Aus dem Experimental and Clinical Research Center
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

The prevalence of pleural and pericardial fluids in healthy premenopausal women - detection and quantification by cardiovascular magnetic resonance

zur Erlangung des akademischen Grades
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Preamble

Part of this work was a scientific presentation at the Society for Cardiovascular Magnetic Resonance (SCMR) Congress in 2018, Barcelona.

Title: ‚Small pericardial and pleural effusions – always a sign for inflammation? A CMR study in healthy females' - Agnieszka Töpper, MD [1,2]; Yashraj Bhoyroo MD [1,2]; Stephanie Funk MD [1]; Edyta Blaszczyk MD [1]; Ludger Heisterkamp MD[3]; Oliver Ehrling[1]; Elke Nickel[1] and Jeanette Schulz-Menger, MD [1,2]

This scientific work has been submitted for publication and has not been yet published.

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3. List of Abbreviations

CMR	Cardiovascular Magnetic Resonance
CMR1	Cardiovascular Magnetic Resonance scan at early follicular phase
CMR2	Cardiovascular Magnetic Resonance scan at luteal phase
CRP	C-Reactive Protein
ECG	Electrocardiography
ECRC	Experimental and Clinical Research Center
EDV	End-Diastolic Volume
EF	Ejection Fraction
ESV	End-Systolic Volume
FSH	Follicle Stimulating Hormone
FW	Fat-Water
FOV	Field of View
FA	Flip angle
GRE	Gradient Echo Sequence
Hs Troponin	High Sensitive Troponin
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVEF1	Left ventricular ejection fraction at early follicular phase.
LVEF2	Left ventricular ejection fraction at luteal phase.
MOLLI	Modified Look-Locker Inversion Recovery
MRI	Magnetic Resonance Imaging
MC	Menstrual Cycle
MDC	Max Delbrück Center for molecular medicine
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
PE	Pericardial Effusion
PLE	Pleural Effusion
PF	Pericardial Fluid
PLF	Pleural Fluid

ROI	Region Of Interest
SSFP	Steady-state free precession
T	Tesla
TI	Inversion Time
TER	RF spin echo
TSH	Thyroid Stimulating Hormone
TR	Repetition Time
TE	Echo Time
TT	Trigger Time
TD.	Difference in time of formation of RF spin echo (TER) and gradient echo (TE)
VLA	Vertical Long Axis

4. Abstract

Objectives: Small amounts of pericardial fluids (PF) and pleural fluids (PLF) are frequent incidental findings during routine cardiovascular magnetic resonance (CMR). The clinical significance of these incidental findings in individuals in the absence of inflammation and/or heart failure remains confusing. Furthermore, it is also common knowledge that premenopausal women experience fluid retention and body mass fluctuations commonly known as 'bloating'. We aimed to investigate the presence and/or changes in pericardial and pleural fluids in healthy premenopausal women over the course of the menstrual cycle by using cardiovascular magnetic resonance, and also to develop reliable and reproducible methods of quantifying pleural and pericardial fluids.

Methods: Healthy premenopausal women were prospectively included and underwent CMR at day 5 of the Menstrual Cycle (Day 3-7, CMR1) and between day 25 and the first day of flow (CMR 2). 35 of 147 healthy females were eligible. Follicular stimulating hormone at CMR 1 confirmed the premenopausal state. A two-sided p value <0.05 was considered statistically significant for all tests.

Results: 30 participants (mean age 31 years) completed both CMR. All participants had normal LV morphology and function. Both PLF and PF were detectable at both time points in 28/30 (93%). The mean amount of PLF for CMR 1 was 9.80 ± 6.1 ml and for CMR 2 was 9.53 ± 5.7 ml, respectively (p=0.742); the mean amount of PF for CMR 1 was 10.07 ± 6.7 ml and for CMR 2 was 9.10 ± 5.8 ml, respectively (p=0.425). The amount of PLF and PF did not differ significantly between both time points. Absolute values did not exceed 26 ml and 34 ml for pleural and pericardial fluid, respectively. No relevant correlation was found between the fluids and progesterone, estradiol, TSH, hsCRP and hsTroponin levels as well as the WBC count.

Conclusion: CMR has the unique capability to detect small effusions without any contrast media application. Small amounts of fluid are assessable in healthy females independent of the phase of the MC and - in the absence of other pathologies - should not be misinterpreted as inflammatory reaction.

Hintergrund: Kleine Mengen an Perikardflüssigkeiten (PF) und Pleuraflüssigkeiten (PLF) sind häufige zufällige Befunde während der routinemäßigen kardiovaskulären Magnetresonanztomographie (CMR). Die klinische Bedeutung dieser zufälligen Befunde bei Personen ohne Hinweis auf Entzündung und/oder Herzinsuffizienz ist unklar. Darüber hinaus ist allgemein bekannt, dass Frauen vor der Menopause unter Flüssigkeitsretention und Schwankungen des Körpergewichts leiden, die allgemein als „Bloating" bezeichnet werden. Das Ziel unserer Studie war das Vorhandensein und/oder die Veränderungen von Perikard- und Pleuraflüssigkeiten bei gesunden prämenopausalen Frauen im Verlauf des Menstruationszyklus mithilfe CMR genauer zu untersuchen und zuverlässige und reproduzierbare Methoden zur Quantifizierung von Pleura- und Perikardflüssigkeiten zu entwickeln.

Methoden: Gesunde prämenopausale Frauen wurden prospektiv eingeschlossen und am 5. Tag des Menstruationszyklus (Tag 3-7, CMR1) sowie zwischen dem 25. Tag und dem ersten Tag der Menstruation (CMR 2) einer CMR unterzogen. 35 von 147 gesunden Frauen erfüllten die Einschlusskriterien. Das FSH, während CMR1 bestätigte den prämenopausalen Zustand. Ein zweiseitiger p-Wert <0,05 wurde für alle Tests als statistisch signifikant angesehen.

Ergebnisse: 30 Teilnehmer (Durchschnittsalter 31 Jahre) absolvierten beide CMR Untersuchung. Alle Teilnehmer hatten eine normale linksventrikuläre Morphologie und Funktion. Sowohl PLF als auch PF waren zu beiden Zeitpunkten in 28/30 (93%) nachweisbar. Die mittlere Menge an PLF für CMR 1 betrug 9,80 ± 6,1 ml und für CMR 2 9,53 ± 5,7 ml (p = 0,742), die mittlere Menge an PF für CMR 1 betrug 10,07 ± 6,7 ml und für CMR 2 betrug 9,1 ± 5,8 ml jeweils (p = 0,425). Die Menge an PLF und PF unterschied sich zwischen beiden Zeitpunkten nicht signifikant. Die absoluten Werte überstiegen 26 ml und 34 ml für Pleura- bzw. Perikard Flüssigkeit nicht. Es wurde keine relevante Korrelation zwischen PLF, PF und Progesteron-, Östradiol-, TSH-, hsCRP- und hsTroponin-Spiegeln sowie der WBC-Zahl gefunden.

Fazit: CMR ist in der Lage, kleine Ergüsse ohne Kontrastmittelanwendung zu erkennen. Kleine Flüssigkeitsmengen können bei gesunden Frauen unabhängig von der Phase des Menstruationszyklus beurteilt werden und sollten in Abwesenheit anderer Pathologien nicht zwingend als Entzündungsreaktion interpretiert werden.

5. Introduction

Small amounts of pericardial fluids (PF) and pleural fluids (PLF) are frequent incidental findings during routine cardiovascular magnetic resonance (CMR). While they seem to be related to inflammatory reactions of the body due to different pathological causes, such as infectious, neoplastic, connective tissue disorders and cardiopulmonary diseases (1–4), they are also commonly detected in completely healthy individuals. The clinical significance of these incidental findings in individuals in the absence of inflammation and/or heart failure remain confusing and cannot be underestimated.

On the other hand, it is well documented in the literature that pleural and pericardial effusions are associated with increased mortality. Friedrich et al. described these fluids as add-on criteria for the assessment of acute myocarditis (5). A study of patients with human immunodeficiency virus infection showed that a small pericardial effusion was associated with shortened survival (6,7). According to Frohlich et al., haemodynamically non-relevant pleural effusions are associated with adverse outcome in patients with chronic heart failure (8). Interestingly, similar findings have been reported in healthy subjects. Different authors have reported fluids in pleural and pericardial space as being found frequently among healthy subjects with the help of ultrasound or magnetic resonance (9–12).

Furthermore, it is also common knowledge that premenopausal women experience fluid retention and body mass fluctuations commonly known as 'bloating'. This was investigated by White and al. (13) and a significant fluctuation in fluid retention in the body throughout the menstrual cycle was identified, where fluid retention peaked on day one of menstrual flow and then reached its lowest point immediately after the menstrual cycle. Fluid retention then saw a gradual rise from five days prior to ovulation up until the next onset of flow (13–15). One hypothesis is that the bloating sensation associated with menstruation could be a result of fluid retention shifts and hormonal changes throughout the menstrual cycle. Interestingly, another study carried out on young female athletes showed that athletic performance may be affected by fluid retention during menstruation (16). It has been well documented that sex hormones affect fluid regulation in the body in different ways. While the activation of the renin-angiotensin-aldosterone system in the luteal phase can cause body fluid accumulation (17,18), some studies have shown that sodium and water reabsorption is enhanced when estrogen and progesterone are

presented together (19,20). There are currently no existing data in the literature regarding fluid retention in the pericardial and the pleural spaces during the menstrual cycle. The frequent detection of pleural and pericardial fluids in healthy people is thus a challenge regarding appropriate interpretation and clinical decision-making and poses a diagnostic dilemma to physicians. Moreover, there is a lack of reliable and easily reproducible methods for the quantification of PLF and PF. Different methods of quantification have been discussed (21–25), but to date there has been no attempt to systematically quantify PLF and PF using CMR.

A reproducible and reliable method to quantify PLF and PF using CMR is needed from the clinical point of view to define new reference values for these fluids, which in turn would facilitate their interpretation in the clinical routine.

5.1 Background

5.1.1 The Pericardium and Pericardial Fluid

The normal pericardium comprises an outer fibrous layer and an inner serous layer and is approximately 1-2 mm thick (26). It is located inside the middle mediastinum posteriorly to the sternum and the cartilages of the third to seventh left rib. Laterally, it is held together with the mediastinal parietal pleura (27). It is a rigid, avascular, fibrous sac and its primary function is minor anchoring, lubrication, preventing distention of cardiac chambers and optimizing diastolic filling (26). It contains a lubrication fluid that separates the visceral and parietal layers. The main purpose of the pericardial fluid is to lubricate the pericardial space during normal heart function (28). In adult humans about 20–60 mL pericardial fluid is considered to be physiological (average 15–35 mL) (27,28).

5.1.2 The Pleura and Pleural Fluid

The visceral pleura is a thin serous layer coating the lungs whereas the parietal pleura lines the thorax, mediastinum, and diaphragm (27,29,30). The pleural space extends from the root of the neck, 3 cm above the midpoint of the clavicle, behind the abdominal cavity, in the costodiaphragmatic recess, to the twelfth rib above the kidney (31).

The parietal layer predominantly produces around 2400 ml of fluid daily and is reabsorbed by the visceral layer (29,30). It is understood that the physiological range of PLF volume

is between 4-18ml. This volume is maintained by the balance between hydrostatic and oncotic forces in the visceral and parietal pleural vessels and lymphatic drainage (32,33). When this balance is disturbed, it causes pleural effusion (21).

5.1.3 The Menstrual Cycle

The menstrual cycle (MC) can be summarized into three separate phases over a period of 28 days. It consists of the menstrual (days 1-5), proliferative (days 6-14), and secretory (days 14-28) phases (13, 30). Ovulation occurs at day 14 in an average 28 Day Cycle (31). At the end of the proliferative phase a high level of 17-beta-estradiol is produced due to follicular maturation, which creates a positive feedback for FSH and LH production. This in turn produces high levels of FSH and LH and is refered to as the LH surge. After the ovulatory process, 17-beta-estradiol levels decrease significantly (31). The secretory phase always occurs from day 14 to day 28 of the cycle. Progesterone is the predominant hormone during this phase and helps to prepare the corpus luteum and the endometrium for possible fertilisation. If fertilisation does not occur, it leads to the regression of the corpus luteum and serum levels of 17-beta-estradiol and progesterone drop rapidly (31). The endometrium layer can then not be maintained, and this process is called menstruation. It is considered as day 0 to day 5 of the next menstrual cycle (31).

5.1.4 Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance is being increasingly used in clinical practice and is rapidly gaining importance in cardiology as an emerging noninvasive method that offers superior structural and dynamic assessment of cardiac function (17). The most frequent indications are inflammatory and ischemic heart disease as well as cardiomyopathies. It is also a very reliable method for the diagnosis of rare diseases such as amyloidosis, sarcoidosis and other systemic diseases as well as congenital heart diseases (34,35).

Due to the wide spatial coverage of this imaging technique, it provides additionally complementary information on structures adjacent to the heart, including the mediastinum, lung fields, chest wall, and upper abdomen. The acquisition of imaging field

data outside the heart offers the opportunity for detection of noncardiac abnormalities (36). Compared to MRI of other body parts, CMR faces specific challenges from cardiac and respiratory motion, thus requiring synchronous cardiac and respiratory gating or breath-holding techniques to overcome motion artifacts (37). Since CMR is noninvasive and free of radiation, it is a very suitable method for the monitoring of treatment effect and follow-up of disease progress.

6. Aims and Objectives

The aim of this work was to investigate the presence and/or changes in pericardial and pleural fluids in healthy premenopausal women over the course of the menstrual cycle using cardiovascular magnetic resonance.

Developing reliable and reproducible methods of quantifying pleural and pericardial fluids that could be used in daily routine was a further important part of my work.

Moreover, defining reference values for pleural and pericardial effusions in CMR would facilitate the interpretation of these incidental fluids in clinical routine and help with diagnosis as well as clinical management of patients.

7. Material and Methods

7.1 Study Design

We designed a prospective single center study. Ethical approval of the Ethics committee of the Charité-University of Medicine, Berlin (approved on 02/03/2016, ref : EA1/054/16) was granted for all study procedures and all participants gave written informed consent.

7.2 Study Process

147 women were screened between March 2016 and December 2017. The volunteers were recruited via emails and word-of-mouth, primarily from Helios Hospital Berlin-Buch, MDC and Charité Medical University, Berlin. The participants were all required to complete a questionnaire and give written consent before the first CMR examination. A revocation of the consent was possible at any time of the study and without giving reasons. The exact timing of the scanning sessions were determined following self-report of menses onset.

7.3 Inclusion and Exclusion Criteria

Each candidate was carefully selected after conducting a detailed anamnesis including medical history status (especially signs of impaired cardiovascular status and hormonal abnormalities like thyroid function abnormalities) as well as careful gynaecological history and eligibility for CMR scan.

Table 1: An overview of specific inclusion and exclusion criteria for the study

Inclusion Criteria	Exclusion Criteria
1) Healthy premenopausal women between 18-45 years old	1) Pacemakers or any other metal implants, ferromagnetic surgical staples or clips, intracranial aneurysm staples
2) Regular menstrual cycles	2) Pregnancy or recent pregnancy in the past 1 year, breast feeding in the past 6 months
3) Participants could be on birth control, so long as the method did not hinder them from menstruating each month.	3) Irregular menstrual cycles
4) Ability to give written agreement and agree to terms and conditions of the study.	4) Claustrophobia
	5) Presence of cardiac, pulmonary or systemic diseases as well as malignancy

7.4 Purpose of Blood samples

Blood samples were acquired at Scan 1 (MC day 3-5) from each candidate to:

1. exclude the presence of inflammation (C-reactive protein, blood counts)

2. confirm the premenopausal state (FSH, Progesteron, Estradiol, LH)

3. exclude the presence of acute myocardial injuries and heart failure (NT-proBNP, hs Troponin)

7.5. The Study Procedure

The CMR Scans were performed at the Berlin Ultrahigh Field Facility at the Max Delbrück Center (MDC) for Molecular Medicine with a 3-Tesla MR Scanner (Verio, Siemens Healthineers, Germany). Participants were thoroughly informed about the purpose and contents of the study, the pseudonymization of their data, and the purpose and importance of acquiring blood samples. They were also informed about the risks and possible complications of taking a blood sample and carrying out a conventional cardiovascular MR.

Blood sampling was obtained around day 5 (Day 3-7) of menstrual cycle to confirm the premenopausal state (follicular stimulating hormone, FSH) and to exclude an inflammatory state of the body as well as acute myocardial injury and heart failure. The protocol included two native CMR scans during the menstrual period: scan I (early follicular phase) and scan II (luteal phase), as well as blood sampling at the time of scan I. Blood samples were acquired in an EDTA Monovette (Blood counts, NT-proBNP, hs Troponin) and a serum monovette (Crp, FSH, Progesterone, Estradiol, LH).

The scans were carried out by experienced technicians and were accompanied at all times by a physician with CMR experience. Each scan was pseudonymized and obtained a personal identification number. The Dicom data of each scan were saved initially on a portable drive and then transferred to a study server (M-Drive) in ECRC (Experimental and Clinical Research Center, MDC and Charite). This ensured that the Dicom data were secured twice.

CVI 42 (Circle Inc., Client Version 5.6.2 (634), Calgary, Canada) was used to assess LV volumes, LV mass and LV ejection fraction and the data and postprocessing contours were secured on the study server of the ECRC (M-Drive). LV contouring of the endocardial and epicardial surfaces was performed on the short-axis cine images in end-diastole and end-systole. The volume and mass were adapted for body surface area.

7.6 Safety

A proper preparation of each volunteer before the CMR scan was carried out by our technicians in order to prevent accidents and complications as well as to ensure the safety of patients and personnel. Each participant was carefully informed about safety-related aspects of MRI and the possible effects of the powerful magnetic field of the MRI system on metal objects in or near the patient, as well as possible heating produced by the strong magnetic field used in imaging. They were also warned about potential claustrophobic sensations that can be induced by the relatively restricted space around the patient inside the MRI system.

(a) Patient Preparation:

(i) A printed standardised questionnaire was handed to each volunteer before the scan and they were required to input information about age, sex, weight, height, the presence of body metal parts, previous diseases, operations, etc. The physician reviewed the form and he/she conducted a brief verbal interview to verify the information on the form and to allow for discussion of concerns that the patient might have.

(ii) Detailed information was provided and the physician explained to each volunteer about:
- the narrow bore with restricted space and the possibility of claustrophobia
- the extreme noise produced during the scan and the mandatory use of a MR compatible headphone
- the requirement to hold their breath on command during the scan
- the possibility of interaction and communication with the technicians or the physician at all times throughout the scan, if necessary, by pressing the alarm button
- the approximate duration of each scan

(iii) If the volunteer agreed to the conditions, written consent was required before the scan.

The following safety measures were considered:

1) Candidates were required to change into a MR safe gown, which we provided. As an alternative, they could wear their own clothes as long as there were no metals parts on them.
2) All metallic objects were required to be removed before entering the MR environment or MR system room.
3) Only MRI-safe devices, equipment and materials (e.g., ECG leads, electrodes) were allowed.
4) A MR-compatible headphone was used during the MRI scan to avoid potential hearing damage. This also allowed candidates to listen to music or the radio if they wanted to.

5) An intercom was used to ensure communication with the candidates at all times during the scan.

6) Emergency resuscitation practice was always in place (a defibrillator and an emergency cart with a full set of emergency drugs within reach).

(b) Patient Positioning

1) The patient was positioned in a supine position with the head towards the magnet (headfirst supine).

2) The patient was positioned over the spine coil and the ECG electrodes were connected.

3) A dedicated 32-channel phased-array cardiac coil was placed on the chest and the straps were securely tightened to prevent respiratory artefacts.

4) Cushions were placed under the head and legs for extra comfort, if required.

7.7 Scan Protocols and Acquisition of Images

The scan protocols for the study included:

1. Scout imaging - coronal, transaxial, sagittal. In general, these are single heartbeat acquisitions acquired in 1 breath-hold. They are required to localise and plan the sequences.

Figure 1: Scout images from left to right, (i) coronal (ii) transaxial (iii) sagittal. Images obtained from one of our scans.

2. Full coverage of the thorax using transaxial true fast imaging with steady-state free precession (SSFP, slice thickness 6/0mm, echo time (TE) 2.1ms, repetition time (TR) 4.3ms, flip angle (FA) 54°) for assessment of pleural effusions.
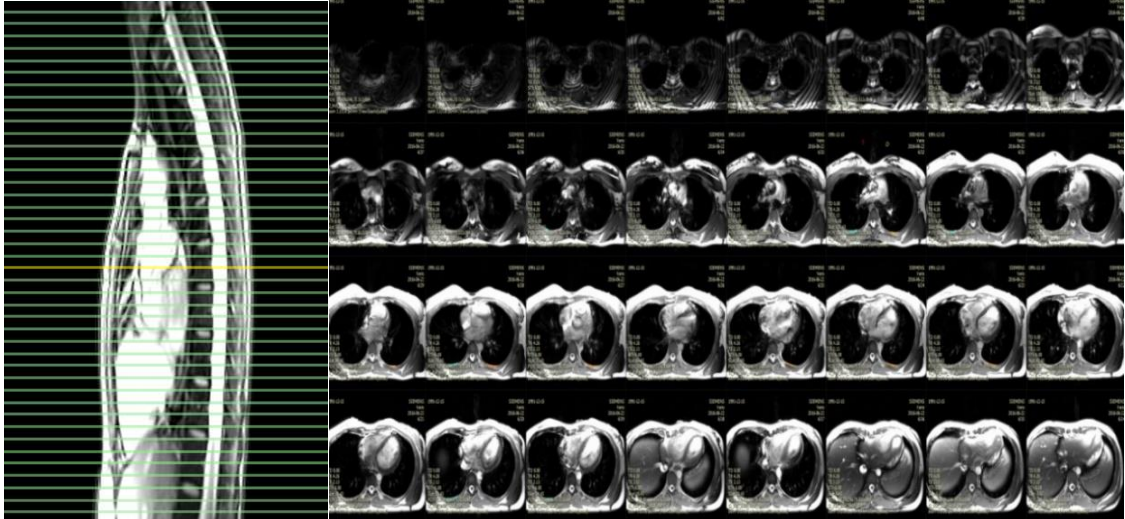
Figure 2: Full coverage of thorax using transaxial true fast imaging with steady-state free precession.

3. Cardiac cine MRI sequences are achieved by acquiring multiple images throughout the cardiac cycle and are used for the assessment of the cardiac function (37) as well as wall motion abnormalities and the quantification of LV and RV parameters. Data acquired at different heartbeats is reconstructed to produce an image at each cardiac phase. By acquiring multiple images at multiple cardiac phases, a series of images can be displayed as a movie (cine) (37).

a) 2 Chamber View: two chamber (vertical) long axis prescribed orthogonal to transaxial scouts aligned through the apex and center of the mitral valve.
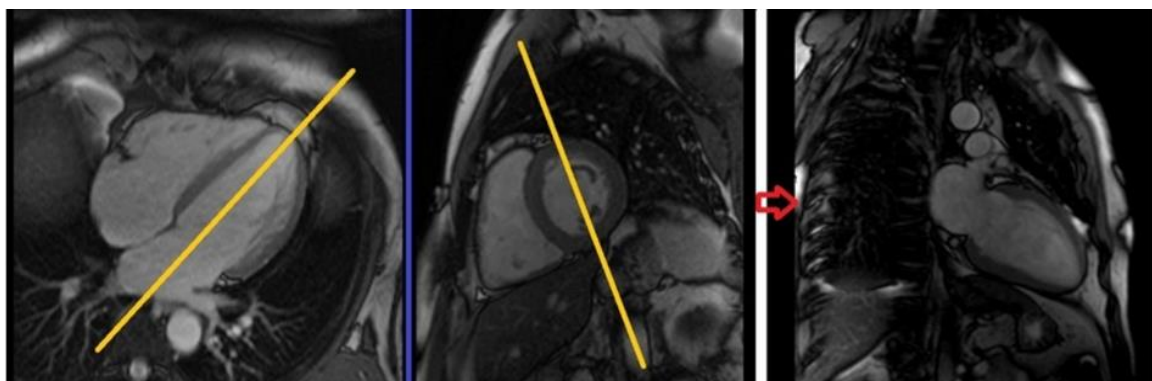
Figure 3: Acquisition of 2 CV. Images obtained from one of the volunteers who participated in the study.

b) 4 Chamber View: four chamber (horizontal) long axis aligned orthogonal to the 2 chamber long axis, passing through the center of the mitral valve and left atrium, and continuing through the long axis of the LV.
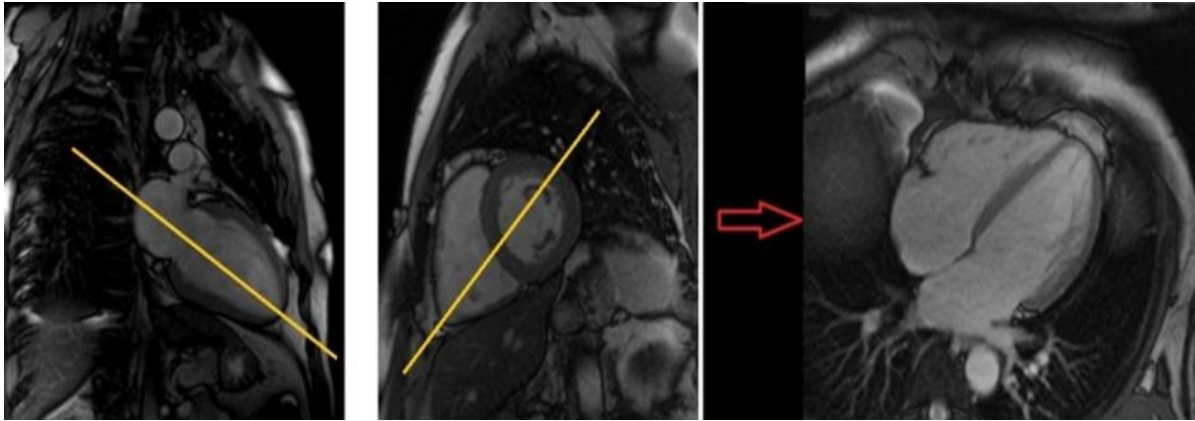
Figure 4 : Acquisition of 4CV. Images obtained from one of the volunteers who participated in the study.

c) 3 Chamber View: the short axis localiser is used and the position block is planned parallel to the line along the centre of the aortic valve and left ventricle and the 2 chamber long axis, passing through the center of the mitral valve and left ventricular apex.
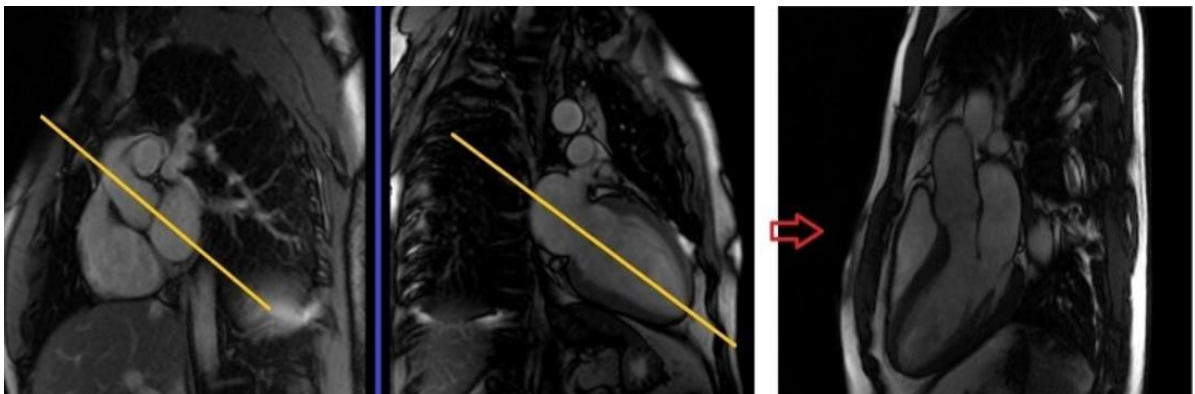
Figure 5 : Acquisition of 3CV. Images obtained from one of the volunteers who participated in the study.

d) Short Axis Cine: state of the art cine SSFP (slice thickness 7/3mm, echo time (TE) 1.3ms, repetition time (TR) 39ms, flip angle (FA) 45°), for assessment of pericardial effusions and of left ventricular (LV) morphology and function.
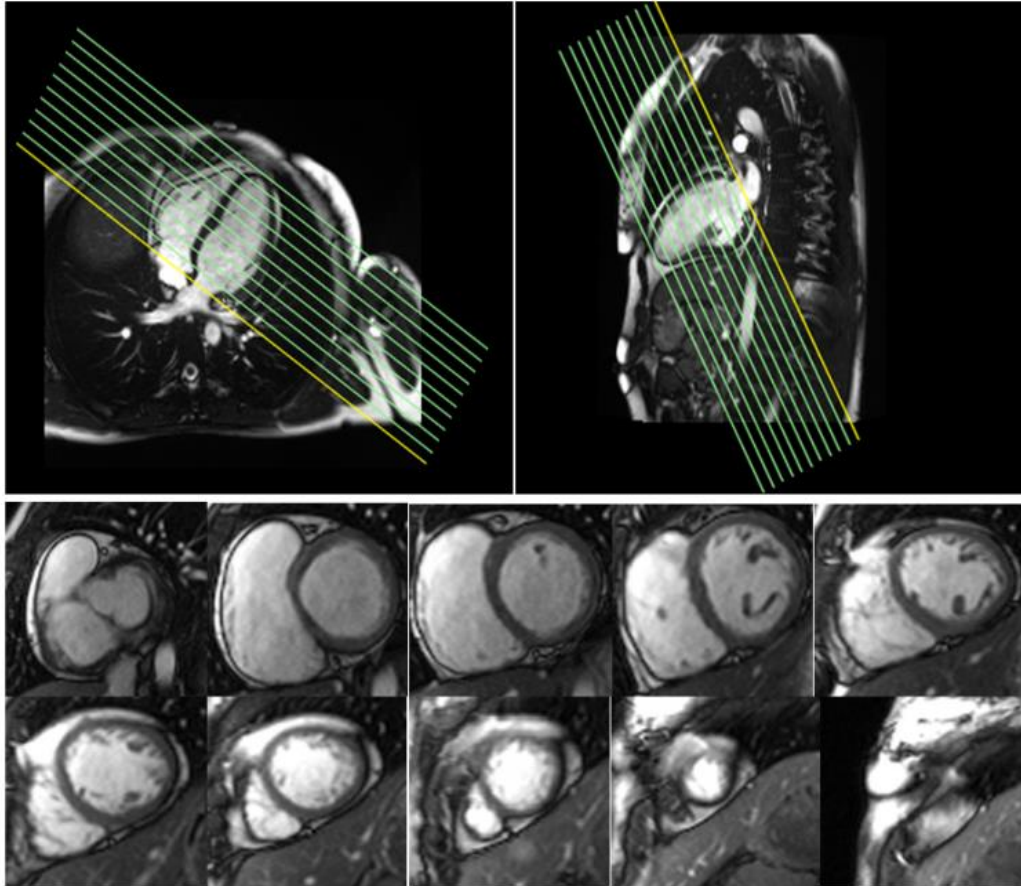
Figure 6:10-12 slices from the VLA and 4ch cine images are used to obtain the Short Axis Cine Stack. Images obtained from one of the volunteers who participated in the study.

4. Differentiation between fat and water was supported by native T1 mapping (MOLLI: 5s(3s)3s; trigger time (TT) 385ms, TE 1.3ms, TR 500ms, incremental TI, FA 35°) positioned similarly to cine SSFP and by fat-water (FW) separated imaging in dedicated slice positions.
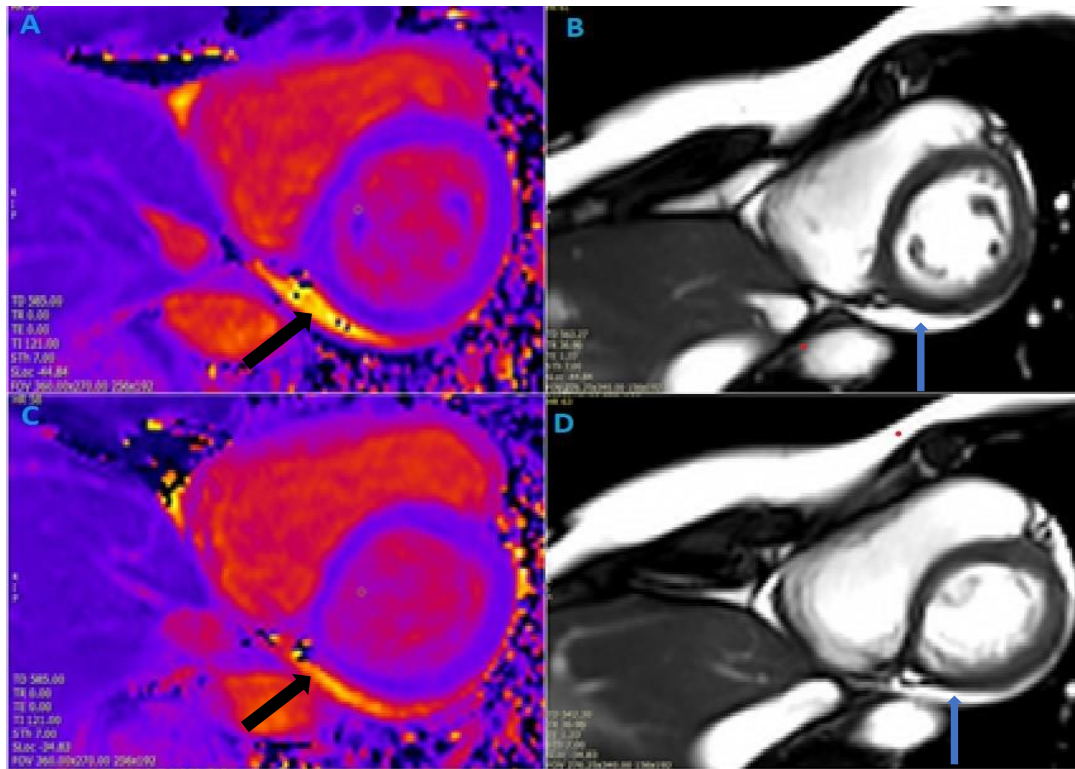
Figure 7: Differentiation between fat and water was supported by native T1 mapping whenever required. Images obtained from one of the volunteers who participated in the study. Cine short axis slices and the corresponding T1 Maps (A: corresponding T1 Map of SAX cine slice B), C is the corresponding T1 Map for Sax Cine slice D. The arrows show pericardial fluid in Cine (Blue arrows), as well as the T1 Maps (Black Arrows).

5. Parameters for the dark blood FW imaging protocol at 3.0T were: double inversion recovery for blood suppression, gradient echo (GRE) with 4 echos and monopolar readout, 977 Hz/pixel bandwidth, echo spacing 14.3 ms with echo times of 1.56, 2.71, 3.87, and 5.02 ms, TD 750 ms TR 87040 and TE 1.56 matrix size of 256 × 192, 360 × 270 mm2 FOV, 6 mm slice thickness, 12° excitation flip angle, breath-hold, 20 views per segment for a total acquisition of 9 heart beats/slice including 1 dummy.

Figure 8: Fat/water separated image in SAX and LAX showing the presence of pericardial fluid. Images obtained from one of the volunteers who participated in the study.
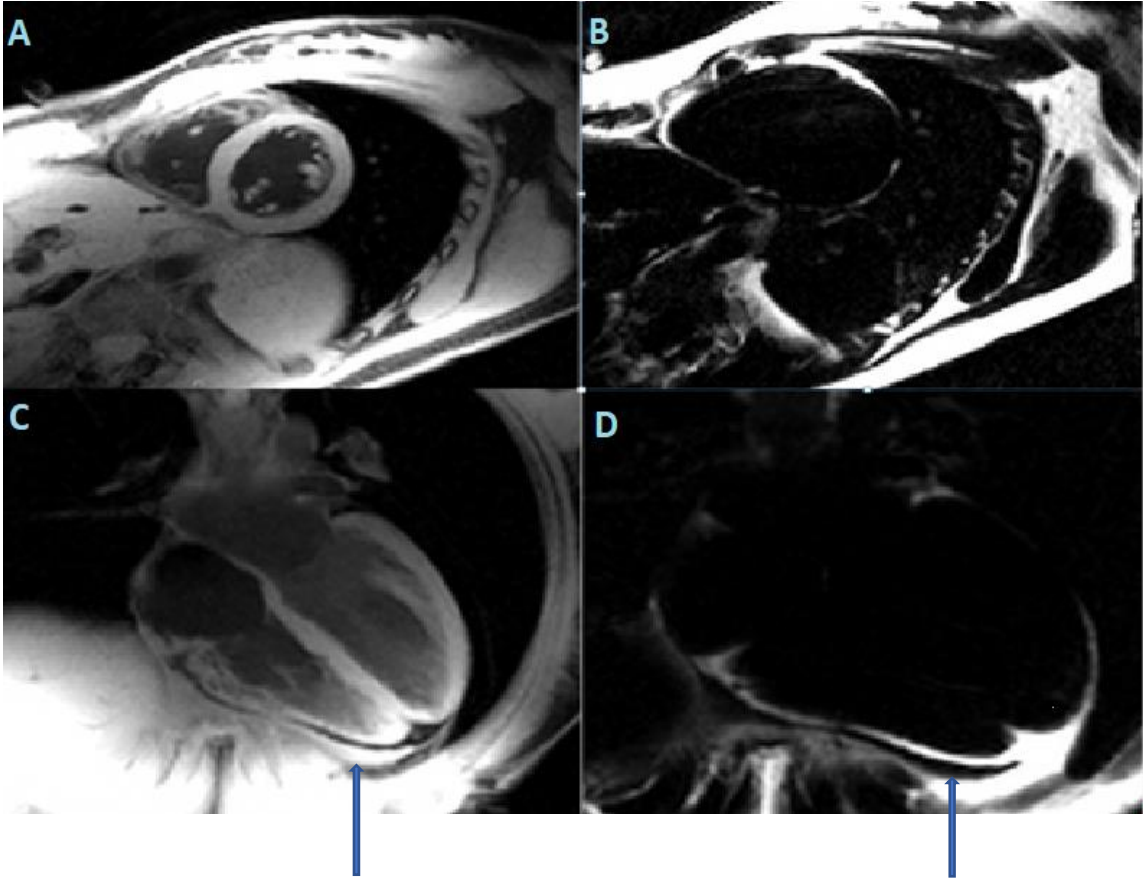
A dedicated fat/water separated image in short axis. Upper row: short axis (A) water and (B) fat. Lower row: 4 CV (C) water and (D) fat. The arrows indicate the presence of pericardial fluid in both fat and water sequences.

7.8 Post Processing

7.8.1 Quantification of LV

For the quantification of LV geometry in the short axis, we used the short 3D module. Using the disc-summation technique, this module is able to analyse a stack of parallel images in long or short axis orientations. This allows for the quantification of the global and regional LV function and volume analysis according to current CMR standards (38). The papillary muscles were excluded in systole and diastole (purple contours). The smallest volume is assumed to be in systole and the largest volume is assumed to represent diastole.
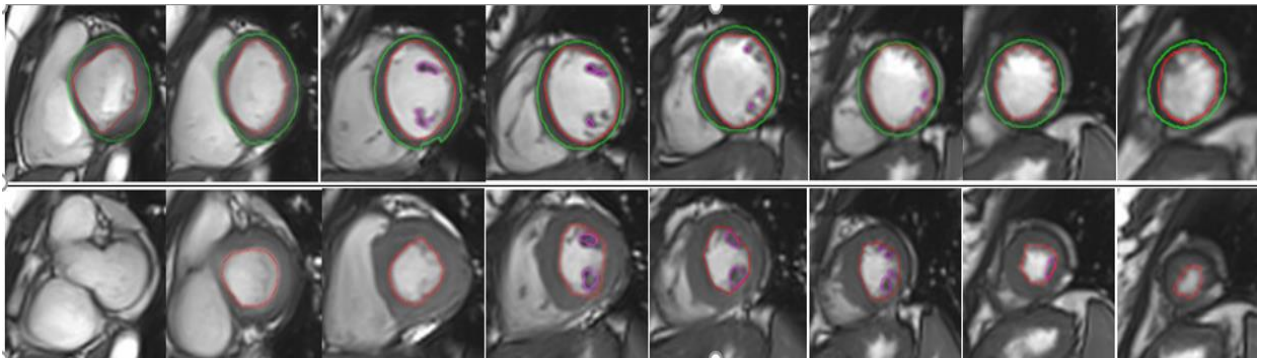
Figure 9: Multi-phase multi-slice SSFP SA cine stack showing endocardial (red), epicardial (green), and papillary muscle (purple) contours at end-diastole (upper row) and at end-systole (lower row). Images obtained from one of our study volunteers.

7.8.2 Quantification of Pleural Fluids

Pleural fluid was quantified by using the true fast imaging with steady-state free precession sequence, as the signal from fluid in the pleural space is well distinguished from other adjacent tissues in this sequence.

Generating new manually composed series for the quantification of Pleural Fluid

CVI 42 does not have any specific tool for the quantification of pleural effusions as this is not performed routinely. It was not possible to use the T2 axial Trufi with the 3D Tool, as it is interpreted as an invalid short axis 3D series. (Figure 10, error shown by arrow).
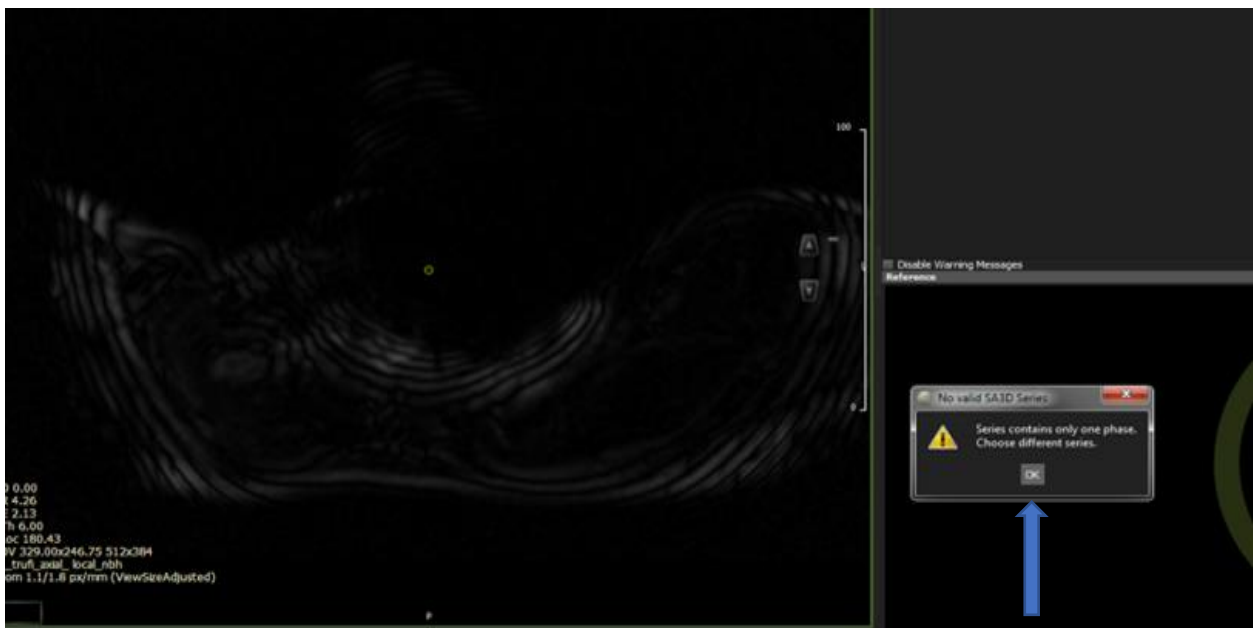
Figure 10: Invalid short axis 3D series.

However, CVI 42 allows images to be added together using the 'series composer' tool (Figure 11, arrow), which enabled us to generate new manually composed series. This was carried out using the following steps:

Step 1:

The T2 Trufi Axial series were dragged into the composer in Phase 1 and Phase 2. A complete series could be dragged directly to the composer as shown below (Figure 11, arrow).

Figure 11: Generating the new manually composed series required the quantification of PLF.

Step 2:

Using the *Apply* tool (shown by arrow) we were able to assemble the newly composed series. The lower window provides a showcase for the newly composed series.
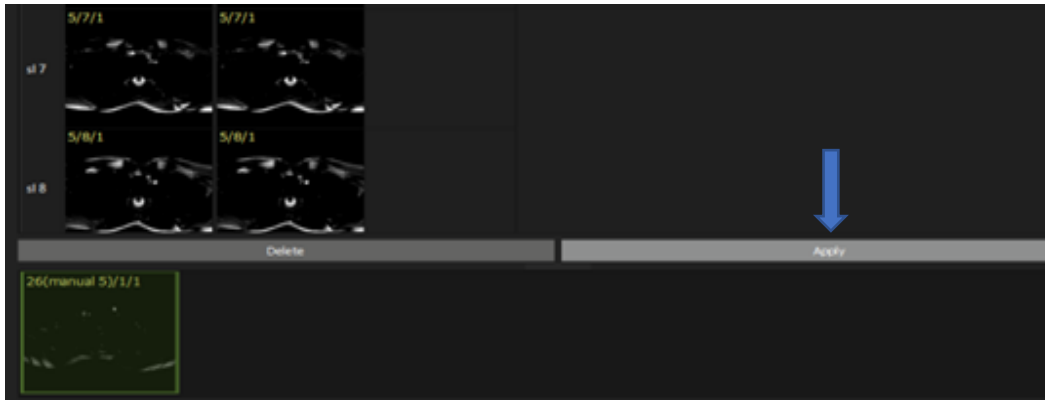
Figure 12: Process of generating new composed series allowing quantification of pleural effusions.

Step 3:

The newly composed series will automatically be added to the list of series (Figure 13).
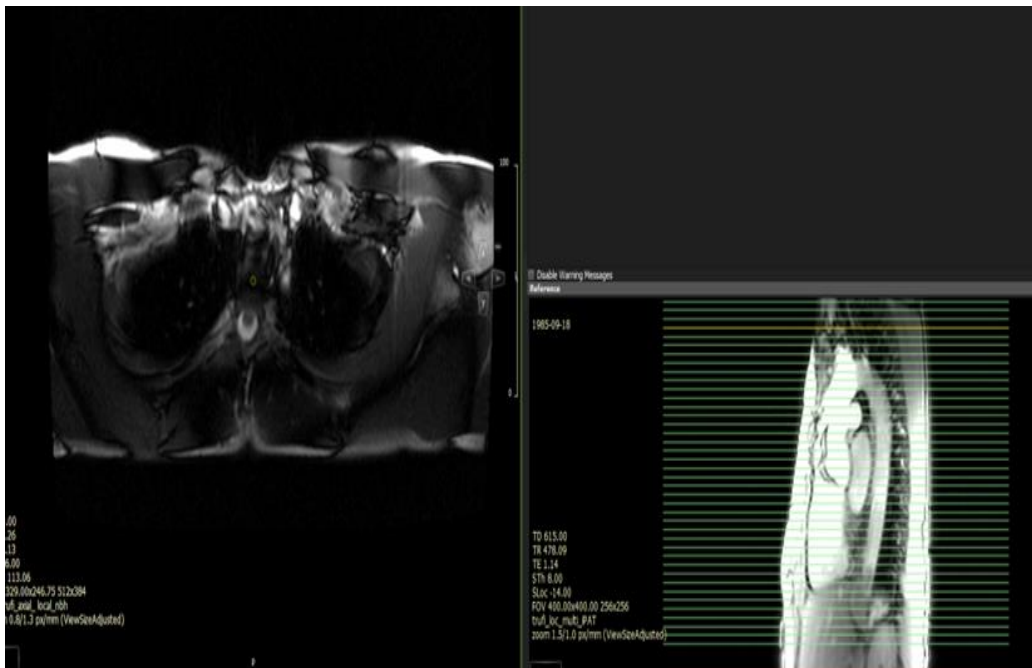
Figure 13: the new series is accepted by CVI 42 and can be used to quantify Pleural fluids.

To establish reproducible quantification for our research purposes, we developed a method to quantify the PLF volumes. We used the disc-summation technique to analyse a stack of parallel images.

- After manually generating the newly composed series of the T2 axial Trufi, the new series could then be used with the 3D module to quantify the pleural effusions. The LA and RA tools were then used to quantify the left and right PLF, respectively.
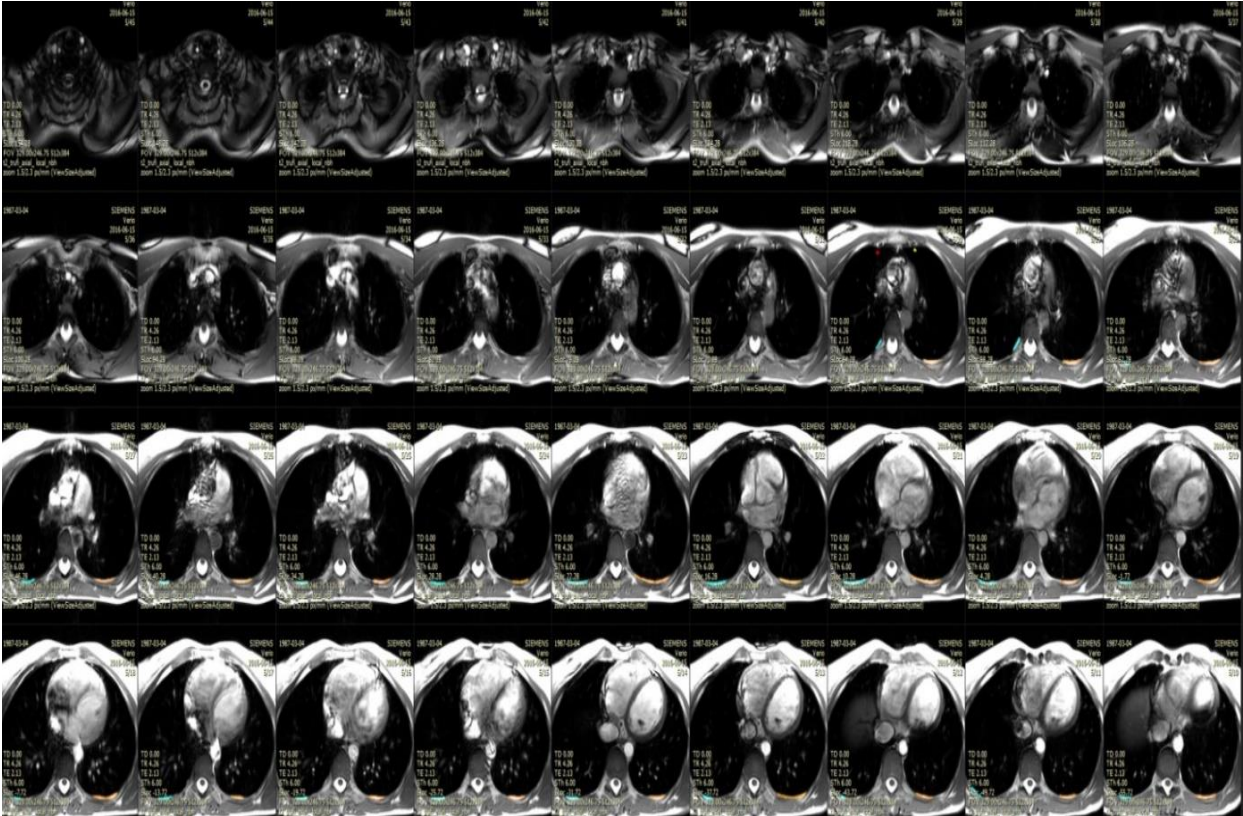
Figure 14: Manually generated new composed series of the T2 axial Trufi.

- CVI 42 only allows the use of the LA and RA tools after the SAX LV endocardial contour and the SAX RV endocardial contour are defined because these tools were created specifically to quantify the LA and RA. Two random regions are marked using the LV and RV tools as shown below (arrows). The left and right pleural volumes were reported as LA and RA volumes, respectively.
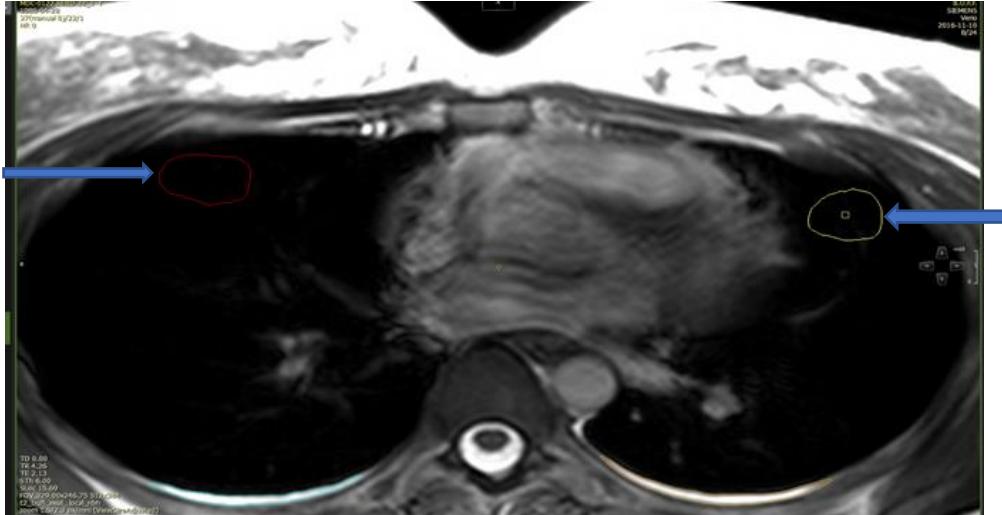
Figure 15: Two random marked regions. The green contour shows the PLF in left-sided pleura and the blue contour shows the PLF in right-sided pleura. Image obtained from one of the volunteers.

- With the newly acquired series, the quantification of the PLF volume was simple. Using the difference in signal intensity between the fluids and the lungs we used the semiautomatic contouring tool (threshold segmentation), as shown below.
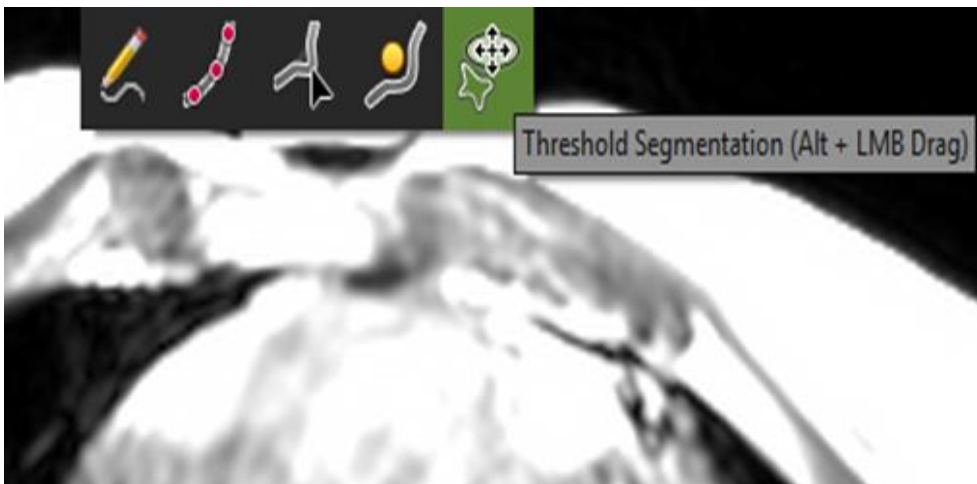
Figure 16: Threshold segmentation tool – semiautomatic contouring tool.

- This allowed for an immediate interaction with the software for manual correction if the semiautomatic contouring was considered unsatisfactory. As shown in the figure below, the automatic tool incorrectly contours part of the rib cage (arrow). This had to be corrected manually.
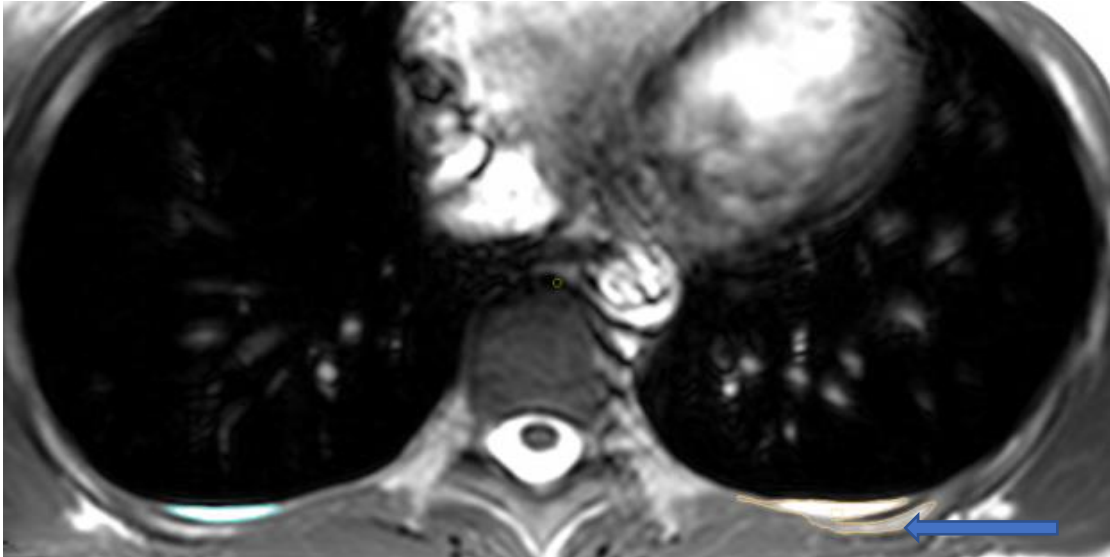
Figure 17: The above image showed unsatisfactory semiautomatic contouring (arrow) and required manual correction.

- With the right amount of contrast, it was simple to differentiate PLF from the lung tissue and neighbouring tissues. A manual correction was required to exclude neighbouring tissues.
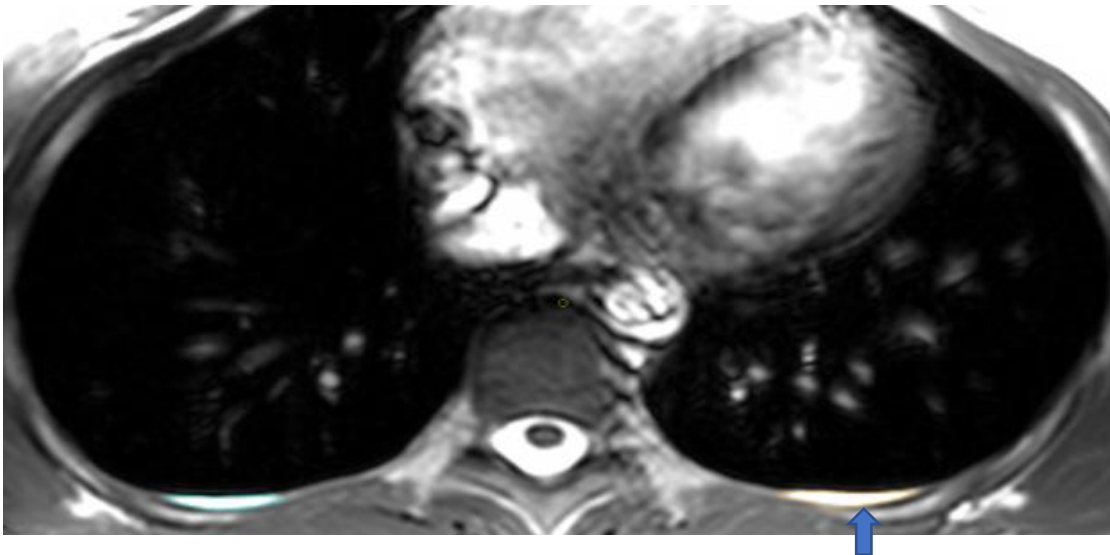
Figure 18: Manual correction following unsatisfactory semiautomatic contouring of the PLF.

- Pleural effusion was quantified if it was present in more than one slice, as judged by the assessing physician for the left and right pleural space separately (Figure 19). The total amount of pleural fluid was calculated by totaling the amounts of

pleural fluid of the right and left side of the pleural space. This was done automatically by CVI 42.
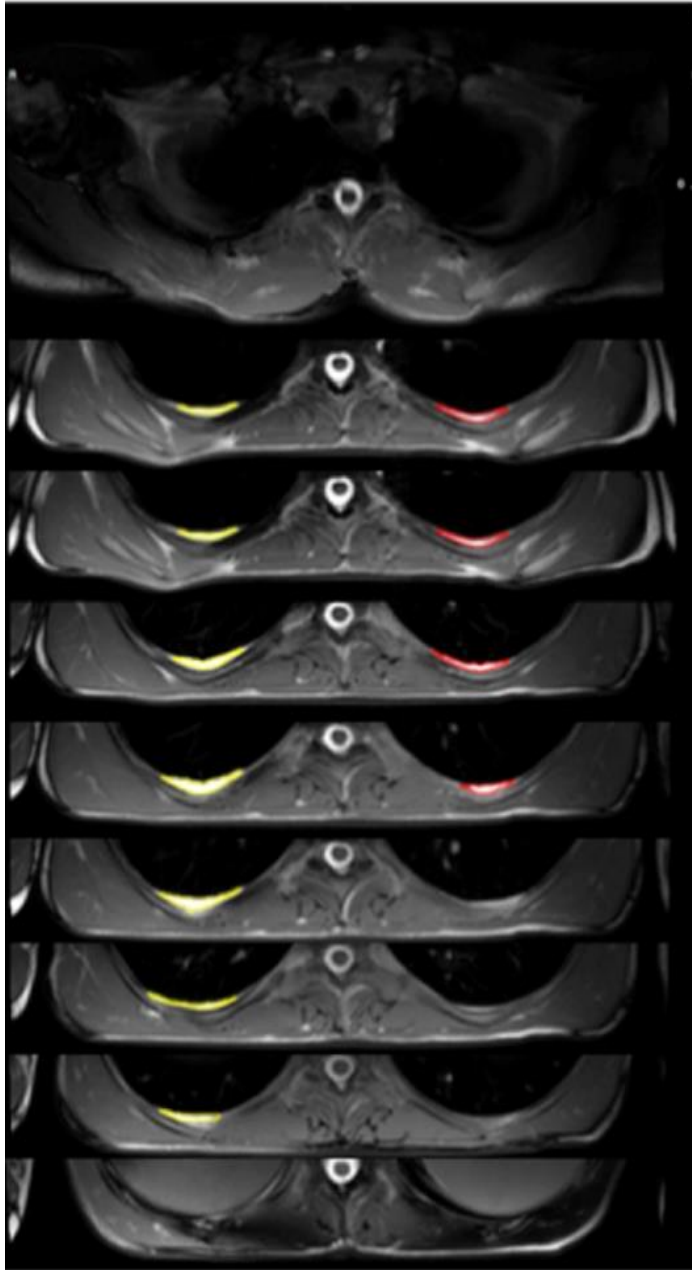
The red ROI shows the pleural fluid in the right pleura, while the yellow ROI shows the pleural fluid in the right pleura. The total PLF was the sum of the volume obtained on both sides.

Figure 19: Quantification of pleural fluids. Images were obtained from one of our volunteers and the images are stacked in accordance with the stack position.

7.8.3 Quantification of Pericardial Fluids

Quantifying pericardial fluid was more challenging because pericardial fat and pericardial fluid have a similar signal intensity in the standard native cine imaging dedicated steady-state free precession (SSFP) sequence. In a few cases, with the help of the T1 native mapping sequence as well as a dedicated fat/water separation technique, it was possible to distinguish between both types of tissue (39). Careful visual comparison to the native T1 mapping at incremental inversion times was performed to distinguish the epi- and pericardial fat tissue from fluid.
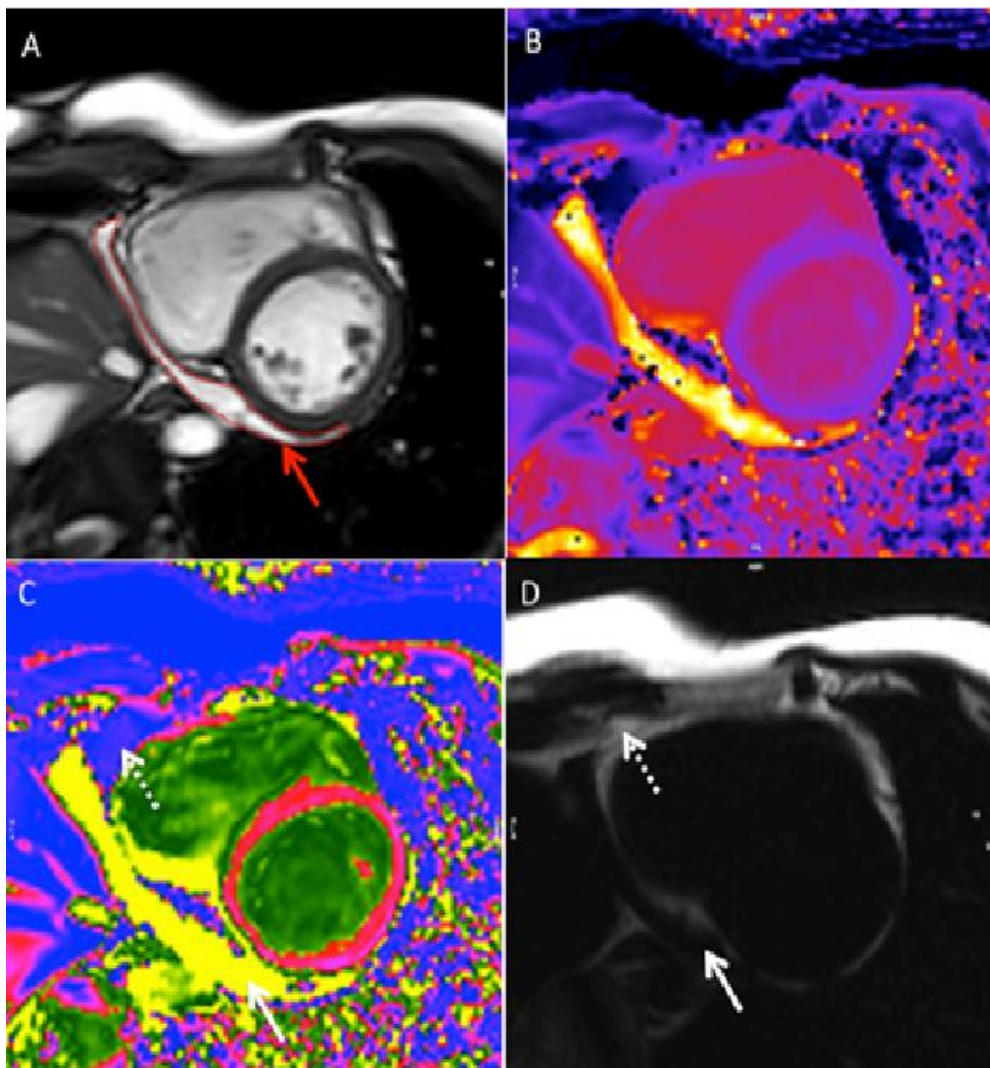
Figure 20: Quantification of Pericardial Fluids using native T1 Mapping and fat/water separation techniques. (A) Cine SSFP with pericardial fluid (ROI shown by the red Arrow); (B) Native T1 Map confirming the Pericardial fluid (PF); (C) Native T1 Map with T1 Values expressed as a colour scale. The small amount of pericardial fat (white dotted arrow) is distinguished from PF (white arrow); (D) A dedicated fat/water separation in the same slice position, fat (white dotted arrow) distinguished from PF (white arrow).

The quantification approach for the pericardial fluid included the following steps:

1. Visual inspection of the SSFP cine images and selection of the end-diastolic phase of the heart cycle.

2. If fluid was present, careful semiautomatic threshold-based visually controlled quantification with the use of multiple regions of interest (ROI) was performed (if appropriate) using the LA and RA tools. If there were more than 2 ROIs, we used the RV tool. The final PF volume was obtained by the totaling of the LA, RA and the RV volumes (in cases where the RV tool was used).

3. Subsequently, correction of ROIs was performed manually, if necessary.
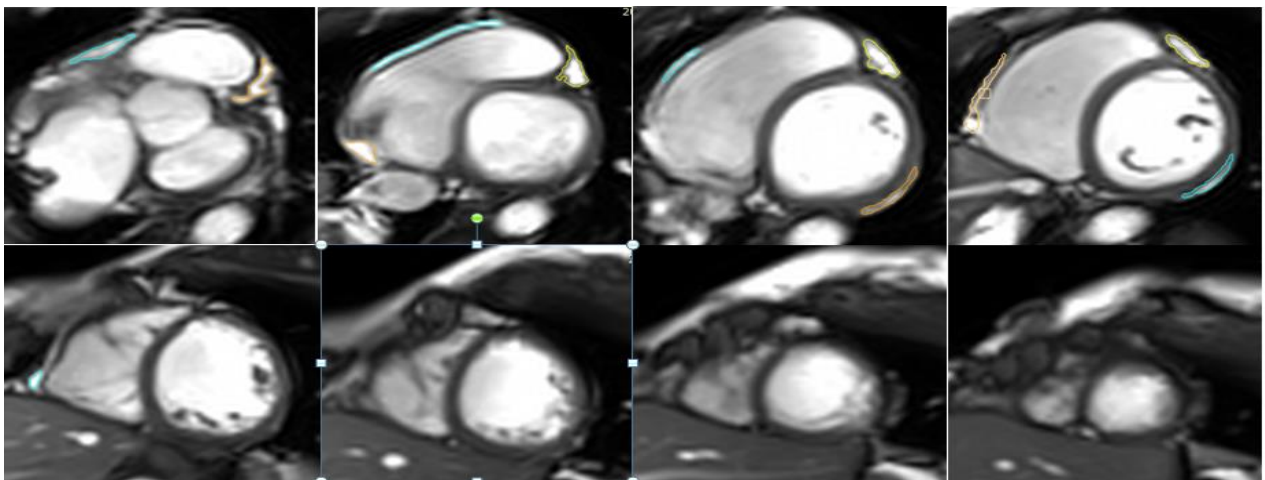
Figure 21: Pericardial Fluids were quantified using the LA, RA und RV tools (yellow, blue and orange, respectively) in each slice and the total amount of PE calculated automatically by CVI 42.

7.9 Interobserver and Intraobserver Reliability

Intraobserver measurements were carried out on 10 randomly chosen volunteers. A second experienced physician with CMR experience performed the interobserver measurements on 10 volunteers.

7.10 Statistical Analysis

Statistical analyses were performed with SPSS Version 24 (IBM SPSS Statistics for Windows, Version 24.0., released 2016. IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means with standard deviations; categorical variables were expressed as percentages and totals. The intraclass correlation coefficient was used to evaluate the interobserver and intraobserver reliability. A two-sided p value <0.05 was considered statistically significant for all tests.

8. Results

8.1 Characteristics of the Volunteers

A total of 147 women were screened between March 2016 and December 2017. 45 (30.6 %) were eligible to take part in the study. 35 (23.8 %) women were recruited. 30 (20.4%) participants (mean age 31 ± 5.4 years) completed both CMR scans. The recruitment process and reasons for exclusion from the study are illustrated in the flowchart below.
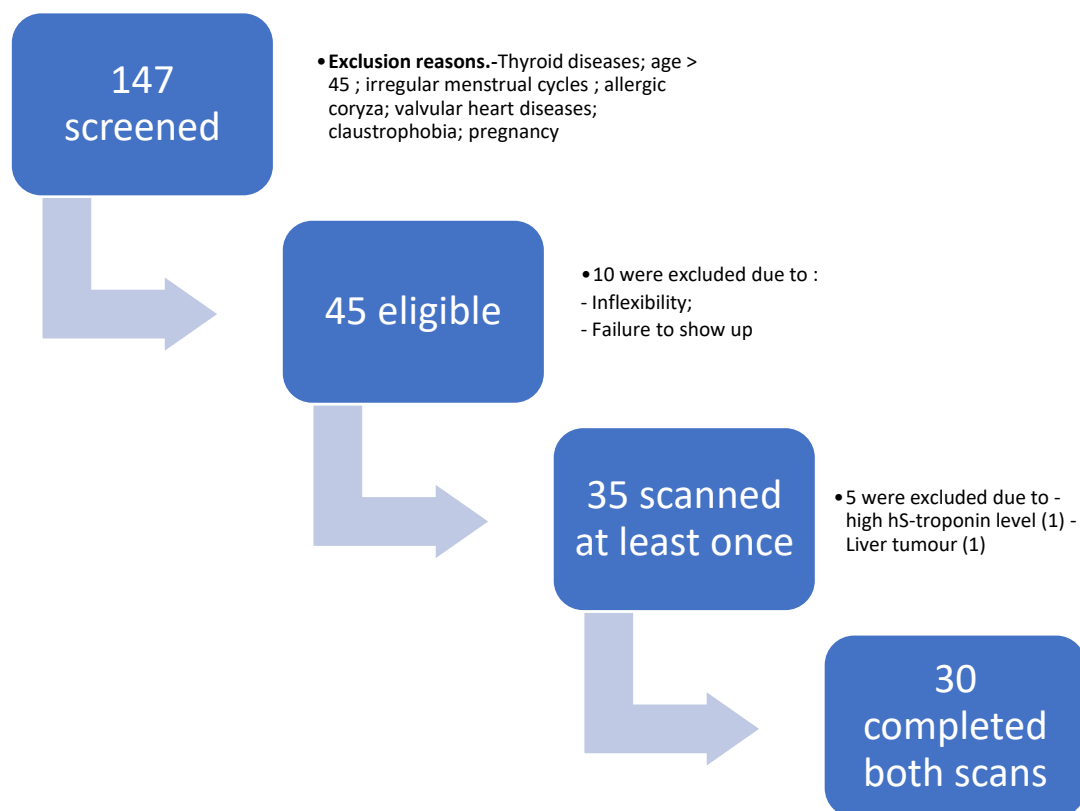
Figure 22: Study flowchart showing a breakdown analysis of screening, recruitment, and protocol completion.

The median body mass index of the study population was 22 ± 2.2 kg/m^2. The mean number of days of the menstrual cycle was 28.47 ± 1.7. The values of the cardiac markers of every volunteer were within normal range. Mean high sensitive Troponin was 3.77 ± 2.4 ng/l and NT-proBNP was 56.80 ± 22.6 ng/l, respectively. Mean high sensitive CRP and Leukocytes were 2.16 ± 2.49 mg/dl and 6.61 ± 1.7 Gpt/l, respectively, which excluded any signs of Inflammation. The mean values of Follicular Stimulating Hormone, Estradiol, and Progesterone were 5.89 ± 2.49 IU/L, 43.56 ± 33.7 ng/l, and 0.74 ± 2.3 ng/ml,

respectively. Out of the enrolled Volunteers, 3 (10%) were smokers and 12 (40%) used contraceptives. In one of the recruited volunteers, a solid tumor of the liver was suspected after the first scan and the candidate was therefore excluded from the study. The above information is summarized in the Table 2.

Basic characteristics	Mean ± SD or %	Normal Values
Age (years)	31±5.4	
Body weight (kilograms)	61.7±6.7	
Body height (centimetres)	166.63±5.7	
BMI (kg/m2)	22±2.2	
Menstrual cycle length (days)	28.47±1.7	
Smokers	3 (10%)	
Contraception	12 (40%)	
Laboratory Findings		
Follicle stimulating hormone (IU/l)	5.89±2.9	1.5-33.4 U/l
Estradiol ng/l	43.56±33.7	25-570
Progesterone ng/ml	0.74±2.3	<1.0*,>10**
High sensitive CRP (mg/l)	2.16±2.49	< 0.3
High sensitive Troponin (ng/l)	3.77±2.4	< 14
White blood cell (Gpt/l)	6.61±1.7	4000-10000
NT-proBNP (ng/l)	56.80±22.6	< 125
Pathological Findings		
Suspected Liver Tumour	1 (3.33%)	
Increased hS-Trop	1 (3.33%)	

Table 2. The basic characteristics of the study population (n=30). Data is presented as number of patients and percentage. Values are n(%) or mean ± SD; hs-CRP – high sensitive C-Reactive Protein, Hs Trop – high sensitive Troponin, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, BMI - Body Mass Index: * Follicular Phase, ** Luteal Phase

MRI Parameters	CMR1 Mean ± SD	CMR 2 Mean ± SD	p-Value
LVEF(%)	67.87 ±4.6	68.40±5.1	0.637
LVEDV (ml)	117.03±16.8	117.93±14.7	0.377
LVESV (ml)	41.23±13.6	38.80±9.8	0.625
PLF (ml)	9.80±6.1	9.53±5.7	0.425
PF(ml)	10.07±6.7	9.10±5.7	0.742

Table 3: Mean left ventricular parameters as well as mean pleural and pericardial effusions in CMR1 and CMR2

8.2 Comparison of LV parameters between early follicular phase (CMR1) and Luteal Phase (CMR2)

Table 4: LV ventricular ejection fraction (LVEF), LVESV (left ventricular end-systolic volume), LVM (Left ventricular mass) and left ventricular end-diastolic volume (LVEDV) between CMR1 and CMR2

Study ID	LVEDV1 (ml)	LVEDV2(ml)	LVESV1(ml)	LVESV2(ml)	LVM1(g)	LVM2(g)	LVEF1(%)	LVEF2(%)
SERO_0002	141	124	79	39	76	87	66	68
SERO_0003	140	134	59	51	71	76	58	62
SERO_0004	117	117	38	34	49	66	67	71
SERO_0006	91	104	28	23	59	63	70	78
SERO_0007	99	109	25	33	72	73	75	69
SERO_0008	144	131	40	50	90	75	73	62
SERO_0009	113	118	39	46	55	57	66	61
SERO_0010	124	118	34	37	72	77	73	69
SERO_0011	129	112	41	38	59	68	68	67
SERO_0012	97	121	29	40	69	70	71	67
SERO_0013	93	110	29	26	52	56	70	76
SERO_0014	140	156	51	46	74	74	64	70
SERO_0015	110	116	38	45	47	63	65	61
SERO_0016	115	119	40	41	59	70	65	65
SERO_0017	118	116	44	29	68	76	62	75
SERO_0018	130	121	43	46	79	49	67	62
SERO_0019	101	102	23	22	57	49	77	78
SERO_0020	100	105	30	30	41	41	70	71
SERO_0021	94	82	24	31	55	63	75	63
SERO_0022	114	112	31	74	66	81	73	74
SERO_0024	114	116	43	37	62	57	62	69
SERO_0025	132	123	40	39	60	74	70	68
SERO_0026	111	109	76	33	58	57	68	70
SERO_0027	99	102	63	36	65	51	64	65
SERO_0028	115	121	42	38	79	69	64	68
SERO_0029	123	116	43	43	70	73	65	63
SERO_0030	146	157	52	38	72	98	64	76
SERO_0032	117	114	38	42	70	91	67	63
SERO_0033	142	136	38	38	97	104	74	72
SERO_0034	102	117	37	36	70	64	63	69
P Value	P: 0.663		P: 0.549		P: 0.347		P: 0.767	
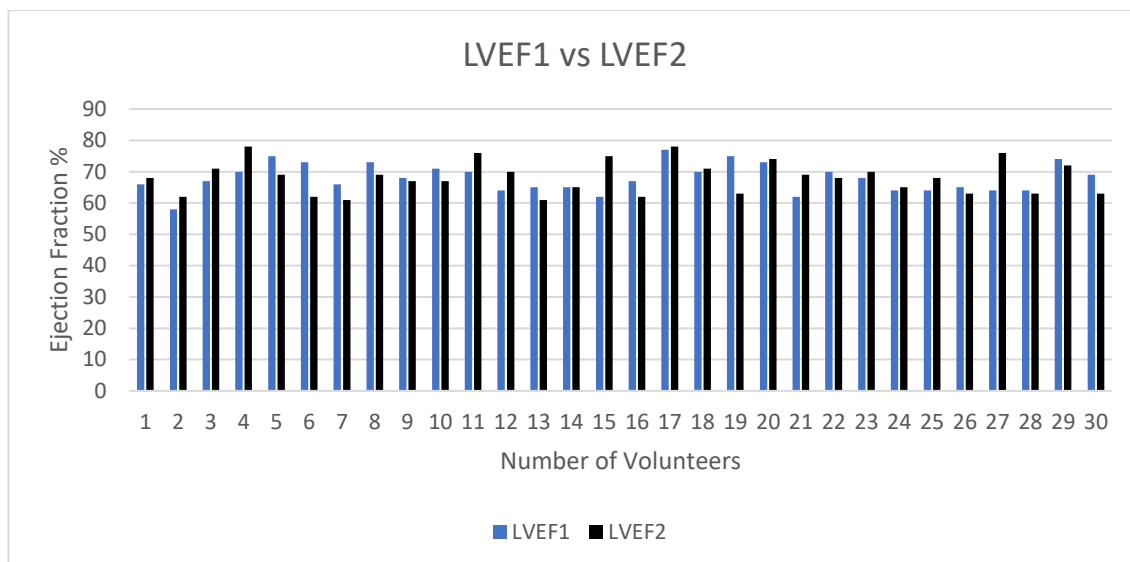
Figure 23: Comparison of the ejection fraction between the first and second scans. A p Value of 0.625 indicated no significant changes.

8.3. Pleural and Pericardial fluids

The table below shows the mean amount of PLF and PF during each scan and the P value in each case.

	CMR1 Mean±SD	CMR2 Mean±SD	p
Pericardial Fluid (ml)	10.07±6.7	9.10±5.8	0.425
Pleural Fluid (ml)	9.80±6.1	9.53±5.7	0.742

Table 5: Mean ± SD and p Values of PLF and PF in CMR1 and CMR2; SD – standard deviation

8.3.1 Comparison of Pleural Fluids between early follicular phase (CMR1) and Luteal Phase (CMR2)

29 (97 %) and 28 (93 %) of the volunteers showed the presence of PLF in CMR1 and CMR2, respectively. The mean PLF for CMR 1 was 9.80 ± 6.1 and for CMR 2 was 9.53 ± 5.7, respectively. The t-test for paired samples resulted in a p value of 0.742 and thus showed that there were no significant differences. The maximum amount of PLF quantified over both scans was 26 ml.

STUDY ID	PLF1	PLF2
SERO_002	15	23
SERO_003	10	5
SERO_004	8	4
SERO_006	5	10
SERO_007	9	9
SERO_008	2	2
SERO_009	3	0
SERO_010	6	7
SERO_011	5	5
SERO_012	10	13
SERO_013	5	9
SERO_014	6	7
SERO_015	11	14
SERO_016	10	12
SERO_017	21	15
SERO_018	13	13
SERO_019	6	10
SERO_020	10	15
SERO_021	7	8
SERO_022	13	17
SERO_024	0	0
SERO_025	26	15
SERO_026	12	5
SERO_027	3	8
SERO_028	6	6
SERO_029	9	5
SERO_030	22	18
SERO_032	15	16
SERO_033	18	13
SERO_034	8	2
p value: 0.425		

Table 6: Pleural fluids in each volunteer in CMR1 and CMR2, respectively
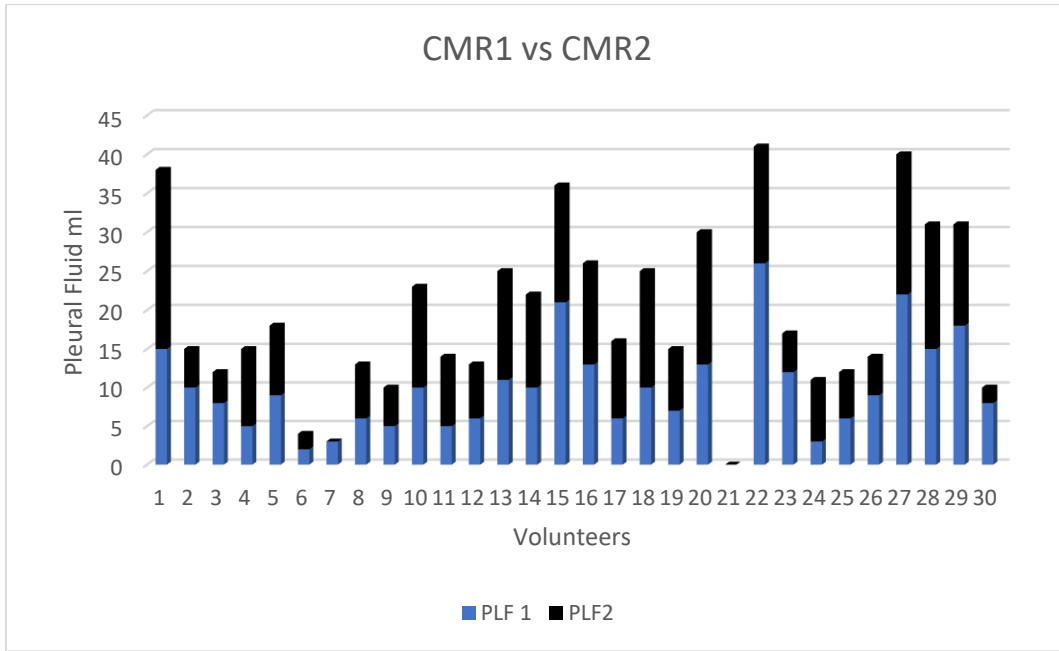
Figure 24: Prevalence of PLF in CMR1 vs CMR2. The differences in pleural fluids between the first and second scans were not relevant (p = 0.742).
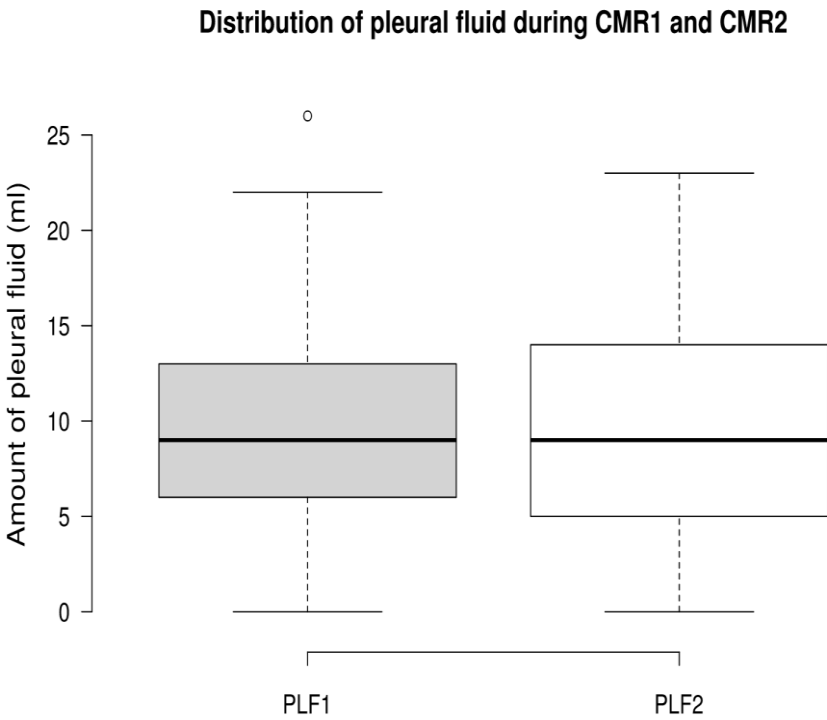
Figure 25 - Distribution (median, quartiles, range) of plural fluids during CMR 1 and CMR 2. PLF1 – distribution of PLF during CMR1 ; PLF2 – distribution of PLF during CMR 2

8.3.2 Comparison of Pericardial Fluids between early follicular phase (CMR1) and Luteal Phase (CMR2)

Pericardial Fluids were detected in 30 (100 %) and 28 (93 %) of the volunteers in CMR1 and CMR2, respectively. The mean PF for CMR 1 was 10.07 ± 6.7 ml and for CMR 2 was 9.10 ± 5.8 ml, respectively. The t-test for paired samples showed no significant difference (p value of 0.425). The maximum amount of PF quantified in all scans did not exceed 34 ml.

Table 7: Pericardial fluids in each volunteer in CMR1 and CMR2, respectively.

STUDY ID	PF1(ml)	PF2(ml)
SERO_0002	19	12
SERO_0003	13	13
SERO_0004	13	8
SERO_0006	5	0
SERO_0007	3	3
SERO_0008	5	5
SERO_0009	4	6
SERO_0010	8	12
SERO_0011	24	9
SERO_0012	9	5
SERO_0013	2	6
SERO_0014	6	7
SERO_0015	11	14
SERO_0016	6	10
SERO_0017	10	8
SERO_0018	14	8
SERO_0019	34	16
SERO_0020	6	0
SERO_0021	7	8
SERO_0022	18	12
SERO_0024	5	5
SERO_0025	19	18
SERO_0026	4	8
SERO_0027	13	15
SERO_0028	6	3
SERO_0029	8	9
SERO_0030	7	5
SERO_0032	9	15
SERO_0033	5	5
SERO_0034	9	28
P value: 0.742		

.
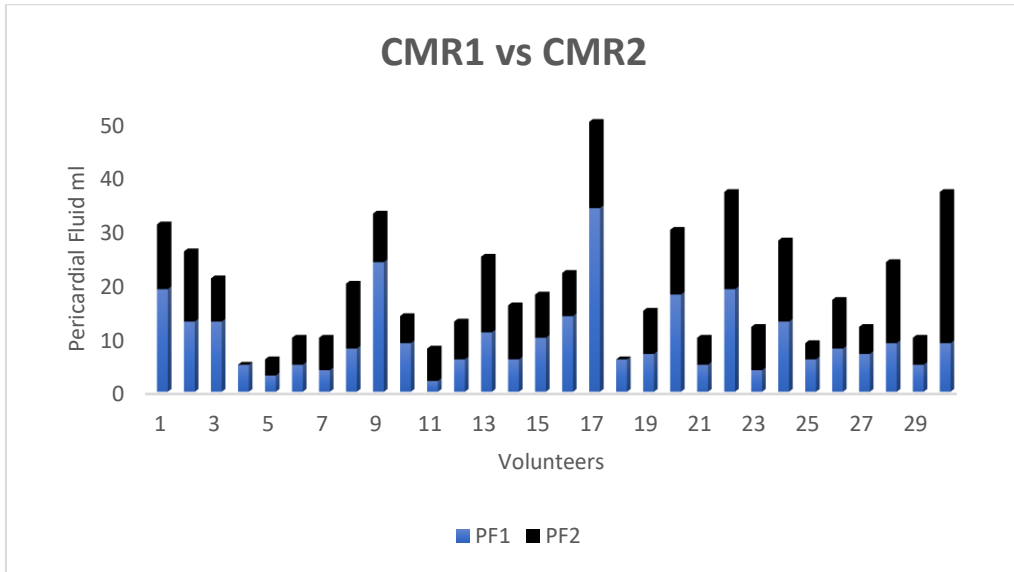
Figure 26: Prevalence of PF in CMR1 and CMR 2. The difference in pericardial fluids in scan1 and scan 2 were not relevant (p = 0.425).
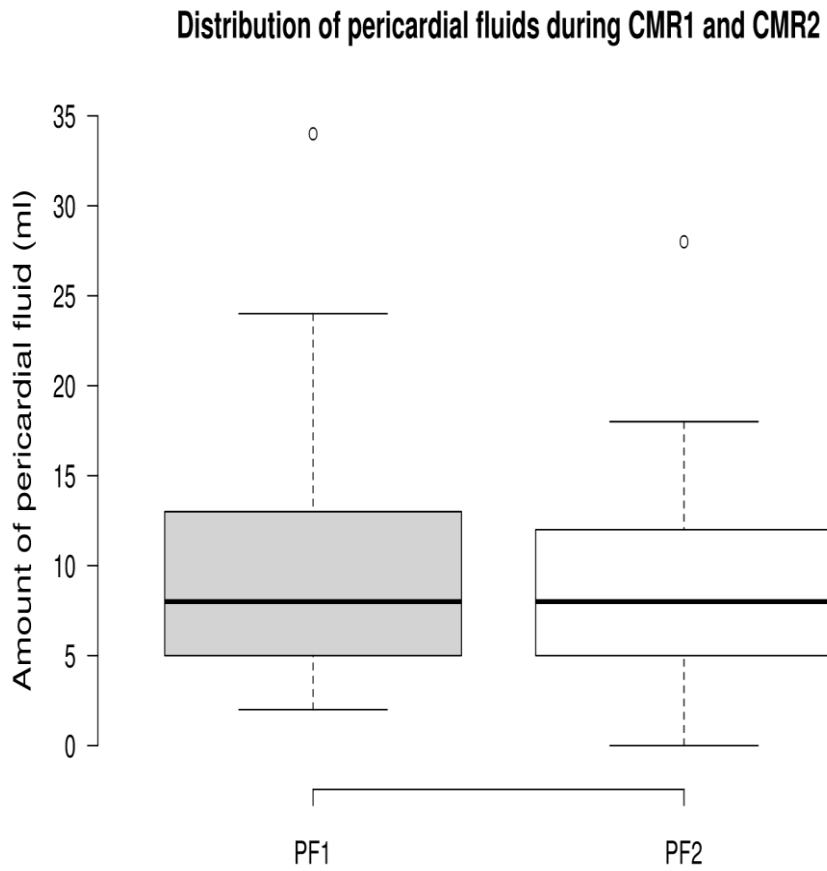
Figure 27: Distribution (median, quartiles, range) of pericardial fluids during CMR 1 and CMR : PF1 – distribution of PF during CMR1 ; PF2 – distribution of PF during CMR 2

8.4 Intraobserver and Interobserver variability

8.4.1 Intraobserver Variability

The quantification of the PLF and PF was carried out on 10 randomly chosen scans. The intraclass correlation coefficient (ICC) index was used for the reliability analysis.

(a) Intraobserver Variability for Pleural Fluids

Intraobserver Variability	PLF	
Sero	Measure 1(ml)	Measure 2(ml)
4	8	6
5	17	20
6	5	8
12	10	7
16	10	7
17	15	14
22	13	12
23	10	12
25	26	25
28	6	8

Table 8: Intraobserver measurement results for PLF; Measure 1: the first quantification, Measure 2: the second quantification
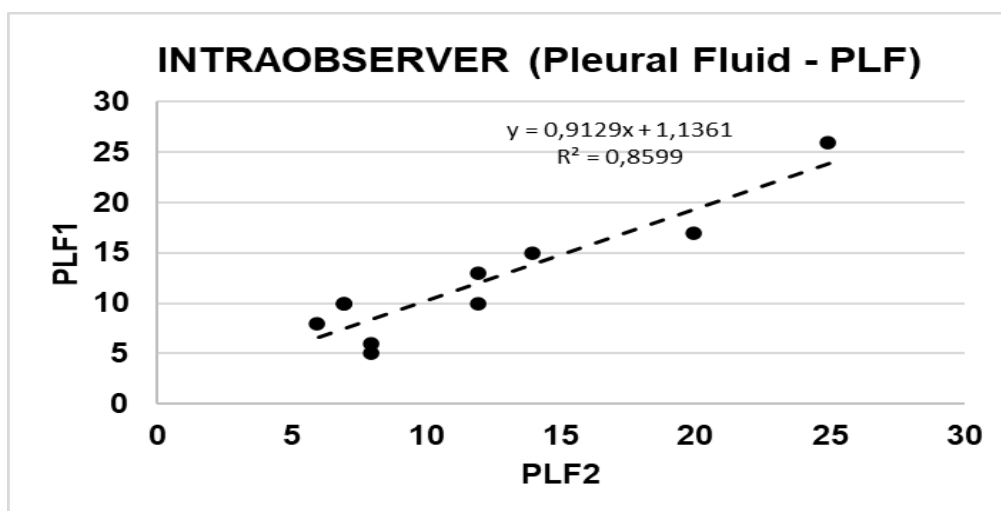
Figure 28: Linear regression analysis graph - intraobserver reliability for PLF.

	Intraclass Correlation	95%-Confidence Interval	
		Lower Bound	Upper Bound
Single Measures	0,927	0,736	0,981
Average measures	0,962	0,848	0,991

Table 9: The intraclass coefficient value and the 95% confidence interval for pleural fluid

Our results showed an intraclass correlation coefficient of 0.962 (95% CI 0.848-0.991), therefore indicating an excellent intraobserver reliability for the pleural fluid.

(b) Intraobserver Variability for Pericardial Fluid

Intraobserver Variability	PF	
Sero	Measure 1 (ml)	Measure 2(ml)
4	13	9
5	5	6
6	5	9
12	9	8
16	6	5
17	8	5
22	18	18
23	15	16
25	19	17
28	5	8

Table 10: Intraobserver measurement results for PF; Measure 1: the first quantification, Measure 2: the second quantification
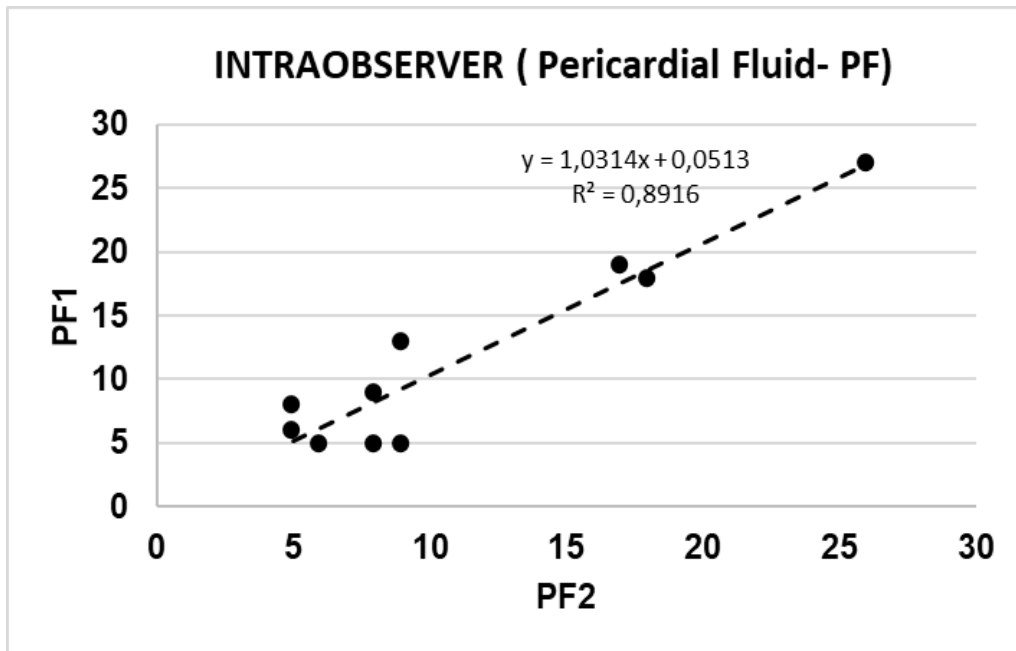
Figure 29: Linear regression analysis graph - intraobserver reliability for PF.

| | | 95%-Confidence Interval | |
	Intraclass Correlation	Lower Bound	Upper Bound
Single Measures	0,885	0,604	0,97
Average measures	0,939	0,753	0,985

Table 11: Intraclass coefficient value and the 95% confidence interval of pericardial Fluid

Our results showed an intraclass correlation coefficient of 0.939 (95% CI 0.753-0.985), thus indicating an excellent intraobserver reliability for the pericardial fluid.

8.4.2 Interobserver Variability

The intraclass correlation coefficient (ICC) was used for the reliability analysis.

a) Interobserver Variability for Pleural Fluids

Interobserver Variability	PLF	
sero	Observer1 (ml)	Observer2 (ml)
4	8	5
5	17	19
6	5	7
12	10	8
16	10	7
17	15	12
22	13	11
23	10	10
25	26	23
28	6	4

Table 12: Interobserver measurement results for PLF; Observer 1 – the first observer, Observer 2 – the second observer
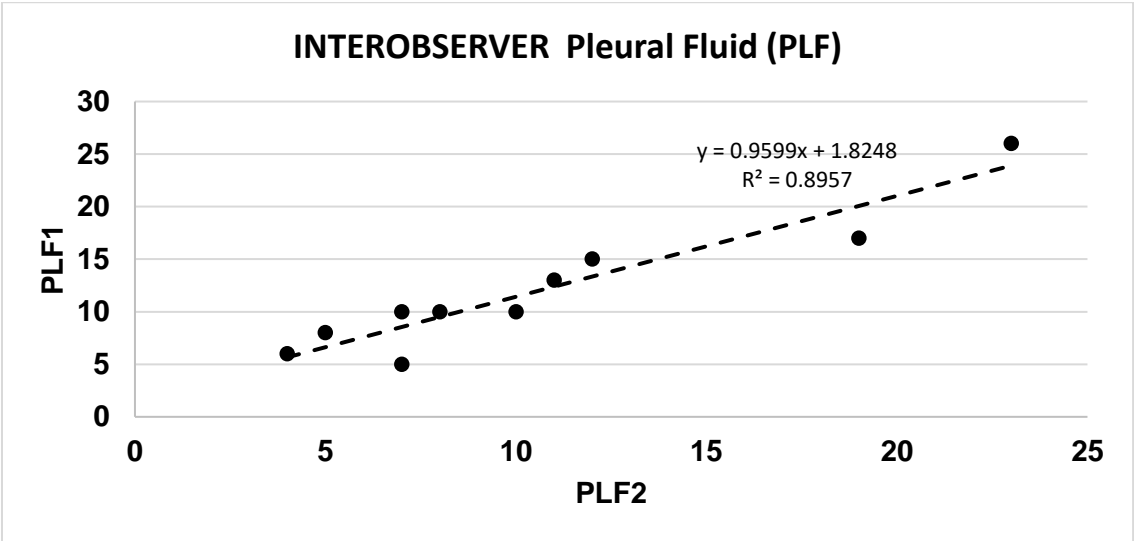
Figure 30: Linear regression analysis graph - interobserver reliability for PLF.

		95%-Confidence Interval	
	Intraclass Correlation	**Lower Bound**	**Upper Bound**
Single Measures	0,946	0,800	0,986
Average measures	0,972	0,889	0,993

Table 13: Intraclass coefficient value and 95% confidence interval for pleural fluid

Our results showed an intraclass correlation coefficient of 0.972 (95% CI 0.889 -0.993), thus indicating an excellent interobserver reliability for the pleural fluids.

b) Interobserver Variability for Pericardial Fluids

Interobserver Variability	PF	
sero	Observer1 (ml)	Observer2 (ml)
4	13	9
5	5	7
6	5	3
12	9	9
16	6	5
17	8	7
22	18	16
23	27	11
25	19	17
28	5	4

Table 14: Interobserver measurement results for PF; Observer 1 – the first observer, Observer 2 – the second observer
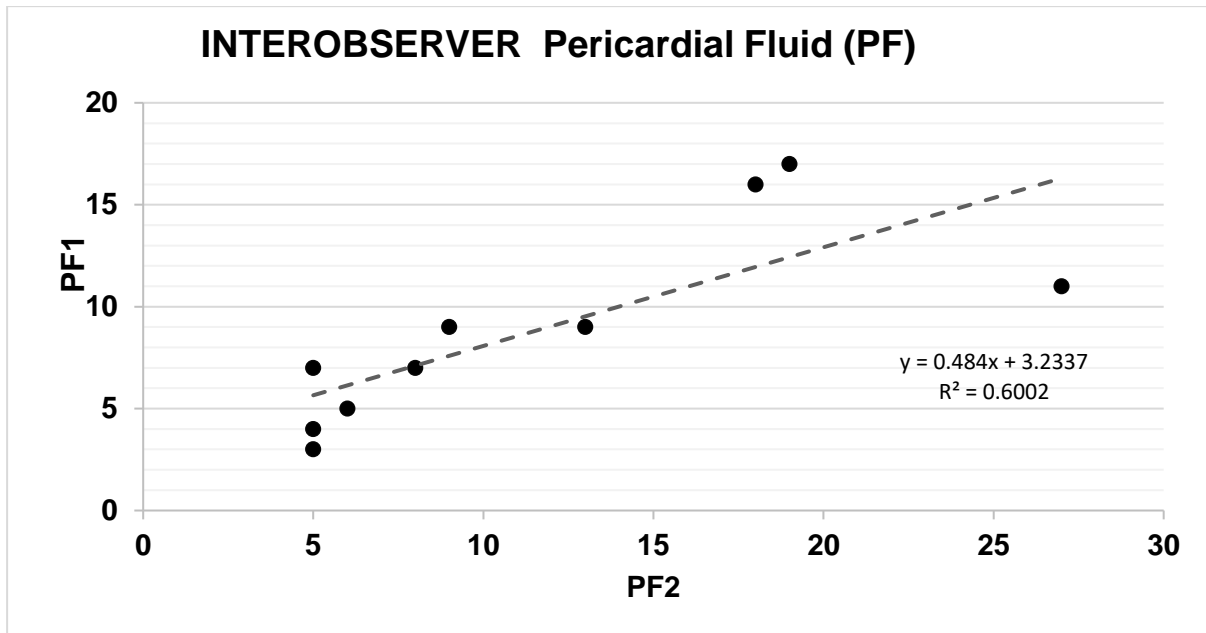
Figure 31: Linear regression analysis graph - interobserver reliability for PF.

	Intraclass Correlation	95%-Confidence Interval	
		Lower Bound	Upper Bound
Single Measures	0,696	0,162	0,915
Average measures	0,821	0,279	0,956

Table 15: Intraclass Intraclass coefficient value and 95% confidence interval for pericardial fluid

The intraclass correlation coefficient was 0.821 (95% CI 0.279-0.956), thus indicating a good interobserver reliability for the pericardial fluids.

9. Discussion

In this study we demonstrated that there were no significant changes in pleural fluid and pericardial fluid over the course of the menstrual cycle. Our results also showed no significant differences in the left ventricular ejection fraction and LV parameters between the luteal and follicular phases. Furthermore, we developed a reproducible method of quantification of PLF and PF with the help of the CVI 42 software and were able to define reference values for PLF and PF in CMR.

9.1 Pericardial Fluid

Our results showed that there were no significant changes in the amount of pericardial fluid (p= 0.742) over the course of the menstrual cycle.

A range from 20–60 mL of pericardial fluid is considered to be physiological (average 15–35 mL) in adult humans (27,28). Some authors have also reported amounts less than 50 ml as normal. The literature available, however, is mostly based on anatomical and pathological studies and does not provide quantitative imaging data (27,28,40,41). Despite growing knowledge about the anatomy, physiology and endocrine function of the pericardium, there is still a scarcity of data describing the prevalence of pericardial fluid in healthy population and a lack of information about changes that occur in healthy premenopausal women during the menstrual cycle.

The presence of PF leads to uncertainty in appropriate evaluation and management of patients, and quite often causes a diagnostic dilemma. In particular, studies carried out in patients with suspected myocardial inflammation and in patients with myocardial infarction have shown contradictory results, thus undermining the diagnostic and prognostic relevance of pericardial effusions in these conditions (11,42–44). Furthermore, while some authors have shown that the volume of pericardial effusion was not related to future clinical events post myocardial infarction, others have claimed that a moderate-to-large pericardial effusion was a marker of poor outcome in patients with STEMI (43,44).

Heindenreich et al. showed in a study of patients with human immunodeficiency virus (HIV) infection that a small pericardial effusion was associated with shortened survival

(6). According to Mitiku et al., the presence of a small asymptomatic pericardial effusion was significantly associated with an increased risk of death (7). A study by Ong et al. showed that the presence of pericardial effusion - when used as an additional diagnostic criterion - could significantly enhance the sensitivity of CMR imaging for detecting myocarditis. They also showed that in patients with recent onset of clinical symptoms, normal left ventricular function and biopsy-proven viral myocarditis, 20% of the patients had PE as the only abnormal finding (11).

Among 9,350 routinely performed echocardiographic examinations, Mitiku et al. detected a small amount of pericardial fluid in 534 (5.7%) patients. Individuals with a request for evaluation of pericardial space and with effusions greater than one centimetre circumference were not included (7). They found a significant association between small, hemodynamically non-relevant pericardial effusion and poorer outcome as well as mortality. But there was no attempt to systematically quantify the amount of existing pericardial fluid. As a consequence, there are no clearly defined normal references and cut-off values.

Conflicting information has been provided by other authors. Lurz et al. demonstrated that pericardial fluid is not specific to myocarditis and therefore its presence does not improve the diagnostic performance of CMR in suspected myocarditis (42). Oflaz et al. found detectable pericardial fluid on echocardiography in 3-4% of their healthy control group in a study dedicated to anorexia (45).

Our data show that even very small amounts of pericardial fluid are detectable by CMR and can be quantified with very good reproducibility. As it is sometimes difficult to distinguish fluid and epicardial fat in the pericardial space on cine imaging, we produced T1 mapping and fat/water separated images as a back up to help with the differentiation between fat and water. But these techniques were rarely required for the differentiation and quantification of the pericardial fluid.

Standard SSFP cine-based quantification is reliable in clinical praxis. In our cohort, the amount of pericardial fluid did not exceed 34 ml – similar upper values are suggested in a study of pericardial fluid collected from 30 patients undergoing elective open heart surgery and suggested in anatomical reports (21,40-41). However, in the above-

mentioned studies, the visibility and detectability of these amounts were not evaluated by CMR. In our study, there were no significant changes in the amount of pericardial fluid during the menstrual cycle and thus no strong correlation to sex hormones.

These insights have not been explored before, but there are similarities with findings regarding the properties of pleural fluid (46). Another noteworthy finding is the correlation of NT-proBNP to the amount of pericardial fluid. Reports describing similar findings in healthy subjects are lacking, and further studies are justified to establish whether the correlation is accidental, or it is preserved and extends to pathological circumstances. Interestingly, one study showed that low serum BNP levels were associated with malignancy in patients with pericardial effusions (47). Limited data has been published regarding this issue in pericardial disease and myocardial inflammation.

Conflicting reports may have a significant impact on patient management. Normal values in CMR would potentially lead to improved diagnostic accuracy and a more consistent interpretation of these findings.

9.2 Pleural Fluid

Our results showed that there were no significant changes in the amount of pleural fluids (p = 0.425) between the two phases of the menstrual cycle.

The physiological PLF ranges from 4 to 18 ml or is approximately 0.1 to 0.3 ml/kg (32). Age related changes in the detection of PLFs was described by Kocijancic et al., with lower frequencies occurring in elders (48). The mean age of the volunteers in our study was 31 (31 $\pm$ 5.4) years, as compared to 53 years in the study performed by Kocijancic et al.

Effusions as small as 5 ml can be detected by ultrasound with high sensitivity (21,25). With appropriate positioning of the patient, even small amounts of PLF can be detected in healthy individuals. A fluid layer as low as 3 mm on average and of up to 5.2 mm thickness in at least one pleural space was detectable in around 32.5 % of the examined healthy subjects and in 22.3 % in repetitive examinations (48). Capper SJ et al. (23) showed that PLF can be detected and quantified using transoesophageal

echocardiography in cardiac surgery patients, with a quantified average detection volume (range) of 125 ml (50– 200 ml) on the left side and 225 ml (150–300 ml) on the right.

Nguyen et al. (24) observed small amounts of pleural fluid in 87% of patients in screening breast MRI. The maximal depth in millimetres was measured at the anterior chest wall and cut-off values of 7 millimetres and 5 millimetres were proposed for the left and right pleural space, respectively. Due to the prone position in the scanner and the lack of information obtainable in whole coverage of the chest, the values obtained are not applicable for CMR, which is usually performed in a supine position. Despite these differences in methodology, the prevalence of pleural fluid is similar. Interestingly, there are other notable observations. First, the pleural fluid layer, if observed, tended to be thicker in women, though there was no sex correlation regarding presence of the fluid itself. Due to the stable amount of fluid over the time period (repetitive examinations), the authors suggested that these findings were probably highly likely to be physiological. Another interesting finding in the same study was that the presence of pleural fluid was less likely with increasing age (24).

The reported prevalence of pleural fluid differs markedly from study to study (97% in our study vs. 32.5% in the study by Kocijancic and 87% in the study by Nguyen). The most important reason is probably the different capability of fluid recognition with the methods utilised. This was also shown by Noppen et al. who used a dedicated pleural lavage technique to quantify the volume. The total amount of pleural fluid in our study was significantly lower in comparison to those reported by Noppen et al. (32). Another technical aspect is the different extent of chest coverage provided due to the specific purposes of each investigation and the subject positioning during the examination. Interestingly, there seems to be a decreasing likelihood of detection with increasing age. It was different in the investigated populations (31 years in our study vs. 43 years in the study by Kocijancic vs. 53 years in the study by Nguyen). Kocijancic et al. evaluated 106 healthy volunteers (44 female) with upright posteroanterior and lateral decubitus chest radiographs as well as decubitus chest ultrasound images. In our study, it was possible to detect and quantify small volumes of PLF - as little as 2 ml.

There are several factors across the previously discussed publications making the proposed cut-off values hardly applicable for cardiovascular MRI. The most important factors to take into account include technical aspects regarding the differentiation from

pericardial fat, the need for systematic volumetric assessment, the different patient position (prone in the case of breast MRI and left or right cubital in the case of sonography or x-ray), the lack of information from whole coverage of the chest, and the non-volumetric (one-dimensional) nature of some of these measurements.

9.3 LV Parameters

We detected no significant changes in LVEF (p =0.637) and LV parameters over the course of the menstrual cycle (LVEDV (p= 0.377) and LVESV (p= 0.625)). The influence on the sex hormones and on the cardiac heart rate has been documented in the literature, whereby the heart rates of patients in the luteal phase is higher than those of patients in the follicular phase (49), but to date there has been no comparison of the changes in cardiac function and LV parameters during the menstrual cycle.

9.4 Intraobserver and Interobserver variability

The techniques which we proposed for the quantification of PLF and PF showed excellent intra-reader reliability for both PLF and PF, as well as excellent inter-reader reliability for PLF and good inter-reader reliability for PF. The main challenge was encountered during the quantification of PF, due to the coexistence of pericardial fat. Fat/water separation techniques and T1 Maps were used in a few cases to help differentiate between fat and PLF.

9.5 Reference Values

Establishing reference values is the key to bringing robust evidence and further insights into different diseases. The cut-off values/normal values proposed in the above discussed publications are not appropriate for usage in CMR. To date there has been no attempt to systematically quantify the amount of pericardial fluid and pleural fluids using CMR. As a consequence, there are no clearly defined normal references and cut-off values.

We demonstrated that our proposed technique of quantification was reproducible with good to excellent reliability. Our results also showed that even small amounts - as little as 2 ml of PLF as well as of PFs - can be detected and quantified by CMR, due to the

extremely high sensitivity of CMR compared to other imaging modalities. The maximum amount of PLF and PF obtained was 26 ml and 34 ml, respectively.

10. Limitations

It was a single-arm, single-center study with a limited sample size.

11. Conclusion

CMR has the unique capability of detecting very small amounts of PLFs and PFs within a fast scan and without the need for any contrast media application. We were able to detect and quantify small amounts - as little as 2 ml of pleural and pericardial fluids in 95% and 93%, respectively - in healthy premenopausal females with the help of CMR. Our results showed that the menstrual cycle does not significantly influence the presence and/or fluctuations of pleural and pericardial fluids. The was also no evidence of a significant change in LV Parameters during the menstrual cycle.

We can therefore conclude that in case of normal LV morphology, and with no signs of Inflammatory conditions, small amounts of pericardial and pleural fluids should not be considered pathological. However, they could be of potential added value for increasing the diagnostic accuracy of CMR in the presence of inflammatory diseases. Furthermore, we demonstrated that it was possible to quantify PLF and PF.

Further software development is desirable, with new postprocessing tools for the quantification of PLF and PF as well as established reference values for PLFs and PFs, and if implemented in clinical routine, would significantly improve diagnostic accuracy.

12. Questionnaire

	Dokumentationsbogen CMR PPF	RB-1
CHARITÉ	AG Kardiale MRT, ECRC, Charité Campus Buch	

Studien ID ⌶_⌶_⌶_⌶_⌶ Allgemeines zu Untersuchung, CMR Protokoll Volunteers
wird vom Studienarzt vergeben

Name: _____   Vorname: _____   D.O.B :   _ _ / _ _ / 2 0 _ _

TT MM JJJJ

Geschlecht: ○ männlich   ○ weiblich

Körpergröße ⌶_⌶_⌶ cm   Gewicht ⌶_⌶_⌶ kg   Blutdruck ⌶_⌶_⌶_⌶ / ⌶_⌶_⌶_⌶ mmHg
systolisch / diastolisch

Datum der Untersuchung 1 : ___ /____/ 20___   Blutentnahme Ja O   Nein O

Datum der Untersuchung 2 : ___ /____/ 20___   Blutentnahme Ja O   Nein O

Straße, Nr.: _____   Tel.: _____

PLZ, Ort: _____   Email: _____

Final 1.0 – 10.02.2016

Studien ID ＿＿＿＿＿＿
wird vom Studienarzt vergeben

CMR Protokoll

Trigger	EKG-Signal: Puls-Signal:	o gut o mäßig o schlecht
Kontrastmittel (falls gegeben)	o ja o nein Art: Menge:	o Gadoteridol o anderes: ＿＿＿＿＿ ＿＿＿＿＿＿ mmol/kg KG
Sequenz	Serien-Nr.	Probleme
TRUFI (ganzen Thorax abdecken)		o keine o ＿＿＿＿＿
cine-SSFP 4CV		o keine o ＿＿＿＿＿
cine-SSFP 3CV		o keine o ＿＿＿＿＿
cine-SSFP 2CV		o keine o ＿＿＿＿＿
cine SSFP RV		o keine o ＿＿＿＿＿
T1 Paket (MOLLI) SAX (7mm/3mm) (Planung wie cine-SSFP)		o keine o ＿＿＿＿＿
Fat-Water 4CV , SAX		o keine o ＿＿＿＿＿
cine-SSFP SAX (7mm/3mm)		o keine o ＿＿＿＿＿

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Studien ID __ __ __ __ __ wird vom Studienarzt vergeben	Anamnese- und Untersuchungsformular zur Untersuchung: „Evaluation mittels kardialer MRT darstellbarer Perikard- und Pleuraergüsse".

Befragungs-/Untersuchungsdatum: _ _ / _ _ / 2 0 _ _

Geburtsdatum _ _ / _ _ _ / 1 9 _ _

---

1. **Leiden Sie an einer Herzerkrankung?** ○ ja ○ nein

   Wenn ja , dann welche _____

2. **Ist eine entzündliche /systemische Erkrankung bei Ihnen bereits bekannt? Wenn ja welche?**

   ○ Rheuma ○Lupus ○Entzündliche Schilddrüsenerkrankung ○Kollagenose ○ Sarkoidose

   ○ Tuberkulose ○ Amyloidose ○ andere-> welche:

3. **Werden Sie derzeit medikamentös behandelt? Wenn ja, welche Medikamente nehmen Sie derzeit ein? / wie lange?**

4. **Ist ein Krebsleiden bei Ihnen bekannt?** ○ ja ○ nein

5. **Symptome und Zeichen**

Luftnot unter Belastung	○ ja, wenn ja: ○ seit : _ _ _ _ (Jahr)	○ nein	○ weiß nicht
bei welcher Anstrengung:	○ bei langsamen Laufen	○ beim Treppensteigern	
	○ nur bei großen Belastungen z.B. Sporttreiben		
Luftnot in Ruhe	○ ja	○ nein	○ weiß nicht
Luftnot nachts, so dass sie aufwachen	○ ja	○ nein	○ weiß nicht
Wasseransammlungen Unterschenkel	○ ja	○ nein	○ weiß nicht
Nächtlicher Husten	○ ja	○ nein	○ weiß nicht
Müdigkeit / Leistungsschwäche	○ ja	○ nein	○ weiß nicht
Nächtliches Wasserlassen ○ ja, wenn ja, wie oft ca. ____ x / Nacht		○ nein	○ weiß nicht

Raucher ○ ja ○ nein (niemals geraucht) ○ Ex-Raucher (≥6 Mon. Clean)→ clean seit wann: _ _ _ _ (Jahr)
→ wenn ‚ja' oder ‚Ex-Raucher': _____ pack years (1 pack year = 20 Zig./d für ein Jahr)

Alkoholkonsum _____ dpw (dpw = drinks per week; 1 drink = 0,25 l Bier oder 0,1 l Wein oder 2 cl Spirituosen ; Bitte durchschnittliche Menge pro Woche angeben.)

Studien ID __|__|__|__|__|__   Anamnese- und Untersuchungsformular zur Untersuchung: „Evaluation mittels
wird vom Studienarzt vergeben   kardialer MRT darstellbarer Perikard- und Pleuraergüsse".

Diese Seite füllen <u>nur</u> weibliche Teilnehmer aus:

Befragungs-/Untersuchungsdatum: _ _ / _ _ / 2 0 _ _
                                  TT MM J J J J

11   Wann war der erster Tag Ihrer letzten Regelblutung? _ _ / _ _ / 2 0 _ _
                                                          TT MM J J J J

12   Kommt Ihre Regelblutung regelmäßig?   ○ ja   ○ nein

13   Wenden Sie derzeit Empfängnisverhütung an?

      ○ hormonhaltige Pille, welche:

      ○ Spirale -> ○ hormonhaltig , ○ nicht hormonhaltig

      ○ andere, welche:

14   Stehen Sie aus irgendwelchen Gründen unter hormoneller Therapie?

      ○ nein   ○ ja , wenn ja welche Präparate werden verabreicht:

15   Stilen Sie gerade?   ○ ja   ○ nein

16.   Treiben Sie Sport regelmäßig? ○ ja   ○ nein

17   Könnten Sie derzeit schwanger sein?   ○ ja   ○ nein

18.   Wie lange dauert Ihr Menstruationszyklus (siehe ★) _____ Tage.

       An welchem Tag findet (ungefähr) ihr Eisprung statt? Am ____ Tag.   ○ weiß nicht

19.   Kreuzen Sie auf dem Schema die Tage an, an welchen Sie zyklusbedingte
Gewichtsschwankungen, Wassereinlagerungen und Völlegefühl merken (sehe auch ★★):

○ ○
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39

Tag1

○ ich leide nicht unter solchen Beschwerden

★ Der erste Tag des Menstruationszyklus ist immer der erste Tag der Regelblutung, hier als Tag 1 markiert.
Setzen Sie bitte bei Frage 17 **zwei** Kreuze auf dem oben gezeigten Schema, einen für **die Dauer des
Zyklus** (nicht die Dauer der Regelblutung!) und einen für ungefähren **Zeitpunkt des Eisprungs.**

★★ Bei Frage 18 können sie **mehrere Tage ankreuzen**, beachten Sie dabei die in der Frage 17 angegebene
Zyklusdauer (wenn Ihr Zyklus z.B. 26 Tage dauert können Sie in Frage 18 nicht höhere Nummer ankreuzen).

Studien ID _|_|_|_|_|_
wird vom Studienarzt vergeben

Datum der Blutentnahme _ _ / _ _ / 20 _ _
$\underset{T\ T}{}$ $\underset{M\ M}{}$ $\underset{J\ J\ J\ J}{}$

Proben ID _|_|_|_|_|_|_|_|_

Keine Blutentname O

Ggf. Labor Aufkleber

Aktuelle Labordiagnostik:

Blutbild:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
Hämoglobin	_____	O mmol/l	O g/dl	O _____
Leukozyten	_____	O 10^9/l = 10^6/ml		O _____
Hämatokrit	_____	O %		O _____
Thrombozyten	_____	O 10^9/l		O _____
Kreatinin (Serum)	_____	O µmol/l=nmol/ml	O mg/dl	O _____
GFR (Serum) *	_____	O ml/min/1,73 m^2		

Inflammation:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
hs CRP	_____	O µmol/l	O U/l	O _____

Kardiale Marker:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
NTproBNP	_____	O µmol/l	O U/l	O _____
hs Troponin	_____	O mmol/l	O mg/dl	O _____

Hormone einfach:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
TSH	_____	O mmol/l	O mg/dl	O _____
Estradiol (E2)	_____	O mmol/l	O mg/dl	O _____
Progesteron	_____	O mmol/l	O mg/dl	O _____
FSH	_____	O mmol/l	O mg/dl	O _____

CHARITÉ	Dokumentationsbogen CMR PPF	RB-6
	AG Kardiale MRT, ECRC, Charité Campus Buch	CMR Q

Studien ID ⎵⎵⎵⎵⎵
wird vom Studienarzt vergeben

Datum der Untersuchung __/__/20__
                        T T M M J J J J

CMR Bewertung /Quantifizierung der PEF und PLF:

Perikardiale Flüssigkeit   ○ ja   ○ nein   ○ unbekannt

Falls Quantifizierung mögich   ○ Menge ⎵⎵⎵⎵ ml

Pleurale Flüssigkeit   ○ ja   ○ nein   ○ unbekannt

Falls Quantifizierung mögich   Menge: rechts ⎵⎵⎵⎵ ml   links ⎵⎵⎵⎵ ml

CMR Bewertung der PEF und PLF:

Perikardiale Flüssigkeit –Hinweise auf entzündliche Genese?

○ ja, welche: ○ nein   ○ unbekannt

Pleurale Flüssigkeit – Hinweise auf entzündliche Genese?

○ ja, welche: ○ nein   ○ unbekannt

CMR Quantifizierung der LV und RV Funktion:

RVEF	⎵⎵⎵ %		LVEF	⎵⎵⎵ %	EDV-Index	⎵⎵⎵
RVSV	⎵⎵⎵ ml		LVSV	⎵⎵⎵ ml	LVM-Index	⎵⎵⎵
RVEDV	⎵⎵⎵ ml		LVEDV	⎵⎵⎵ ml		
RVESV	⎵⎵⎵ ml		LVESV	⎵⎵⎵ ml		

*Abkürzungen:
LVEF   linksventrikuläre Ejektionsfraktion
LVSV   linksventrikulärer Schlagvolumen
LVEDV   linksventrikulärer enddiastolischer Volumen
LVESVI   linksventrikulärer endssystolischer Volumen

RVEF   rechtsventrikuläre Ejektionsfraktion
RVSV   rechtsventrikulärer Schlagvolumen
RVEDV   rechtsventrikulärer enddiastolischer Volumen
RVESV   rechtsventrikulärer endssystolischer Volumen

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Studien ID ⌐⌐⌐⌐⌐
wird vom Studienarzt vergeben   **Allgemeines zu Untersuchung, CMR Protokoll FU Volunteers**

Trigger	EKG-Signal:	systolisch / diastolisch
		o gut o mäßig o schlecht
	Puls-Signal:	

Kontrastmittel (falls gegeben)	o ja o nein Art: Menge:	o Gadoteridol o anderes: _____ _____ mmol/kg KG
Sequenz	Serien-Nr.	Probleme
TRUFI (ganzen Thorax abdecken)		o keine o _____
cine-SSFP 4CV		o keine o _____
cine-SSFP 3CV		o keine o _____
cine-SSFP 2CV		o keine o _____
cine SSFP RV		o keine o _____
T1 Paket (MOLLI) SAX (7mm/3mm) (Planung wie cine-SSFP)		o keine o _____
Fat-Water 4CV , SAX		o keine o _____
cine-SSFP SAX (7mm/3mm)		o keine o _____

Studien ID ⌴⌴⌴⌴⌴
wird vom Studienarzt vergeben

Datum der Blutentnahme __/__/20__
T T M M J J J J

Proben ID ⌴⌴⌴⌴⌴⌴⌴⌴

Keine Blutentname ○

Ggf. Labor Aufkleber

Aktuelle Labordiagnostik:

Blutbild:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
Hämoglobin	_____	○ mmol/l	○ g/dl	○ _____
Leukozyten	_____	○ 10^9/l = 10^6/ml		○ _____
Hämatokrit	_____	○ %		○ _____
Thrombozyten	_____	○ 10^9/l		○ _____
Kreatinin (Serum)	_____	○ µmol/l=nmol/ml	○ mg/dl	○ _____
GFR (Serum) *	_____	○ ml/min/1,73 m²		

Inflammation:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
hs CRP	_____	○ µmol/l	○ U/l	○ _____

Kardiale Marker:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
NTproBNP	_____	○ µmol/l	○ U/l	○ _____
hs Troponin	_____	○ mmol/l	○ mg/dl	○ _____

Hormone einfach:

	Messwert	Einheit (Auswahl aus Vorgaben)		andere Einheit
TSH	_____	○ mmol/l	○ mg/dl	○ _____
Estradiol (E2)	_____	○ mmol/l	○ mg/dl	○ _____
Progesteron	_____	○ mmol/l	○ mg/dl	○ _____
FSH	_____	○ mmol/l	○ mg/dl	○ _____

Studien ID ⌐⌐⌐⌐⌐
wird vom Studienarzt vergeben

Datum der Untersuchung __ / __ / 2 0 __
_{T T   M M   J J J J}

CMR Bewertung /Quantifizierung der PEF und PLF:

Perikardiale Flüssigkeit　　　　　○ ja　　○ nein　　○ unbekannt

Falls Quantifizierung mögich　○ Menge ⌐⌐⌐⌐ ml

Pleurale Flüssigkeit　　　　　　○ ja　　○ nein　　○ unbekannt

Falls Quantifizierung mögich　Menge: rechts ⌐⌐⌐⌐ ml　　　links ⌐⌐⌐⌐ ml

---

CMR Bewertung der PEF und PLF:

Perikardiale Flüssigkeit –Hinweise auf entzündliche Genese?

○ ja, welche:　　　　　　　　　　　　　　　　○ nein　　　　○ unbekannt

Pleurale Flüssigkeit – Hinweise auf entzündliche Genese?

○ ja, welche:　　　　　　　　　　　　　　　　○ nein　　　　○ unbekannt

CMR Quantifizierung der LV und RV Funktion:

RVEF	⌐⌐⌐ %	**LVEF**	⌐⌐⌐ %	**EDV-Index** ⌐⌐⌐
RVSV	⌐⌐⌐ ml	**LVSV**	⌐⌐⌐ ml	**LVM-Index** ⌐⌐⌐
RVEDV	⌐⌐⌐ ml	**LVEDV**	⌐⌐⌐ ml	
RVESV	⌐⌐⌐ ml	**LVESV**	⌐⌐⌐ ml	

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*Abkürzungen:
LVEF　　　　linksventrikuläre Ejektionsfraktion
LVSV　　　　linksventrikulärer Schlagvolumen
LVEDV　　　Linksventrikulärer enddiastolischer Volumen
LVESVI　　　inksventrikulärer endssystolischer Volumen

RVEF　　　　rechtsventrikuläre Ejektionsfraktion
RVSV　　　　rechtsventrikulärer Schlagvolumen
RVEDV　　　rechtsventrikulärer enddiastolischer Volumen
RVESV　　　rechtsventrikulärer endssystolischer Volumen

Studien ID ⌐|⌐|⌐|⌐|⌐|
wird vom Studienarzt vergeben

Datum der Befragung __ __ / __ __ / 2 0 __ __
         T T   M M   J J J J

Follow-Up durchgeführt?   ○ ja   ○ nein   ○ unbekannt

Wenn nein Grund: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Tod?   ○ ja   ○ nein

Sind seit der letzten Befragung neue Erkrankungen bei Ihnen bekannt?

Lungenerkrankung: ○ ja   ○ nein/unbekannt

    ○ wenn ja welche:

Entzündliche /systemische Erkrankung *   ○ ja   ○ nein   ○ unbekannt
    ○ wenn ja welche:

        ○ Rheuma   ○ Lupus   ○ Kollagenose   ○ Entzündliche Schilddrüsenerkrankung

        ○ Sarkoidose   ○ Amyloidose   ○ Tuberkulose   ○ andere, welche:

Malignom?   ○ ja   ○ nein   ○ unbekannt

Neue kardiale Diagnosen (Anamnese und Vorbefunde)

Koronare Herzkrankheit   ○ ja   ○ nein   ○ unbekannt

Zustand nach Myokardinfarkt   ○ ja   ○ nein   ○ unbekannt

Sind Sie seit der letzten Untersuchung einmal plötzlich bewusstlos geworden?
        ○ nein
        ○ ja
      ○ Fast bewusstlos („Schwächeanfall" ohne komplette Bewusstlosigkeit)

Herzklappenerkrankung   ○ ja   ○ nein   ○ unbekannt

Angeborener Herzfehler   ○ ja   ○ nein   ○ unbekannt

Erworbener Herzfehler   ○ ja   ○ nein   ○ unbekannt

   wenn ja, welcher: _____

Vorhofflimmern   ○ ja   ○ nein   ○ unbekannt

   wenn ja: ○ paroxysmal   ○ persistierend   ○ permanent

Haben Sie manchmal das Gefühl, Ihr Herz stolpert häufig?
        ○ nein
        ○ selten (mehrfach/Woche)
        ○ gelegentlich (mehrfach/Tag)
        ○ häufig (mehrfach/Stunde)

Herzschwäche (Herzinsuffizienz) ?   ○ ja   ○ nein/unbekannt

        wenn ja: welche Ursache wird vermutet?

Ischämisch ?   ○ ja   ○ nein   ○ unbekannt

Entzündlich?   ○ ja   ○ nein   ○ unbekannt

Andere?   ○ ja, welche:

Kardiomyopathie (primäre Herzmuskelerkrankung)   ○ ja   ○ nein   ○ unbekannt

   wenn ja: Form   ○ dilatative   ○ hypertrophe
                    ○ restriktive   ○ ARVC (arrhythmogene rechtsventr. CM)
                    ○ andere   ○ unbekannt

        familiär   ○ ja   ○ nein   ○ unbekannt

        entzündlich   ○ ja   ○ nein   ○ unbekannt

        toxisch   ○ ja   ○ nein   ○ unbekannt

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Studien ID _|_|_|_|_|
wird vom Studienarzt vergeben

Alkohol und Raucheranamnese

Raucher
- O ja
- O Ex-Raucher (≥6 Mon. clean) → clean seit wann: _ _ _ _ (Jahr)
- O nein (niemals geraucht)

→ wenn 'ja' oder 'Ex-Raucher': _____ pack years (1 pack year = 20 Zig./d für ein Jahr)

Alkoholkonsum _____ dpw   (dpw = drinks per week; 1 drink = 0,25 l Bier oder 0,1 l Wein oder 2 cl Spirituosen ;
Bitte durchschnittliche Menge pro Woche angeben.)

Kardiovaskuläre Interventionen seit Studieneinschluss (Anamnese und Vorbefunde):

Hospitalisierung: O ja   O nein   O unbekannt   RV Schrittmacher (VVI, DDD) O ja   O nein   O unbekannt

Wenn ja bitte die Umstände der Hospitalisierung kurz beschreiben:

Herzklappen-OP   O ja   O nein   O unbekannt

Hospitalisierung wegen: O Herzinsuffizienz O Myokarditis O KHK

O Pulmonal O andere, welche

Koronare Revaskularisation   O ja   O nein   O unbekannt   BV Schrittmacher   O ja   O nein   O unbekannt
(PTCA / Stent / andere PC   (Resynchronisation)

Periphere Revaskularisation   O ja   O nein   O unbekannt   Implantierter Defibrillator   O ja   O nein   O unbekannt
(PTA Nierenarterie, Carotiden,
Extremitätengefäße, Aortenstent)

Bypass-OP   O ja   O nein   O unbekannt   Assist-Devices   O ja   O nein   O unbekannt
→ wenn 'ja, wann   ___ / ___
                     M M / J J J J

Herztransplantation   O ja   O nein   O unbekannt

Sonstige Gefäß-Operation   O ja   O nein   O unbekannt
(Thrombendarterektomie Carotiden, Bypass-OP bei
PAVK, Resektion eines Aortenaneurysmas, u.a.)

Reanimation / Defibrillation   O ja   O nein   O unbekannt   andere: _____

Aktuelle Medikation (regelmäßige Einnahme):   O ja   O nein
wenn ja, welche:

nur bei Frauen: orale Kontrazeptiva   O ja   O nein
postmenopausale Hormone   O ja   O nein

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14. Eidesstattliche Versicherung

„Ich, Yashraj Bhoyroo, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:‚ The **prevalence of pleural and pericardial fluids in healthy premenopausal women - Detection and quantification by cardiovascular magnetic resonance'** selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

[Für den Fall, dass Sie die Forschung für Ihre Promotion ganz oder teilweise in Gruppenarbeit durchgeführt haben:] Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit der Erstbetreuerin, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte. Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe. Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum   Unterschrift des Doktoranden

15. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

16. Acknowledgement (Danksagung)