The role of left atrial fibrosis in mitral valve repair surgery (ALIVE study)

(Version 3.0, December 2021)

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The role of left atrial fibrosis in mitral valve repair surgery (ALIVE study)

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Subsidising party	*Amsterdam UMC Scholarship 2020*
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PROTOCOL SIGNATURE SHEET – Version 3.0 (December 2021)

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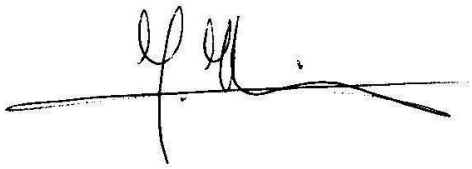
Principal Investigator: **J. Kluin, MD PhD** *Cardiothoracic Surgeon, Department of Cardiothoracic Surgery*		**17-11-2021**
Coordinating Investigator: ***M.J.W. Götte, MD PhD*** *Cardiologist, Department of Cardiology*		**18-11-2021**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

3D	**Three Dimensional**
AE	**Adverse Event**
AF	**Atrial Fibrillation**
AR	**Adverse Reaction**
CMR(I)	**Cardiovascular Magnetic Resonance Imaging**
CV	**Curriculum Vitae**
ECV	**Extra Cellular Volume**
HF	**Heart Failure**
IC	**Informed Consent**
LA	**Left Atrial**
LGE	**Late Gadolinium Enhancement**
LV	**Left Ventricular**
LVEF	**Left Ventricular Ejection Fraction**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MVI	**Mitral Valve Insufficiency**
PC-MRA	**Phase Contrast Magnetic Resonance Angiography**
PH	**Pulmonary Hypertension**
(S)AE	**(Serious) Adverse Event**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Patients with mitral valve insufficiency (MVI) suffer from left atrial (LA) remodeling. Atrial fibrosis is part of this remodeling process. The presence of atrial fibrosis is associated with an increased risk of atrial fibrillation (AF), heart failure (HF), pulmonary hypertension (PH), a reduced quality of life and eventually a shorter life expectancy.

Currently, mitral valve repair surgery is the ultimate treatment for severe primary MVI. The main indications and timing for surgery are severe MVI with symptoms or left ventricular dysfunction. However, the role of atrial fibrosis in this process remains undetermined despite its well-recognized clinical implications.
Characterization of atrial fibrosis patterns in MVI patients might be potentially valuable for the indication and timing of mitral valve repair surgery in order to improve clinical outcomes.

With the introduction of cardiac MRI for the assessment of atrial fibrosis in AF patients suffering from extensive LA remodeling without MVI, the identification of appropriate patients and therapy stratification for cardiac ablation and the associated clinical outcome was significantly improved.

To date, however, MVI patients suffering from LA remodeling have hardly been studied using these new imaging techniques. Therefore, we intend to combine advanced cardiac MRI and post-processing techniques prior to and after mitral valve repair surgery to gain more insight in the clinical implications of atrial fibrosis in this patient population.

It is hypothesized that the atrial fibrosis surface area paradoxically will increase after mitral valve surgery because of global shrinkage of the LA caused by the reversed remodeling process.**[1]** As a consequence, more frequently atrial fibrosis related events including (paroxysmal) AF, may be observed in these patients.

Objective: To assess the effects of (reduced) volume overload on the left atrial wall texture (presence, amount and location of atrial fibrosis) and associated geometry and function in patients with MVI, prior to and after mitral valve repair surgery.

Study design: Single center pilot study.

Study population: The research population consists of MVI patients scheduled for elective surgical mitral valve repair (N=20) according to the current European guideline criteria.

Image data from non-MVI/AF age-sex matched controls (N=10), retrieved from an existing database will be used for reference purposes. These controls have undergone the same MRI scan protocol for another indication.

Main study parameters/endpoints:

The main study parameters are:

1. Severity of MVI prior to and after surgery (defined as regurgitation volume in ml)
2. Left atrial remodelling prior to and after surgery
    - Left atrial volume
    - Calculated left atrial sphericity
    - Estimated wall tension (wall thickness, radius, pulmonary wedge pressure)
    - Mitral regurgitation flow measurement (quantitative)
3. Presence and distribution patterns of LA fibrosis
    - Quantification of fibrosis surface (severity)
    - Geometric distribution of fibrosis (localization)
4. Blood flow patterns in the left atrium (4D flow)
    - Flow velocity (mean and peak)
    - Static fraction
    - Kinetic energy

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

This is a cardiac MRI study with the use of contrast media (Gadolinium).There is no associated additional risk expected for participating patients. There are no direct benefits for individuals participating to our study.

1. INTRODUCTION AND RATIONALE

Patients with mitral valve insufficiency (MVI) frequently suffer from left atrial (LA) remodeling, caused by volume overload and subsequent atrial dilatation.**[1]**

The associated myocardial stretch and increased wall tension, trigger a cascade of pathways leading to the occurrence of atrial fibrosis as part of the remodeling process *(Figure 1)*.**[2]** The clinical relevance of this atrial fibrosis, is that its presence is associated with an increased risk of atrial fibrillation (AF), heart failure (HF), pulmonary hypertension (PH), a reduced quality of life and eventually a shorter life expectancy.**[3, 4]** In addition, in patients suffering from atrial fibrillation (AF), the presence and amount of LA fibrosis was found to be a strong predictor for ablation efficacy and long-term outcome.**[5, 6]**

In daily clinical practice, MVI is managed either by medical or surgical therapy.**[7]** However, since medical therapy is often not sufficient for patients with severe primary MVI, surgical intervention remains the ultimate treatment option for these patients. In general, valve repair is the preferred type of surgery, since it has better clinical results compared to valve replacement.**[8]**
Currently, the indication and timing for valve surgery is mainly based on the severity of MVI and the presence of symptoms and/or severity of left ventricular dysfunction.**[9]**

For clinical decision making and patient stratification for mitral valve surgery, the presence of atrial fibrosis is currently not taken in account, despite its well-recognized clinical implications.

Detection of atrial fibrosis patterns in patients with severe MVI, however, may be potentially valuable for the indication and timing of mitral valve repair surgery to improve clinical outcomes. Improved insight into atrial fibrosis patterns and changes after mitral valve repair due to reverse remodeling, may help clinicians in their clinical decision making and timing for surgery.

Today, quantification of atrial fibrosis can be routinely performed using cardiac magnetic resonance imaging (CMR) techniques and advanced post-processing tools, offering non-invasive tissue characterization in thin-walled structures.**[6]**

To date, MVI patients suffering from LA remodeling have hardly been studied using these new imaging techniques. Therefore, in this study, we want to combine advanced cardiac MRI and

post-processing techniques prior to and after mitral valve repair surgery to gain insight on the clinical role and predictive value of atrial fibrosis in this patient population.

In addition, we aim to assess the effects of (reduced) volume overload on atrial wall texture, geometry and function.

It is hypothesized that the atrial fibrosis surface area paradoxically will increase after mitral valve surgery because of global shrinkage of the LA caused by the reversed remodeling process.**[1]** As a consequence, more frequently atrial fibrosis related events including (paroxysmal) AF, may be observed in these patients.

With this insight, CMR can become clinical valuable for the indication and timing of surgical intervention in these patients. Surgical therapy might be renounced for example when a substantial increase of fibrosis surface is expected post-surgically causing a higher risk for AF, HF, PH and a reduced quality of life. On the contrary, surgical therapy might be considered in an earlier stage of disease when the amount of fibrosis is still limited regarding its expected post-surgical development.

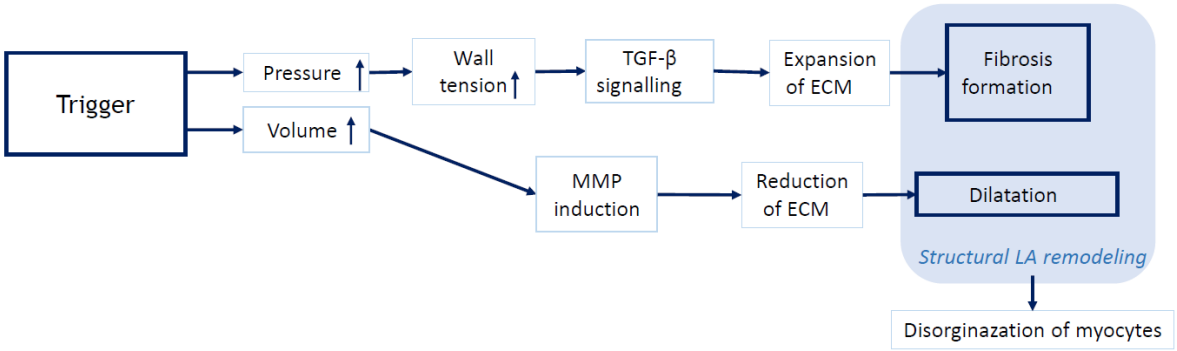


Figure 1. *Pathway to structural LA remodeling caused by a pathological trigger*.

2. OBJECTIVES

Primary Objective:

To assess

- the effects of (reduced) volume overload on the left atrial wall texture (presence, amount and location of atrial fibrosis) and associated geometry and function in patients with MVI, prior to and after elective mitral valve repair surgery.

Secondary Objectives:

To assess;

- the value of LA fibrosis in stratification and timing of mitral valve repair surgery.
- the impact of atrial fibrosis on myocyte contractile function (atrial strain, quantified by CMR).
- whether left ventricular (LV) volume overload results in increased extra cellular volume (ECV) and whether this is reversible after mitral valve repair surgery.
- the impact of LA remodeling on right atrial (RA) function and tissue characteristics.
- the predictive value of LA fibrosis for outcomes of AF and atrial function during post-surgical follow up

3. STUDY DESIGN

This study is designed as a single center pilot study. The aim of this study is to assess the role of left atrial fibrosis and its characteristics prior to and after mitral valve repair surgery in MVI patients.

Study subjects that will be included are MVI patients who meet the criteria for mitral valve repair surgery and are on the waiting list for elective surgery. Exclusion criteria are: AF, history of cardiac surgery, comorbidities, MRI contra-indications. The study subjects are recruited from the Amsterdam UMC surgical waiting list.

The study subjects will visit the AmsterdamUMC hospital (Location VUmc) two weeks prior to mitral valve repair surgery for a CMR scan. This visit will start with checking in- and exclusion criteria using questionnaires regarding medical history and MRI safety. The total duration of the visit, including the CMR scan, will be approximately two hours.

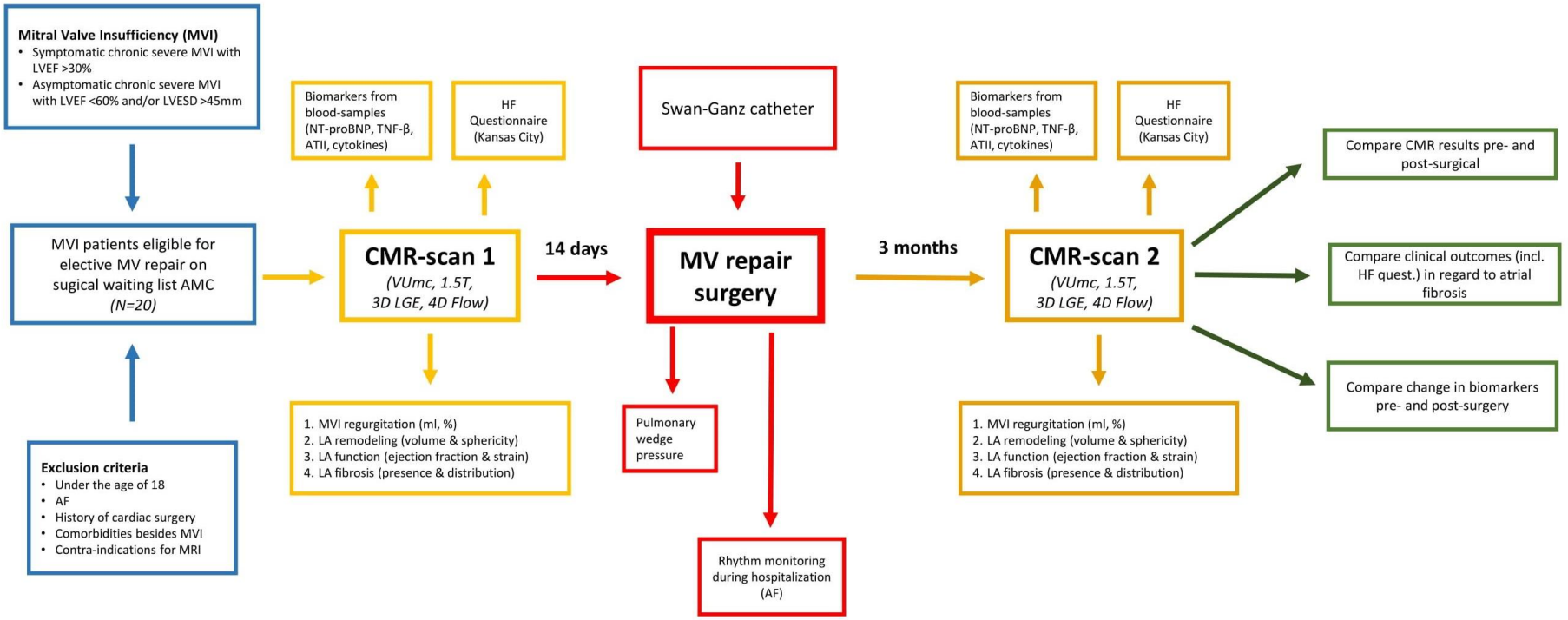
Two weeks later the subjects will undergo mitral valve repair surgery (Location AMC). During anesthesia, a Swan-Ganz catheter will be used for hemodynamic monitoring. This Swan-Ganz catheter is part of the standard care for mitral valve repair surgery.

At three months follow-up, subjects will visit the AmsterdamUMC hospital (Location VUmc) for a second CMR scan to assess reversed atrial remodeling and amount of fibrosis.

Image date from age and gender matched controls will be retrieved from an existing database. The patients in this database have undergone the same MRI scan protocol (for a different medical indication) as scheduled for our study population. Only data from patients without MVI and AF will be used from the database for reference. Absence of MVI and AF will be confirmed by checking ECGs and echocardiography of the control patients.

See *figure 2* for a schematic representation of the study design.

Figure 2. Schematic representation of the study design: Left atrial remodeling in MVI



4. STUDY POPULATION

4.1 Population (base)

The research population consists of MVI patients scheduled for elective surgical mitral valve repair conform the current guideline criteria.

These patients will be recruited from the surgery-waiting list / database of the AUMC after they have been accepted for surgery by a multidisciplinary heart team.

Data from a control group of non-MVI/AF age-sex matched controls (N=10) will be retrieved from an existing database. These controls have undergone the same MRI scan protocol for a different medical indication.

4.2 Inclusion criteria

The following patients will be targeted for inclusion.

- Patients that meet the criteria for elective mitral valve repair surgery according to the European clinical guidelines (class I recommendation);
    - Symptomatic, chronic severe mitral valve insufficiency due to degenerative valve disease with a left ventricular ejection fraction (LVEF) >30%.
    - Asymptomatic, chronic severe mitral valve insufficiency due to degenerative valve disease with a LVEF <60% and/or a left ventricular end-systolic diameter (LVESD) >45 mm.

4.3 Exclusion criteria

Patients that will be excluded from our study are patients;

- not able to provide written informed consent.
- under the age of 18.
- with a history of cardiac surgery
- with AF
- with any comorbidity besides MVI.
- with claustrophobia or any other contra-indication for MRI
    - Each participant will be requested to fill out the “Questionnaire for MRI research with human volunteers” (*“Vragenlijst voor MRI-onderzoek bij testpersonen”*). This standard MRI safety document that is required to be filled in by anybody undergoing MRI scanning contains (among other items) questions on whether

or not the participant has ever had any surgical procedures, has any (metallic) implants or has any other metallic parts in his/her body e.g. splinters.

4.4 Sample size calculation

This study is designed as a pilot study, since we are the first to assess the effect of LA fibrosis and its characteristics prior to and after mitral valve repair surgery.

Therefore we aim to include;

- 20 patients with MVI which are admitted to mitral valve repair surgery

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The main study parameters are:

1. Severity of MVI prior to and after surgery (defined as regurgitation volume in ml)
2. Left atrial remodelling prior to and after surgery
    - Left atrial volume
    - Calculated left atrial sphericity
    - Estimated wall tension (wall thickness, radius, pulmonary wedge pressure)
    - Mitral regurgitation flow measurement (quantitative)
3. Presence and distribution patterns of LA fibrosis
    - Quantification of fibrosis surface (severity)
    - Geometric distribution of fibrosis (localization)
4. Blood flow patterns in the LA (4D Flow)
    - Flow velocity (mean and peak)
    - Static fraction
    - Kinetic energy

Secondary study parameters/endpoints -Fibrosis associated biomarkers derived from blood samples (NT-proBNP, TNF-β, Angiotensin II, cytokines)

-Heart failure symptoms monitoring derived from questionnaire preoperative and at postoperative follow-up

5.1.2 Other study parameters

The following parameters will be recorded for each participant:

- Clinical routine Cardiac MRI parameters (global volumes and function, T1 maps, ventricular fibrosis (LGE))
- Anthropometric data; height, weight
- Clinical information potentially relevant to the study; medical history and medication use

5.2 Study procedures

CMR

We will recruit patients as outlined in paragraph 4.1. Patients will be asked to undergo a cardiac MRI scan protocol at the Amsterdam UMC (Location VUmc) prior to and after surgery. The MRI protocol will be conducted on a 1.5T MRI scanner at the Amsterdam UMC (Location VUmc), with the new 3D whole heart Works In Progress (WIP) package of Siemens. Standard cardiac coils will be used for image acquisition. For triggering, ECG-gating and navigator-gating will be applied.

Intravenous contrast (Gadolinium-based, 0.15mmol/kg) will be administered and total scan time will be approximately 60 minutes.

Abstract outline scan protocol:

1. Localizers
2. LAX cines
3. Contrast administration (Gadolinium)
4. 3D MRA atria/ventricles
5. Flow mitral valve (2D flow)
6. Flow aortic valve (2D flow)
7. 4D Flow scan
8. 3D LGE
9. SAX cines

All scans will be performed using a 1.5 Tesla clinical MRI system (Siemens Sola, Erlangen, Germany) using a 32-channel array coil. The scan protocol included balanced SSFP cine imaging in long axis orientation (two-chamber and four-chamber view). An ECG-gated free-breathing 3D contrast-enhanced MR angiogram (CE-MRA) of the LA and pulmonary veins will be obtained immediately after a 20 mL (1 mL/sec) single dose bolus injection of contrast agent (Dotarem®, Guerbet, Roissy, France) followed by a body weight dependent slow infusion of contrast agent (slow infusion dose; 2.5-30.0 mL, infusion rate; 0.1-0.25 mL/sec) equal to a total dose of 0.4mL/kg. Typical acquisition parameters were: repetition time (TR)/ echo time (TE) 5.5/3.0 ms; flip angle, 25°; in-plane resolution 1.25 × 1.25 mm with slice thickness 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm). Immediately after contrast administration, first 2D flow data at the level of the mitral and aortic valve will be obtained. Then a prospective ECG-gated, 3-dimensional phase-contrast imaging with 3-directional velocity encoding (4D flow CMR) will be performed. Subsequently, high resolution 3D LGE images will be acquired using a navigator-based respiration- and ECG-gated inversion recovery prepared gradient echo pulse sequence applied between 15 and 25

minutes after contrast injection. Voxel size was 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm). Other typical sequence parameters were as follows: TR/TE5.2/2.4 ms; flip angle, 20°. Finally a stack of short-axis cines will be obtained.

In the occurrence of a clinical relevant incidental finding patients will be informed by their treating physician. During the informed consent patients will be notified of this obligation. Patients who refuse to be informed about clinical relevant incidental MRI findings, will be excluded from this study.

MRI processing

Quantification of LA fibrosis will be performed using commercially available ADAS 3D LA image post-processing software (Galgo Medical, Barcelona, Spain) and open-source CEMRG image post-processing software (King's College London, United Kingdom). The 3D LGE images will undergo stringent quality control (i.e. artefacts, proper myocardial nulling) by two experienced readers prior to post-processing and images will be excluded from analysis if quality is deemed insufficient.

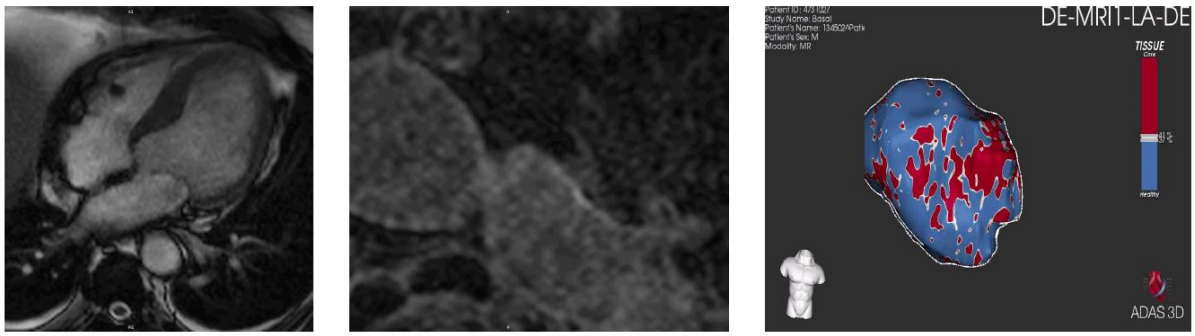


Figure 3. *Left atrial 3D reconstruction from MRI.*

Left Atrial remodeling

LA remodeling will be assessed by quantifying atrial sphericity and calculation of the wall tension calculation using Laplace's law *(T= p x r/2T)*. This calculation includes pulmonary wedge pressure which is determined using peri-operative Swan-Ganz based pressure measurements during anesthesia, and radius based on atrial volume and wall thickness. Also the relation to quantitative MVI will be determined using 4D-flow MRI processing.

Presence and distribution of LA fibrosis

Quantification of fibrosis surface and the distribution of fibrosis will be assessed using LA 3D reconstructions based on 3D MRA data. Output of this data will be as shown below in Figure 4. The left atrial wall is segmented for accurate geometric localization of fibrosis *(Figure 4A)* and the severity of fibrosis will be shown as quantified surface area *(Figure 4B)*.

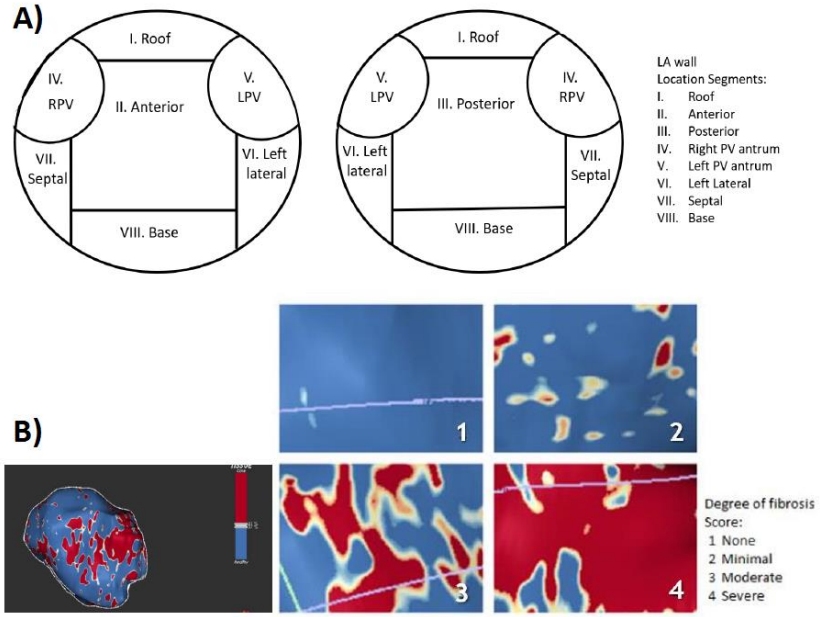


Figure 4. *Left atrial segmentation (A) for accurate assessment of geometric distribution of fibrosis and severity of fibrosis shown as quantified surface (B).*

4D Flow

4D-flow data will be corrected for Maxwell terms in the image reconstruction at the scanner, and velocity aliasing during post-processing. 4D flow data will be co-registered with the cine images to guide left atrial anatomic orientation. Mean and peak flow velocity data will be derived using dedicated research software (MASS version 2017-Exp, Leiden University Medical Center, Leiden, the Netherlands). Furthermore, the volume fraction in the left atrium with a flow velocity below 10cm/s during the entire cardiac cycle will be determined.

Blood samples

Blood samples will be collected two weeks before and 3 months after surgery to assess biomarkers associated with atrial structural remodeling and/or fibrosis (NT-proBNP, TNF-β, Angiotensin II, cytokines).

5.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. This will be correlated with CMR derived LA fibrosis.

5.4 Replacement of individual subjects after withdrawal

Upon withdrawal of a subject, the data collected will not be used for the study and will be deleted.

5.5 Follow-up of subjects withdrawn from treatment

Not applicable.

5.6 Premature termination of the study

Study participants can withdraw their consent at any time during the MRI protocol. However, since patients with claustrophobia will not be included in the study, it is unlikely that patients who have agreed to participate will withdraw during the 45 min MRI protocol. In addition, since all the elements of this study are harmless and carry no risk, it is unlikely that this will occur.

5.7 Potential risk analysis due to COVID-19 regulations

The main risk for our study due to unexpected upscaling of COVID-19 regulations would be the delay of elective surgical mitral valve repair procedures. This would be due to a (temporary) reduced intensive care unit capacity. However, this would not impact the study feasibility, as a consequence the study will take longer to include the target number of inclusions. Other study related procedures would not be affected by COVID-19 as these are reserved for research purposes.

6. SAFETY REPORTING

6.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the researchers will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The researchers will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.2 AEs and SAEs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study considered related to MRI procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

6.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The additional risks associated with participation in this study are considered minimal. Gadolinium is a safe contrast agent, which is frequently used in clinical practice. Intravenous gadolinium administration may cause minimal injection site reactions (e.g. pain, cold or burning sensation). As with other contrast-agents, anaphylactic-like reactions can occur, although this is very unusual.

Nevertheless, the investigators will report all SAEs to the accredited METC without undue delay after obtaining knowledge of the events. The researchers 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 researchers have first knowledge of the serious adverse events.

6.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

6.4 Incidental medical findings

Incidental medical findings for which medical follow-up is required will be reported to the patient self and his/her general practitioner. Patients who do not wish to know about incidental findings are not allowed to participate in this study. This is also mentioned in the informed consent form of this study.

7. STATISTICAL ANALYSIS

7.1 Primary study parameters

CMR qualitative and quantitative analyses will be performed on a dedicated work-station with counseling of investigators experienced in the post-processing of CMR techniques.

The included data will be presented as mean ± standard deviation. Ratios will be given for statistical assessment of non-continuous variables. Correlation analyses will be used to analyze differences between continuous parameters. Confidence intervals (95%) will be used and a $p<0.05$ will be considered statistically significant. Fisher exact test will be performed to verify significance, risk ratio (RR) and 95% confidence intervals. SPSS 26.0 (SPSS Inc, Chicago, IL) for Windows is used to assess statistical analyses.

7.2 Secondary study parameter

Analysis of the obtained bloodsamples for fibrosis associated biomarkers will be performed by the department of laboratory medicine and pathology of the AmsterdamUMC (location AMC).

7.3 Other study parameters

Continuous data will be presented as mean with standard deviation or median with range. Categorical data are presented as proportions. Tables will summarize patient characteristics, clinically relevant parameters and routine MRI parameters (enddiastolic and endsystolic volumes, stroke volume, ejection fraction).

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 2013, Fortaleza, Brazil) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

8.2 Recruitment and consent

Eligible patients will be recruited from a surgery waiting-list/ database of the Heartcenter. Since only healthcare providers with a treatment-relationship with the patient have access the patient record file, the treating physician will be asked for permission by the investigator (S. el Mathari) to contact the patient by phone on his/her behalf to inquire if the patient is interested in study participation. . And if so, patient information will be sent to their home address. Patients will be then given 5 days to read the patient information and to consider the study participation. After this 5-day period, the patients will be contacted again by the aforementioned investigator. If they are willing to participate, the MRI prior to surgery will be scheduled and an MRI slot after surgery will be allocated. Also, the informed consent form will be signed before the first MRI scan is performed.

8.3 Benefits and risks assessment, group relatedness

This is an MRI study with use of contrast media (Gadolinium). Gadolinium-based contrast enhanced imaging is considered the clinical gold standard for identifying cardiac fibrosis in both the ventricles and atria. **[10, 11]** Unfortunately, reliable assessment of atrial fibrosis without use of a contrast agent is currently not feasible.

Although rarely reported in previous literature, nephrogenic systemic fibrosis (NSF) is a more common side effect associated with gadolinium than brain damage. In addition, NSF was more commonly associated with contrast agents with a linear molecular structure. However, in this study we will use the contrast agent gadoterate meglumine (Dotarem®). This is a macrocyclic contrast agent with great stability and low risk profile. **[12]** This favorable profile was recently reconfirmed. In a large cohort, it was demonstrated that gadoterate meglumine is a safe contrast agent. In only 70 (0.12%) out of 35.499 patients who underwent contrast enhanced MRI with gadoterate meglumine, a transient adverse event occurred (urticaria 0.03%, nausea 0.02%, vomiting 0.01%, respectively). In none of the patients NSF was observed. **[13]** Based on these reports, we believe it is safe and justifiable to use gadoterate meglumine for this study at a dose recommended in the literature.

The use of the contrast agent and potential side effects associated with administration, including transient cold/burning sensation, urticaria, nausea and vomiting will be described in the information letter.

There are no direct benefits for individuals participating to our study.

8.4 Compensation for injury

The investigator (AMC) has a liability insurance which is in accordance with article 7 of the WMO.

The investigator (AMC) also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

8.5 Incentives

The subjects will receive no financial compensation or other incentives.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

The participant's identity will remain confidential. His or her name will not be published and will not be disclosed to anyone outside the research group. All personal details and other identifiable data provided or collected during this study will be kept in the strictest confidence. Participants will be assigned a code number following their first contact with the researcher. This number will be used throughout the project and will be the only identifier on physiological archival data and MRI data. No identifiable (e.g. name etc.) of participants will be revealed at scientific meetings, conferences, presentations, publications or any other vehicles of public communication. In any such publication arising from this research the individual results will not be identifiable. Only the research team will have access to the collected data.

- Each researcher will store documents bearing identifiable and personal information in a locked cabinet with access strictly restricted to members of the research group.
- All computerised data/information will be stored on pass-word protected computers, to which only a member of the research team has access.
- Code numbers will be used for all computerised data/information collected. These data are therefore stored in a coded fashion.
- All gathered data/information will be stored for the duration of the study. It will then be kept in a locked cabinet for up to 15 years

9.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

9.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

9.4 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.5 Public disclosure and publication policy

This project is not sponsored and no special arrangements are made regarding the disclosure of publication material and will be disclosed unreservedly.

9.6 Monitoring and Quality Assurance

Monitoring of the conduct of the study by the Clinical Monitoring Center (CMC) of the AmsterdamUMC. The CMC performs quality control measurements to ensure protection of the rights, safety and well-being of the research subjects and scientific quality of the research data. After approval of the protocol by the METC the investigators will have an intake appointment with the CMC to prepare a monitoring plan. The monitoring visits will be planned and the frequency of these visits will be conform the NFU-standards depending on the risk-stratification and duration of the study.

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