Right Ventricular Function after Coronary Artery Bypass Grafting

The SWEDEGRAFT Right-Heart-Substudy

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Supported by:

NIH/NCRR Colorado CTSI Grant Number UL1 RR025780 (REDCap)

Health Research Foundation of Central Denmark Region, Grant Nr. A3057

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ABBREVIATIONS

3D	= Three-dimensional
Borg CR 10®	= BORG category-ratio 10 scale®
CABG	= Coronary Artery Bypass Grafting
CRF	= Case Report File
CTA	= Computerized Tomography coronary angiogram
eGRF/1.73m2 (CKD-EPI)	= Estimated Glomerular Filtration Rate according to the Chronic Kidney Disease EPIdemiology Collaboration equation
eCRF	= Electronic Case Report Form
ECC	= Extracorporeal Circulation
EF	= Ejection Fraction
FAC	= Fractional Area Change
MACCE	= Major Adverse Cardiac and Cerebrovascular Events
NYHA	= New York Heart Association
ProBNP	= Pro B-type Natriuretic Peptide
REDCap	= Research Electronic Data Capture
RV	= Right Ventricular
RV-FWS	= Right Ventricular Free Wall Strain
RV-GLS	= Right Ventricular Global Longitudinal Strain
TAPSE	= Tricuspid Annular Plane Systolic Excursion
WMSI	= Wall motion score index
S’	= Systolic myocardial velocity
SAQ-7	= Seattle Angina Questionnaire 7

SYNOPSIS

Study Title	Right ventricular function after coronary artery bypass grafting
Primary Study Objective	To assess the long-term impact of coronary artery bypass grafting on right ventricular function
Study Design	Prospective observational substudy of SWEDEGRAFT – A Nordic, multicentre, prospective, randomized, register based, clinical trial on no-touch vein graft in coronary surgery
Primary outcome measure	• 3D RV EF • RV-FWS • RV-GLS
Secondary outcome measures	• Fractional Area Change (FAC) • TAPSE • Systolic myocardial velocity (S') • SAQ-7 • NYHA class • Borg CR10® • ProBNP • Saphenous vein graft patency
Study Intervention	Non-emergent CABG with (1) conventional skeletonized saphenous vein grafts (2) no-touch saphenous vein grafts
Duration	SWEDEGRAFT enrollment period: 10/18-04/20 Clinical follow-up: 01/21-11/22
Sample Size	Approximately 200 patients included in the SWEDEGRAFT study at Aarhus University Hospital
Study Population	Elective primary CABG patients with ECC

STUDY TEAM ROSTER

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1. AIM AND STUDY OBJECTIVES

1.1. Hypothesis

We propose that right ventricular (RV) systolic function is essentially preserved two years after coronary artery bypass grafting (CABG). Being a prevalence study, there is no actual hypothesis to test.

1.2. Primary objectives

The primary objective of this study is to investigate whether CABG is associated with reduced depression of RV function after mid-term follow-up.

1.3. Secondary objectives

The secondary objectives of this study are to investigate whether:

- Changes in standard two-dimensional (2D) echocardiographic measures of RV function are reflected by 3D echocardiography
- RV dysfunction is correlated with impaired health-related quality of life as assessed by Seattle Angina Questionnaire-7 (SAQ-7)
- RV dysfunction is correlated with functional capacity as assessed by New York Heart Association (NYHA) class and BORG category-ratio 10 scale (Borg CR10®)
- RV dysfunction is correlated with the degree of revascularization/ graft patency as assessed by computerized tomography coronary angiogram (CTA)
- RV dysfunction is correlated with clinical or biochemical signs of perioperative myocardial damage at the time of surgery
- RV dysfunction is correlated with levels of Pro b-type natriuretic peptide (ProBNP)

2. BACKGROUND AND RATIONALE

2.1. Background

It has become evident that impaired RV function is an important predictor of adverse cardiovascular outcome in patients with ischemic heart disease independent of left ventricular function (Haddad 2008). Early RV failure as assessed by impaired RV ejection fraction through a pulmonary artery catheter is strongly and independently associated with increased two-year mortality (Bootsma 2017). Consequently, it is of major concern that RV dysfunction is a common and well-known phenomenon known to develop during and early after cardiac surgery (Alam 2003, Brookes 1998, Bootsma 2017, David 2006). The phenomenon has been demonstrated to persist for as long as one year after surgery (Roshanali 2008).

A combination of different echocardiographic measures is applied to evaluate RV function as no single method is devoid of limitations, while cardiovascular magnetic resonance serves as gold standard (Mertens 2010). Modern two-dimensional (2D) echocardiographic assessment of RV function commonly includes RV speckle tracking strain analysis, RV fractional area change (RV FAC), tricuspid annular plane systolic excursion (TAPSE), and Doppler-derived RV systolic excursion velocity (S' velocity) (Zaidi 2020 Br. Guidelines, Rudski 2010 Am Guidelines, Lang 2015). Unfortunately, TAPSE and S' velocity have proven to be of limited value in the postoperative setting, due to their angle dependency (Mertens 2010).

3D echo-derived right ventricular ejection fraction (3D RV EF) has been proposed as an accurate parameter of global right ventricular performance as it correlates well to cardiac magnetic resonance (Nagata 2017, Lang 2015). 3D RV EF is not limited to isolated systolic aspects, such as the tricuspid annulus or the free wall of the RV. 3D RV EF appears to be an independent predictor of future adverse cardiac outcome (Nagata 2017). Myocardial strain measurement using speckle tracking echocardiography is a well-established and reproducible method used to reflect the systolic function of the ventricles and carries prognostic information (Kim 2018, Antoni 2010). Unlike other echocardiographic parameters of RV systolic function, strain values can assess intrinsic myocardial performance and can differentiate active movement from passive movement. Strain is a reliable and accurate way to measure RV systolic function and has been validated with MR (Lu 2015, Smiseth 2016).

Because RV global longitudinal strain (RV-GLS) is a global parameter of RV systolic function compared with other conventional parameters, such as TAPSE and tricuspid S' velocity, which represent the displacement degree of the basal segment of the RV free wall, it correlates better with RV systolic function and prognostic power than other conventional parameters (Fine 2013,

Park 2015, Grant 2012). Some authors showed that RV global longitudinal strain free wall (RV-FWS) was better correlated than RV-GLS with RV EF according to cardiac magnetic resonance and it is optional to the user to include septum (Badano 2018).

Several theories on the leading cause behind RV dysfunction after cardiac surgery have been proposed. Cardiopulmonary bypass and cardioplegia are unlikely causes, as the phenomenon has been observed equally following on- and off-pump CABG (Diller 2009). Ischemia has been suggested as an underlying cause for RV dysfunction after CABG. However, RV dysfunction seems to be equally present in patients with and without full revascularization of the right coronary artery (Hedman 2004, Roshanali 2008). Finally, pericardial disruption has been suggested as the most probable cause (Unsworth 2010). Unsworth and colleagues performed serial transoesophageal echocardiographic measurements of RV longitudinal function by S' velocity during CABG. Noteworthy, almost all reduction of RV S' velocity associated with CABG occurred within the first three minutes after pericardial incision.

Few prospective non-randomized studies support the superiority of 3D RV EF over 2D echocardiography for assessment of RV function in the postoperative setting. Keyl et al. conducted a pilot study comparing surgical aortic valve replacement through full sternotomy with transcatheter procedures (Keyl 2016). In both groups, 3D RV EF remained constant. Following open surgery, but not after transcatheter intervention, the geometry of RV contraction was modified as reflected by significantly reduced TAPSE and significantly increased fractional shortening of the RV midcavity transverse diameter. Similarly, Tamborini and colleagues showed in patients undergoing open mitral repair that 3D RV EF was preserved, while TAPSE and S' velocity were significantly reduced up to one-year follow-up (Tamborini 2009). These findings are supported by a previous study which showed no deterioration of RV function after aortic valve replacement through full sternotomy as measured by magnetic resonance imaging (Sandstede 2000). In summary, validated 2D echocardiographic measures for RV function might not reflect the altered RV contraction pattern including paradoxical interventricular septal motion and reduced long-axis function following open cardiac surgery.

Little is known about the prognostic impact of RV dysfunction after cardiac surgery. It may be difficult to assess adverse effects of RV impairment in CABG patients as they may be masked by the beneficial effects of revascularization on left ventricular function. It has been shown that exercise capacity improves three months after CABG despite depressed RV function (Hedman 2008). Furthermore, it has been demonstrated that reduced RV function was not associated with impaired NYHA class at 1-year follow-up (Roshanali 2008).

2.2. Rationale

There remains an unresolved contradiction between the undisputable echocardiographic signs of RV depression after cardiac surgery and the lack of clinical signs of RV failure. This study seeks to contribute to a better understanding of this phenomenon.

We seek to determine the prevalence and scale of RV dysfunction two years after CABG by applying the latest available echocardiographic technology in RV evaluation. We expect the use of 3D imaging to provide better visualization of the RV's complex shape in order to allow definitive assessment of potential RV depression after CABG.

We aim to put the objective findings in relation to patient-reported outcome measures and prognosis. In addition to assessment of functional class by NYHA class, we will inquire into health-related quality of life with the disease-specific Seattle Angina Questionnaire 7 (SAQ-7) and functional capacity with the Borg CR 10® scale. Finally, we aim to examine the prognostic relevance of the phenomenon with a five- and ten-year follow-up of our patients for major adverse cardiac and cerebrovascular events (MACCE).

3. STUDY DESIGN AND OUTCOMES

3.1. Study design

Prospective observational Right-Heart-Substudy of the SWEDEGRAFT trial at Aarhus University Hospital in Denmark. SWEDEGRAFT is a nordic, multicenter, prospective, randomized, register-based, clinical trial (ClinicalTrials.gov Identifier: NCT03501303). Primary objective of the trial is to compare mid-term patency saphenous vein grafts harvested and implanted with the no-touch technique as compared to the conventional skeletonized technique (Ragnarsson 2020).

Patients for the current Right-Heart-Substudy will be recruited amongst the 269 patients included in the SWEDEGRAFT trial at Aarhus University Hospital from 10 September 2018 to 25 May 2020. In the Right-Heart-Substudy, we aim to extend the scheduled two-year follow-up visit with a thorough echocardiographic assessment of the patients' cardiac function and state of revascularization, and to follow our patients' clinical outcome up to 10 years by review of patient electronic. SWEDEGRAFT data obtained under hospitalization (demographics, medical history, randomization, surgery, adverse events), at three-months telephone follow-up (questionnaire), and at two-year follow-up (SAQ-7 questionnaire, ECG, CTA) will be used in analysis and interpretation of the Right-Heart-Substudy results.

3.2. Primary outcome measures

Primary outcome measure is RV function assessed by 3D echocardiography and RV strain measurements derived from two-dimensional speckle-tracking.

3.3. Secondary outcomes measures

At follow-up 24-30 months after surgery:

- Full 2D/3D Echocardiography (specified in 5.3. Endpoint Evaluations)
- Disease-specific health-related quality of life as assessed by SAQ-7
- NYHA class
- Borg CR 10®
- Graft patency as assessed by CTA
- Haemoglobin, ProBNP
- ECG

In-hospital variables:

- RV function decrement (systolic RV function preoperative versus 2-year follow-up) as assessed by 2D echocardiography
- Degree of revascularization according to the operations report (time of intervention)
- Signs of perioperative myocardial damage (CK-MB, ECG, postoperative echocardiography)

At 5- and 10-year follow-up major adverse cardiac and cerebrovascular events (MACCE) according to the electronic patient record:

- Death from any cause (cardiovascular and non-cardio-vascular mortality).
- Myocardial infarction
- Repeat hospitalization due to cardiac cause
- Cerebrovascular accident
- Repeat revascularization

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1. Inclusion criteria

SWEDEGRAFT inclusion criteria:

- First-time non-emergent CABG patients
- Need for at least one vein graft
- Able to provide informed consent and accepted for isolated primary CABG.

Additional inclusion criteria for the Right-Heart-Substudy:

- Ability to meet for follow-up visit

4.2. Exclusion criteria

SWEDEGRAFT exclusion criteria:

- No greater saphenous vein grafts available (previous vein stripping or poor vein quality)
- Age > 80 years at the time of inclusion
- Allergy to contrast dye
- Renal failure with eGFR <15 ml/min at primary inclusion
- Coagulation disorders
- Excessive risk of wound infection
- Participation in other interventional trial on grafts
- Any condition that seriously increases the risk of non-compliance or loss of follow-up
- Pregnant women or women of child bearing potential without negative pregnancy test

Additional inclusion criteria for the Right-Heart-Substudy:

- Inability to cooperate to transthoracic echocardiography

4.3. Study Enrollment Procedures and Informed Consent

At Aarhus University Hospital, 269 patients were enrolled into the SWEDEGRAFT trial. Patients were randomized from 10 September 2018 to 25 May 2020. Per initial SWEDEGRAFT protocol, patients were scheduled for follow-up visit after 2 years including interview (SAQ-7), measurement of eGFR, and electrocardiogram prior to CTA. A current amendment awaits approval to postpone follow-up visit with six months to compensate for the unforeseen delay caused by the COVID-19 pandemic. Consequently, follow-up is due 24-30 months after surgery. Eligible patients will together with the information regarding their scheduled SWEDEGRAFT follow-up visit receive written information regarding the Right-Heart-Substudy ("Deltagerinformation om deltagelse i et videnskabeligt forsøg"), and a brochure regarding

volunteer's rights in a health science research project ("Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forsknings-projekt"). The information will emphasize that participation in any research project is voluntary and that she/he can any time without reason withdraw their consent and drop out. Patients must also be informed that withdrawing from the study will not affect their future medical care, treatment or benefits to which the patient is otherwise entitled. In consideration of the current threat of COVID-19, we chose to refrain from the usual recommendation to bring a companion for the follow-up visit according to hospital policy.

Patients interested in participation will receive verbal information about the project by a research nurse in a quiet and undisturbed environment. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether or not to participate in the study. The investigator is responsible for obtaining written informed consent from all patients prior to enrolment in the study. A copy of the informed consent form will be given to the patient. After informed consent has been obtained, an electronic case report form (eCRF) is created in the Research Electronic Data Capture (REDCap) electronic database hosted at Aarhus University (Harris 2009). Patients will be asked for permission to review their electronic records after five and ten years for clinical follow-up.

4.4. Study duration and follow-up

We expect approximately 90% of the Danish SWEDEGRAFT patients to fulfil the additional inclusion criteria and consent for the Right-Heart-Substudy. To include 230 patients, the approximate duration of the enrolment period is 19 months.

5. MATERIALS AND METHODS

5.1. Screening evaluation

All patients included in the main SWEDEGRAFT study at Aarhus University Hospital scheduled for follow-up visit including CTA are eligible for the current Right-Heart-Substudy.

5.2. Study treatment including perioperative management

All patients included in the SWEDEGRAFT trial at Aarhus University Hospital patients received oral prophylaxis with 75mg acetylsalicylic acid once daily without discontinuation prior to surgery. Anaesthesia was induced and maintained with propofol, sufentanil, rocuronium and sevoflurane. We performed standard CABG with employment of the left internal mammary artery, and either no-touch or conventional great saphenous vein grafts according to their

randomization. We used cardiopulmonary bypass with goal-directed perfusion management and normo- or mild hypothermia (approximately 34°C). Myocardial protection was achieved with intermittent cold antegrade blood cardioplegia (Harefield solution). The pericardium stayed open at the end of surgery in all patients. We intend to register all details of revascularization including graft flow measurements and any cases of incomplete revascularization for retrospective analysis**.**

Postoperative pain was treated with paracetamol, morphine-like analgesics and ketorolac. We resumed acetylsalicylic acid and statin therapy on the first postoperative day. Patients received subcutaneous dalteparin 5000 IE once daily until fully mobilized. Patients were monitored for perioperative myocardial infarction with continuous telemetry, intraoperative transoesophageal echocardiography, focus assessed transthoracic echocardiography at arrival on intensive care (repeated on indication), 12-lead electrocardiograms (at arrival and on morning after surgery), and creatinkinase-MB measurements (every six hours after end of surgery until decreasing CK-MB values).

5.3. Endpoint Evaluations

5.3.1. Follow-up 2D/3D-echocardiography (24-30 months after surgery)

The present Right-Heart-Substudy is designed to gain insight regarding the long-term impact of CABG surgery on right heart function. Hence, we scheduled a full 2D and 3D echocardiography with special focus on RV function at the time of SWEDEGRAFT two-year follow-up. We intend to use a GE VIVID E95 system (GE Medical System, Horten, Norway) with a 2.5-MHz transducer for transthoracic echocardiography.

For all image analysis EchoPAC version 203 (GE-Vingmed Ultrasound, Horten, Norway) will be used. All measurements will be the averaged over three consecutive heart cycles (six in terms of atrial fibrillation) in end-expiration. 3D and 2D echocardiography will be performed according to international guidelines (Lang 2015). In case of poor 3D image quality 2D images and/or a contrast agent (SonoVue/Optison) will be used to opacify both ventricles.

The following parameters will be recorded by 2-dimensional echocardiography: LVEF, left ventricular end-diastolic (LVEDV) and systolic volume (LVESV) is assessed by the biplane disc method. Left and right atrial volume will be assessed by biplane area-length method indexed by body surface area (BSA). The interventricular septum and the posterior wall thickness will be obtained from the parasternal view. LV mass is calculated and indexed according to BSA. RV systolic function is assessed by the 3D-RV EF volumetric method, RV S´ is measured by lateral,

pulsed tissue Doppler velocities. In addition, TAPSE is obtained from the lateral tricuspid plane. RV strain is calculated at the RV free wall (RV-FWS), which is used as the main measure, according to the guidelines, and at the total RV wall, which includes the interventricular septum and free wall (RV-GLS) (Lang 2015).

5.3.2. Preoperative 2D-Echocardiography

A routine 2D-echocardiography has been performed in all patients two to three months prior to CABG at Aarhus University Hospital to assess cardiac function including contractility, chamber size, hypertrophy, valvular dysfunction, and pericardial or pleural effusions. The echocardiographic images were digitally stored for offline analysis using commercially available software (EchoPAC version 203, GE-Vingmed Ultrasound, Horten, Norway).

The echocardiographic RV parameters available on preoperative as compared to follow-up 2D/3D echocardiography including normal cutoff values are depicted in the following chart.

RV Parameters	Preop ECHO	Follow-up ECHO	**Normal cutoff value**	**References**
RV 3D EF Right ventricular ejection fraction (3D)		●	> 45 %	Lang 2015
RV-FWS Right ventricular free wall strain		●	− 28.7% ± 4.1	Meris 2010
RV-GLS Right Ventricular Global Longitudinal Strain	(●)	●	-	-
RV FAC Right ventricular fractional area change	(●)	●	> 35%	Lang 2015
TAPSE Tricuspid Annular Plane Systolic Excursion	(●)	●	> 17 mm	Lang 2015
Tricuspid S' velocity Peak systolic tricuspid annular velocity		●	> 9.5 m/s	Lang 2015
RAV Right Atrial Volume	●	●	< 30 mL/m^2	Lang 2015
RAESA Right Atrial End-Systolic Area	●	●	< 18 mm^2	Lang 2015
RVD Right Ventricular Diameter	●	●	Base <41 mm Midtventricular <35mm Length <83 mm	Lang 2015

5.2.3. CTA

According to the main SWEDEGRAFT protocol, study participants are scheduled for CTA 24-30 months after surgery to assess patency of the saphenous vein grafts. Vein graft patency in patients with conventional skeletonized as compared to no-touch grafts represents the primary endpoint of the SWEDEGRAFT trial. The data set is then sent to Uppsala Clinical Research Center in encrypted form, without patient identification other than study number for further analyses and for compiling the study results. Patency is assessed and classified by blinded and independent cardiac radiologists at a core lab at Uppsala Clinical Research Center.

Prior to CTA, all patients receive a blood sample to measure renal function to ensure an eGRF/1.73m2 (CKD-EPI) ≥ 35 ml/min. The optimal heart rate for CTA is below 60 beats/minute. Thus, an electrocardiogram is performed to exclude bradycardia, atrioventricular block, and cardiac dysfunction. In the electronic patient record it will be noted that the patient has been examined according to the SWEDEGRAFT protocol.

5.2.4. Seattle Angina Questionnaire-7

According to the main SWEDEGRAFT protocol, patients will complete a SAQ-7 questionnaire at two-year follow-up. Patients are asked seven questions in order to measure their current health status with focus on three domains: Physical Limitation, Angina Frequency, and Quality of Life. The SAQ-7 is a well-established, valid, and reliable tool with prognostic value to measure health status in patients with coronary artery disease (Chan 2014). It results three subscales and a summary scale that extend from 0 (worst possible health state) to 100 (best possible health state).

5.2.5. NYHA class

We use the NYHA functional classification system for functional classification of patients with heart failure. The method has been revised since introduction in 1928, most recently in 1994 (Dolgin 1994). Patients are placed in one of four categories based on how much they are limited by dyspnea during physical activity. Appendix 2 displays the official Danish version of the NYHA classification. Limitations of the NYHA functional classification system are its high interoperator variability (Raphael 2007), and the fact that it offers information about the onset of symptoms only (Ponikowski 2016).

5.2.6. Borg CR 10®

The Borg CR10® Scale ranges from 0 "Nothing at all" to the value of 10 "Maximal" with verbal descriptors missing for values 6 and 8. Patients are asked to rate their level of perceived breathlessness (dyspnoea) during exercise. Appendix 3 displays the official Danish version approved by the author in 2007.

5.2.7. Laboratory Examination

According to the SWEDEGRAFT protocol, all patients receive a blood sample to measure renal function to ensure an eGRF/1.73m^2 (CKD-EPI) $\geq$ 35 ml/min prior to CTA. We supplement measurements of haemoglobin, and brain natriuretic peptide (BNP), in order to fully adjust our results for laboratory findings, which are important risk factors for heart failure.

5.2.8. In-hospital details derived from electronic patient record

- Details from the operations report (preoperative lesions, grafts incl. flow and pulsatile index, length of surgery, length of cardiopulmonary bypass, cross-clamp time, areas of incomplete revascularization)
- Signs of perioperative myocardial damage (postoperative CK-MB, ECG, and echocardiography)

5.2.9. Long-term Major Adverse Cardiac and Cerebrovascular Events

According to SWEDEGRAFT protocol, the MACCE rate is registered at 2-year follow-up after review of the electronic patient record. MACCE are defined as:

- Death from any cause (cardiovascular and non-cardio-vascular mortality).
- Myocardial infarction
- Repeat hospitalization due to cardiac cause
- Cerebrovascular accident
- Repeat revascularization

We intend to review the electronic patient record for MACCE 5- and 10 years after surgery in order to correlate cardiac function to long-term clinical outcome.

5.3. Schedule of evaluations

	Initial Hospitalization	24-30 months Follow-up	5-year Follow-up	10-year Follow-up
Initiation procedures				
Eligibility*	●			
Demographics*	●			
Informed consent & randomization*	●			
Surgery*	●			
Investigations				
Echocardiography	●*(2D)	●(2D/3D)		
Haemoglobin, ProBNP		●		
12-lead ECG*		●		
eGFR*		●		
CTA*		●		
SAQ-7*		●		
NYHA class		●		
Borg CR 10®		●		
MACCE		●*	●	●

Borg CR 10®= BORG category-ratio 10 scale; CT= Computed Tomography; eGFR= estimated Glomerular Filtration Rate; ECG= Electrocardiogram; MACCE = Major Adverse Cardiac and Cerebrovascular Events; NYHA= New York Heart Association; Seattle Angina Questionnaire= SAQ-7. * Elements of the main SWEDEGRAFT study to be included in the Right-Heart-Substudy

6. SAFETY ASPECTS

6.1. Insurance

The investigators will be covered by the liability and work injury insurance taken out by Aarhus University Hospital. Participants are covered by the act on complaints and compensation within the health care system.

6.2. Adverse events

All patients included in the study are given standard care. Per SWEDEGRAFT protocol, information about wound healing in the harvesting site on the leg are registered. No adverse events are anticipated in this observational study in conjunction with:

- Transthoracic echocardiography
- Acquisition of the NYHA class and Borg CR 10®
- Determination of haemoglobin and ProBNP in the blood sample drawn for eGFR analysis
- Review of the electronic patient record at 5- and 10-years.

7. STATISTICS CONSIDERATIONS

7.1. General design issues

The SWEDEGRAFT study is an open-label randomized trial. However, evaluation of health status by means of questionnaires and echocardiographies will be performed by a study nurse and investigators blinded regarding the allocation to ensure unbiased ascertainment of outcomes.

7.2. Determination of Sample Size and randomization

The present Right-Heart-Substudy aims to determine the prevalence and scale of RV dysfunction as measured by 3D RV EF two years after CABG. To the best of our knowledge, no prior study has described the prevalence of chronic RV dysfunction after CABG applying this technology. The best prospective study available in this field of enquiry offers a follow-up of up to one year after CABG using 2D echocardiographic measurements (Roshanali 2008).

As a prevalence study there is no hypothesis to test and the size of the study is determined by how accurately we want to determine the prevalence. Based on the formula suggested by Viechtbauer et al., a sample size of N=194 will suffice to identify impaired 3D RV EF (< 45%) with a prevalence down to 2% with a 98% confidence (Viechtbauer 2015). In order to ensure a complete dataset, we aim to include a total of 230 participants.

7.3. Stopping rules

Patients enrolled may withdraw voluntarily from study participation at any time and for any reason. If voluntary withdrawal occurs, the subject will be asked for permission to be followed for clinical outcome.

7.4. Data analyses

Tracking of outcome measures will begin at randomization and continue until death or end of follow-up (10 years after CABG). Continuous variables will be presented as mean ± standard deviation (SD) if normally distributed, otherwise as median with interquartile range (25th and 75th percentile), minimum and maximum values. Discrete variables will be presented in frequencies and percentages. Kaplan-Meier plots will be constructed to visualize time to event variables and log-rank tests will be used.

All statistical analyses will be done using Stata 15.0 (Stata Corp., College Station, USA). Statistical assistance is provided by the Department of Biostatistics, Aarhus University.

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1. Data collection

Study data are collected and managed using REDCap electronic data capture tools hosted at Aarhus University (Harris 2009). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. An eCRF will be constructed for data registration.

Study data from the main SWEDEGRAFT trial are stored in the PheedIT data capture tool hosted at Uppsala Clinical Research Center, and acknowledged as sole property of sponsor Stefan Thelin. We have requested permission from the SWEDEGRAFT sponsor and steering committee to utilize data from Aarhus patients for the purpose of the Right-Heart-Substudy. Relevant data (demographics, medical history, surgery, randomization, 3-month telephone follow-up and the SAQ-7 questionnaire) will be imported into Aarhus University REDCap electronic database for analysis and interpretation of the Right-Heart-Substudy results.

9.2 Data management

Data will be handled, processed, and archived according to the guidelines of the Data Protection Agency. Each participant will be given an identification number at enrolment. Each identification number will have an eCRF. The list over identification codes will be deleted at the end of the study. All trial data including Trial Master File, eCRF, the source datasheet of the CRF, and the list over identification codes will be stored in the external server REDCap with continuous backup. REDCap data are kept for 10 years. Information on study participants will be protected according to the Act of Processing of Personal Data, and the Health Act. No study data will be given to third parties or insurance companies. Clinical findings of relevance for patient health will as soon as available be passed on to the physician responsible for patient care.

9.3. Training

All investigators and research nurses conducting this study provide a Good Clinical Practice certificate prior to start of the study. All technicians performing echocardiographic procedures will be required certification organized by the European Association of Cardiovascular Imaging (EACVI).

10. ECONOMY

The main SWEDEGRAFT study is funded by non-commercial unrestricted grants (Vetenskapsråd 17,2 Millioner SEK, Hjärt-Lungfonden 5 Millioner SEK). Partial salary support for the principal investigator Ivy S. Modrau, and the co-investigator Jesper K. Jensen is provided by a grant of the Health Research Foundation of Central Denmark Region, and the Department of Cardiology at Aarhus University Hospital, respectively. The Department of Clinical Medicine at Aarhus University covers costs for statistical assistance. Expenses for 3D echocardiographies, biochemical analysis, study trial nurse, secretary assistance for data entry, and REDCap datamanager will be applied for at non-commercial private and public foundations.

The funding sources have no role during on protocol, trial conduction, analysis or interpretation of data, and publication of the results. Participation in the study confers no financial benefit on the patients, but the expenses for transportation are reimbursed.

11. ETHICAL CONSIDERATIONS

11.1. Risk of study intervention

We expect an additional expenditure of time (approximately 60-90 minutes for echocardiography, NYHA and Borg CR 10 assessment), but no increased risk for SWEDEGRAFT patients who consent to participate in the Right-Heart-Substudy. The current study involves no increased risk of discomfort or bruising due to blood sampling, as haemoglobin and ProBNP are analyzed in the SWEDEGRAFT blood sample scheduled for control of renal function prior to computed tomography.

We believe that the risk of study participation is minimal and outweighed by the value of the knowledge gained through this study. Participants will not derive any individual benefit from study participation. Costs of transportation to the clinical follow-up visit are refunded through participation in the main SWEDEGRAFT study.

11.2. Conflict of interest

The study has been initiated solely by the investigators. The investigators have no conflict of interest to declare and no commercial interest to conduct the study.

11.3. Approval

The main SWEDEGRAFT study was approved by the regional Human Research Ethics Committee in Uppsala, Sweden (Registration number 2016/363, with amendments 2019-00155 and 2019-04214) and the Central Denmark Region Committees on Biomedical Research Ethics (Identification number 1-10-72-207-18, 2 August 2018; amendments 30 October 2019). Prior to start of the Right-Heart-Substudy, approval will be applied for at both committees. The substudy will be registered at www.clinicaltrials.gov. All patients are required written informed consent before participation. The protocol follows the Declaration of Helsinki-II and Consort guidelines. The trial will be performed in compliance with Good Clinical Practice.

12 COOPERATION AND PUBLICATION POLICYs

The study is performed in collaboration between the Department of Cardiothoracic and Vascular Surgery at Aarhus University Hospital, the Department of Cardiology at Aarhus University Hospital, the Institute for Clinical Medicine at Aarhus University, and the Department of Surgical Science, Thoracic Surgery at Uppsala University. The department of Cardiology at Aarhus University dispose over all the knowledge and equipment needed for carrying out the echocardiographic analyses.

Results, whether positive, negative or inconclusive, will be published in the best peer-reviewed scientific journals possible and be presented at international conferences meetings in the field of cardiology. All above-mentioned investigators are expected to receive authorships according to the Vancouver declaration.

13 PLANNED TIMELINE

Protocol complete	November		2020
Approval from Science Ethics committee	December		2020
Enrollment	January 2021	-	November 2022
Data collection	January 2021	-	November 2032
Data analysis	August 2018	-	December 2032
Publication			2023 and 2032

14 PERSPECTIVES

In Denmark, more than 45 CABG operations are conducted per 100 000 inhabitants per year (Eurostat 2020). The current study will clearly define the prevalence and scope of significant RV depression following this common surgical procedure. We expect to resolve the apparent contradiction of undisputable echocardiographic signs of RV depression after cardiac surgery and the lack of clinical signs of RV failure.

15 REFERENCES

Use the "Insert Citation" button to add citations to this document.

Alam M, Hedman A, Nordlander R, Samad B. Right ventricular function before and after an uncomplicated coronary artery bypass graft as assessed by pulsed wave Doppler tissue imaging of the tricuspid annulus. Am Heart J 2003;146: 520-6

Antoni ML et al. Prognostic Value of Right Ventricular Function in Patients After Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention. Cardiovasc Imaging 2010;3:264-271

Badano LP, Kolias TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2018;19:591-600

Bootsma IT, de Lange F, Koopmans M, Haenen J, Boonstra PW, Symersky T, et al. Right Ventricular Function After Cardiac Surgery Is a Strong Independent Predictor for Long-Term Mortality. J Cardiothorac Vasc Anesth. 2017;31:1656–62. Available from: http://dx.doi.org/10.1053/j.jvca.2017.02.008

Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81

Brookes CIO, White PA, Bishop AJ, Oldershaw PJ, Redington AN, Moat NE. Validation of a new intraoperative technique to evaluate load- independent indices of right ventricular performance in patients undergoing cardiac operations. J Thorac Cardiovasc Surg 1998;116:468–76

Chan PS, Jones PG, Arnold SA, et al. Development and validation of a short version of the Seattle Angina Questionnaire. Circ Cardiovasc Qual Outcomes 2014;7:640–7. doi:10.1161/CIRCOUTCOMES.114.000967

Cohen DJ, Van Hout B, Serruys PW, et al. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. N Engl J Med 2011;364:1016-26.

Dalén M, Oliveira Da Silva C, Sartipy U, Winter R, Franco-Cereceda A, Barimani J et al. Comparison of right ventricular function after ministernotomy and full sternotomy aortic valve replacement: a randomized study. Interact CardioVasc Thorac Surg 2018;26:790–7

David JS, Tousignant CP, Bowry R. Tricuspid annular veloity in patients undergoing cardiac operation using transesophageal echocardiography. J Am Soc Echocardiogr 2006;19: 329-34

Diller G, Wasan B, Kyriacou A, Patel N, Casula R, Athanasiou T, Francis D, Mayet J. Effect of coronary artery bypass surgery on myocardial function as assessed by tissue doppler echocardiography. Eur J Cardiothorac Surg 2009; 34: 995-9

Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994
Eurostat Statistics explained. Cardiovascular diseases statistics [Internet]. 2016 [cited 2020 Sep 29]. Available from:
http://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics

Fine NM, Chen L, Bastiansen PM, et al. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging 2013;6:711-21

Grant AD, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. J Am Coll Cardiol 2012;60:521-8

Haber I, Metaxas DN, Geva T, Axel L. Three-dimensional systolic kinematics of the right ventricle. Am J Physiol Heart Circ Physiol 2005;289:1826–33

Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717–31. doi: 10.1161/CIRCULATIONAHA.107.653584

Hamada-Harimura Y, Seo Y, Ishizu T, Nishi I, Machino-Ohtsuka T, Yamamoto M, Sugano A, Sato K, Sai S, Obara K, Yoshida I, Aonuma K; for the ICAS-HF Investigators. Incremental prognostic value of right ventricular strain in patients with acute decompensated heart failure. Circulation Cardiovascular Imaging 2018;11:e007249.
doi:10.1161/CIRCIMAGING.117.007249

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf. 2009;42:377–81

Hedman A, Alam M, Zuber E, Nordlander R, Samad BA. Decreased right ventricular function after coronary bypass grafting and its relation to exercise capacity: a tricuspid annular motion-based study. J Am Soc Echocardiogr 2004;17(2): 126-31

Iacoviello M, Citarelli G, Antoncecchi V, Romito R, Monitillo F, Leone M, Puzzovivo A, Lattarulo MS, Rizzo C, Caldarola P, Ciccone MM. Right ventricular longitudinal strain measures independently predict chronic heart failure mortality. Echocardiography 2016; 33:992–1000. doi: 10.1111/echo.13199

Il'Giovine ZJ, Mulder H, Chiswell K, Arges K, Tomfohr J, Hashmi A, Velazquez EJ, Kisslo JA, Samad Z, Rajagopal S. Right ventricular longitudinal strain reproducibility using vendor-dependent and vendor-independent software. J Am Soc Echocardiogr 2018;31:721.e5–32.e5. doi: 10.1016/j.echo.2018.01.008

Jamal F, Bergerot C, Argaud L, Loufouat J, Ovize M. Longitudinal strain quantitates regional right ventricular contractile function. Am J Physiol Heart Circ Physiol 2003;285:H2842-7

Keyl C, Schneider J, Beyersdorf F, Ruile P, Siepe M, Pioch K et al. Right ventricular function after aortic valve replacement: a pilot study comparing surgical and transcatheter procedures using 3D echocardiography. Eur J Cardiothorac Surg 2016;49:966–71

Kim HM et al. Myocardial Strain in Prediction of Outcomes After Surgery for Severe Mitral Regurgitation. JACC Cardiovasc Imaging 2018;11:1235-1244. doi: 10.1016/j.jcmg.2018.03.016

Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14

Leong DP, Grover S, Molaee P, et al. Nonvolumetric echocardiographic indices of right ventricular systolic function: validation with cardiovascular magnetic resonance and relationship with functional capacity. Echocardiography 2012;29

López-Candales A, Dohi K, Rajagopalan N, Edelman K, Gulyasy B, Bazaz R. Defining normal variables of right ventricular size and function in pulmonary hypertension: an echocardiographic study. Postgrad Med J 2008;84:40-5

Lu KJ, Chen JX, Profitis K, et al. Right ventricular global longitudinal strain is an independent predictor of right ventricular function: a multimodality study of cardiac magnetic resonance imaging, real time threedimensional echocardiography and speckle tracking echocardiography. Echocardiography 2015;32:966-74

Meluzin J, Spinarova L, Bakala J, Toman J, Krejci J, Hude P, Kára T, Soucek M. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion. A new, rapid, and non-invasive method of evaluating right ventricular systolic function. Eur Heart J 2001;22:340–8

Meris A, Faletra F, Conca C, Klersy C, Regoli F, Klimusina J, Penco M, Pasotti E, Pedrazzini GB, Moccetti T, Auricchio A. Timing and magnitude of regional right ventricular function: a speckle tracking-derived strain study of normal subjects and patients with right ventricular dysfunction. J Am Soc Echocardiogr 2010;23:823–31

Mertens LL, Friedberg MK. Imaging the right ventricle–current state of the art. Nat Rev Cardiol 2010;7:551–63

Morris DA, Krisper M, Nakatani S, Köhncke C, Otsuji Y, Belyavskiy E, Radha Krishnan AK, Kropf M, Osmanoglou E, Boldt LH, Blaschke F, Edelmann F, Haverkamp W, Tschöpe C, Pieske-Kraigher E, Pieske B, Takeuchi M. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: A multicentre study. Eur Heart J Cardiovasc Imaging 2017;18:212–23. doi: 10.1093/ehjci/jew011

Nagata Y, Wu VC, Kado Y, Otani K, Lin F, Otsuji Y, Negishi K, Takeuchi M. Prognostic value of right ventricular ejection fraction assessed by transthoracic 3D echocardiography. Circ Cardiovasc Imaging 2017;10:e005384. DOI: 10.1161/CIRCIMAGING.116.005384

Okada DR, Rahmouni HW, Herrmann HC, Bavaria JE, Forfia PR, Han Y. Assessment of right ventricular function by transthoracic echocardiography following aortic valve replacement. Echocardiography 2014;31:552-7

Park SJ, Park JH, Lee HS, et al. Impaired RV global longitudinal strain is associated with poor long-term clinical outcomes in patients with acute inferior STEMI. JACC Cardiovasc Imaging 2015;8:161-9

Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129-200

Ragnarsson S, Janiec M, Modrau IS, Dreifaldt M, Ericsson A, Holmgren A, Hultkvist H, Jeppsson A, Sartipy U, Ternström L, Per Vikholm MD, de Souza D, James S, Thelin S. No-touch saphenous vein grafts in coronary artery surgery (SWEDEGRAFT): Rationale and design of a multicenter, prospective, registry-based randomized clinical trial. Am Heart J 2020;224:17-24. doi: 10.1016/j.ahj.2020.03.009. Epub 2020 Mar 13.

Raphael C, Briscoe C, Davies J, Whinnett ZI, Manisty C, Sutton R, Mayet J, Francis DP. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart 2007;93:476–82. doi: 10.1136/hrt.2006.089656

Roshanali F, Yousefnia MA, Mandegar MH, Rayatzadeh H, Alinejad S. Decreased Right Ventricular Function after Coronary Artery Bypass Grafting. Tex Heart Inst J 2008;35: 250-5

Rudski LG et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713

Sandstede JJ, Beer M, Hofmann S, Lipke C, Harre K, Pabst T et al. Changes in left and right ventricular cardiac function after valve replace- ment for aortic stenosis determined by cine MR imaging. J Magn Reson Imaging 2000;12:240–6

Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37:1196-207

Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019;55:4–90.

Tamborini G, Muratori M, Brusoni D, Celeste F, Maffessanti F, Caiani EG, Alamanni F, Pepi M. Is right ventricular systolic function reduced after cardiac surgery? A two- and three-dimensional echocardiographic study. Eur J Echocardiogr 2009;10:630–64

Unsworth B, Casula RP, Kyriacou AA, Yadav H, Chukwuemeka A, Cherian A, Stanbridge RL, Athanasiou T, Mayet J, Francis, DP. The right ventricular annular velocity reduction caused by coronary artery bypass graft surgery occurs at the moment of pericardial incision. Am Heart J 2010; 159: 314-22. doi:10.1016/j.ahj.2009.11.013

Viechtbauer W, Smits L, Kotz D, Budé L, Spigt M, Serroyen J, Crutzen R. A simple formula for the calculation of sample size in pilot studies. J Clin Epidemiol 2015;68:1375-9

Zanobini M, Saccocci M, Tamborini G, Veglia F, Di Minno A, Poggio P, Pepi M, Alamanni F, Loardi C. Postoperative echocardiographic reduction of right ventricular function: is pericardial opening modality the main culprit? Biomed Res Int 2017:4808757. doi: 10.1155/2017/4808757