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DISSERTATION

Detektion subklinischer Myokardschäden bei erhaltener
Pumpfunktion mittels kardiovaskulärer
Magnetresonanztomographie
*Detection of subclinical myocardial damage despite a preserved
ejection fraction using cardiovascular magnetic resonance*

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Inhaltsverzeichnis

Abkürzungsverzeichnis	4
Abbildungsverzeichnis	6
Tabellenverzeichnis	7
Abstract (Deutsch)	8
Abstract (English).....	10
1. Einleitung	12
1.1. Die kardiovaskuläre Magnetresonanztomographie (CMR)	12
1.2. Kardiale Beteiligung bei Muskeldystrophien	12
1.2.1. Myotone Dystrophie Typ 2 (DM2)	13
1.2.2. Fazioskapulohumerale Muskeldystrophie Typ 1 (FSHD1).....	14
1.2.3. CMR bei Muskeldystrophien	15
1.3. Myokardiale Deformationsanalyse mittels CMR.....	15
1.4. Kardiale Spätfolgen nach Präeklampsie	16
1.5. Zielsetzung	16
2. Methoden.....	17
2.1. Detektion progressiver Myokardschäden mittels CMR bei Muskeldystrophien	17
2.1.1. Studiendesign	17
2.1.2. Akquise und Auswertung der Bilddaten	17
2.1.3. Statistische Datenanalyse.....	18
2.2. Quantifizierung der myokardialen Deformation mittels Feature Tracking	19
2.2.1. Studiendesign	19
2.2.2. Analyse der Bilddaten	19
2.3. Evaluation kardialer Veränderungen nach Präeklampsie mittels CMR... 	20
2.3.1. Studiendesign	20
2.3.2. Analyse der Bilddaten	20
3. Ergebnisse	21
3.1. Detektion progressiver Myokardschäden mittels CMR bei Muskeldystrophien	21

3.1.1. Funktionelle und morphologische Parameter.....	21
3.1.2. Myokardiale Gewebedifferenzierung.....	21
3.1.3. Myokardiale Deformation	23
3.1.4. Assoziation der myokardialen Gewebeschäden zu Herzrhythmusstörungen	23
3.2. Quantifizierung der myokardialen Deformation mittels Feature Tracking	24
3.2.1. Unterschiede zwischen verschiedenen Auswertemethoden.....	24
3.2.2. Normwertetablierung in Abhängigkeit von Feldstärke und Geschlecht....	25
3.3. Evaluation kardialer Veränderungen nach Präeklampsie mittels CMR... 27	
3.3.1. Funktionelle und morphologische Parameter.....	27
3.3.2. Myokardiale Gewebedifferenzierung.....	27
3.3.3. Myokardiale Deformation	27
4. Diskussion	28
4.1. Progressive Myokardschäden bei Muskeldystrophien.....	28
4.2. Klinische Anwendbarkeit und Nutzen der CMR.....	29
4.3. Zusammenfassung	32
4.4. Limitationen und Ausblick.....	32
5. Literaturverzeichnis	34
Eidesstattliche Versicherung	42
Anteilerklärung an den erfolgten Publikationen.....	44
Auszug aus der Journal Summary List.....	46
Druckexemplare der Publikationen	49
Lebenslauf.....	79
Komplette Publikationsliste	81
Danksagung	83

Abkürzungsverzeichnis

2CV	2-Kammerblick
3CV	3-Kammerblick
4CV	4-Kammerblick
AV-Block	Atrioventrikulärer Block
BMD	Muskeldystrophie Typ Becker
BMI	Body Mass Index
BSA	Body Surface Area
CMR	Kardiovaskuläre Magnetresonanztomographie
DCM	Dilatative Kardiomyopathie
DENSE	Displacement Encoding
DM1	Myotone Dystrophie Typ 1
DM2	Myotone Dystrophie Typ 2
DMD	Muskeldystrophie
ECV	Extrazellulärvolumen
EDMD	Emery-Dreifuss-Muskeldystrophie
EDV	Enddiastolisches Volumen
EDVI	Enddiastolischer Volumenindex
EF	Ejektionsfraktion
EKG	Elektrokardiogramm
FSHD	Fazioskapulohumerale Muskeldystrophie
FSHD1	Fazioskapulohumerale Muskeldystrophie Typ 1
LA	Linker Vorhof
LAEDV	Linksatriales enddiastolisches Volumen
LAEDVI	Linksatrialer enddiastolischer Volumenindex
LAEF	Linksatriale Ejektionsfraktion
LASV	Linksatriales Schlagvolumen
LASVI	Linksatrialer Schlagvolumenindex
LGE	Late Gadolinium Enhancement
LGMD	Gliedergürtelmuskeldystrophie
LV	Linker Ventrikel
LVEDV	Linksventrikuläres enddiastolisches Volumen

LVEDVI	Linksventrikulärer enddiastolischer Volumenindex
LVEF	Linksventrikuläre Ejektionsfraktion
LVM	Linksventrikuläre Masse
LVMi	Linksventrikulärer Masseindex
LV-RI	Linksventrikulärer Remodeling Index
LVSv	Linksventrikuläres Schlagvolumen
LVSvi	Linksventrikulärer Schlagvolumenindex
MOLLI	Modified Look-Locker Inversion Recovery
nsVT	nicht anhaltende ventrikuläre Tachykardie
RA	Rechter Vorhof
RV	Rechter Ventrikel
RVEDV	Rechtsventrikuläres enddiastolisches Volumen
RVEDVI	Rechtsventrikulärer enddiastolischer Volumenindex
RVEF	Rechtsventrikuläre Ejektionsfraktion
RVSv	Rechtsventrikuläres Schlagvolumen
RVSvi	Rechtsventrikulärer Schlagvolumenindex
SENC	Strain Encoding
SSFP	Steady-State-Free-Precession
SV	Schlagvolumen
SVI	Schlagvolumenindex
SVT	Supraventrikuläre Tachykardie(n)

Abbildungsverzeichnis

Abbildung 1. Scan-Protokoll	18
Abbildung 2. Visuelle Überprüfung der Tracking-Qualität	20
Abbildung 3. DM2-Patient mit progredienter intramyokardialer Fibrose und Reizleitungsstörungen	23
Abbildung 4. 34-jähriger asymptomatischer FSHD1-Patient mit einer kurzen Episode einer nicht-anhaltenden ventrikulären Tachykardie im Holter-EKG und Nachweis von LGE	24
Abbildung 5. 2D-Strainanalyse vom linken Ventrikel mittels CVI42 und TomTec	25

Tabellenverzeichnis

Tabelle 1: Vergleich der funktionellen und morphologischen Parameter zwischen Baseline und Follow-up.	22
Tabelle 2: Globaler longitudinaler und radialer Strain in 3 langen Achsen	26
Tabelle 3: Globaler circumferentieller und radialer Strain in 3 kurzen Achsen.	26
Tabelle 4: Globaler circumferentieller und radialer Strain im Kurzachsenpaket.	26

Abstract (Deutsch)

Die kardiovaskuläre Magnetresonanztomographie (CMR) ermöglicht eine präzise Darstellung des Herzens und ist aufgrund der umfangreichen diagnostischen Möglichkeiten nicht mehr wegzudenken. Mithilfe von innovativen Methoden wie der myokardialen Gewebedifferenzierung und der Deformationsanalyse ist es gelungen subklinische Gewebeschäden und Funktionseinschränkungen auch bei erhaltener Ejektionsfraktion (EF) zu identifizieren.

Ziel dieser Arbeit ist es, die Möglichkeiten der CMR zur Identifikation subklinischer Myokardschäden bei erhaltener Pumpfunktion in diversen Krankheitsbildern anzuwenden und den potenziellen klinischen Nutzen zu evaluieren. Dabei liegt der Fokus auf seltene Erkrankungen wie Muskeldystrophien.

In der ersten Studie, einer Follow-up-Studie, wurden 27 Patienten mit myotoner Dystrophie Typ 2 (DM2) und 41 Patienten mit fazioskapulohumeraler Dystrophie Typ 1 (FSHD1) aus publizierten Ausgangsstudien mittels CMR hinsichtlich einer Progression der myokardialen Gewebeschäden und der Entwicklung von Herzrhythmusstörungen untersucht.

In der zweiten Studie wurde die myokardiale Deformation mittels Feature Tracking bei 67 gesunden Probanden analysiert, um Normwerte für den Einsatz in der klinischen Routine zu erheben. Hierbei wurden Einflussfaktoren wie Analysesoftware und Auswertelgorithmen untersucht, um potentielle Fehlerquellen zu identifizieren.

In einer weiteren, dritten Studie wurden 22 Frauen nach einer Präeklampsie hinsichtlich einer kardialen Beteiligung mittels CMR untersucht und mit 22 gesunden Probandinnen verglichen. Hierbei wurden sowohl morphologische und funktionelle Parameter als auch die myokardiale Deformationsanalyse berücksichtigt.

In der Follow-up-Studie konnte mittels CMR in DM2 und FSHD1 bereits innerhalb weniger Jahre eine Zunahme der myokardialen Gewebeschäden und Herzrhythmusstörungen nachgewiesen werden. Bei Patienten mit fokaler Fibrose und/oder Fettinfiltration wurden häufiger Herzrhythmusstörungen registriert. In beiden Patientengruppen fand sich zudem eine Reduktion der longitudinalen Strainwerte.

Um Strainwerte interpretieren zu können, wurden in der zweiten Studie Normwerte für die myokardiale Deformationsanalyse mittels Feature Tracking erhoben. Hierbei ergaben

sich signifikante Unterschiede zwischen unterschiedlichen Softwareherstellern. Ebenfalls wurden die Strainwerte durch die Anzahl der verwendeten Schichten beeinflusst.

In der dritten Studie fand sich, ähnlich wie bei DM2 und FSHD1, auch bei Patientinnen nach Präeklampsie eine Reduktion der Strainwerte im Vergleich zur Kontrollgruppe. Hierbei waren jedoch die circumferentiellen und radialen Strainwerte betroffen. Weiterhin zeigten sich Hinweise für ein atriales Remodeling.

Zusammenfassend konnte das Potenzial der CMR, subklinische Myokardschäden bei erhaltener Pumpfunktion zu detektieren, verdeutlicht werden. Für die Anwendung in der klinischen Routine von Feature Tracking sind standardisierte Bedingungen erforderlich.

Abstract (English)

Cardiovascular magnetic resonance imaging (CMR) allows precise visualization of the heart and has become indispensable due to its extensive diagnostic capabilities. With the help of innovative methods such as myocardial tissue differentiation and deformation analysis, it is possible to identify subclinical tissue damage and functional impairment despite a preserved ejection fraction (EF).

The aim of this work is to exploit the possibilities of CMR to identify subclinical myocardial damage in the presence of preserved pump function in various diseases and to evaluate its clinical utility. The focus was set on rare diseases such as muscular dystrophies.

In the first study, a follow-up study, 27 patients with myotonic dystrophy type 2 (DM2) and 41 patients with facioscapulohumeral dystrophy type 1 (FSHD1) from published baseline studies were evaluated by CMR for progression of myocardial tissue damage and development of arrhythmias.

In the second study, myocardial deformation was analyzed by feature tracking in 67 healthy volunteers to establish normal values for the use in routine clinical practice. Here, influencing factors such as analysis software and segmentation procedure were investigated to identify potential sources of error.

In a further, third study, 22 women after preeclampsia were evaluated for cardiac involvement and compared with 22 healthy subjects. Here, morphologic and functional parameters as well as myocardial deformation analysis were considered.

In the follow-up study, an increase of myocardial tissue damage and cardiac arrhythmias was demonstrated by CMR in DM2 and FSHD1 within only a few years. In patients with focal fibrosis and/or fatty infiltration, arrhythmias were registered more frequently. A reduction of longitudinal strain was found in both patient groups.

To interpret strain values, normal values were obtained in the second study for myocardial deformation analysis by feature tracking. Significant differences were revealed between different software manufacturers. Also, strain values were influenced by the number of slices used.

In the third study, similar to DM2 and FSHD1, a reduction of strain values was found in patients after preeclampsia compared to the control group. Here, however,

circumferential and radial strain were affected. In addition, there was evidence for atrial remodeling.

In conclusion, the potential of CMR to detect subclinical myocardial damage despite preserved ejection function was elucidated. Standardized conditions are required for the application of feature tracking in routine clinical practice.

1. Einleitung

1.1. Die kardiovaskuläre Magnetresonanztomographie (CMR)

Die CMR hat als nicht-invasives, röntgenstrahlenfreies Bildgebungsverfahren in den letzten Jahren zunehmend an Bedeutung gewonnen. Sie gilt mittlerweile als Goldstandard zur kardialen Funktionsanalyse und wird bei zahlreichen kardiovaskulären Erkrankungen eingesetzt (1, 2). Da die CMR eine sehr genaue Quantifizierung der Größe und Funktion aller vier Herzkammern ermöglicht, ist sie besonders wertvoll in der Diagnostik früher morphologischer und funktioneller Veränderungen des Herzens.

Mit Hilfe von Late Gadolinium Enhancement (LGE) und parametrischen Mapping-Methoden ist es gelungen, myokardiales Gewebe zu charakterisieren. Durch Kontrastmittelanreicherung in Bereichen mit einem vergrößerten Extrazellularraum, und die dadurch verlängerte T1-Relaxationszeit, kommen narbige und fibrotische Gewebeveränderungen als sogenanntes LGE hyperintens zur Darstellung. Ihre Verteilungsmuster und Lokalisation können zudem die differentialdiagnostische Zuordnung zu einer zugrundeliegenden Erkrankung erleichtern (2, 3). Diffuse Prozesse können mit Hilfe von T1-Mapping (z.B. Fibrose) bzw. T2-Mapping (Ödem) erfasst werden. Bei diesen Methoden werden durch Akquisition multipler Bilder während der Longitudinal- bzw. Transversalrelaxation „parametrische Maps“ generiert, in der die T1- bzw. T2-Relaxationszeiten pixelweise dargestellt werden (2). Darüber hinaus kann auch das Extrazellularvolumen (ECV) quantifiziert werden. Die Darstellung von regionalen Fettinfiltrationen ist durch spezielle Fett-Wasser-separierte-Aufnahmen möglich (4).

Aufgrund dieser umfangreichen diagnostischen Möglichkeiten spielt die CMR nicht nur bei kardiovaskulären Erkrankungen, sondern auch bei Systemerkrankungen wie Amyloidose und Sarkoidose, eine wichtige Rolle (2). Auch bei Patienten mit Muskeldystrophien konnten diese Techniken zum Nachweis einer kardialen Beteiligung erfolgreich eingesetzt werden (5, 6).

1.2. Kardiale Beteiligung bei Muskeldystrophien

Unter Muskeldystrophien werden eine Vielzahl genetisch bedingter Erkrankungen der Skelettmuskulatur subsumiert, die vordergründig durch einen progressiven Muskelabbau mit Muskelschwäche gekennzeichnet sind. Es ist bekannt, dass diese Erkrankungen auch mit einer relevanten kardialen Beteiligung einhergehen können.

Die einzelnen Formen der Muskeldystrophien unterscheiden sich deutlich hinsichtlich des Erkrankungsalters, des klinischen Erscheinungsbildes und des Krankheitsverlaufes (7). Die bekannteste Form ist die Muskeldystrophie Typ Duchenne (DMD), die sich bereits im frühen Kindesalter manifestiert und einen rasch progredienten Verlauf aufweist. Zu den häufigsten hereditären Muskelerkrankungen im Erwachsenenalter zählen die myotonen Dystrophien, welche zusätzlich durch eine myotone Symptomatik gekennzeichnet sind, sowie die Fazioskapulohumerale Muskeldystrophie (FSHD). Eine kurative Behandlung der Muskeldystrophien existiert bislang nicht. Im Fokus der Behandlung aller Muskeldystrophien stehen symptomorientierte Maßnahmen, wie die medikamentöse Symptomlinderung, eine lebenslange Physiotherapie sowie die Behandlung von Begleiterkrankungen, wie beispielsweise einer Herzbeteiligung (8). Letzteres ist insbesondere dahingehend relevant, da die meist sehr jungen Patienten eine schwere Herzinsuffizienz oder lebensbedrohliche Herzrhythmusstörungen entwickeln können (9).

Der Herzmuskel ist bei den verschiedenen Formen der Muskeldystrophien unterschiedlich häufig mitbetroffen (8). Bei der DMD entwickeln nahezu alle Patienten bis zum 18. Lebensjahr eine Herzbeteiligung (10). Sie stellt in dieser Patientengruppe neben dem respiratorischen Versagen die häufigste Todesursache dar (9). Auch bei der Muskeldystrophie Typ Becker (BMD), der DM1, der Emery-Dreifuss-Muskeldystrophie (EDMD) und Unterformen der Gliedergürtelmuskeldystrophie (LGMD) ist eine kardiale Beteiligung häufig vorzufinden (60-90%) (8).

Histologisch finden sich die binde- und fettgewebigen Umbauvorgänge nicht nur in der Skelettmuskulatur, sondern auch im Bereich des myokardialen Reizbildungs- und Reizleitungssystems (11), weshalb angenommen wird, dass diese Gewebsveränderungen im Herzmuskel Überleitungsstörungen und Arrhythmien verursachen und damit einerseits das Risiko für einen plötzlichen Herztod erhöhen und andererseits zur Entwicklung einer dilatativen Kardiomyopathie (DCM) mit progredienter Herzinsuffizienz beitragen (11-13).

1.2.1. Myotone Dystrophie Typ 2 (DM2)

Die myotone Dystrophie Typ 2 (DM2) ist eine autosomal-dominant vererbte Multisystemerkrankung, die auf eine instabile Tetranukleotid-Repeat-Expansion (CCTG-Repeats) im Zinkfinger-9-Gen zurückzuführen ist (14) und mit einer Prävalenz von ca. 1:1800 auftritt (15). Typischerweise manifestiert sich die Erkrankung im Erwachsenenalter mit einem Häufigkeitsgipfel zwischen dem 30. und 50. Lebensjahr (16) und ist charakterisiert durch

proximal-betonte Paresen insbesondere der Kopfbeuger- und Hüftmuskulatur sowie die häufig im Vordergrund stehenden Myalgien. Die myotone Symptomatik ist im Vergleich zur myotonen Dystrophie Typ 1 (DM1) geringer ausgeprägt. Neben den muskulären Beschwerden zeigen sich gehäuft auch extramuskuläre Symptome wie ein präseniler Katarakt, Diabetes mellitus oder Hypogonadismus (16). Die Lebenserwartung ist in der Regel nicht eingeschränkt, jedoch können Myalgien die Lebensqualität deutlich beeinflussen (17, 18).

Bei DM2 sind ca. 20-40 % von einer kardialen Beteiligung betroffen (16, 19). Häufig zeigen sich Reizleitungsstörungen (beispielsweise atrioventrikuläre Blockbilder (AV-Block), Rechtsschenkelblock und Linksschenkelblock) sowie supraventrikuläre und ventrikuläre Arrhythmien (19, 20). In einer Studie von Peric et al. (21) entwickelten 44 % der Patienten eine diastolische Dysfunktion und 18 % eine Kardiomyopathie, insbesondere vom dilatativen Typ. Das Auftreten eines plötzlichen Herztodes oder einer progredienten Herzinsuffizienz wurde lediglich in Einzelfällen beschrieben (22).

1.2.2. Fazioskapulohumerale Muskeldystrophie Typ 1 (FSHD1)

Die Fazioskapulohumerale Muskeldystrophie Typ 1 (FSHD1) ist mit einer Prävalenz von 1:20.000 die dritthäufigste hereditäre Muskeldystrophie und tritt meist in der 2. bis 3. Lebensdekade auf (23, 24). Die Genmutation auf dem langen Arm des Chromosoms 4 (4q35) wird autosomal-dominant vererbt (25). Leitsymptom der Erkrankung ist die meist asymmetrische Schwäche und Atrophie der Gesichts-, Schulter- und Oberarmmuskulatur. Den Krankheitsbeginn kennzeichnet oft eine Schwäche der mimischen Muskulatur im Sinne einer Facies myopathica mit Betonung der runden Gesichtsmuskulatur. Eine Scapula alata kann durch Atrophie der Schultermuskulatur auftreten. Im weiteren Krankheitsverlauf ist häufig auch die Becken- und Rumpfmuskulatur betroffen. Zusätzlich zu den muskulären Symptomen können eine Schwerhörigkeit sowie Netzhautveränderungen auftreten (23, 26). Die Lebenserwartung ist meist nicht reduziert, jedoch sind etwa 20 % der Patienten im Verlauf auf einen Rollstuhl angewiesen (24, 26). Die Häufigkeit einer Herzbeteiligung bei FSHD1 wird als vergleichsweise selten eingeschätzt (5-15%) (8, 23). Beschrieben wurden insbesondere supraventrikuläre Herzrhythmusstörungen wie paroxysmale supraventrikuläre Tachykardien (SVT) und Vorhofflimmern (27). Van Dijk et al. (28) berichteten zudem über ein gehäuftes Auftreten eines inkompletten oder kompletten Rechtschenkelblocks. In Einzelfällen ist auch eine hypertrophe Kardiomyopathie oder progrediente Herzschwäche beschrieben (29, 30).

1.2.3. CMR bei Muskeldystrophien

Eine Herzbeteiligung bei Muskeldystrophien wurde bislang oft erst spät durch eine eingeschränkte Ejektionsfraktion in der Echokardiographie diagnostiziert (5, 12). Mit Hilfe der CMR ist es gelungen, die histologisch nachgewiesenen Umbauvorgänge im Herzmuskel auch bildgebend darzustellen (5, 6). In unseren Pilotstudien (31, 32) haben wir erstmalig auch DM2- und FSHD1-Patienten hinsichtlich einer subklinischen Herzbeteiligung mittels CMR untersucht und konnten bei ca. 26 % der Patienten myokardiale Gewebeschäden wie Fibrose oder Fettinfiltrationen trotz erhaltener Pumpfunktion nachweisen. Die Anwendung der CMR weckt Hoffnung, Patienten mit einer kardialen Beteiligung bereits in einem frühen Stadium zu identifizieren und eine Therapie wie beispielsweise eine frühe Schrittmacherimplantation oder Herzinsuffizienztherapie vor dem Auftreten potenziell lebensgefährlicher kardiovaskulärer Ereignisse einzuleiten.

1.3. Myokardiale Deformationsanalyse mittels CMR

Die myokardiale Deformationsanalyse gewinnt zunehmend an Interesse, da sie den frühen Nachweis einer kontraktiven Dysfunktion in zahlreichen kardiovaskulären Krankheitsentitäten verspricht. In der Echokardiographie ist die Strainanalyse mittels Speckle-Tracking bereits ein in der Klinik etabliertes Verfahren. Ein wesentlicher Limitationsfaktor ist jedoch die reduzierte Bildqualität und eingeschränkte Reproduzierbarkeit infolge der Interoberservervariabilität (33, 34).

Strain ermöglicht nicht nur die Quantifizierung der myokardialen Deformation auf globaler Ebene, sondern kann auch regionale Kontraktilitätsstörungen erfassen. Da die linksventrikuläre (LV-) Kontraktion aufgrund der komplexen myokardialen Architektur in verschiedenen Richtungen erfolgt, unterscheidet man drei Komponenten: longitudinaler und circumferentieller Strain (Verkürzung in longitudinaler bzw. circumferentieller Ausrichtung, negativer Strain) sowie radialer Strain (Wandverdickung, positiver Strain) (35, 36).

Für die Strainanalyse mittels CMR wurden bereits zahlreiche Techniken evaluiert, darunter Strain Encoding (SENC), Displacement Encoding (DENSE) und Tagging, die jedoch alle spezielle Sequenzen erfordern (37-39). Dagegen basiert die Deformationsanalyse mittels Feature Tracking auf Steady-State-Free-Precession (SSFP)-Sequenzen, die auch in der routinemäßigen Funktionsanalyse Anwendung finden. Da keine

zusätzlichen Aufnahmen erforderlich sind, sondern ein Postprocessing erfolgt, stellt Feature Tracking ein vielversprechendes Verfahren für die klinische Routine dar (36). Referenzwerte für die Strainanalyse mittels Feature Tracking wurden bereits publiziert (40, 41) und auch der Einsatz bei kardiovaskulären Erkrankungen wie der ischämischen Kardiomyopathie wurde untersucht (42). Allerdings fehlt es noch immer an standardisierten Auswertalgorithmen dieser relativ neuen Methode, weshalb sich Unsicherheiten in der Interpretation und Vergleichbarkeit der Daten ergeben. Unsere Studie (43) verfolgt das Ziel, verschiedene Einflussfaktoren zu evaluieren und Normwerte für unterschiedliche Auswertalgorithmen zu generieren.

1.4. Kardiale Spätfolgen nach Präeklampsie

Präeklampsie ist eine hypertensive Schwangerschaftserkrankung, die nicht nur das Risiko für einen späteren bzw. persistierenden arteriellen Hypertonus erhöht, sondern auch mit einem langfristig erhöhten Risiko für die Entwicklung schwerwiegender kardiovaskulärer Erkrankungen wie einer Herzinsuffizienz oder koronaren Herzerkrankung einhergeht (44). Da auch hier, ähnlich wie bei den Muskeldystrophien, vor allem junge Patientinnen betroffen sind, ist es sinnvoll, morphologische oder funktionelle Veränderungen des Herzens möglichst früh zu identifizieren, um entsprechende Behandlungsmaßnahmen einzuleiten. Ein Teil dieser Dissertationsarbeit evaluiert den Nutzen der CMR hinsichtlich der frühen Diagnostik myokardialer Folgeschäden nach einer Präeklampsie (45).

1.5. Zielsetzung

Das Ziel dieser kumulativen Dissertationsarbeit ist es, das Potenzial der CMR zur frühen Identifikation von Myokardschäden zu nutzen und in ihrer Anwendung sowie in ihrem potenziellen klinischen Nutzen zu evaluieren.

Zum einen soll die Bedeutung der subklinischen Veränderungen bei DM2- und FSHD1-Patienten in Hinblick auf das myokardiale Remodeling und die Entwicklung von Herzrhythmusstörungen näher untersucht werden. Zudem widmet sich eine Studie der Etablierung myokardialer Deformationsanalysen mittels Feature Tracking und im Rahmen dessen der Identifikation potentieller Fehlerquellen. Das Potenzial dieser relativ neuen Methode soll schließlich sowohl bei DM2 und FSHD1 als auch bei Patientinnen nach Präeklampsie evaluiert werden.

2. Methoden

Im Folgenden werden zunächst die Methoden der Follow-up Studie (46), anschließend die der Feature-Tracking-Studie (43) und zum Schluss die der Präeklampsie-Studie (45) aufgeführt.

2.1. Detektion progressiver Myokardschäden mittels CMR bei Muskeldystrophien

2.1.1. Studiendesign

Aus publizierten Ausgangsstudien (31, 32) wurden 27 von 31 Patienten mit DM2 sowie 41 von 52 Patienten mit FSHD1 prospektiv in unsere Follow-up Studie eingeschlossen. Die Patienten wurden zu kardiovaskulären Symptomen und Ereignissen sowie zur Schwere der Muskelerkrankung befragt. Herzrhythmusstörungen wurden durch ein Ruhe-Elektrokardiogramm (EKG) und Langzeit-EKG über 24-Stunden erfasst (46).

2.1.2. Akquise und Auswertung der Bilddaten

Die CMR-Messungen wurden an einem 1.5-Tesla-Scanner (Magnetom AvantoFit®, Siemens Healthineers, Erlangen) durchgeführt. Das Scan-Protokoll entsprach dem der Ausgangsstudien (31, 32) (Abbildung 1). Zur Beurteilung der kardialen Morphologie und Funktion wurden SSFP cine-Aufnahmen in kurzen Achsen sowie im 2-Kammerblick (2CV), 3-Kammerblick (3CV), 4-Kammerblick (4CV) und in einer langen Achse für den rechten Ventrikel (RV) akquiriert. Zur Darstellung myokardialer Ödeme wurde T2-Mapping im 4CV sowie in 3 kurzen Achsen (basal, mittventrikulär und apikal) durchgeführt. Für die Erfassung diffuser Fibrose mittels T1-Mapping (4CV, 3 kurze Achsen) wurde die Modified Look-Locker Inversion Recovery (MOLLI)-Sequenz angewandt. Fettinfiltrationen wurden mittels Multiecho Sequenz zur Fett-Wasser-Separation (4) in 3 langen und 5 kurzen Achsen identifiziert. 10-15 Minuten nach Kontrastmittelgabe (0,2 mmol/kg Körpergewicht Gadoteridol (ProHance®) bei DM2 bzw. 0,15 mmol/kg Körpergewicht Gadobutrol (Gadovist®) bei FSHD) folgte die Akquise der kontrastmittelgestützten Aufnahmen: LGE-Bildgebung mittels Inversion-Recovery-Sequenz zum Nachweis fokaler Fibrose sowie T1- und ECV-Mapping basierend auf den MOLLI-Sequenzen. Die LGE-Aufnahmen wurden in langen und kurzen Achsen über den gesamten linken Ventrikel (LV) akquiriert (46).

Die Bilddaten wurden mit der Software cvi42® Version 5.3.2 (Circle Cardiovascular Imaging Inc., Calgary, Kanada) analysiert. Die Funktionsanalyse von LV und RV erfolgte in kurzen Achsen (1), die des linken Vorhofs (LA) biplan im 2CV und 4CV und die des rechten Vorhofs (RA) im 4CV (47). Die visuelle Beurteilung der LGE-Aufnahmen hinsichtlich Lokalisation und Transmuralität erfolgte durch zwei unabhängige, erfahrene Ärzte. Intramyokardiales Fett wurde als positiv gewertet, wenn sich dieses in der Fett- und Wasser-separierten Aufnahme zeigte oder aber in einer der separierten Aufnahmen sowie zusätzlich in den cine- und LGE-Bildern. Mittels CMR-Feature Tracking wurde der globale longitudinale Strain in drei langen Achsen (2CV, 3CV, 4CV) gemessen. Patienten mit Nachweis von fokaler Fibrose (positivem LGE) wurden von der Analyse ausgeschlossen (46).

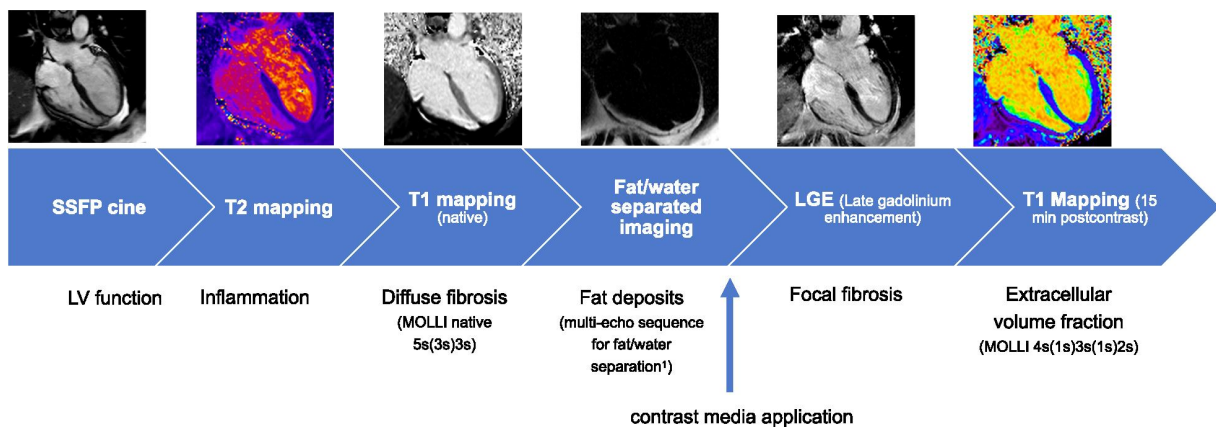


Abbildung 1. Scan-Protokoll. Abbildung übernommen aus Blaszczyk et al. (46)

2.1.3. Statistische Datenanalyse

Die statistische Analyse erfolgte mit der Software IBM® SPSS® Statistics (IBM Corp., Armonk, USA, Version 25). Die Ergebnisse sind als Mittelwerte \pm Standardabweichung angegeben. Die statistische Testung erfolgte mit dem Mann-Whitney-Test und Wilcoxon-Test unter der Verwendung eines Signifikanzniveaus von $p < 0.05$. Korrelationsanalysen wurden mit der Rangkorrelation nach Spearman durchgeführt. Berechnet wurden die Ejektionsfraktion (EF), das enddiastolische Volumen (EDV), Schlagvolumen (SV) sowie die linksventrikuläre Masse (LVM). Die Parameter wurden auf die Body Surface Area (BSA) adjustiert (EDVI, SVI, LVMI) (46).

2.2. Quantifizierung der myokardialen Deformation mittels Feature Tracking

2.2.1. Studiendesign

Das Screening umfasste 243 gesunde Probanden, die an einem 1.5-Tesla- (Magnetom AvantoFit®, Siemens Healthineers, Erlangen) oder 3-Tesla-Scanner (Magnetom Verio®, Siemens Healthineers, Erlangen) in vorangegangenen Studien (31, 47-50) untersucht wurden. Ausgeschlossen wurden Patienten mit kardiovaskulären Risikofaktoren oder Vorerkrankungen sowie einer reduzierten LVEF ($< 55\%$) und pathologischen Befunde im EKG oder in der CMR. Zusätzlich führten unvollständige CMR-Daten ($n = 137$) sowie Abweichungen in der Anzahl der Herzphasen ($n = 41$) zum Ausschluss, sodass letztendlich 67 Probanden in die Studie eingeschlossen werden konnten (43).

2.2.2. Analyse der Bilddaten

Das Postprocessing der Bilddaten erfolgte mit der Software cvi42® (Prototyp Version 5.3.0, Circle Cardiovascular Imaging Inc., Calgary, Kanada). Longitudinaler und radialer Strain wurden in langen Achsen (4CV, 3CV, 2CV) gemessen, circumferentieller und radialer Strain in 3 kurzen Achsen und/oder mittels Kurzachsenpaket. Die manuelle Konturierung des Endo- und Epikards erfolgte in der Enddiastole. Diese musste in allen Schichten in der gleichen Phase vorliegen. Trabekel, Papillarmuskel sowie epikardiales Fett wurden streng ausgeschlossen, ebenso der linksventrikuläre Ausflusstrakt. Die Strainanalyse erfolgte auf globaler sowie segmentaler Ebene basierend auf dem 16-Segmentmodell nach der American Heart Association (51). Zur visuellen Überprüfung der Tracking-Qualität und korrekten Segmentierung wurden spezielle Software-Tools (*Mesh, Boundaries, Myocardial points*) herangezogen (Abbildung 2). Bei fehlerhafter Segmentierung oder inakkuratem Tracking wurden die entsprechenden Segmente ausgeschlossen (43).

Für den Vergleich zwischen unterschiedlichen Software-Herstellern wurden die Bilddaten zusätzlich mittels TomTec Image Arena (Version 1.3.0.91, TomTec Imaging Systems GmbH, Unterschleißheim) analysiert. Die Strainanalyse erfolgte hierbei in 3 langen (4CV, 3CV, 2CV) und 3 kurzen Achsen (basal, mittventrikulär und apikal). Endo- und Epikard wurden manuell in der Enddiastole und Endsystole konturiert, die Tracking-Qualität wurde visuell evaluiert (43).

LV Funktion und Volumina wurden im Kurzachsenpaket berechnet. Aufgrund unvollständiger CMR-Daten oder Artefakten wurden 7 Probanden von der Funktionsanalyse ausgeschlossen (43).

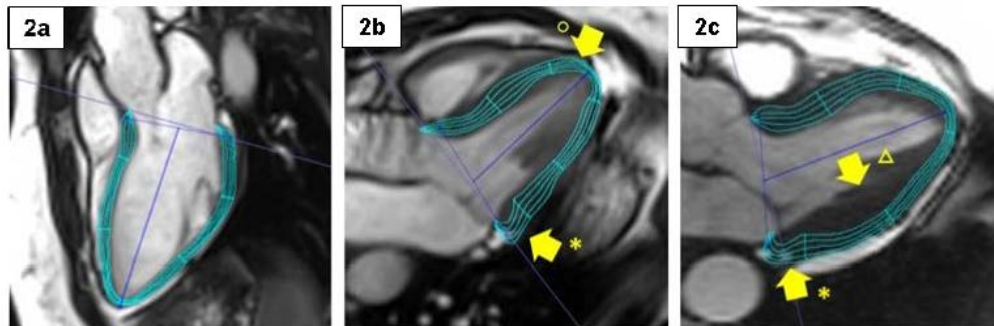


Abbildung 2. Visuelle Überprüfung der Tracking-Qualität. 2a: Korrekte Segmentierung, dargestellt im 3-Kammerblick. 2b: fehlerhafte Segmentierung, bei der das basale Segment relativ kurz ist (*) und sich das apikal septale Segment auf die Gegenseite ausdehnt (°). 2c: Tracking-Konturen folgen nicht dem Endokard (Δ). Abbildung modifiziert nach Lim et al. (43)

2.3. Evaluation kardialer Veränderungen nach Präeklampsie mittels CMR

2.3.1. Studiendesign

In dieser Fall-Kontroll-Studie wurden 22 Frauen mit Präeklampsie in der Vorgeschichte mit 22 gesunden Probandinnen (gematcht nach Alter, Body Mass Index (BMI) und Anzahl der Geburten) hinsichtlich funktioneller und struktureller Myokardveränderungen verglichen. Zu den Ausschlusskriterien zählten Kontraindikationen gegen die CMR-Untersuchung, ein vorbestehender Bluthochdruck sowie kardiovaskuläre Vorerkrankungen. Die CMR-Untersuchung erfolgte an einem 1.5-Tesla-Scanner (Magnetom AvantoFit®, Siemens Healthineers, Erlangen); Kontrastmittel erhielt lediglich die Patientengruppe (0,2 mmol/kg Körpergewicht Gadobutrol (Gadovist®)) (45).

2.3.2. Analyse der Bilddaten

Die Bilddaten wurden mit cvi42® (Circle Cardiovascular Imaging Inc., Calgary, Canada) analysiert. Vorhöfe und Ventrikel wurden hinsichtlich Morphologie und Funktion beurteilt und adjustiert auf die BSA. Zur Gewebecharakterisierung wurden T2- und T1-Mapping sowie LGE-Aufnahmen eingesetzt. Die myokardiale Deformationsanalyse erfolgte mit Feature Tracking (45).

3. Ergebnisse

3.1. Detektion progressiver Myokardschäden mittels CMR bei Muskeldystrophien

27 DM2-Patienten (21 Frauen) und 41 FSHD1-Patienten (12 Frauen) wurden untersucht. Die DM2-Patienten waren im Durchschnitt 9 Jahre älter als die FSHD1-Patienten (58 ± 9 Jahre vs. 49 ± 14 Jahre). Die Follow-up-Zeit betrug $3,9 \pm 0,32$ Jahre bei DM2 und $2,03 \pm 0,10$ Jahre bei FSHD1. Von 68 eingeschlossenen Patienten lehnten 6 eine CMR-Untersuchung ab (46).

3.1.1. Funktionelle und morphologische Parameter

In beiden Patientengruppen war die LVEF normwertig (62 ± 6 % in der DM2-Gruppe, 60 ± 3 % in der FSHD1-Gruppe), jedoch zeichnete sich bei den DM2-Patienten ein signifikanter Abfall der LVEF innerhalb von 4 Jahren ab ($p < 0,01$, siehe Tabelle 1). In beiden Gruppen zeigte sich im Follow-up eine reduzierte RV-Funktion (RVEF 54 ± 4 % bei DM2 und 49 ± 5 % bei FSHD1). Bei FSHD1-Patienten zeigte sich innerhalb des Beobachtungszeitraumes eine signifikante Größenzunahme des linken Vorhofs (LAEDV 54 ± 14 ml vs. 61 ± 14 ml, $p = 0,021$). Das linksatriale Volumen war bei DM2-Patienten erhöht (LAEDV 71 ± 25 ml, LAEDVI 38 ± 25 ml), jedoch ohne signifikante Progression innerhalb der 4 Jahre ($p = 0,275$ bzw. $p = 0,288$). In beiden Patientengruppen vergrößerte sich jedoch die Fläche sowohl des linken als auch rechten Vorhofs (siehe Tabelle 1) (46).

3.1.2. Myokardiale Gewebedifferenzierung

Bei insgesamt 6 DM2-Patienten (27 %) und 15 FSHD1-Patienten (37 %) wurde fokale Fibrose (positives LGE) nachgewiesen. Der Anteil an Patienten mit fokaler Fibrose nahm innerhalb des Beobachtungszeitraumes in beiden Gruppen zu (1 DM2-Patient und 2 FSHD1-Patienten). LGE zeigte ein nicht-ischämisches Muster (intramural und subepikardial) und war bevorzugt in den basal inferolateralen und inferoseptalen Regionen lokalisiert (siehe Abbildung 3). Bei DM2 zeigten Patienten mit fokaler Fibrose eine niedrigere LVEF (59 ± 1 % versus 64 ± 4 %) (46).

Intramyokardiales Fett zeigte sich in 7 DM2- (32 %) und 11 FSHD1-Patienten (28 %). Bei 2 der DM2- (10 %) und 5 der FSHD1-Patienten (12,5 %) war diese in der Ausgangsstudie nicht nachweisbar. Die Fettinfiltration zeigte sich bevorzugt apikal im Bereich des

interventrikulären Septums, bei einem FSHD1-Patienten war sie hingegen in der inferioren Wand lokalisiert (46).

Tabelle 1: Vergleich der funktionellen und morphologischen Parameter zwischen Baseline und Follow-up.

	DM2			FSHD1		
	Baseline n = 31	Follow-up n = 22	p-Wert	Baseline n = 52	Follow-up n = 41	p-Wert
LVEF (%)	68 ± 6	62 ± 6	< 0,01	63 ± 5	60 ± 3	0,762
LVEDV (ml)	126 ± 22	124 ± 29	0,605	128 ± 21	139 ± 34	0,131
LVEDVI (ml/cm)	0,8 ± 0,11	0,73 ± 0,15	0,275	0,70 ± 0,10	0,79 ± 0,17	< 0,01
LVM (g)	104 ± 27	92 ± 24	0,124	99 ± 25	102 ± 24	0,630
LVMI (g/cm)	0,60 ± 0,14	0,54 ± 0,12	0,110	0,56 ± 0,13	0,57 ± 0,12	0,524
LVSV (ml)	85 ± 13	78 ± 17	0,113	80 ± 15	84 ± 18	0,084
LVSVI (ml/m²)	46 ± 6	42 ± 6	0,063	45 ± 8	48 ± 9	0,245
RVEF (%)	59 ± 7	54 ± 4	< 0,01	51 ± 6	49 ± 5	0,104
RVEDV (ml)	140 ± 29	146 ± 33	0,444	160 ± 31	169 ± 28	0,470
RVEDVI (ml/m²)	76 ± 15	79 ± 14	0,456	83 ± 16	88 ± 14	0,422
RVSV (ml)	82 ± 18	80 ± 19	0,932	76 ± 18	83 ± 18	0,082
RVSVI (ml/m²)	44 ± 89	43 ± 8	0,852	40 ± 8	43 ± 8	0,063
LAEF (%)	60 ± 8	57 ± 7	0,392	62 ± 8	60 ± 7	0,452
LAEDV (ml)	63 ± 18	71 ± 25	0,275	54 ± 14	61 ± 14	0,021
LAEDVI (ml/m²)	35 ± 8	38 ± 25	0,288	28 ± 7	32 ± 8	0,027
LA (cm²)	21 ± 3	24 ± 5	< 0,01	19 ± 3	22 ± 3	< 0,01
RA (cm²)	21 ± 3	24 ± 5	0,040	20 ± 3	23 ± 4	0,029

Tabelle modifiziert nach Blaszczyk et al. (46)

Angabe in Mittelwert ± Standardabweichung. Signifikante Unterschiede ($p < 0,05$) sind fettgedruckt dargestellt. Abkürzungen: LVEF = linksventrikuläre Ejektionsfraktion, LVEDV = linksventrikuläres enddiastolisches Volumen, LVEDVI = linksventrikulärer enddiastolischer Volumenindex, LVM = linksventrikuläre Masse, LVMI = linksventrikulärer Massenindex, LVSV = linksventrikuläres Schlagvolumen, LVSVI = linksventrikulärer Schlagvolumenindex, RVEF = rechtsventrikuläre Ejektionsfraktion, RVEDV = rechtsventrikuläres enddiastolisches Volumen, RVEDVI = rechtsventrikulärer enddiastolischer Volumenindex, RVSV = rechtsventrikuläres Schlagvolumen, RVSVI = rechtsventrikulärer Schlagvolumenindex, LAEF = linksatriale Ejektionsfraktion, LAEDV = linksatriales enddiastolisches Volumen, LAEDVI = linksatrialer enddiastolischer Volumenindex, LA = linkes Atrium, RA = rechtes Atrium.

3.1.3. Myokardiale Deformation

Nach Ausschluss der LGE-positiven Patienten zeigte sich sowohl in der DM2- als auch FSHD1-Gruppe eine signifikante Reduktion der globalen longitudinalen Strainwerte (GLS): GLS $-17,9 \pm 1 \%$ versus $-16,8 \pm 4 \%$ ($p < 0,01$) bei DM2 und GLS $-18,3 \pm 1 \%$ versus $-16,4 \pm 1 \%$ ($p < 0,01$) bei FSHD1 (46).

3.1.4. Assoziation der myokardialen Gewebeschäden zu Herzrhythmusstörungen

Es wurden Langzeit-EKGs von 24 DM2- und 34 FSHD1-Patienten ausgewertet. Ein Ruhe-EKG war bei allen Patienten vorhanden (46).

10 von 27 DM2-Patienten (37 %) zeigten neue Erregungsleitungsstörungen und/oder Arrhythmien im EKG. Am häufigsten traten neue SVT auf (7 Patienten). Bei einem Patienten wurde ein bisher unbekannter AV-Block II° diagnostiziert. Zwei weitere Patienten zeigten neue intraventrikuläre Leitungsstörungen (Rechtsschenkelblock, links-anteriorer Hemiblock). In der LGE-positiven-Subgruppe ($n = 5$) hatten 4 DM2-Patienten einen auffälligen EKG-Befund. In der Subgruppe mit nachgewiesener Fettinfiltration zeigten alle 7 DM2-Patienten pathologische EKG-Veränderungen wie supraventrikuläre Arrhythmien, atrioventrikuläre oder intraventrikuläre Leitungsstörungen (46).

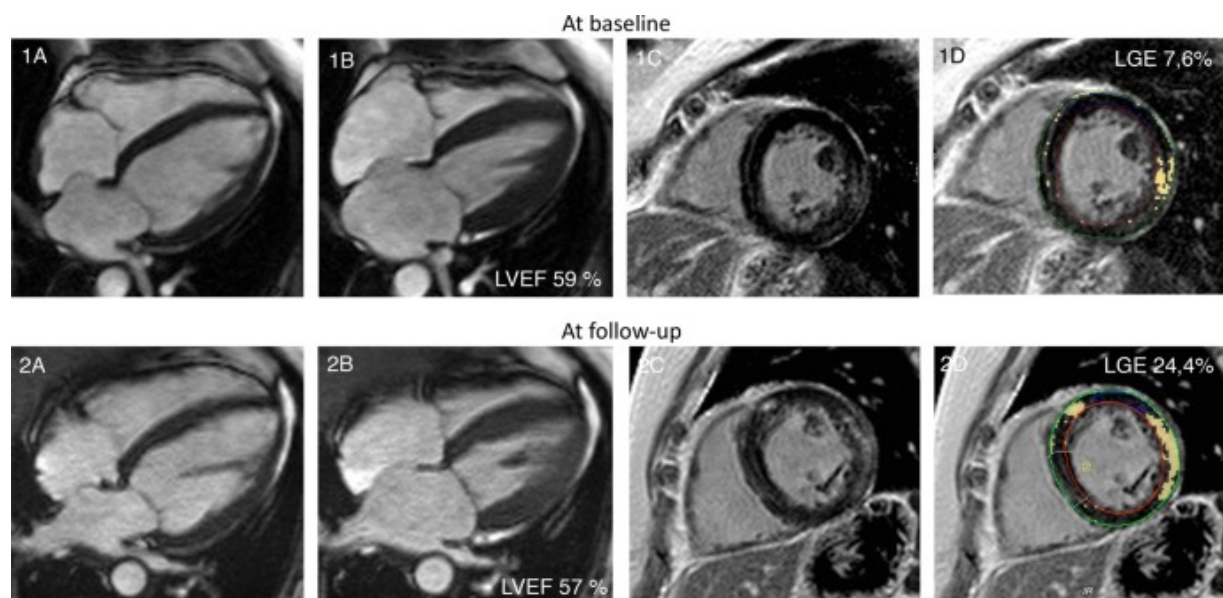


Abbildung 3. DM2-Patient mit progredienter intramyokardialer Fibrose und Reizleitungsstörungen (AV-Block I. Grades, linksanteriorer Hemiblock). 1A-1D bei der Baseline-Untersuchung. 2A-2D zum Zeitpunkt des Follow-Ups. Cine-Bilder im 4-Kammerblick während der Diastole (1, 2 A) sowie Systole (1, 2 B). Late Gadolinium Enhancement (LGE) in den kurzen Achsen (1, 2 C, D). Abbildung übersetzt nach Blaszczyk et al. (46).

Bei insgesamt 10 FSHD1-Patienten (29 %) wurden neue Arrhythmien und/oder Leitungsstörungen detektiert. Ähnlich wie bei DM2 waren gehäuft SVT nachweisbar (8 Patienten). Ein Patient zeigte eine nicht anhaltende ventrikuläre Tachykardie (nsVT; siehe Abbildung 4). Ventrikuläre Arrhythmien wurden bei insgesamt 8 Patienten mit fokaler Fibrose (73 %) und 3 Patienten mit Fettinfiltration (23 %) detektiert. SVT zeigten sich bei 5 Patienten mit Fettinfiltration (45 %) und 3 Patienten mit positivem LGE (60 %) (46).

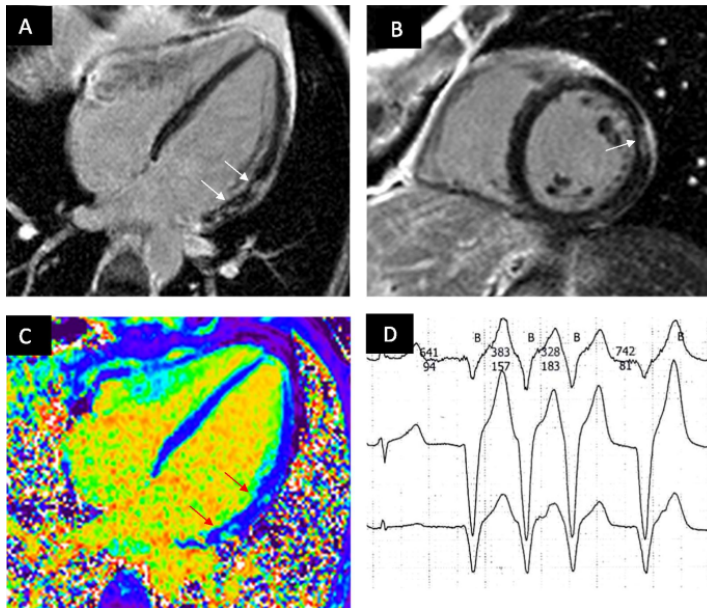


Abbildung 4. 34-jähriger asymptomatischer FSHD1-Patient mit einer kurzen Episode einer nicht-anhaltenden ventrikulären Tachykardie im Holter-EKG (4D) und Nachweis von LGE (4A: 4-Kammerblick; 4B: kurze Achse) in der Seitenwand des linken Ventrikels. Extrazellulärvolumen (ECV)- Map im 4-Kammerblick (4C). Abbildung übersetzt nach Blaszczyk et al. (46).

3.2. Quantifizierung der myokardialen Deformation mittels Feature Tracking

36 gesunde Probanden wurden am 1.5-Tesla- und 31 Probanden am 3-Tesla-Scanner untersucht. Von 67 Probanden waren 31 weiblich, das mittlere Alter lag bei 44 ± 16 Jahren. LV Funktion und Volumina lagen im Normbereich (LVEF 64 ± 4 %, LVEDV 140 ± 33 , LVEDVI 75 ± 15 ml/m², LVM 101 ± 22 g, LVMI 54 ± 9 g/m²) (43).

3.2.1. Unterschiede zwischen verschiedenen Auswertemethoden

Die Strainanalyse ergab signifikant unterschiedliche Werte für circumferentiellen und radialen Strain zwischen der Messung im Kurzachsenpaket und der in 3 kurzen Achsen

($p < 0,001$). Die radialen Strainwerte waren niedriger in 3 langen Achsen als in 3 kurzen Achsen ($p < 0,001$) (43).

Im Software-Vergleich zeigten sich für alle globalen Strainwerte signifikante Unterschiede: In der Auswertung mit TomTec waren die longitudinalen und circumferentiellen Strainwerte negativer ($p < 0,001$ und $p = 0,001$); radialer Strain war signifikant niedriger mit cvi42 ($p < 0,001$) (43).

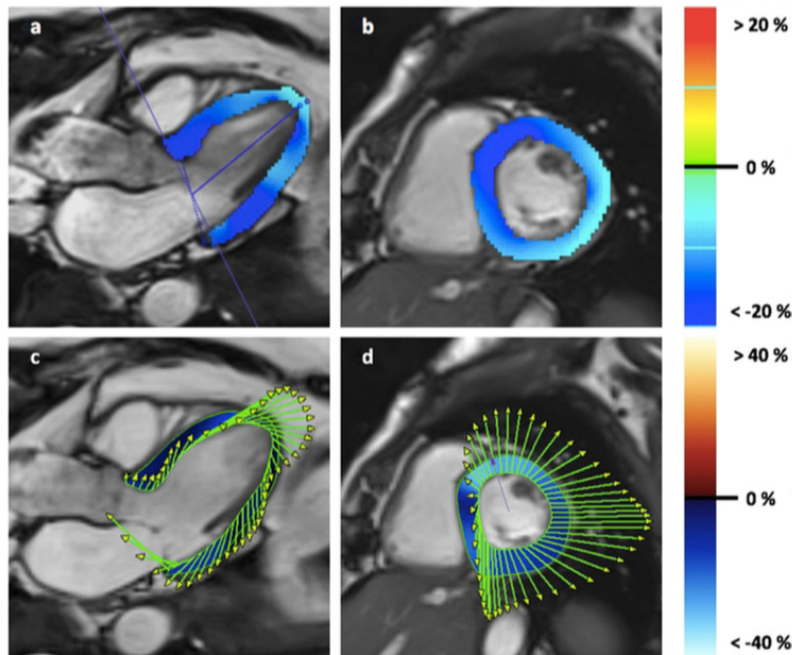


Abbildung 5. 2D-Strainanalyse vom linken Ventrikel mittels Cvi42 (a-b) und TomTec (c-d). Dargestellt ist die Strainanalyse für longitudinalen Strain im 3-Kammerblick (a, c) und für circumferentiellen Strain in der basalen kurzen Achse (b, d). Abbildung modifiziert nach Lim et al.(43).

3.2.2. Normwertetablierung in Abhängigkeit von Feldstärke und Geschlecht

Die Normwerte für die Messungen in langen und kurzen Achsen sind in den Tabellen 2 bis 4 zusammengefasst.

Feldstärke und Geschlecht zeigten keinen Einfluss auf die longitudinalen Strainwerte (siehe Tabelle 2). Radialer Strain war zwar unabhängig von der Feldstärke, ergab jedoch signifikant niedrigere Werte beim männlichen Geschlecht ($p < 0,05$). Dies zeigte sich sowohl für die Messungen in langen Achsen, als auch kurzen. Circumferentieller Strain war nicht abhängig von der Feldstärke ($p = 0,263$), zeigte jedoch ebenfalls Unterschiede zwischen Männern und Frauen ($p = 0,010$, Tabelle 3) (43).

Tabelle 2: Globaler longitudinaler und radialer Strain in 3 langen Achsen

	Longitudinaler Strain (%)				Radialer Strain (%)			
	Mittelwert ± Standardabweichung				Mittelwert ± Standardabweichung			
	cvi42	p-Wert	TomTec	p-Wert	cvi42	p-Wert	TomTec	p-Wert
	-17 ± 2		-20 ± 3		29 ± 5		70 ± 21	
1.5 Tesla	-17 ± 2	0,845	-20 ± 2	0,114	29 ± 6	0,792	78 ± 23	0,002
3 Tesla	-17 ± 2		-21 ± 3		29 ± 5		61 ± 14	
Frauen	-17 ± 2	0,098	-21 ± 3	0,268	31 ± 6	0,033	75 ± 26	0,087
Männer	-17 ± 2		-20 ± 2		28 ± 4		66 ± 15	

Signifikante Unterschiede ($p < 0,05$) sind fettgedruckt dargestellt. Tabelle modifiziert nach Lim et al. (43)

Tabelle 3: Globaler circumferentieller und radialer Strain in 3 kurzen Achsen.

	Circumferentieller Strain (%)				Radialer Strain (%)			
	Mittelwert ± Standardabweichung				Mittelwert ± Standardabweichung			
	cvi42	p-Wert	TomTec	p-Wert	cvi42	p-Wert	TomTec	p-Wert
	-19 ± 2		-21 ± 3		35 ± 7		64 ± 16	
1.5 Tesla	-20 ± 2	0,263	-21 ± 2	0,389	36 ± 8	0,128	57 ± 13	0,001
3 Tesla	-19 ± 2		-21 ± 3		33 ± 6		71 ± 16	
Frauen	-20 ± 2	0,010	-21 ± 3	0,436	37 ± 7	0,014	68 ± 16	0,022
Männer	-19 ± 2		-20 ± 2		33 ± 6		60 ± 15	

Signifikante Unterschiede ($p < 0,05$) sind fettgedruckt dargestellt. Tabelle modifiziert nach Lim et al. (43)

Tabelle 4: Globaler circumferentieller und radialer Strain im Kurzachsenpaket.

	Circumferentieller Strain (%)		Radialer Strain (%)	
	Mittelwert ± Standardabweichung		Mittelwert ± Standardabweichung	
	cvi42	p-Wert	cvi42	p-Wert
	-18 ± 2		29 ± 5	
1.5 T	-18 ± 2	0,855	29 ± 5	0,665
3 T	-18 ± 2		29 ± 4	
Frauen	-18 ± 2	0,029	31 ± 5	0,047
Männer	-17 ± 2		28 ± 5	

Signifikante Unterschiede ($p < 0,05$) sind fettgedruckt dargestellt. Tabelle modifiziert nach Lim et al. (43)

3.3. Evaluation kardialer Veränderungen nach Präeklampsie mittels CMR

22 Frauen mit Präeklampsie in der Vorgeschichte wurden mit 22 Kontrollprobandinnen verglichen. Zwischen den Gruppen gab es keine Unterschiede hinsichtlich Alter, BMI, Anzahl der Geburten und körperlichem Aktivitätslevel, jedoch war der Abstand zur letzten Schwangerschaft in der Patientengruppe kürzer als in der Kontrollgruppe (2 ± 1 Jahre vs. 4 ± 5 Jahre; $p < 0,01$) (45).

3.3.1. Funktionelle und morphologische Parameter

Beide Gruppen zeigten eine erhaltene systolische LV-Funktion (LVEF 61 ± 6 % vs. 63 ± 4 % in der Kontrollgruppe, $p = 0,38$). Es wurden keine signifikanten Unterschiede im LVEDVI ($p = 0,15$) und LVMI ($p = 0,19$) festgestellt. Frauen nach Präeklampsie tendierten zu einer leichten LV-Hypertrophie mit LVSVI 47 ± 7 ml/m² (im Vergleich zu 51 ± 6 ml/m² in der Kontrollgruppe, $p = 0,05$) und LV Remodeling Index (LV-RI) $0,6 \pm 0,1$ (Kontrollgruppe: LV-RI $0,5 \pm 0,1$, $p = 0,06$) (45).

Die linksatrialen Parameter LAEDV und LASV waren bei Frauen nach Präeklampsie um 13 % bzw. 19% erhöht im Vergleich zur Kontrollgruppe (LAEDVI 38 ± 7 vs. 33 ± 6 ml/m², $p = 0,03$, und LASVI 23 ± 6 vs. 19 ± 5 ml/m², $p = 0,04$). Der adjustierte Beta-Koeffizient ergab für die Prädiktion des LAEDV 14,03 ml (95 % Konfidenzintervall: 6,56-21,50; $p < 0,01$) und für die Prädiktion des LASV 10,69 ml (95 % Konfidenzintervall: 3,99-17,38; $p < 0,01$) (45).

3.3.2. Myokardiale Gewebedifferenzierung

Bei keiner der Patientinnen konnten strukturelle Myokardschäden mittels LGE nachgewiesen werden. T1 und T2 Mapping ergaben keine signifikanten Unterschiede in den Relaxationszeiten ($p > 0,05$) (45).

3.3.3. Myokardiale Deformation

Longitudinaler Strain zeigte keine signifikanten Unterschiede zwischen beiden Gruppen (-18 ± 2 % vs. -18 ± 2 %, $p = 0,888$). Radialer und circumferentieller Strain war hingegen bei Frauen nach Präeklampsie signifikant reduziert: 31 ± 7 % vs. 35 ± 7 % ($p = 0,035$) sowie -18 ± 3 vs. -20 ± 2 % ($p = 0,037$) (45).

4. Diskussion

Die dissertationsrelevanten Studien zeigen die diagnostischen Möglichkeiten der CMR, subklinische Myokardschäden bei erhaltener Pumpfunktion zu detektieren und verdeutlichen den klinischen Nutzen der CMR bei seltenen Formen der Muskeldystrophien.

4.1. Progressive Myokardschäden bei Muskeldystrophien

In unserer Follow-up Studie zeigte sich eine Progression myokardialer Gewebeschäden bei DM2- und FSHD1-Patienten innerhalb von nur wenigen Jahren. Arrhythmien und Reizleitungsstörungen scheinen mit dem Auftreten von myokardialer Fibrose und/oder Fettinfiltration assoziiert zu sein (46).

Häufigkeit und Schweregrad einer kardialen Beteiligung variieren deutlich zwischen den verschiedenen Muskeldystrophie-Formen (52). Während zu DM2 und FSHD wenig Daten existieren, wurde die kardiale Mitbeteiligung bei den bekannteren Muskeldystrophie-Formen, der DMD und BMD, ausführlicher untersucht. In diesen Gruppen entwickeln nahezu alle Patienten im Krankheitsverlauf eine Herzbeteiligung, meist als DCM oder in Form von ventrikulären Rhythmusstörungen (12, 53, 54). Bei etwa 70 % der DMD-Patienten konnte fokale Fibrose als mögliches strukturelles Korrelat in der LGE-Bildgebung nachgewiesen werden (6). In unserer Pilot-Studie haben wir DM2- und FSHD1-Patienten mit erhaltener Ejektionsfraktion hinsichtlich einer subklinischen Herzbeteiligung untersucht und bei nahezu 30 % der Patienten fokale Fibrose detektieren können (31, 32). Ähnlich wie auch bei anderen Muskeldystrophie-Formen (55) konnten wir in diesen Patientengruppen nun auch eine Progression des myokardialen Remodelings innerhalb von nur wenigen Jahren nachweisen (46). Bei DM2 zeigte sich zusätzlich ein signifikanter Abfall der LVEF sowie RVEF. Bei DM2-Patienten mit fokaler Fibrose in der LGE-Bildgebung war die LVEF signifikant niedriger als bei Patienten ohne Fibrose (46). Bei den Dystrophinopathien ist bekannt, dass myokardiale Fibrose mit einer reduzierten Ejektionsfraktion und entsprechend auch mit einem erhöhten Risiko für kardiovaskuläre Ereignisse wie plötzlichen Herztod einhergeht (6, 55, 56).

Ähnlich wie bei Myokarditiden und Systemerkrankungen ist das LGE bei Muskeldystrophien durch ein nicht-ischämisches Muster geprägt. Meist ist dieses subepikardial oder intramural lokalisiert, kann sich im Verlauf aber auch transmural sowie

in benachbarte Segmente ausdehnen (12, 13, 57). Transmurales LGE ist verbunden mit einer schlechteren Prognose (13). Bei DM2 und FSHD1 ließ sich Fibrose primär in der inferolateralen Region darstellen (46), ähnlich wie auch in anderen Formen, z.B. DM1 und DMD (12, 57). Bei der DMD war LGE in der lateralen und septalen Wand mit ventrikulären Arrhythmien und einem plötzlichen Herztod assoziiert (56). Bei der DM1 zeigte sich LGE als unabhängiger Prädiktor für supraventrikuläre Arrhythmien (57). In unserer Studie konnten im Follow-up deutlich mehr Herzrhythmusstörungen nachgewiesen werden (46). Ähnlich wie in anderen Studien (19, 20, 27) waren dabei SVT sowie intraventrikuläre Leitungsstörungen vordergründig (46). Patienten mit fokaler Fibrose und/oder intramyokardialer Fettinfiltration zeigten häufiger Erregungsleitungsstörungen und/oder Arrhythmien, sodass hier ein enger Zusammenhang denkbar ist. Fibrose im Bereich der Vorhöfe als mögliches Korrelat der supraventrikulären Rhythmusstörungen lässt sich mit den etablierten Methoden schwer erfassen. In unserer Follow-up-Studie zeigte sich allerdings eine Zunahme der atrialen Volumina, sodass sich auch hier ein Remodeling vermuten lässt (46).

In unserer Studie zeigten alle DM2-Patienten mit Fettinfiltrationen auch EKG-Veränderungen (46). Bei der DCM ist ein Zusammenhang zwischen Fettinfiltrationen und einer LV-Dysfunktion beschrieben (58). Bei Muskeldystrophien wurden diese jedoch bisher unzureichend untersucht, sodass die Relevanz unklar bleibt.

Bei Muskeldystrophien sind häufig junge Patienten betroffen und der Schweregrad einer Herzbeteiligung geht nicht unbedingt mit dem Ausmaß der Muskelschwäche einher (20). Um Patienten mit kardialer Herzbeteiligung früh zu identifizieren, damit diese entsprechend von einer zielgerichteten Therapie wie einer kardioprotektiven Therapie oder einer Schrittmacherversorgung profitieren können, ist ein frühes Screening sinnvoll. Die transthorakale Echokardiographie genießt aufgrund der breiten Verfügbarkeit einen hohen Stellenwert, die diagnostischen Möglichkeiten sind allerdings in Hinblick auf frühe Veränderungen begrenzt, insbesondere bei zusätzlich erschwerten Schallbedingungen und entsprechend reduzierter Bildqualität (34).

4.2. Klinische Anwendbarkeit und Nutzen der CMR

Die CMR ermöglicht eine präzise Beurteilung der kardialen Morphologie und entgegen anderer Bildgebungsverfahren auch die Identifikation subklinischer Gewebeveränderungen, darunter entzündliche, fibrotische und fettige Umbauprozesse. Aufgrund

der vielfältigen diagnostischen Möglichkeiten wird sie nicht nur bei kardiovaskulären Erkrankungen eingesetzt, sondern bietet mit der Myokarddifferenzierung insbesondere bei Systemerkrankungen die Möglichkeit zur diagnostischen und prognostischen Einordnung (2). Die CMR ist der Echokardiographie damit insbesondere in der Frühdiagnostik einer kardialen Beteiligung überlegen. Während die Echokardiographie beispielsweise in nur der Hälfte der DMD- und BMD-Patienten eine reduzierte Pumpfunktion nachweisen konnte, waren bei 70 % der Patienten mit erhaltener Pumpfunktion bereits LGE in der CMR nachweisbar als Hinweis auf eine Herzbeteiligung (5, 6).

In der Präeklampsie-Studie (45) untersuchten wir asymptomatische Frauen nach Präeklampsie hinsichtlich subklinischer kardialer Veränderungen. Wir konnten in dieser Patientengruppe weder fokale Fibrose mittels LGE noch diffuse Prozesse mithilfe parametrischer Mapping-Methoden nachweisen. Dies könnte eventuell der relativ kurzen postpartalen Zeitspanne geschuldet sein. Ob Frauen nach Präeklampsie langfristig strukturelle Gewebeschäden entwickeln, muss mithilfe von Langzeitstudien genauer untersucht werden. Bereits zwei Jahre postpartal zeigten sich allerdings schon morphologische Veränderungen des LA mit einem signifikant erhöhten LAEDV und LASV (45). Atriales Remodeling erhöht nicht nur das Risiko für die Entwicklung einer diastolischen Dysfunktion, sondern auch das für Vorhofflimmern und ischämische Schlaganfälle (59).

Eine weitere Möglichkeit, eine frühe subklinische LV-Dysfunktion zu erfassen bietet die Deformationsanalyse. Die Quantifizierung der Myokarddeformation mithilfe von Strain kann im Gegensatz zur Ejektionsfraktion auch regionale Kontraktilitätsstörungen erfassen. Die Strainanalyse mittels Feature Tracking gewinnt zunehmend an Interesse, da sie entgegen anderer CMR-Techniken nicht der Akquise zusätzlicher Sequenzen bedarf und somit besonders praktikabel für die klinische Routine erscheint (36). In unserer Studie (43) haben wir verschiedene Einflussfaktoren wie Analysesoftware und Auswertelgorithmen untersucht und Normwerte in gesunden Probanden etabliert. Differenzen zwischen unterschiedlichen Softwareherstellern, wie sie auch in anderen Studien beschrieben wurden (60), konnten wir bestätigen (43). Liu et al. (61) konnten innerhalb einer Software Unterschiede zwischen einer dreidimensionalen Analyse und einem zweidimensionalen Ansatz mit einer langen und einer kurzen Achse feststellen. In

unserer Studie (43) zeigten sich sogar signifikante Unterschiede zwischen der Auswertung mit einem Kurzachsenpaket und drei kurzen Achsen. In der bisherigen Literatur wurden für die Normwertetablierung in gesunden Probanden unterschiedliche Herangehensweisen bezüglich der Auswertemethode verfolgt, beispielsweise mit einer langen und einer kurzen Achse, zwei langen und drei kurzen Achsen oder drei langen Achsen und ein Kurzachsenpaket (40, 62, 63). Daraus ergibt sich die Problematik, dass Strainwerte untereinander schwer vergleichbar sind. Derzeit fehlt es an standardisierten Auswertealgorithmen, die jedoch notwendig sind, um Unsicherheiten in der Auswertung und Interpretation von Daten zu vermeiden. Um den klinischen Einsatz zu erleichtern, haben wir geschlechtsspezifische Normwerte für unterschiedliche Auswertealgorithmen erhoben (43).

Abgesehen von den Unsicherheiten, die Feature Tracking als relativ neue CMR-Methode mit sich bringt, konnte ein potenzieller klinischer Nutzen für verschiedene Krankheitsentitäten gezeigt werden. Dass fokale Narben und Fibrosen mit einer Reduktion myokardialer Strainwerte einhergehen, wurde sowohl für ischämische als auch nicht-ischämische Kardiomyopathien wie der DCM gezeigt (42).

In unserer Follow-up-Studie (46) untersuchten wir DM2- und FSHD1-Patienten hinsichtlich einer subklinischen LV-Dysfunktion und konnten mithilfe von Feature Tracking in beiden Patientengruppen eine Reduktion der longitudinalen Strainwerte nachweisen. Bei den FSHD1-Patienten zeigte sich diese Veränderung bereits innerhalb von zwei Jahren, während die LVEF stabil blieb. Unsere Ergebnisse unterstützen damit die Hypothese, dass Feature Tracking im Vergleich zur LVEF früher subklinische Veränderungen der Herzfunktion erfassen kann.

In der Präeklampsie-Studie (45), in welcher wir asymptomatische Frauen mit Präeklampsie in der Vorgeschichte hinsichtlich einer subklinischen LV-Dysfunktion untersuchten, fand sich eine Reduktion der circumferentiellen und radialen Strainwerte. Frühere Studien stellten fest, dass Patientinnen in der Akutphase einer Präeklampsie eine kontraktile Dysfunktion mit pathologischen Strainwerten entwickeln können (64, 65). Unsere Studie konnte zeigen, dass diese Veränderungen auch noch Jahre nach der akuten Erkrankung bestehen (45). Der prognostische Wert dieser Erkenntnisse muss in Langzeitstudien erforscht werden.

Die Besonderheit der CMR liegt in der Fähigkeit, subklinische Myokardschäden bei erhaltener Pumpfunktion zu detektieren. Die Ergebnisse unserer Studie unterstützen die

Vermutung, dass Patienten mit Muskeldystrophien und nachgewiesenen Myokardschäden in der CMR häufiger Herzrhythmusstörungen entwickeln und die CMR in dieser Patientengruppe daher nicht nur diagnostischen, sondern auch prognostischen Wert hat (46). Der Mehrwert bestünde darin, durch ein Screening mittels CMR Risikopatienten, die von einer rechtzeitigen gezielten kardialen Therapie profitieren würden, früh zu identifizieren und zu behandeln, um so die Prognose langfristig zu verbessern. Es erfordert Langzeitdaten und Multi-Center-Studien, um die Ergebnisse unserer Studie zu verifizieren.

4.3. Zusammenfassung

CMR ermöglicht sowohl die Detektion subklinischer Myokardschäden bei erhaltener Pumpfunktion als auch deren Progression und Assoziation zu Herzrhythmusstörungen bzw. Überleitungsstörungen. Dies bietet perspektivisch die Möglichkeit, Patienten mit einer kardialen Beteiligung bei Systemerkrankungen wie Muskeldystrophien oder Präeklampsie bereits früh zu identifizieren und eine Therapie vor dem Auftreten potenziell lebensgefährlicher kardiovaskulärer Ereignisse einzuleiten (45, 46).

Die myokardiale Deformationsanalyse mittels CMR-Feature Tracking hat das Potenzial eine subklinische myokardiale Dysfunktion zu detektieren, wird jedoch von verschiedenen Einflussfaktoren, wie der Auswertungsmethode und –software, beeinflusst. Standardisierte Bedingungen sind notwendig, um die Anwendung in der klinischen Routine zu ermöglichen (43).

4.4. Limitationen und Ausblick

Eine Limitation dieser Arbeit liegt in den relativ kleinen Fallzahlen. Bei der Follow-up-Studie ist die Stichprobengröße unter anderem auf eine relativ niedrige Prävalenz beider Erkrankungen zurückzuführen. Zusätzlich waren EKG-Daten aufgrund logistischer Schwierigkeiten nicht bei allen Patienten vorhanden. Nach bestem Wissen ist dies die erste Follow-up-Studie, die eine Progression der Herzbeteiligung bei DM2 und FSHD1 mittels CMR untersucht. Die Studie zeigt, dass kardiales Remodeling bei DM2 und FSHD1 mit der Zeit fortschreitet und allem Anschein nach mit dem Auftreten von Herzrhythmusstörungen assoziiert ist. Die frühzeitige Diagnostik einer subklinischen Herzbeteiligung mittels CMR bietet die Möglichkeit, durch eine rechtzeitige zielgerichtete Therapie die Langzeitprognose dieser relativ jungen Patienten zu verbessern. Multi-

Center-Studien über einen längeren Zeitraum können helfen, den prognostischen Wert des kardialen Remodelings bei diesen Erkrankungen besser einzuschätzen (46).

Die Studie zur Normwertetablierung mittels Feature Tracking ist ebenfalls durch eine kleine, jedoch sorgfältig ausgewählte gesunde Probandengruppe limitiert. Das Screening für die retrospektive Auswertung der Daten mittels Feature Tracking umfasste mehrere prospektive Studien mit geringfügig abweichenden Scanprotokollen. Der Ausschluss von insgesamt 176 Fällen aufgrund inkompletter CMR-Daten wäre mit einem prospektiven Studiendesign vermeidbar gewesen, spiegelt allerdings auch die Schwierigkeiten in der klinischen Routine aufgrund abweichender Rahmenbedingungen wider. In dieser Studie wurden zwar nicht dieselben Probanden am 1.5-Tesla- und 3 Tesla-Scanner verglichen, jedoch waren beide Subgruppen hinsichtlich Alter und Geschlecht gleichmäßig verteilt. Eine wesentliche Schwäche von Feature Tracking liegt darin, dass die Analyse entgegen anderer Verfahren lediglich auf manuell eingezeichneten Konturen basiert und inakkurates Tracking die Werte verzerren kann. Trotz der genannten Limitationen und Einflussfaktoren stellt Feature Tracking ein vielversprechendes Verfahren in der Diagnostik einer subklinischen LV-Dysfunktion und Prädiktion schwerwiegender kardiovaskulärer Ereignisse dar. Es erfordert Studien mit größeren Fallzahlen sowie Langzeitstudien, um die Ergebnisse dieser Studie zu validieren und den potenziellen klinischen Nutzen zu evaluieren. Ferner sind standardisierte Bedingungen notwendig, um eine Anwendung in der klinischen Routine zu ermöglichen (43).

Die Präeklampsie-Studie ist ebenfalls durch einen relativ kleinen Stichprobenumfang limitiert. Alle Patientinnen wurden jedoch individuell nach Alter, BMI und Anzahl der Geburten gematcht und multivariate Analysen wurden zur Minimierung von Störfaktoren angewandt. Die Zeitspanne zur Exposition (Präeklampsie) war mit 2 Jahren relativ kurz. Follow-up-Studien sind notwendig, um zum einen den prognostischen Wert der morphologischen Veränderungen zu evaluieren und zum anderen die potenzielle Entwicklung von Gewebeschäden, wie Fibrose und Entzündungsprozesse im Verlauf erneut zu beurteilen (45).

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Eidesstattliche Versicherung

„Ich, Carolin Lim, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Detektion subklinischer Myokardschäden bei erhaltener Pumpfunktion mittels kardiovaskulärer Magnetresonanztomographie (*Detection of subclinical myocardial damage despite a preserved ejection fraction using 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.

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.org) 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

Anteilerklärung an den erfolgten Publikationen

Carolin Lim hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Blaszczyk E, **Lim C**, Kellman P, Schmachl L, Gröschel J, Spuler S & Schulz-Menger J. Progressive myocardial injury in myotonic dystrophy type II and facioscapulohumeral muscular dystrophy 1: a cardiovascular magnetic resonance follow-up study. J Cardiovasc Magn Reson. 2021;23(1):130.

Beitrag im Einzelnen:

- Beteiligung an der Erstellung des Ethikantrags
- Patientenrekrutierung
- Datenerhebung und -auswertung (Fragebögen, Ruhe- und Langzeit-EKG)
- Beteiligung an den MRT-Untersuchungen und Auswertung der Bilddaten
- Statistische Auswertung eines Teils der Daten
- Beteiligung an der Erstellung des Manuskripts
- Beteiligung an Revision

Publikation 2: **Lim C***, Blaszczyk E*, Riazzy L, Wiesemann S, Schüler J, von Knobelsdorff-Brenkenhoff F, Schulz-Menger J. Quantification of myocardial strain assessed by cardiovascular magnetic resonance feature tracking in healthy subjects – influence of segmentation and analysis software. Eur Radiol. 2021;31(6):3962-72.

*geteilte Erstautorenschaft

Beitrag im Einzelnen:

- Literaturrecherche
- Zusammentragen der Daten
- Etablierung der Auswertemethode und Auswertung der Daten
- statistische Auswertung und Interpretation der Daten
- Entwurf des Manuskripts, aller Tabellen und Abbildungen
- Diskussion mit den Koautoren
- Revision des Manuskripts, der Tabellen und Abbildungen

Publikation 3: Birukov A, Wiesemann S, Golic M, Balogh A, Marko L, Rakova N, Wilck N, Blaszczyk E, **Lim C**, Weiss S, Kräker K, Haase N, Frolova A, Jørgensen JS, Daub S, Müller DN, Herse F, Schulz-Menger J, Dechend R. Myocardial Evaluation of Post-Preeclamptic Women by CMR: Is Early Risk Stratification Possible? JACC Cardiovasc Imaging. 2020;13(5):1291–1293.

Beitrag im Einzelnen:

- Auswertung eines Teils der Daten (Mapping)
- Teilweise Unterstützung bei der Anwendung der Auswertemethode (Feature Tracking)
- Unterstützung bei der Erstellung des Manuskripts
- Beteiligung an Revision

Unterschrift, Datum und Stempel der erstbetreuenden Hochschullehrerin

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Auszug aus der Journal Summary List

Publikation 1:

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Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	10,110	12.740	0.027550
2	MEDICAL IMAGE ANALYSIS	9,028	11.148	0.017100
3	RADIOLOGY	52,731	7.931	0.057130
4	JOURNAL OF NUCLEAR MEDICINE	26,844	7.887	0.032990
5	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	15,787	7.081	0.023630
6	IEEE TRANSACTIONS ON MEDICAL IMAGING	21,657	6.685	0.030060
7	CLINICAL NUCLEAR MEDICINE	5,042	6.587	0.006200
8	NEUROIMAGE	102,632	5.902	0.125360
9	Photoacoustics	715	5.870	0.001760
10	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	44,197	5.859	0.042160
11	Circulation-Cardiovascular Imaging	5,574	5.691	0.016320
12	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	13,078	5.571	0.018050
13	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,205	5.361	0.011120
14	INVESTIGATIVE RADIOLOGY	6,136	5.156	0.008830
15	RADIOGRAPHICS	12,418	4.967	0.010750
16	ULTRASCHALL IN DER MEDIZIN	2,185	4.966	0.002530
17	RADIOTHERAPY AND ONCOLOGY	17,774	4.856	0.026510
18	European Heart Journal-Cardiovascular Imaging	6,359	4.841	0.023110
19	HUMAN BRAIN MAPPING	23,094	4.421	0.042760
20	Journal of the American College of Radiology	4,409	4.268	0.010730

Publikation 2:

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Gesamtanzahl: 129 Journale

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1	JACC-Cardiovascular Imaging	8,801	10.975	0.026160
2	MEDICAL IMAGE ANALYSIS	7,694	8.880	0.013370
3	IEEE TRANSACTIONS ON MEDICAL IMAGING	19,545	7.816	0.024990
4	RADIOLOGY	54,641	7.608	0.061300
5	JOURNAL OF NUCLEAR MEDICINE	27,551	7.354	0.037990
6	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	15,406	7.182	0.024760
7	CLINICAL NUCLEAR MEDICINE	4,922	6.498	0.007680
8	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	45,833	6.203	0.046810
9	INVESTIGATIVE RADIOLOGY	6,563	6.091	0.011150
10	Circulation-Cardiovascular Imaging	5,456	5.813	0.018480
11	NEUROIMAGE	99,720	5.812	0.132720
12	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	12,336	5.595	0.020140
13	European Heart Journal-Cardiovascular Imaging	5,498	5.260	0.021650
14	RADIOTHERAPY AND ONCOLOGY	17,873	5.252	0.027470
15	Photoacoustics	512	5.250	0.001330
16	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,113	5.070	0.014020
17	ULTRASCHALL IN DER MEDIZIN	2,238	4.613	0.003700
18	HUMAN BRAIN MAPPING	22,040	4.554	0.043230
19	JOURNAL OF NUCLEAR CARDIOLOGY	3,711	4.112	0.004480
20	EUROPEAN RADIOLOGY	19,597	3.962	0.033870

Publikation 3:

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
 Selected Categories: **“RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING”** Selected Category Scheme: WoS
Gesamtanzahl: 129 Journale


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20	EUROPEAN RADIOLOGY	19,597	3.962	0.033870

RESEARCH

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Progressive myocardial injury in myotonic dystrophy type II and facioscapulohumeral muscular dystrophy 1: a cardiovascular magnetic resonance follow-up study

Edyta Blaszczyk^{1,2}, Carolin Lim^{1,2}, Peter Kellman³, Luisa Schmach¹, Jan Gröschel^{1,2}, Simone Spuler⁴ and Jeanette Schulz-Menger^{1,2*} 

Abstract

Aim: Muscular dystrophy (MD) is a progressive disease with predominantly muscular symptoms. Myotonic dystrophy type II (MD2) and facioscapulohumeral muscular dystrophy type 1 (FSHD1) are gaining an increasing awareness, but data on cardiac involvement are conflicting. The aim of this study was to determine a progression of cardiac remodeling in both entities by applying cardiovascular magnetic resonance (CMR) and evaluate its potential relation to arrhythmias as well as to conduction abnormalities.

Methods and results: 83 MD2 and FSHD1 patients were followed. The participation was 87% in MD2 and 80% in FSHD1. 1.5 T CMR was performed to assess functional parameters as well as myocardial tissue characterization applying T1 and T2 mapping, fat/water-separated imaging and late gadolinium enhancement. Focal fibrosis was detected in 23% of MD2) and 33% of FSHD1 subjects and fat infiltration in 32% of MD2 and 28% of FSHD1 subjects, respectively. The incidence of all focal findings was higher at follow-up. T2 decreased, whereas native T1 remained stable. Global extracellular volume fraction (ECV) decreased similarly to the fibrosis volume while the total cell volume remained unchanged. All patients with focal fibrosis showed a significant increase in left ventricular (LV) and right ventricular (RV) volumes. An increase of arrhythmic events was observed. All patients with ventricular arrhythmias had focal myocardial changes and an increased volume of both ventricles (LV end-diastolic volume (EDV) $p=0.003$, RVEDV $p=0.031$). Patients with supraventricular tachycardias had a significantly higher left atrial volume ($p=0.047$).

Conclusion: We observed a remarkably fast and progressive decline of cardiac morphology and function as well as a progression of rhythm disturbances, even in asymptomatic patients with a potential association between an increase in arrhythmias and progression of myocardial tissue damage, such as focal fibrosis and fat infiltration, exists. These results suggest that MD2 and FSHD1 patients should be carefully followed-up to identify early development of remodeling and potential risks for the development of further cardiac events even in the absence of symptoms.

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Keywords: Magnetic Resonance Imaging, Facioscapulohumeral muscular dystrophy type 1, Myotonic dystrophy type 2, Fat, Fibrosis, Remodeling

Introduction

Muscular dystrophy (MD) is a group of genetic and progressive diseases with primary symptoms of skeletal muscle pain and weakness. In some MD, such as Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), cardiac involvement is well known. Myocardial fibrosis detected by cardiovascular magnetic resonance (CMR) enables the prediction of cardiac events in DMD/BMD patients independently when compared with reduced left ventricular (LV) ejection fraction (LVEF). Interestingly, in patients with preserved LVEF, there is added value of focal fibrosis [1–3]. Focal fibrosis may occur in up to 90% of these patients, leading to heart failure and sudden cardiac death (SCD) in some cases [4].

Myotonic dystrophy type II (MD2) and facioscapulohumeral muscular dystrophy type I (FSHD1) have gained an increasing awareness during the last years. There is a suspicion that MD2 as well as FSHD1 could be underdiagnosed due to frequently mild symptoms and slower progression in females. Late onset and a slower progression seem to lead to a rate of 20% misdiagnosed patients [5]. MD2 and FSHD1 are mainly recognized as muscular diseases with rare cardiac involvement.

MD2 is an autosomal dominant inherited multi-systemic muscle disease. The mutation frequency constitutes 1:1830 [6]. Patients often notice the first symptoms quite late, at the age of 37 ± 15 years [7], suffering from muscle weakness, myotonia and muscle pain.

FSHD1 is an autosomal dominant disorder and the third most common inherited muscle disease with an incidence of 1: 8.000–1: 20.000 [8]. Diagnosis of FSHD1 is often suspected in patients with presence of progressive asymmetric weakness of the face and shoulder muscles. However, 10–25% of patients are wheelchair-dependent [9].

Arrhythmias in both patient groups are known but its relation to myocardial injury as well as evidence for progression of myocardial changes still remains unknown. Trevisan et al. reported arrhythmic events in 12% of FSHD-patients [10], whereas in MD2 different forms of arrhythmias were reported in 17% to 36% of patients [11].

In our pilot studies, we were able to identify myocardial injury, like fat infiltration and focal fibrosis, in over 26% of MD2 and FSHD1 patients with preserved LVEF [12, 13].

Table 1 Overview of muscular dystrophies and their associated cardiac abnormalities

Disease	Cardiologic manifestations				
	Clinical			CMR	
	Cardiac involvement (%)	Possible phenotype of the involvement	Conduction disturbances/ Arrhythmias	Extension of late gadolinium enhancement	Presence of fat infiltration
Duchenne muscular dystrophy	Up to 90	DCM	Sinus tachycardia, Ventricular tachycardias	+++	+
Becker muscular dystrophy	60–70	DCM	AV nodal and bundle branch blocks	+++	No data
Emery-Dreifuss muscular dystrophy	50–90	DCM, HCM, LVNC, biatrial dilation	Bradycardias (AV blocks), Tachycardias (SVTs)	Rare, if present associated with tachycardias	Rare
Limb girdle muscular dystrophy	25–90	DCM, HCM	SVTs, Ventricular tachycardia	++	+
Myofibrillar myopathy	40–60	DCM, HCM, LVNC	Complete AV Block	no data	No data
Facioscapulohumeral muscular dystrophy	5–25	DCM (rare)	RBBB, SVTs	+ / + +	+
Myotonic dystrophy type 1	60–80	DCM, HCM	AV Blocks, RBBB/LBBB QTc/QRS prolongation, PVC, Ventricular Tachycardia, Atrial fibrillation, Atrial flutter	++	No data
Myotonic dystrophy type 2	Up to 25	DCM, HCM	Atrial fibrillation	+ / + +	+

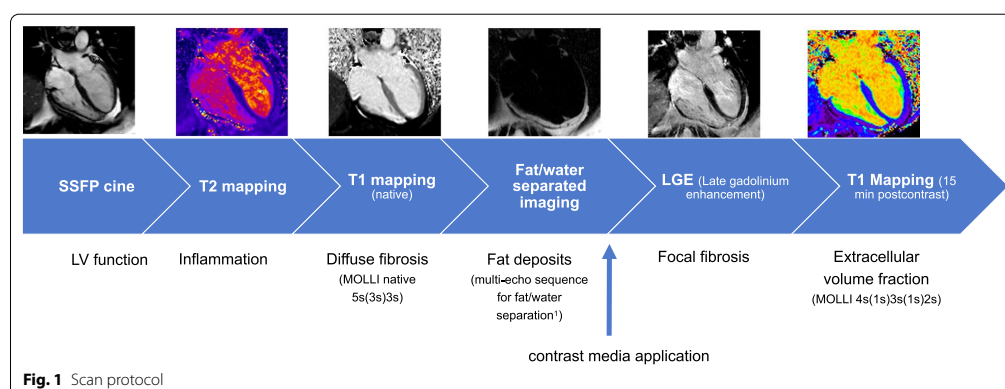


Fig. 1 Scan protocol

Due to individual predispositions, even mild initial dysfunction may lead to severe heart failure over months to years [14, 15]. However, systematic follow-up analysis in patients with MD2 and FSHD1 are lacking. Table 1 provides an overview of the most common muscular dystrophies and their associated cardiac abnormalities.

The aim of this study was to investigate a potential progression of the cardiac remodeling processes, including focal myocardial injury and function, in patients with MD2 and FSHD1 by applying serial CMR. Furthermore, we evaluated its relation to arrhythmias and conduction abnormalities.

Methods

Follow-up was performed in 83 patients with genetically confirmed diagnosis of MD2 and FSHD1 who had previously participated in our studies [12, 13].

A detailed medical history was recorded including symptoms related to cardiovascular diseases, medication and cardiovascular risk factors. Known myocardial infarction or myocarditis were considered as exclusion criterion to avoid an overlap with myocardial injury due to a different cause. Blood pressure was taken before and after CMR. Assessment of heart rhythm abnormalities was based on a 12-lead electrocardiogram (ECG) and on 24 h ECG-monitoring. Patients were also considered at risk of SCD according to the Groh-criteria: no sinus rhythm, PR interval ≥ 240 ms, QRS duration ≥ 120 ms, second- or third-degree atrioventricular block [16].

Significant arrhythmias were defined as frequent premature ventricular contractions (PVC ≥ 1000 /24-h), episodes of non-sustained ventricular tachycardia (NSVT), runs of supraventricular tachycardia (SVT) and 2nd/3rd degree atrioventricular (AV) block.

The local university ethical board approved the study (EA1/042/17) and all subjects gave written, informed consent.

Cardiovascular magnetic resonance

CMR protocol

CMR was performed on a 1.5 T scanner (MAGNETOM AvantoFit[®], Siemens Healthineers, Erlangen, Germany) using a 32-channel surface coil.

Cine imaging was performed applying a balanced steady state free precession (bSSFP) sequence to determine the global cardiac performance. We acquired the following long axis views for the LV: four chamber (4Ch), three chamber (3Ch) and two chamber (2Ch) views and for the right ventricle (RV) a single long axis view (echo time (TE) 1.2 ms; repetition time, 33 ms; voxel size $1.8 \times 1.8 \times 6.0$ mm³) as well as a short axis (SAX) package (TE 1.2 ms; repetition time, 63 ms; voxel size $1.4 \times 1.4 \times 7.0$ mm³) to cover the LV.

For myocardial tissue differentiation parametric T1- and T2-mapping, fat/water-separated imaging and focal fibrosis imaging (late gadolinium enhancement, LGE) were acquired. An overview of the scan protocol is provided in Fig. 1.

A multi-echo sequence was used for fat/water-separation [17] in 4ch view and five SAX slices (gradient echo sequence (GRE), double inversion recovery dark blood preparation, four echoes with monopolar readout, TR 824 ms, TE 1.6–3.9–6.2–8.6 ms, slice thickness 6 mm).

We used the same contrast agent as in the previous studies (0.2 mmol/kg body weight of gadoteridol for MD2 and 0.15 mmol/kg body weight of gadobutrol for FSHD1). [12, 13].

LGE was performed in the same slice position as cine imaging in 4Ch, 3Ch, 2Ch views and SAX orientations

(gradient echo sequence, breath-held segmented protocol with 10 ms echo spacing, TE of 5.2 ms, and slice thickness of 7 mm) 10–15 min after administration of contrast agent.

T2- and T1-mapping were performed in basal, mid and apical slices as described [12, 18]. Calculations were carried out for each segment and for each slice. Motion-corrected T2 mapping was based on a fast low angle shot (FLASH) gradient echo sequence in 4Ch and SAX views as basal, mid-ventricular and apical slices. T2 maps were based on images with T2 preparation at times of 0/30/55 ms, and slice thickness of 6.0 mm, TR 251.49 ms and TE 1.32 ms.

Motion-corrected T1 mapping based on Modified Look-Locker Inversion Recovery (MOLLI) technique was performed before and 15 min after contrast media application using for T1 native: 5 s(3 s)3 s and for T1 post-contrast: 4 s(1 s)3 s(1 s)2 s pattern in 4Ch view and three SAX views with basal, mid-ventricular and apical slices (imaging parameters: TR=281.64 ms (4ch) and 332.67 ms (SAX), TE=1.12 ms, slice thickness 6.0 mm, GRAPPA acceleration factor 2).

Data analysis

In the first paper (2016) we used cvi42 (version 4.1.2, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). The analysis of the MD2 cohort at follow-up was performed in 2018/2019. At that timepoint, we switched to cvi42 (version 5.3.2, Circle Cardiovascular Imaging). Because of potential influences and possible inconsistencies between different software versions, a quality assurance test was performed (re-evaluation of the baseline results with the new version in a randomly chosen subgroup). There were no significant differences between the quantitative results. For the FSHD1 group we used the same version of Circle software (version 5.3.2, Circle Cardiovascular Imaging) for both baseline and follow up evaluations.

Sax cine images were used to determine LVEF and right ventricular (RV) ejection fraction (RVEF), volumes and LV mass by drawing endo- and epicardial contours (papillary muscles as part of the mass) at the end of the systolic and diastolic phases [19].

We quantified the left atrium (LA) area based on the biplanar approach using 2- and 4ch. For right atrium (RA) quantification 4Ch view cine images in LV systole were used. Furthermore, LA volume and ejection fraction were quantified based on the biplanar approach [20].

The quantitative analysis of mapping was performed as average value for slice as well as for each segment. The region-of-interest ROI was defined by the delineation of the endocardial and epicardial border of the myocardium. To ensure that blood or extra myocardial tissue

were not included, endo- and epicardial offset of 5% was used. The segments were defined following the American Heart Association (AHA) segment model. The qualitative survey implied the exclusion of segments in case of artifacts (e.g., caused by susceptibility effects or unintended thoracic motion) or wrong motion correction.

The visual evaluation of the LGE images was performed by two independent, experienced readers (SCMR Level III) to assess presence, number and location of focal scars.

Quantification of LGE was performed with the established semi-automated signal threshold versus reference mean (STRM) method [21]. On all LGE images, endocardial and epicardial contours were manually traced and ROIs were defined in hyperenhanced and remote myocardium.

LGE was defined as myocardial signal intensity plus 3 standard deviations (SD) above remote, normal-appearing myocardium. The automated LGE detection could be manually corrected by the reader for a specific location to exclude obvious artifacts. After segmentation, myocardial and scar tissue (in %) were calculated [21, 22].

Fibrosis volume and the total cell volume were derived using extracellular volume fraction (ECV) and the following formulas [23]:

$$\text{Fibrosis volume} = \text{ECV} * \text{LVmass} / \text{myocardial density} *$$

$$\text{Cell volume} = ((1 - \text{ECV}) * \text{LV mass}) / \text{myocardial density} *$$

$$*\text{myocardial density} = 1.05 \text{ g/m.}$$

Fat/water-separation imaging was analyzed using pre-defined criteria. A suspected region was considered positive if the intramyocardial fat was detectable (a) in the fat-separated image (hyperintense) and in the water-separated image (hypointense) or (b) detected in one of the separated images as well as in the cine imaging and LGE. Within the LV segmental analysis was performed following the AHA segment model [24].

Global longitudinal strain (GLS) using CMR feature tracking was assessed from the 4Ch, 3Ch, and 2Ch images. Endo- and epicardial contours were manually drawn in end-diastolic phase, defined as the phase with the largest LV volume. Trabeculae, papillary muscles, pericardium, and epicardial fat were consequently excluded from contouring [25].

Statistical analysis

The statistical analysis was performed using SPSS® (version 25, Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New

Table 2 Characteristics of patients with muscular dystrophy II (MD2) at follow-up

	Presence of Late Gadolinium Enhancement		
	All (n = 22)	No (n = 17)	Yes (n = 5)
Age (years)	58 ± 9	57 ± 9	61 ± 10
Male sex, n (%)	6 (27.3)	4	2
Heart rate (beats per minute)	69 ± 9	68 ± 9	72 ± 11
Systolic BP (mmHg)	130 ± 16	127 ± 16	139 ± 16
Diastolic BP (mmHg)	75 ± 10	73 ± 10	81 ± 9
Arterial hypertension, n (%)	7 (31.8)	4	3
Hyperlipidemia, n (%)	16 (72.7)	13	3
Diabetes mellitus, n (%)	3 (13.6)	3	–
Smoking, n (%)	2 (9.1)	1	1
Cardiac symptoms			
Asymptomatic, n (%)	16 (72.7)	11	2
Palpitations, n (%)	6 (27.3)	4	2
Chest pain, n (%)	1 (4.5)	1	0
Fatigue, n (%)	5 (22.7)	4	1

Data are shown as mean values ± standard deviation (SD) according to the AHA-segment model. BP blood pressure

Table 3 Characteristics of patients with Facioscapulohumeral muscular dystrophy type 1 (FSHD1) at follow-up

	Presence of Late Gadolinium Enhancement		
	All (n = 40)	No (n = 26)	Yes (n = 14)
Age (years)	49 ± 14	47 ± 14	54 ± 11
Male sex, n (%)	29 (70.7)	9 (36)	3 (21.4)
Heart rate (beats per minute)	74 ± 13	76 ± 13	71 ± 14
Systolic BP (mmHg)	129 ± 15	127 ± 16	132 ± 15
Diastolic BP (mmHg)	79 ± 10	79 ± 9	79 ± 11
Arterial hypertension, n (%)	8 (20)	1	7
Hyperlipidemia, n (%)	7 (17.5)	3	4
Diabetes mellitus, n (%)	3 (7.5)	1	2
Smoking, n (%)	5 (12.5)	3	2
Cardiac symptoms			
Asymptomatic, n (%)	29 (70.7)	19	10
Palpitations, n (%)	8 (12.2)	6	2
Chest pain, n (%)	1 (2.4)	1	0
Fatigue, n (%)	6 (14.6)	4	2

Data are shown as mean values ± standard deviation (SD) according to the AHA-segment model. BP blood pressure

York, USA). All results are shown as mean ± standard deviation. Normal distribution was analyzed graphically using the Kolmogorov–Smirnov test. For comparing FSHD1/MD2 patients before and after the follow-up period we used the Mann–Whitney-U test. A p value < 0.05 was considered to indicate a statistically significant difference. Intra- and inter-observer reproducibility was analyzed using intra-class correlation coefficient (ICC) and 95% confidence interval (CI). ICC was classified as poor (ICC < 0.4), good (ICC = 0.4–0.75) or excellent (ICC > 0.75). Images were analyzed twice by blinded readers.

Results

CMR analysis in MD2 and FSHD1 patients

Follow-up was available for 27 of 31 MD2 (87%) patients (follow up 3.9 ± 0.3 years) and 41 of 52 (80%) FSHD1 patients (follow up 2.0 ± 0.1 years). Six patients refused follow-up CMR. Twenty-two patients with MD2 and 40 subjects with FSHD1 underwent CMR with contrast. Baseline characteristics of patients at follow-up are shown in Tables 2 and 3. Some patients during the observation period received medications that could reduce the progression of cardiac remodeling and fibrotic processes: 10/22 MD2 and 7/41 FSHD1 patients received angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), only 3 patients in both groups received β-blockers.

Myotonic dystrophy type II

Individual and mean changes between both baseline and follow-up groups are displayed in Fig. 2.

Remodeling

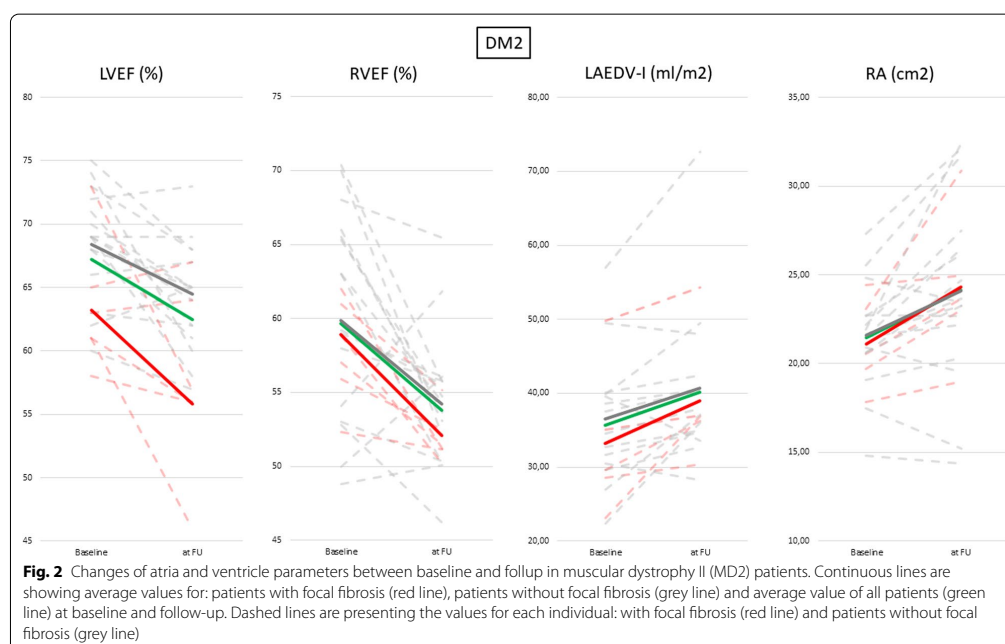
Left ventricular and right ventricular chamber anatomy

LVEF stayed within normal range, however was statistically lower at follow up (LVEF_{baseline} 68 ± 6% vs LVEF_{FU} 62 ± 6%, p = 0.001). After a mean observational period of four years, MD2 patients presented with significantly lower and mildly impaired RVEF compared to their baseline examinations (RVEF_{baseline} 59 ± 7 vs RVEF_{FU} 54 ± 4%, p = 0.001). Both ventricles showed no significant changes in volume during the course of time (LV end-diastolic volume (LVEDV) p = 0.605 and indexed LVEDV (LVEDVI) p = 0.275, RVEDV p = 0.444 and RVEDVI p = 0.456.) (Table 4).

At follow up patients with focal fibrosis showed significantly lower LVEF (LVEF_{LGE+} 59 ± 2% vs LVEF_{LGE-} 64 ± 4%, p = 0.005), however it still remained in normal ranges. LVEDV and LVEDVI did not change at follow up (LVEDV_{LGE+} 142 ± 38 vs LVEDV_{LGE-} 119 ± 25 ml p = 0.127, LVEDVI_{LGE+} 0.81 ± 0.19 ml/m² vs LVEDVI_{LGE-} 0.70 ± 0.13, p = 207).

Left atria and right atria quantification

We observed significant increase of the LA and RA areas (LA_{baseline} 21 ± 3 vs LA_{FU} 24 ± 5 cm², p = 0.014, RA



baseline 21 ± 3 vs RA_{FU} 24 ± 5 cm², $p = 0.040$), however LA volume showed no significant changes (for LAEDV $p = 0.275$ and for LAEDVI $p = 0.288$) (Table 4).

We observed an excellent intra- and inter-observer reproducibility for ventricular and atrial assessment in both groups. ICC was 0.091 for intra-observer and 0.892 for inter-observer analysis.

Myocardial tissue differentiation

Parametric mapping, cell and fibrosis volume

We performed T2 and T1 mapping at baseline and during follow-up. Native T1 values remained stable (MD2: basal $p = 0.066$, mid $p = 0.258$, apical $p = 0.163$), but ECV dropped significantly (MD2: basal $p = 0.014$, mid $p < 0.01$, apical $p < 0.01$). T2 decreased significantly as well (MD2: basal $p < 0.01$, mid $p < 0.01$, apical $p < 0.01$).

While the cell volume remained constant, patients at follow-up presented with lower fibrosis volume (MD2 cell volume basal $p = 0.409$, mid $p = 0.553$; fibrosis volume basal $p = 0.055$, mid $p = 0.009$) (Table 4).

Focal fibrosis and its relation to cardiac remodeling

In the MD2 group, new focal fibrosis could be identified in 1 of 22 patients, (5%, female) at follow up. It was located in the basal segments of the inferolateral and

inferoseptal wall. At follow-up, an increase of focal fibrosis was observed. In total 6/22 (27%, 3 women) MD2 patients had focal fibrosis (see Fig. 3 and Table 5).

Focal fat

New focal fat infiltration was observed in 2 of 22 patients (10%, both females), mostly located in the apical part of the interventricular septal wall (Fig. 4). Overall, fat infiltration was present in 7/22 (32%, all females) patients at follow-up.

Myocardial deformation- global longitudinal strain (GLS)

GLS was significantly lower in MD2 patients at follow in comparison to baseline (GLS_{MD2 LGE (-)} baseline $-17.9 \pm 1.0\%$ vs. GLS_{MD2 LGE (-)} at follow up $-16.8 \pm 4.0\%$, $p < 0.01$). LGE (+) patients were excluded to avoid the influence of known focal fibrosis.

Heart rhythm abnormalities and its relation to myocardial tissue changes

12-lead ECG was available in all patients, Holter-ECG in 24/27 patients.

New arrhythmic events or conduction abnormalities were recorded in 10/27 patients (37%). New episodes of SVT occurred in 7 patients while a new AV block type 2

Table 4 CMR parameters of patients with MD2 and FSHD1 at baseline and at follow-up

Parameter	MD2			FSHD1		
	Baseline (n = 31)	Follow-up n = 22	p-value	Baseline n = 52	Follow-up n = 41	p value
LVEF (%)	68 ± 6	62 ± 6	< 0.01	63 ± 5	60 ± 3	0.762
LVEDV (ml)	126 ± 22	124 ± 29	0.605	128 ± 21	139 ± 34	0.131
LVEDVI (ml/cm)	0.80 ± 0.11	0.73 ± 0.15	0.275	0.70 ± 0.10	0.79 ± 0.17	< 0.01
LV mass (g)	104 ± 27	92 ± 24	0.124	99 ± 25	102 ± 24	0.630
LV mass index (g/cm)	0.60 ± 0.14	0.54 ± 0.12	0.110	0.56 ± 0.13	0.57 ± 0.12	0.524
LV stroke volume (ml)	85 ± 13	78 ± 17	0.113	80 ± 15	84 ± 18	0.084
LV stroke volume index (ml/m ²)	46 ± 6	42 ± 6	0.063	45 ± 8	48 ± 9	0.245
RVEF (%)	59 ± 7	54 ± 4	< 0.01	51 ± 6	49 ± 5	0.104
RVEDV (ml)	140 ± 29	146 ± 33	0.444	160 ± 31	169 ± 28	0.470
RVEDVI (ml/m ²)	76 ± 15	79 ± 14	0.456	83 ± 16	88 ± 14	0.422
RV stroke volume (ml)	82 ± 18	80 ± 19	0.932	76 ± 18	83 ± 18	0.082
RV stroke volume index (ml/m ²)	44 ± 89	43 ± 8	0.852	40 ± 8	43 ± 8	0.063
LAEF (%)	60 ± 8	57 ± 7	0.392	62 ± 8	60 ± 7	0.452
LAEDV (ml)	63 ± 18	71 ± 25	0.275	54 ± 14	61 ± 14	0.021
LAEDVI(ml/m ²)	35 ± 8	38 ± 25	0.288	28 ± 7	32 ± 8	0.027
LA (cm ²)	21 ± 3	24 ± 5	< 0.01	19 ± 3	22 ± 3	< 0.01
RA (cm ²)	21 ± 3	24 ± 5	0.040	20 ± 3	23 ± 4	0.029
Native T1 basal (ms)	1029 ± 30	1015 ± 38	p = 0.066	1010 ± 26	991 ± 24	< 0.01
Native T1 mid (ms)	1012 ± 38	998 ± 30	p = 0.258	991 ± 39	989 ± 30	p = 0.102
Native T1 apical (ms)	1018 ± 50	999 ± 32	p = 0.163	983 ± 41	970 ± 40	p = 0.203
ECV basal (%)	26 ± 3	24 ± 3	< 0.01	26 ± 3	22 ± 2	< 0.01
ECV mid (%)	26 ± 2	24 ± 2	< 0.01	26 ± 3	23 ± 3	< 0.01
ECV apical (%)	29 ± 3	26 ± 2	< 0.01	27 ± 3	24 ± 2	< 0.01
T2 basal (ms)	51 ± 2	49 ± 2	< 0.01	50 ± 4	47 ± 2	< 0.01
T2 mid (ms)	52 ± 3	49 ± 3	< 0.01	51 ± 3	47 ± 2	< 0.01
T2 apical (ms)	55 ± 4	50 ± 2	< 0.01	53 ± 3	48 ± 2	< 0.01
Cell volume basal (ml)	72 ± 18	68 ± 17	p = 0.409	71 ± 19	74 ± 22	p = 0.308
Cell volume mid (ml)	70 ± 19	76 ± 17	p = 0.553	71 ± 20	73 ± 22	p = 0.361
Fibrosis volume basal (ml)	25 ± 9	20 ± 7	p = 0.055	24 ± 8	20 ± 7	p = 0.023
Fibrosis volume mid (ml)	26 ± 7	21 ± 6	< 0.01	23 ± 7	22 ± 7	p = 0.032
GLS (%) LGE(-) patients	-17.9 ± 1	-16.8 ± 1	< 0.01	-18.3 ± 1	-16.4 ± 1	p < 0.01

Data are shown as mean values ± standard deviation (SD) according to the AHA-segment model. Significant differences (p < 0.05) are highlighted in bold

BMI body mass index, BSA body surface area (Mosteller), HR heart rate, BP blood pressure, LVEF left ventricular ejection fraction, LVEDV left ventricular end-diastolic volume, LVEDVI left ventricular end-diastolic volume index, LVESV left ventricular end-systolic volume, LA left atrium, RA right atrium, GLS global longitudinal strain, ECV extracellular volume fraction

was detected in only 1 patient. Two patients displayed new conduction abnormalities, specifically right bundle branch block and left anterior hemiblock. Positive Groh-criteria (AV block type 1) could be identified in only one patient. Arrhythmias or conduction disturbances were observed in all seven patients with fatty infiltrations and 4 of 6 patients with focal fibrosis. See Table 5.

Facioscapulohumeral Muscular Dystrophy 1 (FSHD1)

Individual and mean changes between baseline and follow-up in both groups are displayed in Fig. 5.

Remodeling

Left ventricular and right ventricular chamber size and function

During the follow up period, LVEF remained within the normal range (LVEF_{baseline} 63 ± 5% vs LVEF_{FU} 60 ± 3%, p = 0.762). There was no significant progression of RV dysfunction, however RVEF in FSHD1 patients was mildly impaired (RVEF_{baseline} 51 ± 6 vs RVEF_{FU} 49 ± 5%, p = 0.001). Volume in both ventricles stayed within normal range during the course of time, however LVEDVI increased significantly at follow-up (LVEDV p = 0.131

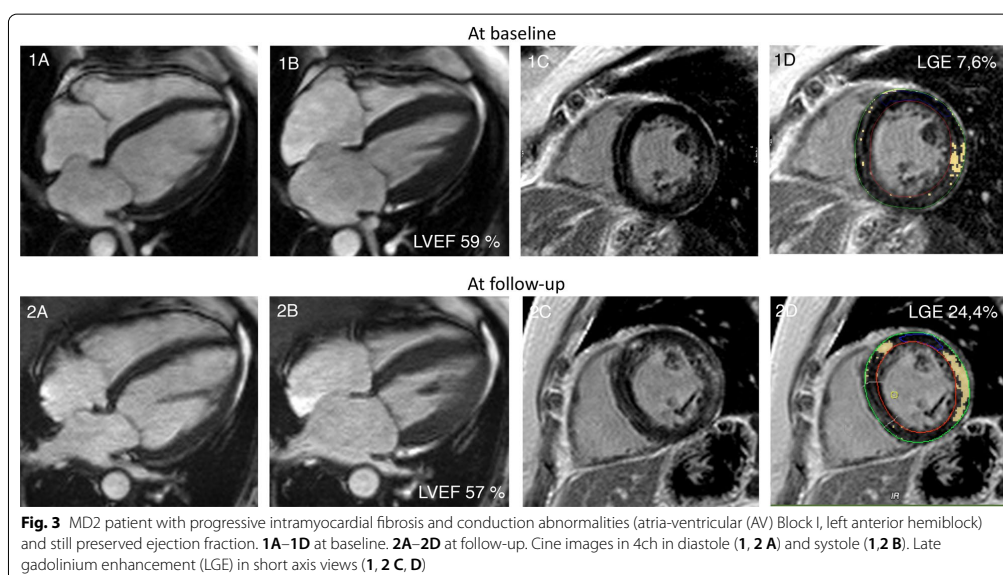


Fig. 3 MD2 patient with progressive intramyocardial fibrosis and conduction abnormalities (atria-ventricular (AV) Block I, left anterior hemiblock) and still preserved ejection fraction. **1A–1D** at baseline. **2A–2D** at follow-up. Cine images in 4ch in diastole (**1, 2 A**) and systole (**1, 2 B**). Late gadolinium enhancement (LGE) in short axis views (**1, 2 C, D**)

and LVEDVI $p=0.013$, RVEDV $p=0.470$ and RVEDV-I $p=0.422$; Table 4).

Quantification of the left atria and right atria size

We observed a significant progression of both LA and RA areas (LA_{baseline} 19 ± 3 vs LA_{FU} 22 ± 3 cm², $p < 0.001$, RA_{baseline} 20 ± 3 vs RA_{FU} 23 ± 4 cm², $p=0.029$) as well as LA volume (for LAEDV $p=0.271$ and for LAEDVI $p=0.227$).

Myocardial tissue differentiation

Parametric mapping, cell and fibrosis volume

We performed T2 and T1 mapping at baseline and during follow-up. Native T1 values dropped in basal slices but remained stable in mid and apical slices (FSHD1: basal $p=0.001$, mid $p=0.102$, apical $p=0.203$). ECV dropped significantly within three whole slices (basal $p < 0.001$, mid $p < 0.001$, apical $p < 0.001$). T2 mapping values decreased significantly similarly as in MD2 patients (basal $p < 0.001$, mid $p < 0.001$, apical $p < 0.001$). Interestingly, we observed the same phenomenon to that in MD2 patients regarding the cell and fibrosis volume. While the cell volume remained constant, patients at follow-up presented a statistically lower volume of fibrosis (cell volume $p=0.306$, mid $p=0.361$, fibrosis volume basal $p=0.023$, mid $p=0.032$). We included detailed information in the table with the CMR parameters (Table 4).

Focal fibrosis and its relation to cardiac remodeling

In the FSHD1 group, new focal fibrosis was detected in 2 of 40 patients (6%, male). The fibrosis was located inferolateral and inferoseptal. Overall, in 15 of 40 (37%, 3 females) patients focal fibrosis could be identified. The pattern of the fibrosis was non-ischemic with an intramural and subepicardial distribution (Fig. 6). During the follow-up we also observed a quantitative increase in focal fibrosis (Table 5).

At follow up, patients with focal fibrosis showed no significant changes in LVEF (LVEF_{LGE+} $60 \pm 7\%$ vs LVEF_{LGE-} $60 \pm 6\%$, $p=0.356$), as well as in LVEDV and LVEDVI (LVEDV_{LGE+} 152 ± 46 vs LVEDV_{LGE-} 132 ± 23 ml $p=0.242$, LVEDVI_{LGE+} 0.86 ± 0.23 ml/m² vs LVEDVI_{LGE-} 0.74 ± 0.10 , $p=0.131$).

Focal fat

New focal fat infiltration was observed in 5 of 40 patients (13%, 1 female). Majority was located in the apical part of the interventricular septal wall. In one patient the infiltration was found in the inferior wall (Fig. 7). Intramyocardial fat could be detected in 12 of 40 patients (30%, 3 female).

Myocardial deformation- global longitudinal strain (GLS)

To avoid the influence of known focal fibrosis, after exclusion of LGE (+) patients, GLS was significantly lower in FSHD1 patients at follow in comparison to

Table 5 Clinical characteristics and imaging findings according to the distribution of late gadolinium enhancement (LGE) and fat infiltration in DM2 and FSHD1 patients at baseline and at follow-up

Type of Arrhythmias	All DM2 patients		DM2 LGE (+)		DM2 Fat (+)	
	Baseline (n = 32)	Follow-up n = 22	Baseline (n = 5)	Follow-up n = 6	Baseline n = 6	Follow-up n = 7
SVT (n)	2	9	–	5	–	5
Non-sustained VT n (n)	–	–	–	–	–	–
Frequent PVC ($\geq 1000/24h$) (n)	–	–	–	–	–	–
AV Block I (n)	4	5	2	2	2	2
AV Block II (n)	–	1	–	–	–	–
LBBB	1	1	1	1	1	1
RBBB	1	2	–	1	–	–
LAH	2	3	–	1	–	–
<i>LGE location and global volume</i>			5	6		
Inferolateral basal (n)	5	6	5	6	1	3
Anterolateral basal (n)	–	2	–	2	–	–
Septal (n)	1	1	1	1	–	–
LGE area - mean (%)			8.4	17.6		
Fat apical					6	7
<i>Medical therapy</i>						
Beta blockers (n)	1	3	–	1	–	1
ACE, Sartans (n)	4	10	1	2	–	2

Type of Arrhythmias	All FSHD1 patients		FSHD1 LGE (+)		FSHD1 Fat (+)	
	Baseline (n = 52)	Follow-up (n = 40)	Baseline (n = 13)	Follow-up (n = 15)	Baseline (n = 7)	Follow-up (n = 12)
SVT (n)	1	8	1	3	–	5
Non-sustained VT n (n)	1	2	1	2	1	1
Frequent PVC ($\geq 1000/24h$) (n)	2	11	1	8	2	3
AV Block I (n)	1	3	1	1	–	1
AV Block II (n)	–	–	–	–	–	–
LBBB	–	–	–	–	–	–
RBBB	–	–	–	–	–	–
LAH	–	–	–	–	–	–
<i>LGE location and global volume</i>			13	15	2	3
Inferolateral basal (n)	7	7	7	7	–	–
Anterolateral basal (n)	2	1	2	1	–	–
Septal (n)	3	3	3	3	–	–
Inferior (n)	1	3	1	3	–	–
LGE area - mean (%)			18.6	28.9		
Fat apical					7	12
<i>Medical therapy</i>						
Beta blockers (n)	1	4		1	1	3
ACE-I, ARBs (n)	2	7	1	3	1	2

SVT = supraventricular tachycardia, VT = ventricular tachycardia, PVC = premature ventricular contractions, LBBB = left bundle branch block, RBBB = right bundle branch block, LAH = left anterior hemiblock, LGE = late gadolinium enhancement. ACE-I = angiotensin-converting enzyme (ACE) inhibitors, ARBs = angiotensin II receptor blockers

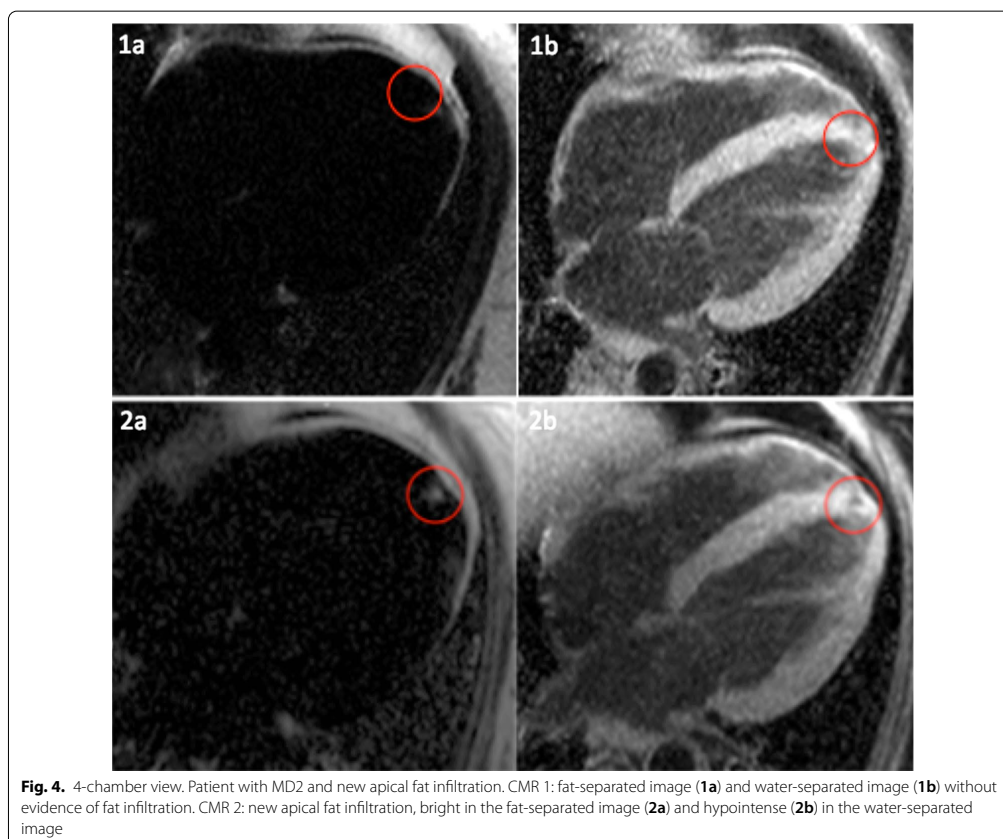


Fig. 4. 4-chamber view. Patient with MD2 and new apical fat infiltration. CMR 1: fat-separated image (**1a**) and water-separated image (**1b**) without evidence of fat infiltration. CMR 2: new apical fat infiltration, bright in the fat-separated image (**2a**) and hypointense (**2b**) in the water-separated image

baseline ($GLS_{FSDH1} LGE (-)_{baseline} -18.3 \pm 1\%$ vs. $GLS_{FSDH1} LGE (-)_{at follow up} -16.4 \pm 1\%$, $p < 0.01$).

Heart rhythm abnormalities and its relation to myocardial tissue changes

12-lead ECG was available in all patients, Holter-ECG in 34 of 40 patients (85%) with the diagnosis of FSHD1. The lack of data was due to patient related reasons.

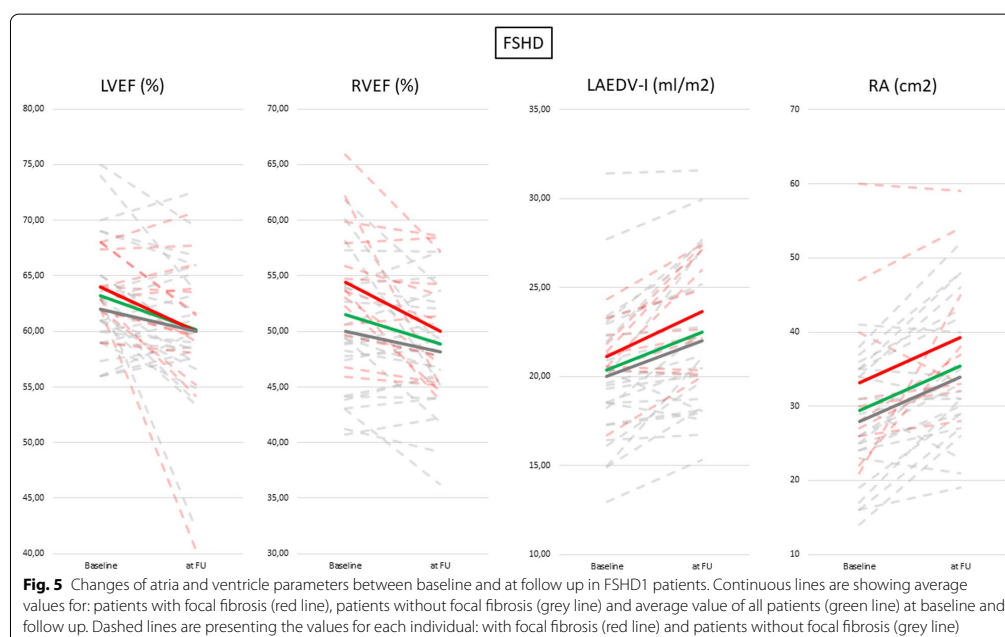
New arrhythmic events were recorded in 10 of 34 patients (29%). NSVT was detected in one patient, runs of SVT in eight patients. Groh-criteria could not be identified. Holter was not available in 5/34 patients with focal fibrosis and/or fat infiltration. Ventricular arrhythmias (PVC > 1000) were observed in 8 patients with focal fibrosis and 3 patients with fat infiltration. SVTs were present in 5 patients with fatty infiltrations and 3 patients with focal fibrosis (Table 5).

Discussion

In this study, we demonstrate that cardiac remodeling is progressive in both MD2 and FSHD1. Even in the absence of significant cardiac symptoms we observed a progression of structural and functional changes regarding all cardiac chambers.

The incidence of myocardial tissue changes such as focal fibrosis and fat infiltration was also higher at follow-up. There seems to be a relationship between structural abnormalities and abnormal heart rhythms and conduction abnormalities/disturbances. To the best of our knowledge, this is the first follow-up study applying CMR in patients with MD2 and FSHD1.

In inherited neuromuscular disorders such as DMD and BMD the development of a cardiomyopathy and/or heart failure is the second most important cause of death after respiratory failure. LV focal fibrosis was described in approximately 70% of these patients [26, 27]. The

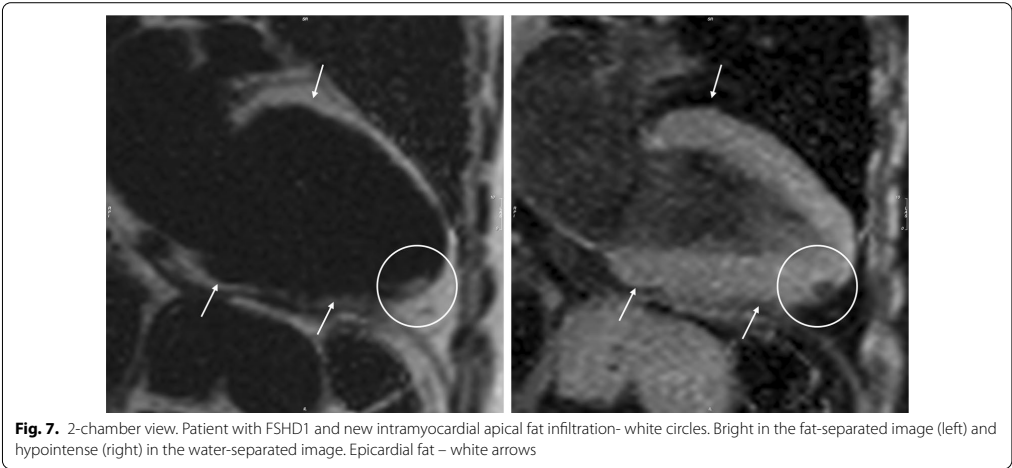
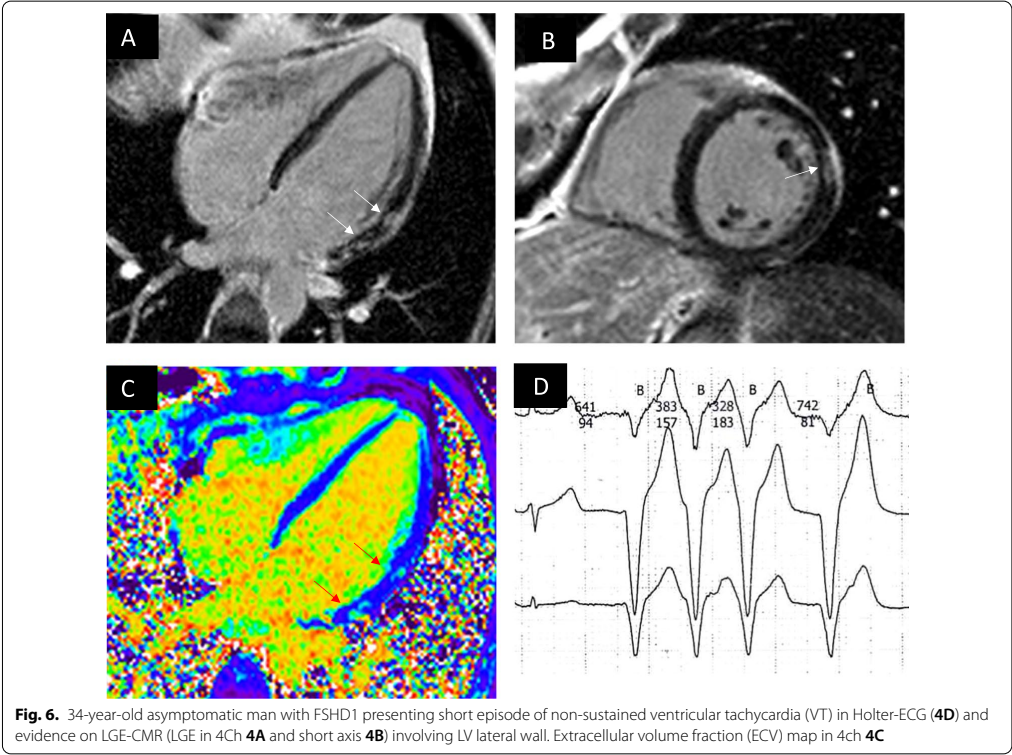


progression of myocardial fibrosis in other forms of MD are already well known [27, 28]. Furthermore, follow-up studies performed in DMD carriers showed progressive myocardial changes such as focal fibrosis and impaired LVEF [29]. In our study, we found that almost 30% of patients with MD2 and FSHD1 had focal fibrosis despite a preserved LVEF. However, in FSHD1 patients RVEF was mildly impaired starting already at baseline. During follow-up the remodeling of ventricle and atria was progressive. LV and RV functions worsened in both patient groups. Furthermore, we observed an increase of atrial size which was more evident in patients with known supraventricular arrhythmias. In almost 26% of patients with MD2, diabetes mellitus was already present at baseline. With this being a traditional cardiovascular risk factor associated with vascular events, it could contribute to cardiac remodeling, nevertheless all patients with focal fibrosis showed a non-ischemic LGE pattern.

Myocardial fat infiltration is a less studied matter in comparison to focal fibrosis as detection of fat by applying CMR is challenging. Thanks to recent technical developments identification of even small changes is feasible [17]. A correlation between fatty infiltration and arrhythmia frequency is already known in different diseases. Lu et al. reported the presence of myocardial fat in dilated cardiomyopathy (DCM) patients and its significant

relationship to LV global function as well as a possible influence on the prognosis of DCM [30]. However, larger data sets are still missing and fatty remodeling seems to be underestimated and understudied. Fat within apical septum was reported also in healthy, however in our study focal fat infiltration was present in a much higher percentage of the studied cohort (30% of MD2 and FSHD1 patients). Especially in our MD2 patient group, all arrhythmic events were associated with the presence of fatty infiltrations, possibly underlying the impact on conduction abnormalities as discussed below.

In most patients with MD the LV is affected, presenting with a dilatation or reduced LVEF. However, over a span of the last few years there has been increasing awareness of the potential impact of RV impairment. RV and atrial remodeling may also dominate with clinical manifestations in neuromuscular diseases. These findings are often combined with rhythm- and conduction abnormalities [31]. Cardiac conduction abnormalities and atrial tachyarrhythmias are commonly observed in inherited MD and may also evolve from myocardial remodeling [32]. In patients with myotonic dystrophy type 1 (MD1), rhythm and conduction abnormalities are the dominant features of cardiac involvement, while heart failure seems to not be the most frequent finding in this entity. Asymptomatic MD1 patients with Groh-criteria were at higher



risk of SCD when compared to those with normal ECGs. In Emery Dreifuss MD cardiac involvement is predominantly identified by conduction defects and atrial fibrillation/flutter. These patients often show atrial dilation in different stages [32, 33].

Patients with MD2 and FSHD1 are known to suffer from supraventricular arrhythmias as well as conduction disturbances like AV blocks [11]. In our group we observed the progression of atrial enlargement and a decrease of atrial function. This may explain the progression of SVT. Recently published studies have shown that multiple atrial premature contractions and SVTs predict stroke recurrence in patients with cryptogenic stroke without atrial fibrillation and may be a reproducible marker of atrial myopathy [33, 34]. Interestingly, Winterholler et al. showed an increased risk for ischemic strokes in DMD patients. It is suspected that cardioembolic stroke is an under-recognized complication in patients with MD [34–36].

Parametric mapping is a method that brings unique quantitative diagnostic information concerning the myocardium.

In our cohorts we observed an increase of the number of focal myocardial changes as well as a worsening of GLS. T2 decreased significantly. T1 values stayed stable in most segments while ECV dropped significantly in both groups. The correlation of the EVC to the LV-morphology showed, that meanwhile the cell volume stayed constant, the volume of fibrosis was lower at follow-up. The cause for the decrease remains speculative (possible cardioprotective medication, progressive fat infiltration?). We have further discussed progressive fat infiltration as a possible explanation, as one could expect especially in this disease, further remodeling in this direction. However, we refused this possibility because T2 decreased. The explanation remains speculative, but an influence of anti-remodeling medications and myocardial deoxygenation could explain the observed mapping variations. We assume, that the decrease of T2 can be explained by T2* effects and may reflect a deterioration of myocardial oxygenation that may play a role in the further development of fibrosis. It was previously shown, that lower T2* mapping values are related to alterations in the myocardial microcirculation. Manka et al. showed that BOLD CMR (blood oxygen level dependent) at rest revealed significantly lower T2* values for segments supplied by >50% stenosed vessels [37]. Friedrich et al. presented the decrease of signal intensity during adenosine perfusion imaging within segments related to coronary artery stenoses >75% [38]. Significant changes were also found in hypertensive patients compared to healthy controls [39].

We assume that the decrease of ECV at follow-up is probably related to a change of therapy between the two time points. The cardioprotective medication was optimized including ACE inhibitors. This may play a role in regards to the myocardial tissue changes within the whole group. Interestingly, Raman et al. could further show, that ACEI and mineralocorticoid receptor antagonists have an influence on fibrosis in MD [40]. There is no systematic CMR analysis investigating the effects of beta receptor blockade. This thesis is supported by our calculations, which show a reduced fibrosis volume with an unchanged total cell volume. Further follow-up trials will help to increase the understanding of these phenomenon's and to define its impact on the patient prognosis.

Quantification of myocardial deformation is of growing interest in CMR. Although relatively new, CMR feature tracking has been performed in various myocardial diseases like cardiomyopathies, aortic valve diseases or myocardial infarction. It allows quantification of global and regional myocardial deformation offering additional information beyond ejection fraction and has the potential to detect subclinical myocardial dysfunction in patients with non-ischemic heart disease even in preserved ejection fraction and without wall motion abnormalities [41, 42].

In our cohort, GLS was significantly lower at follow up although global LV function was preserved. That could also be shown in patients without focal myocardial injury. It seems that a volumetric approach using LVEF may be less reliable during the first years of follow-up regarding the early phase of subclinical LV remodeling.

In our study we observed a remarkably fast progressive decline of the cardiac morphology and function as well as a progression of rhythm disturbances including arrhythmias, even in asymptomatic patients (see Fig. 5). Both ventricles as well as atria were affected. The changes occurred within 2–5 years. This underlines the need for routine ECG or echocardiographic testing even in asymptomatic patients. Currently, routine ECG and/or echocardiographic exams are only indicated in symptomatic FSHD1 patients.

Further multi-center follow-up studies are needed to understand the relation between cardiac remodeling in MD and the outcome. However, regular use of CMR for follow-up in these patients may provide a valuable risk stratification tool in the future.

Limitations

Our sample size is relatively small, but both cohorts are recognized as rare diseases and this is the first follow-up study in this cohort. It was not possible to

perform ECG-monitoring in all patients due to logistical reasons. This is an observational prospective cohort study, therefore there was no randomization into different treatment groups. Nevertheless, there is a potential impact of many other factors like progressive fat infiltration as well as the received therapy during the follow-up period, which should be taken into consideration. Currently, there are not enough data to report outcome analysis.

Conclusions

Patients with MDs gain an increasing awareness in cardiology. We observed a remarkably fast progressive decline of cardiac morphology and function as well as a progression of rhythm disturbances including arrhythmias, even in asymptomatic patients. These changes occurred within a short period of time. It seems that a potential association between an increase of arrhythmias and progression of myocardial tissue damage such as focal fibrosis and fat infiltration exists. Our data suggest that these patients should be carefully followed to identify early development of remodeling and potential risks for the development of further cardiac events even in the absence of symptoms.

Longitudinal multi-center trials with a larger sample size will help to define the impact of our findings as well as further demonstrate a correlation between myocardial injury and arrhythmias in regards to long-term prognosis and therapeutic decision-making.

Abbreviations

2Ch: Two chamber; 3Ch: Three chamber; 4Ch: Four chamber; ACE: Angiotensin converting enzyme; AHA: American Heart Association; ARB: Angiotensin receptor blocker; AV: Atrioventricular; BMD: Becker muscle dystrophy; bSSFP: Balanced steady state free precession; CMR: Cardiovascular magnetic resonance; DMD: Duchenne muscle dystrophy; ECG: Electrocardiogram; ECV: Extracellular volume fraction; FSHD1: Facioscapulohumeral muscular dystrophy type 1; GLS: Global longitudinal strain; GRE: Gradient echo; LA: Left atrium/left atrial; LAEDV: Left atrial end-diastolic volume; LAEDVI: Left atrial end-diastolic volume index; LGE: Late gadolinium enhancement; LV: Left ventricle/left ventricular; LVEDV: Left ventricular end-diastolic volume; LVEDVI: Left ventricular end-diastolic volume index; LVEF: Left ventricular ejection fraction; MD: Muscular dystrophy; MD1: Myotonic dystrophy type 1; MD2: Myotonic dystrophy type 2; MOLL: Modified Look-Locker inversion recovery; NSVT: Non-sustained ventricular tachycardia; PVC: Premature ventricular contractions; RA: Right atrium/right atrial; ROI: Region of interest; RV: Right ventricle/right ventricular; RVEDV: Right ventricular end-diastolic volume; RVEDVI: Right ventricular end-diastolic volume index; RVEF: Right ventricular ejection fraction; SAx: Short axis; SCD: Sudden cardiac death; STRM: Signal threshold versus reference mean; SVT: Supraventricular tachycardia.

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Authors' contributions

All authors participated in the discussion of the concept of the study. EB and JSM conceived the study design. EB and CL obtained CMR images and analyzed CMR scans. EB, CL, JG, PK, SS, LS and JSM analyzed the data. EB, JSM drafted the manuscript. As authors, we attest to each of our substantial contributions to the manuscript and critical revision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study design was approved by the local ethics committee (The ethical board of the Charité University Medicine Berlin, EA1/042/17) and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Consent for publication

All authors approved the manuscript and are aware of the data.

Competing interests

EB, CL, JG, PK, SS, LS and JSM declare that they have no competing interests.

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Quantification of myocardial strain assessed by cardiovascular magnetic resonance feature tracking in healthy subjects—influence of segmentation and analysis software

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Abstract

Objectives Quantification of myocardial deformation by feature tracking is of growing interest in cardiovascular magnetic resonance. It allows the assessment of regional myocardial function based on cine images. However, image acquisition, post-processing, and interpretation are not standardized. We aimed to assess the influence of segmentation procedure such as slice selection and different types of analysis software on values and quantification of myocardial strain in healthy adults.

Methods Healthy volunteers were retrospectively analyzed. Post-processing was performed using CVI⁴² and TomTec. Longitudinal and radial_{Long axis (LAX)} strain were quantified using 4-chamber-view, 3-chamber-view, and 2-chamber-view. Circumferential and radial_{Short axis (SAX)} strain were assessed in basal, midventricular, and apical short-axis views and using full coverage. Global and segmental strain values were compared to each other regarding their post-processing approach and analysis software package.

Results We screened healthy volunteers studied at 1.5 or 3.0 T and included 67 (age 44.3 ± 16.3 years, 31 females). Circumferential and radial_{SAX} strain values were different between a full coverage approach vs. three short slices (−17.6 ± 1.8% vs. −19.2 ± 2.3% and 29.1 ± 4.8% vs. 34.6 ± 7.1%). Different analysis software calculated significantly different strain values. Within the same vendor, different field strengths (−17.0 ± 2.1% at 1.5 T vs. −17.0 ± 1.7% at 3 T, $p = 0.845$) did not influence the calculated global longitudinal strain (GLS), and were similar in gender (−17.4 ± 2.0% in females vs. −16.6 ± 1.8% in males, $p = 0.098$). Circumferential and radial strain were different in females and males (circumferential strain −18.2 ± 1.7% vs. −17.1 ± 1.8%, $p = 0.029$ and radial strain 30.7 ± 4.7% vs. 27.8 ± 4.6%, $p = 0.047$).

Conclusions Myocardial deformation assessed by feature tracking depends on segmentation procedure and type of analysis software. Circumferential_{SAX} and radial_{SAX} depend on the number of slices used for feature tracking analysis. As known from other imaging modalities, GLS seems to be the most stable parameter. During follow-up studies, standardized conditions should be warranted.

Trial registration Retrospectively registered

Key Points

- Myocardial deformation assessed by feature tracking depends on the segmentation procedure.
- Global myocardial strain values differ significantly among vendors.
- Standardization in post-processing using CMR feature tracking is essential.

Keywords Magnetic resonance imaging · Left ventricular function · Software · Myocard · Healthy volunteers

Carolin Lim and Edyta Blaszczyk contributed equally to this work.

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Abbreviations

AHA	American Heart Association
CMR	Cardiovascular magnetic resonance
CS	Circumferential strain
GCS	Global circumferential strain
CV	Chamber view
GLS	Global longitudinal strain
GRE	Gradient echo sequence
LAX	Long axis
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEDVI	Left ventricular end-diastolic index
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MOLLI	Modified look-locker inversion-recovery
RS	Radial strain
SAX	Short axis
SD	Standard deviation
SSFP	Steady-state free precession

Background

Quantification of myocardial deformation applying myocardial strain is of growing interest in cardiovascular magnetic resonance (CMR). For a few years, it has been applied in research, and different vendors have developed post-processing tools [1].

Myocardial strain allows quantitative measurement of global but also regional myocardial function and deformation offering additional information beyond ejection fraction [2, 3]. It enables early detection of subclinical myocardial dysfunction in patients with ischemic and non-ischemic heart disease and in preserved ejection fraction without wall motion abnormalities [2, 4–14].

Left ventricular deformation can be quantified in three dimensions: longitudinal and circumferential strain which show ventricular shortening in longitudinal and circumferential directions (negative strain) and radial strain that characterizes wall thickening (positive strain) [15].

Assessment of myocardial regional function is well known in echocardiography using speckle tracking [12, 15, 16] but is also increasingly investigated in CMR using different techniques, such as strain encoding (SENC) [17, 18], displacement encoding (DENSE) [19], and tagging [17, 18, 20–22]. Feature tracking is a tool which in contrast to the methods mentioned above enables post-processing analysis of myocardial strain based on routine steady-state free precession (SSFP) cine images as acquired for the assessment of left ventricular (LV) function and volume [8, 16, 23]. It avoids acquisition of additional images and saves time [23]. Pre-existing contours for calculation of LV function can be used for strain analysis making it a timesaving method. For those

reasons, feature tracking seems to be a beneficial tool, e.g., for follow-up examinations.

Even though publications regarding CMR strain analysis exist, standards for image acquisition and interpretation are still not established. Different vendors and different analysis procedures such as slice selection procedures, even within the same software, can heavily influence deformation values. This may lead to uncertainties in comparison and interpretation of data. We aimed to analyze the influence of segmentation procedure such as slice selection on values of quantification of myocardial strain in healthy adults. Additionally, we intended to analyze the influence of different software packages and to provide regional strain quantification.

Methods**Study population**

We retrospectively screened 243 truly healthy subjects, who were prospectively examined in former studies [24–28]. Exclusion criteria were known cardiovascular risk factors, any pre-existing diseases or medications, impaired LV ejection fraction (LVEF) (<55%), or pathological findings in 12 lead ECG or CMR. Incomplete CMR data for feature tracking analysis led to exclusion. That included lack of long-axis (LAX) or short-axis (SAX) slices ($n = 137$) or variable number of cardiac phases ($n = 41$). The ethics committee approved all studies. Informed written consent was obtained in concordance with the Helsinki Declaration.

CMR acquisition

CMR was performed at 1.5-T and 3-T scanners. At 1.5 T (Magnetom Avanto), a 12-channel radio frequency coil was used and at 3 T (Magnetom Verio, both Siemens Healthineers) a 32-channel radio frequency coil. SSFP cine images were acquired during repeated breath-holds for LV in 4-chamber-view (4CV), 3-chamber-view (3CV), 2-chamber-view (2CV), and at least three SAX slices (SAX full coverage and/or three SAX slices in basal, midventricular, and apical plane). Recently, detailed sequence parameters were published [24–29]: at 1.5 T: repetition time 2.8 ms, slice thickness 6 mm, flip angle 80 degrees, echo time 1.2 ms, field of view $276 \times 340 \text{ mm}^2$, matrix 156×192 , voxel size $1.4 \times 1.4 \times 7 \text{ mm}$, 30 cardiac phases; and at 3 T: repetition time 3.1 ms, slice thickness 6 mm, flip angle 45 degrees, echo time 1.3 ms, field of view $276 \times 340 \text{ mm}^2$, matrix 156×192 , voxel size $1.4 \times 1.4 \times 7 \text{ mm}$, 30 cardiac phases.

Two independent experienced readers (SCMR level III) performed the visual evaluation of the cine images.

LV function and volumes were quantified in a whole SAX stack according to the recommendation of the SCMR [30] applying CVI⁴² software (Version 4.1.2, Circle Cardiovascular Imaging Inc.). Endo- and epicardial contours were manually drawn in end-diastolic and end-systolic phase. Papillary muscles were excluded from the LV volume.

Feature tracking

Feature tracking analysis was performed retrospectively using CVI⁴² software (prototype version 5.3.0, Circle Cardiovascular Imaging Inc.). Longitudinal strain and radial_{LAX} strain (RS) were assessed in three LAX views: 4CV, 3CV, and 2CV (Fig. 1). Circumferential strain (CS) and RS_{SAX} were analyzed using three SAX slices (basal, mid-ventricular, and apical) in all subjects (Fig. 1). If available, strain was additionally assessed using a SAX full coverage (Fig. 2). Endo- and epicardial contours were manually drawn in end-diastolic phase, defined as the phase with the largest LV volume. End-diastolic phase had to be identical in all SAX and LAX slices of one subject. Trabeculae, papillary muscles, pericardium, and epicardial fat were consequently excluded from contouring. Left ventricular outflow tract (LVOT) was completely excluded in all SAX slices if seen in diastolic and/or systolic phases (Fig. 2). 2D strain analysis was assessed globally and segmentally for longitudinal, RS_{LAX}, CS, and RS_{SAX} strain. Segmentation included both possibilities of slice selection (three slices versus the whole stack) and the segmentation of the left ventricle according to the AHA 17-segment model [31]. We excluded the apex (segment 17) from feature tracking analysis; so far, the 16 segment model was

used. Tracking quality and segmentation were evaluated using software tools like mesh, boundaries, or myocardial points. If contours did not follow the epi- or endocardial borders correctly, delineation was retraced and adjusted. In case of remaining tracking issues, all corresponding segments were excluded. Also, incorrect segmentation (see Fig. 3) led to exclusion. Excluded segments were not considered for global strain assessment.

Strain results were compared between field strengths (1.5 T and 3 T) and between different numbers of SAX slices (three SAX slices versus full coverage) in CS and RS_{SAX}, as well as RS between LAX and SAX analysis.

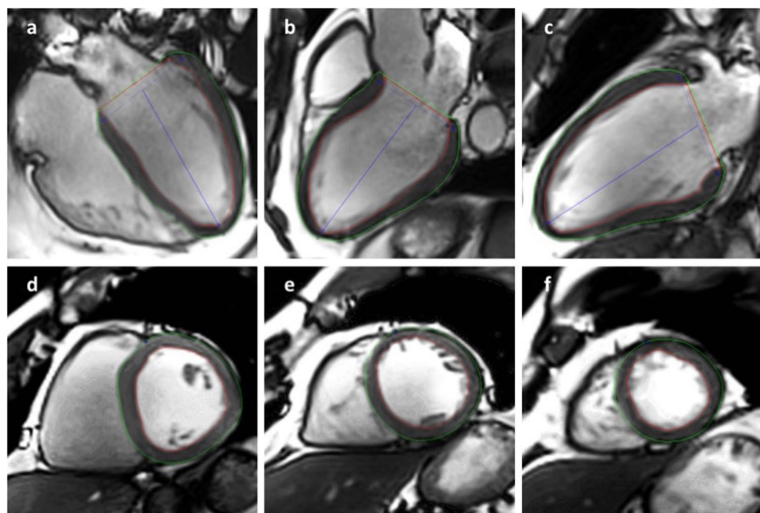
Bulls-eye plots visualizing segmental strain values were created using the Python package Matplotlib.

Global strain analysis was repeated by the same observer (intra-observer) and by a different observer (inter-observer) in the same randomly selected subjects ($n = 10$).

Software comparison

All images were also analyzed with TomTec Image Arena (version 1.3.0.91, TomTec Imaging Systems GmbH) (Fig. 4). 4CV, 3CV, and 2CV were used for longitudinal and transversal (radial_{LAX}) strain. CS and RS_{SAX} were assessed using three SAX slices (basal, midventricular, and apical). Endo- and epicardial contours were manually drawn in end-diastolic and end-systolic phases. Trabeculae and papillary muscles were excluded from analysis, as well as LVOT. Tracking quality was checked manually, specifically whether contours followed endo- and epicardial borders correctly and were adjusted if necessary. Myocardial strain was analyzed on a global and segmental level.

Fig. 1 Post-processing using 2D strain analysis by CVI⁴². Endo- (red) and epicardial (green) contours were manually drawn in end-diastolic phase in long axis (a–c) and short axis (d–f). 4-chamber-view (a), 3-chamber-view (b), and 2-chamber-view (c) were included in long-axis strain analysis. For short-axis strain, contours were drawn in three short-axis slices: basal (d), mid-ventricular (e), and apical (f)



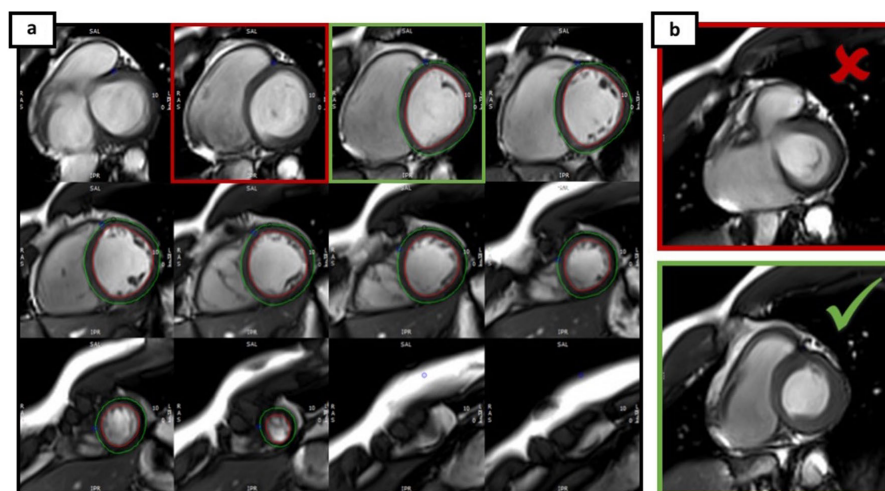


Fig. 2 Strain analysis using full coverage (CVI⁴²). Endo- and epicardial contours were drawn in end-diastolic phase (a). If LVOT was visible in end-systolic phase (b, marked red), slices were excluded. The first slice

used for analysis was chosen as the most basal slice that did not show LVOT in any end-diastolic (a, marked green) and end-systolic phase (b, marked green)

Three LAX (4CV, 3CV, 2CV) and three SAX slices using the exact same slice number were considered for software comparison.

analyzed using intra-class correlation coefficient (ICC) and 95% confidence interval (CI). ICC was classified as poor (ICC < 0.4), good (ICC = 0.4–0.75), or excellent (ICC > 0.75) [1].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistic version 23. We calculated mean values and standard deviation (SD) as well as median and interquartile ranges (IQR) for demographic parameters, LV function, and strain measurements. Volumes were indexed to body surface area (BSA) and height. The non-parametric Mann-Whitney *U* test for unpaired samples was used for comparisons of strain parameters between gender, analysis software, and field strength. Differences were considered to be statistically significant at $p < 0.05$. Intra- and inter-observer reproducibility were

Results

Basic data

Sixty-seven healthy subjects ($n = 36$ at 1.5 T and $n = 31$ at 3 T) were included and analyzed (mean age 44.3 ± 16.3 years, $n = 31$ females). The proportion of men and age between the field strength groups was equalized. The 1.5 T group had 19 (52.8%), while the 3 T group accounted for 17 (54.8%) male

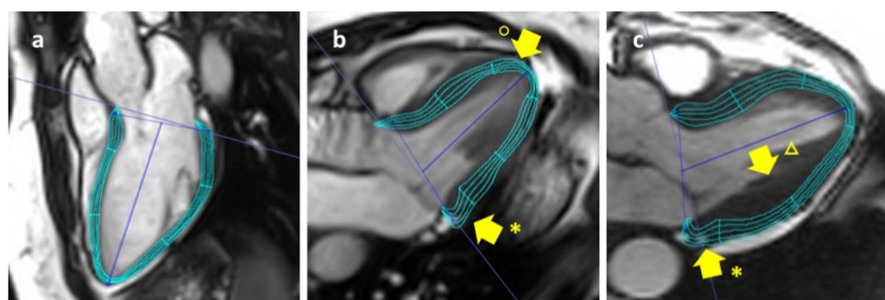
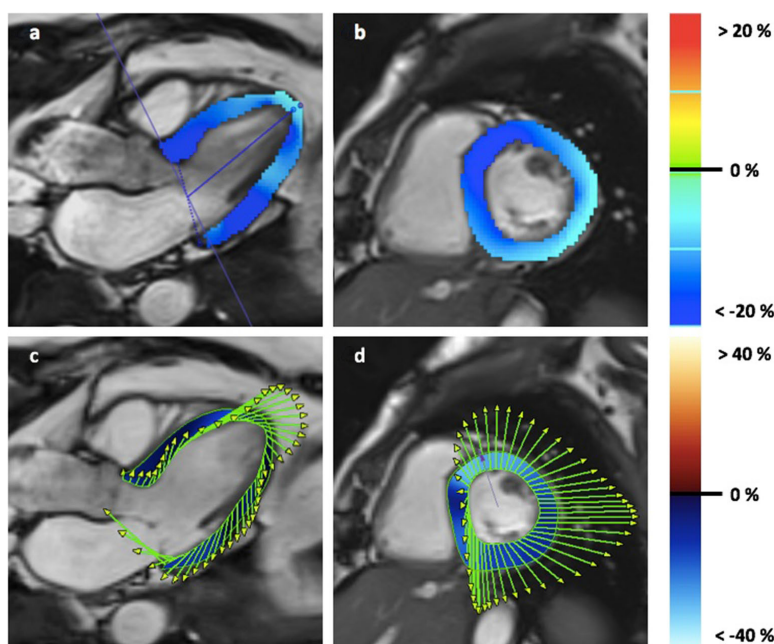


Fig. 3 Quality assessment for accurate tracking and correct segmentation applying CVI⁴². a Optimal segmentation. b and c show incorrect segmentations in 3-chamber-view: the basal inferolateral segments are

relatively short (*) and the apical septal segment extends to apical lateral (°). Additionally, contours do not follow endocardial borders accurately (Δ)

Fig. 4 2D strain analysis of the left ventricle using different post-processing software. Strain was analyzed using CVI⁴² (a–b) and TomTec software (c–d). Longitudinal and radial_{LAX} strain were assessed in 4CV, 3CV (a, c), and 2CV; circumferential and radial_{SAX} strain were analyzed in basal (b, d), medial, and apical short-axis slice



subjects. Mean age was 45.0 ± 16.39 years at 1.5 T versus 43.48 ± 16.33 years at 3 T ($p = 0.739$).

All volunteers had normal LV function ($LVEF 64.1 \pm 4.2\%$) without wall motion abnormalities. Demographic parameters as well as LV function and volumes are summarized in Table 1. Seven subjects had to be excluded from 3D LV function analysis due to incomplete SAX package ($n = 6$) or artifacts ($n = 1$).

Feature tracking quality

In all 67 subjects, strain was analyzed in 4CV, 3CV, 2CV, and three SAX slices. Sixty-one subjects were additionally analyzed by CVI⁴² using a full coverage. Using CVI⁴², we could include 1020 segments (95.1%) for longitudinal strain and 1033 segments (96.4%) for RS_{LAX} . In total, 1064 segments (99.3%) for RS_{SAX} and 1064 segments (99.3%) for CS were analyzed. In the SAX, strain analysis using SAX full coverage 966 segments (99.0%) from each of RS_{SAX} and CS could be included.

For analysis with TomTec, 1059 segments (98.8%) could be included for longitudinal strain, 1056 segments (98.5%) for RS_{LAX} , 1071 segments (99.9%) for RS_{SAX} , and 1070 segments (99.8%) for CS.

Reasons for exclusion were inaccurate tracking or incorrect segmentation.

Table 1 Basic characteristics of the study population

	Mean \pm SD	Median	Q1	Q3
Demographic parameters				
Gender (female male)	31 36			
Age (years)	44.3 ± 16.3	45.0	28.0	59.0
Height (cm)	174.1 ± 8.6	173.0	168.0	180.0
Weight (kg)	74.4 ± 13.0	73.0	64.0	81.6
BMI (kg/m^2)	24.6 ± 3.9	24.2	21.8	27.1
BSA (m^2)	1.9 ± 0.2	1.9	1.8	2.0
HR (1/min)	72.8 ± 11.7	71.0	65.8	79.1
Systolic BP (mmHg)	128.1 ± 14.1	128.0	117.0	137.0
Diastolic BP (mmHg)	73.6 ± 11.7	75.0	68.0	79.0
LV function and volumes				
LVEF (%)	64.1 ± 4.2	64.0	60.4	67.2
LVEDV (ml)	139.9 ± 33.2	135.0	112.2	157.9
LVEDVI (ml/m^2)	74.5 ± 15.1	76.1	62.6	83.3
LVEDVI (ml/cm)	0.8 ± 0.2	0.8	0.7	0.9
LVESV (ml)	51.1 ± 15.0	47.5	40.8	60.4
LVM (g)	101.0 ± 22.3	97.9	88.7	110.9
LVMi (g/m^2)	53.7 ± 9.0	54.2	48.3	57.7
LVMi (g/cm)	0.6 ± 0.1	0.6	0.5	0.6
SV (ml)	89.2 ± 20.2	88.0	75.6	101.1
SVI (ml/m^2)	47.5 ± 9.4	46.6	39.2	54.8
SVI (ml/cm)	0.5 ± 0.1	0.5	0.4	0.6

Data are shown as mean values \pm standard deviation (SD), median, and interquartile ranges (Q1 and Q3)

BMI body mass index, BSA body surface area (Mosteller), HR heart rate, BP blood pressure, LVEF left ventricular ejection fraction, LVEDV left ventricular end-diastolic volume, LVEDVI left ventricular end-diastolic volume index, LVESV left ventricular end-systolic volume, LVM left ventricular mass, LVMi left ventricular mass index, SV stroke volume, SVI stroke volume index

Influence of slice selection on circumferential and radial_{SAX} strain using CVI⁴²

CS and RS_{SAX} measurements assessed by a stack of short axes covering the whole LV differ significantly from those assessed using three short axes: global CS $-19.2 \pm 2.3\%$ (median -19.0% , IQR -20.6 to -17.9%) in 3 SAX vs. $-17.6 \pm 1.8\%$ (median -17.7% , IQR -18.6 to -16.7%) in full coverage ($p < 0.001$) and global RS_{SAX} $34.6 \pm 7.1\%$ (median 33.4% , IQR 29.9 – 38.8%) in 3 SAX vs. $29.1 \pm 4.8\%$ (median 29.1% , IQR 26.2 – 31.9%) in full coverage ($p < 0.001$) (for details, see Table 2).

Using three SAX slices, no differences were found for global strain measurements between 1.5 T and 3 T: global CS $-19.6 \pm 2.3\%$ (median -18.9% , IQR -21.3 to -18.0%) at 1.5 T vs. $-18.8 \pm 2.2\%$ (median -19.0% , IQR -20.5 to -17.6%) at 3 T ($p = 0.263$) and for global RS_{SAX} $36.0 \pm 7.5\%$ (median 33.4% , IQR 29.9 – 38.8%) at 1.5 T vs. $33.0 \pm 6.2\%$ (median 32.6% , IQR 28.9 – 37.3%) at 3 T ($p = 0.128$). However, some segmental strain values differed significantly between field strengths for both CS and RS_{SAX} (for details, see supplemental material online additional file 1).

Using SAX full coverage, both global and segmental strain values did not show any significant difference between field strengths: CS $-17.7 \pm 1.8\%$ (median -17.7% , IQR -18.8 to -16.6%) at 1.5 T vs. $-17.6 \pm 1.8\%$ (median -17.6% , IQR -18.5 to -16.9%) at 3 T ($p = 0.85$) and global RS_{SAX} $29.4 \pm 5.1\%$ (median 29.6% , IQR 25.9 – 32.3%) at 1.5 T vs. $28.7 \pm 4.5\%$ (median 28.7% , IQR 26.6 – 31.1%) at 3 T ($p = 0.665$) (for details, see supplemental material online additional file 1).

In both, three selected slices and a whole SAX stack global circumferential and radial_{SAX} strain differed significantly between genders (for details, see Table 2). Gender-related strain values are visualized in the supplemental material additional file 2.

Assessment of radial strain in long- and short-axis views

Global radial strain acquired in LAX (radial_{LAX}) versus SAX (radial_{SAX}) differed significantly: global radial_{LAX} $29.1 \pm 5.3\%$ (median 29.1% , IQR 25.1 – 32.8%) versus global radial_{SAX} $34.6 \pm 7.1\%$ (median 33.4% , IQR 29.9 – 38.8%) ($p < 0.001$).

Longitudinal strain using CVI⁴²

Longitudinal strain did not show any significant difference for both global and segmental strain measurements between 1.5 T and 3 T: $-17.0 \pm 2.1\%$ (median -17.0% , IQR -18.4 to -15.3%) vs. $-17.0 \pm 1.7\%$ (median -17.1% , IQR -18.0 to -15.8%) ($p = 0.845$ accordingly). No significant differences have been found between females and males: $-17.4 \pm 2.0\%$

(median -17.7% , IQR -18.4 to -15.8%) and $-16.6 \pm 1.8\%$ (median -16.6% , IQR -18.0 to -15.3%) ($p = 0.098$). On a segmental level, only AHA segment 5 (basal inferolateral) showed a significant difference between genders: $-25.8 \pm 5.9\%$ (median -26.7% , IQR -30 to -22.8%) in females versus $-23.3 \pm 5.0\%$ (median -23.4% , IQR -27.5 to -18.4%) in males ($p = 0.048$). Segmental strain measurements for longitudinal strain are presented in Fig. 5.

Software comparison

Strain measurements assessed with TomTec software were significantly different to those assessed with CVI⁴² (Table 3). GLS was $-17.0 \pm 1.9\%$ (median -17.0% , IQR -18.4 to -15.6%) for CVI⁴² and $-20.5 \pm 2.7\%$ (median -20.2% , IQR -22.6 to -18.8%) for TomTec ($p < 0.001$). Significant differences were also found for most segmental strain values (for details, see supplemental material online additional files 3–6).

Gender-related global strain values using TomTec are summarized in Table 2. Unlike differences in global RS_{SAX}, GLS and global CS were not associated with gender.

Intra- and inter-observer reproducibility (CVI⁴²)

GLS reproducibility was as follows: ICC was 0.941 (95% CI 0.759–0.985) for intra-observer and 0.829 (95% CI 0.273–0.958) for inter-observer analysis. We observed an excellent intra- and inter-observer reproducibility across all global strain measurements (for details, see supplemental material 7). Intra-observer agreement was best for CS (ICC 0.977, 95% CI 0.907–0.994) and lowest for RS_{LAX} (ICC 0.930, 95% CI 0.715–0.983). Inter-observer agreement was best for radial_{SAX} strain (ICC 0.975, 95% CI 0.889–0.994) and lowest for longitudinal strain (ICC 0.829, 95% CI 0.273–0.958).

Discussion

In this study, we aimed to increase knowledge about influencing factors on strain results obtained by CMR feature tracking. We focused on the segmentation procedure and on the comparison of software packages of two different vendors.

For the first time, we showed that CS and RS_{SAX} were dependent on the number of slices used for feature tracking analysis. Previous published studies considered a different number of slices for strain analysis making it difficult to compare strain values to each other. While some used one LAX and one midventricular SAX slice [20, 32, 33], others included two LAX and three SAX views [34, 35] or considered all three LAX views and a SAX full coverage [36]. The variation in analysis procedure like slice selection may lead to different quantitative results and consequently to uncertainties and

Table 2 Global strain values based on field strength, gender, and different post-processing software

	Longitudinal strain (%)				Radial _{LAX} strain (%)				p value	Q1	Q3	Median	Q1	Q3	p value
	Mean ± SD	Median	Q1	Q3	Mean ± SD	Median	Q1	Q3							
CVI ^{d2}	1.5 T	-17.0 ± 1.9	-17.0	-18.4	-15.6	29.1 ± 5.3	29.1	25.1	32.8	0.792	0.033	29.1 ± 5.3	25.1	32.8	0.792
	3 T	-17.0 ± 2.1	-17.0	-18.4	-15.3	29.1 ± 5.8	28.8	25.1	33.6						
	Females	-17.0 ± 1.7	-17.1	-18.0	-15.8	29.1 ± 4.6	29.4	26.3	32.5						
TomTec	Males	-17.4 ± 2.0	-17.7	-18.4	-15.8	30.7 ± 5.7	29.9	26.3	34.0	0.098	0.002	27.4 ± 4.5	24.4	30.4	0.087
	1.5 T	-16.6 ± 1.8	-16.6	-18.0	-15.3	70.1 ± 21.0	65.2	56.0	79.7						
	3 T	-20.5 ± 2.7	-20.2	-22.6	-18.8	77.8 ± 22.9	78.1	59.1	93.5						
CVI ^{d2}	Females	-20.2 ± 2.3	-19.8	-22.1	-18.3	60.9 ± 14.1	60.1	52.6	72.2	0.114	0.0268	66.1 ± 15.1	57.9	89.0	0.087
	Males	-20.7 ± 3.2	-20.3	-23.2	-19.3	74.9 ± 25.9	75.3	57.9	89.0						
	3 T	-20.3 ± 2.2	-19.9	-22.4	-18.7	Full coverage	61.2	55.5	77.8						
TomTec	1.5 T	-19.2 ± 2.3	-19.0	-20.6	-17.9	Mean ± SD	Mean	Q1	Q3	0.263	0.010	-17.6 ± 1.8	-18.6	-16.7	0.855
	3 T	-19.6 ± 2.3	-18.9	-21.3	-18.0	Full coverage	Median	Q1	Q3						
	Females	-18.8 ± 2.2	-19.0	-20.5	-17.6	Mean ± SD	Mean	Q1	Q3						
TomTec	Males	-20.0 ± 2.2	-20.0	-21.5	-18.4	17.7 ± 1.8	-17.7	-18.8	-16.6	0.389	0.436	-17.6 ± 1.8	-18.5	-16.9	0.029
	1.5 T	-18.6 ± 2.1	-18.4	-20.1	-17.8	18.2 ± 1.7	-18.2	-19.0	-17.4						
	3 T	-20.7 ± 2.6	-20.8	-23.1	-18.7	17.1 ± 1.8	-17.4	-18.5	-16.2						
CVI ^{d2}	Females	-20.6 ± 2.4	-20.5	-22.5	-18.6	Mean ± SD	Mean	Q1	Q3	0.001	0.006	29.1 ± 4.8	29.1	31.9	0.665
	Males	-21.0 ± 2.8	-21.1	-23.4	-19.0	Full coverage	Median	Q1	Q3						
	3 T	-20.9 ± 2.8	-20.8	-23.4	-19.5	Mean ± SD	Mean	Q1	Q3						
TomTec	1.5 T	-20.5 ± 2.5	-20.6	-22.9	-18.6	29.4 ± 5.1	29.6	25.9	32.3	0.128	0.014	28.7 ± 4.5	28.7	31.1	0.006
	3 T	34.6 ± 7.1	33.4	38.8	35.8	30.7 ± 4.7	29.7	28.2	32.9						
	Females	36.0 ± 7.5	34.1	41.3	37.3	27.8 ± 4.6	28.0	25.0	31.2						
TomTec	Males	33.0 ± 6.2	32.6	37.3	34.3	29.1 ± 4.8	29.1	26.2	31.9	0.001	0.022	29.4 ± 5.1	29.6	32.3	0.665
	1.5 T	36.9 ± 7.2	37.1	42.3	39.6	Full coverage	Median	Q1	Q3						
	3 T	32.7 ± 6.4	31.6	36.2	34.2	Mean ± SD	Mean	Q1	Q3						
CVI ^{d2}	Females	63.7 ± 16.0	64.1	74.9	69.6	29.1 ± 4.8	29.1	26.2	31.9	0.001	0.006	28.7 ± 4.5	28.7	31.1	0.006
	Males	57.4 ± 12.7	56.0	47.1	69.6	30.7 ± 4.7	29.7	28.2	32.9						
	3 T	71.0 ± 16.4	70.2	85.3	85.3	27.8 ± 4.6	28.0	25.0	31.2						
TomTec	1.5 T	67.8 ± 16.4	70.8	77.6	77.6	Full coverage	Median	Q1	Q3	0.001	0.022	29.4 ± 5.1	29.6	31.1	0.006
	3 T	60.2 ± 15.0	57.2	49.8	49.8	Mean ± SD	Mean	Q1	Q3						
	Females	67.8 ± 16.4	70.8	77.6	77.6	Full coverage	Median	Q1	Q3						
TomTec	Males	60.2 ± 15.0	57.2	49.8	49.8	Mean ± SD	Mean	Q1	Q3	0.001	0.022	29.4 ± 5.1	29.6	31.1	0.006
	1.5 T	34.6 ± 7.1	33.4	38.8	35.8	30.7 ± 4.7	29.7	28.2	32.9						
	3 T	36.0 ± 7.5	34.1	41.3	37.3	27.8 ± 4.6	28.0	25.0	31.2						

Global strain values are given as mean ± standard deviation (SD), median, and interquartile range (Q1 and Q3). Significant differences are shown in italics LAX: long axis, SAX: short axis

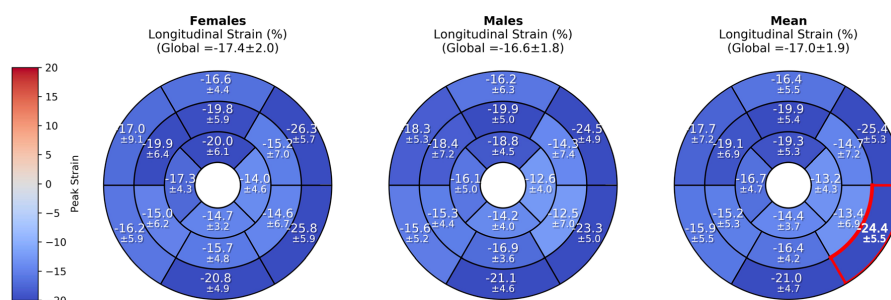


Fig. 5 Gender-related mean values for longitudinal strain using CVI⁴². Segmental values are provided as mean (in %) ± standard deviation in a bulls-eye plot according to the AHA segment model [31]. Segment 5 (marked red) differed between genders ($p = 0.048$)

difficulties in comparison and interpretation. Significant variations among vendors are already known in echocardiography and CMR-FT and this should be considered when performing serial studies [37]. A recent study by Liu et al compared 3D strain analysis (three LAX slices and SAX full coverage) with 2D analysis using one horizontal LAX and one midventricular SAX slice showing notable differences [38]. In our study, we detected differences for CS and RS_{SAX} between three SAX slices and full coverage using CVI⁴². Of note, both parameters were significantly higher using 3 SAX slices vs. full coverage; one should assume that partial volume effects, mainly effecting an apical slice, may influence the results. Furthermore, vendors may use a different way of pixel definition leading to a different boundary detection.

Radial strain assessed in LAX and SAX slices differed significantly. There is no broad experience in using radial_{LAX} strain yet, but when SAX slices are missing, assessment of radial strain in LAX can add information.

Among different types of post-processing software, both global and segmental strain values differed significantly.

These findings indicate that strain values are not comparable between different software applications. Our findings in terms of differences among post-processing software packages are mostly in accordance with previous published data [1, 20, 38]. Barreiro-Pérez et al showed variability among different vendors (TomTec, CVI⁴², Medis, Medviso) in GLS and RS measurements, but not in CS [1]. In our study, strain values were significantly lower using CVI⁴², but these findings conform with previous studies [20, 38]. Cao et al compared different sequences and different post-processing software [20], detecting notable differences between all CMR techniques. However, the proper validation of most analysis procedures as well as absolute and objective reference values is yet to be established. While DENSE, SENC, and tagging, techniques for measuring three-dimensional motion and deformation, require dedicated sequences, feature tracking analysis is based on routine SSFP cine images. However, FT is based on contours only and does not follow intrinsic myocardial contraction. Moreover, the influence of field strengths seems to not be relevant. Schuster et al showed similar results for myocardial

Table 3 Global myocardial strain compared between different post-processing software

	CVI ⁴²				TomTec				<i>p</i> value
	Mean ± SD	Median	Q1	Q3	Mean ± SD	Median	Q1	Q3	
Global longitudinal strain (%)	-17.0 ± 1.9	-17.0 ± 1.9	-17.0	-18.4	-20.5 ± 2.7	-20.2	-22.6	-18.8	< 0.001
1.5 T	-17.0 ± 2.1	-17.0 ± 2.1	-17.0	-18.4	-20.2 ± 2.3	-19.8	-22.1	-18.3	< 0.001
3 T	-17.0 ± 1.7	-17.0 ± 1.7	-17.1	-18.0	-20.8 ± 3.2	-20.7	-23.1	-19.2	< 0.001
Global circumferential strain (%)	-19.2 ± 2.3	-19.0	-20.6	-17.9	-20.7 ± 2.6	-20.8	-23.1	-18.7	0.001
1.5 T	-19.6 ± 2.3	-18.9	-21.3	-18.0	-20.6 ± 2.4	-20.5	-22.5	-18.6	0.076
3 T	-18.8 ± 2.2	-19.0	-20.5	-17.6	-20.9 ± 2.8	-21.1	-23.4	-19.0	0.001
Global radials _{SAX} strain (%)	34.6 ± 7.1	33.4	29.9	38.8	63.7 ± 16.0	64.1	51.1	74.9	< 0.001
1.5 T	36.0 ± 7.5	34.1	30.2	41.3	57.4 ± 12.7*	56.0	47.1	69.6	< 0.001
3 T	33.0 ± 6.2	32.6	28.9	37.3	71.0 ± 16.4*	70.2	60.5	85.3	< 0.001
Global radial _{LAX} strain (%)	29.1 ± 5.3	29.1	25.1	32.8	70.1 ± 21.0	65.2	56.0	79.7	< 0.001
1.5 T	29.1 ± 5.8	28.8	25.1	33.6	77.8 ± 22.9*	78.1	59.1	93.5	< 0.001
3 T	29.1 ± 4.6	29.4	26.3	32.5	60.9 ± 14.1*	60.1	52.6	72.2	< 0.001

Global strain values are given as mean ± standard deviation (SD), median, and interquartile ranges (Q1 and Q3). Radial_{SAX} and circumferential strain were assessed using three short-axis slices (basal, midventricular, apical). Significant differences ($p < 0.05$) are shown in italics. * $p < 0.05$ between 1.5 T and 3 T within one software

strain among 1.5 T and 3 T applying TomTec [32]. This agrees with our results since field strength did not influence global values of longitudinal, RS_{LAX} , RS_{SAX} , and CS strain using CVI⁴².

Reference values for CMR feature tracking analysis have been published, mainly focused on global left ventricular strain. Most studies performed feature tracking via TomTec [36, 39, 40]. Liu et al were the first to establish normal ranges for CVI⁴² using 3D strain analysis [38]. However, regional deformation was only acquired for CS. Regional assessment of myocardial strain is less validated, but may reveal further information compared to global values as single regions of the myocardium can be injured even though global strain is in normal range. We added knowledge on reference values for myocardial strain in healthy subjects using CVI⁴² and TomTec.

Unlike most studies showing greater deformation in females resulting in more negative strain [36, 39–42], we did not find gender-related differences for global longitudinal strain. The larger magnitudes of global CS in females having more negative strain values also agree with the findings reported by Andre et al and Peng et al [40, 41]. However, the higher global radial strain values in females contradict former findings [36, 40].

In accordance with our findings, CMR feature tracking has shown fair reproducibility in previous studies [34]. In fact, strain assessment is influenced by observer experience, but reproducibility may be optimized by training [43, 44]. Most studies indicate better reproducibility for global rather than segmental strain analysis with global CS being the most and global radial strain being the least reproducible measurement [20, 33, 35, 36, 42].

However, analysis methods throughout all studies were not standardized until now. CMR feature tracking–derived strain seems to be influenced by many factors including software package and the applied approach of image processing; thus, reference values should be derived from similar approaches. Currently, no gold standard exists. There is no defined “right” or “wrong” as in most of the publications that evaluate differences between post-processing software or sequences. But there is a need to understand that the application of different approaches may lead to different results.

CMR feature tracking is a promising tool that enables early detection of subtle myocardial dysfunction and prediction of major adverse cardiovascular events [5–7]. Standardization is needed if assessment of myocardial deformation including feature tracking should enter clinical routine.

Limitations

This study is limited by a relatively small, but carefully and well-characterized healthy study cohort. As our analysis was performed retrospectively in prospectively enrolled volunteers, scan protocols were slightly different. This led to

exclusion of 176 subjects due to incomplete CMR data. This may be preventable by a prospectively designed study, but our settings also reflect potential difficulties in clinical routine.

Our statistical analysis was only descriptive and exploratory. It indicates that differences among vendors or segmentation procedures may exist, but further validation remains necessary.

The CMR examinations performed at 1.5 T and 3 T did not contain the same subjects, but showed an equal distribution regarding gender and age. In accordance with our results, pre-existing studies have also shown that field strength does not influence global strain values [32].

CMR feature tracking is less validated for regional strain and radial_{LAX} strain, but they can presumably reveal different physiological mechanisms of the myocardium. Regional assessment is limited by inaccurate tracking or incorrect segmentation which may distort segmental strain values. We provide numbers, but long-term studies have to show the potential significance before CMR-FT may enter clinical routine.

Conclusion

Myocardial deformation assessed by feature tracking depends on segmentation procedure and type of analysis software. Circumferential_{SAX} and radial_{SAX} depend on the number of slices used for feature tracking analysis. As known from other imaging modalities, GLS seems to be the most stable parameter. Standardized conditions should be considered.

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was not required for this study because we screened healthy subjects, who were prospectively examined in former studies and written informed consent was obtained from all subjects (patients) in all former studies.

Ethical approval Institutional Review Board approval was not required because we screened healthy subjects, who were prospectively examined in former studies. The ethical committee had approved all former studies.

Methodology

- retrospective
- observational
- performed at one institution

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weight >120 kg), pre-existent hypertension (>140/90 mm Hg) before index pregnancy, or previous diagnosis of cardiovascular disease. In total, 22 cases and 22 control subjects were enrolled. Participants were matched by age, body mass index (BMI), and parity. Control subjects did not receive any contrast agent; cases received 0.2 mmol/kg body weight of gadobutrol during the CMR procedure. The study (PPC1 [Post-Pregnancy Cardio Trial]; [NCT03313063](#)) was approved by the institutional review board of the Charité - Universitätsmedizin Berlin and performed according to the Second Declaration of Helsinki. All participating women provided written informed consent.

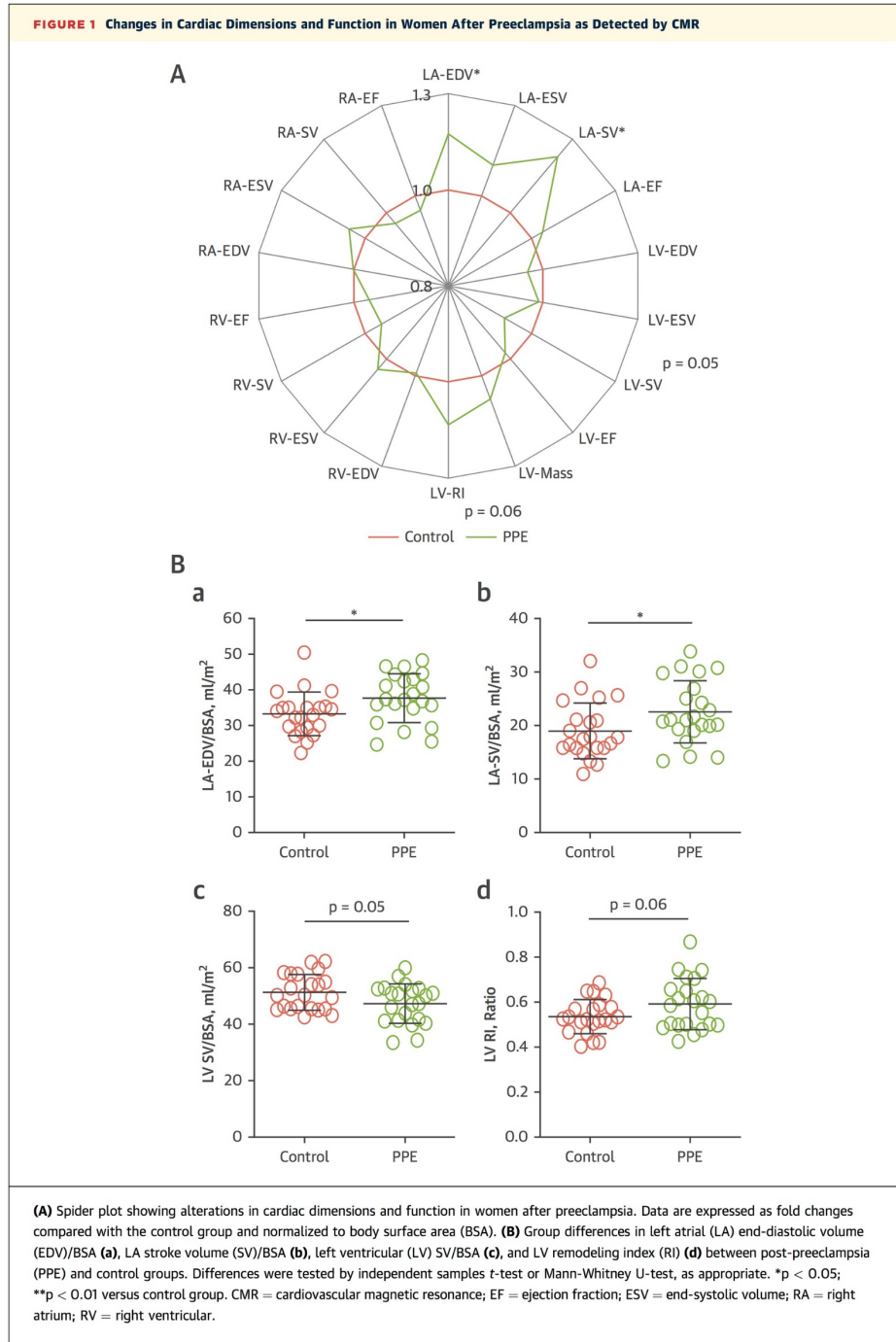
Women in both groups did not differ in their age, BMI, parity, smoking status, body composition, or physical activity status (as measured by the bioelectrical impedance and 6-min walking test). However, the time interval from the most recent pregnancy was slightly shorter in the post-preeclamptic group (2.00 ± 1.00 years vs. 4.00 ± 5.25 years; $p < 0.01$). The post-preeclamptic group showed a 13% increased left atrial (LA) end-diastolic volume (EDV) (37.69 ± 6.83 ml/m² vs. 33.27 ± 6.09 ml/m²; $p = 0.03$) and a 19% increased LA stroke volume (SV) (22.57 ± 5.83 ml/m² vs. 18.99 ± 5.22 ml/m²; $p = 0.04$) (all normalized to body surface area [BSA]), with a slight increase in left ventricular (LV) hypertrophy because LV SV normalized to BSA was 47.28 ± 7.03 ml/m² versus 51.30 ± 6.33 ml/m² ($p = 0.05$) and the LV remodeling index was 0.59 ± 0.11 versus 0.54 ± 0.08 ($p = 0.06$) ([Figure 1](#)). Associations between history of preeclampsia and changes in LA dimensions became even stronger after adjustment for BMI, age, parity, diastolic blood pressure, smoking status, and post-partum interval. The adjusted β coefficient for prediction of LA EDV was 14.03 ml (95% confidence interval: 6.56 to 21.50) ($p < 0.01$); the adjusted β -coefficient for prediction of LA SV was 10.69 ml (95% confidence interval: 3.99 to 17.38; $p < 0.01$). The associations between LV remodeling and history of preeclampsia disappeared after correction for diastolic blood pressure. Enlarged LA area size was already found in women with preeclampsia during the acute phase of the pregnancy disorder (2). Our findings pointed toward LA enlargement as a persistent pathophysiological residue sustained by preeclampsia and corroborated the hypothesis that cardiac alterations in post-preeclamptic women were persistent and did not resolve after a complicated pregnancy. According to the American Society of Echocardiography and the European Association of Echocardiography guidelines on evaluation of diastolic function, the recommended upper normal LA volume indexed to BSA is 34 ml/m²

Myocardial Evaluation of Post-Preeclamptic Women by CMR

Is Early Risk Stratification Possible?



Preeclampsia is a life-threatening disorder associated with long-term cardiovascular risk (1). We investigated cardiac alterations in post-preeclamptic women and control subjects using cardiovascular magnetic resonance (CMR) imaging. Diffuse injury of the myocardium was assessed by parametric mapping, focal injury was assessed by late gadolinium enhancement imaging, and cardiac function was evaluated by cine imaging and tissue tracking (strain). Exclusion criteria were CMR incompatibility (metal implants, kidney insufficiency [glomerular filtration rate <30 ml/min], claustrophobia, contrast medium allergy, current pregnancy or lactation, body



(3). In this study, post-preeclamptic women showed LA volume/BSA above this cutoff. LA enlargement is an integrative marker of pathophysiological processes, such as LV diastolic dysfunction, atrial fibrillation, and stroke (3,4).

CMR tissue tracking analysis revealed reduced global radial strain (GRS) and global circumferential strain (GCS) in the post-preeclamptic group (mean difference \pm SEM: $4.56 \pm 2.08\%$; $p = 0.03$; and $-1.60 \pm 0.71\%$; $p = 0.03$, respectively). Abnormalities in myocardial mechanics could occur before or simultaneously with hypertrophic remodeling and typically predated the development of cardiac fibrosis (5). We did not detect differences in focal or diffuse myocardial tissue composition between the groups.

CMR imaging is able to identify subtle cardiac end-organ damage, indicating diastolic dysfunction as early as 2 years after preeclampsia. LV deformation measured with GCS and GRS was significantly reduced in post-preeclamptic women. A history of preeclampsia is associated with cardiac end-organ damage (LA remodeling), even after adjustment for blood pressure and other clinical and demographic characteristics. Follow-up studies are needed to identify the critical window when morphological tissue differentiation (e.g., progression to myocardial fibrosis or inflammation) occurs in post-preeclamptic patients.

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Lebenslauf

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

Komplette Publikationsliste

Artikel:

1. Blaszczyk E, **Lim C**, Kellman P, Schmacht L, Gröschel J, Spuler S & Schulz-Menger J. Progressive myocardial injury in myotonic dystrophy type II and facioscapulohumeral muscular dystrophy 1: a cardiovascular magnetic resonance follow-up study. *Journal of Cardiovascular Magnetic Resonance*. *J Cardiovasc Magn Reson*. 2021;23(1):130.
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Vorträge und Posterpräsentationen (wissenschaftliche Kongresse):

1. Blaszczyk E, **Lim C**, Grieben U, Kellman P, Schmacht L, Spuler S, Schulz-Menger J. Progressive myocardial injury in myotonic dystrophy type II (DM2) – CMR-Follow-up study. Posterpräsentation CMR 2018 The Joint EuroCMR / SCMR Meeting (Barcelona, Spanien).
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