Trials

STUDY PROTOCOL

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The effects of percutaneous branch pulmonary artery interventions in biventricular congenital heart disease: study protocol for a randomized controlled Dutch multicenter interventional trial

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Abstract

Background Branch pulmonary artery (PA) stenosis is one of the most common indications for percutaneous interventions in patients with transposition of the great arteries (TGA), tetralogy of Fallot (ToF), and truncus arteriosus (TA). However, the effects of percutaneous branch PA interventions on exercise capacity remains largely unknown. In addition, there is no consensus about the optimal timing of the intervention for asymptomatic patients according to international guidelines. This trial aims to identify the effects of percutaneous interventions for branch PA stenosis on exercise capacity in patients with TGA, ToF, and TA. In addition, it aims to assess the effects on RV function and to define early markers for RV adaptation and RV dysfunction to improve timing of these interventions.

Methods This is a randomized multicenter interventional trial. TGA, ToF, and TA patients ≥ 8 years with a class IIa indication for percutaneous branch PA intervention according to international guidelines are eligible to participate. Patients will be randomized into the intervention group or the control group (conservative management for 6 months). All patients will undergo transthoracic echocardiography, cardiac magnetic resonance (CMR) imaging, and cardiopulmonary exercise testing at baseline, 6 months, and 2–4 years follow-up. Quality of life (QoL) questionnaires will be obtained at baseline, 2 weeks post intervention or a similar range for the control group, and 6 months follow-up. The primary outcome is exercise capacity expressed as maximum oxygen uptake (peak VO_2 as percentage of predicted). A total of 56 patients (intervention group $n=28$, control group $n=28$) is required to demonstrate a 14% increase in maximum oxygen uptake (peak VO_2 as percentage of predicted) in the interventional group compared to the control group (power 80%, overall type 1 error controlled at 5%). Secondary outcomes include various parameters for RV systolic function, RV functionality, RV remodeling, procedural success, complications, lung perfusion, and QoL.

Discussion This trial will investigate the effects of percutaneous branch PA interventions on exercise capacity in patients with TGA, ToF, and TA and will identify early markers for RV adaptation and RV dysfunction to improve timing of the interventions.

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Keywords Congenital heart disease, Intervention, Pulmonary stenosis, Right ventricle, Exercise capacity

Introduction

Background and rationale {6a}

Postoperative survival of patients with transposition of the great arteries (TGA), tetralogy of Fallot (ToF), and truncus arteriosus (TA) has increased over the last decades due to advances in operative techniques and perioperative care [1–4]. Despite the fact that postoperative survival has increased, morbidity of these patients has shown to increase during long-term follow-up [5–9]. Also, long-term follow-up studies show that there is a high need for interventions. In patients with d-TGA, 20% requires at least one intervention after a follow-up of 43 years [10]. In ToF, the intervention rate is even 44% after a follow-up of 35 years and in patients with TA 82% after a follow-up of 10 years [11, 12]. Right ventricular outflow tract (RVOT) obstructions, which mainly includes percutaneous branch pulmonary artery (PA) interventions, are the most common indication for interventions [10, 12–15]. Branch PA stenosis results in redistribution of blood flow, possibly resulting in a ventilation perfusion mismatch, reduced ventilatory efficiency, and reduced exercise capacity [16–18]. In addition, branch PA stenosis leads to increased RV pressures and RV hypertrophy, which are independent risk factors for a poor outcome [8, 19]. Therefore, reduced exercise capacity, RV maladaptation to the increased afterload, and subsequently RV dysfunction and RV failure might contribute to the morbidity of these patients. However, the effects of percutaneous branch PA interventions on exercise capacity, RV adaptation, and RV function remain largely unknown. Moreover, there is no consensus about the optimal timing for percutaneous interventions for branch PA stenosis in asymptomatic patients according to international guidelines.

Objectives {7}

This randomized-controlled multicenter trial aims to identify the effects of percutaneous interventions for branch pulmonary artery (PA) stenosis on exercise capacity in patients with TGA, ToF, and TA. In addition, it aims to assess the effects on RV function and to define early markers for RV adaptation and RV dysfunction to improve timing of these interventions.

Trial design {8}

In this randomized controlled multicenter trial, percutaneous branch PA interventions are compared to conservative management for branch PA stenosis to assess the effects on exercise capacity in patients with TGA, ToF, and TA. In addition, this trial aims to investigate the effects on RV function and to define early markers for RV dysfunction and adaptation to improve timing of these interventions. This trial is not designed to demonstrate superiority of percutaneous branch PA interventions because there is uncertainty regarding its potential benefits on exercise capacity and RV function. The patient allocation ratio is 1:1. Patients in the control group (conservative management) are allowed to cross over to the treatment group after 6 months follow-up or sooner in case of symptoms.

Methods: participants, interventions, and outcomes

Study setting {9}

The trial will be conducted in three large congenital cardiac centers for congenital heart disease in the Netherlands: University Medical Center Utrecht (sponsor), Erasmus Medical Center Rotterdam, and Center for Congenital Heart Disease Amsterdam-Leiden (CAHAL).

Eligibility criteria {10}

Patient eligibility will be assessed by study investigators according to the inclusion and exclusion criteria that are displayed in Table 1. Inclusion and exclusion criteria are based on international guidelines and normal reference values from literature [20–25].

Who will take informed consent? {26a}

Patients will be recruited by the investigator during their regular outpatient clinic visit and during multidisciplinary team meetings at the participating centers. Written informed consent will be obtained according to the regulations of the CCMO prior to randomization.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Additional consent provisions for collection and use of participant data and biological specimens is not applicable; no ancillary studies are being performed during this trial.

Interventions

Explanation for the choice of comparators {6b}

The intervention group consists of TGA, ToF, and TA patients who will undergo a percutaneous intervention

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Definition
TGA, ToF, or TA patients ≥ 8 years of age	
At least one class IIa criteria for percutaneous branch PA intervention:	
• Decreased exercise capacity	< 18 years [23]
	• ♂ < 35 ml/kg/min
	• ♀ < 30 ml/kg/min
	≥ 18 years [24]
	• ♂ < 27 ml/kg/min
	• ♀ < 19 ml/kg/min
• Unbalanced PA perfusion	PA perfusion ≤ 35%/65% using CMR
	> 2/3 using echocardiography
• Elevated RV/LV pressure ratio	≥ 50% stenosis using non-invasive imaging
• Significant unilateral PA stenosis	40–70% stenosis using non-invasive imaging
• Borderline bilateral PA stenosis	≥ moderate using echocardiography
• Progressive tricuspid regurgitation	• < 18 years RVEF ≤ 55% [22]
	• ≥ 18 years RVEF < 50% [25]
• Persistent decreased RV function	
Exclusion criteria	
Physical or mental contraindications for one of the study examinations	
Class I criteria for percutaneous branch PA intervention:	
• Symptoms related to branch PA stenosis	Doppler peak gradient > 64 mmHg
• Severe branch PA stenosis	
• Shunt via ASD or VSD	• < 18 years RVEF ≤ 55% [22]
• Recently developed RV dysfunction	• ≥ 18 years RVEF < 50% (25)

ASD atrial septal defect, *CMR* cardiac magnetic resonance imaging, *LV* left ventricle, *PA* pulmonary artery, *RV* right ventricle, *RVEF* right ventricular ejection fraction, *TA* truncus arteriosus, *ToF* tetralogy of Fallot, *TGA* transposition of the great arteries, *VSD* ventricular septal defect

for branch PA stenosis according to routine clinical practice. The control group consists of TGA, ToF, and TA patients with a similar degree of branch PA stenosis compared to the intervention group who will undergo conservative management for 6 months according to routine clinical practice. Due to lack of consensus about the optimal timing of the intervention for asymptomatic patients according to international guidelines, these groups are the comparators of choice. Patients in the control group are allowed to cross over to the treatment group after 6 months follow-up or sooner in case of symptoms or if deemed necessary by the treating cardiologist.

Intervention description {11a}

The intervention consists of a percutaneous PA intervention, which is the treatment of choice for branch PA stenosis according to international guidelines [20, 21]. During this intervention, a stent will be placed in one of the branch pulmonary arteries under conscious anesthesia during right heart catheterization (RHC) to relieve the stenosis. The route of access, use of further interventional techniques (e.g., 3D rotational angiography), and stenting equipment are at the discretion of the operator and according to routine clinical practice at the participating center.

Criteria for discontinuing or modifying allocated interventions {11b}

Patients (or its legal representative) have the right to withdraw from the trial at any time and for any reason without any consequences. If they decide to withdraw, all examinations will be stopped. The investigator can decide to modify the intervention, in case of symptoms, or even withdraw a patient from the study for urgent medical reasons. The reason for premature discontinuation will be documented, and data collected up to that moment will be used. Patients who withdraw will be followed up according to routine clinical practice by their cardiologist and will not be replaced by new patients.

Strategies to improve adherence to interventions {11c}

Improvement of adherence to the study protocol will be optimized by organizing training sessions by the study team for the health professionals involved.

Relevant concomitant care permitted or prohibited during the trial {11d}

No specific concomitant care is permitted or prohibited during the trial since all patients will be treated according to routine clinical practice.

Provisions for post-trial care {30}

An insurance contract to cover damage to patients for injury or death caused by any activities of the study is present at the sponsor and is in accordance with the legal requirements in the Netherlands (Article 7 Medical Research Involving Human Subjects Act (WMO)). This applies to damage that becomes apparent during or within 4 years after the study has been completed.

Outcomes {12}

Primary outcome

The primary endpoint is maximum oxygen uptake (expressed as peak VO_2 in percentage of the predicted value based on age, gender, height and body weight) and is assessed at 6 months follow-up [26].

Secondary outcomes

Secondary endpoints that will be compared between the intervention group and control group are presented in Table 2. They include parameters for exercise capacity, RV systolic function, RV remodeling, RV functionality and adaptation, lung perfusion, procedural success, peri- and post-procedural complications, and quality of life.

Participant timeline {13}

Examinations at baseline

Patients from both groups will undergo the same examinations at baseline as part of routine clinical practice: conventional transthoracic echocardiogram (TTE), cardiopulmonary exercise testing (CPET), conventional CMR, and quality of life (QoL) questionnaires (Figs. 1 and 2). CMR in the interventional group will be performed as close as possible prior to the intervention but maximal 4 weeks prior to the intervention.

Examinations during the procedure

Pre- and post-procedural routine hemodynamic RV and PA pressure measurements will be collected in the intervention group (Figs. 1 and 2). Additional RV-pressure volume (PV) loop analysis will be performed a subgroup (the intervention group of the UMC Utrecht).

Examinations at follow-up

Patients from both groups will undergo the same series of examinations during follow-up. QoL questionnaires will be obtained at approximately 2 weeks post-intervention for the intervention group or a similar time range for the control group. At approximately 6 months follow-up (within 6-week time range), all patients will undergo similar examinations compared to baseline as part of routine clinical practice: conventional TTE, CPET, conventional CMR, and QoL questionnaires. In addition, conventional TTE, CPET, and conventional CMR will be performed during 2–4 years follow-up to assess the long-term effects of percutaneous PA interventions (Figs. 1 and 2).

Sample size {14}

No randomized controlled trials have been performed about percutaneous branch PA intervention vs. conservative management for branch PA stenosis in CHD. Observational studies about the effect of percutaneous branch PA interventions on exercise capacity in CHD are present but scarce. A power calculation was performed to estimate the number of patients needed to draw conclusions on the occurrence of an increased exercise capacity (expressed as maximum oxygen uptake) after a percutaneous intervention for branch PA stenosis. We estimated a difference of 14% increase in maximum oxygen uptake (peak VO_2 expressed as percentage of predicted) in the interventional group compared to the control group using previous observational studies from the literature [27]. Under the assumption of a 14% increase in peak VO_2 (% predicted), $\sigma = 18\%$, and 10% correction for potential loss to follow-up, we determined that inclusion of 56 patients (28 interventional group and 28 controls) would be required with an alpha of 0.05 and a power of 0.80.

Recruitment {15}

Patients will be recruited at three large congenital cardiac centers for congenital heart disease in the Netherlands

Table 2 Secondary endpoints

Domain	Parameter	Additional information parameter	Unit	Method	Timepoint
Exercise capacity	Peak workload	Maximum wattage	% predicted	CPET	Baseline, FU: 6 M, 2–4Y
	VE/VCO2 slope	Ventilatory efficiency (minute ventilation relative to carbon dioxide elimination)	-	CPET	Baseline, FU: 6 M, 2–4Y
RV systolic function	RVEF	-	%	CMR	Baseline, FU: 6 M, 2–4Y
	RV strain	Myocardial deformation	%	Speckle tracking echocardiography	Baseline, FU: 6 M, 2–4Y
	RV strain	Myocardial deformation	%	CMR feature tracking	Baseline, FU: 6 M, 2–4Y
	RV FAC	-	%	Echocardiography	Baseline, FU: 6 M, 2–4Y
	TAPSE	-	mm	Echocardiography	Baseline, FU: 6 M, 2–4Y
RV remodeling	RVEDV	-	ml/m^2	CMR	Baseline, FU: 6 M, 2–4Y
	RV mass	-	g/m^2	CMR	Baseline, FU: 6 M, 2–4Y
RV functionality and adaptation	RV end-systolic elastance (Ees)	Load-independent parameter for RV contractility	mmHg/ml	PV loop analysis	RHC
	Arterial elastance (Ea)	Measure of RV afterload	mmHg/ml	PV loop analysis	RHC
	RV-PA coupling (Ees/Ea)	Efficiency energy transfer from RV to PA	-	PV loop analysis	RHC
	RV end-diastolic elastance (Eed)	Parameter for RV diastolic stiffness	mmHg/ml	PV loop analysis	RHC
Lung perfusion	LPA and RPA lung perfusion	-	%	CMR	Baseline, FU: 6 M, 2–4Y
Procedural success	Procedural success yes/no	-	-	-	RHC
Complications	Peri- and post-procedural complications	-	-	-	RHC
Quality of life	Quality of life	-	-	PedsQL questionnaire	Baseline, FU: 2W

CMR cardiac magnetic resonance imaging, *CPET* cardiopulmonary exercise testing, *FAC* fractional area change, *FU* follow-up, *LPA* left pulmonary artery, *M* months, *PA* pulmonary artery, *PV* pressure–volume, *RHC* right heart catheterization, *RPA* right pulmonary artery, *RV* right ventricle, *RVEDV* right ventricular end-diastolic volume, *RVEF* right ventricular ejection fraction, *TAPSE* tricuspid annular plane systolic excursion, *W* weeks, *Y* years

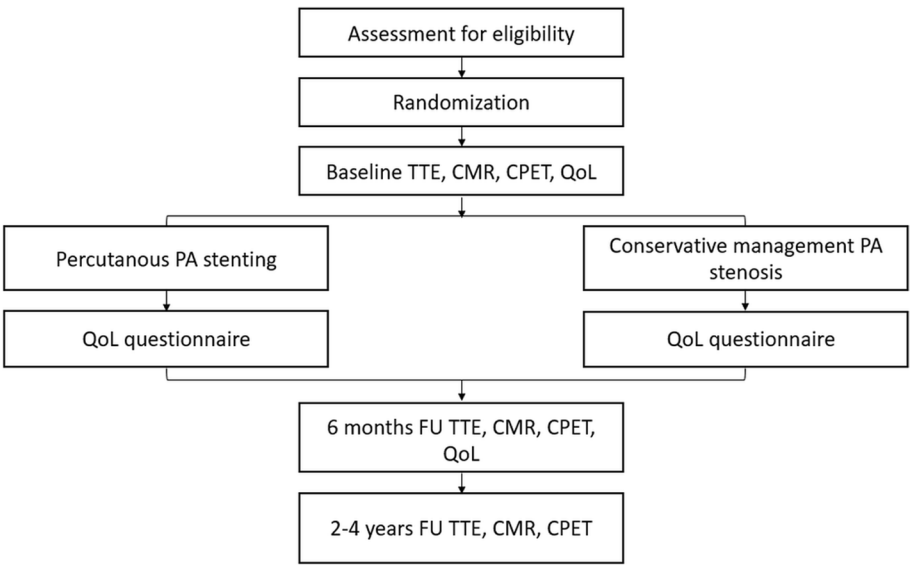

Fig. 1 Study design flowchart. CMR, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise test; FU, follow-up; QoL, quality of life; PA, pulmonary artery; TTE, transthoracic echocardiography

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT**	$-t_1$	0	*2wk*	*6mo*	*2-4 yrs*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Percutaneous PA intervention		◆———	———	———◆	
Conservative management (control)		X	X	X	
ASSESSMENTS:					
Baseline variables *Medical history, socio-demographic data*	X				
Primary outcome *Maximal oxygen uptake*	X			X	
Secondary outcomes RV systolic function, RV functionality, RV remodeling, procedural success, complications and lung perfusion	X			X	X
Secondary outcomes *QoL*	X		X	X	

Fig. 2 Schematic of participant timeline in the trial. QoL, quality of life; PA, pulmonary artery; RV, right ventricle

(University Medical Center Utrecht (sponsor), Erasmus Medical Center Rotterdam, and Center for Congenital Heart Disease Amsterdam-Leiden (CAHAL)) to achieve adequate participant enrolment.

Assignment of interventions: allocation

Sequence generation {16a}

Patients with be randomized intro variable block sizes (block sizes 2 and 4) using a digital internet tool (CASTOR). Stratification will not be conducted due to the low number of patients. In addition, the effects of presence of a functioning pulmonary valve will be analyzed during post hoc analysis since only a small part of the study population will have no functioning pulmonary valve and it will not influence the primary endpoint. The effect of center variability is considered negligible given the fact that subjects are treated according to routine clinical practice.

Concealment mechanism {16b}

The trial uses a concealment mechanism through computerized randomization, ensuring that neither the patient nor the researcher is aware of the allocation until after enrolment and randomization are completed.

Implementation {16c}

Randomization will take place after written informed consent. Randomization of the intervention will be performed by the investigator using a digital internet tool (CASTOR).

Assignment of interventions: blinding

Who will be blinded {17a}

Subjects and professionals will not be blinded since it is impossible due to the nature of the trial and subjects are treated according to routine clinical practice.

Procedure for unblinding if needed {17b}

This is an open-label trial design, and therefore unblinding is not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

TTE

Conventional TTE will be performed in all patients at baseline, 6 months follow-up, and 2–4 years follow-up. The protocol focusses on RV function, including global ventricular function, ventricular dimensions, RV free wall global longitudinal strain, TAPSE, and RV FAC. A

RV focused apical 4-chamber view with frame rate as high as possible is required to obtain RV strain and RV FAC. In addition, velocity and gradients over cardiac valves and in the PAs (pulsed/continuous wave Doppler) and information about cardiac valve insufficiency are collected.

CPET

CPET will be performed in all patients using an electronical brake cycle ergometer at baseline, 6 months follow-up, and 2–4 years follow-up. Before exercise, respiratory flow-volume loops will be acquired, and maximal voluntary ventilation will be determined. Workload will be increased by 10 to 25 watts in a ramp wise manner, depending on the individually predicted maximum exercise capacity, until maximum workload is being obtained. Maximum effort will be defined as peak respiratory exchange ratio (RER) of greater than 1.0 for children and 1.1 for adults. The CPET protocol emphasizes on maximum oxygen uptake (peak VO_2 expressed as percentage of predicted based on age, gender, height and body weight) [26]. Maximum oxygen uptake is defined as the highest value of oxygen consumption during the last 30 s of peak exercise. A 12-lead ECG will be continuously recorded, and a finger pulse oximeter is used for continuous measurement of arterial oxygen saturation. The following additional parameters will be assessed: peak workload, peak heart rate, and ventilatory efficiency (minute ventilation relative to carbon dioxide elimination [VE/VCO_2 slope]).

CMR

Conventional CMR will be performed on a 1.5- or 3.0-T MRI scanner in all patients at baseline, 6 months follow-up, and 2–4 years follow-up. The CMR protocol includes standard steady-state free processing (SSFP) cine images (2,3,4-chamber) and a stack of short-axis SSFP images to assess biventricular volumes, mass, and function. Additional strain analysis will be performed using CMR Feature Tracking during post-processing to gain insight into myocardial deformation. Through-plane images will be obtained, if possible, from the neo pulmonary valve and PAs to determine flow (ml) and regurgitation. Q-flow analysis might be hampered by previous stents in situ during or during follow-up CMR in the intervention group.

QoL questionnaires

PedsQL questionnaires will be used during this study to assess QoL. It is a systematic, valid, and reliable tool that will be used to score physical, emotional, social, and professional domains. Questionnaires are adjusted to the age category and additional specific questionnaires apply for parents of children up to 16 years of age.

RV pressure–volume analysis

RV-PV loop analysis will be used to assess the interaction between the RV and PA load in a subgroup (the intervention group of the UMC Utrecht) using the well-described single-beat and multi-beat method [28, 29]. Pulmonary arterial elastance (Ea), considered mainly a reflection of pulmonary vascular resistance (PVR), will be calculated as RV systolic pressure (RV Psys)/stroke volume [30]. RV end-systolic elastance (Ees), considered a load-independent measure of ventricular contractility, will be obtained in two different manners, according to the single-beat and multi-beat method. Using the single-beat method, Ees will be calculated as (RV maximal isovolumic pressure (RV Piso)-RV Psys)/stroke volume. Piso is based on the prediction of maximal pressure if RV contraction remained isovolumic and will be computed by sine wave extrapolation using RHC RV pressure values recorded before maximal first derivative of pressure development over time (dP/dt) and after minimal dP/dt [28, 31, 32]. RV pressure curves will be averaged over multiple beats to reduce respiratory variations. In contrast to the single-beat method, RV Ees will be obtained using a 7Fr conductance catheter (CA-71083-PL, CD Leycom, Zoetermeer, the Netherlands) when using the multi-beat method. Two injections of 10 cc 5% NaCl and CO according to Fick principle will be used for calibration. Sequentially resting PV loops will be recorded. Subsequently, preload alterations will be executed using passive leg raises, vena cava superior occlusion, or a volume challenge, resulting in a stepwise shift of RV end-systolic pressure points to calculate Ees as described before [29]. Afterwards, RV pulmonary arterial (RV-PA) coupling will be calculated as the ratio of Ees/Ea and represents the efficiency of mechanical energy transfer from the RV to the pulmonary vasculature. In addition, RV end-diastolic elastance (Eed) will be obtained by fitting a curve through (0.0), the begin-diastolic and end-diastolic points on the pressure–volume curve. Eed will be calculated as the slope of this curve at end-diastolic volume and represents RV diastolic stiffness [33].

Plans to promote participant retention and complete follow-up {18b}

There are no plans to promote participant retention and complete follow-up since everything is according to routine clinical practice.

Data management {19}

Data managers from the University Medical Center Utrecht, the Netherlands (sponsor), will supervise and assist

data management during the trial. A data management system (Castor Electronic Data Capture) will be used to enter data in electronic case report forms (eCRFs). QoL questionnaires will be answered and stored in CASTOR. Informed consent and end-of-trial dates will be recorded in the electronic patient dossier, and signed paper forms will be stored at the participating center. (S)AEs will be recorded in the eCRF. At final analyses, data files will be extracted from CASTOR into IBM SPSS to be analyzed. The databases will be kept for 15 years in accordance with the "richtlijn Kwaliteitsborging 2020" by the CCMO and the NFU. These 15 years will start after the last examination of the last participant. After those 15 years, the principal investigators per location will commission to destroy all the data and documents (including original offline documents). This process will be reported.

Confidentiality {27}

All patient data will be pseudonymized and presented with their study identification number. The unique participant number is safeguarded by the principal investigators per center. The CASTOR database is secured using role-based access: the study team will have access after permission from the principal investigators. Source data and signed informed consent forms will be stored safely in each participating center. Pseudonymized imaging data will be shared using the Research Imaging Architecture Exchange (RIA-X) software platform of the sponsor. Access to medical records for verification and auditing purposes by the accredited METC, regulatory authorities (e.g., inspectors of the Dutch Health Care Inspectorate), auditors, and monitors will be required, and permission from each subject will be obtained as part of the consent process. The handling of personal data from patients is in accordance to the *EU General Data* Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (Dutch: UAVG).

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies is not applicable as no biological specimens are being collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Primary analysis

Statistical analysis will be performed using IBM SPSS Statistics (SPSS Inc. version 29.0.1, Chicago, Illinois, USA). Differences in maximum oxygen uptake between the intervention and control group will be obtained using a 2-tailed unpaired independent samples *t*-test or Mann–Whitney test. Comparisons in change in exercise capacity from baseline between the interventional group and control group adjusting for the influence of baseline scores will be performed using an analysis of covariance (ANCOVA).

Secondary analysis

Differences in binary or categorical variables between the intervention and control group will be obtained using the χ^2 test or Fisher exact test. Differences in continuous variables for RV function and remodeling, RV-PA coupling, lung perfusion, and QoL between the intervention and control group will be obtained using a 2-tailed unpaired independent samples test or Mann–Whitney test. Comparisons between baseline and follow-up for exercise capacity, RV function and remodeling, RV-PA coupling, lung perfusion, and quality of life will be analyzed using a 2-tailed paired samples *t*-test or Wilcoxon signed rank test. Pearson correlation will be used to assess the correlations between continuous variables of exercise capacity, RV function and remodeling, RV-PA coupling, lung perfusion, and QoL.

Interim analyses {21b}

There are no interim analyses performed during this trial.

Methods for additional analyses (e.g., subgroup analyses) {20b}

There will be no stratification during this trial. The effects of presence of a functioning pulmonary valve will be analyzed during post hoc analysis. No other subgroup analyses will be performed during this trial.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Due to the prospective study design, the amount of missing data will be reduced to a minimum. In case of missing data, data imputation will be used, in cooperation with a statistician.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The full protocol and statistical code will be available from the coordinating principal investigator (J.M.P.J Breur) on reasonable request. Due to the nature of the data, the dataset will only be available after a granted collaboration which is in is in line with the original informed consent signed by the study participants. This only accounts for the data of participants who gave informed consent for using their data for other research.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating principal investigator of the sponsor (J.M.P.J. Breur) takes full responsibility for the trial. The principal investigators per participating center take supervision of the trial at their study site, responsibility for the decision about patient inclusion, and medical responsibility of the subjects. The investigator is responsible for trial registration, coordination study visits, annual safety reports, identification of potential subjects, and informed consent. Data managers from the sponsor organize data capture and safeguard quality and data. An independent study monitor, Julius Clinical Research B.V (Zeist, The Netherlands), will be designated by the sponsor and will perform routine inspections at all study sites to secure integrity of the study and to secure the quality of the collected data. There is no trial steering committee or stakeholder and public involvement group.

Composition of the data monitoring committee, its role and reporting structure {21a}

In agreement with the advice from the Medical Research Ethical Committee of the University Medical Center Utrecht, the Netherlands (METC NedMec), a data safety monitoring board (DSMB), has not been appointed for this study.

Adverse event reporting and harms {22}

Adverse events (AEs)

Participating study sites will be asked to report all AEs, whether or not considered related to the percutaneous intervention for branch PA stenosis or the conservative management, to the coordinating principal investigator.

Serious adverse events (SAEs)

All participating study sites will be asked to report all SAEs within 24 h after obtaining knowledge of an event to the study sponsor. All SAEs must be documented in the eCRF within 24 h by the investigator at the study site. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Frequency and plans for auditing trial conduct {23}

An independent study monitor, Julius Clinical Research B.V (Zeist, The Netherlands), was appointed by the sponsor to monitor the trial. According to the advice from the Medical Research Ethical Committee of the University Medical Center Utrecht, the Netherlands (METC NedMec), the estimated risk for the trial is considered negligible. This complies with an initiation visit, one visit during the trial, and an close-out visit at each participating center to check the investigation file, informed consents, inclusion and exclusion criteria, source data, and (S)AEs.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority but will be recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers, and other contact details of involved persons mentioned in the submitted study documentation.

Dissemination plans {31a}

Results of this trial will be reported in international peer-reviewed journals.

Discussion

This is the first randomized controlled trial about percutaneous branch PA interventions in patients with CHD. The trial aims to identify the effects of percutaneous interventions for branch PA stenosis on exercise capacity in patients with TGA, ToF, and TA. In addition, it aims to assess the effects on RV function and to define early markers for RV adaptation and RV dysfunction to improve timing of these interventions.

Considerations for percutaneous PA interventions

Percutaneous PA interventions are considered carefully and sets challenges, especially in pediatric patients. Mechanisms of PA stenosis development differ between different types of congenital heart diseases. In patients with TGA, PA stenosis is a result of adjacent structures and the used surgical technique. As a result of the LeCompte maneuver during the surgically correcting arterial switch operation, the PA is positioned anterior of the aorta [34]. This might result in stretching of the PAs over the aorta or compression of the PAs by a dilated neo-aorta, making them prone to PA stenosis [35]. In contrast, PA stenosis in ToF and TA are non-compliant lesions caused by scarring at surgical anastomosis or shunt sites [36, 37]. PA stenosis is preferably treated percutaneously using balloon angioplasty (BA) or stent implantation. BA

is a treatment option that can be used throughout the lifespan of a patient but might be less effective for compliant PA stenosis [38]. On the other side, stent implantation is nowadays feasible from a young age onwards because modern stents can reach a final adult diameter but is limited by serial dilatation of the stent to adjust for somatic growth. In addition, patients who undergo percutaneous PA interventions (BA and stent implantation) are prone for reinterventions for PA stenosis due to fibrosis, elastic recoil of the vessels, and intima proliferation [38]. Moreover, percutaneous PA interventions can generally be performed safely but serious complications can occur which should be taken into account [38–41]. These factors create a challenge to limit the number of interventions but to avoid missing potential health benefits on short and long-term. However, the effects of percutaneous branch PA interventions on exercise capacity, RV adaptation, and RV function remain largely unknown. Moreover, there is no consensus about the optimal timing for percutaneous interventions for branch PA stenosis in asymptomatic patients according to international guidelines. Therefore, this randomized-controlled multicenter trial will try to identify the effects on exercise capacity and RV function and to define early markers for RV adaptation and RV dysfunction to improve timing of these interventions, to minimize the number of interventions, and to optimize the outcomes.

Trial status

Recruitment has started in April 2023 and is expected to be completed end 2026. The final protocol version is version 2.0, February 2023.

Abbreviations

ASD	Atrial septal defect
BA	Balloon angioplasty
CHD	Congenital heart disease
CMR	Cardiac magnetic resonance imaging
CPET	Cardiopulmonary exercise testing
Ea	Arterial elastance
eCRF	Electronic case report form
Eed	End-diastolic elastance
Ees	End-systolic elastance
Ees/Ea	Right ventricular to pulmonary arterial coupling
FAC	Fractional area change
FU	Follow-up
PA	Pulmonary artery
Piso	Isovolumic pressure
Psys	Systolic pressure
PV	Pressure-volume
PVR	Pulmonary vascular resistance
QoL	Quality of life
RHC	Right heart catheterization
RV	Right ventricle
RVEDV	Right ventricular end-diastolic volume
RVEF	Right ventricular ejection fraction
RVOT	Right ventricular outflow tract
SSFP	Stead-state free processing
TA	Truncus arteriosus
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography
TGA	Transposition of the great arteries
ToF	Tetralogy of Fallot
VSD	Ventricular septal defect

Authors' contributions {31b}

RSJ, MV, GJK, and JMPJB drafted the study protocol and design. All authors were involved in the design of the study. RSJ is responsible for daily research management and communications through clinical centers. JMPJB is the coordinating principal investigator of the project. JMPJB, TBK, and NAB are principal investigators at the participating centers. All authors read, critically reviewed, and approved the final manuscript.

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Availability of data and materials {29}

The protocol and statistical code are available from the coordinating principal investigator (J.M.P.J Breur) on reasonable request. Due to the nature of the data, the dataset will only be available after a granted collaboration which is in is in line with the original informed consent signed by the study participants. This only accounts for the data of participants who gave informed consent for using their data for other research.

Declarations

Ethics approval and consent to participate {24}

This trial is carried out in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice. The trial was approved by the Medical Research Ethical Committee of the University Medical Center Utrecht, the Netherlands (METC NedMec) (reference number: NL81160.041.22). Written informed consent will be collected from all patients and parents or legal guardians (if applicable) prior to study participation.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

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