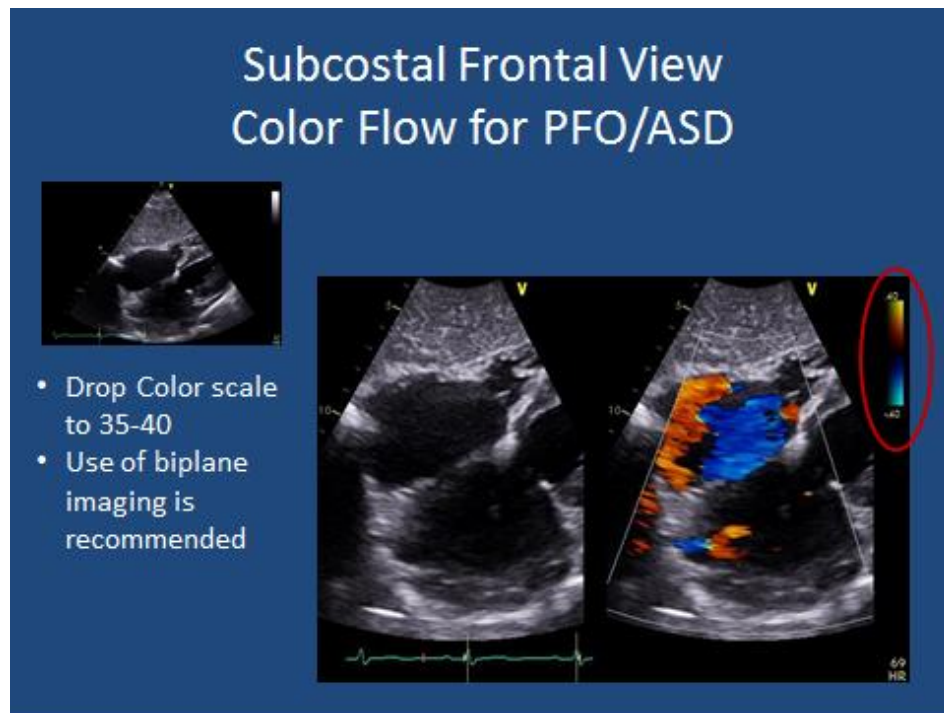
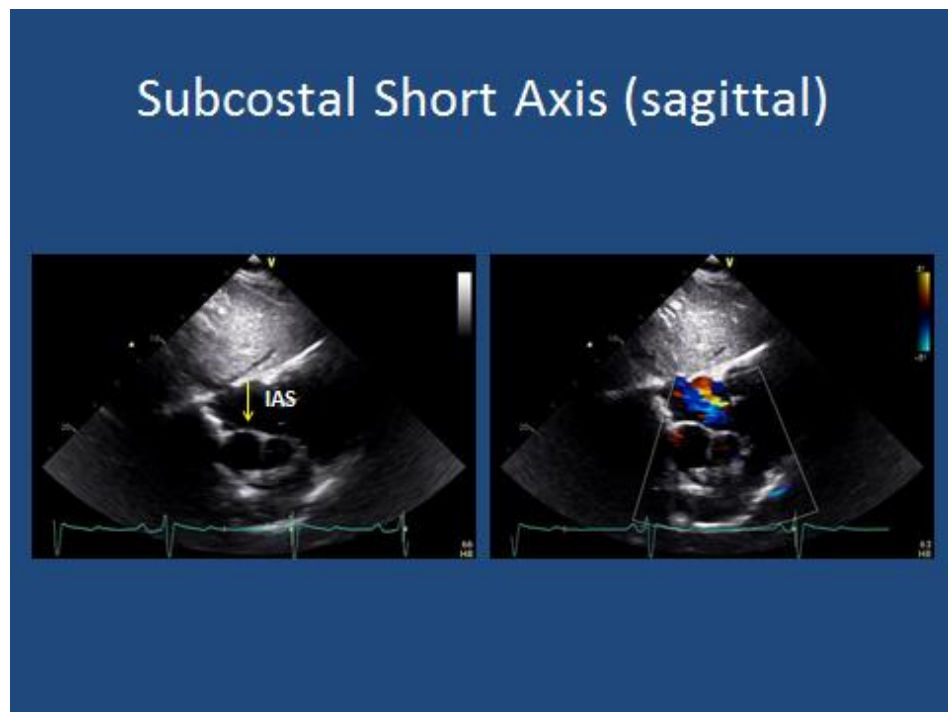


Figure 17



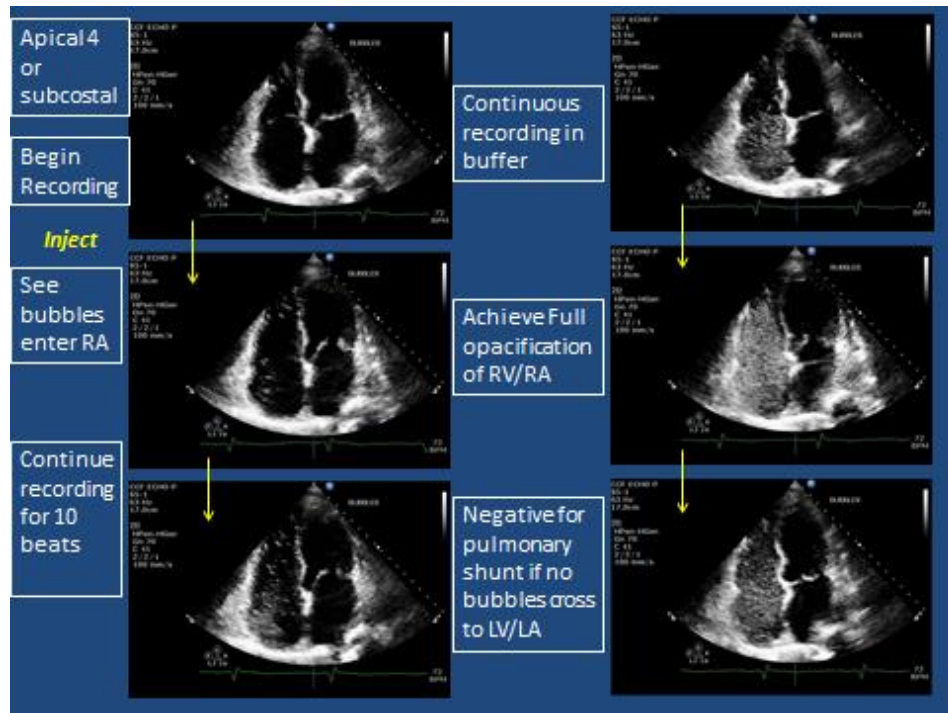
5.6.18 Bubble Study: Include assessment of the IAS for a PFO or ASD shunt with and without color flow Doppler.

Study subjects without known congenital systemic to pulmonary shunts, who did not have an agitated saline test on their prior echo, will need to undergo a peripheral IV line insertion and injection of the agitated saline (bubble study) in order to rule out intra-cardiac shunt.

When a shunt is suspected an agitated saline bubble study should be performed from the A4C view (or subcostal as necessary). Recording should be initiated prior to injection. After visualization of the bubbles into the right atrium continue recording for at least 10 beats to identify intra-cardiac or intra-pulmonary shunting. (See Figure 18) Study subjects without known congenital systemic to pulmonary shunts, who did not have an agitated saline test on their prior Echo, will need to undergo a peripheral IV line insertion and injection of the agitated saline (“bubble study”) in order to rule out intracardiac shunt.

Please Note: A bubble study is not required for Follow-up (L-PVDOMICS) ECHO exams, as one, if necessary, would have already been performed during the Baseline Evaluation exam.

Figure 18



5.6.19 Agitated Saline Technique: Attach two 10-ml syringes using a three way stopcock to an intravenous line. One syringe should be filled with 8ml physiologic saline and the other with 1 ml air, draw 1 ml of blood in to the air filled syringe. Begin mixing by reverse flushing between both syringes until an adequate amount of micro-bubbles are present. (J Am Soc Echocardiogr 2015;28:255-63.)

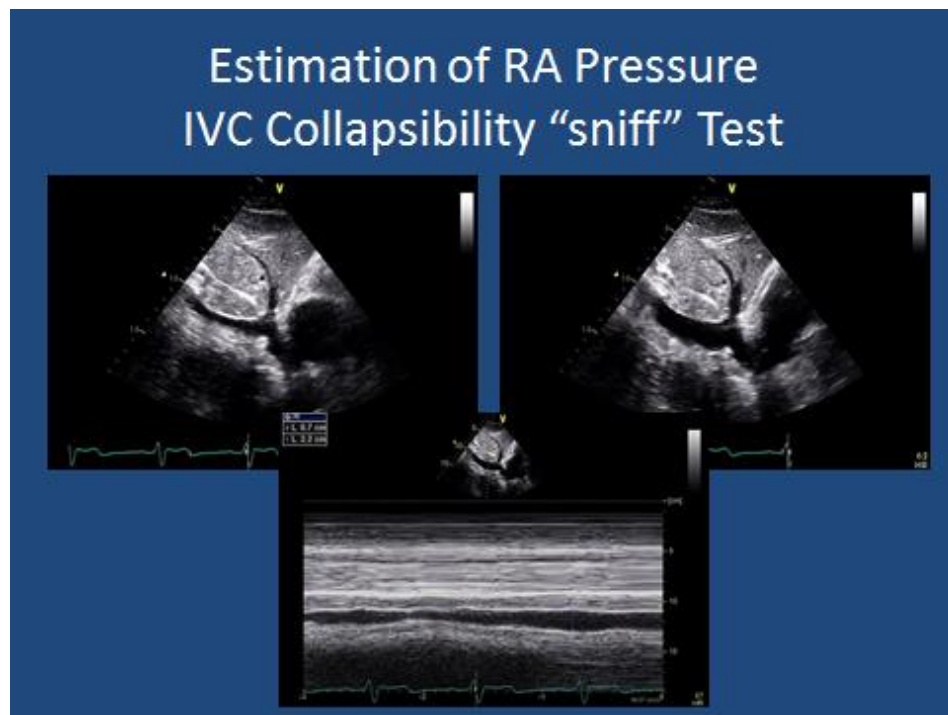
5.6.20 TR Enhancement: An agitated saline bubble study may enhance a weak or difficult to detect tricuspid regurgitation jet. Wait for jet washout to prevent blooming artifact. (See Figure 19)

Figure 19



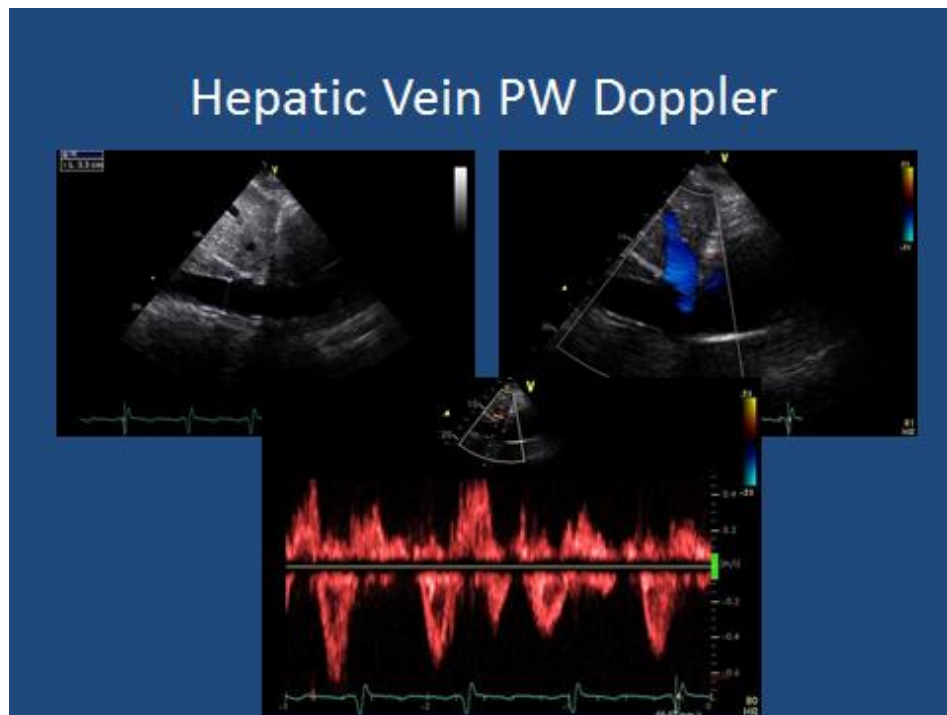
5.6.21 Subcostal View: The subcostal view permits imaging and measurement of the IVC, allowing for assessment of RA pressure with inspiratory collapsibility. Linear M-mode measurement of IVC is performed during inspiratory sniff. (See Figure 20)

Figure 20



5.6.22 Hepatic Vein Doppler: Align the PW Doppler sample volume parallel to hepatic vein (HV) flow.
(See figure 21)

Figure 21



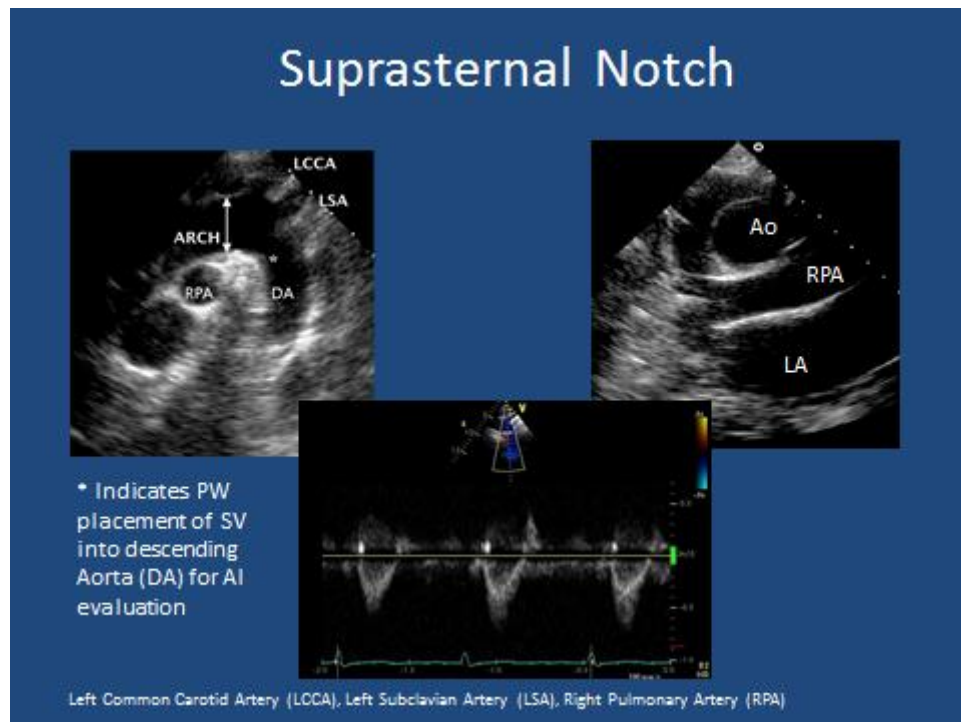
5.6.23 Abdominal Aorta: Just below the IVC the abdominal aorta can be seen in its long axis. Strong pulsations and continuous flow on CFD will help identify from the IVC. (See Figure 22)

Figure 22



5.6.24 Suprasternal Notch: PW/CW Doppler from the suprasternal notch to identify abnormal flow in valvular and congenital heart disease, PEDOFF imaging should also be considered from this window. (See Figure 23)

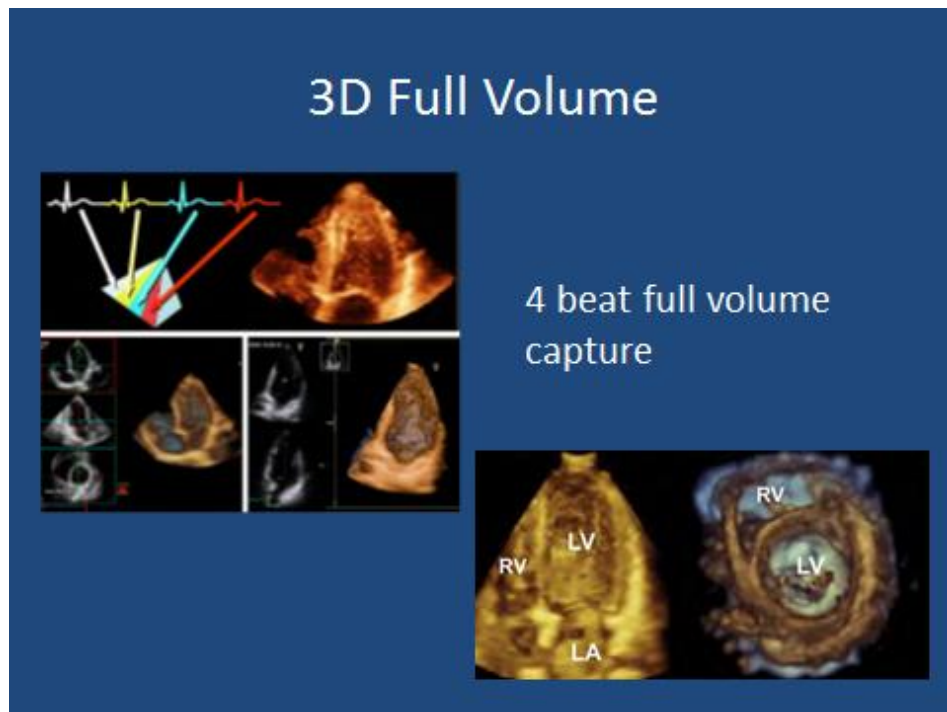
Figure 23



5.7 Part II 3D Optional Research Protocol

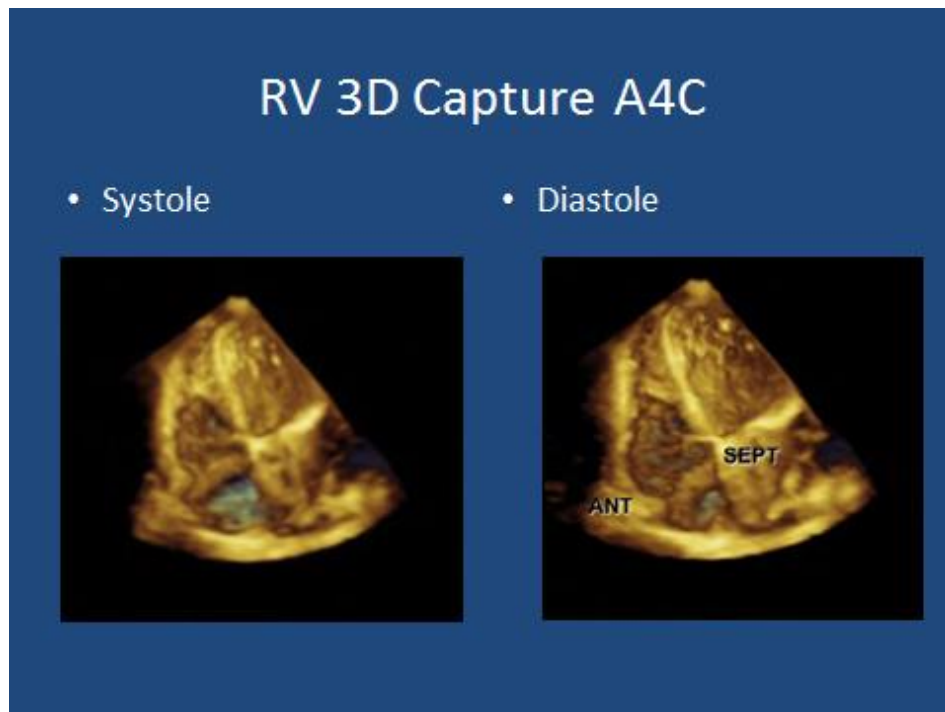
- 5.7.1 3D LV Full Volume:** ECG 4 beat full volume capture.
Check for stitching artifact and optimize gain settings.
(See Figure 24)

Figure 24



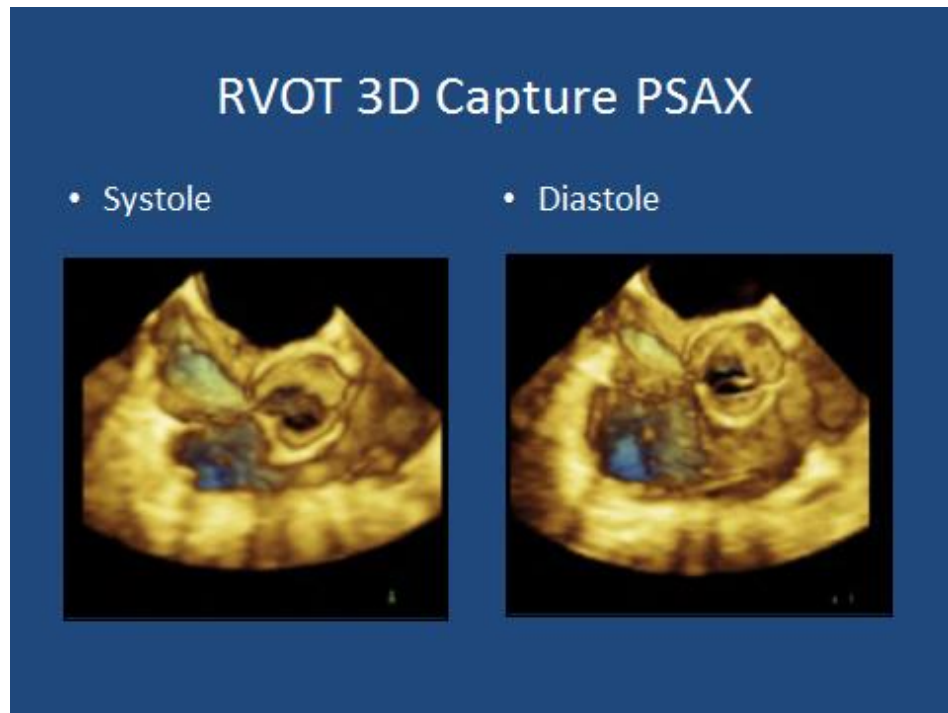
5.7.2 3D RV Full Volume: RV focused 4C view, ECG 4 beat full volume capture. Check for stitching artifact and optimize gain settings. (See Figure 25)

Figure 25



5.7.3 RVOT 3D PSAX: ECG 4 beat full volume capture.
Check for stitching artifact and optimize gain settings.
(See Figure 26)

Figure 26



5.8 (Appendix 1) PVDOMICS Transthoracic Echo Protocol**Goals:**

- General cardiac and valvular anatomy and function
- Systolic function
- Diastolic function
- Hemodynamic assessment:
 - Valvular pathology quantitation
 - Calculation of Qp and Qs
 - CVP and PAP estimate-Tricuspid valve regurgitation peak velocity

PART 1: Mandatory (clinical protocol)

- All images should be collected in one 4-5 beat loop for a total of 4-5 complete cardiac cycles
- Collect images during breath hold for best image optimization
- Agitated saline (with a few drops of blood) may be necessary to assure peak TR velocity jet is achieved
- Contrast enhancement when clinically indicated

Table 1: Echo Protocol Imaging Acquisition

PLAX	• Increased depth field of view (FOV) • Decreased depth FOV • Focus on LVOT with and without zoom mode (include annulus, sinus and STJ) • Move up an intercostal space to better visualize proximal ascending aorta • M-Mode AO Root • M-Mode MV • M-Mode LV • Color Doppler on Aortic Valve (AV) • Color Doppler on Mitral Valve (MV)
-------------	--

RV Inflow	• 2D RV Inflow • Color Doppler across valve • CW Doppler across valve- <i>Please attempt and record, even if incomplete signal or insufficient TR</i>
PSAX	• 2D view at 3 valve level, PV, AV, TV • Zoom the AV to visualize all leaflets • Color AV • Optimize 2D image of RVOT at PV level • Color across PV level • CW Doppler of PV • PW Doppler across RVOT proximal to valve tips, SV 3-4mm • Standard 2D of PA include bifurcation if possible-may need to move to higher ICS • Color across TV • CW of TV • 2D view at the MV level • Color across MV • 2D view at the basal, mid and apical LV levels (<i>collected at frame rates between 60-90 FPS</i>)
Apical 4CH	• Apical 4 chamber view at increased depth (including entire atrial borders) • Apical 4 chamber view at increased depth (including entire atrial borders) <i>collected at frame rates between 60-90 fps.</i> • Dedicated 2D LV Image (reduced depth to focus on LV) • Dedicated 2D LV Image (reduced depth to focus on LV) <i>collected at frame rates between 60-90 FPS</i> • Color across MV, CW Doppler across MV • PW MV inflow, SV at 2.0 mm at leaflet tips • PW MV inflow, SV at 2.0 mm at mitral annular level • PW Doppler Pulmonary Veins (SV 3-4 mm) • MV annular tissue Doppler (septal and lateral mitral annuli) (SV 5-6 mm) • PW TV inflow (held apnea) , CW across TV • Dedicated RV 2D Image (reduced depth) • Dedicated RV 2D Image (reduced depth) <i>frame rates between 60-90 FPS</i> • TV annular tissue Doppler (lateral wall) (SV 5-6 mm) • TAPSE (align M-mode cursor parallel to RV lateral wall) • Zoom, Color and Doppler IAS, assess for ASD flow

	• Zoom, Color and Doppler IVS (down to apex) assess for VSD flow
Apical 5CH	• Apical 5 chamber view at increased depth • Color Doppler LVOT • PW Doppler LVOT • Perform valsalva if systolic anterior motion of the MV is suspected • CW Doppler across AV (parallel to flow) • For suspected/known AS, obtain CW Doppler peak systolic velocities from multiple transducer positions (including PEDOFF imaging)
Apical 2CH	• Apical 2 chamber view at increased depth (including entire atrial borders) • Apical 2 chamber view at increased depth (including entire atrial borders) collected at frame rates between 60-90 FPS • Dedicated 2D LV Image (decreased depth to focus on LV) • Dedicated 2D LV Image (decreased depth to focus on LV) collected at frame rates between 60-90 FPS • Color Doppler MV • CW Doppler if indicated
Apical 3CH (Apical Long)	• Apical 3 chamber view at increased depth (including entire atrial borders) • Apical 3 chamber view at increased depth (including entire atrial borders) collected at frame rates between 60-90 FPS • Dedicated 2D LV Image (decreased depth to focus on LV) • Dedicated 2D LV Image (decreased depth to focus on LV) collected at frame rates between 60-90 FPS • Color across MV • Color across AV • PW Doppler of LVOT if indicated
Subcostal	• 2D 4 chamber image • Zoom on RV free wall for RV thickness • Zoom on IAS • Color, lower color scale to 35-40 cm/sec, then PW Doppler if shunt is suspected followed by CW Doppler • 2D image of IVC during normal respiration • M-mode IVC to document respiratory collapse with “sniff”

	• Color Doppler IVC • Color and PW Doppler on hepatic vein • Visualize abdominal aorta, then color and PW Doppler
Suprasternal Notch	• 2D Image of aortic arch • Color Doppler of aortic arch • PW Doppler • 2D Continuous Wave Doppler, PEDOFF if indicated
Agitated Saline	• Bubble study at rest • Bubble study with valsalva for suspicion of PFO or pulmonary shunt • May be used to enhance an insufficient TR jet • No bubble study required for Follow-up studies (L-PVDOMICS)
Contrast Enhancement for LVO and EBD	• Consider echo contrast study for LV/RV opacification if endocardial definition is sub-optimal per ASE guidelines • Obtain all standard views without contrast prior to performing contrast imaging. • Additionally contrast may be used for Doppler enhancement

Note: If contrast was administered on the initial study, please use contrast on all follow up studies.

Part II Optional Research Protocol**1. 3D Full volume LV and RV dataset (4 beat acquisition is preferable) for the 3D LV and RV volume, function and strain measurements****Table 2 3D Protocol Imaging Acquisition**

3DLV	• Full volume PLAX of LV • Full volume apical 4 of LV
3DRV	• Full Volume Apical 4 of RV • Full Volume RVOT

Above images should be obtained using best possible image optimization algorithms, including automated options offered by the vendors

Best results are expected in patients with regular RR intervals and optimal Echo windows. Optimize frame rates.

5.9 Appendix 2**Longitudinal PVDOMICS (L-PVDOMICS) Clinical Echocardiography Sonographer Guide of Additional Variables to be captured.**

This is a request by Dr. _____ the PI from your institution. This patient is enrolled in the L-PVDOMICS research study with a grant from the National Institutes of Health to study pulmonary vascular disease. We are asking your help to collect a few additional variables during your normal clinical echo exam. **Please change your ECG capture to collect a three beat loop.**

Additional PVDOMICS Variables:

1. PLAX:
 - a. 2D RV Inflow view
 - b. With color Doppler across TV valve
 - c. CW Doppler for TR - Please show attempt, even if incomplete signal or insufficient jet
 - d. PW Doppler of TV inflow at leaflet tips, SV 1-2mm
2. PSAX:
 - a. 2D image of RVOT at PV level for linear measure of RVOT
 - b. Further rotation to include image of the PA bifurcation
 - c. Color Doppler across PV
 - d. PW Doppler across RVOT proximal to valve tips, SV3- 4mm
 - e. CW if PI present
3. Apical 4C dedicated RV view: **Adjust frame rates to 60-80 fps, collect(2) 3 beat loops**
 - a. Focused RV view at reduced depth (for strain and area analysis)
 - i. Modified view may be substituted if better quality
 - b. TAPSE, run m-Mode parallel to RV free wall while perpendicular to TV annulus
 - c. TV annular Tissue Doppler (lateral annulus)(SV 5-6)(S')
 - d. PW Doppler of TV inflow at leaflet tips, SV 1-2mm
 - e. CW for peak TRV
4. Apical Views: **Adjust frame rates to 60-80 fps, collect(2) 3 beat loops**
 - a. Collect A4C LV at reduced depth , three beat loop (for strain analysis)
 - b. Collect A2C LV at reduced depth , three beat loop
 - c. Collect A3C LV at reduced depth , three beat loop

We sincerely appreciate your dedication to patient care in collecting these extra parameters. Your PVDOMICS study coordinator will make arrangements to have the study copied to disc. If you have any questions or have information to share about this study please contact: _____ at _____.

Thank you!

6 Echo Scan Submission Procedure

6.1 Echo Scan Submission Instructions

- 6.1.1 Please observe all HIPAA rules and regulations.** For the purpose of confidentiality, all references to a specific subject must be made by the Subject ID Number. Please do not use subject names or any personal information to label the exam.
- 6.1.2** Before the sonographer begins an echo study, secure the study assigned Subject ID from the site coordinator. Enter the Subject ID in the echo system's ID field designated LAST NAME as PVD and designated FIRST NAME left blank and designated Medical Record Number (MRN) with the two digit site and four digit subject number followed by two digit alpha as assigned by the DCC. **Ex: 110001-AB.**(See example section 7.2.8)
- 6.1.3** Exams that need to be labeled under patient identifiers need to be anonymized before sending to the Core Lab through AG Mednet. The instructions below show how to hide patient identifiers on the imaging screen for Philips, GE and Siemens ultrasound systems. (See anonymizing instructions section 7.1.3.1)
- 6.1.4** L-PVDOMICS exams performed clinically will likely have patient Protected Health Information. Exams should be labelled correctly in the AG Mednet portal as in 6.1.2 described above. Sites are responsible for ensuring all clinically collected ECHOs submitted to the Imaging Core Lab are fully de-identified using the AG Mednet pixel de-identification tool to redact all Protected Health Information (PHI) before pushing the ECHO. ECHOs received at ICL containing PHI will be rejected with site notification via a query and must be resubmitted after complete de-identification of all PHI.

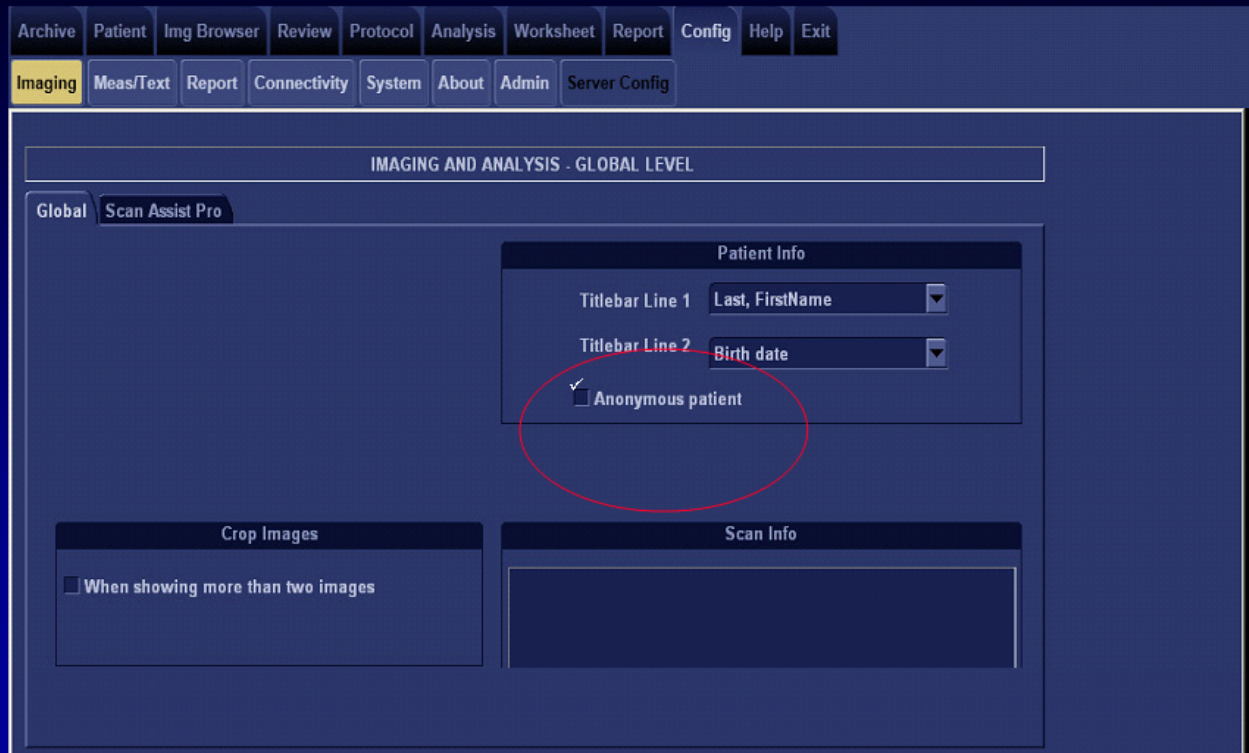
6.1.4.1 Anonymization Instructions for Philips Ultrasound Systems

- Instructions for anonymizing a study:
 - Select “Name ID” from the top row of the ultrasound machine keyboard



6.1.4.2 Anonymization Instructions for GE Ultrasound Systems

- Instructions for anonymizing a study:
 - Config---Imaging---☒ Anonymous patient



6.1.4.3 Anonymization Instructions for Siemens System

- Instructions for anonymizing Siemens System :
 - Before beginning exam select “Hide Name” from the top row of the ultrasound machine keyboard



- 6.1.5** Acquire images per study protocol keeping subject positioning and plane orientations optimal throughout the study.
- 6.1.6** Download the echo in RAW data format to DVD (see section 7.4 for archiving instructions)
- 6.1.7** Follow AG Mednet instructions (see section 10) for digital transmission to the Imaging Core Lab.
- 6.1.8** Make one copy of each echo study per DVD and upload from this media to the AG Mednet website location. Retain this copy of the study with site records.
- 6.1.9** Please copy only one echo study to a disc.

6.2 Transmitting Echo Images to Imaging Core Lab

- 6.2.1 AG Mednet is a web-based diagnostic imaging network, which enables sites to send diagnostic image exams electronically and securely to the Imaging Core Lab. AG Mednet will provide tools and training to de-identify exams, complete transmittal forms electronically and complete other trial specific tasks.
- 6.2.2 The DCC has provided an Echocardiogram (ECHO) Transmittal Form # 250 (see example 7.2.8) to be completed by the study qualified sonographer and submitted to the study coordinator (or designee) for use in completing the electronic transmittal information prior to uploading the study to AG Mednet.
- 6.2.3 No fields may be left blank. You will be unable to upload images to AG Mednet until **all required fields on the electronic transmittal form are complete**. If you have questions about completing the electronic Echo Transmittal Form, refer to the AG Mednet User Guide or contact AG Mednet.
- 6.2.4 Errors on the Echo Transmittal Form should be crossed out with a single line, not obliterated, with the correction inserted, and the change initialed and dated.
- 6.2.5 Never use correction fluid/tape, erase or obliterate information.
- 6.2.6 If there are questions about completing the hardcopy Echo Form # 250, refer to example 7.2.8, or contact an Imaging Core Lab team member for assistance.
- 6.2.7 An Imaging Core Lab Study Team Contact Information sheet is located in the front of this manual for reference.

It is important to transfer image exams to the core lab as they are collected. This practice will prevent a backlog of analysis at the core lab. Please, no bulk sending.

6.2.8 Echo form # 250

Revision of 01/15/2016

Form #250
Page 1 of 2

PVDOMICS Study Echocardiogram (ECHO) Transmittal Form #250

Instructions: This form is used for both uploading data to AG Mednet for the Imaging Core Lab (ICL) and uploading data to the DCC database. Review MOP Chapter 60 prior to testing.

Study Coordinator Completes Questions 1-5.

1. Identification Number 110001

2. Alphacode AB

3. Date of ECHO (mm/dd/yyyy) 12012015

4. Gender (0=Male, 1=Female)..... 0
5. Visit Type 2
1=Qualification, 2=Baseline, 3=Follow-up

Sonographer Completes Questions 6-12.

6. a. Was blood pressure measured at the beginning of ECHO 1
0=No, BP measures not collected, 1=Yes
- b. If yes, blood pressure measures (mmHg) (systolic/diastolic) 110 / 070
7. Agitated saline contrast (0=No, 1=Yes) 0
8. a. Contrast enhancement for left ventricular opacification (LVO) 1
0=No, contrast agent not collected, 1=Yes
- b. If yes, name of contrast agent used 3
1=Optison
2=Definity
3=Lumason
8=Other, specify _____
- c. Total contrast volume (mL) 02

Comments Technically difficult study.

9. a. Username of ECHO Sonographer who performed echocardiogram..... SMITHCA
- b. Name of ECHO Sonographer who performed ECHO Cathy Smith

Revision of 01/15/2016 Pt ID 110001 ACAB Date of ECHO 12/01/2015 Form #250
Page 2 of 2

Ultrasound Equipment Used for this ECHO

10. Ultrasound manufacturer name Philips
11. Model # IE-33
12. Serial # 12345

Transmission Details for ECHO to AG Mednet – Coordinator completes Q13 through end of form.

13. Method of transmission (1=Digital transfer, 8=Other, specify.....) ... 1
14. Date ECHO file transmitted (mm/dd/yyyy) 12/01/2015
(Date file transmitted must be greater or equal to the date the form is completed.)

200. Date this form completed (mm/dd/yyyy) 12/01/2015

201. Username of person completing/reviewing completeness of this form SMITHCA

Clinical Center Use Only

Date Form Entered (mm/dd/yyyy) ____/____/____

Username of person entering this form _____

6.3 Archival Instructions

- 6.3.1 Complete the Echo Data Worksheet carefully and completely while scanning. This is treated as a source document and may be subject to inspection by regulatory authorities.
- 6.3.2 Archive the echo study to digital media (DVD) immediately from the ultrasound system that was used to acquire the images (before archiving to Picture Archiving and Communication System [PACS]). **Please Note: Image files not stored in RAW/NATIVE DICOM format cannot be analyzed completely.**

6.4 GE System Specific Instructions for Archive Export (RAW DICOM Data)

- 6.4.1 Archive all studies immediately after image acquisition.
- 6.4.2 Select Archive screen and log in as administrator (ADM). Password should be: ulsadm (all lower case)

SEARCH / CREATE PATIENT More

Last Name Patient ID
First Name Birthdate (mm/dd/yyyy) Age
Category Sex ☐ female ☒ male

Patient List 1 records fetched of total 36 (☐ Show All)

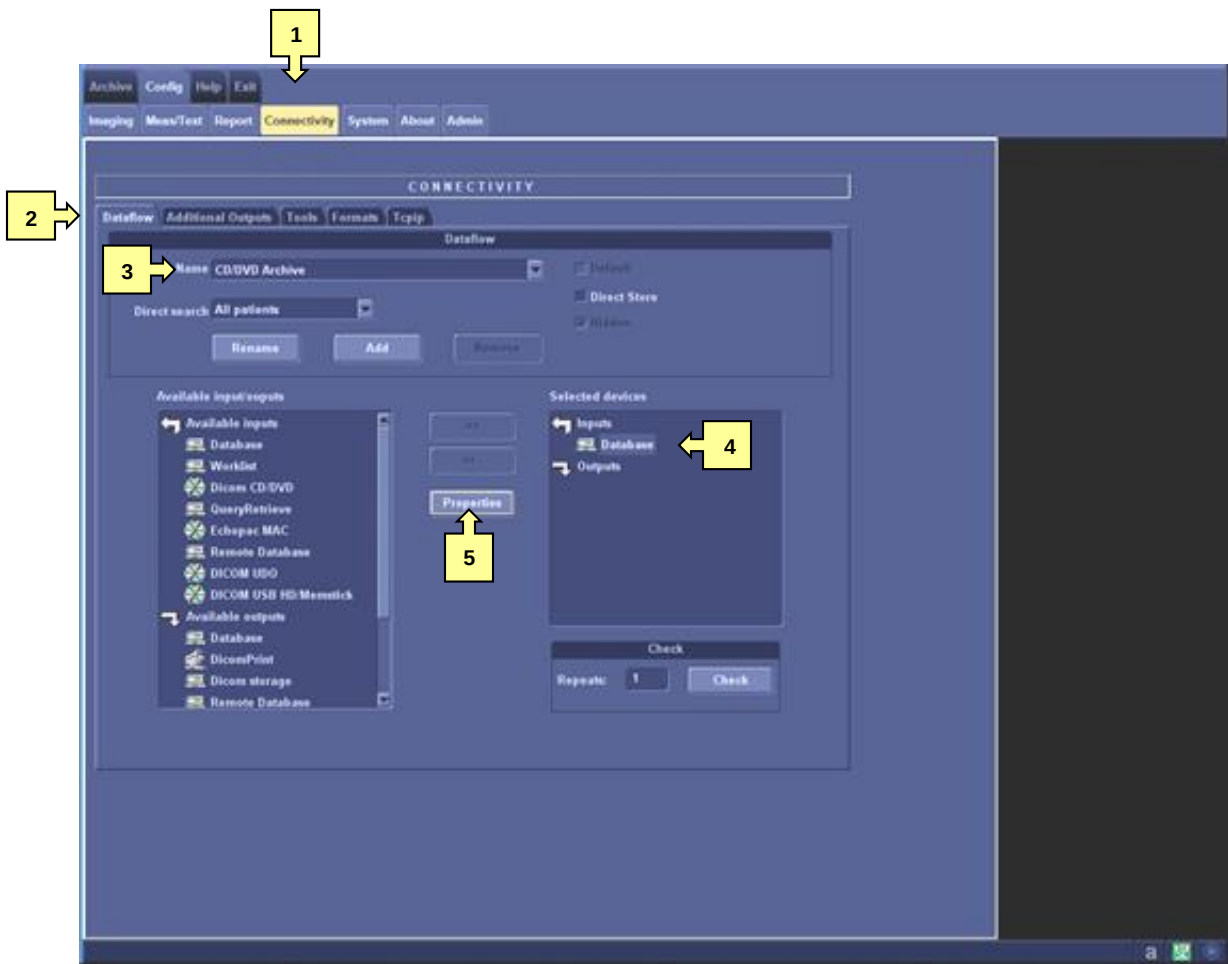
Last Name	First Name	Patient ID	Birthdate	Exam Date	img	Str	Rep	Size	Code
PVD		110001-AB		12/01/2015					

Dataflow Operator

CREATE PATIENT SELECT PATIENT CLEAR SEARCH EXPORT IMPORT More

6.4.3 System Setup

- 1) In the **Configuration** screen, select “**Connectivity**.”
- 2) On the Connectivity screen, choose “**Dataflow**” from the top row of options.
- 3) Select **CD/DVD Archive** from the drop down menu in the “**Name**” section.
- 4) Highlight **Database** in the “**Selected devices**” region; then the Properties button will appear.
- 5) Activate the **Properties button**.



- 6.4.4** After activating the Properties button, a new window will appear. Check ☒ “**Allow Raw Data**,” and “**Allow Multiframe**”; then change the “**Max Framerate**” to **Full**.

The screenshot shows the 'Database properties' dialog box. The 'Image Settings' section is highlighted with red circles around the 'Allow Raw Data' and 'Allow Multiframe' checkboxes, and the 'Max Framerate' dropdown menu which is set to 'Full'.

Database properties

IP-address: (MyComputer) 0.0.0.0

Name: CD/DVD Archive

Db name: JJ05.402A.51015-CDRW

File destination

\\127.0.0.1\CDRW ☒ Removable

Image Settings

☒ Allow Raw Data ☐ Raw Compr. ☒ Allow Multiframe

Max Framerate: Full Compression: Jpeg Quality %: 90

Retry

Max #: 2

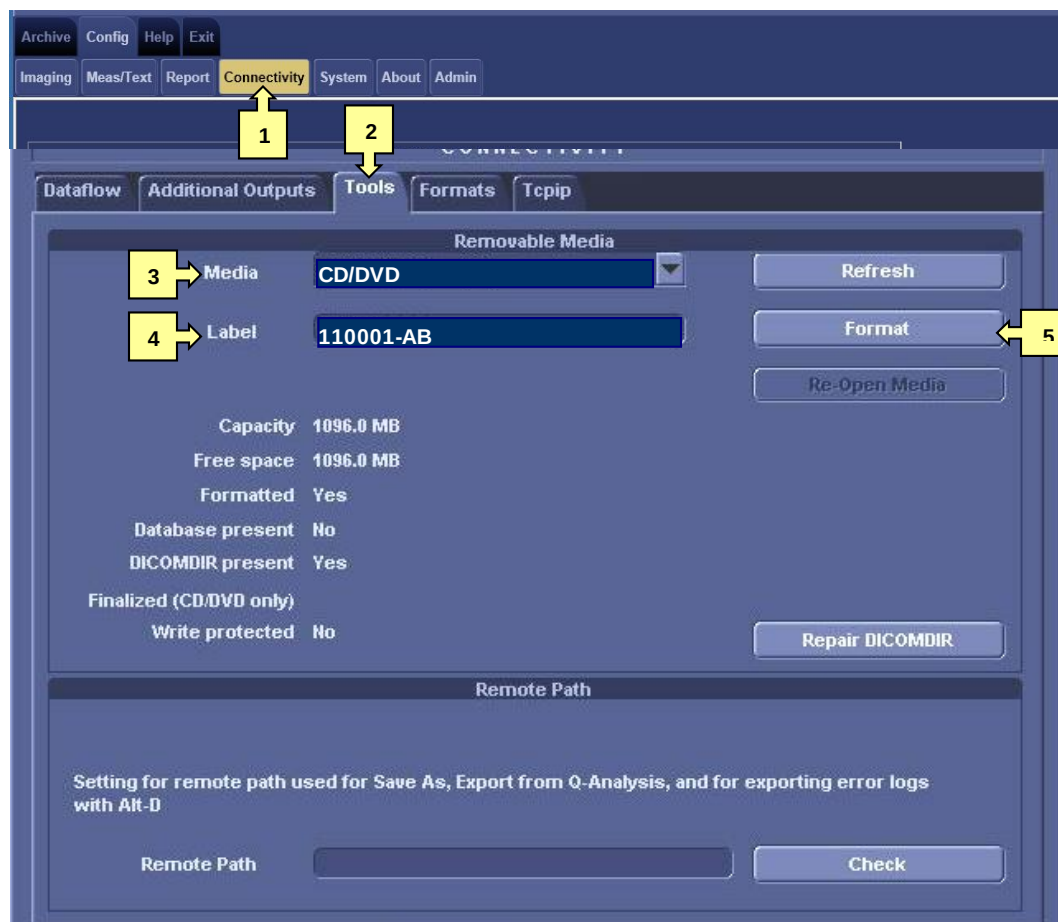
Interval: 1 [S]

Timeout: 3

OK Cancel

6.4.5 Formatting DVD

- 1) In the **Configuration** screen, select “**Connectivity**.”
- 2) On the Connectivity screen, choose “**Tools**” from top row of options.
- 3) In the Tools screen, the media type should be set to “**CD/DVD**.”
- 4) Type in the **label** for the DVD (**4 digit site and 3 digit subject number**).
- 5) Make sure the DVD is in the drive, and select “**FORMAT**.”
- A dialog box will appear to confirm that you wish to format the DVD– select OK.
- Once the DVD is formatted, exit the configuration screen.



6.4.6 Exporting a study from Internal Hard Drive to DVD

- Select **Archive** screen and set “Dataflow” to read “**Local Archive – Int. HD**”
- Select **EXPORT** from the screen
- The export dialog box will appear. The FROM box should read “**Local Archive – Int. HD**” and the TO box should read “**CD/DVD Archive**” from the drop down menus. Select OK.

The screenshot shows the 'SEARCH / CREATE PATIENT' window. The 'Dataflow' dropdown is set to 'Local Archive - Int. HD'. The 'EXPORT' button is highlighted with a red circle. The 'Patient List' table shows one record for 'PVD' with Patient ID '110001-AB' and Exam Date '12/01/2015'.

Last Name	First Name	Patient ID	Birthdate	Exam Date	Img	Str	Rep	Size	Code
PVD		110001-AB		12/01/2015					

- A screen of patients on the hard drive will appear. Select the patient/subject you wish to export to the DVD, and select **COPY**.
- Once the study has been exported to a DVD, select **DONE** to finish the copy procedure.
- Select **F3 or Alt-E** from the keyboard to eject the DVD.

EXPORT PATIENT Archive More

Last Name: PVD Patient ID: 110001-AB
First Name: Birthdate: (mm/dd/yyyy) Age:
Sex: ☐ female ☐ male

Patient List 1 records fetched of total 36 (Show All)

Last Name	First Name	Patient ID	Birthdate	Exam Date	Copied	Status Msg
PVD		110001-AB		07/14/2015		

☐ Delete selected patient(s) after copy ☒ Copy Images

Export from: Local Archive - Int. HD Operator: ADM

COPY SELECT ALL DONE More

Retain a copy of the DVD on site with study-related records.

If there are problems downloading the study to a DVD, please contact your local GE application specialist.

6.5 Philips System Specific Instructions for Archive Export (NATIVE DICOM data)

6.5.1 Archive all studies immediately after image acquisition

6.5.2 Machine set-up

- Select machine “**setup**” on the top row of the keyboard to activate set-up screen.
- Select the “**Print/Network**” tab on the left side of the screen (fourth selection down).

PHILIPS

Printer/Capture Device Selection Global Config Network

System Settings
Analysis Config
Annotate
Print/Network
Audio/Video
Protocols
Data Security
Config/Test
About

Cancel
Done

Live Capture Type

- ☐ Prospective
- ☐ Retrospective
- ☒ Accept Prior to Store

Acquisition Compression

Clip
Lossy Medium

See device Advanced Properties for still frame compression options.

Print Format

Full Screen Display Area

Acquire Key While Frozen ☐ ☐

Control Panel Print Key ☐ ☐

Send Report

- ☐ To Report Printer
- ☐ To Report Server

Image Export

Format

Export Map Configuration
Export Optimized for LCD

☒ Export Retired SOP Classes

Frame Rate
Acquisition Rate

VCR Image Capture Format

Capture Map Configuration
DICOM GSDF Enabled

Large 3D Volume Acquisition

- ☒ Allow Large 3D Volume Acquisition

Minimum of QLAB 5.0 required for acquisition of large 3D volumes

Send Images/Clips

Send Images/Clips

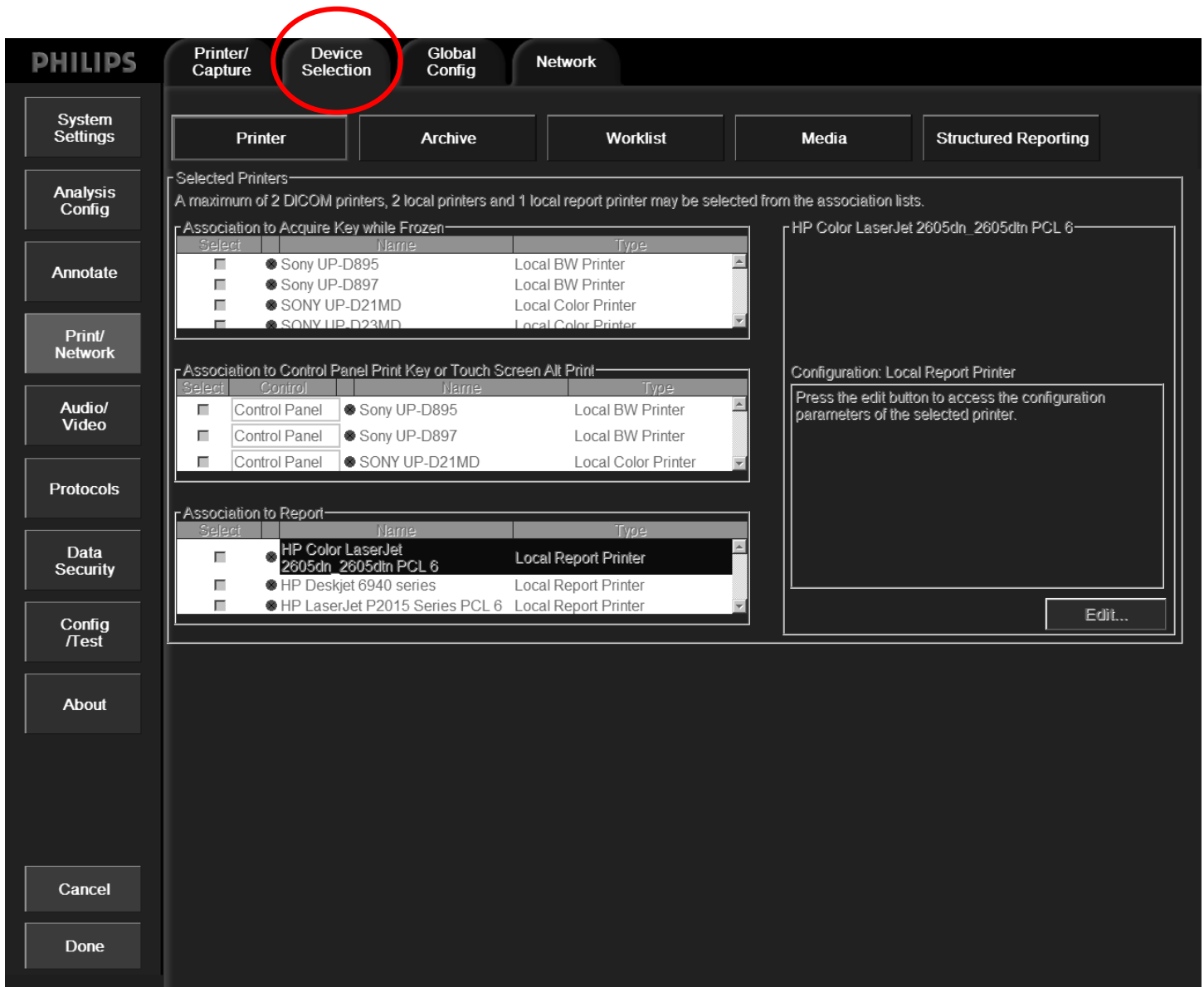
- ☐ After Each Print/Acquire
- ☐ At End of Exam

☒ Automatic Printer Choice

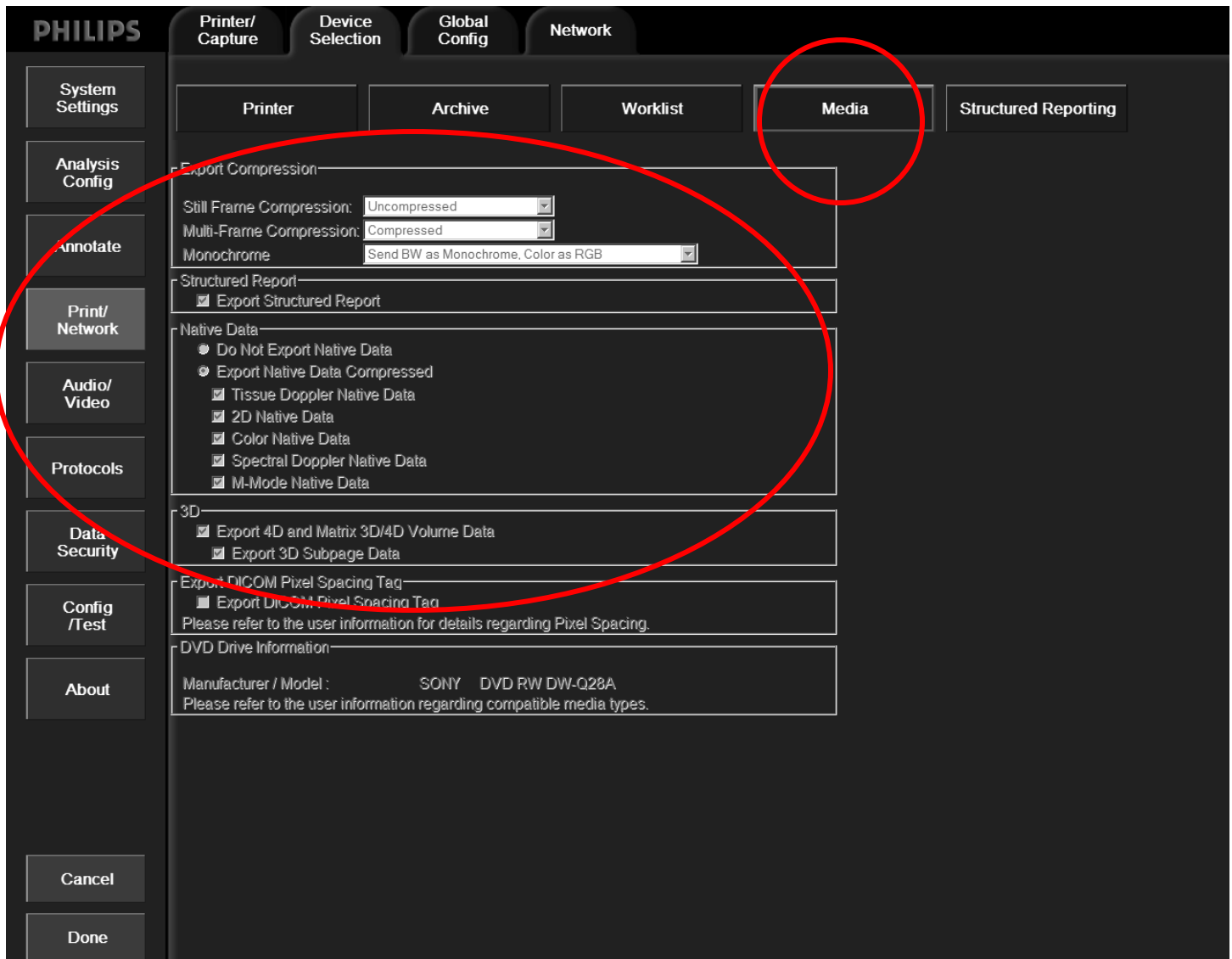
Append from Image Review

- ☒ Create Study Instance UID

- On the Print/Network screen, select **“Device Selection”** from the top row of option.

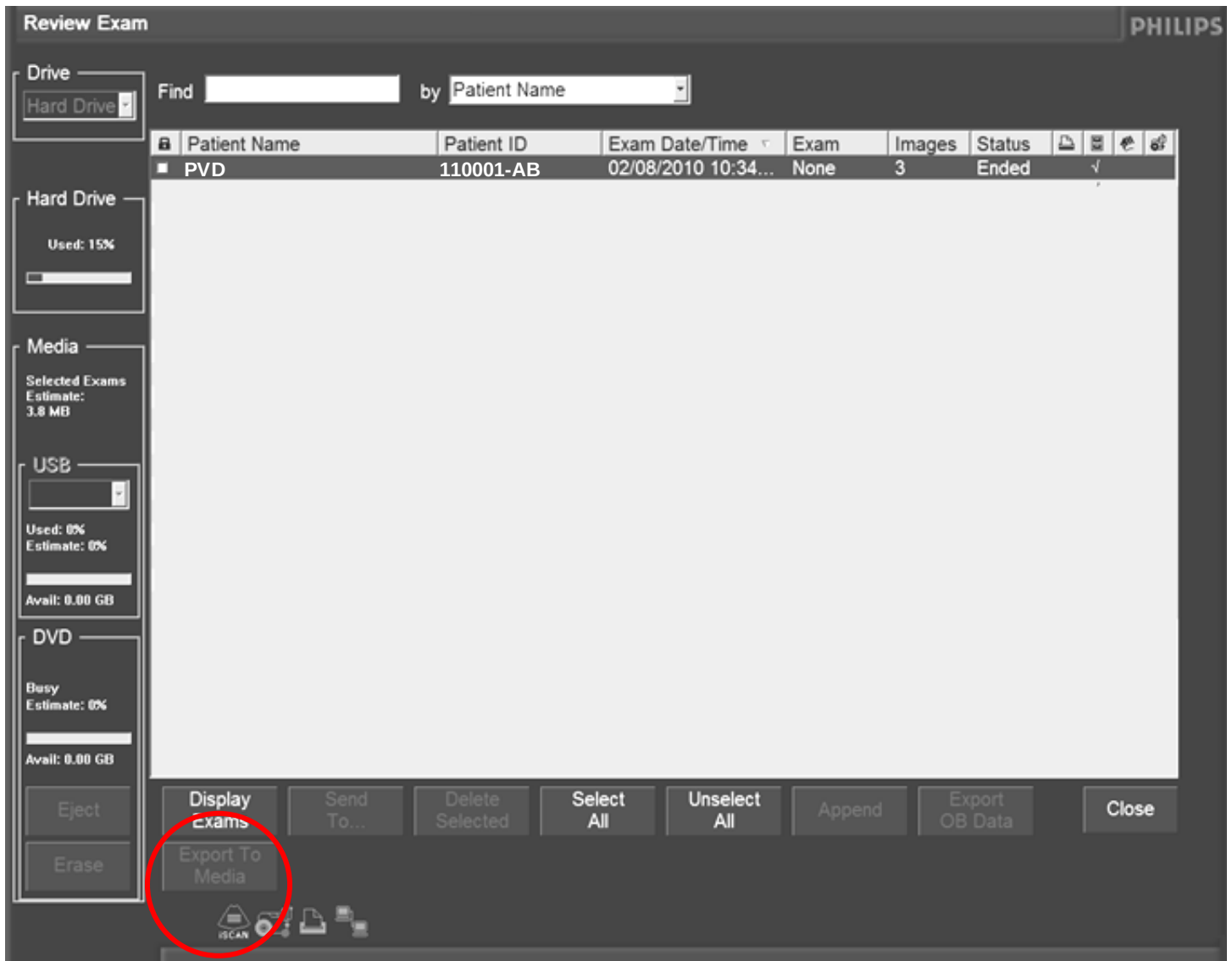


- On the Device Selection screen, select “**Media**” from the second row of options.
 - Export Compression
 - Still Frame Compression: Uncompressed
 - Multi-Frame Compression: Compressed
 - Monochrome: Send BW as Monochrome, Color as RGB
 - Native Data
 - Select Export Native Data Compressed
 - ☒ Check Tissue Doppler Native Data
 - ☒ Check 2D Native Data
 - ☒ Check Color Native Data
 - ☒ Check Export 4D and Matrix 3D/4D Volume Data
 - ☒ Check Export 3D Subpage Data

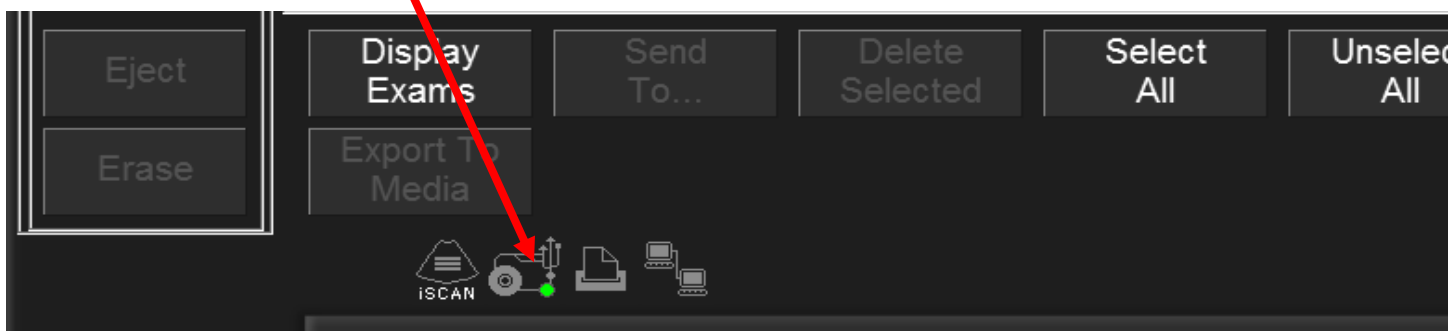


6.6 Exporting a study from internal hard drive to DVD

- Select **“Review”** on left side of control panel to activate the review screen.
- Select (highlight) subject from the exam list.
- On the review screen select **“Export To Media”**
 - Text box will appear
 - Choose **“DVD”** and **“Export to Media”**
 - Select **“OK”** to process selections



- Green Icon at bottom left of the screen shows active copying.



Retain the DVD on site with study-related records.

If there are problems downloading the study to a DVD, please contact your local Philips application specialist.

7 Echo Quality Control Process

7.1 Echo Critique

Echocardiograms will be monitored for adherence to the study protocol as well as quality. The Imaging Core Lab will provide feedback in the form of a critique to the sites and the DCC via email for each study submitted.

7.2 Query Notification

The study coordinator (or designee) and the sponsor will receive an email from the C5R ICL asking for the resolution of any issues that were found during the quality control (QC) process. Prompt response is required from the site study coordinator.

7.2.1 Echo Data Queries

- Review the variable name, reported value, and comments/suggestions
- Record the corrected, missing, or illegible information in the resolution box

7.2.2 Echo Media Queries

- Review the issue and comments/suggestions
- Record the corrected information and/or comments of action taken (for example: sent Imaging Core Lab new images via AG Mednet).

7.2.3 Echo Data Clarification Form (DCF)

Please print your name, sign and date (mm/dd/yyyy) in the space provided. The C5R ICL will not consider corrections recorded on the DCF unless signed and dated by site personnel completing the form. A signature indicates your agreement that the data should be changed as indicated on the DCF.

- Ensure all fields of the Data Clarification Form (DCF) are

complete.

- If you have questions about completing the form, refer to the Echo Data Clarification Form example (see example 8.3.1), send an email, or telephone an Imaging Core Lab team member for assistance.
- An Imaging Core Lab Study Team Contact Information sheet is located in the front of this manual for reference.

7.3 Resolution and Return of Data Clarification Form (DCF)

The study center contact person must fax the completed Data Clarification Form to the Imaging Core Lab within five business days at 216-445-4419. The study center will keep a copy of the DCF on site with the corresponding study files.

7.3.1 Echo Data Clarification Form (DCF) Example

 C5Research Cleveland Clinic Coordinating Center for Clinical Research	Imaging Core Lab 9500 Euclid Avenue JJ-65 Cleveland, OH 44195 Fax: 216-445-4419
Data Clarification	
PVDOMICS	
Site Name: Brigham and Women's Hospital Operator: Exam Date: 12/1/2015 Visit: Baseline	Site Code: 11 Subject: 110001-AB Modality: ECHO Equipment: Philips IE-33 Exam Types: TTE

Media Critique
Digital Data stored in correct format?

Comment: The exam contains minimal images for this study. (29 images only).

Please re-upload the complete echo exam and forward to the Imaging Core Lab.

Sign and Date this DCF and return fax this query to the Imaging Core Lab as soon as possible for echo processing to be continued.

Response: _____

Signature: _____ **Date:** _____

Print Name: _____

7.4 Unresolved Query Process

- 7.4.1** If the Imaging Core Lab does not receive the faxed resolution within a reasonable time frame, a follow-up email will be sent to the site study coordinator and copied to the DCC indicating a second request for immediate attention/resolution of the data clarification.
- 7.4.2** If the DCF is returned and all the issues are not resolved, the ICL will re-send an updated DCF for complete resolution of outstanding issues. The study center will complete the form, sign it, and fax it to the ICL.
- 7.4.3** Save a copy of this DCF with the site study files.
- 7.4.4** Ensure all fields of the DCF are complete.
- 7.4.5** An Imaging Core Lab Study Team Contact Information sheet is located in the front of this manual for reference.

8 Imaging Core Replacement/ Inactivation Process

In the event that an image exam must be replaced or inactivated due to a submission error, this process will be followed:

- ICL to initiate query to site and DCC designee asking for clarification. ICL will not process clarification received from site until sponsor designee(s) verifies the accuracy with signature on inactivation form.
- The site monitor or designee will verify the date and subject ID on the Inventory/Quality Report to ensure accuracy.
- ICL will update the Inventory Report, PACS system and C5Research Clinical Data Management (CDM).
 1. Rename incorrect Echo as INACTIVE.
 2. Proceed with normal processing of replacement Echo, i.e. check-in, import and analysis.
- Prior to data transfer, ICL will send DCC's Data Management team and C5Research CDM Replacement Echo spreadsheet containing cumulative list of studies that have been renamed.
 1. DCC will update their DM team in preparation for successful receipt of transfer.

9 Electronic Submission Overview

9.1 AG Mednet

9.1.1 AG Mednet is a web-based diagnostic imaging network, which enables sites to send diagnostic image exams electronically and securely to the Imaging Core Lab.

9.1.2 AG Mednet will provide tools and training to:

- De-identify exams
 - Site is responsible for correctly de-identifying study within the AG Mednet portal.
- Complete transmittal forms electronically
- Complete other trial-specific task

9.2 Electronic Submission Process

9.2.1 All data should be acquired in DICOM format and submitted electronically via a web-based interface to the Imaging Core Lab using the AG Mednet Desktop Agent.

9.2.2 Upload time is dependent on site speed network connection, but the transfer runs in the background so site staff can leave the computer running or work on other applications.

9.2.3 Sites are informed via email of electronic submission as soon as transfer has completed.

9.2.4 AG Mednet is an intuitive system and can run from a networked PC with **Java 8 plug-in installed**. This plug-in ensures AG Mednet will run within the web browser. It is likely that you already have Java 8 installed.

10 Forms

DCC website for all study forms for downloading and printing:

<http://qhsapps.ccf.org/pvdomics/>

L-PVD Forms that are available for data entry are linked on the PVDOMICS website under Longitudinal PVDOMICS (L-PVDOMICS) Study (https://qhsapps.ccf.org/pvdomics/General_info.htm)

11 References

American Society of Echocardiography Guideline and Standards documents:
www.asecho.org

Guidelines for the Echocardiographic Assessment of Atrial Septal Defect and Patent Foramen Ovale: From the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. (J Am Soc Echocardiogr 2015;28:910-58.)

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