Supplemental Material

Table S1. Current List of Participating centers and investigators in the MASTER Study

	Center / Affiliation	Country	City	Principal Investigators	CO-Investigators
1	Hospital Italiano de Buenos Aires - Unit Internal Medicine Department/Hypertension Section	Argentina	Buenos aires	Waisman G	Jessica Barrochiner
2	Favaloro Foundation - Metabolic Unit, Hypertension	Argentina	Buenos aires	Sanchez R	Paula Catalano MD, Agustin J Ramirez MD, JP Manganiello MD
3	Department of Cardiology. Hospital Español de Mendoza	Argentina	Mendoza	Renna N	Alfredo Astesiano
4	Medical University Graz, Department of Cardiology	Austria	Graz	Perl S	Prof Zweiker, Dr. Niederl
5	Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical Colleges	China	Beijing	Zhang Y	Xueli Jiang, Ken Chen, Jia Ma
6	Shanghai Institute Of Hypertension	China	Shanghai	Wang J	Changyuan Liu, Yi Chen, Lei Lei, Yan Li, Shaokun Xu
7	Peking University First Hospital - Cardiology	China	Beijing , District: Xicheng	Huo Y	Zhang Yan, Gao Lan, Wang Shixuan
8	The Center of Hypertension of the Peoples Hospital of Xinjiang Uyghur Autonomous Region/Hypertension Center	China	Urumqi, Xinjiang Uygur Autonomous Region	Li N	
9	University of Zagreb School of Medicine, University Hospital Center Zagre/Dept of Nephrology, Hypertension, Dialysis and Transplantation	Croatia	Zagreb	Jelaković B	Ana Vrdoljak, Zivka Dika
10	Dharma Vira Heart Center, Sir Ganga Ram Hospital - Cardiology	India	New Delhi	Madan K	Dr. JPS Sawhney,Dr. Manish Sharma
11	Istituto Auxologico Italiano - Ospedale San Luca	Italy	Milano	Bilo G	
12	University of Padova Dipartimento di Medicina DIMED Padua	Italy	Padova	Palatini P	Dr Claudio Fania,Francesca Saladini
13	Centro Ipertensione AOU Città della Salute e della Scienza di Torino - Internal Medicine and Hypertension Division, Department of Medical 14Sciences	Italy	Torino	Veglio F	Dr. Chiara Fulcheri,Dr. Franco Rabbia
14	Ce15ntro Ipertensione Arteriosa, Sezione di Medicina Interna - Azienda Ospedaliera di Terni - Università degli Studi di Perugia	Italy	Perugia	Pucci G	

15	JB Lab and Clinic	Korea	Seoul	Park J B	
16	Dongguk University - Ilsan Hospital - Cardiovascular center	Korea	Goyang-si, Gyeonggi-do	Rhee M Y	
17	Medical University in Gdansk - Department of Hypertension and Diabetology	Poland	Gdansk	Chrostowska M	Krzysztof Narkiewicz, Anna Szyndler, Michal Hoffmann, Ewa Swierblewska, Jacek Wolf
18	Clinical County Hospital Univesity of Medicine and Pharmacy Tirgu Mures/Department of Internal Medicine	Romania	Tirgu Mures	Podoleanu C	
19	EMERGENCY CLINICAL HOSPITAL OF BUCHAREST/CARDIOLOGY	Romania	Bucharest	Dorobantu	Dr. Alexandra Paval
20	Almazov Federal North-West Medical Research Centre, Saint-Petersburg, Russia - ITMO University, Saint-Petersburg, Russia	Russia	Saint-Petersburg	Konradi. A	Zvartau N, Ionov M
21	Excellence Centre for Hypertension of the Clinical Centre of Serbia, Belgrade	Serbia	Belgrade	Stojanovic M	Obrenović-Kirćanski, Stojanov Vesna, Radivojevic Nenad, Marijanovic Marija, Simic Dragan, Parapid Biljana
22	University of Valencia and INCLIVA Research Institute, Valencia, CIBERObn, ISCIII, Madrid, Spain	Spain	Valencia	Redon J	Fernando Martinez
23	Hypertension Clinic, Hospital de Sagunto, Valencia, Spain - Universidad CEU Cardenal Herrera, Ciencias de la Salud, Valencia, Spain	Spain	Valencia	Rodilla E	
24	Hospital Mutua TerrassaUniversity of Barcelona	Spain	Barcelona	De la Sierra A	
25	Hospital Clinic of Barcelona, Spain	Spain	Barcelona	Domenech M	Dr. Javier Sobrino, Dr. Antonio Coca
26	Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden	Sweden	Stockholm	Kahan T	Kristina Björklund-Bodegård
27	Fundacion Venezolana de Hipertension Arterial/Instituto de Enfermedades Cardiovasculares de LUZ	Venezuela	Maracaibo	Octavio JA	Dr. Eglé Silva, Dr. Mayela Bracho, José J, Villasmil, Freddy Madueño, Carlos Esis, Greily Bermúdez, Estílita Paredes, Pablo Amair

Operators Manual MASTER Study

CLINICAL HISTORY

Past medical history (including family history, hypertension history, cardiovascular risk factors, other relevant clinical information) and drug history will be taken according to the data collection form in the eCRF. Current drug therapy will be recorded in detail giving names and daily doses of all drugs.

ANTHROPOMETRIC MEASURES

Calibrated standard equipment will be used to measure height and weight.
To determine waist circumference, the upper hip bone is located and a measuring tape will be placed around the abdomen (ensuring that the tape measure is horizontal). The tape measure should be snug and not cause compressions on the skin.
Body surface area (BSA) will be calculated from height and weight according to the Du Bois formula .
BSA [m^2] = 0.007184 × (height [cm])0.725 × (weight [kg])0.425.
Body mass index (BMI) will be calculated from height and weight according to BMI [kg/m^2] = weight [kg] / (height [m])^2 .
These calculations will be done in the data analysis phase.

PHYSICAL EXAMINATION

Physical examination will be carried out mainly in order to exclude obvious secondary causes of hypertension and to detect previously unknown heart, vascular, renal or other disease.

LABORATORY TESTS

The co-primary end point of UAE will be evaluated from morning spot urine samples and expressed as albumin/creatinine ratio (UACR, mg/g). Spot urine samples will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when the ABPM device will be removed.

Blood samples will also be obtained for determination of serum creatinine, glucose, HbA1c, uric acid, Na+, K+ and lipids as well as to create a study biobank.

HOME BLOOD PRESSURE MONITORING (HBPM)

Devices will be provided to the patients only for the duration of home monitoring period (7 days). Alternatively, patients may use their own validated BP device.

When providing the device to the patient the investigator will instruct the patient:

• On the required monitoring schedule (see below)

• To perform readings in standard conditions (after 5 minutes of rest, having abstained from smoking, exercise or caffeine intake for the past 30 minutes, in sitting position, with the arm supported on the heart level, in a quiet room, not talking during the measurement

• To obtain morning BP readings before or at the time of antihypertensive drug intake

• To register the measured BP and HR values immediately in the provided log sheet (see Figure 1). This log sheet will be provided to the centers in Word format, so that you are free to translate it in your local language.

HBPM will be performed over 7 consecutive days preceding the study visits. Two measurements should be obtained in the morning and two in the evening at 1-2 minute intervals and measurement results should be recorded in a provided log sheet (Appendix 1). This log sheet will serve as Source Document for the Home BP values.

If, on the other hand, the BP device allows export of the data as a .csv file, this csv file can be uploaded in the eCRF, according to the instructions in the eCRF manual.

Values obtained on the first day will be discarded and the average of all the remaining scheduled readings will be calculated and used in the analyses.

Figure S1. Home Blood Pressure Log

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HOME BLOOD PRESSURE LOG

Section to be filled in by Investigator:

Screening ID: |__|__|__|__|__|__|__|__|__|__| Randomization ID: |__|__|__|__|

Device model: _____

Visit: O Screening 2
O Follow-up 3
O Follow-up 9
O Premature discontinuation visit

Section to be filled in by Patient:

Day	Date	Morning				Evening			
		Time	SBP	DBP	HR	Time	SBP	DBP	HR
1									
2									
3									
4									
5									
6									
7									

Notes: _____

Section to be filled in by the investigator: Mean SBP (days 2-7): |__|__|__|.|__| mmHg
Mean DBP (days 2-7): |__|__|__|.|__| mmHg
Mean HR (days 2-7): |__|__|__|.|__| /min

Note for the Investigator: This log must be filled in manually, scanned and uploaded as pdf file in the eCRF.

OFFICE BLOOD PRESSURE MEASUREMENT (OBPM)

The MASTER study requires the use of the specifically provided **A&D TM2430** device for office SBP, DBP and HR measurement.

Measurement will be performed after several minutes of rest and with the subject having abstained from smoking, strenuous exercise or caffeine intake in the period preceding the measurements.

Three blood pressure readings will be obtained at intervals of at least 1 minute with the participant being seated in a quiet room. A standard bladder (12-13 cm long, 35 cm wide) will be used, but a larger and a smaller bladder will be available for large and thin arms, respectively. All three measurements will be stored in the e-CRF, and their average will be taken to indicate office BP at each visit.

An additional measurement will be obtained with the patients standing upright for one minute (unless the patient is unable to stand).

Blood pressure will be measured on both arms during the first visit and the arm with the higher systolic value will be used again during all subsequent visits.

A&D UA-651BLE device – source data:

The supplied device UA-651BLE is equipped with Bluetooth communication which connects to the A&D connect app available for iPhone and Android devices. The data can be downloaded directly after each single measurement when the device is paired with e.g. smartphone.

Once the data are on the mobile device, access the data table and use the “share” function to export the data in **csv** format. Then remove the readings one by one (slide with the finger sideways on a single reading and a delete button will appear).

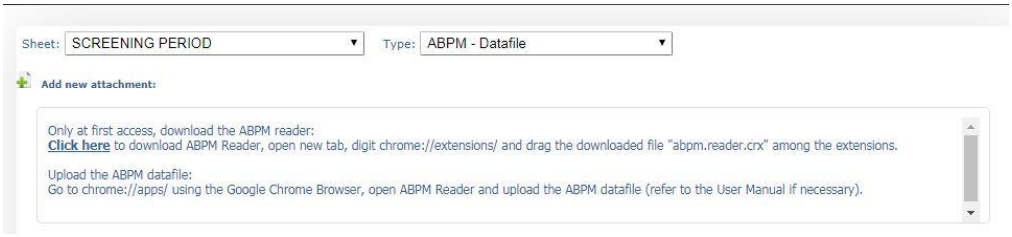
csv files should be uploaded on the eCRF as source documents.

24 H AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

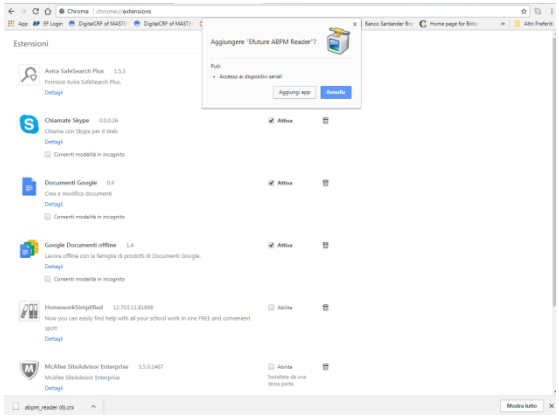
Ambulatory Blood Pressure Monitoring (ABPM) will be carried out as follows:

- The MASTER study requires the use of the specifically provided **A&D TM2430** device. This device allows direct upload of the datafile to the eCRF (see ahead).
- For more information, please check the attached TM2430 Data Sheet and Instruction Manual.
- ABPM will be performed:
    - In Group 1: during screening period, every twelve months during follow-up, and at the final visit.
    - In Group 2: during screening period, at three months, six months and every six months thereafter during follow-up, and at the final visit.
- Each monitoring should start in the morning, after the subject has taken his/her morning medication. Patients will be sent home (to perform the recording in conditions as close as possible to daily life) and asked to come back the following day for the device removal.
- The cuff will be applied on the non-dominant arm unless the patient presents a major (>10 mmHg) between arm difference in BP; in that case the arm with higher BP should be used.
- The patient will be instructed:
    - to fill the attached diary form (see Figure 1) with reference to his/her main daily activities and quality of night time sleep. This diary will be provided to the centers in Word format, so that you are free to translate it in your local language.
    - to keep the arm still and to avoid any movement during each automatic blood pressure measurement
    - to attend her/his usual daily activities (avoiding major physical activity)
    - not to remove the cuff during the recording period
- The device will be set to take automatic readings every 15 minutes at daytime (6:00 to 22:00) and every 20 minutes at night-time (22:00 to 6:00) and not to display the measured readings
- The device should be removed after 25 hours of recording to ensure a complete coverage of all hours. ABPM files, with the accompanying diary, will be uploaded on the study website for immediate quality check.

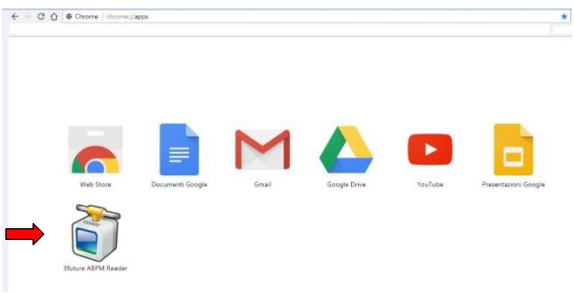
- Recordings of inadequate quality (less than 65% of the expected BP readings, 3 or more hours with no valid readings, 2 or more consecutive hours without valid readings) should be repeated by the centre in the same treatment condition.
- Attach the digital datafile to the eCRF in the “Upload attachments” section, under the heading “ABPM-datafile”:
    - Please use the **Google Chrome browser**!
    - The ABPM datafile has to be uploaded DIRECTLY from the **A&D TM2430** device to the eCRF, by an ABPM-reader APP that was specifically designed for this study.
    - At the first access: (1) download the “abpm_reader.crx” file by clicking “Click here”.



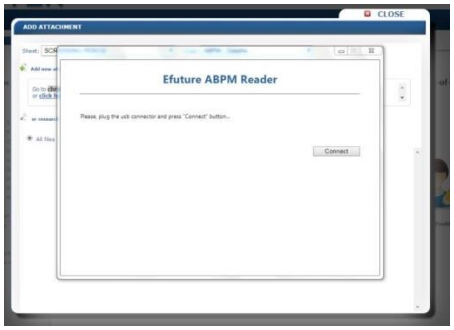
    - (2) Then drag the file among the extensions on the web page “chrome://extensions/”. (Please note that Step (1) and (2) need to be performed only once).



    - Once installed, go to “chrome://apps/ and open the ABPM reader icon.

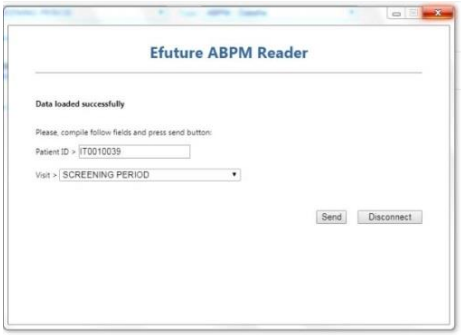


- Click on the Efuture ABPM reader icon, plug the USB connector and press “Connect”

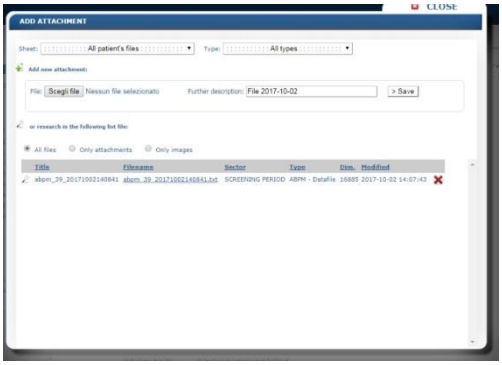


- Press red button on **A&D TM2430** device

- Fill in the patient Screening ID and corresponding visit



- “Data loaded successfully” and “Disconnect”. You will find the attached datafile in the uploaded files list



- Once the ABPM datafile has been uploaded, the raw data (including all individual measurements) of each recording will be examined by the ABPM Core Laboratory in Milan for quality control and analysis.

- ABPM data of patients randomized to group 1 (Office BP) will not be available to the investigators in charge of treatment decisions; for these patients only feedback concerning the quality of the ABPM data file will be returned. You will receive feedback from "masterdata@auxologico.it"
- ABPM data of patents randomized to group 2 (Ambulatory BP) will be available to the investigators in charge of treatment decisions; for these patients feedback concerning quality of the ABPM datafile AND mean BP values will be returned. You will receive feedback from "masterdata@auxologico.it"

- For each ABPM recording the following variables will be computed:
    - 24h, daytime and night-time average BP and heart rate (HR) values
    - SBP and DBP variability calculated as the standard deviation (SD) of the average 24h, day and night values, and as the "weighted" 24h SD, as well as Average Real Variability (AVR) and as ambulatory arterial stiffness index (AASI)
    - Nocturnal BP falls and night/day SBP and DBP ratios
    - Average morning (7-11 a.m.) SBP/DBP values and morning BP surge (defined as the difference between the lowest BP before the morning rise and the highest BP after awakening)
- Figure S2. ABPM Diary

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AMBULATORY BLOOD PRESSURE MONITORING DIARY

Section to be filled in by Investigator:

Screening ID: |__|__|__|__|__|__|__|__|__| **Randomization ID:** |__|__|__|__|

Visit:

O Screening
O Follow-up 1 (only Group 2)
O Follow-up 2 (only Group 2)
O Follow-up 3
O Follow-up 4 (only Group 2)
O Follow-up 5
O Follow-up 6 (only Group 2)
O Follow-up 7
O Follow-up 8 (only Group 2)
O Follow-up 9
O Premature discontinuation visit

Date: |__|__| / |__|__| / |__|__|__|__| (dd/mm/yyyy)

Time recording started: |__|__|:|__|__| (hh:mm)

Section to be filled in by Patient:

Time of: sleep: |__|__|:|__|__| (hh:mm) **awakening:** |__|__|:|__|__| (hh:mm)

Morning drug intake time: |__|__|:|__|__| (hh:mm)

Quality of sleep: O Bad O Average O Good

Please record below any major event that might have affected your blood pressure

Time	Activity/posture/symptoms

Comment:_____

Note for the Investigator: This log must be filled in manually, scanned and uploaded as pdf file in the eCRF

ECHOCARDIOGRAPHIC SPECIAL PROCEDURES

1-Certification of Echo's:

It is essential that all sonographers at participating sites produce the highest possible quality in acquired echo images. The echo operator(s) of each participating center must perform one sample echocardiographic examination, following the instructions described in this manual. This Certification Echo must be submitted to the Core Echocardiography Laboratory (hereafter designated as "Core Echo Lab") through the eCRF (www.master.digitalcrf.eu) for assessment and subsequent certification of adequate quality.
The submitted Certification Echo must:

- be clearly labeled as a "Certification Echo"
- be of good quality and all images should be clear
- be compatible with the instructions contained within this document
- include all required views outlined in the echo protocol contained in this manual

The Core Echo Lab will provide feedback to the site within *10 business days* of receipt of the Certification Echo.
Once the Certification Echo is deemed acceptable, the Core Echo Lab will e-mail a site Certification Form to the site's Principle Investigator.

2-Echocardiographic Media and Data Flow:

The participating center must:

- save the echo data in universal DICOM format.
- unite the requested views/images for each single echocardiography examination in one single data folder.
- name this data folder, according to the patient's screening ID and follow-up visit, as follows:

Follow-Up visit	Requested folder name
Certification Echo	Certification Echo
Screening period - Baseline	ScreeningID-BA
Follow-up 3	ScreeningID-FU3
Follow-up 5	ScreeningID-FU5

Follow-up 7	ScreeningID-FU7
Follow-up 9	ScreeningID-FU9
Premature discontinuation	ScreeningID-PD

- upload the data folder directly to the electronic CRF, according to the eCRF attachment manual.
- keep a copy of the echo data folder in the Investigator Site File, for the entire duration of the study.

NOTE: If the participating site cannot upload the echo data directly to the eCRF, the site investigator(s) will need to make alternative arrangements with the Data Management team for transmitting the required echo data.

The Data Management team:

- downloads the echo data from the eCRF
- forwards the echo data to the Core Echo Lab for blinded centralized reading.
- eliminates the echo data from the eCRF, in order to free digital space in the platform.
- archives a copy of the echo data for the entire duration of the study.

3-Instructions for Performing Echocardiograms:

Recommendations on this manual have been based on the up-to date evidence and consensus provided by current guidelines listed in the reference section at the end of this manual (1-4).

A Core Echo Lab certified sonographer should obtain all study echos on a given subject. If possible, identify one or two sonographers in your Echo Lab to perform all echos related to this study.

A. Echocardiographic Equipment

Use the highest possible frequency (2.5-5.0 MHz) transducer to allow adequate penetration for endocardial border definition. It is advisable to use the same transducer frequency for all the studies on a given patient. Tissue harmonic imaging may be used, at the discretion of the sonographer and investigator, unless this worsens endocardial border definition.

B. Subject Identification on Recorded Images

The echo media (CD) and other materials received by the Core Echo Lab should not contain the subject's name or medical record number. Only the subject's assigned study screening ID should be used.

C. Subject Preparation

Electrocardiographic (ECG) leads (3-lead) should be placed and an ECG signal in which the QRS complex is clearly identifiable should be visible on the echocardiographic monitor.

4- Echocardiographic Quality

Echocardiograms should be obtained in a manner that is most consistent with good-quality subject care. However, subject comfort and safety shall always be the primary concern. Subject co-operation and comfort are essential in obtaining high quality echocardiographic images.

Importance of High Quality Echos

The Core Echo Lab relies heavily on sites performing high quality echos. Quantitative measurements entail manually tracing the endocardium and Doppler envelopes at various periods in the cardiac cycle. Even when images are of good quality, this can be extremely difficult, and it is therefore critically important that the best possible endocardial definition and Doppler signal are obtained.

Optimizing Endocardial Border Definition

Sonographers and the individual echo investigator should optimize endocardial border definition at their own discretion, using any machine-specific optimizations. Please do not use automatic border detection systems, as found on certain machines. Furthermore, adjust the transducer depth range to maximize the dimensions of the chamber of interest.

Instructions for Image Acquisition

The required echo views and echo-Doppler data should be obtained in the order outlined in the Table. Further details, specific to each echo view, can be found in the section: "Instructions for Obtaining Required Echocardiographic Views".

Recording should start once the view is optimized and end after the required number of cardiac cycles has been recorded for each required view.

At least **5 cardiac cycles** per view are required for digitally stored studies (in DICOM format).

Doppler Recordings:

With all spectral Doppler recordings, set the Nyquist limit at 50-70 cm/sec, adjusting to ensure a well-defined jet. The Nyquist limit must be documented on the image. Ensure the color sector remains as narrow as possible to obtain the best frame rate. However, the color sector should be of adequate size to capture the entire regurgitant jet.

For continuous wave and pulsed wave Doppler images, use a standardized sample volume (5 mm is recommended). Care should be taken to align the Doppler signal parallel to the presumed direction of flow. Adjust the gain to obtain a clear flow signal and the baseline and scale (80 cm/sec) to capture the peak flow velocity. Reset scale if necessary to optimize the flow signal. Record at 100 mm/sec sweep speeds for the required number of beats (as outlined above).

5- Required Echocardiographic Views

Echocardiographic Examination and Acquisition

A subset of a standard echocardiographic examination will be performed. The following table resumes the required views for each echo study:

Table S2. Required Echocardiographic Views

VIEW	REQUIREMENTS
A. Parasternal Long Axis View	1. 2D 2. M-mode across the LV base (where MV leaflet tips meet chordae) 3. Color flow Doppler of mitral valve 4. 2D parasternal long-axis view, which depicts the aortic root and the proximal ascending aorta
B. Parasternal Short Axis View: MV Level	1. 2D 2. M-mode across the LV base (where MV leaflet tips meet chordae)
C. Parasternal Short Axis View: Mid-papillary Level	1. 2D 2. M-Mode
D. Parasternal short Axis View: Aortic valve, RV Inflow-outflow View	1. 2 D 2. Continuous wave (CW) Doppler of tricuspid regurgitant (TR) jet if present.
E. Apical 4-Chamber View	1. 2D - include entire four cavities 2. 2D- focused on left ventricle and left atrium only 3. Color flow Doppler of mitral valve and tricuspid valve - include entire LA and RA cavity 4. CW Doppler of TR jet if present 5. Mitral inflow: PW Doppler 6. PW Doppler pulmonary vein recordings guided by color Doppler 7. Mitral annular Doppler Tissue Imaging (DTI) at the medial (septal) and at the lateral corner of the mitral annulus
F. Apical 5-Chamber View	1. 2D 2. LV outflow tract pulsed wave (PW) Doppler 3. Aortic valve color Doppler and CW Doppler
G. Apical 2-Chamber View	1. 2D - include entire LA and LV cavities 2. Color flow Doppler of mitral valve

H. Apical 3-Chamber View	1. 2D 2. Aortic valve color Doppler
I. Subcostal View	1. Four chambers view 2. Inferior vena cava - 2D (image at *rest* and with *inspiration* to assess for respiratory change in IVC diameter)

6-Instructions for Obtaining Required Echocardiographic Views:

The required echo views and echo-Doppler data should be obtained in the order outlined in the table. At least 5 cardiac cycles per view are required. For M-mode and Doppler recordings, use at least 100 mm/sec sweep speeds.

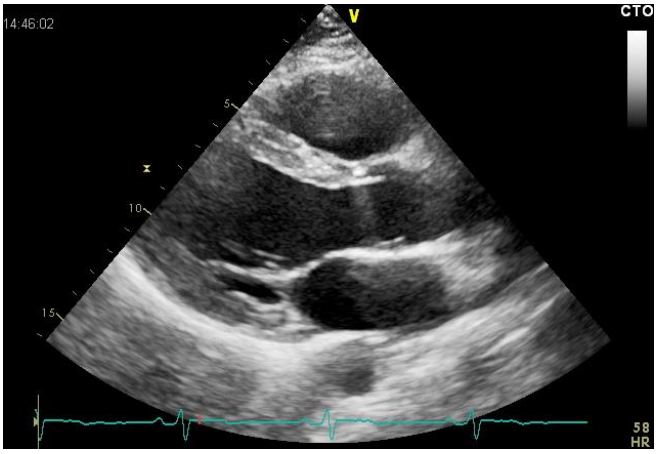
NOTE: Please record *moving* images, rather than still images, for all data except for spectral Doppler and M-mode recordings. Do NOT record measurements on the echo study submitted. The Echo Core Lab will visualize all the cardiac cycles and perform all measurements

PARASTERNAL VIEWS:

A. Parasternal Long Axis View

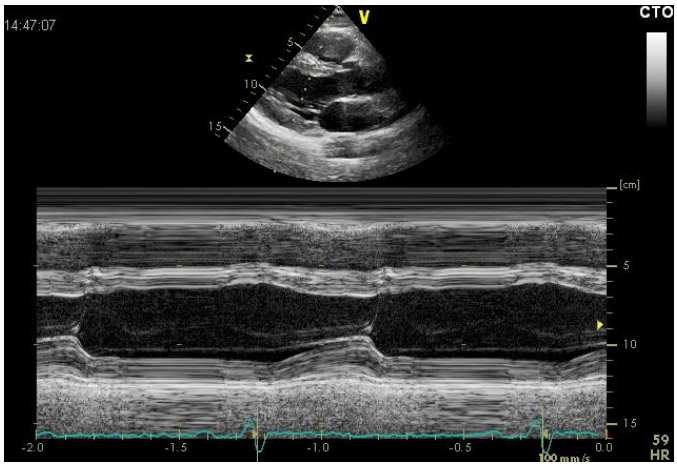
2D

This view is best obtained with the transducer positioned at the left sternal border, angled to ensure the longest apex-base view of the left ventricle (LV). It is important to acquire the true long axis of the LV and to avoid any foreshortening of the LV. The LV outflow tract should be visualized with only minimal angulation of the proximal interventricular septum (IVS) as it meets the anterior aortic wall. The anterior and posterior mitral valve (MV) leaflets and the right and non-coronary cusps of the aortic valve (AV) must also be visible.



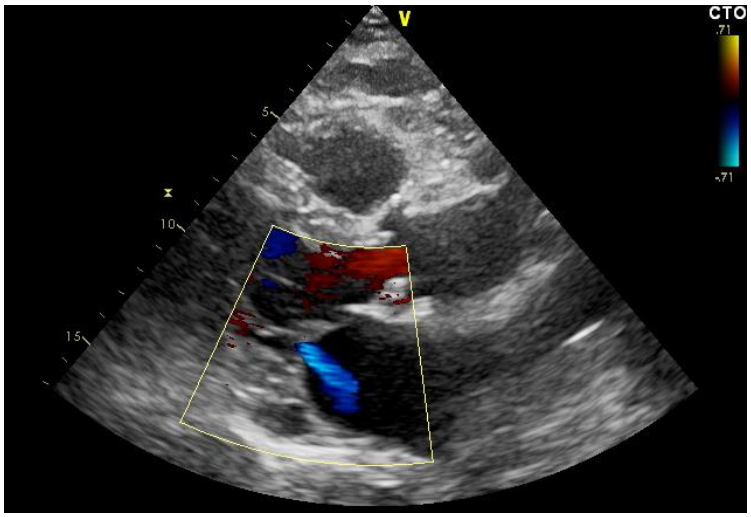
M-mode across the LV base

M-mode recording of the LV should be made with the cursor directed at or below the MV leaflet tips. The interventricular septum (IVS) and the posterior wall (PW) should be clearly visible.



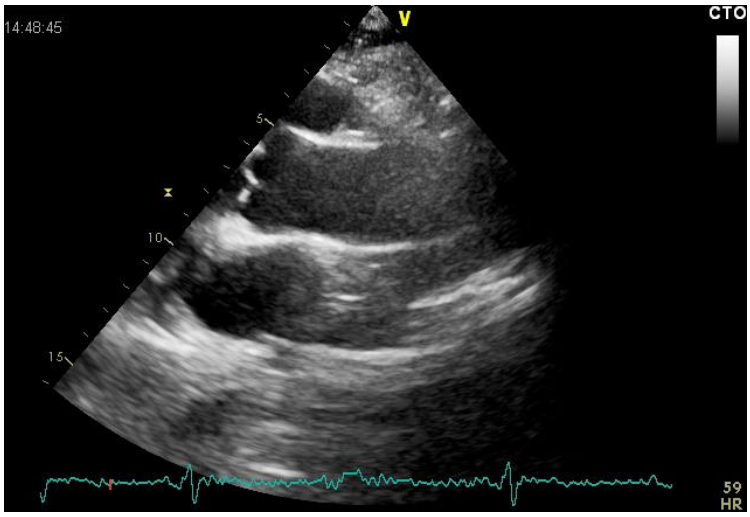
Colour flow Doppler of MV

With the optimized 2D view, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



Ascending aorta

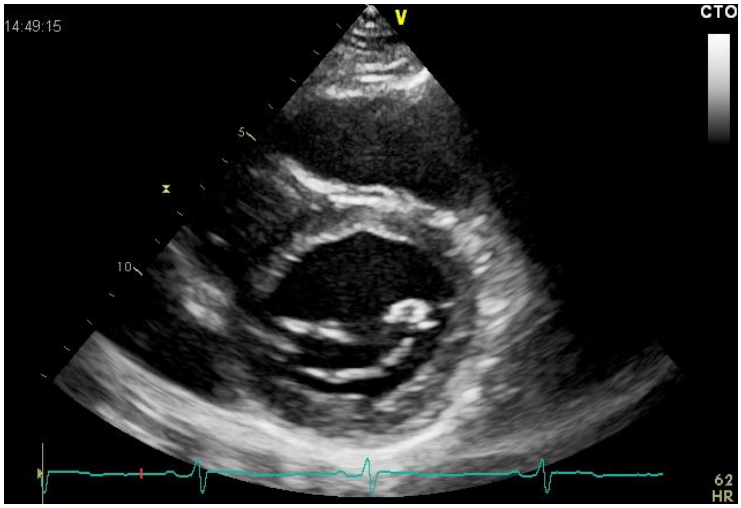
The parasternal long-axis view, which depicts the aortic root and the proximal ascending aorta. This plane is slightly different from that of the long axis of the left ventricle. Acquisition of this LV longaxis view may be performed from different intercostal spaces and at various distances from the left sternal border. The tubular ascending aorta is often not adequately visualized from a standard parasternal window. In these instances, moving the transducer closer to the sternum may allow visualization of a longer portion of the ascending aorta.



B. Parasternal Short Axis View: MV Level

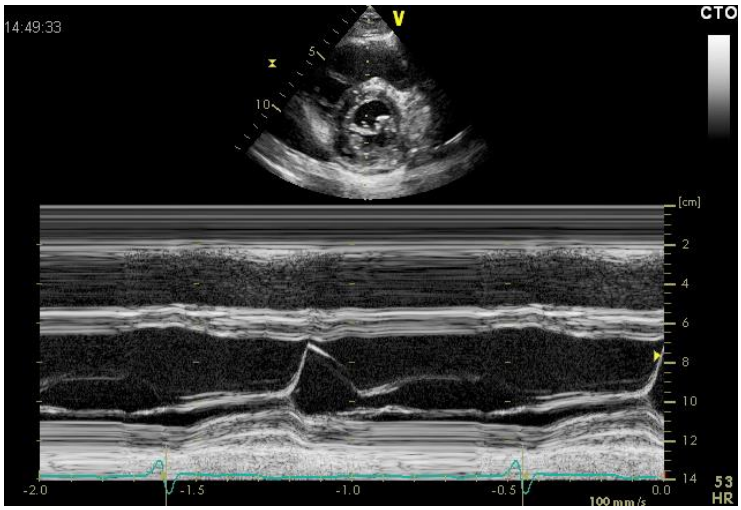
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and with superior or inferior angulation. The LV cavity should be visualized as a circular conformation with the depth adjusted to optimize the LV chamber dimensions. The mitral valve, with both anterior and posterior mitral valve leaflets, should be clearly visible.



M-Mode across the LV base

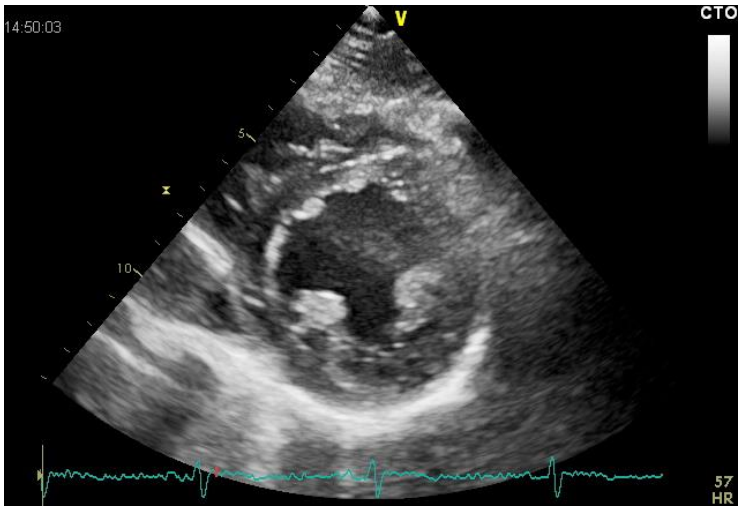
M-mode recording of the LV (for quantification of the LV mass) should be made with the cursor aligned through the middle of the circular LV, where the MV leaflet tips meet the chordae. The mitral valvular apparatus should be visible in this image.



C. Parasternal Short Axis View: Mid-papillary Level

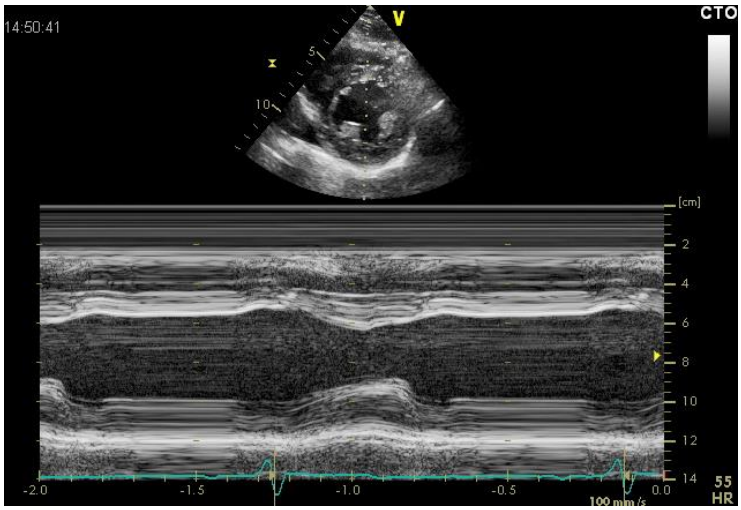
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and angled interiorly from the MV level. The LV should be visualized as a circular conformation with the depth adjusted to optimize the LV chamber dimensions. Both of the papillary muscles must be clearly visible.



M-Mode

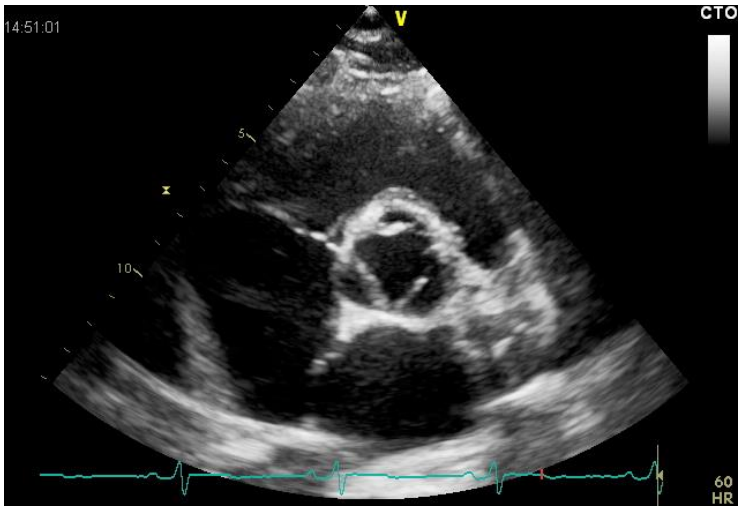
M-mode recording of the LV should be made with the cursor aligned through the middle of the circular LV.



D. Parasternal Aortic valve and Right Ventricular Inflow-outflow View

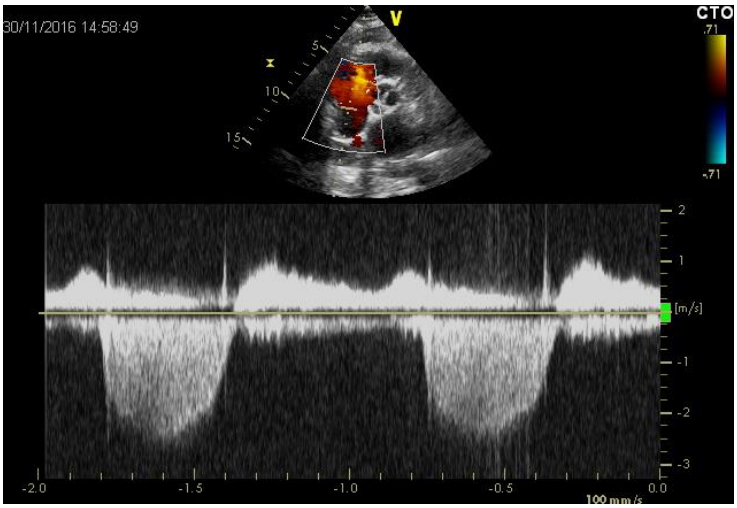
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and with superior angulation. The aortic valve, with its cuspids, should be clearly visible, as well as right ventricular inflow and outflow.



Continuous wave (CW) Doppler of tricuspid regurgitant (TR) jet

The cursor should be directed along the long axis of the RV and through the middle of the TV, parallel to the flow of the TR jet.



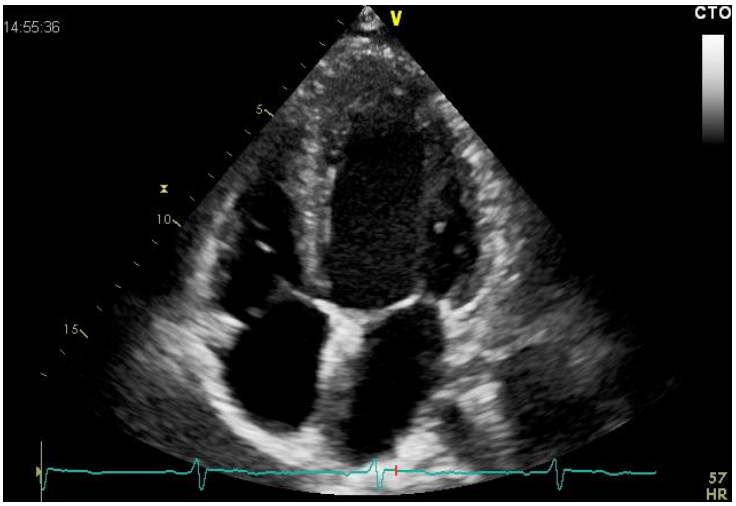
APICAL VIEWS

The apical views are obtained by placing the transducer laterally and inferiorly at the apex and moving superiorly and medially until the cardiac chambers are visualized.

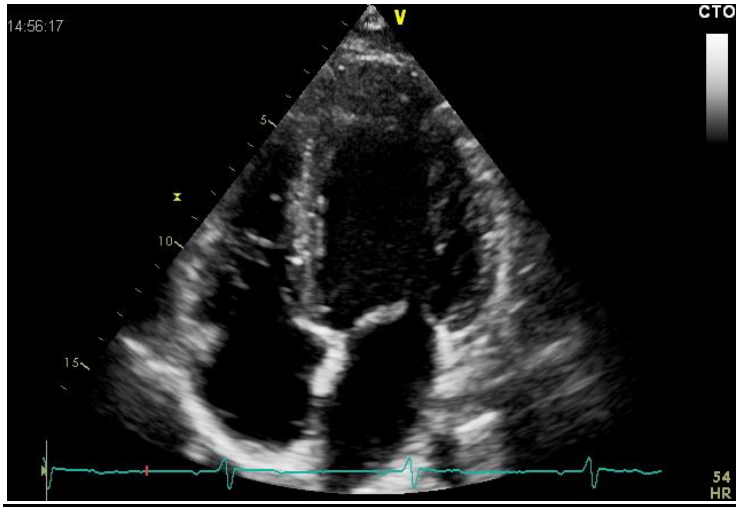
E. Apical 4-Chamber View

<u>2D – 4 chambers</u>

The image should be properly aligned to capture the entire four chambers. The interventricular septum should be as parallel as possible to the superior-inferior direction and the entire LV endocardium must be visualized in both systole and diastole. It is important to adequately visualize the apex and lateral LV free wall. Avoid foreshortening or elongating the RV or LV chambers.

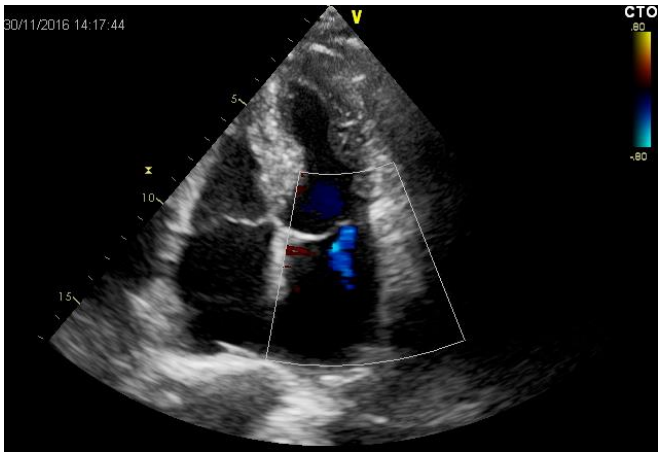


2D focusing only left chambers



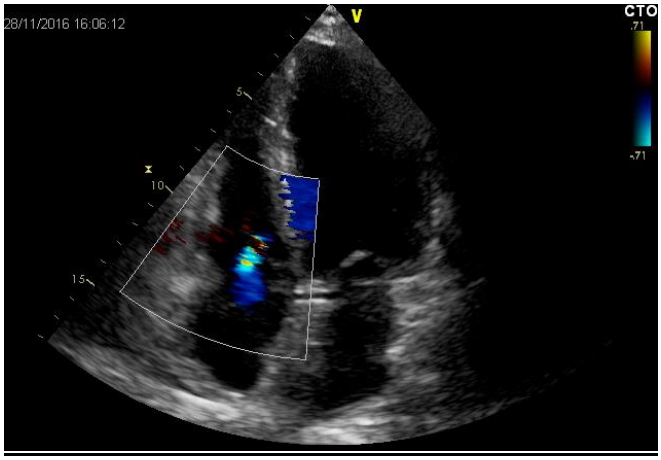
Color flow Doppler of MV

With the optimized 2D apical 4 chamber view, and the LV and LA seen in full, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



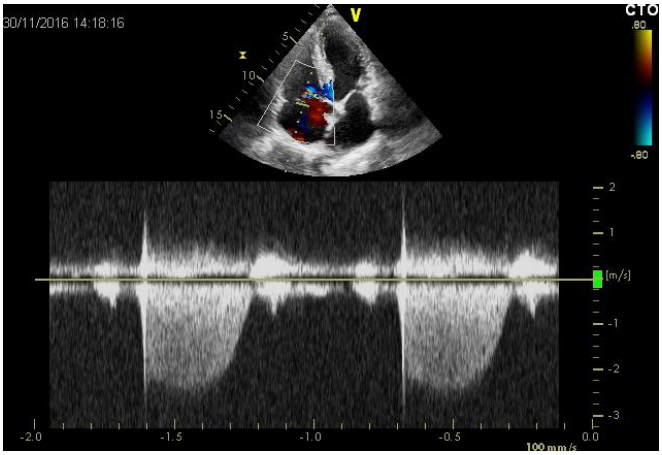
Color flow Doppler of TV

With the optimized 2D apical 4 chamber view and the entire RA seen and the tricuspid valve (TV) leaflets now clearly visible, place the color sector over the TV.



CW Doppler of TR iet

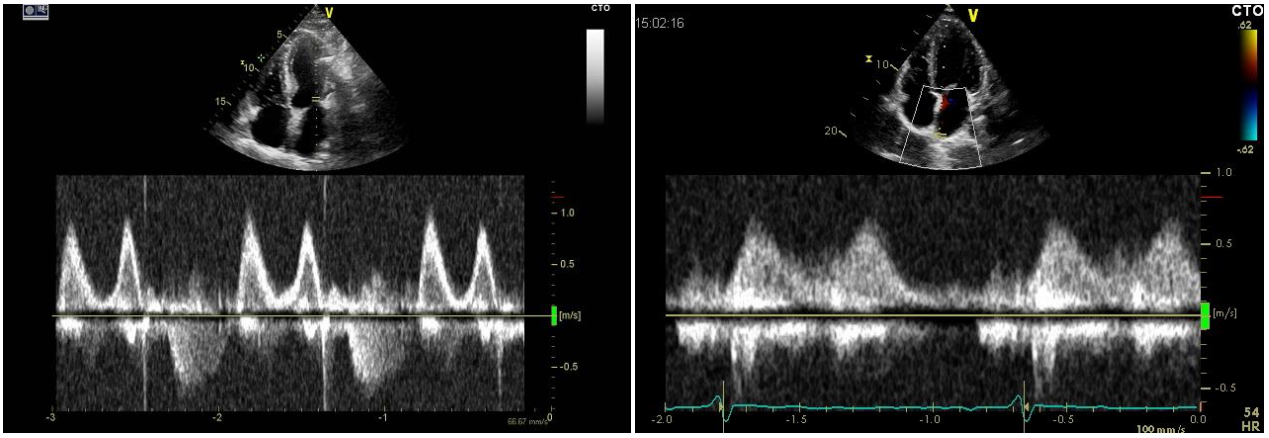
The cursor should be directed along the long axis of the right ventricle (RV) and through the middle of the TV, parallel to the TR flow.



PW Doppler

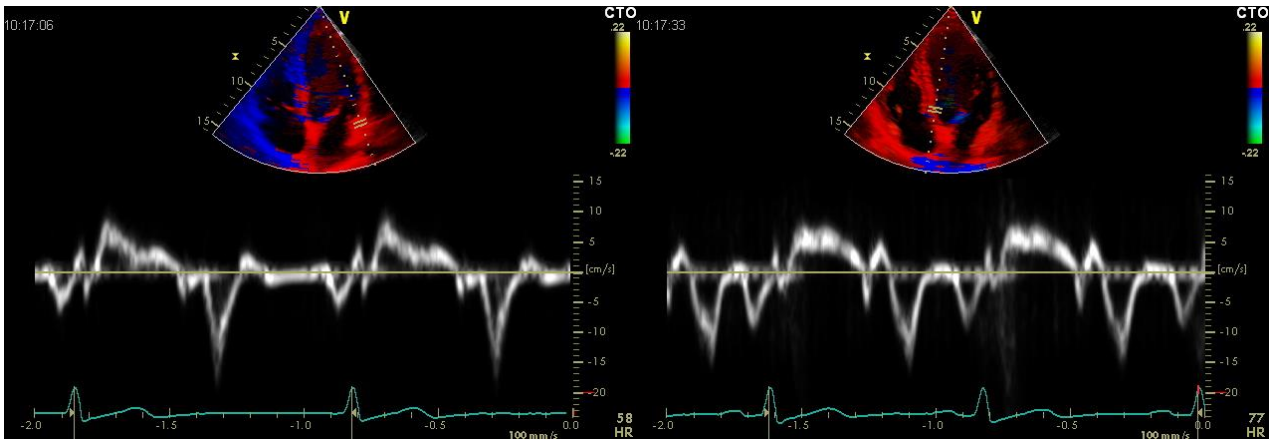
a. PW Doppler transmitral flow recordings with sample volume at leaflet tips during diastole

b. PW Doppler right superior pulmonary vein recordings guided by color Doppler



DTI PW Doppler

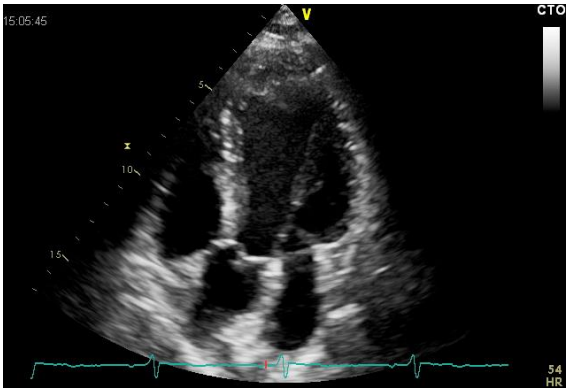
PW tissue Doppler imaging (DTI) is performed in the apical views to acquire mitral annular velocities. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5–10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Record a minimum of 5 cardiac cycles at a sweep speed of 100 mm/sec.



F. Apical 5-Chamber View

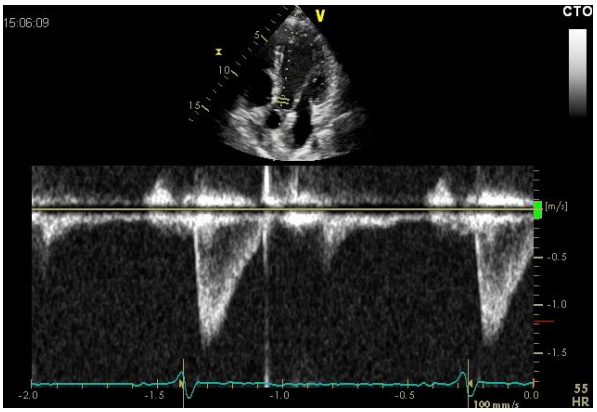
2D

Five-chamber view should include the left ventricular outflow tract (LVOT) and the aortic valve (AV) cusps. Be careful to maintain maximal LV length, to visualize all 4 cardiac chambers and to optimize endocardial definition.



LV outflow tract PW Doppler

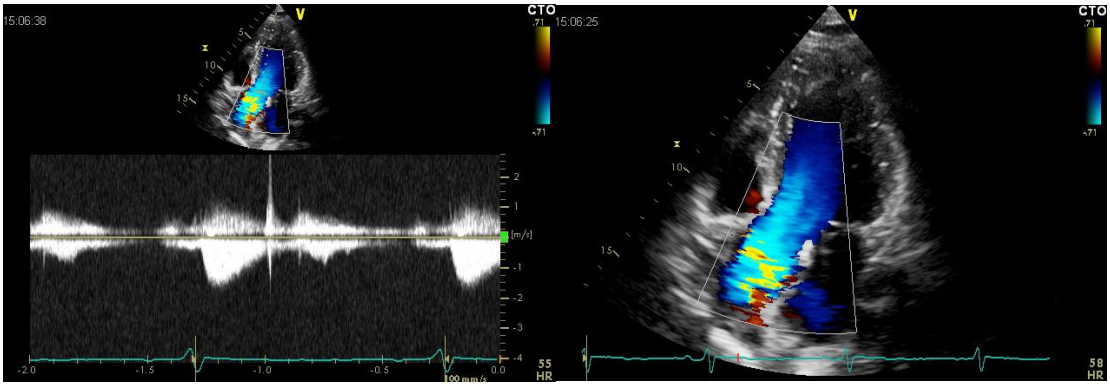
Place the color sector over the LVOT and aortic valve. Align the PW signal parallel to the direction of LVOT flow and position the PW Doppler sample (5 mm sample volume size) within the LVOT 5-10 mm proximal to the AV. Adjust the baseline and Doppler scale to visualize the peak wave velocity.



Aortic CW Doppler and color Doppler

Still in the five-chamber view, the cursor should be directed along the long axis of the LVOT and AV cusps. Adjust the gain to obtain a clear LVOT flow signal and the baseline and scale to capture the peak velocity.

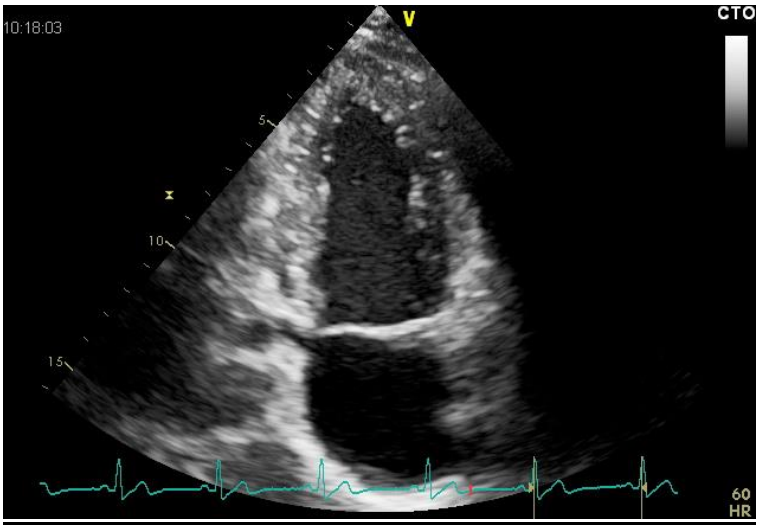
With the optimized 2D apical 5-chamber view, place the color sector over the aortic valve.



G. Apical 2-chamber view

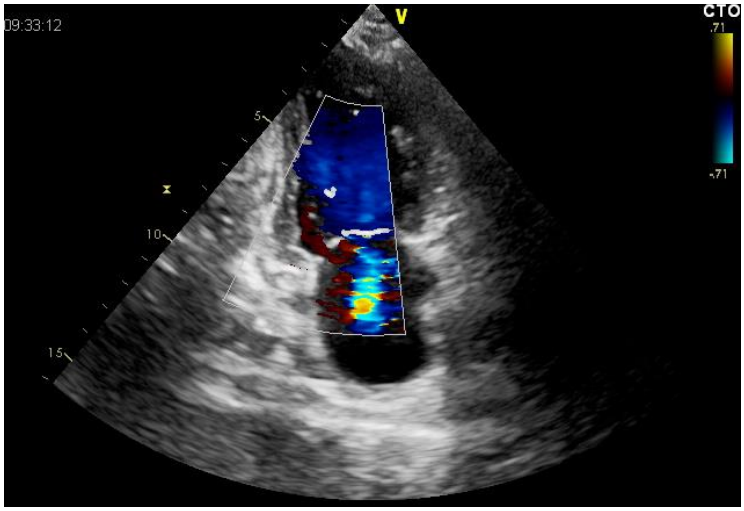
2D

LV and left atrium cavities should be entirely visualized. In particular, for LV, ensuring the entire LV endocardium is visualized in both systole and diastole. Ensure that the LV apex is not cut off.



Color flow Doppler of MV

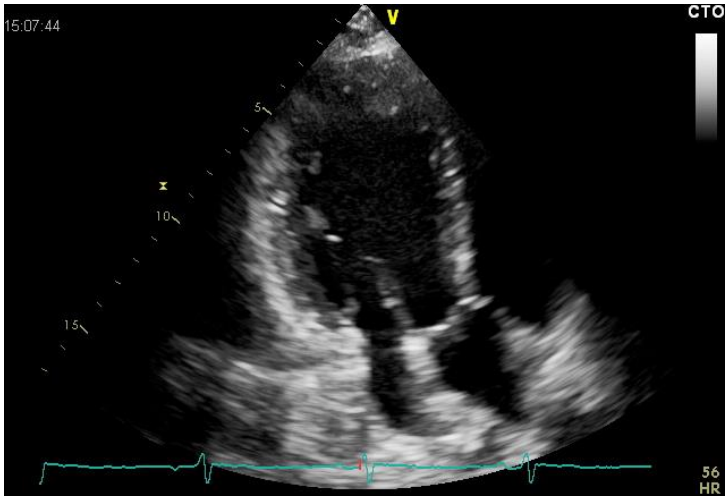
With the optimized 2D apical 2 chamber view, and the LV and LA seen in full, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



H. Apical 3-Chamber View

2D

Visualize the entire LV, as well as the MV and the LA, similar to the parasternal long axis view. Again, it is important to properly align the image and not to foreshorten the LV.



Color flow Doppler of aortic valve

With the optimized 2D apical 3-chamber view, place the color sector over the aortic valve.

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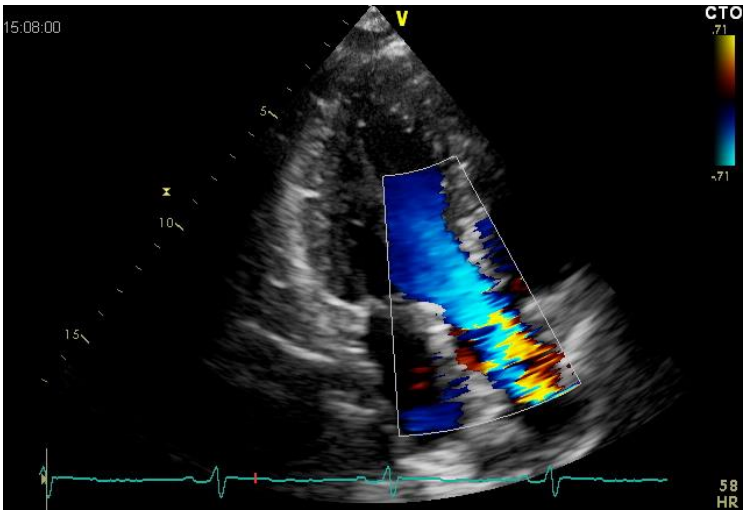
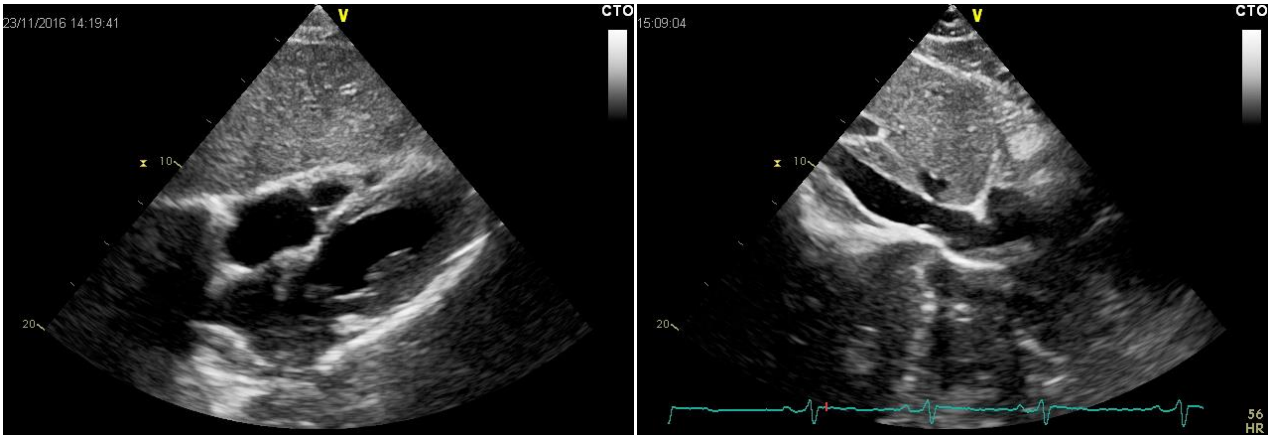


I. Subcostal View

2D

With the transducer in the subcostal position obtain a 4-chamber view.
Then, angulate the transducer to visualize the proximal inferior vena cava (IVC) where it meets the right atrium. Ask the patient to sniff or inspire - this maneuver will reveal if the IVC diameter changes with inspiration.



7-Contact Information

For technical echo-related questions, please direct all questions and inquiries to masterdata@auxologico.it

8-Supplemental References for echocardiographic procedures

1. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39 e14.

2. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the Use of Echocardiography in Adult Hypertension: A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr. 2015;28(7):727-54.

3. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.

4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

ELECTROCARDIOGRAPHY

Electrocardiographic assessment of LV mass

Standard 12-lead ECG will be recorded at 50 mm/s speed. There must be at least one 1 mV square calibration pulse and a time scale to facilitate analysis. Tracings must show at least 3 beats per lead and a rhythm strip of at least 10 s duration. Artefacts due to loose leads are not acceptable. Standard filter settings according to local practice should be chosen, and settings have to be recorded on the printout. The digital ECG file will be uploaded on the web based platform

Recording recommendations:

1. *Description*

The description is written for the mode "automatic system". Please read the manual of the ECG device for other modes.

2. *Installation*

The electrocardiograph is put aside the top of an examination couch of the patient's bed. The power supply comes from either the net or network-independent chargeable battery. It is important for a trouble-free operation that the power line does not go in parallel to the lines of the electrodes.
Operational check: Switching on equipment at the on-off key button.

3. *Preparations*

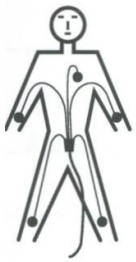
The patient/test person lies on the examination couch with undressed upper part of the body and free ankles. In males, disturbing hair-growth on the chest must be shaved off. The patient must lie relaxed, a pleasant room temperature is necessary.

4. *Attaching the electrodes for the standard derivations*

Carefully laying out the electrodes is required for an accurate ECG result. For the standard derivations 4 extremities and 6 chest wall derivations must be laid out. Contact spray on the skin (see below) is sprayed on. Important: Spray on the skin not on the electrodes.

5. *Extremity derivations*

The positions of the extremity derivates are as follows:
Right arm: Red line
Left arm: Yellow line
Left leg: Green line
Right leg: Black line



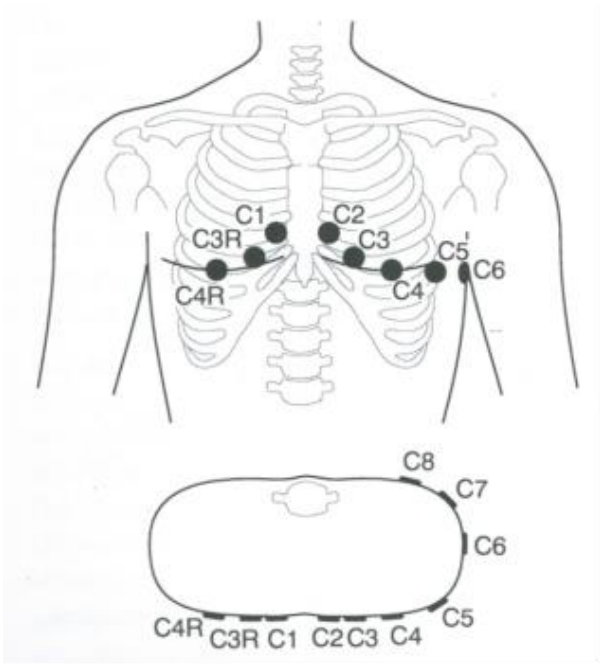
richtig

falsch

6. *Chest wall derivations*

Right	Wrong

C1: In the 4th Intercostal Space at the right sternal site
C2: In the 4th Intercostal Space at the left sternal site
C3: On the 5th rib between C2 and C4
C4: In the 5th Intercostal Space on the left medioclavicular line
C5: On the height of C4 (horizontal) in the front left axillary line
C6: On the height of C4 (horizontal) in the middle left axillary line



7. *Remarks:*

Laying out the chest wall electrodes, it is very important for the derivations V4-V6 proceeding on a horizontal line. So please do not follow the anatomical course of the 5th Intercostal Space as it is often misunderstood.
The 1st Intercostal Space is found directly below the clavicle; the 1st rib cannot be felt. Therefore the 1st Intercostal Space lies below the clavicle; the 2nd is the first palpable Intercostal Space.

8. *ECG writing*

Push the operating button and follow the menu for entering the patient data.
Press button "filters" for excluding muscle artefacts with the arrow keys.

The patient must lie quietly and eased and breathe normally (about 6/minutes).
Start ECG writing by pressing the suitable button.

With the control mode “Automatic” 12 derivations are taken simultaneously, analysed and the ECG distributes over a period of 10 sec. automatically.

Check the ECG tracing on the paper, provide with necessary specific data in handwriting.
If necessary: Do a copy by pressing the specific button.

Analyses:

- ECGs will be analysed for criteria of left ventricular hypertrophy by each centre; requested parameters must be inserted in the ECG sheet of the eCRF; the eCRF will automatically calculate ECG-LVH indices.

- The ECG will also be evaluated by the Central Reading Centre (Prof. R. E. Schmieder, Erlangen, Germany). In order to ascertain adequate source documents, before starting the study:

    - In case of ECG recorder with digital output, a sample file will be requested by the General Coordinating Center in Milan; this file will be checked by the Central Reading Centre
    - In case of ECG recorder without digital output, the General Coordinating Center in Milan will request a high quality scanned ECG (1200 dpi); this file will be checked by the Central Reading Centre for adequate quality.

- The source file has to be attached to the eCRF; the Central Monitoring Team will forward them to the Central Reading Centre in Germany

The following ECG indices of LVH will be calculated:

- Sokolow-Lyon Index
  SV1 + RV5 or RV6 ≥ 3.5 mV, The higher value should be documented.
- Cornell Voltage Index
  S in V3 + R in aVL > 2.4 mV (men)
  S in V3 + R in aVL > 2.0 mV (women)
- Cornell Voltage Product

(RaVL + SV3) × QRS duration	≥244.0 mVms	(men)
(RaVL + SV3 + 0.8 mV) × QRS duration	≥244.0 mVms	(women)

ECG determination of LV mass

ECG represents the most available method to evaluate LV mass in daily clinical practice. A recent meta- analysis of 26 studies comprising a large hypertensive population of 40444 subjects, found Sokolow-Lyon voltage criteria to be the most commonly used method for determination of ECG-LVH in clinical practice. However, the Cornell voltage product represented the most sensible, accurate index for detection of ECG-LVH in particular in female and obese subjects (1). Also, the recent ROADMAP study (2) found the Cornell Product to be the most accurate index of LVH; moreover, the ability to express results as continuous variables with this index allows to perform more comprehensive statistics. On the basis of these findings, the MASTER study will evaluate ECG-LVH primarily with the Cornell Voltage Product, and also with Cornell Voltage Index and Sokolow-Lyon Index.

Supplemental References for electrocardiography

1. Schillaci G, Battista F, Pucci M. A review of the role of electrocardiography in the diagnosis of left ventricular hypertrophy in hypertension. J Electrocardiol. 2012 45(6):617-23
2. Raff U, Ott C, Ruilope LM, Menne J, Haller H, Schmieder RE. Prevention of electrocardiographic left ventricular remodeling by the angiotensin receptor blocker olmesartan in patients with type 2 diabetes. J Hypertens. 2014 Nov;32(11):2267-76