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***Article***

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# Comprehensive Long-Term Follow up of Adults with Arterial Switch Operation–European Collaboration for Prospective Outcome Research in Congenital Heart Disease (EPOCH-ASO)–Study Design and Protocols

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**Abstract: Background:** Long-term outcomes in adults with prior arterial switch operation (ASO) have not yet been well defined. The aim of this study is to elucidate incidence and predictors of adverse cardiac outcomes in a prospectively followed cohort of adults after their ASO. **Methods:** The comprehensive long-term follow up of adults with ASO is a project within the European collaboration for prospective outcome research in congenital heart disease (EPOCH). It is designed as a prospective, international multicenter cohort study. Consecutive patients (age ≥ 16 years) with prior ASO will be included at 11 European tertiary care centers. Participants will be followed according to a standardized protocol following international recommendations, including standardized protocols for imaging and for exercise testing. **Results:** Main outcome measures are all-cause and cardiac-related mortality, rate of cardiac re-intervention, neo-aortic dissection, myocardial infarction, stroke, infective endocarditis, sustained atrial and ventricular arrhythmias, new-onset or worsening pulmonary hypertension or heart failure. Secondary endpoints are frequency and progression of right ventricular outflow stenosis, neo-aortic root dilatation, neo-aortic valve regurgitation and ventricular

dysfunction. The impact of demographic, anatomic (e.g., coronary artery anatomy) and functional variables on the above-mentioned outcomes, as well as quality of life and incidence of pregnancy related complications will also be assessed. **Conclusion:** The prospective, international, multicenter EPOCH-ASO study will provide a better understanding of adverse outcomes and their predictors in adults after ASO. The results of the EPOCH-ASO study may help to optimize future care of this novel patient cohort in adult cardiology.

**Keywords:** Transposition of the great arteries; arterial switch operation; coronary artery anomaly; outcome

## 1 Introduction

Complete transposition of the great arteries (TGA) accounts for 3 percent of all congenital heart lesions and for 20 percent of all cyanotic heart defects [1–3]. Without intervention, survival beyond the neonatal period is unlikely [4]. With the advent of open-heart surgery, the atrial switch operation has become the standard repair operation for many decades before it was superseded by the arterial switch operation (ASO) [5–10]. The ASO, first successfully performed by Dr. Adip Jatene in 1975, has become the standard operation at most centers since the late 1980s with very low operative mortality and excellent childhood survival [11–15]. Therefore, adult patient cohorts after ASO are rapidly evolving. Although good long-term outcomes are expected, preliminary studies in young adults have shown several areas of concern, including dilatation of the neo-aortic root and malfunction of the neo-aortic valve, obstruction of the right ventricular outflow (RVO) and concerns about long-term patency and dysfunction of the re-implanted coronary arteries [15–26].

In this manuscript, we describe the setting and organization of our prospective, international, multicenter cohort study in adults after childhood ASO. Our aim is to define frequency of and risk factors for adverse events in a large cohort of adults after ASO. The study will eventually provide better identification of patients at risk, improve follow-up protocols and may aid to improve long-term outcomes within this novel patient cohort in adult congenital heart disease.

## 2 Methods

### *2.1 Setting and Study Population*

EPOCH (European collaboration for Prospective Outcome research in Congenital Heart disease) is a research initiative among several European tertiary care centers for adults with congenital heart disease. Its aim is to design and execute multicenter outcome studies in the field of adult congenital heart disease. A complete list of participating centers and investigators is shown in Appendix 1. EPOCH-ASO is a research project of the EPOCH-consortium, designed as a prospective, multicenter, international cohort study of adults after the ASO. The study is registered at ClinicalTrials.gov (Identifier: NCT04335448).

All adults (≥16 years) with TGA or a Taussig-Bing anomaly who underwent repair by an ASO, and who are actively followed at one of the participating centers will be enrolled. Exclusion criteria are incapability of giving informed consent and previous heart transplant. Enrollment started in October 2019. The cohort will be prospectively followed according to a standardized follow-up protocol, detailed below, based on recommendations in current guidelines for the management of adults with congenital heart disease [27,28].

### *2.2 Platform of EPOCH-ASO*

The EPOCH-ASO platform is a web-based data management system and electronic database (secuTrial®). The required application software is implemented on a central server at the University Hospital Zurich and maintained by the Clinical Trial Unit of the University Hospital Zurich, Switzerland.

Access can be obtained from any personal computer using some of the most popular internet browsers (e.g., Microsoft Internet Explorer, Mozilla Firefox, and Apple Safari). The secuTrial® system complies with all regulatory requirements regarding data safety. Each participant will be pseudonymized (depersonalized) and participants' data will be entered by center representatives or trained study nurses.

## 3 Results

### *3.1 Study Plan*

Enrollment into the study will occur at routine clinic visits. Follow-up visits will occur at least every 24 months or more frequently if indicated in an individual patient. A framework of minimal requirements of follow-up is outlined in Tab. 1.

**Table 1:** Framework and timing of follow-up visits and examinations

| Visit | Baseline* | Follow-up† |
|---|---|---|
| Informed Consent | X | |
| Eligibility criteria | X | |
| Demographics | X | |
| Medical history | X | |
| Clinical examination | X | At least every 24 months |
| Evaluation of quality of life (LAS and SWLS) | X | At least every 24 months |
| 12-lead electrocardiogram (ECG) | X | At least every 24 months |
| Holter-ECG | (X) | If clinically indicated |
| Transthoracic echocardiogram | X | At least every 24 months |
| Cardiac magnetic resonance imaging | X‡ | At least every 60–72 months |
| Coronary computed tomography angiography | X§ | If clinically indicated |
| Cardiopulmonary exercise testing | XI | At least every 60–72 months |
| Blood analysis | X | At least every 60–72 months |

(X) If clinically indicated; * baseline examinations; † minimal follow-up interval according to international guidelines of 2 years; ‡ if not performed within the last 3 years from baseline; § if not already performed at the age of 16 years or later; I if not performed within the last 2 years from baseline; LAS: linear analog scale; SWLS: satisfaction with life scale; ECG: electrocardiogram, NT-proBNP: N-Terminal fraction of pro Brain Natriuretic Peptide.

#### *3.1.1 Data Collection and eCRF-Forms*

There are three different types of electronic case reports forms (eCRF): a baseline form, a visit form and an outcome form. The information contained in these forms will be collected at routine clinic visits and entered electronically (eCRF) into the electronic databased platform (secuTrial®). Adverse events are recorded and entered into the eCRF continuously as they occur.

#### *3.1.2 Baseline Examinations*

Inclusion into EPOCH-ASO will occur at the time of routine clinic visits at the participating centers. All patients will undergo physical examination, basic blood work testing (including N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP) levels and measurement of blood lipids), 12-lead electrocardiogram (ECG), comprehensive transthoracic echocardiography and cardiopulmonary exercise testing. As part of these routine clinic visits, quality of life will be assessed by a linear analog scale (LAS) [29,30] and the Satisfaction with Life Scale (SWL) [31]. If no contraindications are present and unless already available within the last 3 years prior to study inclusion, cardiac magnetic resonance imaging (CMR) will be performed for evaluation of RVO obstruction, neo-aortic root dilatation and neo-aortic valve regurgitation

[27]. In order to evaluate the anatomy and integrity of the coronary arteries, all patients will undergo coronary computed tomography angiography (CCTA). If CCTA was already performed prior to inclusion at ≥ 16 years of age, this test will be analyzed as baseline CCTA. In case of any cardiac intervention between baseline CMR/CCTA and the time of inclusion into EPOCH-ASO, these investigations will be repeated.

Baseline characteristics include the original cardiac anatomy at birth, including all associated congenital cardiac defects. When TGA is accompanied by other heart defects such as a ventricular septal defect (VSD) or aortic coarctation, the condition is described as complex TGA. If TGA occurs without associated defects it is denominated simple TGA. Detailed coronary artery anatomy and pattern will be recorded [32].

Details and timing of prior surgical and interventional procedures will be recorded after careful review of interventional and operative notes. All cardiac complications until inclusion into EPOCH-ASO will be extracted from chart review.

All study investigations will be standardized among participating centers as detailed below.

#### *3.1.3 Timing of Routine Follow-Up Visits and Follow-Up Examinations*

Frequency of routine follow up will be performed according to the clinical status of the individual patient, following general recommendations in published guidelines [27,28]. A framework of minimal requirements of follow-up examinations is outlined in Tab. 1.

### *3.2 Outcomes*

The main outcome measures of the study are the incidence of major adverse cardiac events. Secondary endpoints are deterioration of cardiac function and functional capacity. Type and definitions of primary and secondary outcomes are outlined in Tabs. 2 and 3, respectively. All major adverse cardiac events will be reviewed periodically within the steering committee by means of videoconferences.

A predefined list of potential predictors for the development of primary endpoints is presented in Tab. 3.

**Table 2:** Definition of primary outcomes

| Outcome | Definition/Description |
|---|---|
| **All-cause mortality** | Determination of cause of death |
| **Cardiac-related mortality** | |
| Sudden cardiac death | Death that ensues unexpected within one hour of onset of symptoms. |
| Myocardial ischemic death | Death related to acute myocardial infarction. |
| Heart failure death | Death that is primarily caused by heart failure. |
| Perioperative/peri-interventional death | Death within 30 days or during the hospital admission after a cardiac intervention. |
| **Re-intervention** | Includes all types of cardiac re-intervention with detailed analysis of the indication of re-intervention. |
| **Neo-aortic dissection** | Aortic dissection with entry within the neo-aortic root. |
| **Myocardial infarction** | Defined according to the Fourth Universal Definition of Myocardial Infarction [33]. |
| **Arrhythmias** | |
| Atrial arrhythmias | Atrial arrhythmias with a duration of > 30 seconds, or requiring anti-arrhythmic medication or ablation procedures. |
| Ventricular tachycardia | Sustained ventricular tachycardia (heart rate > 100/min) for at least 30 seconds or requiring electrical cardioversion/defibrillation. |

**Table 2 (continued).**

| Outcome | Definition/Description |
|---|---|
| **New onset/worsening heart failure** | Hospital admission for heart failure or initiation of heart failure medication for symptoms of heart failure (excludes initiation of medication for asymptomatic deterioration of ventricular function), according to the current ESC guidelines [34]. |
| **Stroke** | Focal neurological symptoms and confirmation of cerebral ischemia or infarction by cerebral magnetic resonance imaging or computed tomography. |
| **Infective endocarditis** | Defined according to the modified Duke's criteria, according to the current ESC guidelines [35]. |
| **Pulmonary hypertension** | Defined as an increase in mean pulmonary arterial pressure (PAPm) ≥20 mmHg at rest as assessed by right heart catheterization [36]. |

ESC: European society of cardiology.

**Table 3:** Secondary outcomes and potential predictors of mortality and morbidity outcomes

| Secondary outcomes/potential predictors for the development of primary endpoints | Definition/Description/Aim |
|---|---|
| Right ventricular outflow stenosis | At least 1 of the following criteria:<br>- Branch pulmonary artery minimal diameter: maximal diameter ≥ 1:2 on CT or MRI<br>- Echocardiographic systolic peak gradient across branch pulmonary arteries >16 mmHg (peak velocity >2.0 m/s)<br>- Estimated right ventricular systolic pressure >40 mmHg (determined by RV/RA-pressure gradient and estimated central venous pressure, see echocardiography protocol for details) |
| Coronary anatomy | To study the impact of coronary artery anatomy and type of coronary reimplantation on cardiovascular morbidity, ventricular function and functional capacity with a specific focus on presence of coronary artery obstruction, acute proximal angulation and inter-arterial or intramural course. |
| Neo-aortic root dilatation | Dilatation of the neo-aortic root corrected for age- and gender with a Z-score ≥ +2.0 determined by echocardiography, cardiac CT or cardiac MRI. |
| Progression of neo-aortic root dilatation | Increase of neo-aortic root dilatation of ≥3 mm, determined with the same imaging modality and appropriate side-by-side comparison of actual images. |
| Neo-aortic regurgitation | Assessment by echocardiography:<br>- Mild, moderate, severe [37]<br>Assessment by CMR:<br>- Regurgitation fraction and volume by flow measurements in proximal aortic root |

(Continued)

**Table 3 (continued).**

| Secondary outcomes/potential predictors for the development of primary endpoints | Definition/Description/Aim |
|---|---|
| Progression of neo-aortic regurgitation | Increase >1 grade (echocardiography)<br>Increase of regurgitant fraction >10% on CMR |
| Left ventricular systolic dysfunction | Echocardiography:<br>- LVEF biplane Simpson < 52% for men and <54% for women [38]<br>CMR:<br>- LVEF <52% |
| Left ventricular diastolic dysfunction | Echocardiography:<br>- Defined according to the current recommendations for the evaluation of left ventricular diastolic function by the ASE and the EACI [39]. |
| Worsening left ventricular function | Decrease of LVEF > 5% |
| Right ventricular dysfunction | Echocardiography [38]:<br>- At least 2 of the following<br>• FAC <30%<br>• TAPSE <18 mm<br>• TAPSE S' <10 cm/s<br>CMR:<br>- RVEF <50% |
| Worsening right ventricular function | Echocardiography (not valid in case of worsening tricuspid regurgitation)<br>- At least 2 of the following [38]:<br>• Decrease in Fac >10%<br>• Decrease in TAPSE >5 mm<br>• Decrease in TAPSE S' >3 cm/s<br>CMR:<br>- Decrease in RVEF >5% |
| Functional capacity | As determined by cardiopulmonary exercise testing (see specific section). |
| Pregnancy | To study the impact of pregnancy on mortality and cardiovascular morbidity. |

CT: computerized tomography; MRI: magnetic resonance imaging; RV: right ventricle; RA: right atrium; RF:regurgitation fraction; LVEF: left ventricular ejection fraction; ASE: America society of echocardiography; EACI: European association of cardiovascular imaging; CMR: cardiac magnetic resonance; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; RVEF: right ventricular ejection fraction. Reference values for aortic Z-scores according to Campens et al. [40].

### *3.3 Standard Operating Procedure (SOP) for Study Procedures*

In order to standardize and harmonize cardiac imaging (echocardiography, CMR and CCTA) and cardiopulmonary exercise testing, standardized operating procedures (SOP) were developed for these investigations. These SOPs, as outlined below, contain minimum requirements for image acquisition and reporting of results. All SOPs are based on recommendations of national and international guidelines and imply measurements commonly used in clinical practice. The essence of the SOPs is outlined below, while the complete SOPs are available as supplement tables (Appendix 2) or under: http://www.sacher-registry.com/epoch/.

#### *3.3.1 SOP for Transthoracic Echocardiography*

All patients will undergo a comprehensive standard transthoracic echocardiographic examination, according to international recommendations [38]. The echocardiographic examination will specifically focus on qualitative and quantitative assessment of the left and right ventricular dimensions, systolic and diastolic function, neo-aortic root dimensions and neo-aortic valve function as well as obstruction within the right ventricular outflow (including assessment of branch pulmonary artery stenosis, if technically feasible).

#### *3.3.2 SOP for Cardiopulmonary Exercise Testing*

Cardiopulmonary exercise testing will be performed preferably on a cycle ergometer but a treadmill can be used instead, if clinically indicated (e.g., patients with pacemakers requiring pacemaker accelerometer sensor function to maintain chronotropic competence). Follow-up examinations for individual patients must use the same test modality as with the initial investigation. Before exercise, respiratory flow loops will be acquired and maximal breathing capacity determined. A ramp protocol will be used, individualized to the patient's expected exercise capacity with the aim of exercise duration of 8–12 minutes. Details on specifics of recording and protocols are outlined in the supplements. For follow-studies, identical ramp protocols must be used for the individual patient. Measurements and reporting of data from exercise testing will follow the recommendations of the European Association for Cardiovascular Prevention and Rehabilitation [41].

#### *3.3.3 SOP for Cardiac Magnetic Resonance Imaging*

Among patients without contraindication a CMR will be performed. The CMR protocol will specifically focus on biventricular volumes and function (including late gadolinium enhancement sequences to detect myocardial scars), neo-aortic root dilatation and quantification of neo-aortic valve regurgitation. In addition, the protocol includes assessment of branch pulmonary artery stenosis and pulmonary artery flow distribution. A semi quantitative evaluation of myocardial perfusion will be performed by the analysis of myocardial perfusion first-pass perfusion images as previously described [42,43].

#### *3.3.4 SOP for Coronary Computed Tomography Angiography*

Before the CCTA examinations, beta-blockers will be given if heart rate >65/min unless contraindicated, to optimize acquisition. Data acquisition will be performed prospectively with ECG-triggered sequential scan or retrospectively with ECG-gated spiral scan. Acquisition includes the entire heart and proximal pulmonary artery branches. Inclusion of the thoracic aorta and aortic arch is optional, if good quality images from cardiac magnetic resonance imaging are available within the last 3 years prior to CCTA. The specific focus of analysis of the CCTA will be the origin and the proximal course of the re-implanted coronary arteries. This includes detailed analysis of coronary ostial dimensions and geometry as well as angles of coronary artery takeoff and potential length of inter-arterial or intramural course. To minimize bias in image analysis, the analysis of proximal coronary artery anatomy will be performed by experienced observers in a core lab.

### *3.4 Analysis Plan and Statistical Considerations*

Given that enrollment started by the end of 2019 and all patients after the ASO are seen at least every 24 months in outpatient clinic, we expect that the majority of eligible adults followed at the participating centers will have been enrolled until the end of 2021. It is thus planned to perform a descriptive cross-sectional characterization of the study cohort by the end of 2021. Analyses of primary and secondary outcomes are planned at least every five years. Dedicated biostatisticians at the Clinical Trial Unit of the University Hospital Zurich Switzerland, or the other corresponding units of the other participating centers will support statistical analysis of data. Investigator initiated sub-studies are encouraged and research proposals with a specific research aim and a study plan can be submitted to the steering committee at any time. The steering committee will decide mutually upon acceptance of the research proposal. Publication of sub-studies within EPOCH-ASO is regulated by the steering committee of EPOCH by means of a publication strategy.

## 4 Discussion

Cohorts of adult survivors after the ASO are rapidly evolving. Although we generally expect a good long-term outcome for these patients, experience taught us that there is no cure for congenital heart disease [44]. Indeed, preliminary analyses of outcomes of young adults after the ASO have shown several areas of concern [45–47]. These include particularly dilatation of the neo-aortic root, regurgitation of the neo-aortic valve and obstruction of the RVO [15,17–19,21–23,25,26]. These may affect ventricular function and have an impact on long-term outcomes. Furthermore, complications of the re-implanted coronary arteries due to geometric distortion or altered vasomotion require our attention [16]. In adulthood, the frequency of cardiac structural and functional deterioration, their predictors and their impact on adverse outcomes are largely unknown.

Only a better knowledge of all of these factors will allow early detection of patients at risk and will potentially allow appropriate indication and timing of preventive interventions to reduce the risk of complications and hence improve long-term outcomes. EPOCH-ASO has the potential to fill some of these gaps in our knowledge. Given the multicenter nature of the study, we expect to enroll up to 700 adults after ASO within 2 years, which will create a large cohort that will allow valid estimates of the frequency and predictors of these adverse outcomes.

Several studies have documented impaired cardiopulmonary exercise capacity in patients after the ASO [47]. This has mainly been attributed to right ventricular outflowright ventricular outflow obstruction and neo-aortic valve dysfunction [48–50]. However, the extent of impaired exercise capacity of adults after the ASO, their course over time and its impact on long-term outcomes remains to be elucidated. A better understanding of factors contributing to limited exercise capacity may allow tailored treatment strategies and have the potential to improve quality of life.

The prospective nature of the project with clearly defined follow-up protocols will help to identify predictors of adverse outcomes and will improve the validity of the collected data. As learnt from other multicenter registries, larger patient cohorts provide a better base for data analysis and allow a greater granularity of data analysis [51,52]. Only such precise data will inform us on optimal strategies for conduction of prospective-ideally randomized-studies comparing different treatment strategies, which will finally improve patient outcomes.

## 5 Limitations

The nature of this prospective registry will only allow defining associations between potential predictors and adverse outcomes. We hope that the results of the EPOCH-ASO study will alleviate the planning of prospective, ideally randomized trials to test preventive strategies for improved outcomes.

Although ideally all investigations were analyzed within a core-laboratory, funding of our project currently does not allow core-laboratory analyses of all imaging and exercise data. Currently only CCTA is planned to be analyzed in a core-lab.

## 6 Conclusions

The prospective, international multicenter EPOCH-ASO study will provide a better understanding of adverse outcomes and their predictors in a large cohort of adults after the arterial switch operation. The results of the EPOCH-ASO study may help to optimize the future care of this novel patient cohort in adult cardiology and may inform us about the optimal targets for planning prospective trials to compare treatment strategies.

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**Availability of Data and Materials:** Not applicable for this manuscript.

**Ethical Considerations:** The study will be carried out according to the ICH GCP Guidelines. It has been submitted to the responsible ethics committee and to the competent authorities. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities will be implemented. So far, ethical approval for the participating centers located in Amsterdam, Barcelona, Basel, Bern, Geneva, Lausanne, Valencia, Vienna and Zurich has been obtained. The available ethical approvals can be downloaded from http://www.sacher-registry.com/epoch/.

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**Conflicts of Interest:** There are no conflicts of interest to disclose.

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## Appendix 1

**Infrastructure of EPOCH**

**Steering Committee** (in alphabetical order)

J. Bouchardy, BJ. Bouma, L. Dos, H. Gabriel, P. Gallego, M. Greutmann, M. Ladouceur, M. Schwerzmann, D. Tobler

**Participating Centers** (in alphabetical order)

Austria: University Hospital Vienna; France: CHU Paris IdF Ouest - HEGP Hôpital Européen Georges Pompidou; Netherlands: Netherlands: Amsterdam University Medical Center, location AMC; Spain: Hospital Universitario y Politécnico La Fe Valencia, Hospital Universitari Vall d'Hebron Barcelona, Hospital Universitario Virgen del Rocio, Sevilla; Switzerland: University Hospital Basel, University Hospital Inselspital Bern, University Hospital Geneva, University Hospital Lausanne, University Hospital Zurich.

**Electronic Data Capture and Statistical Analyses (CTU University hospital Zurich)**.

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**Appendix 2**

**Standard Operating Procedures**

**Study Specific SOP**

| | | |
|---|---|---|
| **Title:** | Cardiopulmonary exercise testing (CPET) SOP EPOCH CPET | |
| **Doc Name:** | SOP_CPET_01 | |
| **Version:** | 1 | |
| **Effective Date:** | 25.09.2019 | |
| | Name, Function | Date |
| **Author** | Markus Schwerzmann | 28.04.2019 |
| **Release by PI** | Matthias Greutmann | 25.09.2019 |

## 1 Purpose

The purpose of this SOP is to describe the standards for performing a cardiopulmonary exercise test as part of the EPOCH studies.

## 2 Scope

The SOP is valid for all clinical research functions participating at EPOCH ASO STUDY and aims to improve the comparability of CPET exams performed at different investigating sites. The SOP shall set a common standard for the performing a cardiopulmonary exercise test in compliance with GCP, other SOP and regulatory requirement(s).

## 3 Abbreviations

| | |
|---|---|
| CPET | Cardiopulmonary exercise testing |
| ECG | electrocardiogram |
| FVC | forced vital capacity |
| FEV | forced expiratory volume |
| $FEV_1$ | forced expiratory volume in the first second |
| $VO_2$ | oxygen consumption |
| $VCO_2$ | carbon dioxide production |
| $PETO_2$ | partial pressure of end-tidal oxygen |
| $PETCO_2$ | partial pressure of end-tidal carbon dioxide |
| VE | ventilation |
| HR | heart rate |
| HRR | heart rate recovery |
| RQ | respiratory quotient ($VCO_2/VO_2$) |

## 4 Procedure

### *4.1 General*

| Responsibility | Procedure |
|---|---|
| Study nurse and/or cardiologist | Plan CPET study, inform patient to bring sports gear and to only eat a light meal before the CPET |
| | Prepare a room with ECG, spiroergometry system and electronically braked cycle ergometer |

### *4.2 Study Preparation*

| Responsibility | Procedure |
|---|---|
| Assistant doctor and/or sports scientist | Measure patient height and weight |
| | Connect Twelve-lead ECG with patient laying down<br>✓ Measure resting ECG and HR<br>✓ Measure resting blood pressure (≥5 min of laying down) with an automatic device twice on the right arm and once on the left arm. The lowest value is taken.<br>✓ Register ECG date, HR and rhythm on CRF sheet |
| | Perform spirometry 3 times<br>✓ Register best performance FVC and $FEV_1$ on CRF sheet |
| | CPET on cycle with ergometry, ECG registration and blood pressure measurement<br>✓ Connect gas analyser and perform local calibration protocol before every CPET<br>✓ Make sure patient cannot to see the amount of Watt during cycling. RPM should be visible. |

### *4.3 Performing Study*

| Responsibility | Procedure |
|---|---|
| Study nurse and/or cardiologist | Test protocol for $VO_2$ peak:<br>✓ Start recording<br>✓ 3 min resting phase sitting quietly on ergometer without talking<br>✓ Measure baseline blood pressure in second minute and HR in third minute while sitting on the bicycle<br>✓ Cycle for 3 min at 0 Watt for RAMP 5 protocol or at 20 Watt for other protocols with a RPM between 60–80<br>✓ Choose individualized RAMP protocol resulting in optimal test duration 8–12 min |

(Continued)

**(continued).**

| Responsibility | Procedure |
|---|---|
| | ○ RAMP 10 (10 Watt/min)<br>○ RAMP 15 (15 Watt/min)<br>○ RAMP 20 (20 Watt/min)<br>✓ Use the same protocol for follow-up testStart RAMP and let patient cycle between 60–80 RPM<br>**Protocol for treadmill:**<br>✓ Start recording<br>✓ The initial speed of 3 km/h will be maintained for the first 2 minutes and, thereafter, an increase of 0.3 km/h for every subsequent minute was added.<br>✓ The initial slope will be zero, increasing 1.4% after the second stage until a maximum of 12%.<br>✓ Twelve-lead ECG (CS-200) recordings will be obtained and blood pressure will be measured with a sphygmomanometer at baseline and at the end of every stage.<br>✓ Criteria for test termination will be lack of increase in oxygen uptake ($VO_2$), physical exhaustion or the reiterated request of the patient.<br>✓ A $VO_2$ plateau, or ventilatory threshold plateau if the former was lacking, will be considered criteria for maximal exercise test.<br>Terminate the test when patient is exhausted despite verbal encouragement:<br>✓ Aim at RQ >1.1<br>✓ Aim at Borg scale (6–20) > 17<br>After termination of the test, let the patient continue cycling for at least 1 min at 5 watt and at 60 RPM<br>✓ Register reason for test termination and BORG score on CRF sheet<br>✓ Register HR after 1 min<br>Stop data recording only shortly before patient dismounts from the ergometer |

### *4.4 Results/Report*

| Responsibility | Procedure |
|---|---|
| PI of each centre | Analyse data locally (nor core lab)<br>The following data should be collected and reported:<br>- bicycle/treadmill<br>- peak Watt<br>- peak Watt % predicted<br>- peak $VO_2$, defined as the highest value of oxygen consumption during the last 30 s of peak exercise<br>- peak $VO_2$ % predicted |

**(continued).**

| Responsibility | Procedure |
|---|---|
| | - $VE/VCO_2$ slope*<br>- $O_2$ pulse trajectory*<br>- $VO_2$/delta Watt trajectory*<br>- Arrhythmias at 12-lead ECG<br>- ST-segment depression (J-point during exercise)<br><br>Reporting of these data will follow the recommendations of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR/AHA joint scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations, Eur. Heart J. 2012:33; 2917–2927) |

## Appendix 3
## Study Specific SOP

| | | |
|---|---|---|
| **Title:** | Transthoracic Echocardiography (TTE), EPOCH-ASO | |
| **Doc Name:** | SOP_ECHO_01 | |
| **Version:** | 1 | |
| **Effective Date:** | 25.09.2019 | |
| | Name, Function | Date |
| **Author** | Berto Bouma<br>Matthias Greutmann | 15.06.2019 |
| **Release by PI** | Matthias Greutmann | 25.09.2019 |

### 1 Purpose/Scope

The purpose of this standard operating procedure (SOP) is to describe the standards for performing a transthoracic echocardiography (TTE) as part of the EPOCH-ASO study. The SOP is valid for all clinical research functions participating at EPOCH-ASO and aims to improve the comparability of echocardiography exams performed at different investigating sites. The SOP shall set a common standard for the performing of an echocardiographic study in compliance with GCP, other SOP and regulatory requirement(s).

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## 3 Abbreviations

| | |
|---|---|
| PW | Pulsed wave Doppler |
| CW | Continuous wave Doppler |
| PR | Pulmonary regurgitation |
| RV | Right ventricle |
| LVOT | Left ventricular outflow tract |
| TAPSE | Tricuspid annular plane systolic excursion |

## 4 Procedure

Transthoracic echocardiography

### *4.1 Requirements/Responsibilities*

| Responsibility | Procedure |
|---|---|
| Study physician/echo technician (dedicated by the study site) | Performing a full echocardiographic study following the protocol outlined in detail in this SOP |
| Core lab | Not determined |

### *4.2 Detailed Echocardiography Protocol*

| Responsibility | Procedure |
|---|---|
| General requirements | • For each view: Record at least 2 consecutive loops (beware of extra-systole)<br>• Gain and depth settings must be optimized for each view<br>• All echocardiographic studies must be recorded with ECG<br>• For images for strain analysis a framerate of 50–90 should be obtained |
| Detailed echocardiography protocol | **Parasternal views:**<br>**1.) Parasternal long-axis**<br>• Overview<br>• Parasternal long axis view optimized for neo-aortic valve and aortic root, with and without color<br>• Parasternal long axis with detailed recording of the neo-aorta (including measurement LVOT)<br>• Parasternal long axis optimized for mitral valve, with and without color<br>**2.) Parasternal short-axis**<br>• Parasternal short axis view optimized for neo-aortic valve, with and without color<br>• Parasternal short axis view optimized for pulmonic valve, with and without color, if possible.<br>• High parasternal short axis view optimized for pulmonary artery including the branches, with, without color and cw.<br>• Short axis view at mid-ventricular level (please ensure that the entire RV-wall is within the scanning sector) with frame rate 50–90/sec<br>• Parasternal short axis view optimized for tricuspid valve regurgitation jet, with and without color<br>**3.) RV-inflow view with and without color**<br>**Apical views:**<br>**4.) Apical views**<br>• 4-chamber view overview: at least 2 recordings<br>• 2-chamber view overview<br>• 3-chamber (apical long axis) overview<br>• 4-chamber view focused on left atrium<br>• Measurement of LVef and LV volumes<br>• Measurement of left and right atrium volume<br>**Additional apical assessment of left ventricle**<br>• LV-optimized 4CV-view (frame rate: 50–90/sec) At least 2 recordings<br>• 2-chamber view (frame rate: 50–90/sec): at least 2 recordings<br>• 3-chamber view (frame rate: 50–90/sec): at least 2 recordings |

(Continued)

**(continued).**

| Responsibility | Procedure |
|---|---|
| | • Tissue Doppler lateral mitral valve annulus– optimized for systolic and diastolic flow velocities (S', E', A') |
| | • PW at tips of mitral valve leaflets (to obtain E and A velocity) |
| | **Apical assessment of LVOT, mitral regurgitation, pulmonary regurgitation** |
| | • Mitral valve with color 4,2 and 3 chamber view (including attempt for PISA in case of > minor MR) |
| | • CW mitral valve to record mitral regurgitation max. velocity (optimized gain settings) if there is mitral regurgitation |
| | • LVOT with and without color |
| | • LVOT CW and PW |
| | • Pulmonic valve from 5CV with and without color Doppler, if possible |
| | • Pulmonic valve regurgitation CW (to obtain diastolic pulmonary artery pressure) |
| | **Apical 4-chamber view RV-assessment** |
| | • RV-optimized view (frame rate: 50–90/sec): At least 2 recordings |
| | • M-Mode lateral tricuspid valve annulus, maximal sweep speed (2 recordings) |
| | • Tissue-Doppler lateral tricuspid valve annulus – optimized for systolic and diastolic flow velocities (S', E', A') |
| | • PW at tips of tricuspid valve leaflets (to obtain E and A velocity) |
| | • Tricuspid valve annulus maximal diameter |
| | **Apical 4-chamber view tricuspid regurgitation assessment:** |
| | • With normal color baseline including zoom modality (for Vena contracta) |
| | **CW measurements:** |
| | • TR with optimized scale settings for measurement |
| | • TR with optimized scale settings for measurement of PISA (entire TR-spectrum, optimized gain settings |
| | **Subcostal view** |
| | • Inferior vena cava with inspiration (5 loops) |
| | • Hepatic vein velocities (PW) |
| | **Suprasternal view** |
| | • Aortic arch with and without color Doppler and PW & cw in descendens |
| | • PA branches if possible |

### *4.3 Results/Report*

| Responsibility | Procedure | | |
|---|---|---|---|
| PI of each center | Standard-measurements as outlined in the detailed protocol | | |
| | **Measurement** | **Result** | **Unit** |
| | Weight | | kg |
| | Height | | cm |
| | BP systolic<br>BP diastolic | | mmHg<br>mmHg |
| | HR | | Beats/min |
| | Estimated left ventricular function<br>- Visual estimation<br>0: None<br>I: Mild dysfunction<br>II: Moderate dysfunction<br>III: Severe dysfunction | | -<br>ml<br>ml<br>%<br>% |
| | - LV volumes systolic<br>- LV volumes diastolic ml<br>- LV EF %<br>- LV-GLS % | | |
| | LVEDD<br>LVESD<br>LA-M-Mode<br>Posterior wall thickness<br>Septal wall thickness | | mm<br>mm<br>mm<br>mm<br>mm |
| | Right ventricular enddiastolic area<br>Right ventricular endsystolic area<br>FAC (score)<br>TAPSE<br>TAPSE S’ | | $cm^2$<br>$cm^2$<br>%<br>mm<br>cm/s |
| | Tricuspid valve regurgitation<br>0: None<br>I: Mild<br>II: Moderate<br>III: Severe | | Grade:<br>0: None<br>I: Mild<br>II: Moderate<br>III: Severe |
| | Peak systolic RA-RV gradient | | mmHg |
| | Inferior vena cava width–maximum | | mm |
| | Inferior vena cava width–minimum | | mm |
| | Estimated enddiastolic pulmonary pressure (pressure gradient PA/RV–as measured from PR-signal) | | mmHg |
| | Maximal/mean pressure gradient across the Pulmonic valve | Max.<br>Mean | mmHg<br>mmHg |

(Continued)

**(continued).**

| Responsibility | Procedure | |
|---|---|---|
| | Neo-aortic valve regurgitation<br>0: None<br>I: Mild<br>II: Moderate<br>III: Severe<br>guidelines | 0: None<br>I: Mild<br>II:<br>Moderate<br>III: Severe<br>guidelines |
| | Diameter of neo-aortic root:<br>(all measurements inner-to-inner edge, enddiatolic)<br>Sinus Valsalva<br>Sinotubular junction<br>Aorta ascendens | mm<br>mm<br>mm |

## Appendix 4
## Study Specific SOP

| | | |
|---|---|---|
| **Title:** | Cardiac magnetic resonance imaging (CMR), EPOCH-ASO | |
| **Doc Name:** | SOP_CMR_01 | |
| **Version:** | 1 | |
| **Effective Date:** | 25.09.2019 | |
| | Name, Function | Date |
| **Authors** | Laura Dos, Pastora Gallego | 23.09.2019 |
| **Release by PI** | Matthias Greutmann | 25.09.2019 |

### 1 Purpose

The purpose of this SOP is to describe the standards for image acquisition, image analysis and reporting of cardiac mangnetic resonance tomography for assessment of cardiac anatomy and function as part of the EPOCH-ASO study.

### 2 Scope/Objectives

The SOP is valid for all clinical research functions participating at EPOCH-ASO study and aims to improve the comparability of CMR exams performed at different investigating sites. The SOP shall set a common standard for image acquisition, image analysis and reporting of results. The CMR protocol is in compliance with GCP, other SOP and regulatory requirement(s).

The general objectives of the standardized CMR-protocols part of the EPOCH-ASO study are:

(1) To describe the standards for CMR examinations in adults with TGA after ASO as part of the EPOCH-ASO study
(2) To improve comparability among examinations performed at different centers by different operators.
(3) To detect and quantify aortic dilatation and regurgitation

(4) To detect, localize and quantify right ventricular outflow tract obstructions and to evaluate pulmonary branches anatomy.
(5) To detect myocardial fibrosis and ventricular dysfunction
(6) To study the aortic arch

## 3 Abbreviations

| | |
|---|---|
| CMR | Cardiac magnetic resonance imaging |
| LGA | Late gadolinium enhancement |

## 4 Procedure

### *4.1 Study Preparations/Requirements*

| Responsibility | Procedure |
|---|---|
| Radiologist/ cardiologist | • Blood pressure at the time of examination<br>• Measure patient height and weight<br>• Hematocrit for those who performe T1-mapping and ECV |

### *4.2 Performing Study*

| | Procedure *(in brackets: estimated time for image acquisition)* |
|---|---|
| **Mandatory** | 1. Three-plane localizing images (3 min.)<br>2. ECG-gated cine SSFP imaging of the ventricles *(10–12 min)* a short axis stack covering both ventricles from base to apex (slice thickness 8 mm, no slice gap, in-plane resolution 1.3–1.7 $mm^2$, 25 cardiac phases)<br>- three-, four- and two-chamber planes,<br>- LVOT long-axis plane<br>- RV outflow tract long-axis plane and double oblique RVOT plane.<br>3. ECG-gated cine SSFP imaging stack in short axis to the neoaortic root (slice thickness 5 mm, no slice gap). *(2–3 min)*<br>4. ECG gated cine SSFP imaging stack in an axial plane to image the branch pulmonary arteries (slice thickness 8 mm, slice gap 2 mm) with extending the stack to the ascending aorta (above the surgical suture) in order to image the descending aorta on the same plane (aortic distensibility)<br>- ECG-gated cine LPA and RPA *(2 min)*<br>- perpendicular long axis (planned from the transaxial view)<br>- double oblique perpendicular planned from the previous LPA/RPA long axis cine<br>5. Gadolinium contrast-enhanced 3D angiography *(2–3 min)* timing focused on:<br>- pulmonary arteries<br>- second run for aortic arch and descending aorta |

(Continued)

**(continued).**

| | Procedure *(in brackets: estimated time for image acquisition)* |
|---|---|
| | 6. ECG-triggered (at end-diastole) and respiratory navigator gated 3D CA imaging (voxel size 1.5 × 1.5 × 1.5 mm) (*4–5 min)*<br>*Optional (CT coronary angiography comparisons): best planned para-sagittal/para-aortal to capture end-diastolic neo-aortic root and coronary arteries (appr. 90 slice per slap)* |
| | 7. ECG-gated velocity-encoded cine for measurements in the main, left, and right pulmonary arteries, and ascending aorta *(3–4 min)*<br>- velocity adjustments according to highest velocity (aorta 150 cm/s, MPA/PRA/LPA > 150 cm/s);<br>- *Optional: confirmation of ascending aorta flow can be performed by comparing it with the sum of the SVC and descending aorta flows (with 90 cm/s).* |
| | 8. ECG gated LGE imaging in ventricular long- and short-axis planes (slice thickness 8 mm, no slice gap, in-plane resolution 1.3–2.0 $mm^2$, end-diastolic phase) *(8–10 min)* |
| **Optional** | It requires additional software or experience and may thus be not available at all institutions: |
| | 9. T1-map of 1 short axis slice (copy image position of a SAX cine at the boarder basal to midventricular). *(0.5 min)* |
| | 10. Post-contrast T1-map of 1 short axis slice (copy image position of the same cine slice as pre-contrast, point 3 with same FOV and image position). *(0.5 min)* |
| | 11. *A vasodilator stress protocol at baseline *(6–7 min)* |
| | 12. *4D-Flow: PC-VIPR sequence, retrospective ECG-gating, free-breathing. VENC 200 cm/s. FOV 400 × 400 × 400, isotropicvoxel 2.5 × 2.5 × 2.5 $mm^3$, flipangle 8°, temporal resolution *(15–45 sec)* |
| | *To be acquired only in the baseline MR examination |

### *4.3 Results/Report*

| Responsibility | Procedure |
|---|---|
| CMR specialists | |
| Mandatory | CMR reports should comprehensively address the most common postoperative sequelae and include the following information:<br>- LV and RV volume, EF, mass, and regional function<br>- Presence of focus of myocardial fibrosis and ischemic/embolic scars. If applicable, diffusse myocardial fibrosis and ECV<br>- Extent of (LV) and RV outflow tract obstruction<br>- Extent of pulmonary artery obstruction and calculation of the branch pulmonary artery flow distribution<br>- Neoaortic root size and quantitation of neoaortic valve regurgitation (regurgitant volumen and fraction)<br>- Aortic arch morphology, extent and severity of vascular stenosis<br>- Presence of residual atrial septal defects and VSDs, and calculation of the pulmonary-to-systemic flow ratio (Qp/Qs) |

**(continued).**

| Responsibility | Procedure |
|---|---|
| **Optional** | - Quantitation of significant AV or neopulmonary valve regurgitation (regurgitant fraction and volume)<br>- If applicable, description of the CA origins, proximal course, and degree of obstruction (CT examination as gold standard)<br>- Presence and quantitation of aortopulmonary collateral vessels flow.<br>- Aortic distensibility (used for research purpose) |

## Appendix 5
## Study Specific SOP

| | | |
|---|---|---|
| **Title:** | Coronary Computed Tomography (CTCA), EPOCH-ASO | |
| **Doc Name:** | SOP_CTCA_01 | |
| **Version:** | 1 | |
| **Effective Date:** | 25.09.2019 | |
| | Name, Function | Date |
| **Authors** | Magalie Ladouceur, Daniel Tobler | 23.09.2019 |
| **Release by PI** | Matthias Greutmann | 25.09.2019 |

### 1 Purpose

The purpose of this SOP is to describe the standards for image acquisition, image analysis and reporting of computed cardiac tomography for assessment of coronary arteries (CTCA) as part of the EPOCH-ASO study.

### 2 Scope/Objectives

The SOP is valid for all clinical research functions participating at EPOCH-ASO study and aims to improve the comparability of CTCA exams performed at different investigating sites. The SOP shall set a common standard for image acquisition, image analysis and reporting of results. The CTCA protocol is in compliance with GCP, other SOP and regulatory requirement(s).

The general objectives of the standardized CTCA-protocolas part of the EPOCH-ASO study are:

- To estimate origin and quality of each main coronary arteries (LM, LAD, Cx, RC), cardiac valves, the entire thoracic aorta and pulmonary arteries with enhanced CT. If the thoracic aorta and aortic arch have been comprehensively imaged by means of cardiac/aortic magnetic resonance imaging within the last 3 years prior to CTCA, the inclusion of the thoracic aorta and the aortic arch may be omitted in the CTCA-protocol.
- To detect abnormal origin and course of proximal coronary arteries presenting a risk for potential stenosis and/or occlusion.
- To detect dilatation and all other abnormal geometry features of the thoracic aorta.
- To detect obstruction all along the right ventricular outflow tract, which includes proximal pulmonary arteries?
- To limit X-Ray radiation in this young population.

## 3 Abbreviations

| | |
|---|---|
| CT | Computed tomography |
| CTCA | Computed tomography coronary arteriography |
| LCA | Left coronary artery |
| RCA | Right coronary artery |
| LAD | Left descending artery |
| CX | Circumflex artery |

## 4 Procedure

### *4.1 Study Preparations/Requirements*

| Responsibility | Procedure |
|---|---|
| Radiologist/ cardiologist | All examinations will be performed with a bitube Siemens or >= 128 detector rows system in other vendors. The effective temporal resolution should be < 140 ms per slice. Patient characteristics (age, body size indices, blood pressures) at time of CT. Patient will be isocentering in CT gantry, with ECG leads and arm positioning. No sedation will be necessary |

### *4.2 Performing study*

| Responsibility | Procedure |
|---|---|
| Radiologist/ cardiologist | Measure patient height and weight |
| | **Data acquisition** will be performed prospectively with ECG-triggered sequential scan or retrospectively ECG-gated spiral scan depending on local expertise for cardiac examination and equipment. Data parameters will the following: slice collimation 0.5–0.6 mm (the smallest one), tube voltage 70–100 kV in order to decrease the Dose Length Product (DLP), tube current will dependent on local expertise, tube modulation and patient weight.<br>Diastolic imaging of the heart (70–80% of the RR interval coverage) and of the great vessels will be acquired with full coverage in no more than 4 cardiac cycles depending of the equipment. Iterative reconstruction algorithm will be used according to local expertise for cardiac examination and equipment. Heart rate during scan acquisition will be recorded, or ECG's will be saved during acquisition and kept in the patient folder. The CT scanning will be performed with intravenous contrast enhancement. Volume and rate of contrast injection will depend on patient size and circulation; 100 ml of maximal volume of a solution with ≥300 ml/l of an iodinated contrast medium will be used, depending on local expertise and tube voltage. The scan delay will be determined using a bolus tracking technique. Biphasic injection is warmly recommended since opacification of the right ventricular outflow tract and the pulmonary arteries is necessary. (60 ml at 4.5 ml/sec of pure iodinated CM followed by 20 ml of diluted CM can be an example of injection protocol). To optimize acquisition, beta blockers and sublingual Nitrate will be given if heart rate >65/min unless contraindication. |

**(continued).**

| Responsibility | Procedure |
|---|---|
| | Acquisition will include the entire heart, thoracic aorta and proximal PA branches within the field of view optimized to patient size. |
| | **Reconstruction process** will be performed using one series with 0.5–0.625 mm and no gap between slices with less than 220 mm FOV if possible. Iterative reconstruction and optimal filter could be used based on the local expertise and CT system. |

### *4.3 Analysis of the Data*

Coronary arteries will be analyzed using axial slices and, if necessary, with the aid of post-processing tools such as multiplanar reconstruction, maximum-intensity thin-slab projection and 3-dimensional reconstruction. Analysis will be limited to 6 coronary artery segments: ostia of the left and right coronary artery, left main coronary artery, and the proximal segments of the left anterior descending, left circumflex, and right coronary artery. In both modalities, the following features will be assessed additionally for the purposes of the current study [1]:

(1) Minimum and maximum diameters: at the most narrowed location and the normal distal reference segment; coronary lesions will be graded using visual assessment, and classified as either normal or having >50 or <50% stenosis (3 classes) after being also quantitatively estimated as a percentage of reduction of the coronary artery diameter in % (Fig. 1).

(2) Proximal vessel morphology: categorize proximal vessel morphology as: (i) normal, (ii) 'oval' (<50%), and (iii) 'slit-like' narrowing (≥50% reduction in minimum diameter in the absence of coronary artery disease). (Fig. 2) [2,3].

(3) Length of narrowing: centerline length of vessel narrowing extending from the most proximal segment to the normal caliber distal reference (Fig. 3) [1].

(4) Acute angle: defined as the presence or absence of acute angle take-off <45° between (a) the plane formed by the ostium centre to a point 5 mm along the vessel centerline, and (b) a plane tangent to the aorta in multiplanar axial reconstruction at the level of the ostium (Fig. 4) [3,4],

(5) Intramural course: defined as (i) presenct, (ii) absent, or (iii) indeterminate (Fig. 4) [1].

(6) Vessel take-off level: categorized as at/above or below the aortic valve commissure (Fig. 4) [1].

(7) Ostia type: defined as (i) separate, (ii) shared, or (iii) branch vessel (Fig. 5) [1].

(8) Coronary pattern will be described using the classification of Yacoub et al. [1,5].

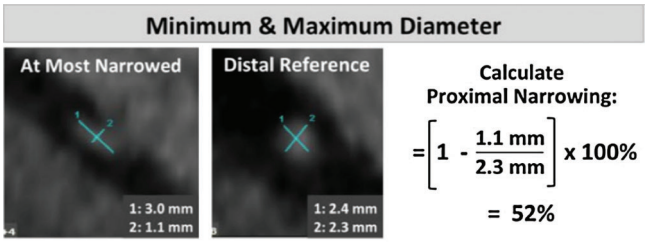


**Figure 1:** Minimum & Maximum ostial coronary artery diameter

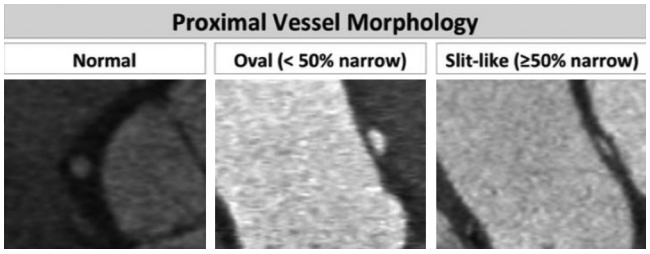


**Figure 2:** Proximal vessel morphology

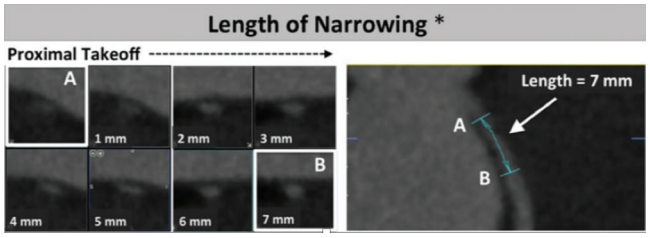


**Figure 3:** Length of narrowing

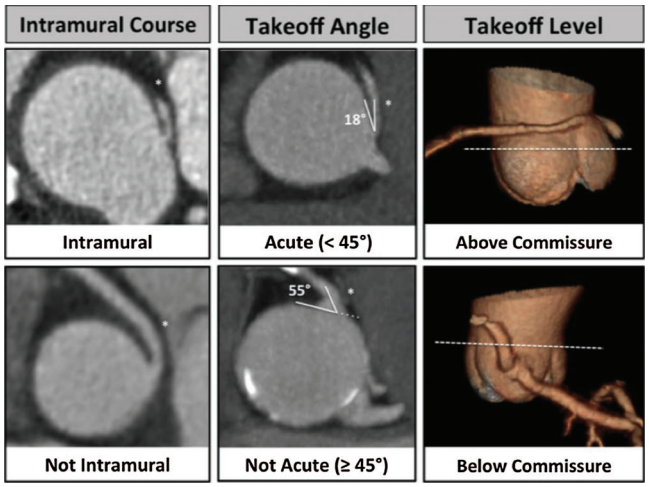


**Figure 4:** Course, angle and takeoff level of coronary arteries

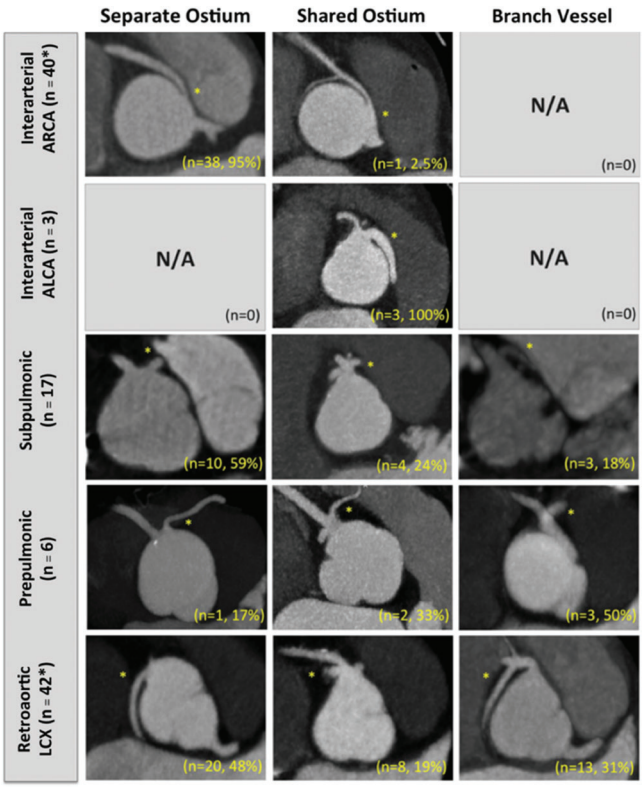


**Figure 5:** Type and branching of coronary ostias

Right ventricle outflow tract, pulmonary annulus, main pulmonary artery and pulmonary arteries will be also assessed with a measurement of the narrowest diameter at each level in views obtained orthogonal to the centerline of the corresponding vessel. -All diameters will be measured perpendicular to the centreline of the pulmonary artery, during end-diastole

Finally, the maximal diameters at level of aortic annulus, sinus of Valsalva, sino-tubular junction and the ascending and descending aorta (next to the left pulmonary artery) will be measured in orthogonal views of the ascending aorta.

- All diameters will be measured perpendicular to the centreline of the aorta
- All aortic diameters are measured with the inner edge to inner edge convention, during end-diastole
- The dimeter of the sinus of Valsalva will be the maximal diameters among the 3 diameters obtained by measurements sinus to sinus.
- Ascending and descending aorta will be measured in the same plane than the pulmonary artery bifurcation.

### *4.4 Results/Report*

| Responsibility | Procedure |
|---|---|
| PI of each center/Corelab | Analyse data locally and in core lab<br>The following data should be collected and reported:<br>These measurements must be reported for LCA (if separate ostia: for LAD and CX) and RCA<br>- CA anatomy type<br>- Minimum/maximum diameter of proximal coronary arteries<br>- Proximal narrowing (see text for details)<br>- Proximal vessel morphology: Normal, oval, slit-like<br>- Length of narrowing<br>- Takeoff angle<br>- Takeoff level<br>- Neo-Aortic diameters<br>- Aortic root level<br>- Ascending aorta<br>- Aortic arch<br>- Diameter of proximal branch pulmonary arteries |

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