CLINICAL RESEARCH PROTOCOL

1. TITLE OF THE STUDY

Assessment of outcomes of reverse remodeling of the left ventricle in patients with aortic valve insufficiency after surgical correction

Protocol version 1.1

Last updated: 20/03/2024

Clinical trials Organization's Unique Protocol ID: 173538086

2. SPONSORSHIP

None, initiative study

3. DETAILS

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NCT: **********

4. SIGNATURES

RESEARCHERS' SIGNATURES

I agree to conduct the study described above in accordance with the protocol, GCP, and applicable regulatory requirements. All information related to the study will be treated confidentially.

Full Name	Position	Signature	Date
Charchyan Eduard Rafaelovich, MD, PhD, professor	corresponding member of the RAS, head of the cardiac surgery department No. 1 Petrovsky National Research Center of Surgery		01.05.2024
Bulynin Andrey Andreevich	cardiovascular surgeon of the cardiac surgery department No. 1 BUZ VO 'Voronezh Regional Clinical Hospital No. 1'		01.05.2024

5. CONFIDENTIALITY POLICY

This document contains confidential information that should not be disclosed outside the research team, regulatory authorities, and members of the local ethics committee.

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6. HISTORY OF CHANGES

Version	Approval Date	Summary of Changes
Version 1.0	01.11.2023	Initial Draft
Version 1.1	20.03.2024	Changes made regarding the development of the information booklet

7. PROTOCOL SYNOPSIS

Study Title	Assessment of the left ventricle reverse remodeling outcomes in patients with aortic valve insufficiency after surgical correction
Sponsor	Investigator-Initiated Study
Study Phase	Phase III
Hypothesis	We hypothesize that surgical correction of functional mitral regurgitation during interventions for chronic aortic valve insufficiency in patients with significant dilatation of the left heart chambers affects the reverse remodeling of the left ventricle in the postoperative period.

Research objectives and tasks	Research objective: To assess myocardial reverse remodeling in patients with significant left ventricular dilation caused by chronic aortic regurgitation, depending on the degree of mitral valve insufficiency and surgical approach. Main objectives of the study: 1. To evaluate the short-term and long-term outcomes of aortic valve replacement for aortic valve insufficiency in patients with significant left ventricular dilation 2. To compare the results of myocardial reverse remodeling depending on the strategy regarding functional mitral valve insufficiency at 3 and 12 months post-surgery 3. To determine preoperative predictors of an unfavorable left ventricle function and architecture recovery prognosis. 4. Assess the patients life quality 12 months after surgery 5. Develop a clinical protocol for simultaneous surgical treatment of mitral regurgitation during aortic valve replacement in patients with significant left ventricular myocardial remodeling caused by chronic aortic regurgitation
Study design	This study is a multicenter, comparative, prospective

Inclusion criteria	1. *Age over 18 years* 2. *Proposed primary elective surgical intervention for chronic aortic regurgitation* 3. *Presence of functional mitral regurgitation* 4. *Left Ventricular End-Diastolic Volume 250 ml≥*
Exclusion criteria	1. *Infectious endocarditis* 2. *Previous myocardial infarction* 3. *Necessity for simultaneous myocardial revascularization* 4. *Acute aortic regurgitation* 5. *Previously established left ventricular dilation not associated with the development of aortic regurgitation* 6. *Lack of informed consent*
Number of study subjects	120 patients

Investigated procedure	It is planned to study the initial and long-term results of left ventricle reverse remodeling in patients with aortic regurgitation, depending on the strategy chosen for the correction of functional mitral regurgitation and its severity.
Duration of observation	12 months after surgical treatment
Methods of statistical evaluation	The determination of the significance of differences between quantitative data of unrelated samples will be carried out using the Student's t-test under the condition of normal distribution; in the case of non-normal distribution, the Mann-Whitney test, White's test, Van der Waerden test, and Kolmogorov-Smirnov test are planned to be used. In the case of analyzing the significance of differences in quantitative data in related samples with a normal distribution, the paired Student's t-test is planned to be used; in the case of non-normal distribution, the Wilcoxon test and sign test will be used. Qualitative data analysis will be performed using the $\chi 2$ test and the McNemar test. To assess the reliability of the relationship between quantitative data, regression analysis, Pearson's correlation coefficient, Spearman's rank correlation coefficient, and Kendall's correlation coefficient are planned to be used. Descriptive and analytical statistical methods will be finalized after analyzing the sample size. To eliminate the influence of differences in baseline clinical parameters on the study outcome, a propensity score matching analysis (PSM) is planned between the ordinary 'Unmatched' groups using the nearest neighbor matching method for 1:1 pair matching. Demographic data and clinical indicators will be presented using descriptive statistics (absolute indicators and percentage shares for categorical variables, or mean ± standard deviation for normally distributed continuous variables; for continuous variables with non-normal distribution, the median and interquartile range will be specified). The significance of differences in repeated measurements will be analyzed using ANOVA.

Sample size	Considering a clinically significant difference in left ventricle volumes 12 months after surgery, equal to 15 ml/m^2, with a power of 80% and alpha of 5%, the sample size should be at least 64 patients in each group. *The sample size usually depends on the standard deviation, which is determined based on the results of similar studies or, more often, a pilot study. Approximate indicators will be obtained by February 2024 after analyzing the RCHC sample within the framework of the dissertation research.*

8. ABBREVIATIONS

AAo – ascending aorta
AVOA – amplitude of aortic valve opening
AML – anterior mitral leaflet
Ao – aorta
AoArch – aortic arch
AoRoot – aortic root
AoV – aortic valve
AR – aortic regurgitation
AS – aortic stenosis
ASA – atrial septal aneurysm
ASD – atrial septal defect
ASE – American Society of Echocardiography
AVA – aortic valve area
BSA – body surface area
CFD – color flow Doppler
CI – cardiac index
CO – cardiac output
CS – coronary sinus
CWD – continuous wave Doppler mode
DAO – descending aorta
EDV – end-diastolic volume
EF – ejection fraction
EPSS – E point to septal separation of the mitral valve
ESV – end-systolic volume
A5CV – apical five-chamber view
A4CV – apical four-chamber view
IVC – inferior vena cava
IVS – interventricular septum
LA – left atrium

LAA – left atrial appendage

LAX – long axis

LAX Ao – longitudinal section of the aorta

LAX LV – longitudinal section of the left ventricle

LAX RVIT – longitudinal section of the right ventricular inflow tract

LAX RVOT – longitudinal section of the right ventricular outflow tract

LCC – left coronary cusp

LPA – left pulmonary artery

LV – left ventricle

LVEF – left ventricular ejection fraction

LVIDd – left ventricular internal diameter in diastole

LVIDs – left ventricular internal diameter in systole

LVIDV – left ventricular internal diastolic volume

LVISV – left ventricular internal systolic volume

LVOT – left ventricular outflow tract

LVPW – inferolateral wall of the left ventricle

M-mode – M-mode

MR – mitral regurgitation

MS – mitral stenosis

MVA – mitral valve area

NCC – non-coronary cusp

PA – pulmonary artery

PAP – pulmonary artery pressure

PG – pressure gradient

PHT – pressure half-time

PML – posterior mitral valve leaflet

PR – pulmonary regurgitation

PS – pulmonary stenosis

PV – pulmonary valve

PWD – pulsed wave Doppler mode

RA – right atrium

RAP – right atrial pressure

RVWT – right ventricular wall thickness

RVIT – right ventricular inflow tract

RVOT – right ventricular outflow tract

RVSP – right ventricular systolic pressure

SAM – systolic anterior motion

SAX APEX – short axis at the apex level

SAX BASE – short axis at the base level

9. INTRODUCTION

9.1 Introduction and Research Hypothesis

During surgical intervention for aortic valve insufficiency accompanied by hemodynamically significant functional mitral regurgitation, the surgeon faces the question of whether intervention on the mitral valve is necessary. Secondary MR of varying degree is found in 60%-75% of patients who have undergone aortic valve replacement. [1]

We hypothesize that the chosen strategy regarding moderate mitral regurgitation during the correction of aortic valve lesion in patients with significant left ventricular remodeling plays a crucial role in the course of reverse LV remodeling when assessed by transthoracic echocardiography 12 months post-surgery.

9.2 General Information

Adaptation of the cardiovascular system to increased preload is observed in a number of quite physiological conditions: child growth, pregnancy, intensive aerobic training, as well as in pathological processes: atrioventricular valve insufficiency, or systemic arteriovenous shunt. [2, 3]

9.3 Study Rationale

The heart is a terminally differentiated organ with very limited reparative capabilities at the cellular level. The number of heart cells does not change over a lifetime; according to some data, the volume of cellular repair does not exceed 1% of the cellular mass per year. Cardiomyocytes are incapable of completing mitosis due to the presence of a rigid cytoskeleton and, consequently, the impossibility of cytokinesis. Repair and compensation at the cellular level with the inability of cytokinesis involves a multiple increase in intracellular elements without completed division, which causes an increase in cytoskeleton stiffness. Aortic valve insufficiency is the third most common valvular heart defect. Severe and significant aortic valve insufficiency is associated with hemodynamically significant functional mitral valve insufficiency in more than one-third of cases. Aortic valve insufficiency should be considered pathogenetically and hemodynamically as a pressure and volume overload, while mitral regurgitation is a typical variant of isolated volume overload. Pressure overload causes cardiomyocyte hypertrophy due to the parallel layering of sarcomeres and disruption of energy couplings. Subsequent metabolic changes induce apoptosis and autophagy of cardiomyocytes with a progressive loss of functional cardiac cell mass; in the remaining functional

cardiomyocytes, polyploidization occurs, and simultaneously, a humoral response arises, the prolonged tension of compensatory mechanisms of which leads to worsening myocardial dysfunction. With volume overload, there is a progressive expansion of the left ventricular cavity due to the addition of new sarcomeres in sequence with the existing ones. Prolonged existence of volume overload also ultimately leads to the loss of functional cardiac cell mass and the development of systolic and diastolic heart failure. It should be noted that the elongation of the left ventricular cross-sectional circumference along the short axis due to progressive dilation, according to the Frank-Starling law, requires supraphysiological preload to achieve optimal contraction strength. Functional mitral regurgitation is a variant of increased preload. A sharp decrease in left ventricular preload with hemodynamically effective correction of functional mitral regurgitation simultaneously with the correction of the aortic defect can potentially impair left ventricular contractility in the early stages of reverse remodeling. It is evident that postoperative regression of mitral regurgitation is possible in cases where the reverse development of changes that caused mitral regurgitation is possible. For example, with normal sizes of the left ventricle and atrial tethering of the mitral valve against the background of persistent atrial fibrillation, isolated correction of aortic valve insufficiency is not able to reverse the arrhythmogenic fibrosis of the left atrium and, consequently, improve the grading of mitral regurgitation. Mitral regurgitation against the background of a significant increase in the end-systolic size of the left ventricle and a decrease in contractility may be characterized by a favorable prognosis of reverse development after correction of the aortic defect, provided there are no other causes of mitral regurgitation.

There is a limited number of research studies dedicated to the reverse remodeling of the left ventricular myocardium and the spontaneous regression of functional mitral regurgitation after surgical correction of aortic stenosis; the degree of study of this issue in the context of aortic valve insufficiency is even lower. In the available studies, the main focus is on assessing the impact of hemodynamically significant functional mitral regurgitation, which has not undergone surgical correction during aortic valve replacement, on immediate and long-term survival, as well as the course of the mitral regurgitation itself. In many studies, fundamentally different causes of functional mitral regurgitation—such as aortic stenosis and aortic valve insufficiency—are not distinguished. None of the studies found evaluate the course of reverse remodeling of the left ventricle depending on the chosen strategy regarding the mitral valve. The obtained results and conclusions on the aforementioned issues are contradictory, exacerbating the ambiguity of the scarce data. There are also no studies that include patients exclusively with severe forms of left ventricular remodeling against the background of chronic aortic regurgitation. The duration of hemodynamically significant aortic valve insufficiency and the age of manifestation, as well as the patient's gender, are rarely analyzed. Thus, the study of reverse remodeling of the left ventricular myocardium in patients with chronic aortic valve insufficiency against the background of functional mitral regurgitation is of interest, remains unexplored, and is clinically relevant.

10. OBJECTIVES AND ENDPOINTS OF THE STUDY

To study the impact of the volume of surgical treatment for chronic aortic valve insufficiency on the rate and degree of reverse myocardial remodeling in patients with significant left ventricular dilation against the background of chronic aortic regurgitation, depending on the degree of mitral valve insufficiency.

10.1 Objectives

Primary objective:

1. To assess the impact of functional mitral regurgitation on the rate and degree of reverse myocardial remodeling in patients with significant left ventricular dilation against the background of chronic aortic valve insufficiency after surgical correction of the aortic defect.

Secondary objectives:

1. To assess the relationship between the severity of preoperative functional mitral valve insufficiency and the patient's life quality 12 months after surgery.

Research objectives:

1. To assess the relationship between severity of functional mitral regurgitation and diastolic dysfunction of the left ventricle at 3 and 12 months after surgical correction of aortic regurgitation.
2. To assess the relationship between the severity of functional mitral regurgitation and the dynamics of left atrial volume, evaluated by transthoracic ECHO-CG, at 3 and 12 months after surgical correction of aortic regurgitation.

10.2 Study endpoints

Primary endpoints:

1. *Reduction of the left ventricle end-diastolic volume at 3 and 12 months after surgical correction of aortic regurgitation*
2. *Freedom from readmission for heart failure related conditions 12 months after surgery*

Secondary endpoints:

1. Patient quality of life according to the EQ-5D-5L questionnaire results.

Exploratory endpoints:

1. Left ventricle ejection fraction at 3 and 12 months after surgical correction of aortic regurgitation

2. Diastolic function of the left ventricle based on echocardiography results, assessed preoperatively and at 3 and 12 months after surgical correction of the aortic regurgitation (mean E/e', DT)
3. Indexed to BSA volume of the left atrium (according to transthoracic echocardiography results) preoperatively, as well as at 3 and 12 months after surgical treatment

*BSA – body surface area, calculated using the Mosteller formula

11. Study design

11.1 General Provisions

A multicenter controlled comparative prospective cohort study is planned.

It is known that chronic aortic valve insufficiency leads to significant remodeling of the left ventricle and development of functional mitral regurgitation. On one hand, residual mitral regurgitation may complicate the postoperative period by increasing the preload on the left ventricle; however, a dilated left ventricle after surgical correction of the aortic defect still requires supraphysiological preload during the most vulnerable period of early rehabilitation. As the volume of the left ventricle regresses, functional mitral regurgitation is also capable of regressing. A significant scientific task is to address the role of functional mitral regurgitation in the reverse remodeling of the left ventricle after correction of chronic aortic valve insufficiency.

11.2 Definition of the study group

Patients who have undergone open surgical correction of aortic valve insufficiency with large eccentric left ventricle remodeling (EDV more than 250 ml). Men and women over 18 years old.

11.2.1 Inclusion Criteria

Potential study subjects must meet the following criteria:

1. *Age over 18 years*
2. *Planned primary elective surgery for chronic aortic regurgitation*
3. *Presence of functional mitral regurgitation*
4. *Left Ventricular End-Diastolic Volume ≥ 250 ml*

11.2.2 Non-inclusion Criteria

1. *Infectious endocarditis*
2. *Previous myocardial infarction*
3. *Necessity of simultaneous myocardial revascularization*
4. *Acute aortic valve insufficiency of any etiology*
5. *Previously established left ventricular dilation not associated with the development of aortic regurgitation*
6. *Permanent or persistent form of atrial fibrillation*

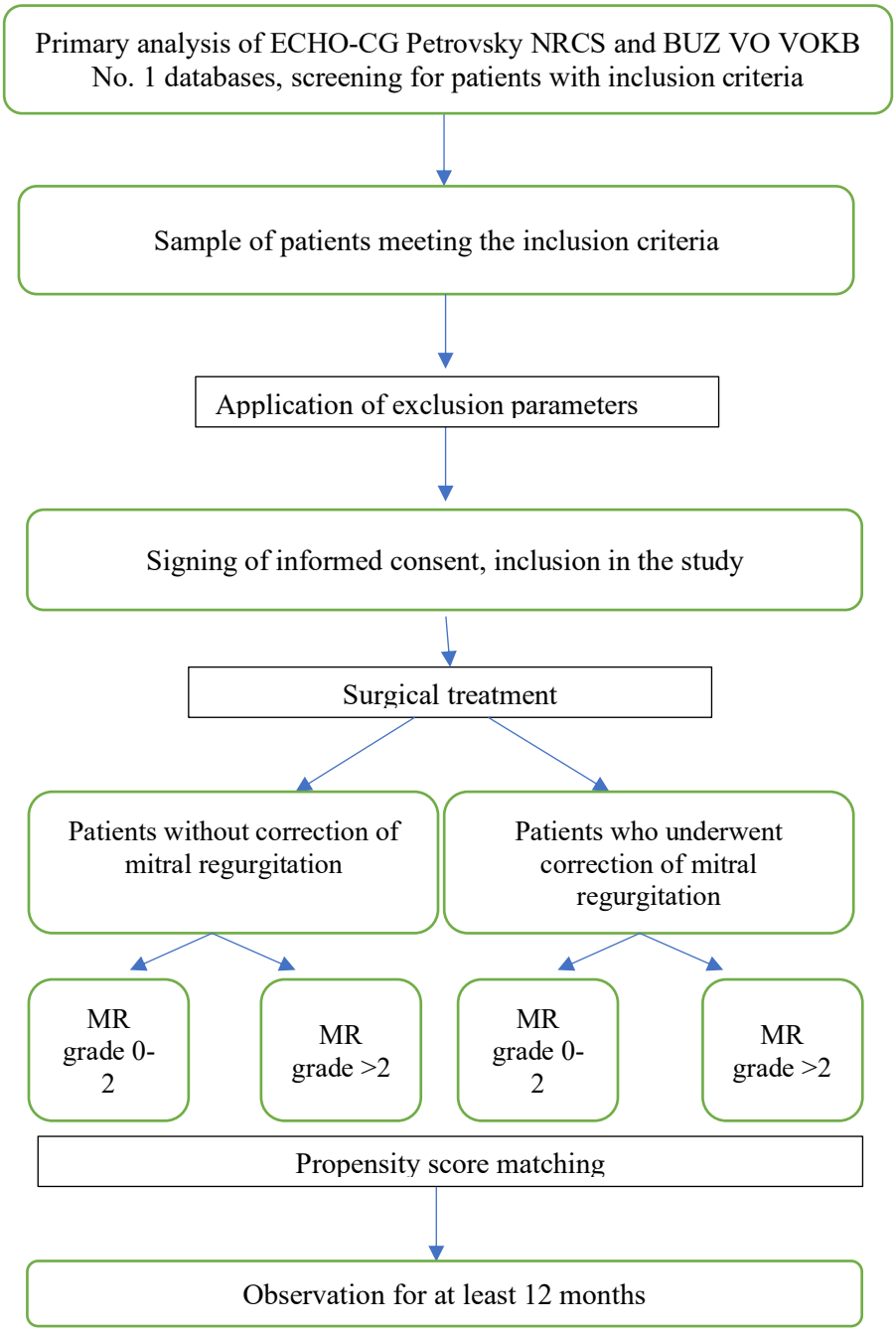
7. *Ongoing pregnancy within the first 12 months after surgery*
8. *Simultaneous participation in other studies*
9. *Implanted heart pacemaker*
10. *Refusal to sign informed consent*

During the population analysis, the research team reserves the right to add new exclusion criteria if required to achieve sample representativeness, due to the clinical situation, or common sense.

11.2.3 Exclusion Criteria

1. *Acute coronary event diagnosed within 12 months after surgical correction of the aortic defect.*
2. *Need for resynchronization therapy or permanent right ventricular pacing in the first 12 months after surgery.*
3. *Re-do cardiac surgery for any reason within 12 months after the operation.*

Figure 1. 'Principle scheme of forming the study working sample'



12. ASSESSMENT METHODS AND PROCEDURES

An informed consent will be obtained from each subject prior to conducting any procedure related to the protocol of this study.

12.1 Preliminary Screening (Visit 0)

As part of the clinical work at the Petrovsky NRCS and BUZ VO VOKB No. 1, a screening of the medical documentation of patients scheduled for surgical treatment for aortic valve insufficiency will be conducted. Subjects who meet the inclusion criteria and do not have any exclusion criteria will be offered participation in the study.
Patients may also be initially referred by other specialists from other medical institutions for planned surgical treatment of chronic aortic regurgitation.

Subjects who express interest in participating in the study will be invited to Examination 1.

During Examination 1, patients will be offered an informational brochure, developed by the research team in collaboration with the Petrovsky NRCS research development department (print run of 200 copies), containing comprehensive information revealing the potential benefits and risks of participating in the study. After reviewing the information and having all relevant clarifying questions answered by the researcher, the subject will be given sufficient time to sign the voluntary informed consent. Voluntary informed consent must be obtained exclusively by a specialist qualified as a cardiologist or cardiovascular surgeon. Prior to obtaining voluntary informed consent, it is not possible to carry out any of the procedures provided for in this study.

Examination 2 is carried out on the 2nd day after surgical treatment of aortic valve insufficiency in the intensive care unit before leaving for the specialized department intensive care unit.

12.2 Early postoperative examination (Examination 2)

An assessment of the surgical treatment initial results of will be conducted: stability of the pre-perfusion period, dosage of perioperative pharmacological support medications, features of the surgical intervention, and indicators of the body's internal environment. Mandatory study – transthoracic or transesophageal ECHO-cardiography.

12.3 Assessment 9-14 days after surgery (Examination 3)

A comprehensive assessment of the inpatient treatment stage is planned, according to Table 1.

12.4 First outpatient visit (Examination 4)

Routine registration of parameters reflecting the rate of reverse remodeling of the left ventricle, associated parameters, patient life quality, and analysis of adverse events occurring from Examination 3 to Examination 4 is planned.

In the event that the patient cannot or does not wish to attend the examination, comprehensive information and task resolution will be conducted by phone. If the visit is postponed for any reason, the schedule of subsequent examinations will not be modified.

Table 1. Procedures provided by the study protocol

Examination Number	0	1	2	3	4	5
Planned activities	**Screening**	**Inclusion in the study**	**ICU**	**11 days**	**3 months**	**12 months (EOS)**
				± 2 days	**± 7 days**	**± 14 days**
Assessment of eligibility for study participation	**x**					
Familiarization with the conditions of participation in the study and possible risks		**x**				
Signing the informed consent		**x**				
Medical history collection		**x**				
General clinical evaluation		**x**	**x**	**x**	**x**	**x**
Anthropometry (height without shoes and weight in light clothing)		**x**			**x**	**x**
ECHO-cardiography		**x**	**x**	**x**	**x**	**x**
Questionnaire completion		**x**		**x**	**x**	**x**
6-minute walk test		**x**		**x**	**x**	**x**
ECG		**x**	**x**	**x**	**x**	**x**
Assessment of complications since the previous examination			**x**	**x**	**x**	**x**
NT-proBNP (optional)		**x**			**x**	**x**
Myocardial MRI with gadolinium contrast enhancement (optional)		**x**				**x**

12.4 Outcome assessment

12.4.1 History taking

Detailed recording of medical history and life history is planned during Examination 1.

12.4.2 Demographic data

The date of birth and gender of each study participant will be entered into the database during Examination 1.

12.4.3 Objective examination

A standard clinical examination is provided as part of Examinations 1-5.

12.4.4 Height and weight

Height in centimeters and weight in kilograms will be assessed during Examinations 1, 4, 5. Body weight will be recorded to the nearest 0.1 kilogram [kg] in light clothing without shoes. Height will be recorded to the nearest 1 cm without shoes.

12.4.5 Electrocardiography (ECG)

A standard 12-lead ECG (after 5 minutes of rest) will be performed (at Examination 1 (baseline), examinations 3, 4, 5 according to the standard method (paper speed 50 mm/sec, amplitude 10 mm/mV, with at least 5 seconds of recording available for each lead). Recording will be conducted using an automatic recorder with digital signal processing capability. Heart rate will be assessed, and potential disturbances in heart rhythm, conduction, and repolarization parameters, such as QT interval prolongation or atrioventricular block, will be recorded.

12.4.6 ECHO-cardiography

ECHO-cardiography will be performed as part of Examinations 1-5. It is planned to perform transthoracic ECHO-cardiography and transesophageal intraoperative ECHO-cardiography. The scope of the study during Examinations 1, 3-5 will correspond to the minimum transthoracic EAUD protocol (https://easud.org/sites/default/files/manuals/tte_protokol_eaud.pdf). Examination 2 may be significantly hindered due to unsatisfactory visualization. All DICOM images obtained during the examination of each study participant will be stored in RAW format on a common DICOM server for all research centers. A selective cross-analysis of the standardized set of DICOM data, in accordance with EAUD, is planned to be conducted by physicians with more than 5 years of experience in cardiovascular imaging in the ultrasound modality.

- *The assessment of myocardial contractility will be performed using the Simpson Biplane method, the General Electric "auto EF" algorithm, and Speckle Tracking analysis based on General Electric algorithms.*
- *The standard transthoracic protocol in all cases will be supplemented by myocardial strain analysis with the recording of initial RAW DICOM data, as well as Global Longitudinal Strain, Strain Rate, and myocardial mechanical dispersion.*

12.4.7 Questionnaires

1. *EuroQOL*-5D (EQ-5D): EQ-5D is a standardized instrument for assessing the respondent's quality of life: in the form of a health profile - five questions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with five levels of severity, and a score obtained using the EQ-VAS visual analog scale.

The questionnaire will be offered for completion during Examinations 1 and 3-5. The questionnaire is available only in Russian. Patients who do not have proficiency in Russian at the level of writing and reading will be excluded from periodic testing.

12.4.7 6-Minute Walk Test

This test is one of the methods for diagnosing heart failure, but it is used more for determining the functional class rather than confirming it. It also involves determining the endurance of patients to assess the effectiveness of therapy.

The test is easy to perform, does not require complex equipment, and can be conducted both in inpatient and outpatient settings. The test allows for the assessment of patients' daily activity levels, and its results correlate well with quality-of-life indicators; moreover, they can be used as additional criteria for evaluating the effectiveness of treatment and rehabilitation of patients.

The methodology for conducting this test involves using a straight corridor familiar to the patient, with zero incline and length markings every 3 meters, and separate markings for turnaround points are provided. After a preliminary rest period of 10 minutes, the subject's pulse rate and blood pressure are measured. If there are no contraindications to performing the test, the subject is instructed to cover the maximum distance in 6 minutes, without running or sprinting, but a reduction in walking pace and short breaks are allowed. The time interval is measured by starting a countdown timer, which loudly signals with a sound at the end of 6 minutes. The doctor assesses the distance covered and the functional class.

13.11 Definition of the term 'End-of-study'

The date of completion of the study is considered to be the day on which the last subject included in the study underwent Examination 5.

Other aspects of study completion

The principal investigator has the right to terminate the study at any time based on clinical or organizational considerations, while ensuring the interests of the study participants are protected.

The completion of the study will be reported to the local ethics committee within 90 days, or within 15 days if there was an early termination of the study. All researchers will inform the study participants about the premature termination, ensuring the continuation of qualified dynamic monitoring for previously included participants.

A report on the conducted study will be compiled within 12 months from the date of study completion.

15. PROTOCOL COMPLIANCE

The researchers ensure compliance with the study protocol. In case,
the researcher believes that a deviation from the protocol will optimize the study process or allow for obtaining extremely significant additional results, this should be considered an amendment to the protocol. If this amendment is not approved by the local ethics committee, it cannot be implemented. Thus, all proposed deviations from the protocol must be reported to the principal investigator and the local ethics committee. If approved, the changes made will be reflected in the 'History of Changes' section of the research protocol.

15.1 Amendments to the Protocol

Any changes to the protocol must be agreed upon in writing with the principal investigator and the local ethics committee. The above does not apply to protocol changes aimed at the immediate safeguarding of the health and safety of the research participant. The principal investigator should be notified of this fact within 10 working days.

16. ACCESS TO STUDY DATA

Direct access will be provided to authorized representatives of the institutions where the study is conducted, as well as regulatory officials for monitoring, auditing, and inspections related to the study.

17. DATA PROCESSING AND STORAGE

17.1 Data collection, primary information, and individual registration cards (IRC)

All documentation related to the study, as well as information concerning the patients participating in it, is strictly confidential. The researcher must ensure the anonymity of the volunteers. In the IRK and other documents, volunteers should not be identified by their first and last names. The identification of volunteers is carried out using the first letters of the volunteer's last name, first name, and patronymic (FIO), date of birth (DD.MM.YYYY), and an individual number assigned to the volunteer upon inclusion in the study. Each volunteer is assigned a unique number by the Researcher, consisting of numeric and alphabetic designations, with the following structure: eight digits arranged sequentially from left to right, digits 1 to 6 are defined for this study by the following sequence: 11-RIS, which is the same for all volunteers, and the last two digits correspond to the serial number of the volunteer upon admission to the research center. Thus, the data provided by the Researcher for the identification of volunteers have the following format:

digits 1-3 - the first letters of the volunteer's last name, first name, and patronymic; digits 4-11 - the volunteer's date of birth (DD.MM.YYYY);

digits 12-19 - a unique number assigned to the volunteer by the Investigator responsible for conducting the clinical trial, consisting of numerical and/or alphabetical designations and entered into the Clinical Trial Protocol. The Investigator must maintain a separate Identification Log of individual numbers, last names, dates of birth, addresses, phone numbers, and medical documentation numbers (if available). The researcher must keep documents strictly confidential that are not intended for disclosure in general cases, in particular, signed Informed Consent Forms and the Identification Log.

The report and study documents will use only the initials, birth dates, and unique numbers of participant, which are part of the Individual Identification Code. The Individual Identification Code is established by the insurer after obtaining permission from the Ministry of Health and Social Development of the Russian Federation to conduct a clinical trial, based on the data provided by the Researcher of the volunteer participating in the clinical trial. The assigned individual identification code is not subject to change.

All data about the volunteer obtained during the study is first entered into the primary documentation (documentation of the medical institution or physician maintained at the research center) and then transferred to the Individual Registration Card of the volunteer.

The data contained in the IRK must match the data in the primary documentation. The IRK must be completed no later than 5 days after the volunteer's visit to the research center. The IRK is maintained in digital format. Logging of changes made is mandatory. The principal investigator bears the final personal responsibility for the accuracy and authenticity of all clinical, instrumental, and laboratory data entered into the IRK.

All records and documents related to the clinical study, including Individual Registration Cards, patient information sheets, and volunteer lists, are retained at the clinical institution where the study is conducted for 15 years after the study's completion.

18. ETHICAL ASPECTS

18.1 Ethical principles of conducting the study

The study will be conducted in accordance with the current version of the Declaration of Helsinki, the provisions of the National Standard of the Russian Federation GOST R52379-2005 on Good Clinical Practice dated April 1, 2006, and the Order of the Ministry of Health of the Russian Federation dated April 1, 2016. No. 200n 'On the approval of the rules of good clinical practice' and the provisions of Good Clinical Practice (GCP).

The material for conducting the study will be collected at two clinical sites: Petrovsky NRCS, Moscow and BUZ VO VOKB No.1, Voronezh.

By signing the study protocol, the researcher agrees to adhere to the instructions and procedures described therein, as well as the principles of Good Clinical Practice, which they comply with. Regulatory approval will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be obtained before the patient undergoes any study-related procedures, including screening tests to determine eligibility criteria.

Approval for conducting the study is planned to be obtained at both centers from the local ethics committee of the RCHC.

18.2 Approvals

The study protocol, informed voluntary consent form, individual patient registration card, and questionnaire forms must be approved by the local ethics committee and other regulatory officials, in accordance with current legislation, before the initiation of the study.

18.3 Informed Voluntary Consent

The investigator must obtain written informed consent from each participant prior to their participation in the study and before any study-related procedure is undertaken. Thus,

informed consent must be obtained at Examination 1 before performing any study-related procedure. Before this, the investigator or their representative must inform each participant about the objectives, benefits, risks, and requirements related to the study.

Only a qualified physician can obtain informed consent.

The participant will be provided with an information and consent form written in clear and simple manner. He/she should be given enough time to clarify the details of the study and make an informed decision about participation. The researcher must answer all relevant questions that may arise from the patient.

Two originals of the voluntary informed consent form must be completed, dated, and personally signed by the participant and the person responsible for obtaining informed consent. The participant will be provided with one signed original, and the second original will remain with the Investigator.

The obtaining of informed consent must be clearly documented in the participant's individual registration card. The following aspects must also be recorded in the subject's medical record:

• The date the informed consent form was provided to the subject.

• The date written informed consent was obtained.

• The name of the person who obtained the informed consent.

• Any other relevant information regarding the consent acquisition process.

Each patient included in the clinical study must have an individual participant card, which reflects data allowing the identification of the clinical study. (In particular, the study title, patient identifier in the study, date of signing the informed consent, 'date of completion of patient participation,' which must be filled in at Examination 5, the principal investigator's name, and the research group's contact number must be specified).

18.4 Patient Confidentiality

Researchers ensure the confidentiality of participants, who will be identified only by their subject identification number in any database. All documents will be stored in a secure location. The study was conducted in accordance with the 'Personal Data Protection' law.

19. FUNDING

The study is initiative-driven, and no sponsorship is provided.

20. CLINICAL TRIAL REPORT AND PUBLICATION POLICY

20.1 Clinical trial report

The clinical trial report must be prepared and signed by all study participants within 12 months after the completion of the study.

20.2 Publication Policy

The results of this study will be published in reputable medical journals. The information obtained may provide impetus for further research on reverse remodeling of the left ventricle in patients with chronic aortic regurgitation.
Principle investigator is responsible for publishing the data obtained in this study.

21. PROPOSED STUDY SCHEDULE

Start date: May 2024

End date: May 2029

Report preparation date: within 12 months from the end of the study

22. APPENDICES

22.1 Appendix 1. "EQ-5D Quality of Life Questionnaire"

Title in Russian: Quality of Life Questionnaire EQ-5D
Original title European Quality of Life Questionnaire (EQ-5D)
Source:
Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul; 33(5): 337 - 43. doi: 10.3109/07853890109002087. PMID: 11491192.
Brooks R, Boye KS, Slaap B. EQ-5D: a plea for accurate nomenclature. J Patient Rep Outcomes. 2020 Jul 3; 4(1): 52. doi: 10.1186/s41687-020-00222-9. PMID: 32620995; PMCID: PMC7334333.
Russian population health-related quality of life indicators calculated using the EQ-5D-3L questionnaire/E.A. Aleksandrova, A.R. Khabibullina, A.V. Aistov [et al.]//Siberian Scientific Medical Journal. - 2020. - Vol. 40. - No. 3. - P. 99 - 107. - DOI 10.15372/SSMJ20200314.

Type - questionnaire
Purpose: assessment of quality of life

English EQ-5D-Y-5L Paper Self-Complete

Under each heading, please choose the ONE answer that best describes your health TODAY.

MOBILITY *(walking about)*
I have no problems walking about ☐
I have a little bit of a problem walking about ☐

I have some problems walking about ☐
I have a lot of problems walking about ☐
I cannot walk about ☐

LOOKING AFTER MYSELF

I have no problems washing or dressing myself ☐
I have a little bit of a problem washing or dressing myself ☐
I have some problems washing or dressing myself ☐
I have a lot of problems washing or dressing myself ☐
I cannot wash or dress myself ☐

DOING USUAL ACTIVITIES *(for example, going to school, hobbies, sports,playing, doing things with family or friends)*

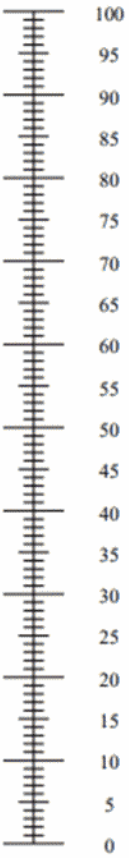
I have no problems doing my usual activities ☐
I have a little bit of a problem doing my usual activities ☐
I have some problems doing my usual activities ☐
I have a lot of problems doing my usual activities ☐
I cannot do my usual activities ☐

HAVING PAIN OR DISCOMFORT

I have no pain or discomfort ☐
I have a little bit of pain or discomfort ☐
I have some pain or discomfort ☐
I have a lot of pain or discomfort ☐
I have extreme pain or discomfort ☐

FEELING WORRIED, SAD OR UNHAPPY

I am not worried, sad or unhappy ☐
I am a bit worried, sad or unhappy ☐
I am quite worried, sad or unhappy ☐
I am really worried, sad or unhappy ☐
I am extremely worried, sad or unhappy ☐

	The best health you can imagine
• *We would like to know how good or bad your health is TODAY.* • *This line is numbered from 0 to 100.* • *100 means the best health you can imagine. 0 means the worst health you can imagine.* • *Please mark an X on the line to show how your health is TODAY.* • *Now, write the number you marked on the line in the box below.* YOUR HEALTH TODAY = ☐	

22.2 Appendix 2. “Minimal Transthoracic Echocardiography Protocol”

Minimum transthoracic echocardiographic protocol: recommendations of the Eurasian Association of Specialists in Ultrasound and Functional Diagnostics

B.V. Blagodir
Recommendations adopted on 27.09.2018. (voting protocol No. 1 from 28.09.2018).

1. *Introduction.*

Recent advancements in echocardiography have facilitated the integration of new principles and methodologies into the routine work of an echocardiographer. This necessitates the implementation of a minimal echocardiographic protocol to ensure the quality collection of necessary data, improve quality, and standardize the performance of transthoracic echocardiographic examinations. The Eurasian Association of Ultrasound and Functional Diagnostics Specialists (EAUD) organized on 27.09.2018. The forum 'Ural Echocardiographic Protocol,' where 44 specialists unanimously voted for its adoption.

EAUD offers a minimal step-by-step protocol for comprehensive echocardiographic examination to obtain the most detailed information about the heart, its structures, and the assessment of cardiac function. When pathological morphological and/or functional abnormalities are detected, additional data is required, which is not included in this guideline and will be considered in subsequent guidelines.

2. *Requirements for the ultrasound device.*

- *2D mode with Tissue Harmonic Imaging (THI)*
- *Standard M-mode*
- *CFD*
- *PWD*
- *CWD*
- *TDI-PW*
- *ECG module for image synchronization and highly accurate verification of the corresponding phase of the cardiac cycle.*

3. *Preparation for the study.*

a. Familiarize yourself with the referral, indications, and diagnosis.

b. Preparation of equipment: electrodes, ultrasound gel, clean bed linen, sensor.

c. Familiarize yourself with the medical documentation and previous echo reports for comparison.

g. Enter the patient's data into the ultrasound device, check the name, date of birth, height, weight, and medical record number.

d. Ask the patient to lie down on the couch, attach 3 ECG electrodes, and adjust the height of the couch.

e. Start scanning with either the left or right hand.

- It depends on the features of the echo lab and/or personal preferences. It's better to be proficient with both hands.
- Scanning with the right hand – the patient lies with their back to you. The patient's body should be embraced with the hand. The patient can lean on you. For the right hand, this is a comfortable position, as it relieves tension. This position may be suboptimal in the operating room, in case of injury, as well as in cases of hygiene issues with the patient.
- Examination with the left hand – the patient is lying face towards you. The hand is placed on the couch. The patient requires a pillow behind their back. This position provides better visibility of the sensor and the patient's chest, allowing contact with it. This position is not optimal if the patient has a cough, so if they are not wearing a mask, you need to provide one for yourself.

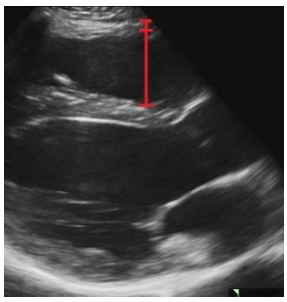
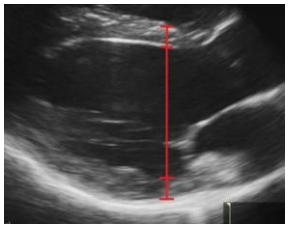
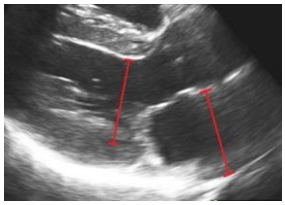
f. Patient position.

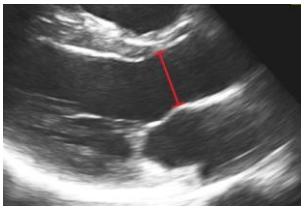
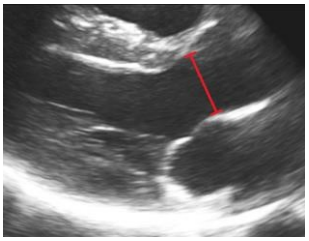
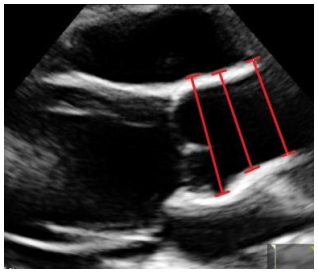
- Subcostal access – the patient lies on their back.
- Suprasternal access – the patient lies on their back, chin up, and turns their head slightly to the left.
- Right parasternal access – the patient lies on their right side.

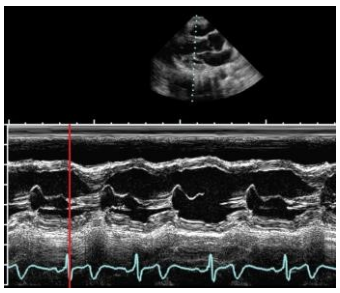
4. *Duration of the study.*

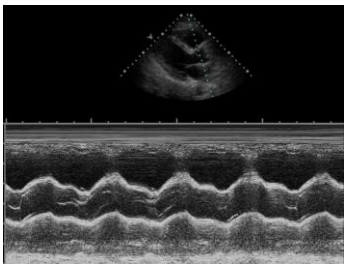
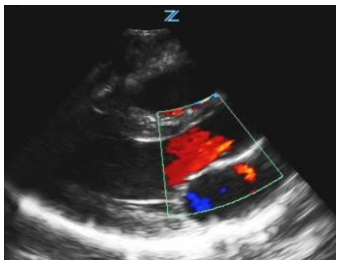
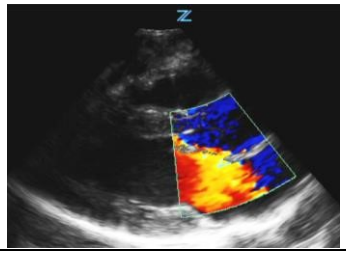
The average duration of one study, including patient preparation, familiarization with medical documentation, obtaining images, quantitative calculations, and report writing, is 40-45 minutes. However, for a complete study, some patients require more time to obtain additional information, while others require less time.

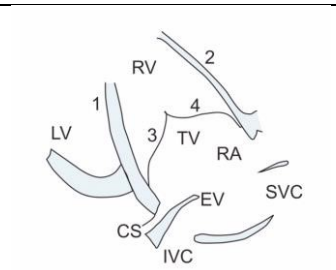
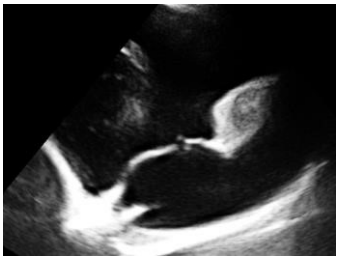
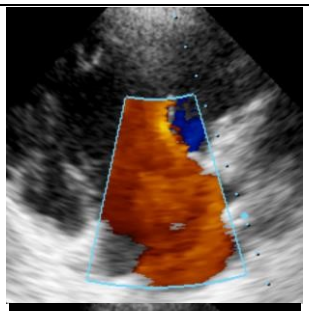
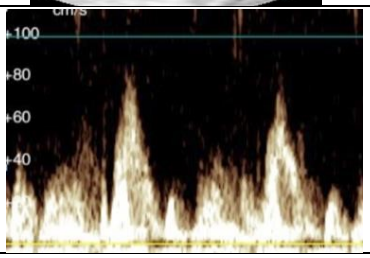
Section (mode)	Measurements	Exclude	Image

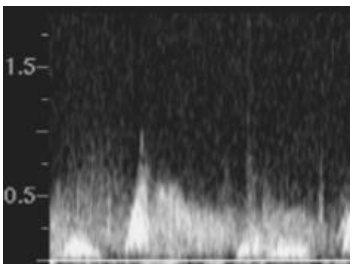
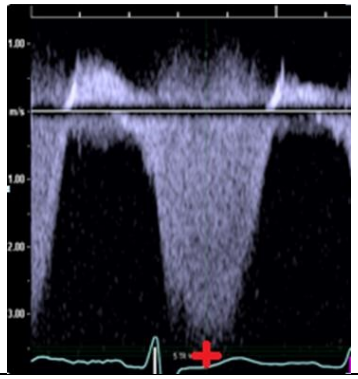
LAX LV (2D)	*At the end of diastole:* ***a. Right ventricle*** RVWTd, RVOTprox. IVSd, LVIDd, LVPWd. **b. Left ventricle:** IVSd, LVIDd, LVPWd, LVmass, RWT. *At the end of systole:* LVIDs, LA diam *Note:* 1. *The linear dimensions of the left ventricle are measured just beyond the ends of the mitral valve leaflets.* 2. *EF LV by Teicholz can be used to assess the overall contractile function of the left ventricle only in the absence of*	• chamber dilation • wall thickening • contractility impairment • valve anomalies. • Left ventricular hypertrophy • Normal values: RVWT (1 – 5 mm) RVOTprox (20 – 30 mm) IVS (female 6-9 mm; male 6-10 mm) LVIDd (female 37.8-52.2 mm; male 42.0-58.4 mm) PWT (female 6-9 mm; male 6-10 mm) LVIDs (female 21.6-34.8 mm; male 25.0-39.8 mm) LA (female 27 – 38 mm; male 30 – 40 mm) LVmass (female 67-162 g, male 88-224 g) RWT (≤0.42) EF LV 53-73%	  
	local contractility disorders!		

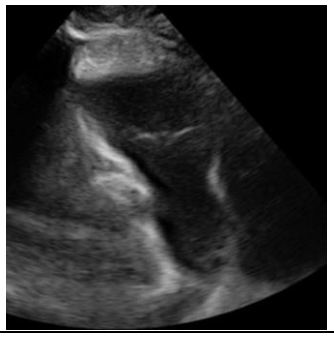
LAX Ao (2D)	*In mid-systole:* LVOT diam – I-I method AoAnnulus – I-I method Note: LVOTdiam measurement is conducted proximal and parallel to the plane of the aortic valve from the inner edge of the septal endocardium to the inner edge of the anterior leaflet of the mitral valve within 5-10 mm from the aortic valve. *At the end of diastole:* AoSinus (L-L method) STJ (L-L method) AoAsc prox (L-L method)	• LVOT obstruction • Aortic dilation • Aortic calcification • Aortic dissection Normal values: LVOTdiam (18-22 mm) AoAnnulus (female 22-25 mm, male 23-29 mm) AoSinus (female 27-33 mm, male 31-37 mm) STJ (female 23-29 mm, male 26-32 mm) AoAsc prox (female 23-31 mm, male 26-34 mm)	  

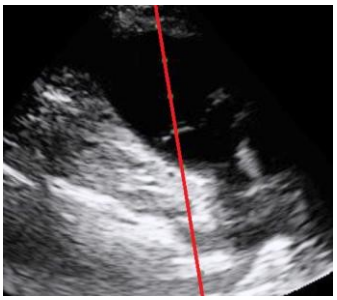
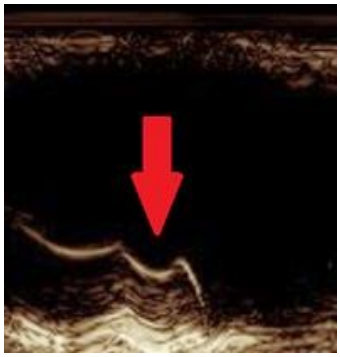
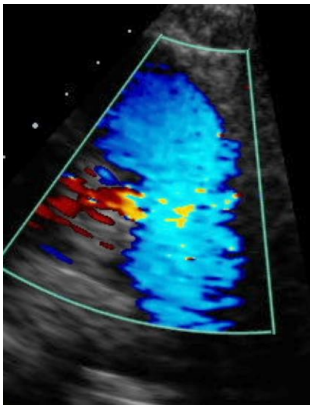
LAX LV (M-mode)	*M-mode at the level of the mitral valve:* DE amp EF slope EPSS	• Contractility impairment/ dyssynchrony/ paradoxical motion. • Mitral valve prolapse. • Early closure of the mitral valve (indicates increased left ventricular end-diastolic pressure – LVEDP). • Hemodynamic compromise in the presence of exudative pericarditis. Normal values: DEamp 18-28 mm EF slope 70-150 mm/sec EPSS ≤ 8 mm	

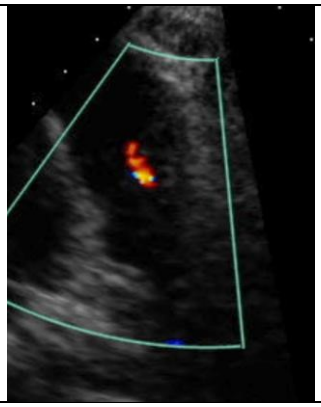
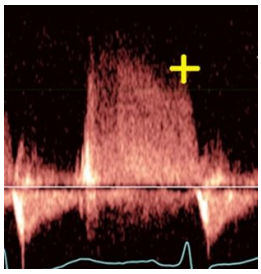
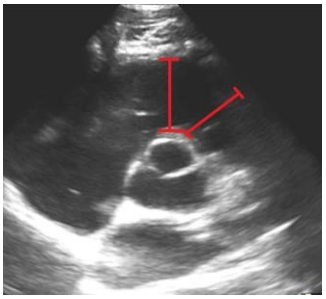
	M-mode at the level of the Valsalva sinuses: AVOA	• Restriction of aortic valve opening • Early opening of the aortic valve • Mid-systolic closure of the aortic valve Normal values: ASC 15-26 mm	
LAX LV (CFD)		• LVOT obstruction • aortic stenosis • aortic regurgitation • mitral stenosis • mitral regurgitation • Ventricular septal defect	 

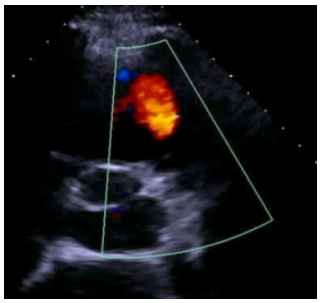
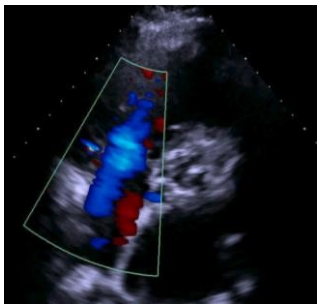
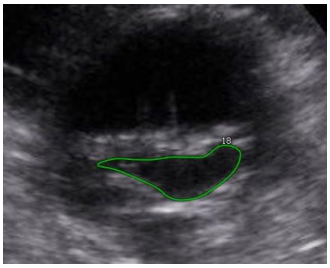
LAX RVIT (2D)	Diameter of the coronary sinus (CS)	• prolapse/elongation of the leaflets • myxomatous / thickening / calcification with / without restriction of excursion • flailing tricuspid valve leaflet dilation of the tricuspid valve annulus • dilation of the coronary sinus Normal values: CS diam (4-10 mm)	 
LAX RVIT (CFD)		Evaluate the flow from the left atrium to the left ventricle • tricuspid stenosis • tricuspid insufficiency	
LAX RVIT (PWD)	VE VA	Right ventricular filling pattern	

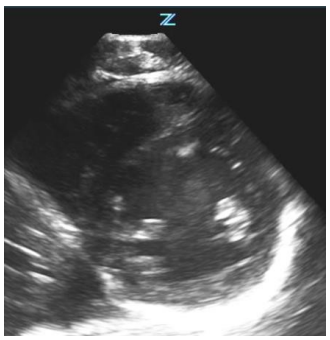
LAX RVIT (CWD)	TV Vmax TR Vmax	• Tricuspid stenosis • Tricuspid insufficiency • Calculate RVSP/SPAP Normal values: TV Vmax 30-70 cm/s TRVmax ≤ 2.5 m/s RVSP/SPAP ≤ 25 mm Hg	 
LAX RVOT (2D)	RVOTdistal MPAdiam* RPAdiam** LPAdiam**	• Dilation of the right ventricle • RVOT obstruction • Subvalvular pulmonary stenosis • Semilunar prolapse	

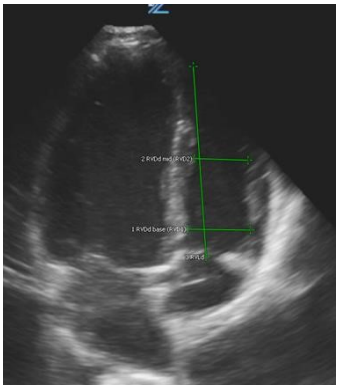
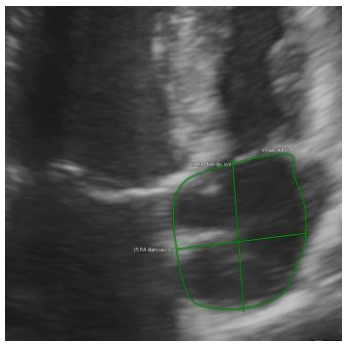
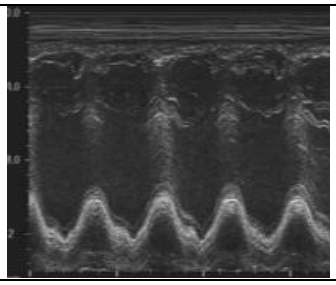
		pulmonary valve • Thickening/calcification of the pulmonary valve cusps with/without restriction of mobility • Dilation of the pulmonary artery • Narrowing of the pulmonary artery (supravalvular pulmonary stenosis)	

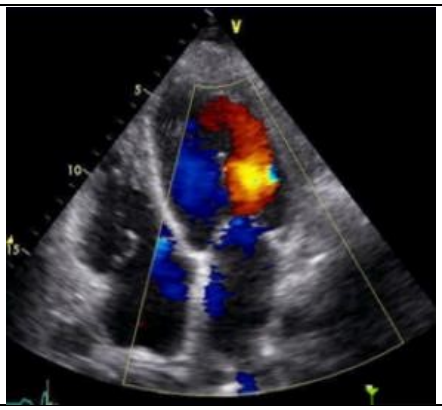
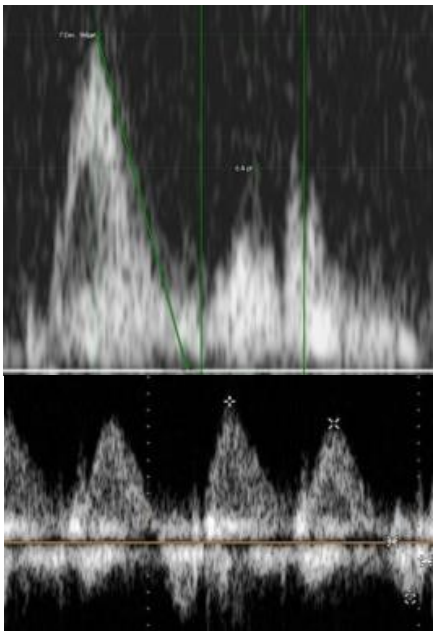
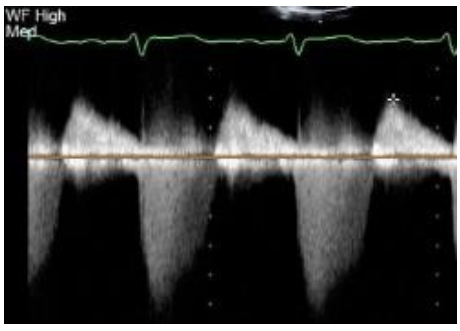
LAX RVOT (M-mode)	Amplitude of the a-wave *Note:* Normally, the a-wave is present on the motion graph of the right posterior cusp. Amplitude of the a-wave is 2.7 mm. Absence or reduction of the amplitude of the a-wave < 2 mm, mid-systolic closure (W-flight) indicates the presence of pulmonary hypertension	Pulmonary hypertension	 
LAX RVOT (CFD)		• • Pulmonary stenosis • Pulmonary regurgitation Patent ductus arteriosus (PDA) *Note:* Moderate pulmonary regurgitation is a variant of normal.	

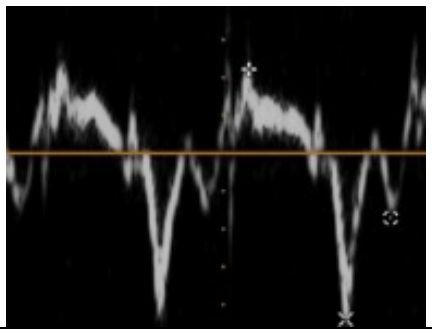
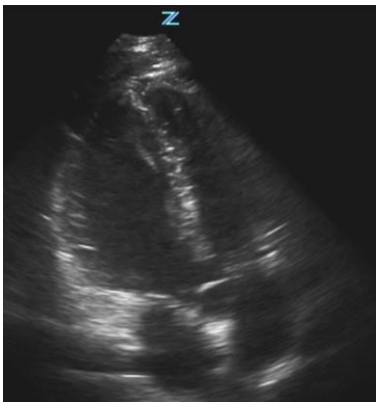
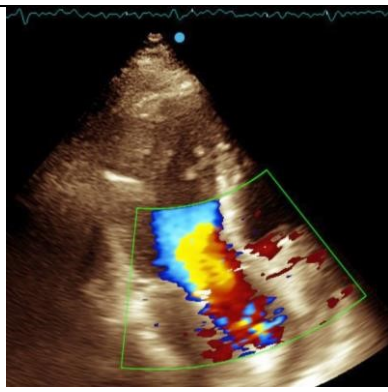
			
LAX RVOT (PWD)	Vmax RVOT PGmax RVOT	RVOT obstruction	
LAX RVOT (CWD)	PV Vmax PV Gmax PV Gmean PVA EDPR	• Pulmonary stenosis • Pulmonary regurgitation • Pulmonary hypertension Normal values: PV Vmax 60-90 cm/s EDPR 0-5 mm Hg Note: An increase in EDPR of more than 5 mm Hg indicates the presence of pulmonary hypertension.	
SAX BASE (2D)	RVOTprox RVOTdistal MPAdiam* RPAdiam** LPAdiam** *if the diameter of the MPA is greater than that of the Ao **as needed	• Dilation of the right ventricle • Prolapse/elongation • Myxomatous/thickening/calcification of the tricuspid and pulmonary valves with/without restriction of excursion • Flailing TV leaflet • Dilation of the TV annulus (TVannulus) • RVOT obstruction Normal values: RVOTprox 21-30 mm RVOTdistal 17-27 mm	

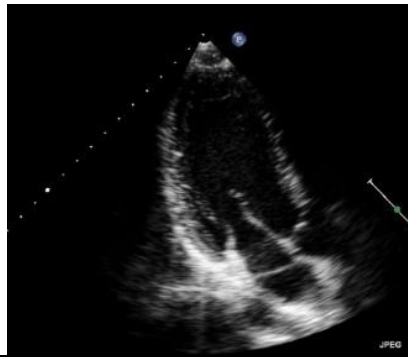
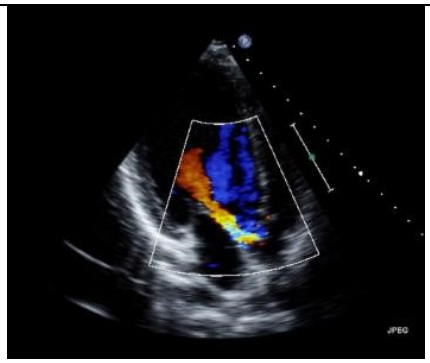
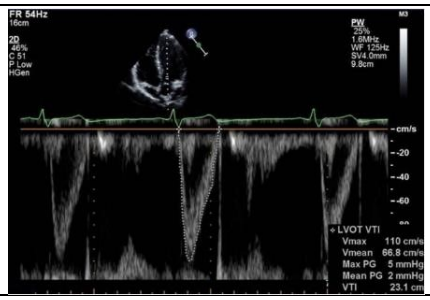
SAX BASE (CFD)		• Tricuspid stenosis • Tricuspid regurgitation • Pulmonary stenosis • Pulmonary regurgitation • RVOT obstruction • Ventricular septal defect • Atrial septal defect	
		• Elongation and bulging of the atrial septum • Atrial septal aneurysm	
SAX BASE (CWD)	TV Vmax TR Vmax TVA PV Vmax PV Gmax PV Gmean PVA EDPR	• Tricuspid stenosis • Tricuspid regurgitation • Pulmonary stenosis • Pulmonary regurgitation • RVOT obstruction	
SAX BASAL/MV (2D)	MVA (planimetry)	• Prolapse/elongation of leaflets. • Myxomatous/thickening/calcification with/without restriction of excursion. • Local contractility disorder at the basal level	 

SAX LV (MID/APEX) (2D)		Hypo-, a-, dyskinesia of the walls. Dilation of the right ventricle	

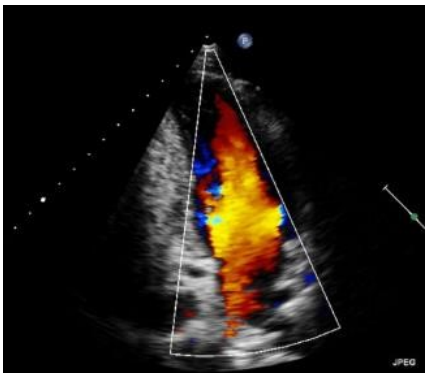
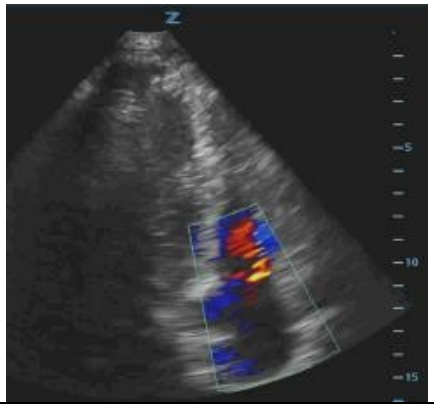
A4CV (2D)	EDVi ESVi EF LV LAVi RVD1 RVD2 RAsax RAlax RAA RAVi	• Dilation of chambers • Hypertrophy • Reduction of global function • Valvular dysfunction Normal values: EDVi (female <61 ml/m^2, male <74 ml/m^2) ESVi (female <24 ml/m^2, male <31 ml/m^2) EF LV (female >52%, male >54%) LAVi (<34 ml/m^2) RVD1 (25-41 mm) RVD2 (19-35 mm) RAlax (<53 mm) RAsax (<44 mm) RAA (<18 cm^2) RAVi (female 15-27 ml/m^2, male 18-32 ml/m^2) Note: LAV is calculated using the disk summation method RAV is calculated using the area-length method	   
A4CV (M-mode)	TAPSE	Right ventricular dysfunction Normal value: TAPSE >17 mm	

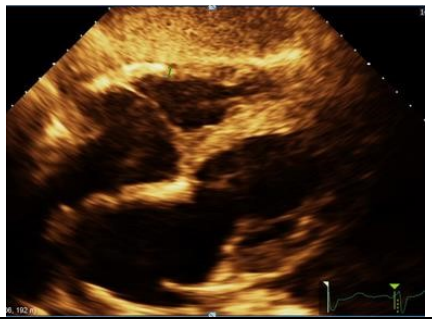
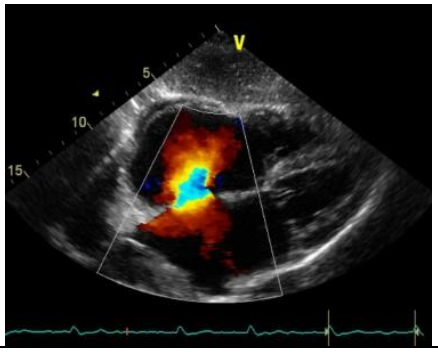
A4CV (CFD)		• Mitral stenosis • Mitral regurgitation • Tricuspid stenosis • Tricuspid regurgitation • Atrial septal defect • Ventricular septal defect	
A4CV (PWD)	VE MV VA MV E/A MV DT MV Adur VE TV VA TV E/A TV DT TV S D ARdur	• Diastolic dysfunction of the left ventricle • Diastolic dysfunction of the right ventricle Normal values: E/A MV 1.0-1.5 DT MV 160-220 msec S>D AR<150 msec Adur<ARdur	
A4CV (CWD)	MV Vmax MR Vmax MVA TV Vmax TR Vmax TVA RVSP/SPAP	• Mitral stenosis • Mitral regurgitation • Tricuspid stenosis • Tricuspid regurgitation • Pulmonary hypertension	

A4CV (TDI PW)	e' lat E/e' lat e' med E/e' med E/e' avg	Diastolic dysfunction of the left ventricle Normal values: e' lat >10 cm/s e' med >7 cm/s E/e' lat <13 cm/s E/e' med <15 cm/s E/e' avg <14 cm/s	
A5CV (2D)		• Mitral stenosis • SAM with/without LVOT obstruction • Aortic sclerosis/stenosis • Dilation of chambers • Local contractility of the ventricular walls	
A5CV (CFD)		• LVOT obstruction • Mitral stenosis • Mitral regurgitation • Aortic stenosis • Aortic valve insufficiency • Ventricular septal defect	
A5CV (CWD)	MV Vmax MR Vmax MV PHT AoV Vmax AR PHT LVOT Vmax TV Vmax TR Vmax RVSP/SPAP	• LVOT obstruction • Mitral stenosis • Mitral regurgitation • Aortic stenosis • Aortic valve insufficiency	

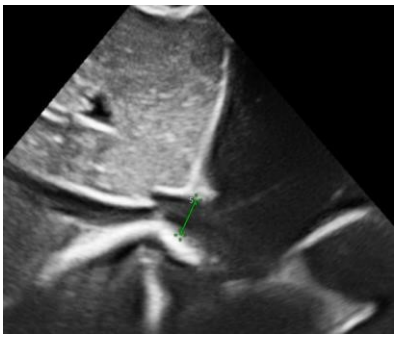
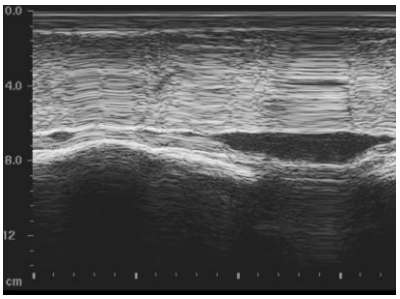
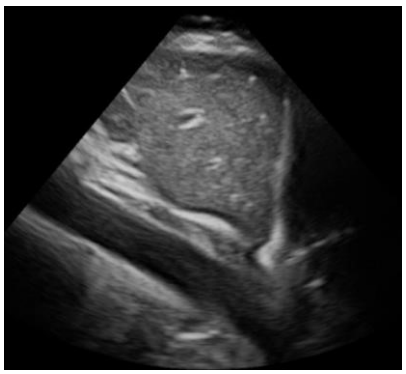
3C (2D)		• Dilation of chambers • Reduced contractility • Left ventricular hypertrophy • LVOT obstruction	
		Pathology of the mitral and and aortic valves Aortic aneurysm	
3C (CFD)	MV Vmax MR Vmax AoV	• Mitral stenosis • Mitral regurgitation • Aortic stenosis • Aortic regurgitation • LVOT obstruction	
3C (PWD)	LVOT Vmax	LVOT obstruction	
3C (CWD)	MV Vmax MR Vmax MVA AoV Vmax AR PHT AVA	• Mitral stenosis • Mitral regurgitation • Aortic stenosis • Aortic valve insufficiency	

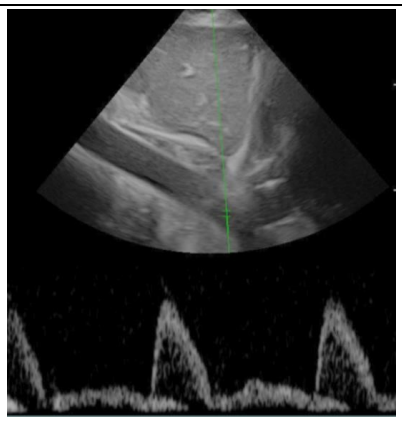
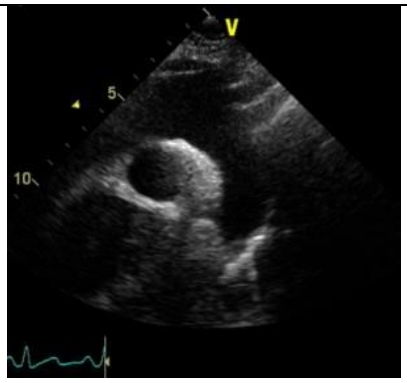
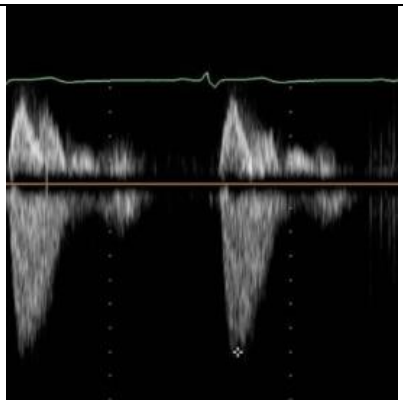
2C (2D)	EDVi ESVi EF LV LAVi	• Dilation of chambers • Dilation of the DAO • Thrombosis of the left atrial appendage • Local contractility disorder • Reduced contractility of the left ventricle	

2C (CFD)		• Mitral stenosis • Mitral regurgitation	
2C (CWD)	MV Vmax MR Vmax MVA	• Mitral stenosis • Mitral regurgitation	
3C RVIT (CFD, CWD)	TV Vmax TR Vmax RVSP/SPAP	The best section that provides the ideal Doppler angle for assessing tricuspid regurgitation and calculating RVSP/SPAP in cases where other sections had a suboptimal Doppler angle.	

Sub A4CV (2D)	RVWT	• Right ventricular hypertrophy • Pericardial effusion • Lipohypertrophy of the interatrial septum • Hemodynamic compromise in tamponade	
Sub A4CV (CFD)		• Atrial septal defect • Ventricular septal defect • Mitral regurgitation • Tricuspid insufficiency	

Sub SAX BASE (2D, CFD)		Atrial septal defect (ASD) Note: This is the ideal section for assessing the atrial septal defect, as it provides the ideal Doppler angle.	

Sub IVC (2D / M-mode)	IVC diam insp IVC diam expir	• Dilation of the inferior vena cava • Assess the inspiratory collapse of the inferior vena cava • Determine the right atrial pressure (RAP) (**RAP = 3/8/15**). Note: IVC diameter according to the ASE guidelines is measured at the entry proximal to the hepatic vein. Normal values: IVC diam expir (12-21 mm).	 
Sub DAO (2D)	DAO diam	• Dilation • Aneurysm • Dissection • Atherosclerosis Normal values: DAO diam (<30 mm).	

Sub DAO (PWD)	PSV AT	• Distal effects of aortic coarctation • Distal effects of aortic stenosis Normal values AT <80 msec Hemodynamically significant proximal events: AT ≥100 msec.	
Supra LAX (2D)	AAo diam AoArch diam DAO prox	• Aneurysm • Dissection • Atherosclerosis • Coarctation	
Supra LAX (CFD / PWD)	PSV AAo PSV DAO	Dissection Coarctation Normal values: PSV AAo (< 200 cm/s) PSV DAO (<200 cm/s)	

23. REFERENCES

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