



# **Concordance between stress CMR and coronary angiography in pediatric patients with suspected coronary artery disease.**

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## 1. BACKGROUND

Transposition of the great arteries, the most common cyanotic congenital heart lesion found in neonates, accounts for 5%–7% of congenital cardiac malformations.

Arterial switch surgery is now the treatment of choice for transposition of the great arteries. In this procedure, the aorta and main pulmonary artery are transected, switched, and re-anastomosed to the correct ventricle. The coronary arteries and a small portion of aortic sinus are excised when the aorta is transected and are re-implanted once the aorta is connected to the left ventricular outflow tract.

Most complications and mortality occur within the first year of life, and are secondary to myocardial ischemia or infarction associated with relocation of the coronary arteries at surgery. Nonetheless, follow-up studies have revealed a significant prevalence (7-8%) of coronary stenosis, occlusions and late death in an otherwise symptom-free patient population.

Other pathologic condition affecting coronary arteries during pediatric age, with a lower incidence than transposition of coronary arteries, are: Kawasaki disease, primary dilatative cardiomyopathy of undetermined nature, ALCAPA syndrome and other coronary artery anomalies of origin and pathway, coronary fistula, coronary atresia, familial hypercholesterolemia, bicuspid aortic valve, chest pain or dispnea related to exercise of suspected coronary nature.

Following current practice, pediatric patients affected by or with suspected coronary artery disease undergo to Exercise Test, Eco stress and Coronary Angiography. While coronary angiography (CA) is considered the gold standard for detection of coronary lesions necessitating possible interventions, CA is a invasive and x-ray exposing technique which cannot be included in regular follow-up in asymptomatic children.

Cardiovascular Magnetic Resonance imaging (cMRI) provides both morphologic and functional information that can be decisive in the treatment of neonates and infants with congenital heart disease. Thanks to its non-invasiveness and lack of ionizing radiation, cMRI is now becoming a major imaging tool in pediatric congenital heart disease.

In recent years, pharmacological stress testing has evolved as an alternative to physical exercise for the detection of inducible myocardial ischemia. In adult patient affected by atherosclerotic coronary disease, myocardial perfusion cMRI can be performed at rest and during stress with pharmacologically induced coronary vasodilatation. This defines myocardial viability and the stress/rest perfusion deficit, while a bolus of gadolinium contrast agent is being administered. The clinical value of stress perfusion cMRI is similar to that of myocardial scintigraphy, with the advantages that cMRI perfusion is performed over a single 45-



minute session, with no radiation exposure, as compared to two long sessions of scintigraphy.

Surgical revascularization or angioplasty are therapeutic options for coronary lesions even in infants and children. Pharmacological stress induced cMRI could provide crucial information such as coronary arteries origin and proximal pathway, wall motion abnormalities, myocardial perfusion and viability, enabling accurate monitoring of symptomatic and non-pediatric patients.

Feasibility and safeness of stress cMRI in pediatric patient is already well established by studies and clinical experience published (JCMR 2009;29:313-319; JCMR 2014, 16 (Suppl 1):P128; JACC 2016 Vol. 67, Issue 13; JCMR 2009, 11:51; Cardiology in the young Vol. 20/Issue 4/August 2010, pp 410-417; JCMR 2013, 15 (Suppl): P298). Stress cMRI is already included in the clinical current practice of major international Pediatric Hospital (GOSH London, Children Hospital Boston).

We would build a prospective series of stress cMRI exams in pediatric symptomatic and non-patients, with suspected or previously diagnosed coronary artery disease, and we would put the results in comparison with ECG, Exercise test, stress Cardiac Ultrasound and Angiography. At the end of the study, if supported by results, our aim is to replace the current diagnostic procedure (ECG, Exercise test, stress Cardiac Ultrasound and Angiography) which need long hospitalization, expose the patient to radiation dose, is uncomfortable for the patient, and is characterized by a non-negligible risk due to invasive procedure, with a single exam (stress cMRI) which is dose-free, minimal risk related, without hospitalization, and less expensive for our National Care System.

## 2. OBJECTIVES

### **Primary Objective:**

- To verify the concordance between stress cMRI and conventional technique (angiography, eco-stress) in evaluation of pediatric patient with suspected coronary artery disease.

### **Secondary Objectives:**

- To optimize the scan protocol and the sequence parameters
- To investigate the clinical compliance of stress induced cardiac MRI in pediatric patients
- To test the ability of stress cMRI to visualize coronary arteries morphological irregularities, the corresponding wall motion abnormalities and perfusion - viability features
- To find a correlation between cMRI data and clinical status and other diagnostic tools, parameters and variables.
- To demonstrate the advantage of stress cMRI over cMRI in evaluation of pediatric patient with



suspected coronary artery disease.

**Primary Endpoint:**

- Agreement of results between stress cMRI and the current practice constituted by Exercise test, Stress Cardiac Ultrasound and Invasive Angiography.

**Secondary Endpoints:**

- Efficacy of stress cMRI: Predictive value of stress cMRI to determine the incidence of post-surgical complication of switch repair, and other pathological conditions affecting coronary arteries in natural history
- Safety: to investigate Advers Events (AE) to Contrast Medium and pharmacological stress agent

### 3. STUDY DESIGN:

Mono-centre, pilot, prospective interventional study.

cMRI exam with injection of Contrast Medium is considered a safe and robust technique to study congenital heart disease in pediatric patient. At Gaslini Institute, our Cardio-Radiology team accounts for more than 1000 cMRI exams of congenital heart disease performed in pediatric patients, without major adverse events reported.

Furthermore, in our centre, Dobutamine is routinely administered to all patients during diagnostic stress procedures (Stress Cardiac Ultrasound and Invasive Angiography), which correspond to the current practice to investigate coronary arteries anomalies according to international guidelines.

Therefore, stress cMRI with Dobutamine stress agent (stress cMRI), from a procedural perspective, represent the combination of two orders of exams routinely performed (cMRI and stress diagnostic series of exams) without additional risk for the patient, but with the advantage of non-invasiveness and lack of radiation, less laborious for the Patient and less expensive for the Healthcare.

### 4. STUDY PROCEDURES

The study population will be recruited, over a period of approximately 24 months, from children attending the ward and the outpatient clinics of the cardiologic paediatric unit, in accordance with the following inclusion criteria.



4.1 Inclusion Criteria are: Between 8 and 18 years-old patients symptomatic and non, with suspected or previously diagnosed coronary arteries disease: Coronary artery re-implantation after arterial switch, ALCAPA Syndrome, other anomalies of origin or pathway, replacement of aortic valve with pulmonary autograft (Ross procedure), Kawasaki disease, primary dilatative cardiomyopathy, coronary atresia, familial Hypercholesterolemia, bicuspid aortic valve, chest pain, exertional dyspnea of suspected coronary artery nature, coronary artery fistula.

4.2 Exclusion criteria are: General contraindication to MRI (non MRI compatible device: vascular clips, foreign bodies, coronary and peripheral artery stents, aortic stent grafts, prosthetic heart valves and annuloplasty rings, cardiac occluder devices, vena cava filters and embolisation coils, haemodynamic monitoring and temporary pacing devices, haemodynamic support devices, permanent cardiac pacemakers and implantable cardioverter-defibrillators, retained transvenous pacemaker and defibrillator leads, cochlear implants, claustrophobia, pregnancy and postpartum), contraindication to contrast agent (renal insufficiency, hypersensitivity to the Dotarem active substance or to any of the excipients:), contraindication to stress agent (hypersensitivity to Dobutamine active substance or to any of the excipients; severe arterial hypertension ( $\geq 220/120$  mmHg), unstable angina pectoris, significant aortic stenosis, complex cardiac arrhythmias including uncontrolled atrial fibrillation, hypertrophic obstructive cardiomyopathy, myocarditis, endocarditis, pericarditis, uncontrolled congestive heart failure, previous manifestations of hypersensitivity to dobutamine, refuse to join the protocol and relative off-label procedures.

A total number of 15 patients fitting the above criteria is the target of our study.

### 4.3 Study Procedure

#### METHOD

- 1) Ask for permission of local ethic board
- 2) Identify all patients in follow-up at Gaslini Institute, with suspected or previously diagnosed coronary arteries disease
- 3) Patients selection based on inclusion criteria
- 4) Patient call and first clinical visit, which includes explanation of research protocol and consent form signature
- 5) Stress CardiacMRI scan, ECG and Stress Cardiac Ultrasound exam, Exercise Test, Coronary Angiography.



### EXAM PREPARATION

Patients were asked to abstain from caffeine intake and to refrain from taking anti-anginal medications including beta-blockers 24 h prior to the exam. Theophylline must not be used for at least 12 hours before exam. Dipyridamole must not be used for at least two days before exam

Doctor have to explain to patient and parent the tasks of the exam, the benefits and the risks related to the subadministration of medications, including the Dobutamine. In particular, parents have to sign the consent form for off-label use of Dobutamine, consent form for Contrast Medium injection (Dotarem, Guerbet ITALY), and metal check list for in order to exclude patients with contraindications to MRI.

Nurse staff, under the supervision of a Doctor, should provide peripheral venous cannulation, thoracic four-lead VCG signal placement for MRI cardiac synchronization and thoracic twelve-lead electrodes for cardiac activity monitor.

Total Dotarem dose to inject during exam is calculated by the formula 0,1 mmol/kg.

Baseline HR and BP were obtained at rest prior to stress exam in the supine position. Peak HR was defined as the highest HR during the stress perfusion scan. Peak BP was defined as the BP corresponding to HR peak. Heart rate response (HRR) and blood pressure response (BPR) were calculated ( $\text{HR response} = [(\text{HR}_{\text{peak}} - \text{HR}_{\text{baseline}})/\text{HR}_{\text{baseline}}] \times 100$ ;  $\text{BP response} = [(\text{BP}_{\text{peak}} - \text{BP}_{\text{baseline}})/\text{BP}_{\text{baseline}}] \times 100$ ).

Proper hospital clothes and bladder emptying before entering MRI scanner room are recommended.

A 12-lead ECG was performed before and after the exam. Owing to magnetohydrodynamic effects causing ECG signal distortion, ECG tracing during examination was used only for gating purposes. Oxygen saturation, blood pressure (BP), and HR were monitored throughout the exam.

### Cardiac MRI PROTOCOL

MRI scanner: Philips Achieva 1.5 T. 32 Channel Cardiac Coil.

A. Scout sequences

B. SSFP 2-Chamber left, SSFP 2-Chamber right, SSFP 4-Chamber

C. DOBUTAMINE in increments of 10  $\mu\text{g}/\text{kg}$  body weight/minute every 3 minutes starting at 10  $\mu\text{g}/\text{kg}$  body weight/minute until target heart rate [ $85\% \times (220 - \text{age})$ ] reached.



- D. Dotarem injection (0,1 mmol/kg, 2 ml/sec) when the target heart rate is reached
- E. Stress perfusion Images in Short Axis and 4-Chamber
- F. Cine Short Axis from base to apex for volumetric analysis
- G. Late Gadolinium enhancement
- H. Rest perfusion Images in Short Axis and 4-Chamber
- I. 3D Navigated SSFP in transversal plane
- L. Aorta and Pulmonary flow

Patients were queried about their symptoms before and after Dobutamine administration. Sublingual nitroglycerine and iv metoprolol are available for severe and persistent chest pain during or after the exam.

#### STAFF, MEDICAL AND TECHNICAL EQUIPMENT

Hospital staff involved in stress cMRI exam is composed by: Radiologist, Cardiologist, Radiographer, Nurse. In case of necessity, first aid is guaranteed by Radiologist and Cardiologist in site, but in-Hospital Anesthetist Resuscitator is 24 hours 365 day ready to intervene for emergency related to MRI exams.

Emergency medical supplies, in recovery room: metoprololo, esmololo, nitroglycerine, adrenaline, betametasona

Medical device MRI compatibile, in scanner room: Contrast Medium pump, Dobutamine pump, cables and electrodes for four-lead VCG signal, cables and electrodes for cardiac monitoring, sat O<sub>2</sub>, heart rate and arterial blood pressure devices

Medical device not MRI compatibile, in control room: Contrast and Dobutamine pump command module, vital parameter monitor (12 lead ECG trace, blood pressure, heart rate, sat O<sub>2</sub>).

Medical device not MRI compatibile, in recovery room: vital parameter monitor (12 lead ECG trace, blood pressure, heart rate, sat O<sub>2</sub>), defibrillator

#### ADVERSE EVENTS

Potential side-effects stress-related: can start soon after Dobutamine injection and are usually over within 30 minutes. They don't usually need any treatment. They are: headache, dizziness, shortness of breath, chest pain, flushing, stomach discomfort.





Potential side-effects contrast agent-related: can partially present overlapping features with side-effects stress-related. They are: headache, dizziness, shortness of breath, chest pain, flushing, nausea, injection site pain, injection site coldness, burning sensation, feeling cold, rash, somnolence, fatigue, dizziness, vomiting, pruritus, paresthesia, dysgeusia, pain in extremity, anxiety, hypertension, palpitations, oropharyngeal discomfort.

Potential stress-related adverse events are:

Myocardial ischaemia: fatal cardiac arrest, life-threatening ventricular arrhythmias, and myocardial infarction may result from the ischaemia induced by pharmacologic stress agents.

Sinoatrial and atrioventricular nodal block: may depress the sinoatrial (SA) and arterioventricular (AV) nodes and may cause first, second or third-degree AV block, or sinus bradycardia.

Hypotension: may induce arterial vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.

Bronchoconstriction: may cause bronchoconstriction and respiratory compromise. For patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD) or asthma, appropriate bronchodilator therapy and resuscitative measures should be available prior to administration.

Potential contrast agent-related adverse events are:

Bradycardia, tachycardia, arrhythmia, anaphylactoid reactions including cardiac arrest, respiratory arrest, cyanosis, pharyngeal edema, laryngospasm, bronchospasm, angioedema, conjunctivitis, ocular hyperemia, eyelid edema, lacrimation increased, hyperhidrosis, urticarial, coma, convulsion, syncope, presyncope, parosmia, tremor.

During our study, all side effects and adverse events will be recorded in the registry for further analysis.

Adverse events will be coded using the MedDRA dictionary that provides the primary system organ class and preferred term information. All other information collected (e.g. severity, relationship to study treatment) will be tabulated and listed as appropriate. Adverse events will also be summarized by SMQ.

### OTHER EXAMS

**Stress Cardiac Transthoracic Ultrasound** is performed by a Cardiologist with at least 5 years of experience in Congenital Heart Disease Ultrasound, without knowing the result of Cardiac MRI, in a window time of 3 month before or after Cardiac MRI. Stress Cardiac Transthoracic Ultrasound exam protocol includes evaluation of origin and proximal pathway of coronary arteries, left chamber function, wall motion



abnormalities, systolic wall thickening, abnormal echogenicity of myocardium. Results are reported according to 17 segments classification (AHA). Cardiologist analyses right ventricle outflow tract (RVOT), main pulmonary artery and branch pulmonary arteries diameter, morphology and flow. The greatest velocity detected by echocardiography across the pulmonary valve, pulmonary trunk, or pulmonary branches was used in the analysis as an index of RVOT obstruction.

**Exercise test** is performed by a Cardiologist with at least 5 years of experience in Congenital Heart disease CPEX, without knowing the result of Cardiac MRI, in a window time of 3 month before or after Cardiac MRI. The peak exercise oxygen uptake ( $VO(2)$ ), and heart rate were recorded and are expressed as the percentage of predicted values.

**Coronary Angiography** is performed by a Interventional Cardiologist with at least 5 years of experience in Congenital Heart disease Angiography, without knowing the result of Cardiac MRI, in a window time of 3 month before or after Cardiac MRI. Exam protocol includes evaluation of origin and pathway of coronary arteries, RVOT morphology and pressure, main pulmonary artery and pulmonary branches morphology, diameter and intraluminal pressure.

ECG, Stress Cardiac Ultrasound, Exercise test, Coronary angiography are performed the same day.

#### 4.4 STATISTICAL CONSIDERATIONS

Data will be described as means, standard deviation (SD) and medians with a range for continuous variables, while absolute and relative frequencies will be used for categorical variables.

Categorical data will be compared by chi-square test or by Fisher's exact test in case of expected frequencies  $<5$ . Comparisons of quantitative variables will be performed by Student's t test for paired data or Wilcoxon test. Concordance between MRI- and traditional test will be determined by the Kappa statistical method as described by Landis and Koch, and  $\kappa$  will be interpreted as follows:  $\kappa$  value of 0 indicates poor agreement;  $\kappa$  value of 0.01–0.20, slight agreement;  $\kappa$  value of 0.21–0.40, fair agreement;  $\kappa$  value of 0.41–0.60, moderate agreement;  $\kappa$  value of 0.61–0.80, substantial agreement; and  $\kappa$  value of 0.81–1; almost perfect. p-value less than 0.05 will be considered statistically significant, and all p-values will be based upon two tailed tests. Statistical analysis will be performed using SPSS for Windows (SPSS Inc, Chicago, Illinois USA).

#### 4.5 ETHICAL CONSIDERATIONS AND INFORMED CONSENT

This Study will be conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and all its revisions, pertinent national laws and regulations, as well



as the International Conference on Harmonization (ICH)'s Good Clinical Practice, taking into account the Directive 2001/20/EC of the European Parliament and of the Council April 2001. Approval of the EC/IRB must be obtained before initiation of the study.

### **Informed consent**

The Principal Investigator (PI) is responsible for the collection of the written informed consent from each parent/patient participating in the study, after clear explanation of the study objectives, design, methods, potential benefits and hazards, data protection/confidentiality. The PI must specify to parents/patient that they are free to refuse to participate in the study and can withdraw from the study at any time and for whatever reason, without any prejudice on the quality of care that the patient has the right to expect.

It is recommended that parents/patients should have adequate time between being given the information on the study and being asked to sign the Informed Consent Form (ICF).

The ICF must be dated and signed off by either the PI and the patient (and/or their legal representative(s)) in duplicate. One copy of the ICF will be kept by the patient/parents and the original ICF will be kept by the PI.

## **5. DATA MANAGEMENT**

### **5.1 DATA SHEETS**

Data sheets will be completed as the form attached.

### **5.2 DATA STORAGE AND ELABORATION**

In accordance with the directives 2001/20 Ethical Committee of the European Parliament and of the Council of April 4, 2001, and the corresponding national laws, all data will be handled strictly confidentially. Throughout documentation and analysis, participants into this Registry will be identified only by the unique patient code. Identifying information will not be published. Submitted data will stored electronically into a specific database located at Radiology Dept. of the Istituto Giannina Gaslini, Genova, Italy. Storing procedures will be provided by the local Data Manager under the Registry Coordinator supervision.

Data elaboration will be conducted only by approved operators.

## **6. FINAL REPORT OF THE RESULT OF THE STUDY**

### **Result publication and communication policies**

The study's principal investigator will undertake to draw up a final report and a scientific article, and to publish the results on completing the study in a peer-reviewed journal.



The patient's data will be made public in anonymous form and will be presented just as group data.

## **7. FUNDING**

No sponsor study. The study will receive an external financial support by GUERBET Group, under the formula IIS (Investigator Initiated Study). The collaboration will be ruled by the contract between Gaslini Institute and Guerbet Group.

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