

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

DISSERTATION

Standardisierung innovativer Sequenzen der kardiovaskulären
Magnetresonanztomographie
Evaluierung der Reproduzierbarkeit verschiedener Hersteller und
Feldstärken

Standardization of innovative cardiovascular magnetic resonance
sequences
Evaluating the reproducibility of different vendors and field
strengths

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Abkürzungsverzeichnis

2D-Fluss-MRT	Zweidimensionale zeitaufgelöste Phasenkontrast-MRT
4D-Fluss-MRT	Dreidimensionale zeitaufgelöste Phasenkontrast-MRT mit dreidirektionaler Geschwindigkeitskodierung
CI	Konfidenzintervall
CMR	Kardiovaskuläre Magnetresonanztomographie
CoV	Variationskoeffizient
EF	Ejektionsfraktion
EPI	Echo-planar Imaging
fSENC	Fast Strain-encoding
FT	Feature Tracking
GCS	Globaler zirkumferentieller Strain
GLS	Globaler longitudinaler Strain
ICC	Intraklassen-Korrelation
MRT	Magnetresonanztomographie
MTRA	Medizinisch-technische*r Radiologieassistent*in
SD	Standardabweichung
SENC	Strain-encoding
SNR	Signal-to-Noise-Ratio
SSFP	Steady-state free precession
STE	Speckle-Tracking-Echokardiographie
VENC	Velocity encoding
WSS	Wandscherkräfte

Abstrakt

Die kardiovaskuläre MRT (CMR) ist als nicht-invasives Verfahren zur Diagnostik kardiovaskulärer Erkrankungen bereits in die aktuellen Leitlinien integriert. Durch die Entwicklung innovativer Sequenzen konnte das Spektrum klinischer Indikationen in den letzten Jahren zunehmend erweitert werden. Die dreidimensionale zeitaufgelöste Phasenkontrast-MRT (4D-Fluss-MRT) kann durch die Quantifizierung und Visualisierung kardialer Hämodynamik einen wichtigen Beitrag zum Verständnis kardiovaskulärer Pathophysiologie sowie zur Diagnostik und Therapiesteuerung von Erkrankungen leisten. Fast Strain-encoding (fSENC) ermöglicht als neue Methode die Erfassung myokardialen Strains innerhalb weniger Sekunden. Der Transfer dieser Sequenzen in die klinische Routine erfordert ein Bewusstsein für Störfaktoren.

Ziel dieser Arbeit ist die Evaluation potenzieller Störfaktoren wie unterschiedliche MRT-Hersteller oder Feldstärken als Beitrag zur Standardisierung innovativer CMR-Sequenzen.

15 gesunde Proband*innen wurden mittels 4D-Fluss-MRT an 3T-Scannern dreier verschiedener Hersteller (GE, Philips, Siemens) untersucht. Als hämodynamische Vergleichsparameter wurden Vorwärtsflussvolumen, maximale Flussgeschwindigkeit und Wandscherkräfte in neun Ebenen bestimmt (1). Des Weiteren wurde die aortale Hämodynamik von zehn gesunden Proband*innen via 4D-Fluss-MRT an drei verschiedenen Feldstärken (1,5T, 3T, 7T) sowie drei unterschiedlichen Sequenzen am 1,5T-MRT untersucht (2). Die Reproduzierbarkeit der fSENC wurde ebenfalls an drei MRT-Geräten unterschiedlicher Hersteller bei 15 gesunden Proband*innen evaluiert. Zur Strain-Analyse wurden globaler zirkumferentieller Strain und globaler longitudinaler Strain genutzt (3). Zusätzlich wurden Scan-Rescan-Reproduzierbarkeit und Intra- und Interobserver-Variabilität beurteilt (1-3).

Die hämodynamischen Parameter in der 4D-Fluss-MRT unterschieden sich signifikant zwischen den Scannern dreier verschiedener Hersteller und überschritten jeweils den durch die Intraobserver-Analyse definierten Äquivalenzbereich (1). Die Darstellung der 4D-Fluss-MRT gelang bei allen Feldstärken mit suffizienter Bildqualität. Die Ergebnisse aller hämodynamischen Parameter waren zwischen den Feldstärken ebenfalls nicht äquivalent (2). In den fSENC-Messungen zeigte sich zwischen den drei MRT-Geräten ein

geringer, jedoch statistisch signifikanter Bias (3). Die Scan-Rescan- sowie Intra- und Interobserver-Reproduzierbarkeit erzielten gute bis exzellente Ergebnisse (1-3).

Zusammenfassend werden durch die spezifischen Protokolle an MRT-Geräten unterschiedlicher Hersteller oder Feldstärken signifikante Unterschiede in den Ergebnissen innovativer CMR-Sequenzen hervorgerufen. Diese Erkenntnis sollte insbesondere bei der Durchführung multizentrischer Studien und Follow-up-Untersuchungen beachtet werden. Für eine optimierte Etablierung in der klinischen Routine ist eine weitere Standardisierung dieser Sequenzen daher essenziell.

Abstract

Cardiovascular magnetic resonance (CMR) has already been established in current guidelines as a non-invasive method for diagnosis of cardiovascular diseases. The development of innovative sequences has fostered an increase in the range of clinical indications during the past years. Three-dimensional time-resolved phase-contrast magnetic resonance (4D Flow MR) enables quantification and visualization of cardiac hemodynamics and may help in understanding cardiovascular pathophysiology as well as in diagnostics and therapy guiding of diseases. Fast strain-encoding (fSENC) is a novel method that allows the acquisition of myocardial strain within a few seconds. Transferring these sequences into clinical routine requires an awareness of confounders. The aim of this work is the evaluation of potential confounders such as different MRI vendors or field strengths as a contribution to the standardization of innovative CMR sequences.

15 healthy volunteers underwent 4D Flow MR examinations at 3T scanners of three different vendors (GE, Philips, Siemens). Forward flow volume, peak velocity and wall shear stress as hemodynamic parameters were investigated in nine planes (1). Furthermore, the aortic hemodynamics of ten healthy volunteers were examined using 4D Flow MR at three different field strengths (1.5T, 3T, 7T) and three different sequences on 1.5T MRI (2). The reproducibility of fSENC was also evaluated on three scanners from different vendors in 15 healthy volunteers. Global circumferential strain and global longitudinal strain were determined for strain analysis (3). In addition, scan-rescan reproducibility as well as intra- and interobserver variability were examined (1-3).

4D flow derived hemodynamic parameters differed significantly between scanners of the three different vendors and exceeded the equivalence range defined by intraobserver-analysis (1). 4D Flow MR displayed sufficient image quality at all field strengths. The results of all hemodynamic parameters were also non-equivalent between field strengths (2). In the fSENC measurements, there was a slight but statistically significant bias between the three scanners (3). Scan-rescan as well as intra- and interobserver reproducibility yielded good to excellent results (1-3).

In summary, specific protocols used at scanners from different vendors or field strengths lead to significant differences in the results of innovative CMR sequences. This finding should be taken into account when conducting multi-center studies or patient's follow-up examinations. Further standardization of these sequences is essential for implementation in clinical routine.

1. Einleitung

1.1 Technik und klinische Relevanz der kardialen 4D-Fluss-MRT

Die kardiovaskuläre Magnetresonanztomographie (CMR) hat in den letzten Jahren zunehmend an Bedeutung für die nicht-invasive Diagnostik kardiovaskulärer Erkrankungen gewonnen und ist bereits für einige klinische Fragestellungen als Goldstandard etabliert. Insbesondere für die Bestimmung kardialer Funktion und ventrikulärer Volumina sowie zur Charakterisierung von Myokardgewebe gilt sie als Methode der Wahl. Mit der kontinuierlichen Entwicklung neuer technischer Sequenzen geht eine zunehmende Erweiterung des klinischen Indikationsspektrums einher (4, 5).

Phasen-Kontrast-Techniken ermöglichen die Quantifizierung des pulsatilen Blutflusses im Herzen und den großen Gefäßen. Das Prinzip beruht auf einer Phasendifferenz bewegter Spins (z.B. in Gefäßen) im Vergleich zu angrenzenden stationären Spins (z.B. in Gefäßwänden). Der Phasenshift von stationären Spins wird mit Hilfe eines bipolaren Gradienten kompensiert, wodurch die Phase stationärer Spins unverändert bleibt. Bei sich bewegenden Spins hingegen kann aufgrund des Ortswechsels keine vollständige Kompensation erfolgen. Es kommt zu einer Phasenverschiebung, die bei linearen Magnetfeldgradienten proportional zur Geschwindigkeit ist und dadurch eine Geschwindigkeitsbestimmung ermöglicht. Eine korrekte Geschwindigkeitszuordnung ist hierbei nur für Phasendifferenzen zwischen -180° und $+180^\circ$ möglich. Die Kodierungsgeschwindigkeit (Velocity encoding, Venc) ist der Geschwindigkeitsbereich, welcher der maximalen Phasendifferenz von $\pm 180^\circ$ entspricht und bereits vor der Datenakquise festgelegt wird. Der Venc ist dementsprechend definiert als die maximale Geschwindigkeit (positiv oder negativ), die ohne Fehler detektiert werden kann. Überschreitet die tatsächliche Maximalgeschwindigkeit den eingestellten Venc können Aliasing-Artefakte resultieren, welche eine adäquate Quantifizierung des Flusses verhindern. Je höher der Venc ist, desto stärker wird jedoch auch das Hintergrundrauschen, so dass der Venc optimalerweise nur etwas größer als die zu erwartende Maximalgeschwindigkeit gewählt werden sollte. Aliasing-Artefakte können im Preprocessing der Datenauswertung bis zu einem gewissen Maß korrigiert werden (6-8).

Die zweidimensionale (2D = eine Raumrichtung und Zeit) zeitaufgelöste Phasenkontrast-Magnetresonanztomographie (2D-Fluss-MRT) ermöglicht die Detektion eines unidirektionalen Flusses senkrecht zur Messebene. Bereits vor der Datenakquise müssen die zu analysierenden Messebenen einzeln und orthogonal zu den Gefäßen positioniert werden. In der klinischen Routine findet die 2D-Fluss-MRT bereits Anwendung zur Bestimmung von Flussvolumina und -geschwindigkeiten in der Aorta oder der Pulmonalarterie und dient hierbei insbesondere der Diagnostik von Klappenvitien und Shunts (9-11).

Eine vielversprechende Weiterentwicklung dieser Untersuchungstechnik ist die dreidimensionale zeitaufgelöste Phasenkontrast-Magnetresonanztomographie mit dreidirektionaler Geschwindigkeitskodierung (4D-Fluss-MRT). Der vierdimensionale (4D = drei Raumrichtungen und Zeit) Charakter der Bildakquisition ermöglicht die zeitliche Auflösung sowie eine dreidimensionale Analyse des Blutflusses in allen räumlichen Ebenen und dadurch die Visualisierung und Quantifizierung von multidirektionalem Fluss. Es gelingt eine kontrastmittelfreie anatomische Darstellung des kardiovaskulären Systems in hoher Auflösung und gleichzeitig dessen funktionelle Charakterisierung in jeder Ebene innerhalb des Aufnahmevolumens. Anders als bei der 2D-Fluss-MRT, dem bisherigen Standard, bei der die zu analysierenden Ebenen bereits vor der Datenakquise festgelegt werden müssen, ermöglicht die 4D-Fluss-MRT eine retrospektive Analyse aller Lokalisationen innerhalb des Aufnahmevolumens (7, 12).

In der Diagnostik kongenitaler Herzerkrankungen ist die 4D-Fluss-MRT daher bereits in der klinischen Routine verankert (13). Neben einer qualitativen und quantitativen Analyse von Flussgeschwindigkeiten und -volumina können zudem neue Parameter wie Wandscherkräfte (WSS) ermittelt werden (14). Erhöhte WSS treten beispielsweise bei Patient*innen mit Aortenklappenstenosen oder bikuspiden Aortenklappen sowie nach einer Aortenklappenrekonstruktion auf (15-17). Ebenfalls zeigen sich Veränderungen der WSS bei Pathologien der thorakalen Aorta sowie in Systemerkrankungen mit aortaler Beteiligung (18, 19). Weiterhin ist die Quantifizierung von Energieverlusten innerhalb der Aorta möglich. Als Ausdruck eines abnormal erhöhten Flusses und konsekutiv erhöhter ventrikulärer Nachlast lassen sich beispielsweise höhere Energieverluste bei Patient*innen mit bikuspiden Aortenklappen oder Aortenklappenstenosen sowie Aortendilatation beobachten (20, 21).

Durch die Analyse von Blutflüssen sowie die Quantifizierung der Energieverluste und der Wandscherkraftverteilung in der Aorta kann die 4D-Fluss-MRT einen wertvollen Beitrag zum pathophysiologischen Verständnis kardiovaskulärer Erkrankungen leisten und deren Diagnostik und Therapie somit wesentlich beeinflussen. In der klinischen Routine wird sie bisher lediglich in der Diagnostik kongenitaler Herzerkrankungen genutzt. Ein limitierender Faktor für eine breitere klinische Nutzung war neben der besonderen Expertise bei der Datenakquisition und -auswertung dabei insbesondere die notwendige Untersuchungszeit. Durch die stetige technische Weiterentwicklung der 4D-Fluss-MRT-Sequenzen konnte inzwischen eine Scandauer von wenigen Minuten erreicht werden (22). Daher rückt nun die Standardisierung der Methodik zunehmend in den Fokus.

1.2 Standardisierung der kardialen 4D-Fluss-MRT

Für die erfolgreiche Implementierung der kardialen 4D-Fluss-MRT in die klinische Routine ist eine Standardisierung der Methode essenziell. Die Grundlage dafür bildet die kritische Auseinandersetzung mit möglichen Störfaktoren wie beispielsweise dem Einfluss verschiedener MRT-Hersteller oder Feldstärken sowie Standorte auf die Reproduzierbarkeit der Ergebnisse.

Ein Konsensus-Paper mit Empfehlungen zu Sequenz- und Aufnahmeparametern der 4D-Fluss-MRT wurde bereits publiziert (12). Jedoch fehlen bisher standardisierte 4D-Fluss-Sequenzen, die eine breite Nutzung an verschiedenen Zentren sowie unterschiedlichen MRT-Geräten ermöglichen könnten. Die verwendeten 4D-Fluss-Sequenzen unterscheiden sich beispielsweise hinsichtlich ihrer technischen Parameter an den verschiedenen MRT-Geräten, da jeder Hersteller für eine optimale Bildakquise unterschiedliche Einstellungen an der Sequenz vornimmt und höhere Feldstärken ebenfalls Anpassungen der Aufnahmeparameter erfordern.

Für das T1-Mapping, welches zur myokardialen Gewebedifferenzierung dient, konnte bereits eine Variabilität der Ergebnisse in Abhängigkeit von verschiedenen Herstellern oder Feldstärken gezeigt werden (23, 24). Dementsprechend ist auch für die 4D-Fluss-MRT ein Einfluss durch die Nutzung unterschiedlicher MRT-Geräte verschiedener Hersteller oder Feldstärken zu erwarten. Einige Studien zum Vergleich der 4D-Fluss-MRT zwischen verschiedenen Feldstärken oder MRT-Herstellern existieren bereits (25-27). Allerdings fehlen bisher Daten zur Äquivalenz dieser Ergebnisse, die Aussagen

darüber ermöglichen, ob die Unterschiede in den hämodynamischen Parametern innerhalb eines klinisch tolerablen Bereiches liegen. Die unzureichende Datenlage bezüglich der Übereinstimmung hämodynamischer 4D-Fluss-Parameter zwischen verschiedenen MRT-Geräten erschwert daher einen Vergleich von Untersuchungen in der klinischen Praxis und Forschung.

1.3 fSENC als weitere neue Sequenz der kardialen MRT

Myokardialer Strain ist ein Parameter zur Quantifizierung der myokardialen Deformation (28). Insbesondere in der Diagnostik ischämischer und nicht-ischämischer Kardiomyopathien wie z.B. der Herzinsuffizienz mit erhaltener Ejektionsfraktion (EF) oder Chemotherapie-induzierter Kardiotoxizität liefert sie als frühzeitiger Detektionsparameter für kontraktile Dysfunktionen einen Mehrwert gegenüber der konventionellen Bestimmung der EF (29-32). Neben einer Differenzierung zwischen globaler sowie regionaler myokardialer Funktion lässt sich die myokardiale Deformation in drei verschiedenen Ebenen des Herzens (zirkumferentiell, longitudinal, radial) bestimmen. Da sich die Verformung des Myokards relativ auf seine ursprüngliche Form bezieht, handelt es sich bei Strain um eine dimensionslose Einheit, die in Prozent angegeben wird (28).

Die echokardiographische Quantifizierung von myokardialem Strain ist mittels Speckle-Tracking-Echokardiographie (STE) bereits allgemein bekannt und findet regelmäßig Anwendung in der klinischen Diagnostik (28, 30). Im weiteren Verlauf sind für die Strain-Analyse auch verschiedene Techniken der CMR wie beispielsweise Feature Tracking (FT), Tagging oder Strain-encoding (SENC) etabliert worden (33-35).

Das FT ist eine Post-Processing-Methode, die nach Definition der endo- und epikardialen Konturen in einer Phase deren Bewegungen über den gesamten Herzzyklus automatisch verfolgt. Dieses Verfahren ermöglicht eine Strain-Analyse aus regelhaft akquirierten steady-state free precession (SSFP)-cine-Aufnahmen und hat dadurch den Vorteil, dass es keiner zusätzlichen speziellen Sequenz bedarf (33). Beim Tagging dienen zur Detektion der Myokardkontraktion Gitterlinien als Marker, die durch eine lokale Störung der Magnetisierung generiert werden und senkrecht zur Bildebene orientiert sind (35). SENC basiert ebenfalls auf dem Prinzip von Tagging mit dem Unterschied einer parallelen Ausrichtung der Gitterlinien zur Bildebene. Für die Bestimmung von longitudinalem Strain mittels SENC werden daher Kurzachsen-Pakete (basal,

mittelventrikulär, apikal) und für zirkumferentiellen Strain Langachsen-Pakete (2-Kammerblick, 3-Kammerblick, 4-Kammerblick) benötigt (34). Initial waren für die Akquisition über multiple Herzschläge lange Atemanhaltenmanöver notwendig. Fast Strain-encoding (fSENC) ist eine neue Technik in der CMR und ermöglicht die Erfassung myokardialen Strains innerhalb weniger Herzschläge sowie unter freier Atmung (36). Während es für die STE bereits Empfehlungen zur Verwendung desselben Gerätes und derselben Auswertesoftware gibt, fehlen bislang ähnliche Anweisungen für die MRT-Techniken (37). Der Einfluss potenzieller Störfaktoren wie beispielweise unterschiedlicher MRT-Hersteller ist für die Methodik noch unzureichend untersucht und kann zu Unsicherheiten in der Dateninterpretation führen.

1.4 Zielsetzung der Arbeit

Vor dem Hintergrund einer Standardisierung innovativer Sequenzen der CMR ist das Ziel dieser Studien insbesondere die Evaluation potenzieller Störfaktoren, welche die Ergebnisse dieser Sequenzen beeinflussen könnten. Im Mittelpunkt steht hierbei die Reproduzierbarkeit und Äquivalenz aortaler Hämodynamik mittels 4D-Fluss-Messungen, die an MRT-Geräten verschiedener Hersteller oder Feldstärken akquiriert werden. Außerdem wird der Einfluss verschiedener MRT-Geräte auf eine weitere neue Sequenz der CMR, die fSENC, untersucht.

2. Material und Methoden

2.1 Reproduzierbarkeit der kardialen 4D-Fluss-MRT

2.1.1 Vergleich von MRT-Geräten verschiedener Hersteller

2.1.1.1 Studienaufbau und MRT-Protokoll

Es wurden 15 gesunde Proband*innen prospektiv in die „Traveling Volunteers“-Studie (EA2/208/17) eingeschlossen. Bei allen Proband*innen wurden jeweils drei CMR-Untersuchungen an 3T-Scannern verschiedener Hersteller sowie an drei unterschiedlichen Zentren in Deutschland durchgeführt. Folgende drei Zentren nahmen an der Studie teil: das Deutsche Herzzentrum Berlin (Scanner I), das Theresienkrankenhaus Mannheim (Scanner II) und das Max-Delbrück-Centrum in Kooperation mit der Charité - Universitätsmedizin Berlin - Campus Buch (Scanner III). Jedes Zentrum nutzte für die MRT-Untersuchung einen 3T-Scanner eines anderen Herstellers (alphabetisch sortiert): Ingenia (Philips, Best, Niederlande), MAGNETOM Verio (Siemens, Erlangen, Deutschland) und SIGNA Architect (GE Healthcare, Milwaukee, Wisconsin, USA) (1, 3).

SSFP-cine-Aufnahmen ermöglichten die Bestimmung der kardialen Funktion sowie die Verifizierung einer trikuspiden Aortenklappe ohne Vorliegen einer Pathologie. Zur Evaluierung der Reproduzierbarkeit der 4D-Fluss-MRT an Scannern verschiedener Hersteller wurde jeweils eine 4D-Fluss-Aufnahme pro Scanner durchgeführt. Zusätzlich wurde am Scanner III nach einer Pause eine zweite 4D-Fluss-Aufnahme zur Testung der Scan-Rescan-Reproduzierbarkeit akquiriert. Ziel war es, den aktuellen Grad der Übereinstimmung klinisch genutzter aortaler 4D-Fluss-Sequenzen zu beurteilen und einen potenziellen Bias hinsichtlich eines Herstellers auszuschließen. Daher wurden die Unterschiede in den Sequenzparametern der einzelnen 4D-Fluss-Sequenzen beibehalten und nicht an einen bestimmten Hersteller oder eine Sequenz angepasst. Jedes Zentrum nutzte dementsprechend eine individuelle 4D-Fluss-Sequenz unter Beibehaltung der herstellereigenen Parametereigenschaften (siehe Tabelle 1) (1).

Die verschiedenen Planungsschwerpunkte wurden nach den Empfehlungen der jeweiligen Hersteller definiert und gingen daher mit einem unterschiedlichen Fokus und Bildmittelpunkt in den Aufnahmen einher. Am Scanner III umfasste das Aufnahmevolumen die Aorta und an den Scannern I und II das gesamte Herz. Da die 4D-Fluss-Messungen über mehrere Minuten und somit über mehrere Herzphasen akquiriert

werden, wurde zur Synchronisation der Herzphasen an allen Scannern eine EKG-gesteuerte Datenzuordnung (kardiales Gating) genutzt. Am Scanner III wurde eine prospektive EKG-Triggerung verwendet. Zusätzlich wurde eine Atemtriggerung in Navigator-Technik genutzt, um ein freies Atmen zu ermöglichen (1). Hierbei werden lediglich Daten in einem bestimmten Akzeptanzbereich, welcher durch die Zwerchfellposition vordefiniert wird, in die Bildrekonstruktion eingeschlossen (7). An den Scannern I und II wurde hingegen ein retrospektives kardiales Gating ohne Atemtriggerung in Navigator-Technik genutzt. Der Venc wurde basierend auf der klinischen Routine des jeweiligen Zentrums auf 150 cm/s an den Scannern II und III und auf 250 cm/s an Scanner I eingestellt (1).

Tabelle 1 Parameter der 4D-Fluss-MRT an Scannern verschiedener Hersteller (übersetzt und modifiziert nach Demir et al. (1); Lizenznummer: 5300681178987)

	Scanner I	Scanner II	Scanner III
Planungsebene	sagittal	transversal	sagittal
Aufnahmevolument	ganzes Herz	ganzes Herz	Aorta
EKG-Triggerung	retrospektiv	retrospektiv	prospektiv
Respiratorischer Navigator	nein	nein	ja
Echozeit [ms]	2,2	2,0	2,6
Repetitionszeit [ms]	3,5	4,2	5,1
Zeitliche Auflösung [ms]	28	66,8	40,8
Anzahl kardialer Phasen	25 (\pm 0)	25 (\pm 0)	19,2 (\pm 3,4)
Segmentierungsfaktor	2	4	2
Voxelgröße [mm ³]	2,8 x 2,8 x 2,8	2,4 x 2,4 x 2,8	2,7 x 2,3 x 2,6
Rekonstruierte Voxelgröße [mm ³]	1,3-1,9 x 1,3-1,9 x 2,8	1,4-1,5 x 1,4-1,5 x 1,4	2,3 x 2,3 x 2,6
Field of view [mm ³]	270 x 180 x 81,2	380 x 266 x 95,2	360 x 270 x 83,2
Velocity encoding [cm/s]	250	150	150
Flipwinkel [Grad]	5	8	7
Hochfrequenz-Spule	multi-element Array-Spule	multi-element Array-Spule	32-Kanal Körperspule
Parallelakquisitionstechniken*	R = 2	R = 8	R = 5
Untersuchungszeit [min]	10,8 (\pm 1,2)	10,5 (\pm 1,5)	8,0 (\pm 2,2)

*die genutzten herstellerepezifischen Techniken in alphabetischer Folge: kt-ARC, kt-GRAPPA und SENSE.

Anzahl kardialer Phasen und Untersuchungszeit dargestellt als Mittelwerte \pm Standardabweichungen.

R = Beschleunigungsfaktor, kt = k-adaptive-t, ARC = Autocalibrating Reconstruction for Cartesian sampling, SENSE = Sensitivity Encoding, GRAPPA = GeneRalized Autocalibrating Partially Parallel Acquisition.

Der zeitliche Abstand zwischen der ersten und zweiten MRT-Untersuchung (an Scanner I und II) betrug durchschnittlich 103 ± 4 Tage, während zwischen der zweiten und dritten Untersuchung 18 ± 10 Tage lagen (1).

2.1.1.2 Datenanalyse

Für die Auswertung der 4D-Fluss-Aufnahmen wurde die Software CAAS MR Solutions 5.0 (Pie Medical Imaging BV, Maastricht, Niederlande) genutzt. Die einzelnen Schritte der 4D-Fluss-Analyse sind in Abbildung 1 dargestellt. Alle Daten wurden durch eine Untersucherin (AD) mit zwei Jahren Erfahrung in kardialer 4D-Fluss-MRT ausgewertet. Mittels Preprocessing erfolgte zunächst die automatische Korrektur von Phasen-Offsets sowie Aliasing in allen Datensätzen. Zusätzlich wurden alle Bilder manuell auf potenzielle Aliasing-Artefakte untersucht, da eine problemlose Anwendung der Anti-Aliasing-Korrektur an den Datensätzen aus Scanner II nicht möglich war. Dementsprechend wurden Ebenen manuell ausgeschlossen, in denen Aliasing sichtbar war (1).

Für die Segmentierung der Aorta wurde der Startpunkt der Mittellinie im oberen Bereich des linksventrikulären Ausflusstraktes und der Endpunkt in der Aorta descendens unterhalb des Apex definiert. Nach automatischer Generierung einer Mittellinie sowie eines 3D-Volumen-Modells der Aorta für fünf verschiedene Herzphasen konnten die Gefäßwandkonturen anschließend manuell angepasst werden. Für die weitere Auswertung wurde das Aorten-Modell der Herzphase der maximalen Systole ausgewählt. Bei unvollständig abgebildeten Aortensegmenten erfolgte ein Ausschluss des kompletten Datensatzes (1).

Insgesamt wurden neun Ebenen (P1-P9) entlang der Aorta platziert (siehe Abbildung 1c). Die Lokalisationen umfassten jeweils drei Ebenen im Bereich der Aorta ascendens (P1-P3), des Aortenbogens (P4-P6) und der Aorta descendens (P7-P9). Für jede einzelne Ebene wurden die maximale Flussgeschwindigkeit, das Vorwärtsflussvolumen sowie die maximalen und durchschnittlichen WSS bestimmt. Die Konturen der Gefäßwand wurden für die Analyse der Flussparameter aus der Segmentierung der gewählten Herzphase übernommen und konnten zusätzlich für alle Phasen des Herzzyklus manuell angepasst werden. Die identischen Ebenenlokalisationen wurden für die WSS-Analyse automatisch übertragen. Da die WSS-Analyse lediglich in der ausgewählten Herzphase der maximalen Systole erfolgte, war hierbei keine manuelle Anpassung der Gefäßkonturen notwendig (1).

Die Intra- und Interobserver-Variabilität wurde in einer Subgruppe von zehn Proband*innen mit insgesamt 30 Datensätzen evaluiert. Dabei wurde die Analyse nur in den Ebenen der Aorta ascendens (P1-P3) durchgeführt, da die meisten klinisch relevanten Pathologien diesen Abschnitt betreffen (1).

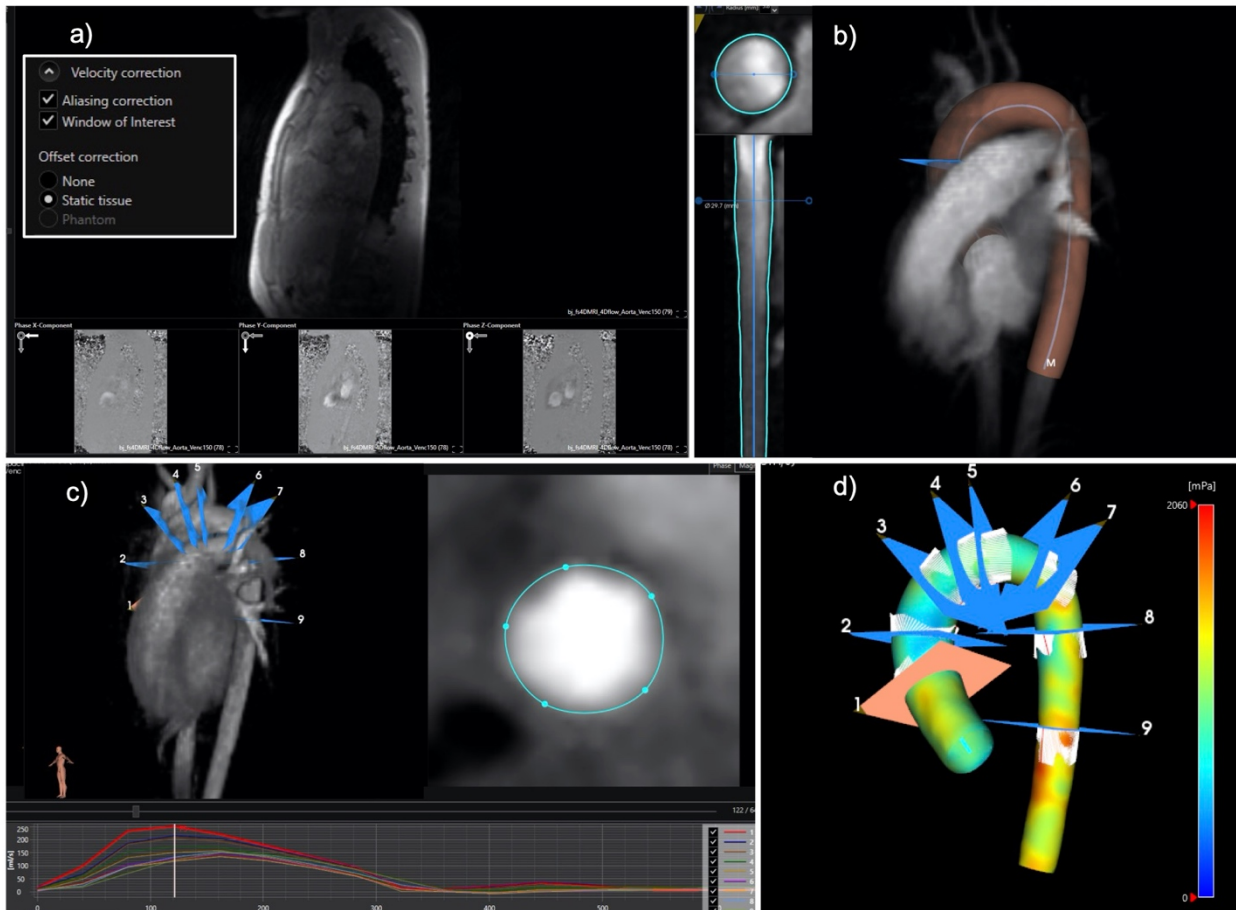


Abbildung 1 4D-Fluss-Auswertung mit CAAS (modifiziert nach Demir et al. (1); Lizenznummer: 5300681178987)

a) Preprocessing mit Korrektur der Phasen-Offsets sowie der Aliasing-Artefakte, b) Segmentierung der Aorta: automatische Generierung eines 3D-Volumen-Modells nach Definition des Start- und Endpunktes der Mittellinie sowie anschließende Optimierung durch eine manuelle Korrektur der Gefäßwandkonturen, c) Lokalisation der neun Ebenen zur Analyse der Flussparameter mit exemplarisch abgebildeten Gefäßkonturen für P1, d) Visualisierung der maximalen WSS in der Herzphase der maximalen Systole.

2.1.1.3 Statistische Auswertung

Die statistische Auswertung wurde mit SPSS (V25.0, IBM Corp., Armonk, NY, USA) und SAS (V9.4, SAS Institute Inc., Cary, NC, USA) durchgeführt. Um die Ergebnisse der drei MRT-Geräte untereinander zu vergleichen, erfolgten Signifikanztestungen mittels

Wilcoxon- und Friedman-Test für jede einzelne Ebene und lineare gemischte Modelle mit wiederholten Messungen für kombinierte Ebenen (P1-P9) und Aortensegmente. Zusätzlich wurden Bland-Altman-Analysen generiert und eine Äquivalenztestung durchgeführt (1). Hierbei wurde das 95%-Konfidenzintervall (CI) der Intraobserver-Differenz des entsprechenden Parameters als Grenze des klinisch akzeptablen Unterschiedes zwischen jeweils zwei Scannern festgelegt (38). Die Ergebnisse zweier Scanner wurden als äquivalent angesehen, sofern ihre Differenz innerhalb des 95%-CI des Intraobserver-Vergleiches lag und dementsprechend die Abweichung ihrer Ergebnisse mit denen der zweimaligen Auswertung durch eine Person vergleichbar war. Zusätzlich erfolgte eine Äquivalenztestung mit Festlegung des 95%-CI der Scan-Rescan-Differenz als tolerable Grenze. Die Scan-Rescan-, sowie Intra- und Interobserver-Variabilität wurde mittels Bland-Altman-Plots sowie durch eine Bestimmung der Intraklassen-Korrelation (ICC) dargestellt. Zusätzlich wurde die Scan-Rescan-Reproduzierbarkeit mittels T-Test oder Wilcoxon-Test geprüft (1).

2.1.2 Vergleich von MRT-Geräten unterschiedlicher Feldstärken

2.1.2.1 Studienaufbau und MRT-Protokoll

Es wurden zehn gesunde Proband*innen ohne kardiovaskuläre Vorerkrankungen in die Studie eingeschlossen. Alle Proband*innen wurden innerhalb weniger Wochen an drei MRT-Geräten unterschiedlicher Feldstärken des Herstellers Siemens (Erlangen, Deutschland) untersucht: 1,5T (MAGNETOM Avanto Fit), 3T (MAGNETOM Verio), 7T (MAGNETOM 7T Forschungsscanner). Zusätzlich wurden am 1,5T-MRT 4D-Fluss-Aufnahmen mit drei unterschiedlichen Prototyp-Sequenzen akquiriert. Die Selektion der einzelnen Sequenzen orientierte sich an deren Verfügbarkeit in der klinischen Routine. Die jeweiligen Sequenzparameter sind in Tabelle 2 dargestellt (2).

Alle Aufnahmen erfolgten mittels EKG-Triggerung sowie Atemtriggerung in Navigator-Technik. Bei fehlerhafter EKG-Triggerung am 7T-MRT wurde zusätzlich ein akustisches Triggersystem (ACT, Easy ACT, MRI.TOOLS GmbH, Berlin, Deutschland) genutzt (39). Die Evaluierung der links-ventrikulären Funktion und der Morphologie der Aortenklappe erfolgte via SSFP-cine-Aufnahmen am 3T-MRT. Zwischen den ersten und zweiten Untersuchungsterminen lagen im Durchschnitt 29 ± 21 Tage, zwischen den zweiten und dritten Untersuchungsterminen 20 ± 11 Tage (2).

Tabelle 2 Sequenzparameter der drei Sequenzen am 1,5T sowie 3T und 7T (übersetzt und modifiziert nach Wiesemann et al. (2); Lizenznummer: 5300690103659)

	1,5T (Sequenz 1)	1,5T (Sequenz 2)	1,5T (Sequenz 3)	3T	7T
Echozeit [ms]	2,4	2,3	2,3	2,6	2,4
Repetitionszeit [ms]	39,2	38,9	38,9	40,8	38,4
Bandbreite [Hz]	450	496	496	450	450
GRAPPA	R = 5	R = 2	R = 2	R = 5	R = 2
Flip-Winkel [Grad]	8	8	8	7	10
Field of view [mm ³]	270-292 x 360 x 62,5	252-270 x 360 x 62,5	270-292 x 360 x 62,5	270 x 360 x 83,2	292 x 360 x 38,4
Matrixgröße	70-90 x 160 x 26	78-91 x 160 x 18	84-91 x 160 x 18	100 x 160 x 32	88 x 160 x 26
Voxelgröße [mm ³]	3,3-3,9 x 2,3 x 2,4	3,2 x 2,3 x 3,5	3,2 x 2,3 x 3,5	2,7 x 2,3 x 2,6	3,3 x 2,3 x 2,4
Rekonstruierte Voxelgröße [mm ³]	2,3 x 2,3 x 2,4	2,3 x 2,3 x 2,4	2,3 x 2,3 x 2,4	2,7 x 2,3 x 2,6	2,3 x 2,3 x 2,4
Anzahl kardialer Phasen	20	18	25	18	20
Velocity encoding [cm/s]	150	150	150	150	150
EKG-Triggerung	prospektiv	prospektiv	retrospektiv	prospektiv	prospektiv
Hochfrequenz-Spule (Empfangskanäle)	30	30	30	32	16
Untersuchungszeit [min]	6,7 ± 8,3	8,5 ± 1,4	8,4 ± 1,5	9,0 ± 1,7	11,2 ± 3,0

R = Beschleunigungsfaktor, GRAPPA = GeneRalized Autocalibrating Partially Parallel Acquisition.

2.1.2.2 Datenanalyse

Die diagnostische Bildqualität jeder einzelnen 4D-Fluss-Aufnahme wurde innerhalb der drei Aortensegmente (Aorta ascendens, Aortenbogen, Aorta descendens) mithilfe von Magnitudebildern sowie der Flussvisualisierung mittels Strömungslinien bewertet und in die Kategorien „nicht-diagnostisch“, „gut“ und „exzellent“ eingeteilt. Segmente von nicht-diagnostischer Qualität, die sich beispielsweise durch das Auftreten von Artefakten, Signalverlust oder Unschärfe kennzeichnen, wurden anschließend von der weiteren Analyse ausgeschlossen (2).

Für die Bildanalyse war eine Kombination dreier Softwareprogramme notwendig. Das Preprocessing der Daten wurde in MATLAB (The MathWorks Inc., USA) und die Segmentierung der Aorta in Mimics (Materialise, Belgien) durchgeführt, während die Platzierung der aortalen Ebenen inklusive Flussvisualisierung in EnSight (V10.0, CEI, Apex, NC, USA) vorgenommen wurde. Insgesamt wurden neun Ebenen entlang der thorakalen Aorta positioniert (siehe Abbildung 2) und die Flussvolumina innerhalb der

Ebenen automatisch quantifiziert. Die maximalen Flussgeschwindigkeiten wurden jeweils für die einzelnen Aortensegmente bestimmt (2).

Die Ermittlung der 3D-WSS erfolgte innerhalb von zehn Segmenten, von denen jeweils vier im Bereich der Aorta ascendens und descendens sowie zwei im Aortenbogen lokalisiert waren. Die Kalkulation der WSS wurde anhand der Herzphase der maximalen Systole sowie der vorausgehenden und nachfolgenden zwei Herzphasen durchgeführt (2).

Alle Daten wurden durch eine Untersucherin mit drei Jahren Erfahrung in kardialer 4D-Fluss-MRT ausgewertet (SW). Eine Subgruppe von Daten (n=18) wurde für die Untersuchung der Inter- und Intraobserver-Variabilität erneut analysiert (2).

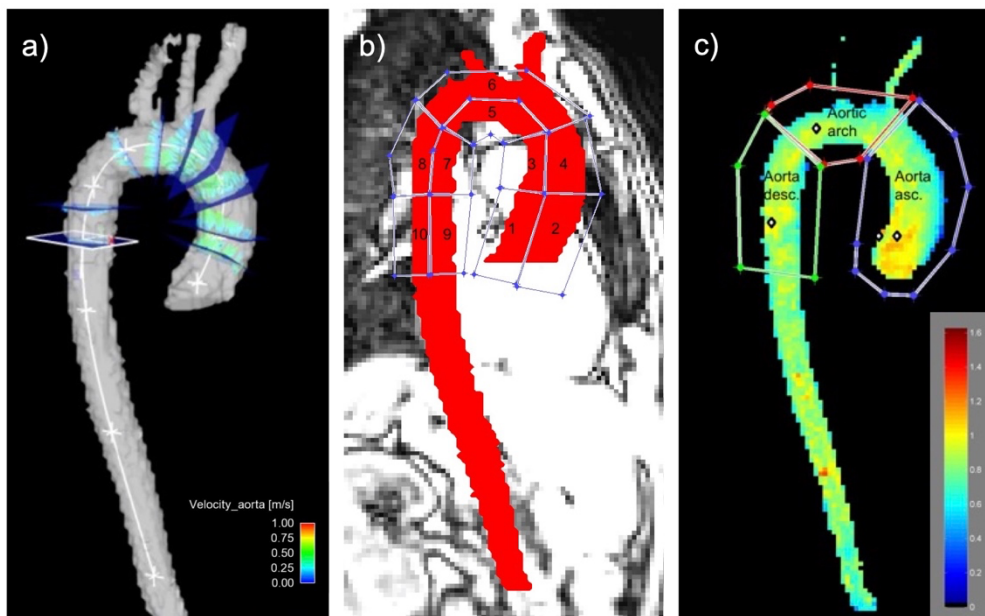


Abbildung 2 Visualisierung der Lokalisationen quantitativer 4D-Fluss-Auswertung (übersetzt aus Wiesemann et al. (2); Lizenznummer: 5300690103659)

a) Quantifizierung des Flusses in neun Ebenen entlang der thorakalen Aorta, b) Untersuchung der WSS innerhalb von zehn Segmenten, c) Evaluation maximaler Flussgeschwindigkeiten innerhalb der drei Segmente Aorta ascendens, Aortenbogen und Aorta descendens.

2.1.2.3 Statistische Auswertung

Die statistische Analyse wurde durchgeführt mit SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) und Graph Pad Prism 6.0 (GraphPad Software Inc., San Diego, California, USA). Um die Unterschiede im Beschleunigungsfaktor sowie der EKG-Triggerung (prospektiv vs. retrospektiv) als potenzielle Störfaktoren einzubeziehen, erfolgte der

Feldstärkenvergleich zwischen 1,5T und 3T mit Sequenz 1 und zwischen 1,5T und 7T zusätzlich mit der Sequenz 2. Die Vergleiche erfolgten sowohl für die gesamte Aorta als auch separat für die Aorta ascendens (2).

Zur Beurteilung klinisch relevanter Unterschiede zwischen den verschiedenen Sequenzen und Feldstärken wurde eine Äquivalenztestung durchgeführt. Hierfür wurden Bland-Altman-Analysen des Intraobserver-Vergleiches erstellt und das 95%-CI der Intraobserver-Differenz als Grenze für den klinisch akzeptablen Unterschied zwischen zwei Feldstärken bzw. Sequenzen festgelegt. Mittels Wilcoxon-Test wurde auf das Vorliegen statistisch signifikanter Unterschiede getestet. Zudem wurden Korrelationstests nach Spearman-Rho durchgeführt, wobei $r \geq 0,5$ als moderate und $r \geq 0,75$ als starke Korrelation definiert wurde (2).

2.2 Reproduzierbarkeit der fSENC als weitere neue Sequenz der kardialen MRT

2.2.1 Vergleich von MRT-Geräten verschiedener Hersteller

2.2.1.1 Studienaufbau und MRT-Protokoll

Die Datenakquisition der fSENC-Messungen erfolgte gemeinsam mit denen der 4D-Fluss-Scans im Rahmen des MRT-Protokolls der „Traveling Volunteers“-Studie sowie unter Einschluss derselben Proband*innen (1, 3). An drei Standorten mit 3T-MRT-Geräten eines jeweils unterschiedlichen Herstellers wurden an 15 gesunden Proband*innen jeweils vier fSENC-Untersuchungen pro Standort durchgeführt. Vorab erfolgten Messungen von Phantomen aus Silikon-Gel mit bekannten mechanischen Eigenschaften. Die technischen Sequenzparameter konnten an den jeweiligen MRT-Hersteller angepasst werden und werden in der Publikation detailliert dargestellt (3).

Eine vollständige fSENC-Untersuchung beinhaltete die Akquisition von drei Langachsen (2-Kammerblick, 3-Kammerblick, 4-Kammerblick) zur Bestimmung des linksventrikulären globalen zirkumferentiellen Strain (GCS) sowie drei Kurzachsen (basal, mittelventrikulär, apikal) für den linksventrikulären globalen longitudinalen Strain (GLS). Gemäß Studienprotokoll wurden zwei fSENC-Messungen mit identischen Einstellungsparametern der Bildplanung nacheinander durchgeführt und nach einer Pause, in der die Proband*innen das MRT-Gerät verlassen konnten, durch zwei weitere Messungen ergänzt (3).

2.2.1.2 Datenanalyse

Alle Bilder wurden durch eine Untersucherin (JE) mit der Software Myostrain 5.0 (Myocardial Solutions Inc., Morrisville, North Carolina, USA) ausgewertet. Für die Bestimmung des linksventrikulären Strain wurden jeweils in den drei Lang- und Kurzachsenbildern die endo- und epikardialen Konturen in der endsystolischen Phase eingezeichnet (siehe Abbildung 3). Für die Kalkulation des segmentalen Strains wurde der linke Ventrikel in den Langachsen automatisch in 21 Segmente und in den Kurzachsen in 16 Segmente unterteilt. Der globale Strain wurde jeweils aus den durchschnittlichen Strainwerten aller Segmente in der endsystolischen Phase ermittelt. Es wurden die Parameter GLS und GCS bestimmt. Datensätze von Proband*innen wurden ausgeschlossen, wenn aufgrund schlechter Bildqualität kein einziges Bild des jeweiligen Kurz- oder Langachsenpaketes ausgewertet werden konnte (3).

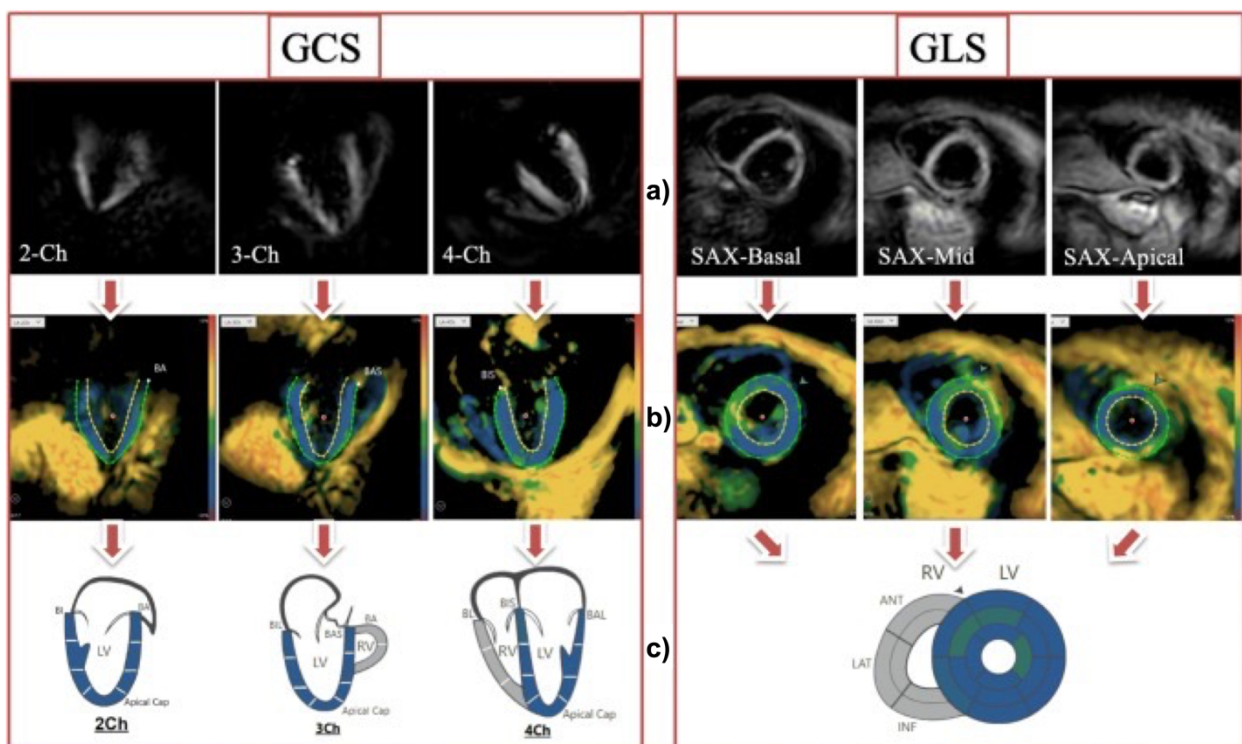


Abbildung 3 fSENC mit farbkodierten Bildern nach Post-Processing sowie myokardialer Segmentierung (übersetzt und modifiziert nach Erley et al. (3); Lizenznummer: 12217251)

a) Darstellung wie auf dem Scanner, b) farbkodierte Bilder in der Software nach dem Post-Processing mit manuell eingezeichneten endo- und epikardialen Konturen in der endsystolischen Phase, blau repräsentiert hierbei Strain im normalen Bereich während der Kontraktion, c) Ergebnisse der Strain-Analyse dargestellt durch eine farbkodierte Karte des Herzens.

Innerhalb einer Subgruppe von neun Proband*innen mit insgesamt 36 Datensätzen wurde die Intra- und Interobserver-Reproduzierbarkeit evaluiert (3).

2.2.1.3 Statistische Auswertung

Für die statistische Analyse wurde SPSS (Version 25.0, IBM Corp., Armonk, NY, USA) verwendet. Die Übereinstimmung in den Ergebnissen der drei MRT-Geräte wurde durch Bland-Altman-Plots dargestellt. Zur Evaluation der Scan-Rescan-Reproduzierbarkeit wurden die fSENC-Aufnahmen vor und nach der Pause jeweils gemittelt sowie einzeln anhand ICC und Variationskoeffizient (CoV) bewertet. Der Wilcoxon-Test und der gepaarte T-Test dienten zur Überprüfung der ermittelten Unterschiede auf Signifikanz. Die Inter- und Intraobserver-Variabilität wurde ebenfalls mittels ICC und CoV getestet (3).

3. Ergebnisse

3.1 Reproduzierbarkeit der kardialen 4D-Fluss-MRT

3.1.1 Vergleich von MRT-Geräten verschiedener Hersteller

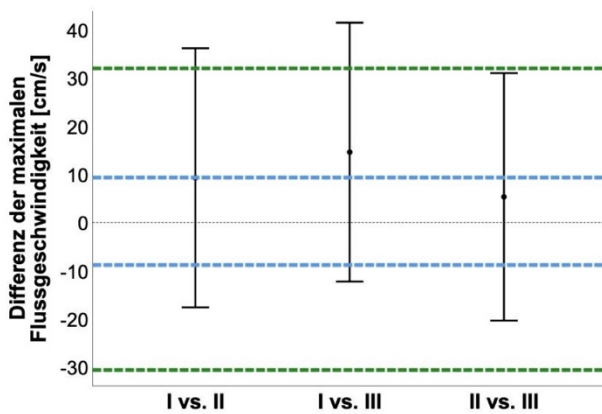
Nur zehn der initial eingeschlossenen 15 Proband*innen (mittleres Alter = 25 ± 5 Jahre, acht davon weiblich) konnten die Studie ohne fehlende Datensätze abschließen. Aufgrund technischer Probleme war die Durchführung von einer MRT-Untersuchung am Scanner II nicht möglich. Drei 4D-Fluss-Messungen vom Scanner I konnten aufgrund inkompletter Rekonstruktionen nach der Datenakquise nicht ausgewertet werden. Eine weitere 4D-Fluss-Aufnahme am Scanner I musste ausgeschlossen werden, da mehrere aortale Segmente durch inakkurate Bildplanung nicht vollständig abgebildet waren. Bei einem Probanden wurde eine Ebene (P2) exkludiert, da diese während der Bildplanung abgeschnitten wurde, während zwei weitere Ebenen (P1, P5) bei zwei anderen Proband*innen auf Grund von Aliasing ausgeschlossen wurden (1).

Das Vorwärtsflussvolumen variierte signifikant zwischen den drei Scannern jeweils in den Ebenen P3-P9 ($59,1 \pm 13,1$ vs. $68,1 \pm 12,0$ vs. $55,4 \pm 13,1$ ml; jeweils $p < 0,01$) sowie im Segment der Aorta descendens ($52,2 \pm 12,4$ vs. $60,7 \pm 13,3$ vs. $50,1 \pm 12,3$ ml; $p < 0,01$). Einzig die Ebene P1 mit Lokalisation am sinotubulären Übergang zeigte keinen signifikanten Unterschied für den paarweisen Vergleich zwischen den Scannern (jeweils $p > 0,1$) sowie den Vergleich aller drei Scanner miteinander ($78,5 \pm 15,1$ vs. $80,3 \pm 15,4$ vs. $79,5 \pm 19,9$ ml; $p > 0,1$). Insgesamt wurden die höchsten Werte für das Vorwärtsflussvolumen aus den Daten des Scanners II ermittelt. Die Scanner I und III zeigten in den Bland-Altman-Analysen zum Vorwärtsflussvolumen die höchste Übereinstimmung (1).

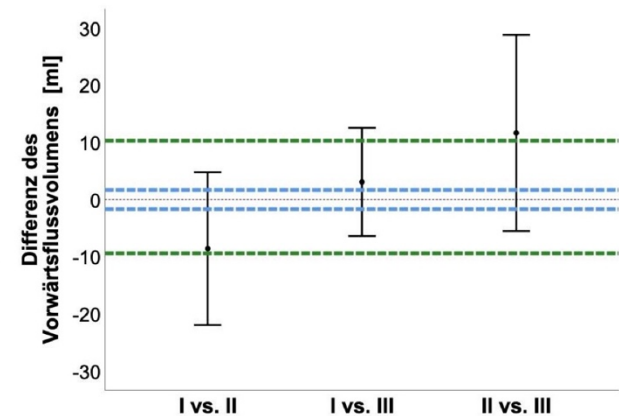
Die maximale Flussgeschwindigkeit unterschied sich signifikant im Segment der Aorta descendens ($125,6 \pm 17,5$ vs. $113,7 \pm 13,2$ vs. $111,1 \pm 19,1$ cm/s; $p < 0,05$) sowie in jeder einzelnen Ebene mit Ausnahme von P1 ($126,4 \pm 16,7$ vs. $119,7 \pm 13,6$ vs. $111,2 \pm 22,6$ cm/s; $p > 0,05$) im Vergleich zweier oder aller drei Scanner miteinander. Die höchsten Werte für die maximalen Flussgeschwindigkeiten resultierten aus den Daten von Scanner I und die geringsten Werte aus denen von Scanner III. Die größte Übereinstimmung in den Bland-Altman-Analysen zur maximalen Flussgeschwindigkeit wurden in den Ergebnissen der Scanner II und III erzielt (1).

Beide Flussparameter waren zwischen den drei Scannern nicht äquivalent, da die Differenzen zwischen je zwei Scannern den Bereich des 95%-CI der Intraobserver-Variabilität überschritten. Auch nachdem das 95%-CI der Scan-Rescan-Variabilität als tolerable Grenze festgelegt wurde, lag nur die Differenz der maximalen Flussgeschwindigkeit zwischen den Scannern II und III innerhalb der Intervallgrenzen und konnte als äquivalent angesehen werden (siehe Abbildung 4) (1).

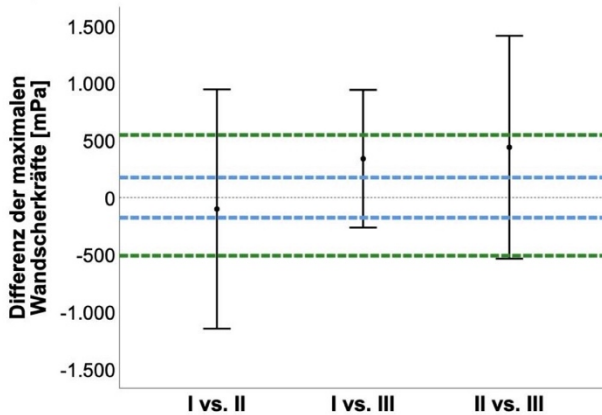
a) Maximale Flussgeschwindigkeit



b) Vorwärtsflussvolumen



c) Maximale Wandscherkräfte



d) Durchschnittliche Wandscherkräfte

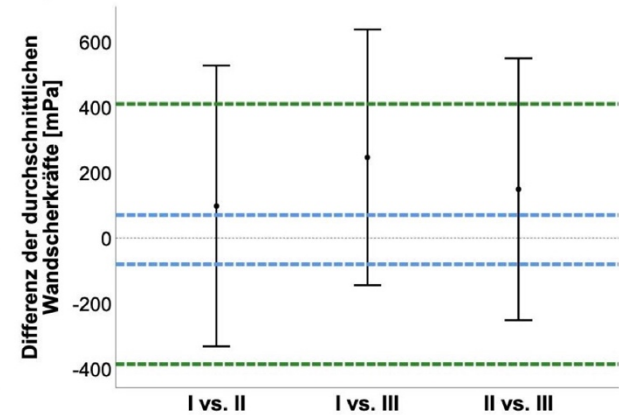


Abbildung 4 Äquivalenztestung mit Bezug auf die Intraobserver- und Scan-Rescan-Variabilität als Vergleich zwischen je zwei Scannern für die Parameter maximale Flussgeschwindigkeit (a), Vorwärtsflussvolumen (b), maximale Wandscherkräfte (c) und durchschnittliche Wandscherkräfte (d) (übersetzt aus Demir et al (1); Lizenznummer: 5300681178987)

Die Äquivalenz von zwei Scannern liegt vor, wenn das 95%-CI ihrer Differenz (dargestellt als graue vertikale Balken) innerhalb der Äquivalenzgrenzen der Intraobserver-Variabilität (blau gestrichelte Linien) oder der Scan-Rescan-Variabilität (grün gestrichelte Linien) liegt. Die gestrichelten Linien stellen den Bereich der Intraobserver- bzw. Scan-Rescan-Variabilität als 95%-CI der Differenz der gemessenen Werte dar.

Die maximalen WSS unterschieden sich signifikant zwischen den drei Scannern für die kombinierten Ebenen P1-P9, die Segmente Aortenbogen sowie Aorta descendens und für alle einzelnen Ebenen außer P1 (1665 ± 363 vs. 1458 ± 434 vs. 1301 ± 243 mPa; $p > 0,05$) und P2 (1530 ± 257 vs. 1762 ± 888 vs. 1294 ± 290 mPa; $p > 0,1$). Auch die durchschnittlichen WSS zeigten lediglich in Ebene P2 (1087 ± 252 vs. 956 ± 320 vs. 919 ± 230 mPa; $p > 0,1$) und dem Segment der Aorta ascendens (1169 ± 210 vs. 1041 ± 285 vs. 971 ± 192 mPa; $p > 0,1$) einen nicht-signifikanten Unterschied im Vergleich aller drei Scanner miteinander. Die geringsten Werte für maximale und durchschnittliche WSS wurden aus den Datensätzen von Scanner III ermittelt (1).

Zwischen den Scannern I und II zeigten sich lediglich bezüglich der durchschnittlichen WSS für die Ebenen P5 ($p < 0,01$), P9 ($p < 0,05$) und für das Aortenbogensegment ($p < 0,05$) sowie die kombinierten Ebenen P1-P9 ($p = 0,01$) signifikante Unterschiede. Hinsichtlich der maximalen WSS war zwischen den beiden Scannern in den Ebenen P1-P9 ($p > 0,1$) und allen Segmenten (jeweils $p > 0,1$) sowie einzelnen Ebenen (jeweils $p > 0,05$) kein signifikanter Unterschied nachzuweisen. Sowohl die Werte für die durchschnittlichen als auch maximalen WSS lagen außerhalb der Bereiche der Intraobserver- und Scan-Rescan- Variabilität und sind dementsprechend als nicht-äquivalent anzusehen (1).

Die ermittelte durchschnittliche Herzfrequenz zeigte keinen signifikanten Unterschied zwischen den verschiedenen 4D-Fluss-Aufnahmen ($69,6 \pm 9,4$ vs. $77,4 \pm 6,8$ vs. $78,9 \pm 13,5$ bpm; $p > 0,05$). Der Blutdruck, welcher vor Akquisition der 4D-Fluss-Scans gemessen wurde, variierte hingegen signifikant (systolisch: $111,0 \pm 10,0$ vs. $121,4 \pm 11,8$ vs. $118,8 \pm 10,1$ mmHg [$p < 0,05$]; diastolisch: $59,8 \pm 5,4$ vs. $69,0 \pm 8,0$ vs. $60,4 \pm 6,1$ mmHg [$p < 0,01$]) (1).

3.1.1.1 Scan-Rescan-Reproduzierbarkeit

Bei allen 15 Proband*innen wurden zwei 4D-Fluss-Messungen am Scanner III durchgeführt, ohne dass ein Ausschluss von Scans oder einzelnen Ebenen im Verlauf notwendig war. Die mittlere Herzfrequenz ($76,1 \pm 11,5$ vs. $76,1 \pm 11,1$ bpm; $p > 0,5$) und der Blutdruck (systolisch: $119,4 \pm 12,0$ vs. $123,7 \pm 17,1$ mmHg [$p > 0,1$]; diastolisch: $61,5 \pm 9,6$ vs. $60,6 \pm 10,5$ mmHg [$p > 0,5$]) zeigten keinen signifikanten Unterschied zwischen beiden Aufnahmen. Ebenfalls wurde kein signifikanter Unterschied für alle untersuchten Parameter in sämtlichen Ebenen und Segmenten ermittelt (alle p -Werte $> 0,1$) (1).

Die Übereinstimmung war exzellent für das Vorwärtsflussvolumen (ICC = 0,98) und gut für die maximale Flussgeschwindigkeit (ICC = 0,83), die durchschnittlichen WSS (ICC = 0,84) sowie für die maximalen WSS (ICC = 0,80). Die Bland-Altman-Analysen zeigten eine gute Übereinstimmung mit engen Konfidenzintervallen. Eine Äquivalenz zwischen den beiden Messungen konnte jedoch nicht aufgezeigt werden, da die Differenzen aller Parameter die Grenzen der Intraobserver-Variabilität überschritten (Abbildung 4) (1).

3.1.1.2 Intra- und Interobserver-Variabilität

Die Bland-Altman-Analysen und ICC belegten eine exzellente Intraobserver-Reproduzierbarkeit für alle evaluierten Parameter (Vorwärtsfluss: ICC = 1,0; maximale Flussgeschwindigkeit: ICC = 0,99; maximale WSS: ICC = 0,99; durchschnittliche WSS: ICC = 1,0). Ebenfalls wurde bezüglich der Interobserver-Reproduzierbarkeit eine exzellente Übereinstimmung für die Parameter Vorwärtsflussvolumen (ICC = 0,99), maximale Flussgeschwindigkeit (ICC = 0,96) und maximale WSS (ICC = 0,92) erzielt. Die durchschnittlichen WSS zeigten eine gute Übereinstimmung (ICC = 0,86) (1).

3.1.2 Vergleich von MRT-Geräten unterschiedlicher Feldstärken

Alle 4D-Fluss-Aufnahmen der zehn gesunden Proband*innen (mittleres Alter = 33 ± 9 Jahre, sechs davon weiblich) wurden am 1,5T- und 3T-MRT erfolgreich akquiriert. Bei 7T hingegen konnten zwei 4D-Fluss-Scans aufgrund technischer Probleme nicht durchgeführt werden. Von den insgesamt 144 evaluierten Aortensegmenten wurde bei zehn die Bildqualität als nicht-diagnostisch eingestuft und diese von der weiteren Analyse ausgeschlossen. Der Großteil hiervon (9/10) war am 7T-MRT generiert worden. 15 Segmente wurden mit einer guten und 119 mit einer exzellenten Bildqualität bewertet (2).

Die Unterschiede zwischen den Feldstärken lagen für alle untersuchten Parameter außerhalb des Äquivalenzbereiches, welcher durch das 95%-CI des Intraobserver-Unterschiedes definiert wurde. Die 4D-Fluss-Aufnahmen der drei Feldstärken wurden somit als nicht-äquivalent eingestuft (siehe Abbildung 5) (2).

Signifikante Unterschiede hinsichtlich des Vorwärtsflussvolumens wurden zwischen 1,5T (Sequenz 1) und 3T sowie zwischen 3T und 7T gefunden ($p < 0,001$), während sich beim Vergleich von 1,5T (Sequenz 1) und 7T kein statistisch signifikanter Unterschied zeigte

($p > 0,5$). Beim alleinigen Vergleich des Vorwärtsflussvolumens in der Aorta ascendens hingegen wurden auch signifikante Unterschiede zwischen 1,5T (Sequenz 1) und 7T gesehen ($p < 0,001$). Ebenfalls zeigten sich signifikant unterschiedliche Werte für das Vorwärtsflussvolumen zwischen 1,5T (Sequenz 2) und 7T ($p < 0,001$). Weiterhin ergab sich eine moderate Korrelation zwischen 1,5T (Sequenz 1) und 3T ($r = 0,7$), 1,5T (Sequenz 1 und 2) und 7T ($r = 0,5$ und $0,6$) sowie zwischen 3T und 7T ($r = 0,5$) (2).

Beim Vergleich der maximalen Flussgeschwindigkeit waren die Differenzen zwischen 1,5T (Sequenz 1) und 3T oder 7T sowie zwischen 3T und 7T statistisch nicht signifikant ($p > 0,1$). Ein signifikanter Unterschied sowohl für die gesamte Aorta als auch für die alleinige Analyse der Aorta ascendens manifestierte sich beim Vergleich zwischen 1,5T (Sequenz 2) und 7T ($p < 0,05$). Die maximale Flussgeschwindigkeit korrelierte moderat zwischen 1,5T (Sequenz 1) und 3T ($r = 0,6$), während suffiziente Aussagen bezüglich der Korrelation am 7T aufgrund der geringen Anzahl vorliegender Werte nicht möglich waren (2).

Bezüglich der WSS ergab sich lediglich zwischen 1,5T (Sequenz 1) und 3T ein signifikanter Unterschied ($p < 0,05$), während die Vergleiche 1,5T (Sequenz 1 und 2) vs. 7T sowie 3T vs. 7T keine statistisch signifikanten Differenzen aufzeigten (jeweils $p > 0,1$). Bei alleiniger Betrachtung der WSS-Werte aus der Aorta ascendens manifestierte sich auch ein signifikanter Unterschied zwischen 1,5T (Sequenz 1 und 2) und 7T ($p < 0,05$). Eine moderate Korrelation wurde zwischen allen Feldstärken außer zwischen 1,5T (Sequenz 1) und 7T ($r = 0,4$) beobachtet (2).

Die Bland-Altman-Analysen zeigten für jeden paarweisen Vergleich der Feldstärken manifeste Unterschiede aller Parameter, während keine systematischen Trends zur Darstellung kamen (2).

3.1.2.1 Reproduzierbarkeit dreier verschiedener Sequenzen am 1,5T-MRT

In den Bland-Altman-Analysen der drei Sequenzen am 1,5T-MRT wurden für jeden paarweisen Vergleich ebenfalls Unterschiede aller Parameter ohne systematisches Muster beobachtet. Lediglich beim Vorwärtsflussvolumen wurden zwischen den Sequenzen 1 und 3 Ergebnisse im Äquivalenzbereich erzielt, so dass sich diese hinsichtlich des Vorwärtsflussvolumens als äquivalent bezeichnen lassen. Bei allen anderen Parametern wurde das 95%-CI der Intraobserver-Reproduzierbarkeit jeweils überschritten (siehe Abbildung 5) (2).

Signifikante Unterschiede hinsichtlich des Vorwärtsflussvolumens wurden zwischen den Sequenzen 1 und 3 sowie den Sequenzen 2 und 3 gefunden ($p < 0,001$), jedoch nicht zwischen den Sequenzen 1 und 2 ($p > 0,1$). Bei alleiniger Betrachtung der Vorwärtsflussvolumina in der Aorta ascendens zeigten sich jedoch signifikante Unterschiede im Vergleich aller Sequenzen ($p < 0,005$). Bezüglich der maximalen Flussgeschwindigkeit wurden für die gesamte Aorta sowie für die Aorta ascendens allein keine signifikanten Unterschiede zwischen den Sequenzen eruiert ($p > 0,5$). Bei Analyse der WSS ergab sich ein signifikanter Unterschied zwischen allen Sequenzen ($p < 0,001$), der auch bei alleiniger Analyse der Aorta ascendens bestehen blieb. Alle Parameter korrelierten moderat bis stark zwischen den unterschiedlichen Sequenzen (je $r \geq 0,5$) (2).

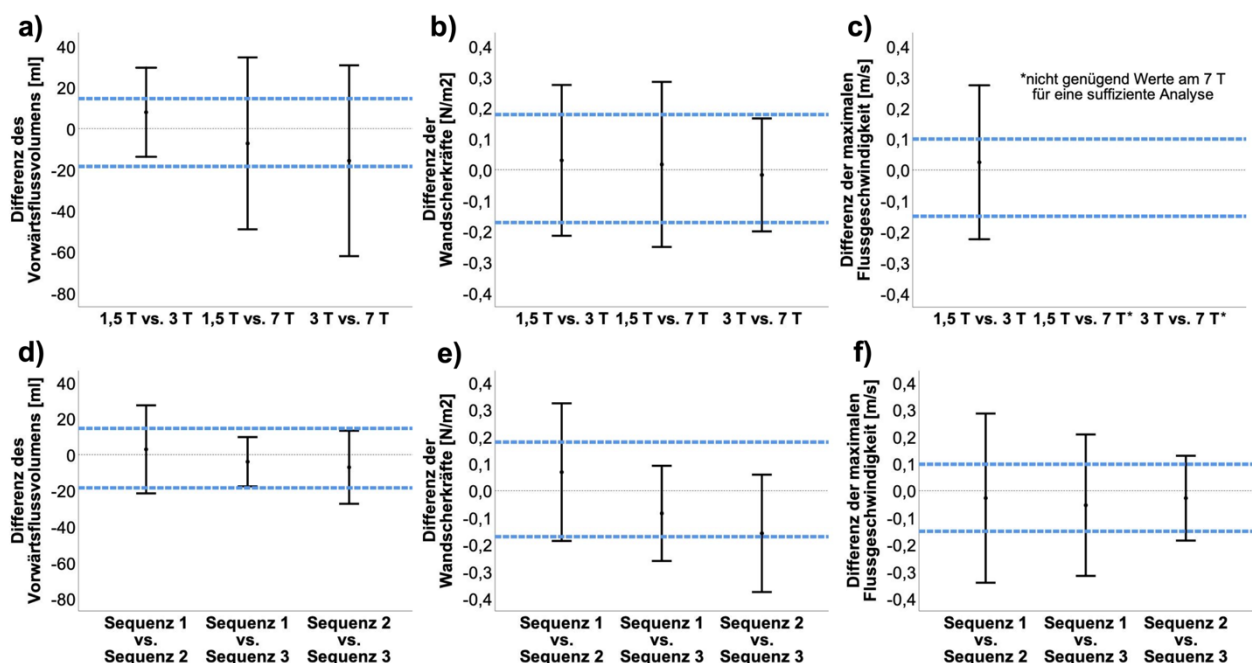


Abbildung 5 Äquivalenztestung mit Bezug auf die Intraobserver-Variabilität als Vergleich zwischen je zwei Feldstärken (a-c) und Sequenzen (d-f) für die Parameter Vorwärtsflussvolumen, Wandscherkräfte und maximale Flussgeschwindigkeit (übersetzt und modifiziert nach Wiesemann et al. (2); Lizenznummer: 5300690103659)

Äquivalenz von zwei Feldstärken bzw. Sequenzen besteht, wenn das 95%-CI ihrer Differenz (dargestellt als graue vertikale Balken) innerhalb der Äquivalenzgrenzen der Intraobserver-Variabilität (blau gestrichelte Linien) liegt.

3.1.2.2 Intra- und Interobserver-Variabilität

Die Bland-Altman-Analysen zeigten eine gute Intra- und Interobserver-Übereinstimmung mit geringem Bias und engen Konfidenzintervallen für alle Parameter. Die Interobserver-

Reproduzierbarkeit war exzellent für die Parameter Vorwärtsflussvolumen (ICC = 0,93), maximale Flussgeschwindigkeit (ICC = 0,99) und WSS (ICC = 0,93) (2).

3.2 Reproduzierbarkeit der fSENC als weitere neue Sequenz der kardialen MRT

3.2.1 Vergleich von MRT-Geräten verschiedener Hersteller

Von den 15 Proband*innen (acht davon weiblich, mittleres Alter = 25 ± 5 Jahre) war die Durchführung der MRT-Untersuchung eines Probanden am Scanner II bedingt durch technische Probleme nicht möglich. Aufgrund von Artefakten wurden weitere fünf fSENC-Messungen von der GLS- und neun von der GCS-Analyse exkludiert, so dass insgesamt 51 Aufnahmen für die Analyse des GLS und 47 Aufnahmen für die Analyse des GCS zur Verfügung standen (3).

Bland-Altman-Analysen zeigten eine gute Übereinstimmung zwischen allen Scannern mit insgesamt geringem Bias (0,01- 1,88%) und 95%-CI mit einer maximalen Spannweite von -5,25% bis 7,68%. Der Bias war sowohl für die GLS- als auch GCS-Analyse am niedrigsten und nicht-signifikant zwischen den Scannern II und III ($p > 0,05$). Zwischen den Scannern I und II sowie I und III hingegen bestand ein größerer Bias (1,21-1,88%), der in der statistischen Testung auch jeweils signifikant war (alle p -Werte $< 0,05$). Bezüglich des 95%-CI lag bei den GLS-Werten eine größere Spannweite vor als bei den GCS-Werten zwischen den MRT-Geräten verschiedener Hersteller (siehe Tabelle 3) (3).

Tabelle 3 Ergebnisse der Bland-Altman-Analysen des fSENC-Vergleiches zwischen MRT-Geräten verschiedener Hersteller (übersetzt aus Erley et al. (3); Lizenznummer: 12217251)

	Bias (%)	95-CI (%)	p-Wert
GLS (n = 51)			
Scanner I vs. II	1,21	-5,25; 7,68	0,012
Scanner I vs. III	1,24	-4,47; 6,92	0,004
Scanner II vs. III	0,01	-4,78; 4,81	0,968
GCS (n = 47)			
Scanner I vs. II	1,14	-2,34; 4,64	<0,001
Scanner I vs. III	1,88	-3,02; 6,79	<0,001
Scanner II vs. III	0,61	-3,99; 5,20	0,083

Die fSENC-Aufnahmen der Gel-Phantome wurden mehrfach wiederholt und die Ergebnisse für mittlere Strain-Werte und deren Standardabweichungen (SD) an den jeweiligen Scanner-Systemen ermittelt ($-28,1 \pm 0,3$ vs. $-23,7 \pm 0,9$ vs. $-26,8 \pm 1,4\%$) (3).

3.2.2 Scan-Rescan-, Intra- und Interobserver-Variabilität

Die Analyse mittels ICC und CoV zeigte insgesamt eine gute bis exzellente Scan-Rescan-Reproduzierbarkeit der gemittelten fSENC-Messungen vor und nach der Pause an allen MRT-Geräten (ICC = 0,63-0,97; CoV = 0,03-0,09). Am Scanner I stellte sich hierbei eine höhere Reproduzierbarkeit für die GCS-Analyse dar, an den Scannern II und III jeweils für die GLS-Analyse. Nur für den Parameter GLS am Scanner I wurde ein signifikanter Unterschied in den gemittelten fSENC-Aufnahmen beobachtet ($p=0,02$) (3).

Unter Betrachtung der Ergebnisse von ICC (0,77-0,99) und CoV (0,02-0,05) ergab sich eine exzellente Intraobserver- und Interobserver-Variabilität mit einer noch höheren Übereinstimmung der Werte der GLS-Analyse (siehe Tabelle 4) (3).

Tabelle 4 Scan-Rescan- sowie Intra- und Interobserver-Reproduzierbarkeit repräsentiert durch ICC (95%-CI) und CoV (\pm SD) (übersetzt und modifiziert nach Erley et al. (3); Lizenznummer: 12217251)

	GLS		GCS	
	ICC (95%-CI)	CoV (\pm SD)	ICC (95%-CI)	CoV (\pm SD)
Scan-Rescan				
Scanner I	0,63 (0,21-0,86)	0,06 (\pm 0,05)	0,82 (0,53-0,93)	0,05 (\pm 0,03)
Scanner II	0,97 (0,90-0,99)	0,03 (\pm 0,02)	0,80 (0,47-0,94)	0,04 (\pm 0,04)
Scanner III	0,82 (0,54-0,94)	0,09 (\pm 0,07)	0,69 (0,29-0,88)	0,07 (\pm 0,05)
Intraobserver	0,99 (0,98-1,0)	0,02 (\pm 0,02)	0,77 (0,47-0,90)	0,05 (\pm 0,04)
Interobserver	0,96 (0,92-0,98)	0,03 (\pm 0,04)	0,82 (0,58-0,92)	0,04 (\pm 0,03)

4. Diskussion

Die vorliegenden Studien zeigen Unterschiede in den Ergebnissen neuer CMR-Sequenzen bei einer Datenakquisition an MRT-Geräten verschiedener Hersteller und Feldstärken. Diese Tatsache verdeutlicht die Notwendigkeit einer Standardisierung dieser Sequenzen über Feldstärken und Hersteller hinweg für eine optimierte Etablierung in der klinischen Routine sowie für forschungsbezogene Fragestellungen.

4.1 Reproduzierbarkeit der kardialen 4D-Fluss-MRT

4.1.1 Vergleich von MRT-Geräten verschiedener Hersteller

Die Anwendung unterschiedlicher herstellerabhängiger Sequenzen an den drei Standorten zeigte signifikante Unterschiede für hämodynamische Parameter der 4D-Fluss-MRT auf. Alle untersuchten Parameter überschritten den Toleranzbereich des Intraobserver-Vergleiches der Äquivalenztestung. Darüber hinaus fanden wir durchweg niedrigere Werte für alle ausgewerteten Parameter am Scanner III, während die höchsten Werte für die maximale Flussgeschwindigkeit am Scanner I und für das Vorwärtsflussvolumen am Scanner II gemessen wurden (1).

Nach unserem Kenntnisstand ist diese Studie die erste, welche den Einfluss von MRT-Geräten dreier unterschiedlicher Hersteller auf hämodynamische Parameter der 4D-Fluss-MRT an gesunden Proband*innen evaluiert.

Watanabe et al. untersuchten bereits anhand von Phantommessungen den Effekt von drei unterschiedlichen 3T-MRT-Geräten der Hersteller GE, Philips und Siemens auf die Flussgeschwindigkeit. Als Phantom wurde ein gerades Rohr in schräger Position verwendet, durch welches eine Flüssigkeit von blutähnlicher Konsistenz gepumpt wurde. Die Ergebnisse ergaben eine gute Genauigkeit der Flussgeschwindigkeitsprofile aller drei Scanner, obwohl in allen MRT-Geräten die maximale Flussgeschwindigkeit im Zentrum des Rohres unterschätzt und wandnah überschätzt wurde. Zusätzlich wurde die zeitlich gemittelte Flussgeschwindigkeit senkrecht zum Zentrum des Rohres gemessen und korrelierte gut mit den Referenzwerten, welche mittels herstellerspezifischer Flussmeter gemessen wurden, zeigten jedoch in den Referenzwerten zwischen den MRT-Geräten

ebenfalls geringe Unterschiede auf (27). Auch in unserer Studie lagen die absoluten Werte der ermittelten maximalen Flussgeschwindigkeiten zwischen den verschiedenen MRT-Geräten nahe beieinander. Zusätzlich wurde eine statistische Analyse inklusive einer Äquivalenztestung als Methode des akzeptierten Unterschiedes aus klinischer Perspektive durchgeführt. Die maximale Flussgeschwindigkeit erwies sich hierbei als stabilster Parameter, da zumindest mit Bezug auf die Scan-Rescan-Variabilität eine Äquivalenz zwischen zwei Scannern erreicht wurde (1).

Die Ebene P1 mit Lokalisation am sinotubulären Übergang kristallisierte sich durch die niedrigste Anzahl an signifikanten Unterschieden der untersuchten Parameter als stabilste Position heraus. Zusätzlich wurde das Herzzeitvolumen einerseits aus den SSFP-cine-Bildern und andererseits aus der 4D-Fluss-Analyse (Vorwärtsflussvolumen an P1 x Herzfrequenz während der 4D-Fluss-MRT) exemplarisch für 15 Proband*innen am Scanner III ermittelt. Die Ergebnisse zeigten keinen signifikanten Unterschied und können dadurch als externe Validierung der mittels 4D-Fluss-MRT erfassten Flussvolumina dienen (1).

Die Stabilität von P1 ist insbesondere von klinischem Interesse, da die Position identisch zu der Lokalisation der routinemäßig genutzten 2D-Fluss-MRT ist und damit eine wichtige Rolle in der Diagnostik von Flussmessungen der Aorta wie Insuffizienzen oder Shunt-Messungen einnimmt (9-11). Vor dem Hintergrund der Tatsache, dass nicht nur die identische Positionierung dieser Ebene herausfordernd bleibt, sondern auch die akkurate Konturierung der Gefäßgrenzen durch die besonders starke translationale Verlagerung im Bereich der Aorta ascendens erschwert wird, mag diese Feststellung überraschend erscheinen (40). Ein Grund für die Stabilität dieser Ebene könnte in ihrer zentralen Lage liegen, unabhängig vom definierten Akquisitionsvolumen (ganzes Herz vs. Aorta). Bekanntlich können Ebenenlokalisationen, welche sich weiter entfernt vom magnetischen Isozentrum befinden, eher zu inakkuraten Flussergebnissen führen. Hauptsächlich wird dies durch Eddy currents verursacht, die Phasen-Offsets bedingen (1, 41).

Um dem entgegenzuwirken, wurde zwar während der Datenanalyse eine Korrektur der Phasen-Offsets mittels linearer Anpassung zum statischen Gewebe durchgeführt, jedoch können auch die Phasen-Offsets selbst zwischen verschiedenen Scannern variieren und Anpassungsmodelle höherer Ordnung für Vergleiche zwischen verschiedenen Scannern erforderlich machen. Weiterhin existiert in der klinischen Auswertung keine gewöhnliche

Technik, um die Präzision der angewendeten Korrekturmethode zu verifizieren, wodurch die Korrektur selbst insuffizient sein könnte (1, 6).

Ursächlich für die signifikanten Unterschiede zwischen den Ergebnissen der drei MRT-Geräte könnte die Variation in den technischen Sequenzparametern sein. Es wurden in dieser Studie bewusst die individuellen und herstellereingepassten 4D-Fluss-MRT-Sequenzen der Standorte verwendet, ohne eine Angleichung der Akquisitionsparameter vorzunehmen, um so die reale klinische Umgebung zu repräsentieren. Der damit einhergehende potenzielle Einfluss verschiedener technischer Parameter auf die erhobenen Ergebnisse wurde in der entsprechenden Veröffentlichung bereits ausführlich diskutiert (1). Die Unterschiede in den Sequenzparametern, wie sie in unserer Studie vorzufinden sind, stellen damit potenzielle Confounder dar. Gleichzeitig repräsentieren sie aber auch das Fehlen von standardisierten MRT-Sequenzen mit einer Anwendbarkeit über verschiedene Hersteller oder Standorte hinweg. Da jedes MRT-Gerät in Abhängigkeit von Feldstärke und/oder Hersteller individuelle Einstellungen benötigt, müssen vermutlich auch weiterhin individuelle Anpassungen vorgenommen werden. Ebenfalls können aus klinischer Erfahrung individuelle und standortassoziierte Anpassungen zur Optimierung des Protokolls notwendig werden (1).

Zudem könnten hämodynamische Veränderungen in den Proband*innen selbst zu den resultierenden Unterschieden beigetragen haben. Als Hinweis dafür kann die signifikante Variation in den systolischen und diastolischen Blutdruckwerten zwischen den verschiedenen 4D-Fluss-Messungen betrachtet werden. Diese physiologischen Veränderungen könnten beispielsweise durch Unterschiede in der Flüssigkeits- oder Nahrungszufuhr vor der 4D-Fluss-MRT entstanden sein, da unsere Proband*innen keiner Flüssigkeits- oder Nahrungskarenz unterlagen (42). Ebenfalls könnten Unterschiede in Akquisitionsdauer und Liegedauer die Hämodynamik beeinflusst haben. Dennoch waren die absoluten Blutdruckwerte sehr ähnlich und die Diskrepanzen aus klinischer Sicht ohne Relevanz, zumal auch die Herzfrequenz nicht signifikant unterschiedlich war (1).

4.1.2 Vergleich von MRT-Geräten unterschiedlicher Feldstärken

Die Akquise von 4D-Fluss-Messungen war an den MRT-Geräten aller drei Feldstärken (1,5T, 3T und 7T) mit einer suffizienten Bildqualität möglich. Die untersuchten 4D-Fluss-

Parameter waren zwischen den verschiedenen Feldstärken nicht äquivalent und signifikante Unterschiede konnten aufgezeigt werden (2).

Strecker et al. verglichen bereits in einer Studie die 4D-Fluss-MRT der Aorta an den Feldstärken 1,5T und 3T bei gesunden Proband*innen und fanden keine signifikanten Unterschiede der evaluierten Parameter. Deren Ergebnisse zeigten zudem eine deutlich bessere Bildqualität am 3T-MRT mit Hinblick auf Flussvisualisierung, Qualität der Phasenkontrast-MRT und Hintergrundrauschen (25). Ergänzend zur Studie von Strecker et al. schlossen wir zusätzlich noch 7T als weitere Feldstärke ein. In Übereinstimmung mit der genannten Publikation sahen wir bei Betrachtung der quantitativen Untersuchungsparameter ähnliche Werte für Flussvolumina, maximale Geschwindigkeit und WSS. In der statistischen Analyse waren jedoch einige dieser Unterschiede signifikant. Zusätzlich wurde in unserer Studie die Äquivalenz zwischen den Ergebnissen der einzelnen Feldstärken untersucht, um eine Austauschbarkeit verschiedener MRT-Geräte aus klinischer Perspektive zu prüfen. Hierbei waren alle evaluierten Parameter zwischen je zwei Scannern nicht-äquivalent und damit nicht austauschbar (2).

Die geringste Bildqualität stammte in unserer Studie aus den Daten der 7T-MRT mit primärer Lokalisation am Aortenbogen und der Aorta descendens als Segmente von nicht-diagnostischer Qualität. Diese Tatsache verhielt sich gegensätzlich zu der zu erwartenden höheren Signal-to-Noise-Ratio (SNR) bei 7T im Vergleich zu 3T oder 1,5T. Beispielweise wurde in der Studie von Hess et al. in der aortalen 4D-Fluss-MRT eine bis zu 2,2-fach höhere SNR für 7T verglichen mit 3T bestimmt (43). Dies ermöglichte z.B. in der Bildgebung intrakranieller Gefäße mittels 7T-MRT eine bessere Darstellung kleiner Gefäße sowie eine optimierte Flussvisualisierung (44). Die geringere Bildqualität bei 7T in unserer Studie wurde vermutlich durch systematisch geringe Flipwinkel verursacht, die von der Einkanal-Sendespule innerhalb des Aortenbogens und der Aorta descendens erzeugt wurden. Eine Adjustierung der Spule, so dass diese die Aorta und nicht das gesamte Herz erfasst, oder die Verwendung einer Multikanal-Sendespule mit Shimming-Funktion könnten dieses Problem beheben (2).

Die klinisch genutzten 4D-Fluss-Sequenzen unterscheiden sich häufig in ihren technischen Parametern geringfügig voneinander, was auch die in unserer Studie beobachteten signifikanten Unterschiede zwischen den Feldstärken mitverursacht haben könnte. Ebenfalls können diese Differenzen durch physiologische Veränderungen in der

Hämodynamik und/oder der Flüssigkeits- und Nahrungszufuhr von den Proband*innen aufgetreten sein, da unsere Proband*innen nicht gefastet hatten (42). Dennoch wurden alle Aufnahmen ungefähr zu gleicher Tageszeit durchgeführt, was zu einem ähnlichen Flüssigkeits- und Nahrungshaushalt geführt haben sollte, zumal beispielweise die drei 4D-Fluss-Messungen bei 1,5T direkt hintereinander durchgeführt wurden (2).

Wie bereits beim Vergleich der MRT-Geräte verschiedener Hersteller beobachtet, kristallisierte sich auch in dieser Studie die maximale Flussgeschwindigkeit als stabilster Parameter heraus. Dies verdeutlichen die nicht-signifikanten Unterschiede in der maximalen Flussgeschwindigkeit zwischen 1,5T und 3T sowie 3T und 7T. Zudem konnten die Ergebnisse zwischen 3T und 7T bei Betrachtung des alleinigen Intraobserver-Vergleiches der Aorta ascendens als äquivalent angesehen werden. Ebenfalls erwies sich die maximale Flussgeschwindigkeit beim Vergleich der drei Sequenzen am 1,5T-MRT als der Parameter mit der geringsten Abhängigkeit. Es wurden keine signifikanten Unterschiede für diesen Parameter ermittelt und zwischen den Sequenzen 2 und 3 lagen die Differenzen nur knapp außerhalb des Intraobserver-Äquivalenzbereiches. Bei Betrachtung des alleinigen Intraobserver-Intervalls aus den Ergebnissen der 1,5T-MRT lagen sie sogar innerhalb der Äquivalenzgrenzen und können als äquivalent bezeichnet werden (2).

Im Vergleich der technischen Parameter der Sequenzen 2 und 3 unterscheiden sich diese lediglich im kardialen Gating (prospektiv und retrospektiv), was die Stabilität der maximalen Flussgeschwindigkeit begründen könnte und eher geringe Unterschiede zwischen den Sequenzen erwarten lässt. Dennoch sahen wir signifikante Unterschiede für die Parameter Vorwärtsflussvolumen und WSS. Da prospektiv getriggerte Sequenzen nicht den kompletten Herzzyklus umfassen und die späten diastolischen Phasen fehlen, lassen sich hierdurch die Unterschiede im Vorwärtsflussvolumen erklären. Unterschiede in der rekonstruierten zeitlichen Auflösung der unterschiedlichen Gating-Techniken könnten zu Veränderungen in den WSS geführt haben. Da die WSS-Analyse fünf Herzphasen umfasst, von denen die mittlere Phase die maximale Systole darstellt, könnte das Intervall der fünf Herzphasen für den retrospektiven Scan vermeintlich kürzer ausfallen und somit die höheren WSS-Werte erklären (2).

4.1.3 Scan-Rescan-, Intra- und Interobserver-Variabilität

Die Intra- und Interobserver-Reproduzierbarkeit der 4D-Fluss-MRT stellte sich in beiden Studien und damit unabhängig von der verwendeten Auswertungssoftware als gut bis exzellent dar (1, 2). Ebenfalls sahen wir hinsichtlich der Scan-Rescan-Reproduzierbarkeit am 3T-MRT keine signifikanten Unterschiede für alle evaluierten Parameter. Im Vergleich zur Intra- und Interobserver-Variabilität zeigte sich in den Ergebnissen der Scan-Rescan-Reproduzierbarkeit jedoch eine größere Varianz. Diese könnte durch Unterschiede in der Repositionierung der Spule oder der Bildplanung ausgelöst worden sein, da die Proband*innen während der Pause das MRT-Gerät verlassen hatten. Zudem war die Liegedauer vor der ersten 4D-Fluss-Messung länger und könnte hämodynamische Veränderungen verursacht haben, wobei sich Blutdruck und Herzfrequenz zwischen beiden Messungen nicht signifikant unterschieden (1).

4.2 Reproduzierbarkeit der fSENC als weitere neue Sequenz der kardialen MRT

4.2.1 Vergleich von MRT-Geräten verschiedener Hersteller

Unsere Ergebnisse der fSENC-Messungen zeigen zwischen den drei MRT-Geräten verschiedener Hersteller einen geringen, jedoch statistisch signifikanten Bias mit weiten Konfidenzintervallen in den Bland-Altman-Analysen. Der Bias zwischen den Scannern I und II sowie I und III war signifikant. Zudem deuten die weiten Konfidenzintervalle darauf hin, dass bei einigen Proband*innen die Unterschiede in den Strain-Werten noch höher liegen könnten als der ermittelte Bias (3).

Nach unserem Kenntnisstand ist dies die erste Studie, die den Einfluss verschiedener Gerätehersteller auf die MRT-basierte Strain-Analyse evaluiert. Eine Verwendung von Ultraschallgeräten verschiedener Hersteller für die Strain-Analyse mittels STE wurde bereits in mehreren Studien untersucht (45-49).

Farsalinos et al. evaluierten die Reproduzierbarkeit des GLS an sieben Ultraschallgeräten verschiedener Hersteller mit deren jeweiligen Softwarepaketen sowie den Produkten zweier unabhängiger Softwarehersteller. Das Kollektiv, bestehend aus 62 Teilnehmenden, umfasste sowohl gesunde Proband*innen als auch Patient*innen mit

niedriger EF (49). In Übereinstimmung mit unserer Studie resultierte ein geringer, jedoch statistisch signifikanter Bias (0,1-3,7%) zwischen den Herstellern (3).

In der Studie von Badano et. al. wurde im Vergleich zweier Hersteller ebenfalls ein signifikanter Bias aufgezeigt, der in der Analyse des GLS (Bias = 1,1%) deutlich geringer ausfiel als in der Analyse des GCS (Bias = 7,0%) (48). Im Vergleich dazu wurden in unserer Studie hingegen ähnliche Werte bei beiden Strain-Analysen beobachtet (3).

Mirea et al. untersuchten in ihrer Studie die Reproduzierbarkeit segmentaler Strain-Auswertung an sieben verschiedenen Ultraschallgeräten und 63 Proband*innen, von denen 58 in der Vorgeschichte bereits einen Myokardinfarkt erlitten hatten. Deren Ergebnisse zeigten, dass sich die Präzision einer Differenzierung zwischen narbigen und gesunden Segmenten signifikant zwischen den Herstellern unterscheidet. Zudem wurden in der segmentalen Strain-Analyse signifikante Unterschiede mit einem maximalen Bias von 4,5% ermittelt. Dementsprechend schlussfolgerten Mirea et al., dass im Gegensatz zur insgesamt gut reproduzierbaren globalen Strain-Analyse hinsichtlich der segmentalen Strain-Auswertung eine höhere Variabilität zwischen Ultraschallgeräten besteht (46, 47). So könnte auch in der Strain-Analyse mittels fSENC eine größere Variabilität in der Präzision segmentaler Strain-Auswertung vorliegen.

Unterschiede in den technischen Charakteristika der verschiedenen Sequenzen stellen auch bei den fSENC-Messungen einen potenziellen Einflussfaktor dar. Während an den Scannern I und II Spiralsequenzen verwendet wurden, wurde am Scanner III eine echoplanare Sequenz (Echo-planar Imaging, EPI) genutzt. Zusätzlich wurden die Akquisitionsparameter der fSENC-Pulssequenzen jeweils durch Experten der verschiedenen Hersteller modifiziert, um an den jeweiligen Hersteller angepasst zu sein und eine optimale Bildqualität zu ermöglichen. Daher unterschieden sich die technischen Parameter zwischen den drei Standorten, was einer realistischen klinischen Perspektive gleichkommt (3).

Um den alleinigen Einfluss der unterschiedlichen Pulssequenzen auf die Strain-Ergebnisse zu evaluieren, wurden vor den In-vivo-Messungen bereits Phantome an den drei Scanner-Systemen untersucht. Hierbei zeigten sich höhere Mittelwerte für die Scanner II und III im Vergleich zu Scanner I in Übereinstimmung mit den Ergebnissen des mittleren GLS und GCS bei unseren Proband*innen. Daraus lässt sich schließen, dass die Pulssequenz selbst bereits zu den Unterschieden in den Strain-Werten beigetragen haben könnte (3).

Weitere mögliche Einflussfaktoren könnten Unterschiede in der Bildplanung durch variierende Trainingsgrade der Medizinisch-technischen Radiologieassistent*innen (MTRA), die Erfahrung in der Datenauswertung oder physiologische Veränderungen in den Proband*innen darstellen. Um den Effekt eines Unterschiedes im Training der MTRAs und während der Datenauswertung zu minimieren, durchliefen alle ein intensives Training zu Bildplanung bzw. Auswertung und absolvierten einen schriftlichen Abschlusstest (3).

Durch die zum Teil längeren Zeiträume zwischen den einzelnen Untersuchungen können Veränderungen in der myokardialen Funktion der Proband*innen ebenfalls nicht ausgeschlossen werden. Alle Proband*innen wurden vor jeder Untersuchung zu ihrem Gesundheitszustand inklusive einer Einnahme neuer Medikamente befragt und wären bei einer relevanten Veränderung ausgeschlossen worden. Teilweise wurden unsere Proband*innen auch zu unterschiedlichen Tageszeitpunkten untersucht, was kurzfristige Unterschiede in der Volumenbelastung des Herzens verursacht haben könnte. Die Herzfrequenzen der Proband*innen waren jedoch nicht signifikant unterschiedlich. Zudem zeigten unsere Ergebnisse eine gute bis exzellente Scan-Rescan-Reproduzierbarkeit der fSENC-Messungen (3). In Übereinstimmung dazu wurde in der Studie von Giusca et al., welche neben elf gesunden Proband*innen auch sieben Patient*innen mit Herzinsuffizienz beinhaltete, eine exzellente Scan-Rescan-Reproduzierbarkeit innerhalb eines medianen Zeitraumes von 63 Tagen ermittelt (50). Der Einfluss kurzfristiger Veränderungen in der myokardialen Funktion beispielsweise durch Volumenunterschiede, Schlagvolumen oder Herzfrequenz sollte daher bei Gesunden gering sein (3).

4.3 Limitationen

Alle drei Studien umfassten nur eine geringe Anzahl gesunder Proband*innen ohne Teilnahme von Patient*innen mit kardiovaskulären Vorerkrankungen. Zudem mussten aufgrund von technischen Problemen, Artefakten oder nicht-diagnostischer Bildqualität in den einzelnen Studien mehrere Untersuchungen ausgeschlossen werden. Um den aktuellen Grad der Standardisierung darzustellen, wurden die individuellen CMR-Sequenzen der Scanner unterschiedlicher Hersteller oder Feldstärken an den jeweiligen

Standorten beibehalten und nicht auf eine angepasste Sequenz adaptiert. Dadurch unterschieden sich die Sequenzparameter zwischen den einzelnen MRT-Geräten geringgradig voneinander, was mitunter durch die Verfügbarkeit der Sequenzen und der Hardware an den unterschiedlichen Scannern verursacht wurde, somit jedoch auch die klinische Umgebung widerspiegelt (1-3).

Zusätzliche Scans mit angepassten Sequenzparametern konnten aus logistischen Gründen nicht durchgeführt werden (1). Dennoch wurden in der Studie zum Feldstärkenvergleich auch verschiedene Sequenzen bei einer Feldstärke miteinander verglichen, um den Einfluss unterschiedlicher Sequenzparameter zu evaluieren (2). Beim fSENC-Vergleich wurden hierfür vorab Phantomuntersuchungen durchgeführt (3).

In allen drei Studien wurde kein Vergleich der Ergebnisse mit der jeweiligen Standard-Methodik, 2D-Fluss-MRT bzw. STE oder Tagging, durchgeführt. Dadurch lassen sich keine Aussagen darüber treffen, welche der Sequenzen an den MRT-Geräten der verschiedenen Hersteller oder Feldstärken die akkuratesten Ergebnisse aufwiesen, was jedoch auch nicht primäres Ziel dieser Studien war. Die unterschiedlichen Zeitintervalle zwischen den einzelnen Untersuchungsterminen an den MRT-Geräten verschiedener Hersteller könnten die Variabilität der hämodynamischen Parameter erhöht haben. Dennoch verhielten sich die Blutdruckwerte der einzelnen Proband*innen ähnlich und die Unterschiede in der Herzfrequenz waren nicht signifikant. Das gesamte Kollektiv war zudem gesund, so dass der Einfluss diesbezüglich eher gering ausfallen sollte (1-3).

4.4 Ausblick

Die stetige technische Weiterentwicklung der 4D-Fluss-MRT führte bereits in den letzten Jahren zu einer deutlichen Reduktion der Akquisitionsdauer, wodurch eine Anwendbarkeit außerhalb der Forschung und ein Transfer in die klinische Routinediagnostik ermöglicht wurde. Gleichzeitig findet gegenwärtig eine immense Progression der Post-Processing-Softwares statt, welche mit intuitiveren und automatisierten Schritten zu einer weiteren Verkürzung der Analysedauer beitragen, während gleichzeitig die Intra- und Interobserver-Reproduzierbarkeit weiter optimiert wird. Eine kritische Auseinandersetzung mit möglichen Störfaktoren wie dem Einfluss verschiedener MRT-Hersteller oder Feldstärken sowie Post-Processing-Tools im Rahmen multizentrischer

Studien ist für die Standardisierung innovativer CMR-Sequenzen essenziell, welche nun immer stärker in den Fokus rückt. Diesbezüglich lieferten unsere Studien bereits erste Erkenntnisse, die im Rahmen größerer multizentrischer Studien mit zusätzlicher Inklusion von Patient*innen weiter eruiert werden sollten. In unserer Arbeitsgruppe findet dafür momentan im Bereich der 4D-Fluss-MRT eine multizentrische Studie zum Vergleich von Scannern verschiedener MRT-Hersteller mit einer größeren Kohorte an gesunden Proband*innen statt. Gleichzeitig werden in einer weiteren Studie drei verschiedene Auswertesoftware evaluiert.

Durch eine fortschreitende Standardisierung der neuen Sequenzen können diese nicht nur ihren Platz in der klinischen Routine finden, sondern auch in verschiedenen Forschungsgebieten durch multizentrische zielgerichtete Studien wertvolle Ergebnisse für Diagnostik und Therapie von Erkrankungen liefern. So könnte die 4D-Fluss-MRT neben einem besseren Verständnis der Pathophysiologie und der Diagnostik von Klappenerkrankungen auch bei der Wahl des individuellen Zeitpunktes für einen Klappenersatz, dessen individueller Anpassung sowie der Evaluation der Therapieeffektivität nach einem Klappenersatz zum Einsatz kommen. Die fSENC als Methode zur Strain-Analyse bietet insbesondere durch die kurze Akquisitionsdauer sowie exzellente Intra- und Interobserver-Variabilität großes Potential. Bei einer weiteren Minimierung potenzieller Confounder könnte sie sich neben der untersucherabhängigen Echokardiographie als frühzeitiger Detektionsparameter kontraktile Dysfunktionen sowie insbesondere zur Verlaufskontrolle myokardialer Funktionen durchsetzen.

4.5 Schlussfolgerungen

Die vorliegenden Studien stellen den gegenwärtigen Stand der Standardisierung innovativer CMR-Sequenzen dar und legen einen besonderen Fokus auf den Einfluss unterschiedlicher Feldstärken und MRT-Geräte verschiedener Hersteller. Diesen potenziellen Störfaktoren kommt sowohl in der Forschung als auch in der klinischen Routine eine besondere Bedeutung zu, weshalb eine Auseinandersetzung mit der Thematik unabdingbar ist.

Bei der Anwendung unterschiedlicher herstellereinspezifischer Sequenzen an drei verschiedenen Scannern (GE, Philips, Siemens) zeigten sich signifikante Unterschiede

der hämodynamischen Parameter in der 4D-Fluss-MRT. Alle untersuchten Parameter überschritten den aus klinischer Sicht tolerablen Äquivalenzbereich der Intraobserver-Variabilität. Die Ebene P1 am sinotubulären Übergang zeichnete sich als stabilste Ebenenlokalisation aus (1). Eine Datenakquisition war an allen drei Feldstärken (1,5T, 3T, 7T) mit suffizienter Bildqualität möglich, mit der insgesamt niedrigsten Bildqualität am 7T-MRT. Ebenfalls waren die Ergebnisse der 4D-Fluss-MRT bei verschiedenen Feldstärken signifikant unterschiedlich und nicht äquivalent (2). Die maximale Flussgeschwindigkeit erwies sich in beiden Studien als Parameter mit der geringsten Abhängigkeit von Feldstärke bzw. Hersteller (1, 2). Die Ergebnisse der fSENC-Messungen an drei MRT-Geräten eines unterschiedlichen Herstellers zeigten insgesamt zwar einen niedrigen, jedoch statistisch signifikanten Bias. Zudem deuteten die breiten Konfidenzintervalle darauf hin, dass Ergebnisse einer Strain-Analyse verschiedener Scanner nicht problemlos austauschbar sind. Ein durchschnittlicher Bias von 0,01-1,88% sollte bei einem Vergleich zwischen verschiedenen Scannern beachtet werden (3). Die Scan-Rescan-Reproduzierbarkeit sowie Intra- und Interobserver-Variabilität erzielten in allen Studien jeweils gute bis exzellente Resultate (1-3).

Unsere Ergebnisse verdeutlichen die Notwendigkeit größerer multizentrischer Studien zur präzisen Identifikation potenzieller Confounder sowie einer weiteren Standardisierung innovativer Sequenzen über Feldstärken und Hersteller hinweg. Erst hierdurch kann eine Etablierung in der klinischen Routine sowie eine zielgerichtete Durchführung diagnostisch und therapeutisch relevanter Studien in der klinischen Forschung erfolgen. Bis dahin sollte die fehlende Austauschbarkeit einzelner Scanner bedacht werden und Follow-up-Untersuchungen sowie longitudinale Studien am selben Scanner durchgeführt werden.

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Eidesstattliche Versicherung

„Ich, Aylin Demir, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Standardisierung innovativer Sequenzen der kardiovaskulären Magnetresonanztomographie – Evaluierung der Reproduzierbarkeit verschiedener Hersteller und Feldstärken“ / „Standardization of innovative cardiovascular magnetic resonance sequences – Evaluating the reproducibility of different vendors and field strengths“ 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 dem/der Erstbetreuer/in, 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

Aylin Demir hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Demir A*, Wiesemann S*, Erley J, Schmitter S, Trauzeddel RF, Pieske B, Hansmann J, Kelle S, Schulz-Menger J. Traveling Volunteers: A Multi-Vendor, Multi-Center Study on Reproducibility and Comparability of 4D Flow Derived Aortic Hemodynamics in Cardiovascular Magnetic Resonance. J Magn Reson Imaging. 2022;55(1):211-22.

*die Autoren teilen sich die Erstautorenschaft dieser Publikation

Beitrag im Einzelnen:

- Literaturrecherche
- Beteiligung an Konzeption und inhaltlicher Ausrichtung (gemeinsam mit SW und JSM)
- Rekrutierung der Proband*innen und Mitorganisation der MRT-Untersuchungen (gemeinsam mit JE und SK)
- Mitbetreuung der Proband*innen während der MRT-Untersuchungen (gemeinsam mit JE)
- Zusammentragung der Datensätze
- Evaluierung verschiedener Post-Processing-Softwares der 4D-Fluss-MRT zur Auswahl einer validen und geeigneten Auswertemethode für die Studie
- Kommunikation mit den entsprechenden Ansprechpartnern der Post-Processing-Software-Hersteller zur Lösung von Problemen
- Erstellung des Auswerteprozesses mit CAAS inklusive Festlegung der Ebenenlokalisationen
- Etablierung der Auswertemethode
- Komplette Datenauswertung (Auswertung aller Daten zur 4D-Fluss-MRT sowie zur linksventrikulären Dimension und Funktion)
- Wiederholte Datenanalyse zur Intraobserver-Reproduzierbarkeit
- Statistische Auswertung und Interpretation der Ergebnisse
- Entwurf des gesamten Manuskripts inklusive aller Tabellen und Abbildungen (Tabellen 1-3, Abbildungen 1-4 sowie in der Online-Publikation die zusätzlichen Tabellen S1-S3 und Abbildung S1 wurden alle von mir erstellt)
- Diskussion mit den Koautor*innen
- Einreichung des Manuskripts für die Publikation
- Revision des Manuskripts, der Tabellen und Abbildungen

Publikation 2: Wiesemann S, Schmitter S, **Demir A**, Prothmann M, Schwenke C, Chawla A, von Knobelsdorff-Brenkenhoff F, Greiser A, Jin N, Bollache E, Markl M, Schulz-Menger J. Impact of sequence type and field strength (1.5, 3, and 7T) on 4D flow MRI hemodynamic aortic parameters in healthy volunteers. *Magn Reson Med.* 2021;85(2):721-33.

Beitrag im Einzelnen:

- Auswertung eines Teils der Daten als Interobserver
- Diskussion im Rahmen der Interobserver-Auswertung
- Kritische Revision der Manuskriptentwürfe, Tabellen und Abbildungen

Publikation 3: Erley J, Zieschang V, Lapinskas T, **Demir A**, Wiesemann S, Haass M, Osman NF, Simonetti OP, Liu Y, Patel AR, Mor-Avi V, Unal O, Johnson KM, Pieske B, Hansmann J, Schulz-Menger J, Kelle S. A multi-vendor, multi-center study on reproducibility and comparability of fast strain-encoded cardiovascular magnetic resonance imaging. *Int J Cardiovasc Imaging.* 2020;36(5):899-911.

Beitrag im Einzelnen:

- Rekrutierung der Proband*innen und Mitorganisation der MRT-Untersuchungen (gemeinsam mit JE und SK)
- Mitbetreuung der Proband*innen während der MRT-Untersuchungen (gemeinsam mit JE)
- Kritische Revision der Manuskriptentwürfe, Tabellen und Abbildungen

Unterschrift des Doktoranden/der Doktorandin

Auszug aus der Journal Summary List und Originalpublikationen


Publikation 1

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
 Selected Categories: **“RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING”** Selected Category Scheme: WoS
Gesamtanzahl: 133 Journale

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

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	EUROPEAN RADIOLOGY	20,761	4.101	0.033260
22	SEMINARS IN RADIATION ONCOLOGY	2,531	4.076	0.003540
23	JOURNAL OF MAGNETIC RESONANCE IMAGING	17,046	3.954	0.024900
24	Biomedical Optics Express	11,090	3.921	0.025030
25	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,656	3.750	0.002940
26	JOURNAL OF DIGITAL IMAGING	2,494	3.697	0.003790
27	MAGNETIC RESONANCE IN MEDICINE	32,159	3.635	0.029700
28	Insights into Imaging	1,948	3.579	0.003260
29	INTERNATIONAL JOURNAL OF HYPERTHERMIA	4,397	3.574	0.004880
30	SEMINARS IN NUCLEAR MEDICINE	2,194	3.544	0.002420
31	AMERICAN JOURNAL OF NEURORADIOLOGY	23,135	3.381	0.027120
32	JOURNAL OF NUCLEAR CARDIOLOGY	3,600	3.366	0.004570
33	MEDICAL PHYSICS	26,445	3.317	0.027280
34	Quantitative Imaging in Medicine and Surgery	1,335	3.226	0.002800
35	NMR IN BIOMEDICINE	7,537	3.221	0.011610
36	Clinical Neuroradiology	935	3.183	0.002710
37	KOREAN JOURNAL OF RADIOLOGY	2,967	3.179	0.004490
38	Ultrasonography	618	3.075	0.001710
39	ULTRASONICS	7,808	3.065	0.008930
40	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	9,045	3.037	0.009790
41	AMERICAN JOURNAL OF ROENTGENOLOGY	32,209	3.013	0.024770
42	Practical Radiation Oncology	1,879	2.948	0.005780

Traveling Volunteers: A Multi-Vendor, Multi-Center Study on Reproducibility and Comparability of 4D Flow Derived Aortic Hemodynamics in Cardiovascular Magnetic Resonance

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 Jochen Hansmann, MD,⁷ Sebastian Kelle, MD,^{2,3,6} and Jeanette Schulz-Menger, MD^{1,2*} 

Background: Implementation of four-dimensional flow magnetic resonance (4D Flow MR) in clinical routine requires awareness of confounders.

Purpose: To investigate inter-vendor comparability of 4D Flow MR derived aortic hemodynamic parameters, assess scan-rescan repeatability, and intra- and interobserver reproducibility.

Study Type: Prospective multicenter study.

Population: Fifteen healthy volunteers (age 24.5 ± 5.3 years, 8 females).

Field Strength/Sequence: 3 T, vendor-provided and clinically used 4D Flow MR sequences of each site.

Assessment: Forward flow volume, peak velocity, average, and maximum wall shear stress (WSS) were assessed via nine planes (P1–P9) throughout the thoracic aorta by a single observer (AD, 2 years of experience). Inter-vendor comparability as well as scan-rescan, intra- and interobserver reproducibility were examined.

Statistical Tests: Equivalence was tested setting the 95% confidence interval of intraobserver and scan-rescan difference as the limit of clinical acceptable disagreement. Intraclass correlation coefficient (ICC) and Bland–Altman plots were used for scan-rescan reproducibility and intra- and interobserver agreement. A *P*-value < 0.05 was considered statistically significant. ICCs ≥ 0.75 indicated strong correlation (> 0.9 : excellent, 0.75 – 0.9 : good).

Results: Ten volunteers finished the complete study successfully. 4D flow derived hemodynamic parameters between scanners of three different vendors are not equivalent exceeding the equivalence range. P3–P9 differed significantly between all three scanners for forward flow (59.1 ± 13.1 mL vs. 68.1 ± 12.0 mL vs. 55.4 ± 13.1 mL), maximum WSS (1842.0 ± 190.5 mPa vs. 1969.5 ± 398.7 mPa vs. 1500.6 ± 247.2 mPa), average WSS (1400.0 ± 149.3 mPa vs. 1322.6 ± 211.8 mPa vs. 1142.0 ± 198.5 mPa), and peak velocity between scanners I vs. III (114.7 ± 12.6 cm/s vs. 101.3 ± 15.6 cm/s). Overall, the plane location at the sinotubular junction (P1) presented most inter-vendor stability (forward: 78.5 ± 15.1 mL vs. 80.3 ± 15.4 mL vs. 79.5 ± 19.9 mL [*P* = 0.368]; peak: 126.4 ± 16.7 cm/s vs. 119.7 ± 13.6 cm/s vs. 111.2 ± 22.6 cm/s [*P* = 0.097]). Scan-rescan reproducibility and intra- and interobserver variability were good to excellent (ICC ≥ 0.8) with best agreement for forward flow (ICC ≥ 0.98).

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Data Conclusion: The clinical protocol used at three different sites led to differences in hemodynamic parameters assessed by 4D flow.

Level of Evidence: 2

Technical Efficacy Stage: 2

J. MAGN. RESON. IMAGING 2022;55:211–222.

Three-dimensional (3D) cine (time-resolved) phase-contrast magnetic resonance with three-directional velocity-encoding (4D Flow MR) allows quantification and visualization of hemodynamics in the heart and great vessels.^{1–3} It has been shown to be useful in different diseases for the evaluation of blood flow patterns and derived hemodynamic parameters, such as wall shear stress (WSS).⁴ WSS is elevated in patients with severe aortic stenosis and/or bicuspid aortic valve, as well as in aortic valve replacements.^{5–8} In systemic diseases with affection of the aorta, WSS is also altered. In patients with Marfan syndrome, these alterations included a local decrease in average WSS in the outer proximal ascending segment and an increase in the inner distal ascending aorta.⁹ This additional information may help with clinical decision-making and therapy guiding in diseases.

The potential of integrating 4D Flow MR into daily clinical routine has been increased due to several image acceleration techniques, such as parallel imaging, yielding scan times for the assessment of aortic flow of under 2 minutes.¹⁰ However, awareness of confounders is now of vital importance for successful implementation in the clinical setting.

4D Flow MR acquisitions have been applied using various protocols and different scanner types.^{1–11} Although the acquisition of the whole heart is routinely recommended in congenital heart diseases, while the acquisition of the aorta is mainly used for aortic and aortic valve diseases, no consensus has been established on which technique to use in adults.^{12,13} Additionally, 4D Flow MR sequences differ between sites with scanners from different vendors regarding their acquisition parameters, as each vendor has made different adjustments in the sequence and in the recommended protocol for optimal acquisition.

For other quantitative parameters like T_1 mapping or myocardial strain, variability of results in dependence on different manufacturers is known, thus indicating that variability may also exist in 4D Flow MR.^{14,15} Without this information on inter-vendor agreement, comparison of 4D Flow MR examinations provided by scanners from different vendors may be difficult in the clinical environment.

Therefore, the aims of this study were to:

1. Examine the inter-vendor comparability and reproducibility of 4D Flow MR derived aortic hemodynamic parameters at scanners of three different vendors in order to evaluate if 4D Flow MR examinations acquired at different sites under diverging conditions are equivalent.

2. Test for scan-rescan reproducibility at one scanner for hemodynamic variability.

3. Determine the intra- and interobserver agreement for evaluation of hemodynamic parameters.

Materials and Methods

Study Population

Ethical approval was obtained by the local ethics committee (approval number EA2/208/17). The study complied with the Declaration of Helsinki. It was registered at the German Clinical Trials Register (registration number: 00013253) and the World Health Organization (universal trial number: U1111-1207-5874). Informed written consent was obtained from each participant prior to study enrollment. Healthy volunteers without a history of cardiovascular diseases were recruited and underwent three cardiovascular MR scans using different scanner types. Cardiovascular MR examinations verified normal left ventricular function and a tricuspid aortic valve without pathology.

Image Acquisition

Volunteers were scanned at three different sites (scanners I–III). Each site was using a 3-T wide-bore scanner of different vendors (scanners sorted alphabetically not corresponding to sites): Ingenia (Philips, Best, The Netherlands), SIGNA Architect (GE Healthcare, Milwaukee, WI, USA), and MAGNETOM Verio (Siemens Healthineers, Erlangen, Germany). The same scan protocol was performed in all volunteers. Heart rate was recorded during each 4D Flow MR acquisition, while blood pressure was measured before each 4D Flow MR scan. At one site (scanner III) an additional 4D Flow MR acquisition for scan-rescan reproducibility was performed after a short break of 20–30 minutes, where the volunteers left the scanner requiring repositioning of the coil and replanning of image acquisition afterwards.

To validate the current level of agreement in 4D flow imaging of the aorta in a real-life setting, the clinical 4D Flow MR sequence of each site was used to image the volunteers. The study refrained of adapting sequence parameters to the published consensus paper as common ground to avoid potential bias favoring one vendor and to reflect the current clinical application of 4D Flow MR sequences.² Acquisition parameters between the scanners varied due to different vendor-provided protocols and each site's individual adjustments for optimal clinical use (Table 1).

The acquisition volume was defined according to the vendor's recommendation: on scanner III the scan covered the aorta, on scanners I and II the whole heart. For cardiac gating, an electrocardiogram (ECG) was used in all cases. On scanner III, prospective cardiac gating was applied along with a cross-paired respiratory navigator placed on the lung–liver interface allowing for free breathing. Retrospective triggered ECG gating without a respiratory navigator

TABLE 1. Sequence Parameters of the Different Scanners

	Scanner I	Scanner II	Scanner III
Acquisition volume	Sagittal Whole heart	Transversal Whole heart	Sagittal Full coverage aorta
ECG gating	Retrospective	Retrospective	Prospective
Respiratory navigator	No	No	Yes
Echo time (msec)	2.2	2.0	2.6
Repetition time (msec)	3.5	4.2	5.1
Temporal resolution (msec)	28	66.8	40.8
Number of cardiac phases	25 (± 0)	25 (± 0)	19.2 (± 3.4)
Temporal segmentation factor	2	4	2
Acquisition voxel size (mm ³)	2.8 × 2.8 × 2.8	2.4 × 2.4 × 2.8	2.7 × 2.3 × 2.6
Reconstructed voxel size (mm ³)	1.3–1.9 × 1.3–1.9 × 2.8	1.4–1.5 × 1.4–1.5 × 1.4	2.3 × 2.3 × 2.6
Field of view (mm ³)	270 × 180 × 81.2	380 × 266 × 95.2	360 × 270 × 83.2
Velocity encoding (cm/s)	250	150	150
Flip angle (degrees)	5	8	7
Radiofrequency coil	Multi-element receive coil array with flexible number of up to 32 elements	Multi-element receive coil array with flexible number of up to 32 elements	32-channel body coil
Parallel imaging ^a	$R = 2$	$R = 8$ kt-acceleration	$R = 5$ kt-acceleration
Encoding scheme	4-point symmetric with Hadamard encoding	4-point symmetric with Hadamard encoding	4-point symmetric with MPS
Sequence	Product sequence	Product sequence	Prototype sequence
Acquisition duration (minutes)	10.8 (± 1.2)	10.5 (± 1.5)	8.0 (± 2.2)

Number of cardiac phases and acquisition duration are presented as mean \pm SD.

ECG = electrocardiogram; R = acceleration factor; kt = k-adaptive-t; MPS = measurement/phase/slice.

^aUsed vendor-specific techniques in alphabetical order: Autocalibrating Reconstruction for Cartesian sampling (ARC), GeneRalized Autocalibrating Partially Parallel Acquisition (GRAPPA), and Sensitivity Encoding (SENSE).

was used at scanners I and II. Based on site routine, the velocity encoding (VENC) value was set to 150 cm/s at scanners II and III, and to 250 cm/s at scanner I. Acquisition time differed between the volunteers, depending on heart rate and breathing quality.

Image Analysis

All 4D Flow MR images were analyzed by a single observer (AD, 2 years of 4D Flow MR experience) using CAAS MR Solutions 5.0 (Pie Medical Imaging BV, Maastricht, The Netherlands).¹⁶ Maxwell fields were corrected in all MR systems automatically during image reconstruction.¹⁷ Background phase offset correction using a linear fit and phase unwrapping were performed in all datasets.^{2,18} In the applied software version, phase unwrapping was not possible for the data acquired at scanner II. Therefore, all images (including those from scanners I and III) were manually screened by the observer (AD) for potential phase aliasing, and in cases where phase aliasing occurred inside a plane region, the plane was excluded.

For segmentation of the aorta, the start point was placed in the upper region of the left ventricular outflow tract and the end point in the descending aorta below the cardiac apex (Fig. 1b). As previously described, a phase-specific segmented 3D aortic surface model was automatically detected for five cardiac phases and the peak systolic phase was selected for implementation of the succeeding analysis steps.^{19,20} If necessary, this 3D volume model was manually corrected by the observer by editing the vessel boundary contours for each aortic 2D plane in the peak systolic phase (Fig. 1c) updating the centerline subsequently. In case of missing or truncated aortic segments, the scan was excluded from further evaluation.

Nine cross-sectional planes were positioned along the centerline (Figs. 1 and 2). Contours of the vessels were projected automatically on each plane based on the 3D segmentation of the selected peak systolic phase and, if needed, manually adapted for all phases along the cardiac cycle. Peak velocity and forward flow volume were evaluated. For WSS analysis the identical plane locations were

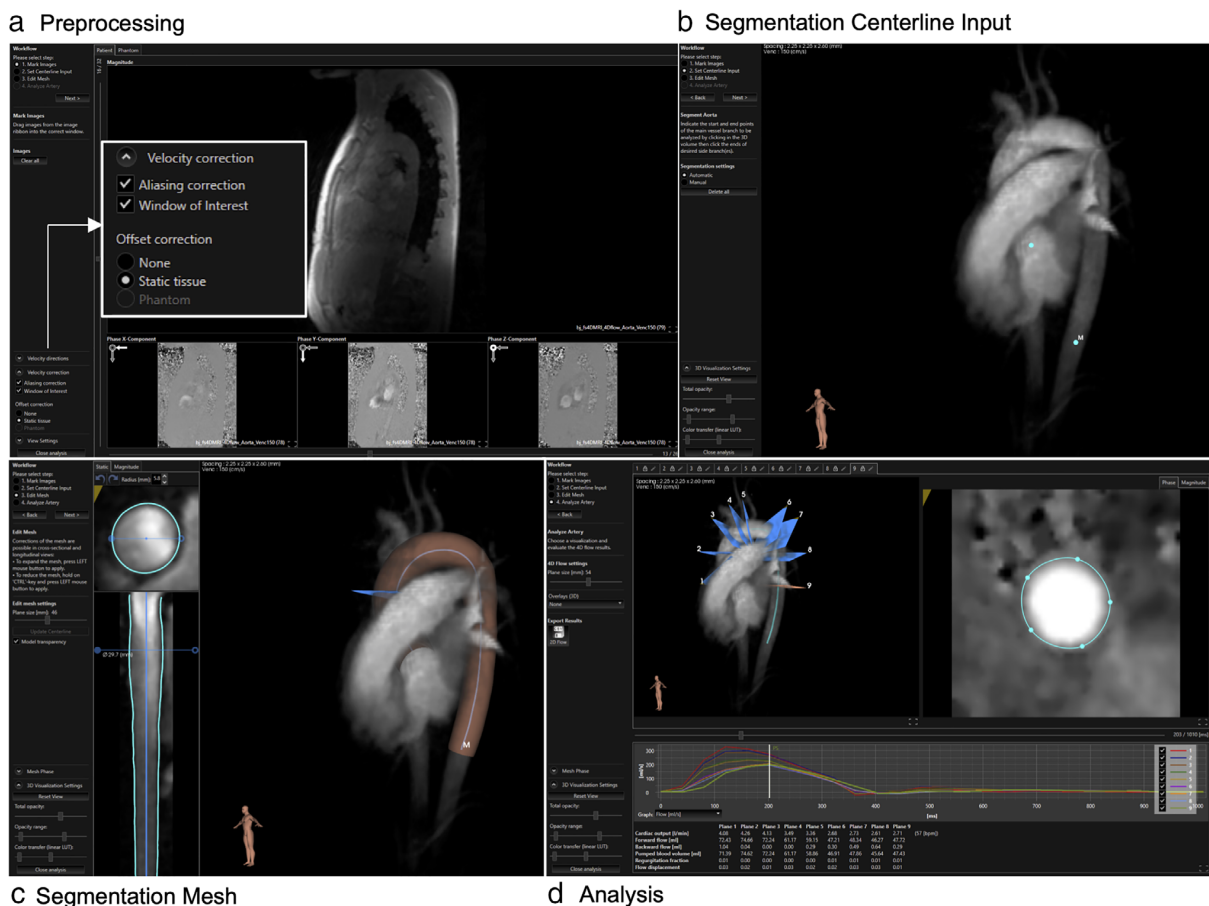


FIGURE 1: Process of 4D Flow MR analysis with CAAS. (a) Preprocessing with background phase offset and aliasing correction. (b) Segmentation of the aorta: determining the start and end point of the centerline using a 3D display of the heart and great vessels. (c) Segmentation of the aorta: editing the Mesh model based on the static tissue for each 2D plane along the aorta in the peak systolic phase. The Mesh model represents a 3D volume model of the aorta for one cardiac phase. It is automatically generated for five cardiac phases (peak systolic phase ± 2 cardiac phases). We selected the peak systolic phase for subsequent manual segmentation and analysis. (d) Localization of the nine planes in the thoracic aorta for analysis of flow parameters with exemplary drawn vessel contours for plane 9.

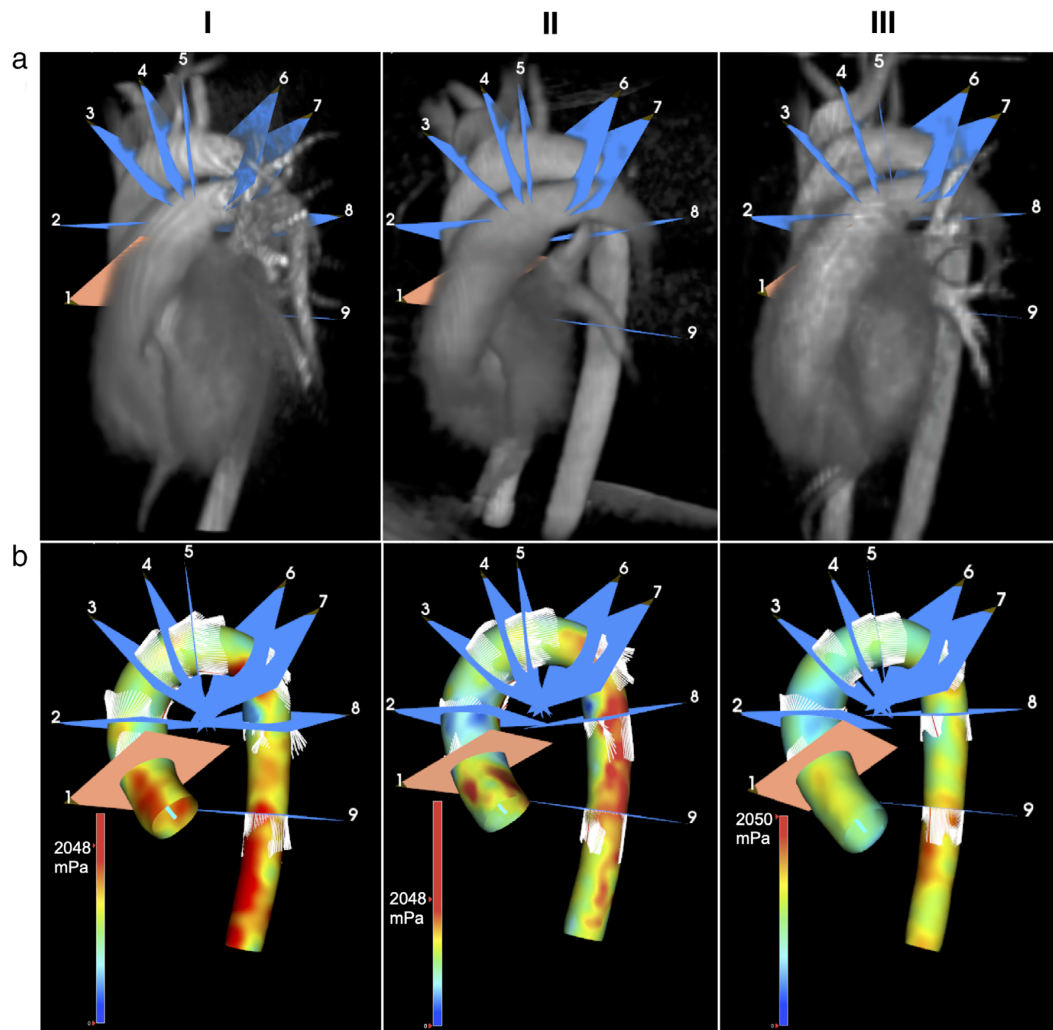


FIGURE 2: Visualization of the 4D Flow MR data obtained by the different scanners for evaluation of flow parameters (a) and wall shear stress (WSS) (b) from one volunteer. (a) Nine cross-sectional planes were positioned along the centerline and perpendicularly to the longitudinal axis of the aortic wall as follows: at the level of the sinotubular junction (P1), in the mid-ascending aorta (P2), proximal to the brachiocephalic trunk (P3), between the brachiocephalic trunk and the left common carotid artery (P4), between the left common carotid artery and the left subclavian artery (P5), at the aortic isthmus (P6), in the descending aorta above the pulmonary artery (P7), in the descending aorta below the pulmonary artery (P8), in the descending aorta below the level of the aortic valve (P9). (b) Distribution of maximum WSS is visualized in a 3D segmented model of the aorta for the peak systolic phase. As shown in the color bar red-colored areas represent highest values for maximum WSS. The color bars were adjusted as far as possible between the three acquisitions for better visual comparison.

automatically transferred. WSS was automatically calculated based on the segmented 3D volume model for the peak systolic phase and extrapolated to the point of zero velocity for defining the location of the aortic wall.²¹ No manual adaptation was necessary. For each plane, the WSS vector along the surface of the 3D model was calculated for 90 wall points. Maximum WSS was determined as the highest of all WSS values and average WSS as the average of all WSS values in the peak systolic phase.

For intraobserver analysis, the scans of all 10 volunteers at all three scanners (30 scans in total) were evaluated twice. All scans were analyzed by a blinded second observer (SW, 5 years of 4D Flow MR experience, >10 years of MR experience) for interobserver analysis as well. Both analyses only included plane positions in the ascending

aorta (P1–P3) as most clinically relevant pathologies occur in this region.

Statistical Analysis

Statistical analyses were performed with SPSS (V25.0, IBM Corp., Armonk, NY, USA) and SAS (V9.4, SAS Institute Inc., Cary, NC, USA). Bland–Altman analyses were generated for agreement of the values acquired at the different scanners. As previously published, for equivalence testing the 95% confidence interval (CI) of the intraobserver difference for each parameter was set as the margin of acceptable disagreement regarding the comparison between vendors.²² Results from two vendors were considered equivalent if the limits of their difference would lie within the 95% CI of

intraobserver difference. Additionally, equivalence was tested using the 95% CI of scan-rescan difference as the accepted range. Significance testing was performed for each plane separately using the Wilcoxon and Friedman tests. Numeric data of the combined planes (eg, P1–P9) were stated as the mean \pm SD of their average value. Linear mixed models with repeated measures taking into account the correlation of multiple observations per patient were additionally applied to determine statistically significant differences jointly for the planes P1–P9 as well as in the ascending aorta (P1–P3), aortic arch (P4–P6), and descending aorta (P7–P9). A hierarchical test strategy was used. Only if significance was shown in the global test (scanner I vs. II vs. III) significance was assessed in the pairwise comparison between two scanners also at a two-sided level of 5%.

Depending on the distribution (normal vs. non-normal), significance of scan-rescan variability was tested with the paired *t*-test or Wilcoxon test. For agreement of scan-rescan reproducibility, Bland–Altman analyses and the intraclass correlation coefficient (ICC) were calculated. ICC was interpreted as follows: >0.9: excellent, 0.75–0.9: good, 0.5–0.75: moderate, <0.5: poor.²³ Intra- and interobserver reliability was determined using the ICC and Bland–Altman plots.

Results

Fifteen healthy volunteers (mean age 24.5 ± 5.3 years, 8 females) without a history of cardiovascular diseases were

enrolled in the study. Baseline characteristics are provided in Table 2. Out of these, 10 volunteers completed the study and could be included in further analysis. Following circumstances resulted in exclusion of the five volunteers. Due to unexpected technical problems, one volunteer could not be scanned at scanner II. Three datasets from scanner I were lost due to incomplete reconstruction after data acquisition. Another 4D Flow MR acquisition obtained at scanner I was excluded as inaccurate image planning led to missing aortic segments. In one volunteer, one plane (P2) had to be excluded as the aortic segment was truncated during image planning, while aliasing led to an exclusion of two additional planes (P1, P5) in two other volunteers. In total, we analyzed 90 segments and 267 planes in 10 volunteers. The time period between the first and second scan sessions (at scanners I and II) was 103 ± 4 days, while the second and third scans were performed within 18 ± 10 days.

Comparison of Different Vendors

Average heart rate did not differ significantly between the scans (69.6 ± 9.4 bpm vs. 77.4 ± 6.8 bpm vs. 78.9 ± 13.5 bpm; $P = 0.067$). Systolic and diastolic blood pressure levels significantly varied (sys: 111.0 ± 10.0 mmHg vs. 121.4 ± 11.8 mmHg vs. 118.8 ± 10.1 mmHg; dia: 59.8 ± 5.4 mmHg

TABLE 2. Baseline Characteristics of the Healthy Volunteers

Variables	Inter-Vendor (<i>N</i> = 10)		Scan-Rescan (<i>N</i> = 15)	
Gender (female)	6		8	
Age (years)	24.1 (± 5.4)		24.5 (± 5.3)	
Height (cm)	174.1 (± 7.2)		173.9 (± 8.8)	
Weight (kg)	66.2 (± 10.5)		65.6 (± 10.6)	
BMI (kg/m ²)	21.7 (± 2.2)		21.6 (± 2.2)	
BSA (m ²)	1.8 (± 0.2)		1.8 (± 0.2)	
LVEDV (mL)	145.4 (± 31.5)		146.6 (± 32.6)	
LVEF (%)	63.8 (± 4.5)		64.7 (± 4.8)	
Heart rate at scanner I (bpm)	69.6 (± 9.4)	$P = 0.067$	76.1 (± 11.5)	$P = 0.986$
Heart rate at scanner II (bpm)	77.4 (± 6.8)		76.1 (± 11.1)	
Heart rate at scanner III (bpm)	78.9 (± 13.5)			
Blood pressure at scanner I (mmHg)	111.0 (± 10.0)/59.8 (± 5.4)	$P = 0.03$ $P = 0.005$	119.4 (± 12.0)/61.5 (± 9.6)	$P = 0.116$ $P = 0.599$
Blood pressure at scanner II (mmHg)	121.4 (± 11.8)/69.0 (± 8.0)		123.7 (± 17.1)/60.6 (± 10.5)	
Blood pressure at scanner III (mmHg)	118.8 (± 10.1)/60.4 (± 6.1)			

Values are presented as mean \pm SD.
BMI = body mass index; BSA = body surface area; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

vs. 69.0 ± 8.0 mmHg vs. 60.4 ± 6.1 mmHg). Figure 2 exemplarily illustrates a visual impression of the analyzed 4D Flow MR data from one volunteer at the three different scanners.

Forward flow volume showed significant differences between all scanners regarding P3–P9 (59.1 ± 13.1 mL vs. 68.1 ± 12.0 mL vs. 55.4 ± 13.1 mL), and for the descending aortic segment (52.2 ± 12.4 mL vs. 60.7 ± 13.3 mL vs. 50.1 ± 12.3 mL) (Tables S1 and S2 in the Supplemental Material). Only P1, located at the sinotubular junction, indicated no difference for pairwise comparison (I vs. II $P = 0.110$; I vs. III $P = 0.646$; II vs. III $P = 0.314$), as well as for comparison of all three vendors (78.5 ± 15.1 mL vs. 80.3 ± 15.4 mL vs. 79.5 ± 19.9 mL; $P = 0.368$). Forward flow volume between the values obtained from scanners I and III agreed best in Bland–Altman analyses (Table 3, Fig. S1 in the Supplemental Material), while the highest values were detected by scanner II. Peak velocity differed significantly between the three scanners within the descending aortic segment (125.6 ± 17.5 cm/s vs. 113.7 ± 13.2 cm/s vs. 111.1 ± 19.1 cm/s) and in a pairwise or three-way comparison within all planes except P1 (126.4 ± 16.7 cm/s vs. 119.7 ± 13.6 cm/s vs. 111.2 ± 22.6 cm/s; $P = 0.097$) (Tables S1 and S2 in the Supplemental Material). Highest values for peak velocity resulted from scanner I, lowest from scanner III. In Bland–Altman analyses the results of scanners II and III were most comparable (Table 3, Fig. S1 in the Supplemental Material). Equivalence could not be concluded for both flow parameters as the range of 95% CI of differences between the scanners exceeded the margin of intraobserver variability. When setting the 95% CI of scan-rescan variability as accepted range, only the difference between scanners II and III for peak velocity laid within the limits and were therefore found to be equivalent (Fig. 3, Table 3).

Maximum WSS varied significantly between all scanners for P1–P9, aortic arch, and the descending aorta as well as all planes separately except P1 ($P = 0.062$) and P2 ($P = 0.121$) (Tables S1 and S2 in the Supplemental Material). Average WSS results were similar, revealing a non-significant difference only for P2 ($P = 0.264$) and the ascending aortic segment ($P = 0.357$). Lowest values for maximum and average WSS resulted from data of scanner III (WSS max: I = 1790.5 ± 172.4 mPa vs. II = 1903.2 ± 430.5 mPa vs. III = 1458.7 ± 238.8 mPa; WSS avg: I = 1344.6 ± 136.9 mPa vs. II = 1251.9 ± 214.2 mPa vs. III = 1102.8 ± 187.6 mPa). Between scanners I and II, no significant difference for maximum WSS in all planes ($P = 0.406$) and segments (ascending: $P = 0.622$, arch: $P = 0.961$, descending: $P = 0.297$) and only significant differences in P5, P9, and the aortic arch for average WSS could be observed (ascending: $P = 0.204$, descending: $P = 0.555$) (Tables S1 and S2 in the Supplemental Material). Both WSS

TABLE 3. Mean Values and Confidence Intervals of Bland–Altman Analyses for Inter-Vendor, Scan-Rescan, Intra- and Interobserver Reproducibility

	Peak Velocity (cm/s)	Forward Flow Volume (mL)	Maximum WSS (mPa)	Average WSS (mPa)
Inter-vendor				
I vs. II	9.28 (36.17; –17.60)	–8.57 (4.80; –21.93)	–100.48 (945.79; –1146.75)	97.71 (527.48; –332.06)
I vs. III	14.19 (41.45; –13.07)	3.01 (12.94; –6.92)	332.12 (935.85; –271.61)	242.53 (635.97; –150.90)
II vs. III	5.23 (30.82; –20.35)	11.54 (28.73; –5.65)	433.78 (1409.89; –542.32)	145.12 (549.81; –259.57)
Scan-rescan	0.69 (31.99; –30.60)	0.51 (10.31; –9.29)	24.01 (548.70; –500.68)	13.05 (412.80; –386.70)
Intraobserver	0.27 (9.34; –8.81)	0.00 (1.66; –1.66)	–0.48 (175.55; –176.51)	–5.54 (69.92; –81.00)
Interobserver	1.92 (16.47; –12.64)	–2.41 (2.78; –7.61)	29.31 (605.41; –546.79)	71.19 (415.85; –273.47)

WSS = wall shear stress.

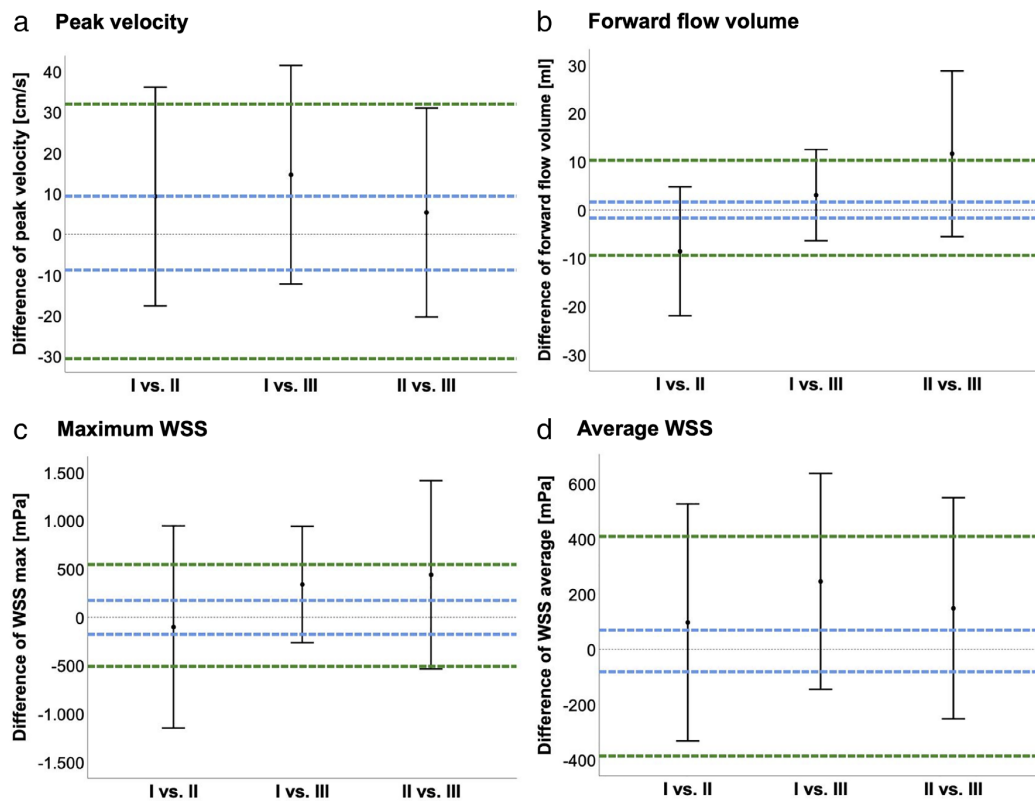


FIGURE 3: Equivalence testing for inter-vendor comparison in relation to intraobserver and scan-rescan variability for peak velocity (a), forward flow volume (b), maximum wall shear stress (WSS) (c), and average WSS (d). Equivalence of two vendors is shown if the 95% confidence interval (CI) for the scanner comparison (indicated as gray vertical bars) lays within the equivalence limits of the intraobserver variability (blue dashed lines) or scan-rescan variability (green dashed lines). The dashed lines display the range of intraobserver/scan-rescan variability as 95% CI of the differences of the measured values.

parameters exceeded the margin of intraobserver and scan-rescan variability as accepted difference (Fig. 3, Table 3).

Scan-Rescan Reliability

All 15 volunteers were scanned twice at scanner III and no acquisition or plane had to be excluded. Average heart rate (76.1 ± 11.5 bpm vs. 76.1 ± 11.1 bpm; $P = 0.986$) and blood pressure (sys: 119.4 ± 12.0 mmHg vs. 123.7 ± 17.1 mmHg [$P = 0.116$]; dia: 61.5 ± 9.6 mmHg vs. 60.6 ± 10.5 mmHg [$P = 0.599$]) did not vary significantly between scan and rescan. No significant difference was found for all parameters in all planes and segments (P1–P9: peak = 102.4 ± 14.6 cm/s vs. 101.7 ± 18.1 cm/s [$P = 0.859$]; forward flow = 60.0 ± 13.2 mL vs. 59.5 ± 13.7 mL [$P = 0.621$]; WSS max = 1470.4 ± 207.8 mPa vs. 1446.4 ± 284.5 mPa [$P = 0.955$]; WSS avg = 1118.3 ± 163.3 mPa vs. 1105.2 ± 211.7 mPa [$P = 0.795$]) (Table S3 in the Supplemental Material). Agreement for forward flow volume was excellent (ICC = 0.98) and good for peak velocity (ICC = 0.83), average WSS (ICC = 0.84), and maximum WSS (ICC = 0.80). Bland-Altman analyses showed good agreement with narrow CI (Table 3, Fig. 4). Equivalence set by the intraobserver variability

could not be concluded as all parameters exceeded the margin (Fig. 3, Table 3).

Inter- and Intraobserver Reliability

Bland-Altman plots and ICC indicated excellent intraobserver reproducibility (forward flow: ICC = 1.0; peak velocity: ICC = 0.99; maximum WSS: ICC = 0.99; average WSS: ICC = 1.0; Table 3, Fig. 4).

Excellent interobserver agreement was achieved for forward flow (ICC = 0.99), peak velocity (ICC = 0.96), and maximum WSS (ICC = 0.92), while average WSS displayed good agreement (ICC = 0.86) (Fig. 4).

Discussion

This study revealed significant differences for 4D flow derived hemodynamic parameters when using vendor-provided and clinical used protocols at three different sites. All parameters exceeded the equivalence range set by the intraobserver analysis. For representation of the real clinical setting and the current level of standardization each site used their individual and vendor-provided standard 4D Flow MR sequence for acquisition. The study results do not provide information

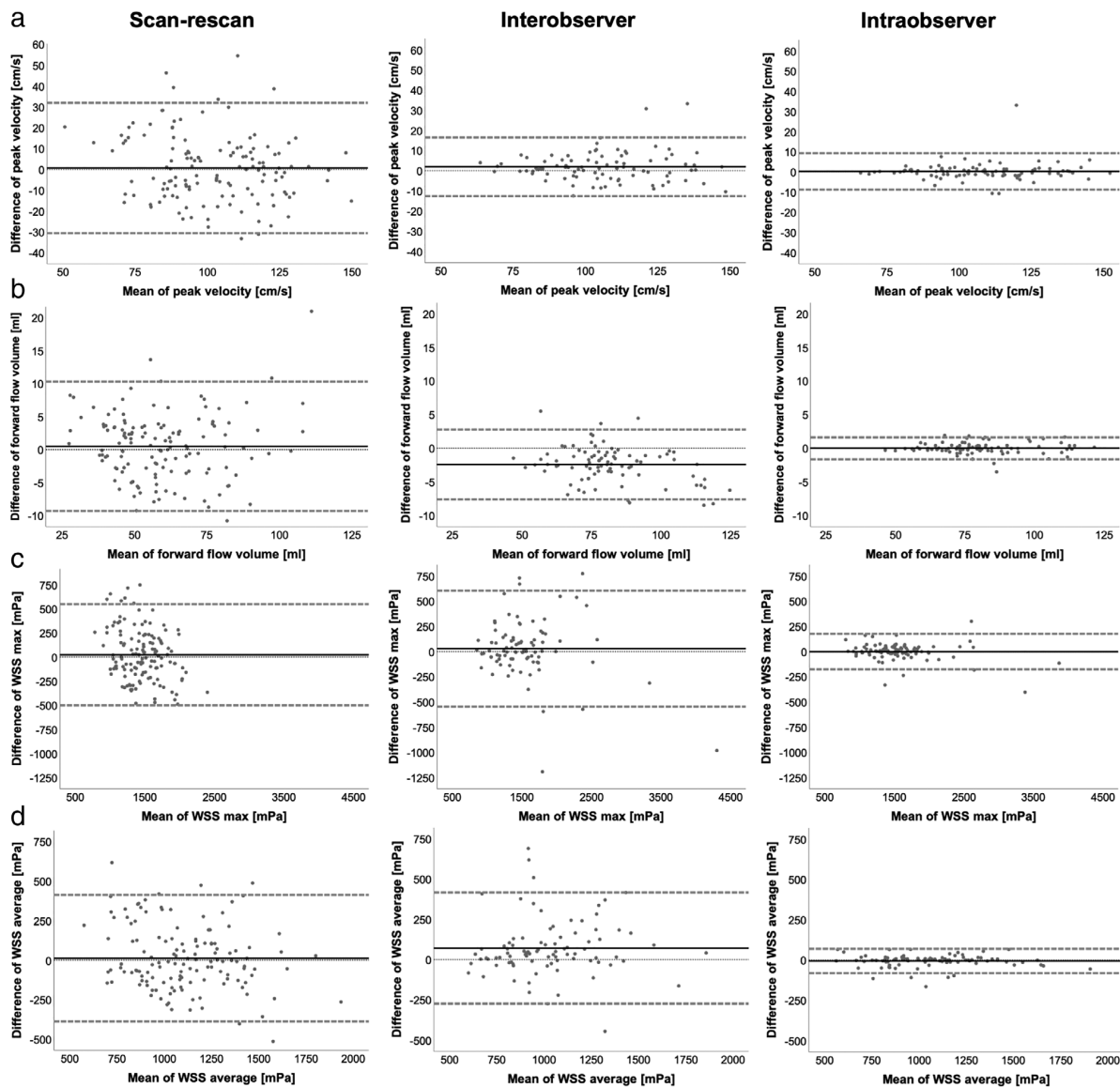


FIGURE 4: Bland–Altman plots for scan-rescan reproducibility and intra- and interobserver variability of peak velocity (a), forward flow volume (b), maximum wall shear stress (WSS) (c), and average WSS (d). Solid black lines indicate mean difference, dashed lines indicate limits of agreement (95% confidence interval of the differences of the measured values).

about which of the 4D flow sequences is the most accurate or precise. However, they show that 4D flow derived hemodynamic parameters cannot easily be compared for a follow-up when a subject is examined at different scanners under diverging conditions, exemplary different vendors, and/or sites. Also, the differences in protocols identify the lack of commercial 4D Flow MR sequences across platforms and centers in the clinical routine, yet reflecting the current status quo. Additionally, many data sets or planes needed to be discarded, highlighting the complexity of this method despite continuous technical development of 4D Flow MR sequences and postprocessing tools.

Bock et al validated 4D Flow MR sequences in a phantom and in vivo comparing flow volumes between a 1.5-T Siemens and Philips scanner, which showed a larger variation of kinetic energy between the two scanner types than between repeated measurements at one scanner.²⁴ This is in line with the findings of this study.

Watanabe et al investigated the impact of changing the vendor of the scanner on flow velocity using a straight-tube phantom. Their results showed satisfying accuracy of flow velocity profiles in all three 3 T scanners (GE, Philips, Siemens).²⁵ Additionally, they measured time-averaged flow velocity perpendicular to the tube central, which

corresponded well with the reference values obtained by a flowmeter for each vendor, but reference values slightly differed between the scanners. Absolute values for peak velocity were also similar between the scanners in the present study. Further, a statistical analysis including equivalence testing as a method for accepted difference range from clinical perspective was performed. Peak velocity was the most stable parameter as equivalence was achieved between two scanners within the limits of scan-rescan variability.

Wen et al evaluated the multicenter reproducibility of neurovascular 4D flow magnetic resonance imaging (MRI) scans on 10 healthy volunteers at three different sites using a 3-T GE scanner with identical coils and acquisition parameters. They observed great multisite reproducibility for measurement of blood flow and good reproducibility for peak velocity in intracranial vessels.²⁶ Their findings suggest the significant disagreement in 4D flow parameters detected in the present study to be rather induced by the vendor-associated difference of acquisition parameters than practical experience in the different sites.

Systolic and diastolic blood pressure levels varied significantly between the scans indicating hemodynamic changes in each volunteer. These physiological changes may have been induced by differences in fluid or food intake before 4D Flow MR acquisition, as the volunteers did not fast.²⁷ However, absolute values of blood pressure levels were similar and from a clinical perspective this discrepancy represents no clinical relevance as heart rate did not differ significantly. Additionally, all three scanners were wide-bore (70 cm) scanners leading to a similar level of rather common claustrophobia induced stress. This minimalizes the potential influence on hemodynamic parameters caused by different levels of claustrophobic stress. Also, in larger bores effects due to a more heterogeneous field are commonly found.

Since the plane at the level of the sinotubular junction (P1) showed the lowest number of significant differences in hemodynamic parameters, we considered this region as the most stable plane location. Additionally, when comparing the cardiac outputs resulting from the cine images and the 4D flow analysis (forward volume at P1 \times heart rate during 4D flow) exemplarily for all 15 volunteers at scanner III, no significant difference could be found. This can serve as an external validation of the 4D flow derived flow volumes in this study.

The stability of P1 is especially interesting for clinical purposes as the position is identical to the localization applied in clinically used 2D flow measurements holding clinical importance for diagnosis of aortic flow measurements.²⁸ This stability could be explained by its central location independent of the defined acquisition volume (whole heart vs. aorta). Plane positions that are more distant from the isocenter of the magnet rather lead to inaccurate flow results mainly caused by eddy currents yielding phase offsets.²⁹

Therefore, background correction has been applied by a linear fit to the static tissue. However, eddy current related phase contributions may vary between scanners and potentially fitting models including higher order terms may be needed for comparisons between different vendors, particularly for the more distant slices. Furthermore, a simple approach to verify the precision of the applied background compensation is missing for clinical routine and the correction may be insufficient.³⁰

The different acquisition volumes applied in this study could represent a factor leading to disagreement in flow parameters due to various isocenter distances regarding P2–P9. Yet, comparison of both whole heart sequences showed significant differences in forward flow volume and peak velocity for many planes and segments, thus demonstrating that the definition of the acquisition volume may not be the only influential factor.

4D Flow MR sequences in this study were scanner-specific containing variations in acquisition parameters which may have contributed to the observed significant differences. Multiple research groups studied the impact of acquisition parameters on results of different flow parameters and WSS. Low spatial resolution had the most influence on WSS leading to underestimation of WSS values.^{31–33} Stalder et al showed with a synthetic model that, eg, for a voxel length of 1 mm WSS is lowered to 60% of its actual value and decreases to above 30% for a voxel length of 10 mm, whereas total blood flow remained comparatively steady.³¹ In this study, the highest acquired voxel size and thereby lowest spatial resolution was obtained at scanner I, but WSS values were lowest at scanner III. Also lower values for forward flow volume and peak velocity were found at scanner III, which should not be affected by the difference in spatial resolution, but which could be related to the different acceleration techniques applied at the scanners (Autocalibrating Reconstruction for Cartesian sampling, Generalized Autocalibrating Partially Parallel Acquisition, Sensitivity Encoding). Highest VENC was set at scanner I and may have induced higher WSS values as Zimmermann et al detected.³³ However, in scans acquired at scanner II, also higher WSS values were measured without significant difference to the values measured at scanner I, although the VENC was lower. Furthermore, varieties in temporal resolution and the amount of reconstructed cardiac phases could have led to determination of slightly different absolute time points of the peak systolic phase between the scans, elevating the variability in WSS results.

Montalba et al showed greater underestimation and variability for flow parameters when using 4D flow acquisitions with lower temporal resolutions.³⁴ In this study, the lowest temporal resolution was obtained at scanner II, but lowest flow parameters resulted from 4D flow images acquired at scanner III. The lowest forward flow volume

could be partly attributed to the difference in ECG gating, as the only prospectively gated sequence, which does not cover the entire cardiac cycle missing the late diastolic phases, was used at scanner III. Although aortic flow is primarily expected in the systolic phases in healthy volunteers, prospective gating could cause lower forward flow volumes missing the early systolic flow due to a delay in detecting the R-wave.

Considering knowledge on the influence of acquisition parameters on the results the differences in protocol settings represent potential confounders and sequence parameters should be matched as far as possible between different scanners. However, as each scanner type presents individual specifications, individual adjustments are needed. Furthermore, individual and site-dependent adjustments in protocol settings can be necessary for optimizing the vendor-provided protocols from a clinical perspective. Additional site-associated influence factors such as potential operator-dependent variabilities in levels of experience with 4D Flow MR planning at the different sites could have caused the differences as well.

Regarding scan-rescan reliability, the results showed no significant differences for all parameters and highlighted forward flow volume as most constant parameter with excellent scan-rescan and intra- and interobserver agreement. Markl et al also found excellent scan-rescan, intra- and interobserver agreement for calculation of total flow and peak velocity vs. greater variability for WSS.³⁵ Compared to flow parameters, evaluation of WSS seems to depend more on the definition of vessel wall contours, leading to more variability by differing segmentation contouring.^{31,33,35} This might explain the wider CI for WSS parameters reached by the interobserver agreement. The broader CI becomes particularly clear outreaching the level of the scan-rescan CI for maximum WSS.

In relation to inter- and intraobserver reproducibility, scan-rescan comparison resulted in higher variability. This may likely be determined by differences in repositioning of the coil and image planning with, eg, various isocenter locations between both acquisitions. Further, length of still recumbency was longer before the first 4D Flow MR acquisition than the rescan and may have induced hemodynamic changes, although blood pressure and heart frequency were similar between both scans. In addition, the scan-rescan difference was statistically non-significant, and ICC reached good-excellent agreement.

Limitations

The study consisted of only a smaller number of healthy volunteers with a high drop-out rate and did not include patients or elderly, but it was already challenging to organize and implement this quantity of scans at different sites throughout Germany. Reflecting the status quo, each site used their individual and vendor-provided standard 4D Flow

MR sequence, instead of agreeing on a common adapted sequence. Thus, acquisition parameters differed between the scans influencing the inter-vendor agreement but reflected the real-life setting and current level of standardization. Additional scans with matched sequence parameters could not be performed for logistical reasons and the study refrained of a comparison of 4D Flow MR results with a reference gold standard, eg, 2D flow acquisitions or invasive hemodynamic measurements. Therefore, the results do not allow conclusions about which of the 4D flow sequences is the most precise or if the differences were more vendor or site associated, but neither of those was actually this study's aim. Also, changes in hemodynamic parameters during the various time between 4D Flow MR examinations at the different sites may have elevated the inter-vendor variability, however as all blood pressure measurements lay within a narrow range and the volunteers were all healthy, the impact should be small.

No adjustment was applied for the significance level due to the explorative character of the study. However, hierarchical testing was used by applying first the global test on differences between scanners before interpreting pairwise comparisons of two scanners.

Conclusion

4D flow derived aortic hemodynamic parameters assessed with various vendor-provided and clinical 4D Flow MR protocols at the three different sites are not equivalent. Overall, the plane positioned at the sinotubular junction showed most inter-vendor stability and agreement. To enable large multicenter studies and patient follow-up examinations at various scanners and sites further investigation of the differences of sequences across centers and vendors is needed. The identification of confounders will help to overcome current limitations. Due to the lack of existing commercial 4D Flow MR sequences for clinical routine across platforms and centers, longitudinal studies and patient's follow-up examinations should take place at the same scanner.

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Publikation 2

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

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
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
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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

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	RADIOGRAPHICS	11,768	3.923	0.009170
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23	MAGNETIC RESONANCE IN MEDICINE	32,648	3.858	0.034990
24	SEMINARS IN NUCLEAR MEDICINE	2,245	3.798	0.002710
25	Journal of the American College of Radiology	4,191	3.785	0.009760
26	JOURNAL OF MAGNETIC RESONANCE IMAGING	17,147	3.732	0.027800
27	KOREAN JOURNAL OF RADIOLOGY	2,687	3.730	0.004800
28	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,552	3.589	0.004020
29	EJNMMI Physics	394	3.475	0.001350
30	NMR IN BIOMEDICINE	7,511	3.414	0.014790
31	MOLECULAR IMAGING AND BIOLOGY	2,543	3.341	0.005360
32	Journal of Cardiovascular Computed Tomography	1,711	3.316	0.004430
33	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,464	3.298	0.002990
34	AMERICAN JOURNAL OF NEURORADIOLOGY	23,231	3.256	0.028010
35	MEDICAL PHYSICS	26,715	3.177	0.030870
36	AMERICAN JOURNAL OF ROENTGENOLOGY	33,633	3.161	0.028540
37	CANCER IMAGING	1,406	3.153	0.002220
38	Quantitative Imaging in Medicine and Surgery	1,072	3.074	0.002420
39	PHYSICS IN MEDICINE AND BIOLOGY	27,458	3.030	0.031970
40	EJNMMI Research	1,408	3.000	0.004320
41	EUROPEAN JOURNAL OF RADIOLOGY	12,871	2.948	0.019480
42	Radiation Oncology	5,669	2.895	0.012980

Impact of sequence type and field strength (1.5, 3, and 7T) on 4D flow MRI hemodynamic aortic parameters in healthy volunteers

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Purpose: 4D flow magnetic resonance imaging (4D-MRI) allows time-resolved visualization of blood flow patterns, quantification of volumes, velocities, and advanced parameters, such as wall shear stress (WSS). As 4D-MRI enters the clinical arena, standardization and awareness of confounders are important. Our aim was to evaluate the equivalence of 4D flow-derived aortic hemodynamics in healthy volunteers using different sequences and field strengths.

Methods: 4D-MRI was acquired in 10 healthy volunteers at 1.5T using three different prototype sequences, at 3T and at 7T (Siemens Healthineers). After evaluation of diagnostic quality in three segments (ascending-, descending aorta, aortic arch), peak velocity, flow volumes, and WSS were investigated. Equivalence limits for comparison of field strengths/sequences were based on the limits of Bland-Altman analyses of the intraobserver variability.

Results: Non-diagnostic quality was found in 10/144 segments, 9/10 were obtained at 7T. Apart for the comparison of forward flow between sequence 1 and 3, the differences in measurements between field strengths/sequences exceeded the range of agreement. Significant differences were found between field strengths/sequences for

forward flow (1.5T vs. 3T, 3T vs. 7T, sequence 1 vs. 3, 2 vs. 3 [$P < .001$]), WSS (1.5T vs. 3T [$P < .05$], sequence 1 vs. 2, 1 vs. 3, 2 vs. 3 [$P < .001$]), and peak velocity (1.5T vs. 7T, sequence 1 vs. 3 [$P > .001$]). All parameters at all field strengths/with all sequences correlated moderately to strongly ($r \geq 0.5$).

Conclusion: Data from all sequences could be acquired and resulting images showed sufficient quality for further analysis. However, the variability of the measurements of peak velocity, flow volumes, and WSS was higher when comparing field strengths/sequences as the equivalence limits defined by the intraobserver assessments.

KEYWORDS

4D flow, 7T, aorta, cardiovascular magnetic resonance imaging, non-invasive hemodynamics, standardization

1 | INTRODUCTION

4D flow has been shown to be a promising tool in cardiovascular MRI for the non-invasive evaluation of hemodynamics in adult and pediatric cardiology.¹⁻³ It can provide both time-resolved visualization of complex flow patterns and quantification of flow velocities and volumes. Furthermore, more advanced parameters such as wall shear stress (WSS) can be derived.⁴

Currently, only a few markers obtained by echocardiography or cardiovascular MRI mainly based on the aortic shape and size help with the decision on the timing and type of surgery in patients with aortic valve pathology and/or aortic aneurysm.^{5,6}

WSS has shown to have great potential in this field as several studies have shown the additional benefit of determining the WSS in different patients with aortic valve pathologies or pathologies of the thoracic aorta.⁷⁻¹⁵ It was shown that hemodynamics were altered in the ascending aorta in the presence of an aortic valve stenosis. Such alterations included a local increase in WSS and were related to stenosis severity.^{9,16} It was also observed that flow patterns were altered and WSS was regionally elevated in the ascending aorta of patients after aortic valve replacement.^{17,18} First follow-up studies have been conducted to evaluate changes in hemodynamics or WSS over time in specific pathologies or after surgery and 4D flow MRI was able to show the longitudinal evolution of already initially abnormal WSS values.^{19,20} Therefore, 4D flow may help with therapy guiding and decision making by providing additional and potentially complementary information.

Since initial studies have demonstrated that certain types of 4D flow scans can be obtained in about 2 min,^{21,22} the implementation of 4D flow in clinical routine is imminent. However, to reach a broad application in clinical routine, standardization and awareness of confounders are essential. Thus, the aim of our study was to evaluate the equivalence of 4D flow MRI-derived aortic hemodynamic parameters at three different field strengths (1.5T, 3T, and 7T). Additionally, we analyzed the equivalence of three different sequence variants at 1.5T.

2 | METHODS

The study included 10 healthy volunteers without any known cardiovascular risk factors or history of cardiac diseases as well as normal left ventricular (LV) function and a tricuspid aortic valve without stenosis or insufficiency as assessed by cardiovascular MRI. Approval of the local Institutional Review Board and informed consent from each participant were obtained.

2.1 | Image acquisition

Each volunteer was scanned three times; in each of these sessions the volunteer was scanned at a single field strength: 1.5T (Magnetom Avanto fit), 3T (Magnetom Verio), and 7T (Magnetom 7T, whole-body research scanner) (all Siemens Healthcare, Erlangen, Germany). At 7T, a local single-channel transmit, 16-channel receive radio-frequency transceiver array was used, which provided an optimized transmit magnetic field pattern within the heart.²³ At 3T, a 32-channel receiver coil and, at 1.5T, an 18-channel anterior surface coil and 12 elements of the spine coil were used. The acquisition volume was defined over the entire thoracic aorta down to the diaphragm. For cardiac gating electrocardiograph (ECG) was used. Due to the magneto-hydrodynamic effect, which increasingly impacts the ECG signal with increasing field strength, we used an acoustic cardiac triggering system (ACT, Easy ACT, MRI.TOOLS GmbH, Berlin Germany) at 7T when ECG detection failed.²⁴ Data acquisition was performed during free breathing using a respiratory navigator placed on the lung-liver interface.

At 1.5T, three prototype 4D flow sequence variants using different scan parameters were applied as listed in Table 1. These three sequence variants were acquired within one scanning session. Parameters for the sequences used at 3T and 7T are also listed in Table 1. The 4D flow sequences were

TABLE 1 Sequence parameters for the three different sequences at 1.5T as well as for 3T and 7T

Field strength (sequence)	1.5T (sequence 1)	1.5T (sequence 2)	1.5T (sequence 3)	3T	7T
TE in ms	2.4	2.3	2.3	2.6	2.4
TR in ms [#]	39.2	38.9	38.9	40.8	38.4
Bandwidth in Hz/pixel	450	496	496	450	450
GRAPPA	R = 5	R = 2	R = 2	R = 5	R = 2
Nominal flip angle in degrees	8	8	8	7	10 ^{##}
Field of view in mm ³	270-292 × 360 × 62.5 [*]	252-270 × 360 × 62.5 [*]	270-292 × 360 × 62.5 [*]	270 × 360 × 83.2	292 × 360 × 38.4
Acquisition matrix (phase encode × readout × slice)	70-90 × 160 × 26	78-91 × 160 × 18	84-91 × 160 × 18	100 × 160 × 32	88 × 160 × 26
Acquired voxel size in mm ³ (phase encode × readout × slice)	3.3-3.9 × 2.3 × 2.4 ^{**}	3.2 × 2.3 × 3.5	3.2 × 2.3 × 3.5	2.7 × 2.3 × 2.6	3.3 × 2.3 × 2.4
Reconstructed voxel size in mm ³ (phase encode × readout × slice)	2.3 × 2.3 × 2.4	2.3 × 2.3 × 2.4	2.3 × 2.3 × 2.4	2.7 × 2.3 × 2.6	2.3 × 2.3 × 2.4
Number of cardiac phases	20	18	25	18	20
Velocity encoding in m/s	1.5	1.5	1.5	1.5	1.5
ECG-gating	prospective	prospective	retrospective	prospective	prospective
Radiofrequency coil (receive channels)	30	30	30	32	16
Acquisition time mean ± SD in min	6.7 ± 1.8	8.5 ± 1.4	8.4 ± 1.5	9.0 ± 1.7	11.2 ± 3.0
Heart rate in beats/min	68.5 ± 8.3	67 ± 8.0	69 ± 8.1	70.4 ± 8.7	60 ± 10.8 [†]

Abbreviations: TE, echo time; TR, temporal resolution; GRAPPA, GeneRALized Autocalibrating Partial Parallel Acquisition; R, acceleration factor; ECG, electrocardiographic.

*The field of view in phase encoding direction was adjusted to the subject's anatomy.

**In two subjects the acquired pixel spacing along the phase encoding axis was increased to 3.9 mm.

#A twofold temporal segmentation factor has been used for all scans.

##The actual flip angle throughout the region of interest varies strongly at 7T.

†The heart rate at 7T is biased by the partially unreliable ECG detection, which may lead to lower heart rates.

selected based on their clinical availability to best represent a routine clinical setting.

Acquisition times for all sequences as well as the heart rates, which were retrospectively obtained from the Digital Imaging and Communications in Medicine (DICOM) data, are also provided in Table 1. Scan time was the longest at 7T, but varied substantially between approximately 8 and 15 min. The reason for such a large range is given by the navigator that failed in 5 of 10 subjects at 7T due to insufficient B_1^+ magnitude to detect the position of the diaphragm. In these subjects the scan efficiency was 100% while the minimal efficiency of 56% was determined for the longest 7T scan. A sandbag was placed on the stomach to minimize respiratory motion. Scan sessions at 1.5T, 3T, and 7T took place within weeks. The first and second scan sessions were performed within 4.2 ± 3 wk (29.3 ± 21.1 days), while the second and the third scan sessions were performed within 2.8 ± 1.6 wk (19.6 ± 10.9 days). For each 4D flow scan, the heart rate was recorded. Additionally, at 3T, steady state free precession (SSFP) cine images for the evaluation of left ventricular function and assessment of the aortic valve were acquired. If significant artifacts occurred, gradient echo sequences were added.

2.2 | Analysis of 4D flow data

The image quality of 4D flow data was evaluated for each subject and for each sequence in magnitude images as well as in streamline visualization (Supporting Information Video S1, which is available online) in three contiguous segments: the ascending aorta, the aortic arch, and the descending aorta. The ascending aorta was defined from the aortic valve to proximal of the brachiocephalic trunk, the aortic arch ended at the aortic isthmus, and the descending aorta ended at the diaphragm. Image quality was graded as published before: 0 = non-diagnostic, 1 = good, 2 = excellent.²⁵ Non-diagnostic quality was defined as presence of artifacts, blurriness, or signal loss across or inside an aortic segment. Good quality was defined as the lack thereof, but challenging delineation or missing supra-aortic branches. In images with excellent quality, the aorta as well as the supra-aortic branches could be easily delineated, no blurriness or artifacts occurred. Segments with non-diagnostic quality were excluded from further analyses.

All remaining segments were analyzed for flow volumes, as well as WSS and peak velocity.^{4,19,26}

Data were corrected online for Maxwell terms. Background velocities were corrected in MATLAB (The MathWorks Inc., USA) by fitting linear spatial gradients to the phase of static tissue, which was subtracted from the velocity data.²⁷ Subsequently, manual segmentation of the aorta was performed (Mimics, Materialise, Belgium). Then, 3D blood flow visualization and manual positioning of 2D planes for flow quantification were conducted (EnSight, Version 10.0, CEI, Apex, NC, USA). Nine cross-sectional planes were positioned perpendicularly to the longitudinal axis of the aortic wall as follows (Figure 1A): in the left ventricular outflow tract (P1), at the level of the sinotubular junction (P2), in the mid-ascending aorta (P3), proximal to the brachiocephalic trunk (P4), between the brachiocephalic trunk and the left common carotid artery (P5), between the left common carotid artery and the left subclavian artery (P6), at the aortic isthmus (P7), in the descending aorta after the isthmus (P8), and in the descending aorta at the level of P2 (P9). Flow within each plane was computed automatically.

3D WSS was calculated using a previously published approach.^{19,26} Briefly, 3D WSS was calculated throughout the entire thoracic aortic wall at peak systole and the two previous and following cardiac time frames, peak systole being defined as the time frame with the highest velocity averaged over the whole aortic volume (MATLAB, The MathWorks Inc., USA). Peak systolic WSS values were then averaged over those five time frames and extracted in 10 segments throughout the thoracic aorta as defined in Figure 1B.

Finally, peak velocities were obtained from velocity maximum intensity projections in the ascending aorta, the aortic arch, and the descending aorta (Figure 1C) (MATLAB, The MathWorks Inc., Natick, MA, USA).²⁸

2.3 | Statistical analysis

To account for the confounding effect of GRAPPA acceleration and prospective vs. retrospective ECG gating, field strength comparison between 1.5T and 3T considered 1.5T sequence 1, while comparison between 1.5T and 7T additionally considered 1.5T sequence 2.

A Wilcoxon signed-rank test was applied to test for statistically significant differences. Correlation was tested by Spearman rho's correlation. A moderate correlation was defined as $r \geq 0.50$, a strong correlation as $r \geq 0.75$.

Comparisons were performed using both the entire aorta and the ascending aorta only, since most abnormal findings in diseased patients are found in that region.

Results are reported for both, all 10 volunteers as well as only those who could be examined at all field strengths.

A subset of the data consisting of all field strengths and sequences was analyzed twice by one observer for intraobserver analysis. The time interval between the first and the second analysis was 9 mo. Bland-Altman analyses were used to assess the intraobserver variability and to set limits of agreement (95% confidence interval [CI] of difference) and

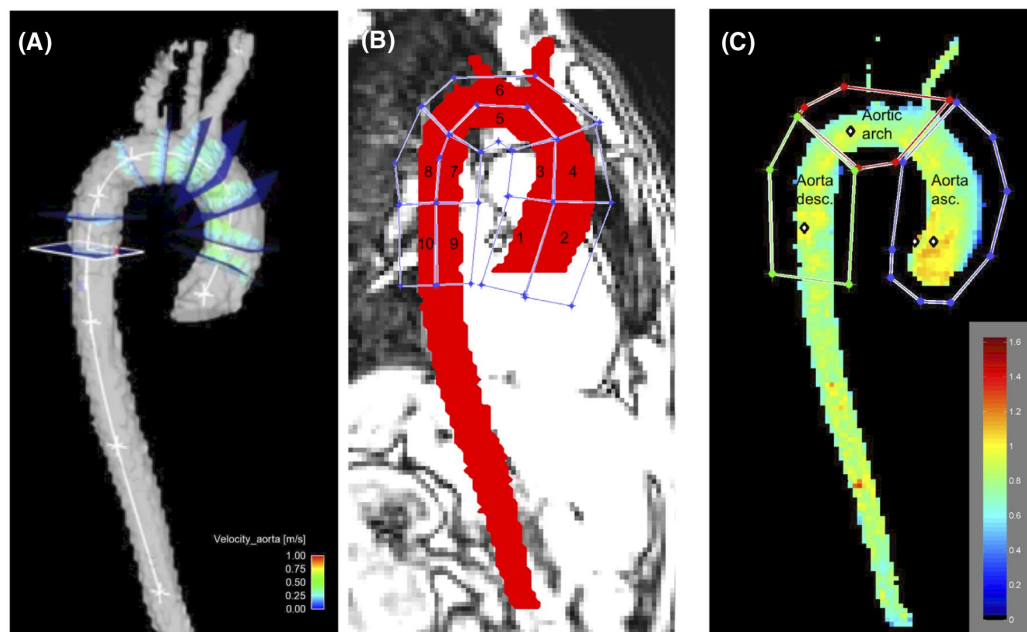


FIGURE 1 Visualization of the locations used for quantitative assessment in the thoracic aorta: flow was evaluated in nine cross-sectional planes (A), WSS was evaluated in 10 wall regions (B), peak velocity was evaluated in the ascending aorta, the aortic arch, and the descending aorta (C)

range of agreement for each aortic parameter, which was used as equivalence range for the comparison of field strengths and sequences for each aortic parameter: equivalence was reached if the limits of the 95% CI of the difference between sequences laid within the limits of the 95% CI defined by the intraobserver analysis.

A subset of data including all sequences and field strengths was used for interobserver analysis. Agreement between the observer was assessed using intraclass correlation coefficient (ICC) and Bland-Altman analysis.

Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and Graph Pad Prism 6.0 (GraphPad Software Inc., San Diego, California, USA). Graphics were created using Graph Pad Prism and plug-in software for MATLAB.

3 | RESULTS

Demographics of the 10 volunteers (6 female, mean age: 33 ± 9 y) are provided in Table 2. Across the study cohort the averaged heart rate was 67.7 ± 8.7 beats/min with no significant differences between the different 4D flow scans.

While at 1.5T and 3T all scans could be completed, at 7T, two sessions could not be performed due to technical problems with the hardware of the scanner. For cardiac gating, we used ACT in one volunteer at 7T, ECG was used in all other scans.

TABLE 2 Baseline characteristics of the healthy volunteers.

n = 10 (6 f/4 m)	Mean \pm SD
Age (yrs)	33 ± 8.9
Height (cm)	170.9 ± 10.1
Weight (kg)	65.2 ± 10
BMI (kg/m^2)	22.2 ± 1.7
LV-EF (%)	63 ± 5

BSA = body-surface-area, LV = left ventricular, EF = ejection fraction.

3.1 | Image quality

In total, 144 aortic segments were evaluated for image quality. Non-diagnostic quality was found in 10 segments (7%) (quality score = 0), 15 (10%) were scored as good (quality score = 1). The remaining 119 (83%) had excellent quality. Of the 10 segments with non-diagnostic image quality, 9 were obtained at 7T: 5 of them were located in the aortic arch, 4 of them in the descending aorta. The remaining segment was obtained during a scan with sequence 1 at 1.5T and was in the aortic arch. Among the 15 segments with good quality, 9 were found in the aortic arch (3 with sequence 1 at 1.5T, 2 with sequence 3 at 1.5T, 3 at 3T, and 1 at 7T), three segments were in the ascending aorta (1 with sequence 1 at 1.5T, and 2 at 3T), and three in the descending aorta (1 with sequence 3 at 1.5T, 1 at 3T, and 1 at 7T).

After exclusion of the aortic segments with non-diagnostic quality, 134 segments remained for further analysis.

3.2 | Intraobserver analysis

Bland-Altman plots (Figure 2) for the intraobserver analysis showed good agreement of all parameters with low bias and narrow 95% CI for the difference of the two assessments by the same observer (forward flow volume: -18.4 ; 14.6 mL; WSS: -0.17 ; 0.18 N/m^2 ; peak velocity: -0.15 ; 0.10 m/s). Also, no clear systematic pattern, for example, increasing or decreasing variability with higher averages, was observed so that sufficient agreement was concluded across the whole range of outcomes.

3.3 | Interobserver analysis

Agreement between the two observers was excellent for forward flow volume (ICC = 0.93), WSS (ICC = 0.93), and

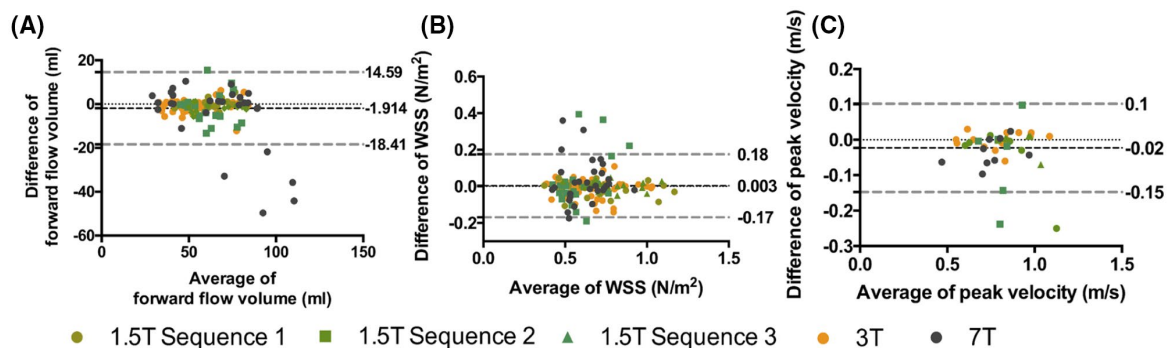


FIGURE 2 Bland Altman analyses for intraobserver analysis of forward flow volume (A), WSS (B), and peak velocity (C). Each field strength is coded in a different color. The three sequences at 1.5T are additionally coded using a different shape

peak velocity (ICC = 0.99). Bland-Altman analyses showed small biases and narrow CI (see Figure 3).

3.4 | Comparison of field strengths

The Bland-Altman analyses of the comparisons of field strengths showed differences in measurements in each pairwise comparison. These differences deviated from zero. No systemic pattern, for example, no increasing or decreasing variability with higher averages, was observed. However, equivalence between field strengths could not be concluded as the 95% CI of differences of measurements between field strength exceeded the range of the intraobserver variability (Table 3A and Figure 4A-C). When exclusively evaluating

the ascending aorta, the numbers only deviated slightly (Table 3A and Figure 4D-F).

Significant differences were found between 1.5T (sequence 1) and 3T as well as 3T and 7T for forward flow ($P < .001$). No difference between 1.5T (sequence 1) and 7T was detected with respect to forward flow ($P = .74$); however, the results of sequence 2 at 1.5T and 7T showed a significant difference ($P < .001$). When comparing only the ascending aorta, forward flow volumes also differed significantly between 7T and sequence 1 at 1.5T ($P < .001$). There was a significant difference in WSS between 1.5T (sequence 1) and 3T ($P < .05$) and no differences between 3T and 7T ($P > .2$) or between 1.5T and 7T with either sequence 1 or 2 ($P > .3$). When analyzing only the ascending aorta, also 7T and 1.5T (sequence 1 and 2) differed significantly ($P < .05$). There was

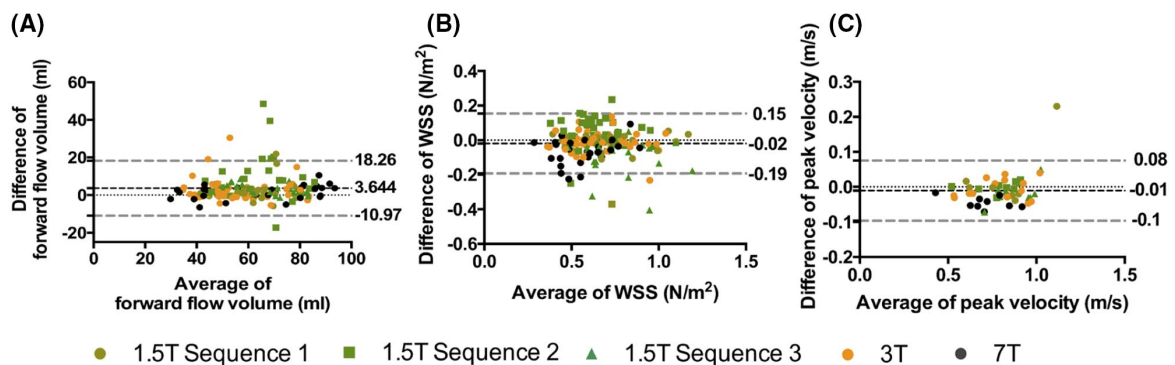


FIGURE 3 Bland Altman analyses for interobserver analysis of forward flow volume (A), WSS (B), and peak velocity (C). Each field strength is coded in a different color. The three sequences at 1.5T are additionally coded using a different shape

TABLE 3 95% CI (confidence intervals) of differences of measurements of forward flow, WSS, and peak velocity for the comparison of field strengths (A) and sequences (B)

	Forward flow (mL)	WSS (N/m ²)	Peak velocity (m/s)
(A) 95% CI of differences of measurements			
1.5T vs. 3T Whole aorta	-14.29-29.05	-0.21-0.27	-0.23-0.27
Ascending aorta only	-15.77-34.76	-0.17-0.27	-0.15-0.26
1.5T vs. 7T Whole aorta	-50.97-34.6	-0.25-0.29	*
Ascending aorta only	-57.02-29.3	-0.19-0.27	-0.21-0.28
3T vs. 7T Whole aorta	-60.03-30.75	-0.2-0.15	*
Ascending aorta only	-72.3-25.79	-0.2-0.19	-0.15-0.12
(B) 95% CI of differences of measurements			
Sequence 1 vs. 2 Whole aorta	-21.42-27.4	-0.17-0.32	-0.34-0.28
Ascending aorta only	-21.88-36.65	-0.12-0.33	-0.31-0.27
Sequence 1 vs. 3 Whole aorta	-17.55-9.75	-0.26-0.09	-0.29-0.19
Ascending aorta only	-18.67-10.45	-0.23-0.11	-0.28-0.2
Sequence 2 vs. 3 Whole aorta	-27.27-13.31	-0.37-0.06	-0.14-0.11
Ascending aorta only	-36.17-13.18	-0.38-0.05	-0.17-0.13

*At 7T too few values could be calculated for an unbiased analysis. As the evaluation of the ascending aorta only contained less values in all comparisons, the amount of values generated at 7T were comparable.

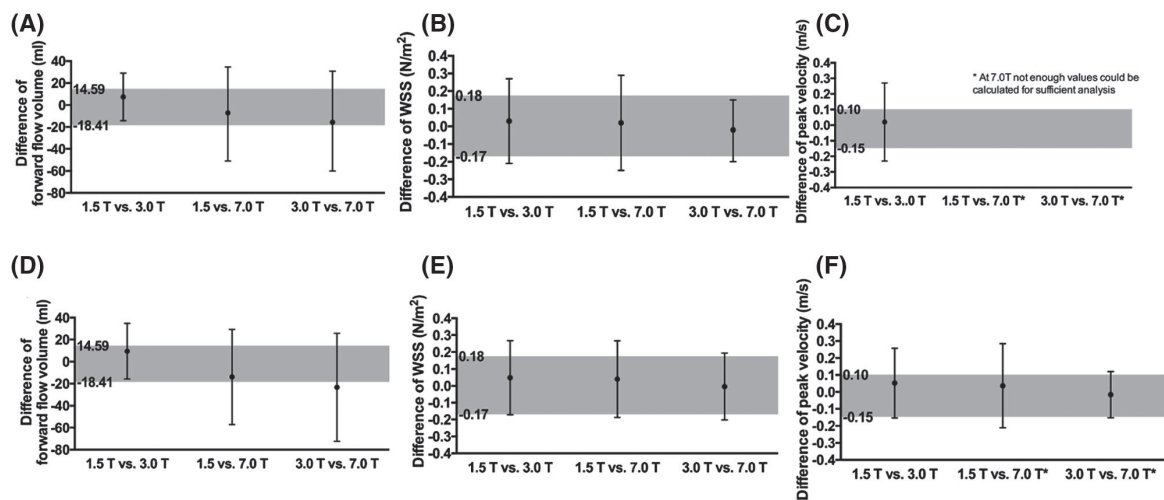


FIGURE 4 Assessment of variability of differences of measurements by field strengths with respect to intraobserver variability for forward flow, WSS, and peak velocity for the whole aorta (A-C) and the ascending aorta only (D-F). The gray area displays the range of intraobserver variability (ie, 95% CI of the differences of intraobserver assessments [Bland-Altman approach]). Black dots indicate mean difference, while black bars indicate 95% CI of the difference between field strengths. As the evaluation of the ascending aorta only contained fewer values in all comparisons, the amount of values generated at 7T were comparable and, therefore, enough for sufficient analysis also in peak velocity

no significant difference in peak velocity between 1.5 (sequence 1) and 3T or 7T and no difference between 3T and 7T ($P > .1$), but a significant difference between 1.5 (sequence 2) and 7T ($P > .01$). This result remained in the analysis of the ascending aorta only.

The results remained the same when evaluating only the eight volunteers that could be examined at all field strengths.

There was a moderate positive correlation for forward flow between 1.5T (sequence 1) and 3T ($r = 0.7$), and between 1.5T (sequence 1 and 2) and 7T ($r = 0.5$, respectively, $r = 0.6$), as well as between 3T and 7T ($r = 0.5$). For WSS, there was a moderate correlation between all field strengths (1.5T sequence 1 and 3T $r = 0.7$, 1.5T sequence 2 and 7T $r = 0.7$, 3T and 7T $r = 0.7$), apart from 1.5T sequence 1 and 7T ($r = 0.4$). Peak velocity correlated moderately between 1.5T (sequence 1) and 3T ($r = 0.6$). At 7T, there were not enough values for a sufficient analysis (Figure 5).

3.5 | Comparison of sequences at 1.5T

The Bland-Altman analyses of the comparisons of sequences at 1.5T showed differences in measurements in each pairwise comparison. These differences deviated from zero. No systemic pattern, for example, no increasing or decreasing variability with higher averages, was observed. Equivalence between sequences could not be concluded for all parameters and comparisons apart from the comparison of forward flow volumes between sequence 1 and 3 as the 95% CI of differences of measurements by sequences exceeded the range of intraobserver variability (Table 3B and Figure 6A-C). When

exclusively evaluating the ascending aorta, the numbers only deviated slightly (Table 3B and Figure 6D-F).

Forward flow volume was found to be significantly different between sequences 1 and 3 and 2 and 3 ($P < .001$), but did not differ significantly between sequence 1 and 2 ($P > .1$). When comparing only the ascending aorta, forward flow volumes differed significantly between all sequences ($P < .005$). There was a significant difference between all three sequences in WSS ($P < .001$). These results remained when analyzing the ascending aorta only. Peak velocity did not differ significantly between any of the sequences ($P > .5$), neither when analyzing the whole aorta nor when analyzing the ascending aorta only. These results remained the same when evaluating only the eight volunteers, that could be examined at all field strengths.

There was a moderate positive correlation for forward flow volume between sequences 1 and 2 ($r = 0.5$) and sequences 2 and 3 ($r = 0.7$) and a strong correlation between sequences 1 and 3 ($r = 0.9$). For WSS, there was a moderate correlation between sequences 1 and 2 ($r = 0.6$) and a strong correlation between sequences 1 and 3 ($r = 0.8$) and between sequences 2 and 3 ($r = 0.75$). Peak velocity correlated moderately between sequences 1 and 3 ($r = 0.6$) and strongly between sequences 2 and 3 ($r = 0.9$) (Figure 5).

4 | DISCUSSION

In this study, 4D flow data from three different sequences at 1.5T, one sequence at 3T, and one sequence at 7T were successfully acquired. The resulting images showed sufficient quality that allowed further analysis, despite challenges

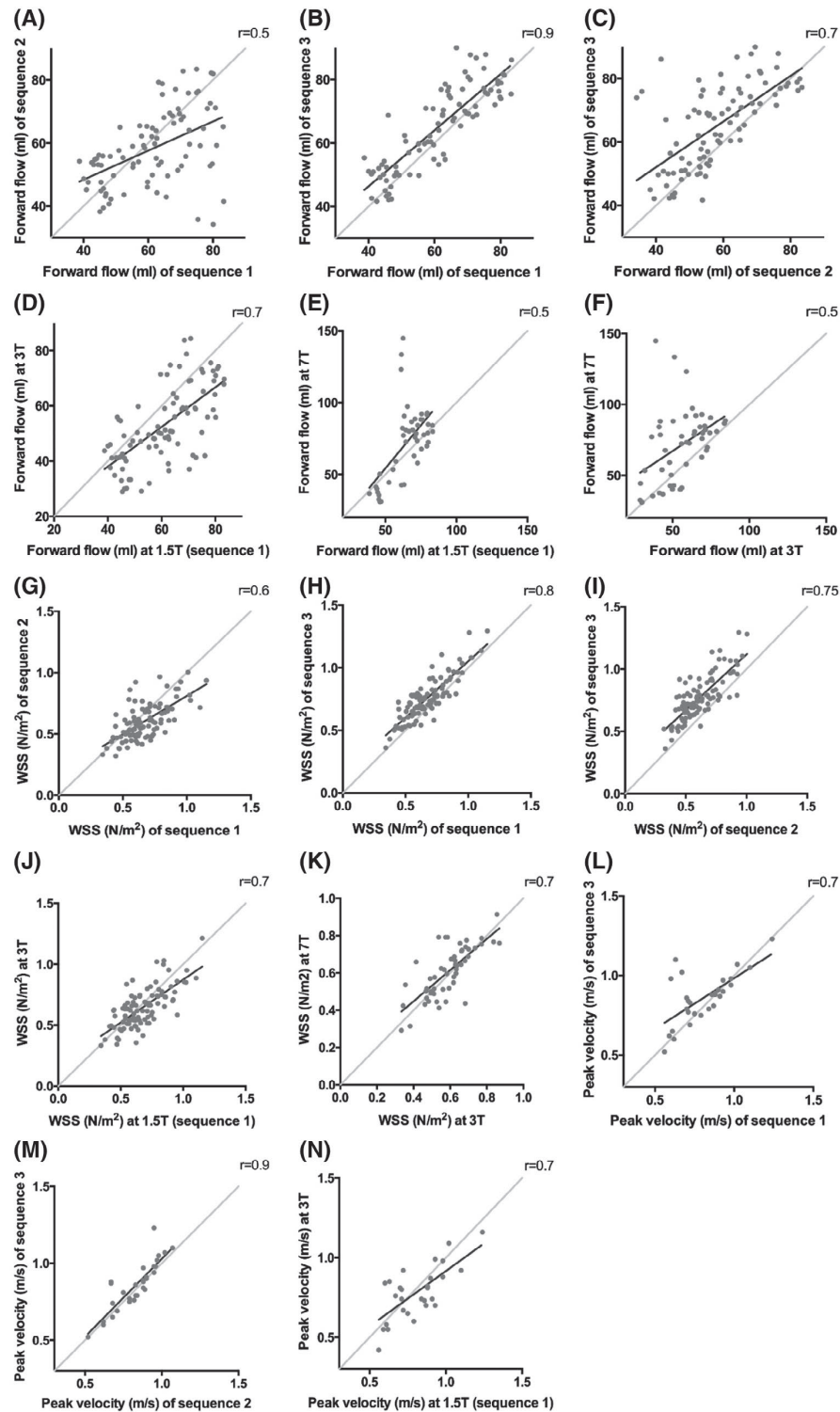


FIGURE 5 Moderate to strong correlation between all sequences and field strengths for all parameters: correlation of forward flow for all sequences (A-C), correlation of forward flow for all field strengths (D-F), correlation of WSS for all sequences (G-I), correlation of WSS for field strengths (J,K), correlation of peak velocity for sequences (L,M), and correlation of peak velocity between 1.5 and 3T (at 7T not enough values for sufficient analysis) (N)

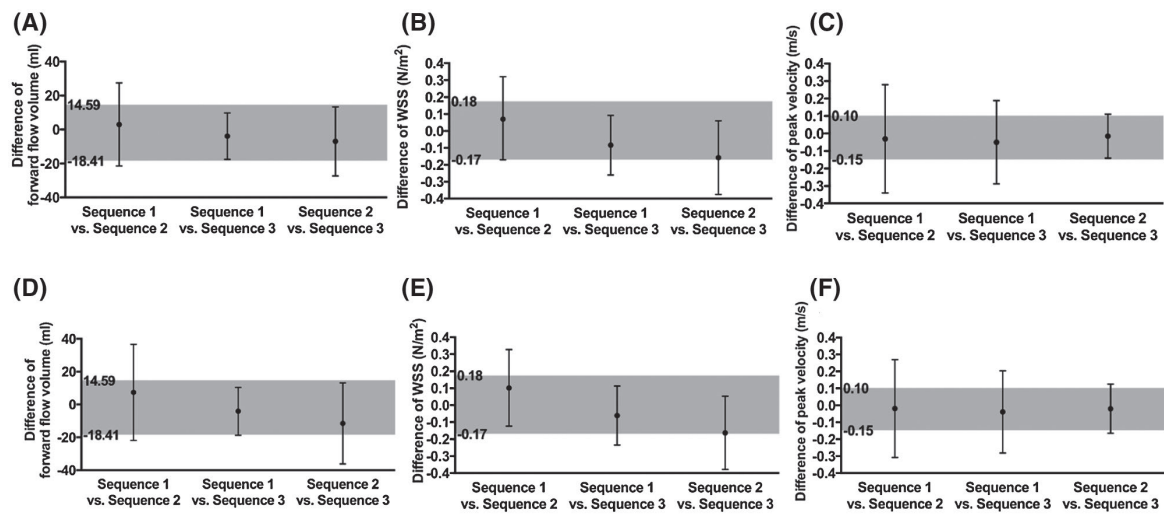


FIGURE 6 Assessment of variability of differences of measurements by sequences at 1.5 T with respect to intraobserver variability for forward flow, WSS, and peak velocity for the whole aorta (A-C) and the ascending aorta only (D-F). The gray area displays the range of intraobserver variability (ie, 95% CI of the differences of intraobserver assessments (Bland-Altman approach)). Black dots indicate mean difference, while black bars indicate 95% CI of the difference between sequences

particularly related to the navigator, the positioning, the ECG, and coil placement at 7T. None of the tested sequences provided results that were equivalent with regard to the intraobserver variability in all parameters and significant differences were revealed. However, some comparisons suggest equivalence and some do not reveal any significant differences (Supporting Information Table S1).

Clinically, the impact of field strengths or sequences on the result is essential for follow-up investigations of a patient since a biased result can lead to a misdiagnosis. By calculating the equivalence, only the existence and amount of a potential bias can be identified, but the chance of misdiagnosing a patient with a certain pathology cannot be determined. For this evaluation, a tolerance range based on a comparison between healthy volunteers and patients with this certain pathology would be required, and the analysis needs to be performed again if the pathology of interest changes. As a first step, we retrospectively investigated data published in a previous study,⁹ where we compared patients with aortic stenosis to healthy volunteers. In this former study, we showed a significant difference between healthy volunteers and patients with aortic stenosis in WSS and an increasing WSS with increasing severity of the stenosis. We re-used the data from this previous publication for a WSS comparison between patients with aortic stenosis (data of the previous study) and healthy subjects (data of the current study). This initial analysis showed that the differences in WSS between healthy volunteers and patients with severe aortic stenosis were larger than the differences in WSS between sequences/field strengths. However, this statement is not generally valid for patients with mild or moderate stenosis, a patient group

of high interest as they are typically diagnosed in this stage. Therefore, such patients could be misdiagnosed if the sequence or field strength changes in follow-up examinations.

Intra- and interobserver analysis show good agreement with low bias and narrow CI. In forward flow volume bias is lower in intraobserver analysis than in interobserver analysis, as expected. However, the 95% confidence interval is slightly larger in intraobserver analysis than in interobserver analysis. In the Bland-Altman plot of the intraobserver analysis, five outliers can be seen. These outliers are all from data acquired at 7T. An explanation for this might be given by insufficient flip angles, which was particularly observed in the descending aorta. Due to the low flip angles, the signal-to-noise ratio (SNR) decreases and might influence the delineation. In WSS, bias is also lower in intraobserver analysis than in interobserver analysis and the CI is similar. Only in peak velocity bias is lower in interobserver analysis than intraobserver analysis. The 95% CI is also slightly larger in interobserver analysis than in intraobserver analysis. However, both show excellent agreement. Peak velocity is measured in three areas of the aorta, and the highest velocity in each of the areas is given. Slight changes in placing the areas can lead to these slight changes in numbers.

4.1 | Image quality

The lowest diagnostic quality was found at 7T, mainly in the aortic arch and the descending aorta. This seems to contradict the expected higher SNR at 7T in comparison to 3T or 1.5T. Indeed, Hess et al showed a higher SNR up to 2.2 times for

4D flow in the aorta at 7T compared with 3T.²⁹ In 4D flow in intracranial vessel imaging, a higher SNR at 7T compared with 3T resulted in a better delineation of small vessels and improved flow visualization.³⁰ The low image quality at 7T in our study was most likely caused by systematically low flip angles generated by the single-channel transmit coil within the arch and descending aorta that resulted in lower contrast. Modifying the hardware of the coil to specifically target the aorta and not the heart (as in the present study) or using a multi-transmit-channel coil combined with radiofrequency shimming could help solving this problem.

The one segment with non-diagnostic quality in sequence 1 at 1.5T was most likely due to a poorly positioned field of view during acquisition.

4.2 | Comparison of field strengths

The potential impact of field strength on the determination of hemodynamic parameters using 4D flow has been investigated before. Strecker et al did not find significant differences in the thoracic aorta of healthy volunteers between 1.5T and 3T.³¹ However, they compared different 4D flow-derived parameters at 1.5 and 3T, while we further included 7T data as well as different sequences. In agreement with Strecker et al, we found a good agreement between quantitative analyses with similar values for flow volumes, peak velocities, and WSS.³¹ In addition, we investigated if these aortic hemodynamic parameters obtained using the different sequences/field strengths were similar enough to be interchangeable. Therefore, we also evaluated equivalence, which could also be interpreted as a tolerance range according to a clinical perspective. Indeed, given the current lack of standardization, it is crucial to foster the clinical use of 4D flow MRI, to establish if sequences/field strengths can be changed for a patient's follow-up investigation without affecting results.

Significant differences were found in our cohort in the comparison of forward flow volumes, WSS, and peak velocity between different field strengths. However, not all comparisons were significantly different: Peak velocity did not differ significantly between 1.5T and 3T as well as 3T and 7T, and the comparison of the results obtained at 3T and 7T could even be considered equivalent with respect to the intraobserver variability in the ascending aorta only. Due to the limited number of datasets for peak velocity at 7T, this conclusion is limited and applies to the ascending aorta only.

Although some comparisons concerning the WSS did not show a significant difference, they exceeded the limits of intraobserver variability and were, therefore, not found to be equivalent. In forward flow, significant differences were found and the respective comparisons between field strengths exceeded the limits of intraobserver variability (Supporting Information Table S1). As in clinical evaluation, differences

in results can lead to a different diagnosis, these differences between field strengths should be taken into account. However, our findings suggest that peak velocity is less dependent on the field strength than WSS and forward flow.

4.3 | Comparison of sequences

Apart from the comparison of forward flow between sequence 1 and sequence 3, none of the compared parameters were equivalent with regard to the intraobserver variability.

The intraobserver variability was determined by analyzing a subset of examinations at all field strengths twice. An additional intraobserver analysis consisting only of examinations at 1.5T revealed a smaller variability resulting in a narrower range of equivalence. A closer look at the comparison of forward flow volumes between sequence 1 and 3 showed that they indeed lay within the range determined by intraobserver variability of all field strengths, but not within the range determined only by intraobserver variability at 1.5T. The comparison of peak velocity between sequence 2 and 3 only slightly exceeded the range of equivalence determined by intraobserver variability of all field strengths. Furthermore, it lay just within the range of equivalence determined by intraobserver variability at 1.5T only. These sequences might, therefore, be equivalent, however, only regarding peak velocity.

Significant differences were found in our cohort in the comparison of forward flow volumes, WSS, and peak velocity between sequences, although not between all parameters in all sequences. For the comparisons of forward flow and WSS significant differences were found. This was supported by the finding of the test for equivalence in these comparisons, as no equivalence between the sequences could be shown there either. In peak velocity, no significant difference was found. As the test for equivalence also already showed only a slight divergence, peak velocity seems to be the parameter least dependent on the type of sequence used.

As sequence 2 and 3 have identical acquisition parameters and differ only in the way of gating (prospectively vs. retrospectively), only minor difference between both sequences could be expected. However, they also show significant differences in forward flow and WSS. Only the comparison of peak velocity shows no significant differences and was found to be equivalent. Differences in forward flow may be explained by the different way of gating applied in sequence 2 and 3. Prospectively gated sequences do not cover the whole heart beat, but miss milliseconds of the diastolic phase, while retrospectively gated sequences cover the entire cardiac cycle. Therefore, differences can be expected already in healthy volunteers, as we showed. This difference is of even higher importance when examining patients with pathologies that affect the diastolic phase of the heart cycle (eg, aortic valve regurgitation). WSS, however, is

measured around peak systolic phase, which cannot be explained by the differences in gating. Interestingly, our data reflect that also WSS differs significantly between sequence 2 and 3, which motivates further investigations on the impact of triggering on derived WSS values.

A moderate to strong positive correlation was found for the comparison of all parameters in all sequences as well as in all field strengths. This means that 4D flow can be used and evaluated in all sequences and at all field strengths with reasonable results. Although the results of the different field strengths and sequences might not be interchangeable, the positive correlation also implies that a transfer might be possible with the establishment of a z-score.³²

So far, 4D flow MRI been applied using various sequence types and at different field strengths. In clinical studies, it has been used at 1.5T^{11,15,18,33,34} and 3T^{9,12-14,35,36} or at both clinical field strengths.^{16,19,20,37-39} Furthermore, 4D flow MRI has been evaluated at 7T.^{29,40} Sequence characteristics ranged from echo time 2.2 to 6.1 ms, echo spacing 4.2 to 6.4 ms, spatial resolution 1.6-4 × 1.5-4 × 2.5-4 mm³, and ECG gating was performed either prospectively or retrospectively.^{13,16,18,36,37} The impact of technical parameters of hemodynamic parameters of 4D flow sequences was also studied by other groups. Carlsson et al compared two 4D flow sequences to determine flow volumes in the whole heart with different acceleration techniques at 1.5T and 3T in healthy volunteers. They found significant differences between both sequences regarding peak blood flow.⁴¹ The influence of different acceleration techniques on 4D flow was also analyzed in a whole heart study⁴² and in brain vasculature⁴³: Garg et al examined 25 volunteers as well as a thoracic phantom with three intracardiac 4D flow sequences with different acceleration techniques. They compared peak velocity and flow volume at the mitral and aortic valve of each 4D sequence. All results obtained by 4D flow sequences correlated well with those obtained by a slice-selective acquisition, but they correlated differently, with one sequence correlating excellently.⁴² Sekine et al examined 16 volunteers with two accelerated 4D flow sequences and one non-accelerated sequence in brain vessels. They measured peak velocity and flow volume. Both accelerated scans agreed well with the non-accelerated sequence. They both underestimated peak velocity and flow volumes in some subjects, but in different vessels.⁴³ Montalba et al could show that spatial and temporal resolution had an impact on the measurement of flow volumes and peak velocity using 4D flow MRI in an aortic phantom.⁴⁴

These studies show that different technical parameters of 4D flow sequences might have an impact on certain clinically important parameters. Clinically used sequences often differ slightly to one another, which might influence the result.

The differences between 4D flow at different field strengths could also be caused by physiological changes of hemodynamics and/or fluid or food intake⁴⁵ of the individual

volunteer, as our volunteers did not fast before conducting the scan. However, all scans were performed at approximately the same time of day resulting in a probable similar food influence on hemodynamics. All scans at 1.5T were performed in one scan without break, which implies a similar impact of food intake on hemodynamics over the whole scan.

Kamphuis et al tested scan-rescan reproducibility of an intracardiac 4D flow sequence. They showed a good reproducibility of 4D flow with good to strong correlation coefficients, depending on the evaluation method.⁴⁶ Stoll et al showed similar results in their study of intracardiac 4D flow scan-rescan assessment.³⁶ This shows that scan-rescan reproducibility for 4D flow is high, which suggests that the effect of changes in hemodynamics between the scans should be small and cannot fully explain the differences we found.

4.4 | Limitations

This study was based on a limited number of healthy volunteers, and no phantom studies were performed. For the establishment of normal values, larger cohorts are needed. Acquisition parameters of the sequences at the different field strengths differ slightly, which is mainly caused by the availability of sequences and the hardware (eg, gradients) at the different scanners, but the parameters reflect the clinical setting.

Scan-rescan variability was not tested in this study, and differences here might also contribute to our findings. Comparison to other studies, however, showed smaller scan-rescan variability than the differences between field strengths/sequences found in our study.

No reference measurement such as 2D phase contrast imaging in selected planes was obtained based on which the LV stroke volume was calculated and compared with the volumes measured by 4D flow imaging. To assess a possible over- or underestimation of flow values, this is of interest for further investigations.

Furthermore, the results for the peak WSS shown in Figure 6 might be biased by the different reconstructed temporal resolution for the retrospective and prospective acquisitions at 1.5T. Since here five cardiac phases at peak systole are selected for both reconstruction types, the resulting interval is shorter for the retrospective scan, which may explain higher WSS values for this acquisition.

5 | CONCLUSIONS

Despite challenges particularly related to the navigator, the positioning, the ECG and coil placement at 7T, data from all sequences have been successfully acquired and resulting images showed sufficient quality that allowed further analysis. The hemodynamic results in this study showed agreement, as

the differences were found to be around zero with a certain variability, but were not found to be equivalent with regard to limits assessed by the intraobserver variability. In our view, this agreement was sufficient for a more detailed evaluation of the differences. The comparison of different hemodynamic parameters between the sequences, respectively, field strengths showed significant differences. Hence, field strength and/or different sequence acquisition parameters of one sequence might have an influence on 4D flow quantitative aortic hemodynamic parameters; therefore, equivalence between these parameters cannot be taken for granted, but should be verified before interpreting results and when conducting longitudinal or cross-center studies.

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CONFLICT OF INTEREST

Ning Jin and Andreas Greiser are full-time employees of Siemens Healthineers.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

TABLE S1 Comparison of forward flow, WSS and peak velocity between field strengths (a) and sequences (b) in a color-coded three-scale metric combining both the statistical and the equivalence testing: Values indicated in red reflect differences in both tests and a change between the respective sequences/field strengths is not recommended. Yellow colored values denote a difference in only one of the tests, changes of sequences/field strengths can be done with careful consideration and keeping this bias in mind. Values in green indicate no differences in both tests, changes are possible. * When comparing the results in the ascending aorta only, the color changes to red

VIDEO S1 Streamlines of one volunteer's aorta at 1.5T (sequences 1-3), at 3T and at 7T

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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

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
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 RADIOLOGY	3,711	4.112	0.004480
20	EUROPEAN RADIOLOGY	19,597	3.962	0.033870

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	RADIOGRAPHICS	11,768	3.923	0.009170
22	Biomedical Optics Express	9,547	3.910	0.021750
23	MAGNETIC RESONANCE IN MEDICINE	32,648	3.858	0.034990
24	SEMINARS IN NUCLEAR MEDICINE	2,245	3.798	0.002710
25	Journal of the American College of Radiology	4,191	3.785	0.009760
26	JOURNAL OF MAGNETIC RESONANCE IMAGING	17,147	3.732	0.027800
27	KOREAN JOURNAL OF RADIOLOGY	2,687	3.730	0.004800
28	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,552	3.589	0.004020
29	EJNMMI Physics	394	3.475	0.001350
30	NMR IN BIOMEDICINE	7,511	3.414	0.014790
31	MOLECULAR IMAGING AND BIOLOGY	2,543	3.341	0.005360
32	Journal of Cardiovascular Computed Tomography	1,711	3.316	0.004430
33	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,464	3.298	0.002990
34	AMERICAN JOURNAL OF NEURORADIOLOGY	23,231	3.256	0.028010
35	MEDICAL PHYSICS	26,715	3.177	0.030870
36	AMERICAN JOURNAL OF ROENTGENOLOGY	33,633	3.161	0.028540
37	CANCER IMAGING	1,406	3.153	0.002220
38	Quantitative Imaging in Medicine and Surgery	1,072	3.074	0.002420
39	PHYSICS IN MEDICINE AND BIOLOGY	27,458	3.030	0.031970
40	EJNMMI Research	1,408	3.000	0.004320
41	EUROPEAN JOURNAL OF RADIOLOGY	12,871	2.948	0.019480
42	Radiation Oncology	5,669	2.895	0.012980

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
43	MAGNETIC RESONANCE MATERIALS IN PHYSICS BIOLOGY AND MEDICINE	1,600	2.836	0.003630
44	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	8,813	2.828	0.011270
45	Clinical Neuroradiology	798	2.800	0.002250
46	Practical Radiation Oncology	1,563	2.794	0.005010
47	RADIATION RESEARCH	8,561	2.779	0.006480
48	SEMINARS IN RADIATION ONCOLOGY	2,395	2.741	0.003600
49	STRAHLENTHERAPIE UND ONKOLOGIE	2,949	2.717	0.004500
50	ULTRASONICS	7,026	2.598	0.009090
51	JOURNAL OF DIGITAL IMAGING	2,191	2.572	0.003680
52	JOURNAL OF BIOMEDICAL OPTICS	13,787	2.555	0.016940
53	Physica Medica-European Journal of Medical Physics	2,641	2.532	0.006270
54	NEURORADIOLOGY	5,656	2.504	0.007020
55	NUCLEAR MEDICINE AND BIOLOGY	3,858	2.492	0.004230
56	ULTRASONIC IMAGING	1,117	2.490	0.000860
57	Diagnostic and Interventional Imaging	1,359	2.486	0.003400
58	JOURNAL OF NEURORADIOLOGY	985	2.467	0.001440
59	Dose-Response	997	2.451	0.001460
60	Zeitschrift fur Medizinische Physik	558	2.322	0.001360
61	ACADEMIC RADIOLOGY	5,625	2.267	0.008230
62	INTERNATIONAL JOURNAL OF RADIATION BIOLOGY	4,537	2.266	0.003740
63	ULTRASOUND IN MEDICINE AND BIOLOGY	10,769	2.205	0.012790
64	International Journal of Computer Assisted Radiology and Surgery	2,416	2.155	0.005160

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
65	Abdominal Radiology	1,420	2.147	0.003820
66	MAGNETIC RESONANCE IMAGING	7,321	2.112	0.009310
67	CLINICAL RADIOLOGY	6,537	2.082	0.008390
68	JOURNAL OF NEUROIMAGING	2,081	2.080	0.004270
69	JOURNAL OF THORACIC IMAGING	1,417	2.078	0.001910
70	NEUROIMAGING CLINICS OF NORTH AMERICA	1,173	2.046	0.001310
71	Brachytherapy	1,797	2.030	0.003400
72	PEDIATRIC RADIOLOGY	6,212	2.022	0.007040
73	JOURNAL OF RADIATION RESEARCH	2,652	2.014	0.004250
74	Magnetic Resonance Imaging Clinics of North America	984	2.011	0.001370
75	Contrast Media & Molecular Imaging	1,241	1.984	0.002140
76	Molecular Imaging	1,078	1.942	0.001190
77	BRITISH JOURNAL OF RADIOLOGY	9,657	1.939	0.011070
78	QUARTERLY JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	1,037	1.931	0.001290
79	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	5,219	1.928	0.007850
80	CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS	1,562	1.894	0.001590
81	ROFO-FORTSCHRITTE AUF DEM GEBIET DER RONTGENSTRAHLEN UND DER BILDGEBENDEN VERFAHREN	1,435	1.882	0.002170
82	RADIOLOGIC CLINICS OF NORTH AMERICA	2,298	1.875	0.001970
83	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	2,949	1.860	0.006790
84	Journal of Contemporary Brachytherapy	628	1.847	0.001300
85	Radiology and Oncology	824	1.846	0.001620



A multi-vendor, multi-center study on reproducibility and comparability of fast strain-encoded cardiovascular magnetic resonance imaging

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Abstract

Myocardial strain is a convenient parameter to quantify left ventricular (LV) function. Fast strain-encoding (fSENC) enables the acquisition of cardiovascular magnetic resonance images for strain-measurement within a few heartbeats during free-breathing. It is necessary to analyze inter-vendor agreement of techniques to determine strain, such as fSENC, in order to compare existing studies and plan multi-center studies. Therefore, the aim of this study was to investigate inter-vendor agreement and test-retest reproducibility of fSENC for three major MRI-vendors. fSENC-images were acquired three times in the same group of 15 healthy volunteers using 3 Tesla scanners from three different vendors: at the German Heart Institute Berlin, the Charité University Medicine Berlin-Campus Buch and the Theresien-Hospital Mannheim. Volunteers were scanned using the same imaging protocol composed of two fSENC-acquisitions, a 15-min break and another two fSENC-acquisitions. LV global longitudinal and circumferential strain (GLS, GCS) were analyzed by a trained observer (Myostrain 5.0, Myocardial Solutions) and for nine volunteers repeatedly by another observer. Inter-vendor agreement was determined using Bland-Altman analysis. Test-retest reproducibility and intra- and inter-observer reproducibility were analyzed using intraclass correlation coefficient (ICC) and coefficients of variation (CoV). Inter-vendor agreement between all three sites was good for GLS and GCS, with biases of 0.01–1.88%. Test-retest reproducibility of scans before and after the break was high, shown by ICC- and CoV values of 0.63–0.97 and 3–9% for GLS and 0.69–0.82 and 4–7% for GCS, respectively. Intra- and inter-observer reproducibility were excellent for both parameters (ICC of 0.77–0.99, CoV of 2–5%). This trial demonstrates good inter-vendor agreement and test-retest reproducibility of GLS and GCS measurements, acquired at three different scanners from three different vendors using fSENC. The results indicate that it is necessary to account for a possible bias (<2%) when comparing strain measurements of different scanners. Technical differences between scanners, which impact inter-vendor agreement, should be further analyzed and minimized.

DRKS Registration Number: 00013253.

Universal Trial Number (UTN): U1111-1207-5874.

Keywords Strain · fSENC · Agreement · Reproducibility · CMR · Cardiac · Magnetic resonance

Abbreviations

CMR Cardiovascular magnetic resonance
 EF Ejection fraction
 EPI Echo planar imaging
 fSENC Fast strain-encoded magnetic resonance imaging
 GCS Global circumferential strain

GLS Global longitudinal strain
 IQR Interquartile range
 LV Left ventricular
 LOA Limits of agreement
 MRI Magnetic resonance imaging
 SAX Short-axis
 SENC Strain-encoded magnetic resonance imaging
 STE Speckle tracking echocardiography
 2-Ch 2-Chamber
 3-Ch 3-Chamber
 4-Ch 4-Chamber

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Introduction

Myocardial strain has proven to be an important parameter for further investigation of myocardial performance in addition to conventionally used volumetric measures, such as ejection fraction (EF) [1–3]. Strain can be determined using echocardiography and cardiovascular magnetic resonance (CMR) imaging. A common technique to measure strain in echocardiography is using speckle tracking (STE). STE is routinely used, for example to identify systolic dysfunction in heart failure patients with preserved EF [4] or as a marker for cardiotoxicity in patients undergoing chemotherapy [5]. An important step towards standardization of STE in preparation for broad clinical use was the recent publication of a consensus document on how strain measurements should be performed [6]. However, strain is not only influenced by measurement methods, but also by image quality, intra- and inter-observer reproducibility, the image acquisition system [7] and the post-processing software used [8, 9]. As the impact of these various factors on strain results remains unclear, guidelines recommend STE to be performed using the same vendor's acquisition system and software for individual patients [9].

As CMR emerged as the reference standard of cardiac morphology and function [10], various acquisition- and post-processing techniques to determine strain using CMR have been explored and validated [11]. Long acquisition times [12] and long breath-holds in patients with cardiac diseases, especially those who suffer from dyspnea, are some of the factors currently limiting use in clinical settings. Furthermore, no standardized approach to measure strain using CMR has been proposed yet, as was the case for STE. The lack of information on the influence of different magnetic resonance scanners and platforms on strain results is one challenge preventing standardization of CMR techniques. Nevertheless, this information is crucial since studies are conducted at different centers with varying scanners, at different field strengths and using different post-processing platforms. Without information on inter-vendor agreement, CMR-strain should only be determined using the same scanner and post-processing software for individual patients, as recommended for STE. Although this measure reduces possible bias on strain results, no comparison can be made between different studies and measurements performed at different centers, hampering the practicality of using strain routinely and the design of multi-center studies to further validate this method.

Strain-encoding (SENC), first described in 2001 by Osman et al. [13], is a novel imaging technique to measure strain. In comparison to myocardial tagging, SENC uses tag planes in which the sinusoidal phase is constant in parallel to the image plane [13]. Therefore, longitudinal

strain is determined using short-axis- and circumferential strain using long-axis views; radial strain is not measurable by SENC. Fast-SENC (fSENC) is a “real-time” scan that acquires all necessary data for one slice within one single heartbeat [14]. Hence, it is insensitive to breathing motion, resulting in a fast magnetic resonance imaging (MRI) exam for the patient at free breathing. Studies have shown that fSENC is equal or even superior to tagging [15] and highly reproducible concerning inter-study, as well as intra- and inter-observer reproducibility [2].

The aim of this study was to examine the inter-vendor agreement and reproducibility of CMR-derived strain, obtained with fSENC in the same group of volunteers at three different sites with individual MRI-platforms and sequences. In particular, our aims were to

1. investigate inter-vendor agreement of fSENC at 3 T using scanners from three major MRI vendors,
2. determine test-retest reproducibility of repeated scans at each scanner and
3. determine intra- and inter-observer reproducibility of the strain measurements.

Methods

Study population and design

Fifteen healthy volunteers with no history of cardiovascular diseases or contraindications against MRI [16] were prospectively identified and recruited for the study after obtaining a written informed consent. The study was approved by the Ethics Committee of the Charité-University-Medicine in Berlin and complied with the Declaration of Helsinki. It was registered at the German Register for Clinical Studies (DRKS) (registration number: 00013253) and the World Health Organization (WHO) (universal trial number (UTN): U1111-1207-5874).

Cardiovascular magnetic resonance imaging

CMR images of all fifteen volunteers were acquired repeatedly at 3 T on three different scanners (names in alphabetical order and not according to site number: Ingenia, Philips, Best, The Netherlands; MAGNETOM Verio, Siemens Healthcare GmbH, Erlangen, Germany; SIGNA Architect, GE Healthcare, Milwaukee, WI, USA). CMR examinations took place within five months at: the German Heart Institute Berlin (site I), the Theresien-Hospital Mannheim (site II) and the Max-Delbrück Center for Molecular Medicine (MDC) in collaboration with Charité University Medicine

Berlin-Campus Buch (site III), each equipped with one of the above listed scanners.

Fast strain-encoding (fSENC)

The techniques applied to the pulse sequence (localized/reduced field-of-view fSENC, interleaved tuning, spiral imaging, ramped flip angle, etc.) to achieve image acquisition in a single heartbeat have been described previously [2, 14, 15]. Prior to in-vivo imaging, studies were performed in vitro with scanning platforms of the three different vendors using phantoms of very similar proportions, made of homogeneous MR-visible silicone gel with known mechanic properties [17]. Periodic non-flat compression and expansion was applied using an MR-compatible air cylinder as described by Osman et al. [17, 18]. Subsequently, scanning of the fifteen volunteers was performed at all three sites. All volunteers were scanned using the same imaging protocol, schematically depicted in Fig. 1. Each volunteer received four fSENC scans per site, adding up to 60 scans. The first two scans were performed consecutively using the same scanning parameters. Afterwards the volunteers left the scanner room for fifteen minutes, followed by two more fSENC acquisitions with the same parameters. Images were acquired in three long-axis views (2-chamber (2-ch), 3-chamber (3-ch), 4-chamber (4-ch)) to calculate left ventricular (LV) global circumferential strain (GCS) and in three short-axis views (SAX- basal, mid-ventricular (mid), apical) to calculate LV global longitudinal strain (GLS). Scanning was performed by the local team of one or two technicians at each site after being trained by the same representatives of the software provider on performing the fSENC acquisitions and completing a written test. Scanning parameters were allowed to be adjusted according to the different scanners, if needed. Heart rate (bpm) and blood pressure (mmHg) were monitored before, during and after the exam. Variables that might influence strain measurements, such as height, weight and smoking behavior, were determined before the scans at every site.

Technical parameters

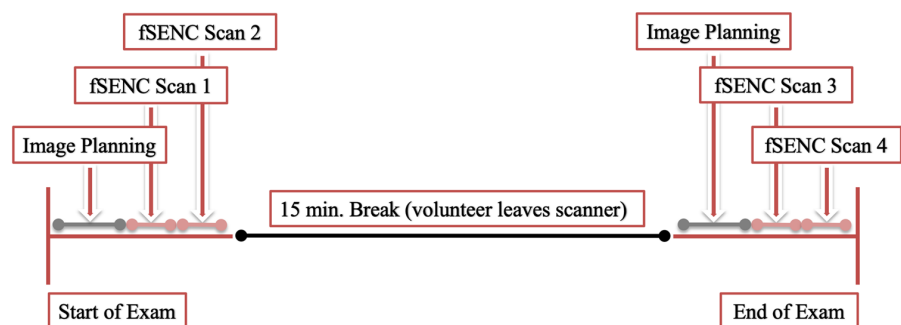
Site I

At site I, images were acquired using a multi-element receive coil array, consisting of an anterior part on the patient's chest and a posterior part embedded in the patient table. A flexible number of up to 32 elements was employed, where the selection of coil elements was performed automatically by the MR software. Image acquisition was triggered on the R-wave using a 4-lead vector ECG. fSENC imaging parameters at site I were: field-of-view = $256 \times 256 \text{ mm}^2$, slice thickness = 10 mm, voxel size = $4 \times 4 \times 10 \text{ mm}^3$, reconstructed images at $1 \times 1 \times 10 \text{ mm}^3$ using zero-filled interpolation (in-plane ZIP 1024), spiral readout (3 interleaves) with acquisition time (TA) = 10 ms, flip angle = 30° , effective echo time (TE) = 0.7 ms, repetition time (TR) = 12 ms, temporal resolution = 36 ms, typical number of acquired heart phases = 22, spectrally selective fat suppression (SPIR), total acquisition time per slice < 1 s (1 heartbeat), total acquisition time per scan = 6 heartbeats.

Site II

At site II, a user-developed sequence was employed. Images were acquired using a multi-element receive coil array, as described for site I. fSENC spiral images were triggered on the R-wave using a 4-lead vector ECG. Field-of-view = $256 \times 256 \text{ mm}^2$, slice thickness = 7–8 mm, voxel size = $4 \times 4 \times 7 \text{ mm}^3$, reconstructed images at $1 \times 1 \times 7 \text{ mm}^3$, single-shot spiral readout (4 interleaves) with acquisition time (TA) = 7.5 ms, flip angle = 20° , effective echo time (TE) = 5.0 ms, repetition time (TR) = 9.1 ms, temporal resolution = 36.4 ms, typical number of acquired heart phases = 18, spectrally selective fat suppression (SPIR), total acquisition time per slice < 1 s (or one heartbeat), total acquisition time per scan = 6 heartbeats.

Fig. 1 Schematic outline showing the scan organization with a total of four fSENC scans per volunteer at every site



Site III

In comparison to the spiral pulse sequence at sites I and II, fSENC at site III is an Echo Planar Imaging (EPI) user-developed pulse sequence [19]. Volunteers were scanned using a 32-channel body coil and image acquisition was triggered on the R-wave using a 4-lead vector ECG. Epi-factor = 9, field-of-view = $450 \times 170 \text{ mm}^2$, slice thickness = 12 mm, voxel size = $4.7 \times 4.7 \times 12 \text{ mm}^3$, reconstructed resolution at $4.7 \times 4.7 \times 12 \text{ mm}^3$, flip angle = 12° , effective echo time (TE) = 1.18 ms, repetition time (TR) = 8.9 ms, temporal resolution = 35.6 ms, centric EPI recording, typical number of acquired heart phases = 22, spectrally selective fat suppression (SPIR). The acquisition happened in a single heartbeat, as for sites I and II. A separate heartbeat was used for EPI phase correction. The total acquisition time per slice was about 2 s (or two heartbeats) and per scan about 12 heartbeats.

Image analysis

All images were analyzed by one observer (JE) using dedicated software (Myostrain 5.0, Myocardial Solutions, Inc.,

Morrisville, North Carolina, USA), after being trained by a representative of the software company and completing a written test, as previously described [20]. Figure 2 demonstrates the process of image analysis, starting with the acquisition of the image on the scanner (1.), proceeding onto the color-coded image on the software, displaying the manually drawn endo- and epicardial contours at end-systole (2.) and onto the result of the strain analysis, represented by a color-coded map of the heart (3.). GCS was quantified in the three long-axis images by drawing epi- and endocardial contours manually at end-systole (as seen in Fig. 2), identified by the size of the heart and the color-coding of the images signaling contraction (blue). Papillary muscles and trabeculae were excluded from the endocardial contour. GLS was quantified using the short-axis images, again by drawing epi- and endocardial contours at end-systole (Fig. 2). The LV was automatically divided into 16 segments in the short-axis views and 21 segments in the long-axis views (according to the AHA model [21]) and segmental strain was calculated by applying an automated tracking algorithm. Peak systolic GCS and GLS were calculated as the average strain of all segments at end-systole in the long- and short-axis views, respectively. Scans were only excluded from the analysis if

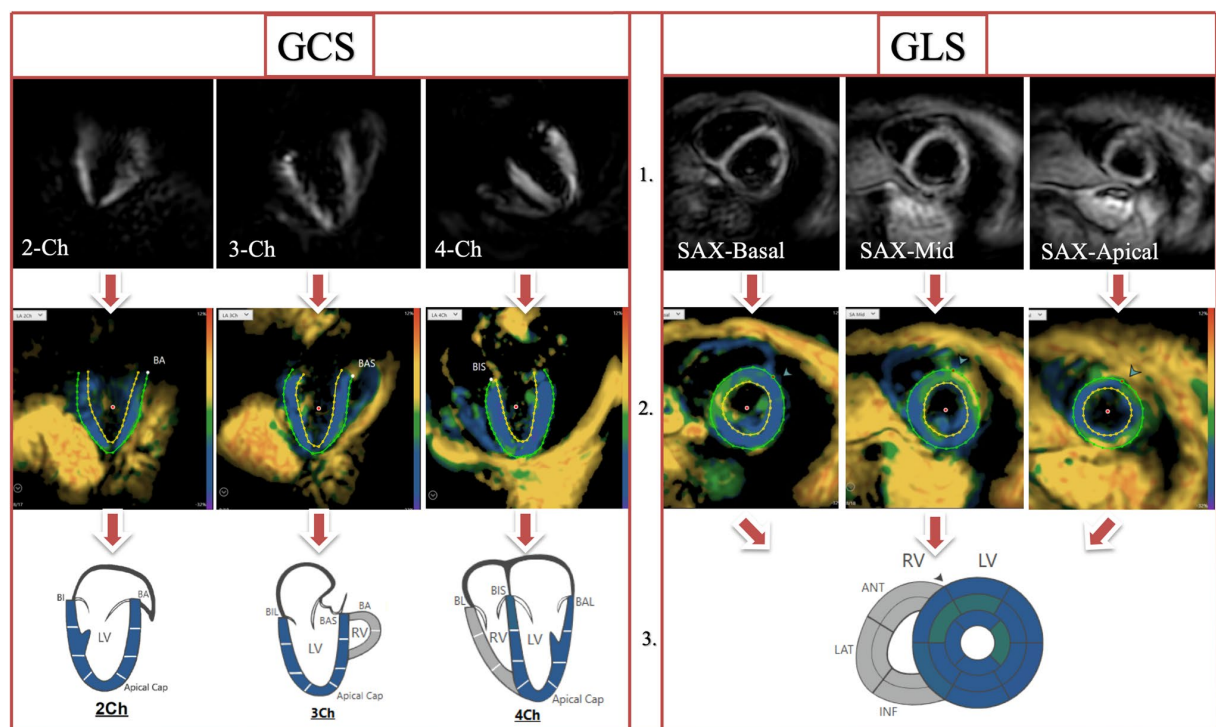


Fig. 2 fSENC- and corresponding color-coded images after post-processing at end-systole (blue representing strain in the normal range during contraction), as well as the myocardial segmentation as illustrated by the software. Legend: 1.=Images as shown on the scanner,

2.=Color-coded images on the software after post-processing, displaying manually drawn epi-and endocardial contours at end-systole, 3.=Results of the strain analysis, represented by a color-coded map of the heart

no view could be analyzed due to insufficient image quality (e.g. GCS could not be determined due to insufficient image quality of the 2-,3- and 4-chamber images). Figure 3 shows exemplary images of the same volunteer at the three sites, as displayed on the scanner and after post-processing.

Intra- and inter-observer reproducibility analysis

Measurements were repeated in a subset of three random volunteers per site (9 volunteers = 36 scans) by the first observer two months after the first analysis and by a second observer who received the same training by software representatives beforehand, blinded to all previous strain measurements. Before repeating the analysis, both observers came to a consensus of excluding volunteers, if both observers considered no view to have the sufficient image quality to determine either GCS or GLS reliably.

Statistical analysis

The distribution of all values was assessed for normality using the Shapiro-Wilks test. Normally distributed data is expressed as mean \pm standard deviation, non-normally distributed data using median and interquartile range (IQR). Inter-vendor agreement between the three sites was

determined using Bland-Altman analysis. Test-retest reproducibility between averaged scans before (average strain of scan 1 and 2) and after the fifteen-minute break (average strain of scan 3 and 4) and between single scans was determined using intraclass correlation (ICC) and coefficients of variation (CoV). Wilcoxon test (for non-normally distributed strain parameters) and paired students t-test (for normally distributed strain parameters) were calculated to determine if differences in strain values between the sites and before and after the break were significant. Intra- and inter-observer reproducibility were analyzed using ICC and CoV. The following levels of agreement were used: excellent for ICC > 0.74, good for ICC 0.6–0.74, fair for ICC 0.4–0.59 and poor for ICC < 0.4 [2, 22]. All values are expressed using p-values and confidence intervals. A p-value of ≤ 0.05 was considered significant in two-tailed tests. Statistical analyses were conducted using SPSS (Version 25.0, IBM Corp., Armonk, NY, USA).

Results

fSENC-image acquisitions of the gel-phantoms were repeated several times. Mean strain and standard deviation were -28.1% (± 0.3) for the system used at site I, -23.7

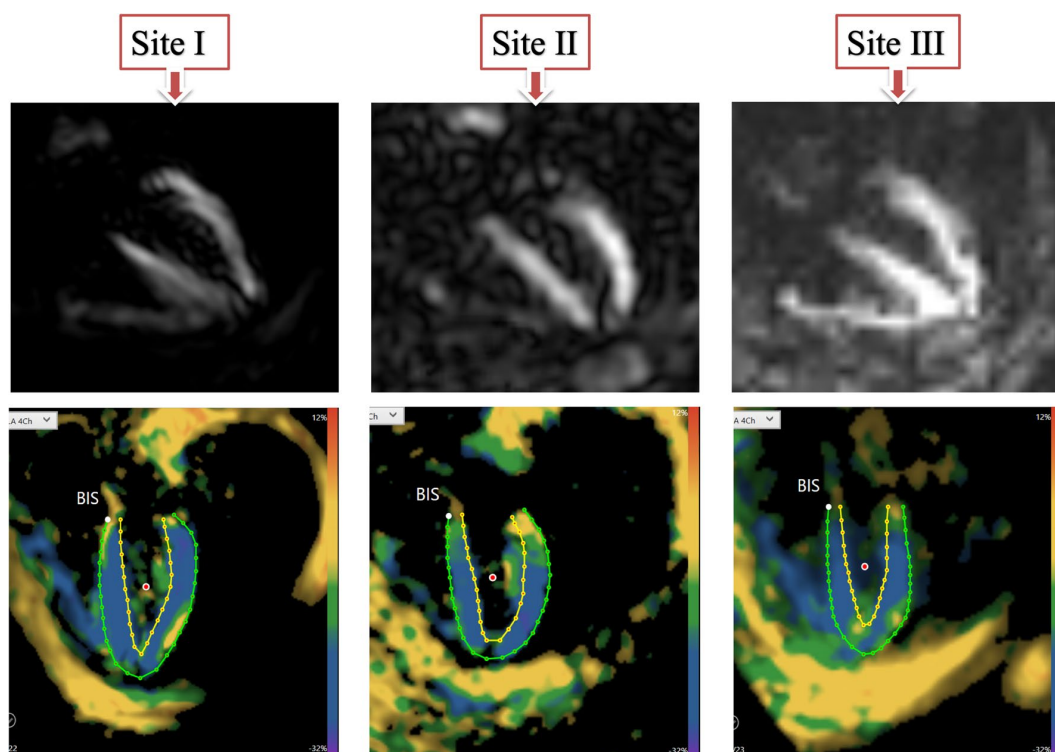


Fig. 3 4-chamber view images of the same volunteer scanned at the three different sites, as shown on the scanner and after post-processing

(± 0.9) for the system used at site II and $-26.8 (\pm 1.4)$ for the system used at site III. Table 1 portrays the baseline characteristics of the volunteers, vital signs and median (IQR) strain values. One complete fSENC-examination including all images was acquired in a median (IQR) scan time of two (1–4) min at all sites. Median image analysis time ranged from 10 to 14 min for one whole examination. A total of four scans were performed for each volunteer (twice before and twice after the break). At site I, one scan had to be excluded from GLS-analysis owing to motion artifacts during acquisition of the short-axis images. At site II, one volunteer could not be scanned due to unexpected technical difficulties. Further four scans were excluded from GLS- and nine from GCS-analysis because of artifacts that would not allow reliable contouring of the heart. At site III, no scan was excluded. A total of 51 scans (85.0%) were left for GLS- and 47 scans (78.3%) for GCS-analysis.

Inter-vendor agreement

Figure 4 shows box and whisker-plots to illustrate the range of strain values with regard to the different sites and the significance level of the differences, as calculated from the Bland-Altman analysis. The range of GLS-measurements was wider than of GCS-measurements. Differences in strain values were significant when comparing site I against either site II or III. Table 2 and Fig. 5 display the results of the Bland-Altman analysis. Inter-vendor agreement was good between all sites, shown by small biases (0.01 – 1.88% strain), but the limits of agreement (LOA) reflected a possible inconsistency regarding individual patients. Biases and limits of agreement were significant when comparing site I against either site II or III.

Table 1 Baseline characteristics of the volunteers (n = 15), median (IQR) scan time and median strain values (IQR) at the different sites

Volunteer characteristics	Site I	Site II	Site III
Female, n (%)	8 (53%)	8 (53%)	8 (53%)
Age (years)	25 (± 5)	25 (± 5)	25 (± 5)
Height (cm)	174 (± 9)	173 (± 8)	174 (± 9)
Weight (kg)	66 (± 11)	66 (± 11)	66 (± 11)
Smoking, n (%)	2 (13%)	3 (20%)	3 (20%)
Blood pressure before exam (mmHg)	123 (± 18)/68 (± 11)	129 (± 18)/74 (± 9)	123 (± 16)/64 (± 9)
Blood pressure after exam (mmHg)	112 (± 17)/61 (± 7)	127 (± 15)/70 (± 7)	120 (± 16)/62 (± 10)
Heart rate before exam (bpm)	74 (± 12)	77 (± 15)	67 (± 12)
Heart rate after exam (bpm)	69 (± 7)	75 (± 11)	76 (± 9)
Scan time (min.)	2 (1–2)	3 (2–6)	3 (1–4)
LV-GLS (%) (n = 51)	-19.2 (-20.5 to -18.0)	-17.8 (-20.0 to -16.4)	-17.9 (-20.0 to -16.0)
LV-GCS (%) (n = 47)	-19.7 (-21.1 to -18.3)	-18.9 (-20.0 to -17.1)	-18.2 (-19.2 to -16.8)

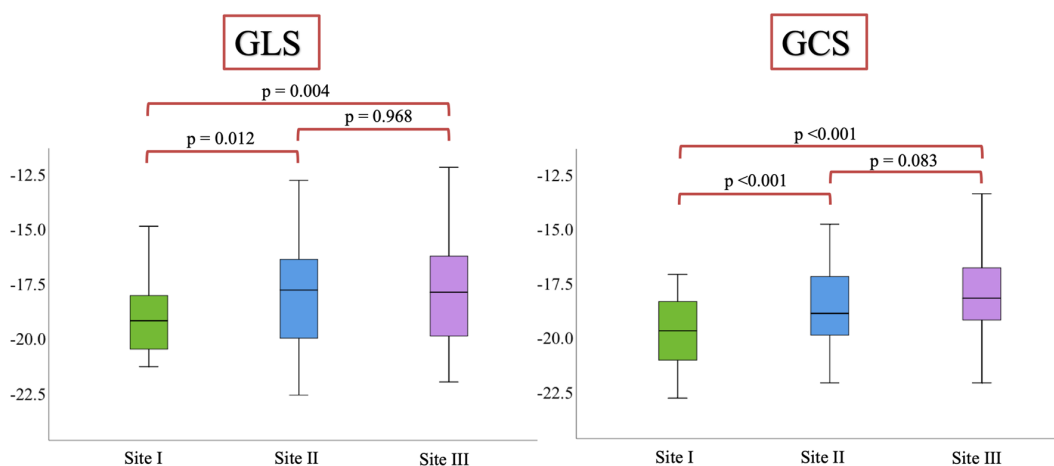


Fig. 4 Box and whisker-plots to illustrate the range of strain values with regard to the different sites and the significance level of the differences

Table 2 Results of the Bland-Altman analysis illustrating inter-vendor agreement

	Bias (%)	LOA (%)	p
LV-GLS (n=51)			
Site I vs. II	1.21	-5.25 to 7.68	0.012
Site I vs. III	1.24	-4.47 to 6.92	0.004
Site II vs. III	0.01	-4.78 to 4.81	0.968
LV-GCS (n=47)			
Site I vs. II	1.14	-2.34 to 4.64	<0.001
Site I vs. III	1.88	-3.02 to 6.79	<0.001
Site II vs. III	0.61	-3.99 to 5.20	0.083

Test-retest reproducibility

Table 3 displays the median (IQR) strain values of the averaged scans before and after the break and the corresponding p-value, as well as the ICC (95% CI) and CoV (\pm sd). As shown by the good- to excellent ICC- and CoV-values, test-retest reproducibility of averaged scans before and after the break was very high for all sites. The highest test-retest reproducibility was observed for LV-GLS at site II (ICC = 0.97) and the lowest for LV-GLS at site I (ICC = 0.63). At site I, test-retest reproducibility was higher for GCS-measures, whereas at site II and III, it was higher for GLS-measures. Nevertheless, differences in median strain between scans before and after the break were mostly insignificant (except for LV-GLS for site I). Table 4 shows the scan-rescan reproducibility between single scans. Overall, scan-rescan reproducibility was good, independent of

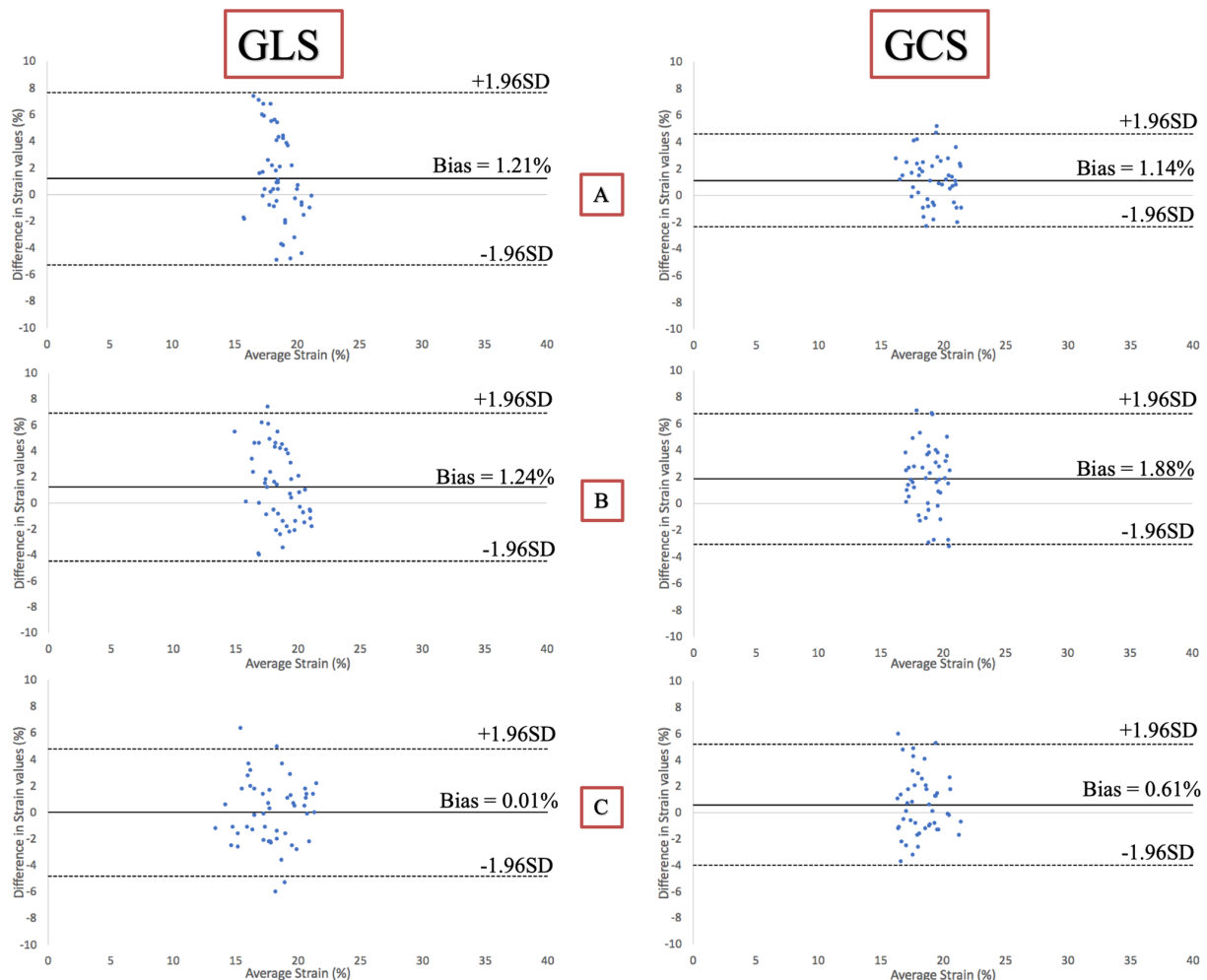


Fig. 5 Bland-Altman analysis comparing GLS and GCS between the different sites. Legend: **a** Site I vs. II, **b** Site I vs. III, **c** Site II vs. III

Table 3 Median (IQR) strain before and after the 15-min break at every site and results of the ICC (95% CI) and CoV (\pm sd) to display test-retest reproducibility

		Median (IQR) strain	p	ICC (95%CI)	p	CoV (\pm sd)
Site I	LV-GLS	–20.1 (–20.9 to –18.3) –19.4 (–20.6 to –17.8)	0.020	0.63 (0.21 to 0.86)	0.002	0.06 (\pm 0.05)
	LV-GCS	–19.0 (–21.1 to –18.3) –19.4 (–21.0 to –18.3)	0.950	0.82 (0.53 to 0.93)	<0.001	0.05 (\pm 0.03)
Site II	LV-GLS	–19.9 (–21.3 to –16.8) –20.1 (–21.2 to –17.0)	0.347	0.97 (0.90 to 0.99)	<0.001	0.03 (\pm 0.02)
	LV-GCS	–17.4 (–19.0 to –16.4) –17.3 (–18.6 to –16.7)	0.307	0.80 (0.47 to 0.94)	<0.001	0.04 (\pm 0.04)
Site III	LV-GLS	–18.8 (–20.2 to –15.1) –18.4 (–19.8 to –16.2)	0.977	0.82 (0.54 to 0.94)	<0.001	0.09 (\pm 0.07)
	LV-GCS	–17.2 (–18.6 to –16.3) –18.5 (–19.5 to –16.5)	0.056	0.69 (0.29 to 0.88)	0.001	0.07 (\pm 0.05)

scanner site (ICC = 0.97–0.70). The highest scan-rescan repeatability could be observed for site II between scans 3 and 4 and 1 and 3, the lowest regarding site I between scans 1 and 3.

Intra- and inter-observer reproducibility

Both observers independently excluded one volunteer out of nine from strain analysis, resulting in 32 scans. Intra- and inter-observer reproducibility were very high overall (Table 5), but even higher for GLS than for GCS.

Discussion

It has been shown that strain, determined using either echocardiography or CMR, is a valuable parameter to determine the impact of coronary artery disease on heart function [12], to detect LV dysfunction, especially in patients with heart failure when EF is still preserved [1, 4, 12, 23] and to reveal diffuse damage to the myocardium due to systemic diseases, such as cardiac amyloidosis [24, 25], sarcoidosis [26] or cardiotoxic effects of chemotherapy [5]. Despite these many possible indications, the use of strain in clinical routine is still challenging due to the impact of intra-, inter-observer- [7] and inter-vendor reproducibility of the different post-processing platforms [8, 9, 27] on strain results, which could also explain the lack of inter-technique agreement between echocardiography and CMR [28]. Therefore, before conducting studies to validate strain techniques in large patient cohorts, it is important to (1) identify the possible factors influencing strain results and to (2) minimize the impact of these factors. To address this issue, we compared GLS and GCS in healthy volunteers, who were all scanned using fSENC at three different sites with MRI scanners from major vendors.

Our results show:

- (1) good inter-vendor agreement of strain measurements using fSENC between all three vendors overall, reflected by small biases but substantial limits of agreement
- (2) very good test-retest reproducibility of fSENC when scanning volunteers again after a fifteen-minute break, regardless of vendor, and
- (3) good to excellent intra- and inter-observer reproducibility of fSENC strain measurements.

To our knowledge, no previous data on inter-vendor agreement of a CMR-technique to determine strain exists. Nevertheless, the influence of different ultrasound systems on 2D- and 3D-STE has been reported previously [7, 29–31]. As in our study, differences in STE-strain measurements between the different vendors were significant [7, 29, 30]. However, the bias between different ultrasound systems was similar or higher (0.1–3.7 [7], 1.1–7.0 [30], 1–1.55% [31]) than the bias between magnetic resonance scanners determined in our study group of fifteen volunteers (0.01–1.88%), with limits of agreement of a similar magnitude. The bias in our cohort of healthy volunteers was significant between site I and II or III. Moreover, the limits of agreement indicate that in some individuals the difference in strain values could be considerably higher than the bias. We believe that this study demonstrates the importance of further exploring inter-vendor agreement in larger cohorts to validate these results and to determine the agreement related to different scanners in patients. Our results indicate that it might possibly be helpful to implement scanner-related normal values and that one should be aware of this possible bias and limits of agreement when comparing strain results acquired at different scanners. This should also play a role when designing classifications based on strain, which determine diagnostic procedures and therapeutic decisions for patients.

An important factor that could influence inter-vendor agreement is the difference in technical characteristics of

Table 4 Scan-rescan reproducibility, represented using ICC (95% CI) and CoV

		ICC (95%CI)	p	CoV (\pm sd)
Site I	GLS			
	Scan 1 vs. 2	0.94 (0.81 to 0.98)	<0.001	0.03 (0.02)
	Scan 2 vs. 3	0.75 (0.16 to 0.92)	0.002	0.07 (0.04)
	Scan 3 vs. 4	0.97 (0.91 to 0.99)	<0.001	0.02 (0.02)
	Scan 1 vs. 3	0.70 (0.15 to 0.90)	0.013	0.06 (0.06)
	Scan 1 vs. 4	0.74 (0.27 to 0.91)	0.007	0.06 (0.06)
	Scan 2 vs. 4	0.79 (0.33 to 0.93)	0.002	0.07 (0.05)
	GCS			
	Scan 1 vs. 2	0.89 (0.68 to 0.96)	<0.001	0.05 (0.06)
	Scan 2 vs. 3	0.83 (0.47 to 0.94)	0.002	0.07 (0.06)
	Scan 3 vs. 4	0.86 (0.56 to 0.95)	0.001	0.05 (0.04)
	Scan 1 vs. 3	0.79 (0.37 to 0.93)	0.004	0.06 (0.04)
	Scan 1 vs. 4	0.86 (0.58 to 0.95)	<0.001	0.05 (0.04)
	Scan 2 vs. 4	0.88 (0.62 to 0.96)	<0.001	0.06 (0.05)
Site II	GLS			
	Scan 1 vs. 2	0.88 (0.61 to 0.96)	<0.001	0.07 (0.07)
	Scan 2 vs. 3	0.94 (0.80 to 0.98)	<0.001	0.04 (0.05)
	Scan 3 vs. 4	0.97 (0.91 to 0.99)	<0.001	0.03 (0.03)
	Scan 1 vs. 3	0.97 (0.89 to 0.99)	<0.001	0.04 (0.03)
	Scan 1 vs. 4	0.94 (0.81 to 0.98)	<0.001	0.06 (0.04)
	Scan 2 vs. 4	0.95 (0.77 to 0.99)	<0.001	0.05 (0.04)
	GCS			
	Scan 1 vs. 2	0.94 (0.79 to 0.98)	<0.001	0.04 (0.04)
	Scan 2 vs. 3	0.89 (0.61 to 0.97)	0.001	0.05 (0.03)
	Scan 3 vs. 4	0.85 (0.52 to 0.96)	0.001	0.05 (0.04)
	Scan 1 vs. 3	0.79 (0.20 to 0.95)	0.013	0.06 (0.04)
	Scan 1 vs. 4	0.85 (0.46 to 0.96)	0.002	0.04 (0.06)
	Scan 2 vs. 4	0.85 (0.50 to 1.00)	0.002	0.05 (0.05)
Site III	GLS			
	Scan 1 vs. 2	0.92 (0.77 to 0.97)	<0.001	0.08 (0.09)
	Scan 2 vs. 3	0.84 (0.51 to 0.95)	0.001	0.10 (0.11)
	Scan 3 vs. 4	0.96 (0.90 to 0.99)	<0.001	0.06 (0.05)
	Scan 1 vs. 3	0.89 (0.67 to 0.96)	<0.001	0.09 (0.09)
	Scan 1 vs. 4	0.89 (0.68 to 0.97)	<0.001	0.10 (0.08)
	Scan 2 vs. 4	0.85 (0.55 to 0.95)	0.001	0.10 (0.08)
	GCS			
	Scan 1 vs. 2	0.90 (0.70 to 0.97)	<0.001	0.06 (0.03)
	Scan 2 vs. 3	0.71 (0.18 to 0.90)	0.012	0.08 (0.06)
	Scan 3 vs. 4	0.85 (0.56 to 0.95)	0.001	0.06 (0.05)
	Scan 1 vs. 3	0.71 (0.12 to 0.90)	0.005	0.08 (0.06)
	Scan 1 vs. 4	0.79 (0.38 to 0.93)	<0.001	0.08 (0.05)
	Scan 2 vs. 4	0.83 (0.50 to 0.94)	0.001	0.07 (0.05)

the pulse sequence at the different scanners. A spiral readout was used at sites I and II, whereas an EPI was used at site III, which may have different properties in terms of geometric distortion and susceptibility to off-resonant spins. Furthermore, the pulse sequence varied with regard to most

Table 5 Intra- and inter-observer reproducibility, reflected by ICC (95% CI) and CoV (\pm sd)

	ICC (95%CI)	p	CoV (\pm sd)
Intra-observer reproducibility			
LV-GLS	0.99 (0.98 to 1.00)	<0.001	0.02 \pm 0.02
LV-GCS	0.77 (0.47 to 0.90)	<0.001	0.05 \pm 0.04
Inter-observer reproducibility			
LV-GLS	0.96 (0.92 to 0.98)	<0.001	0.03 \pm 0.04
LV-GCS	0.82 (0.58 to 0.92)	<0.001	0.04 \pm 0.03

scanning parameters for each scanner. In order to determine the influence of the pulse sequence alone on strain measurements, phantoms were scanned at sites with the three different scanning systems before scanning the volunteers. Mean strain values of the phantoms were higher using the scanning systems at site II and III than using the system at site I, similar to the pattern of median GLS and GCS of the volunteers. This suggests that the pulse sequence itself could contribute to differences in strain values. Other possible variables with impact on inter-vendor agreement are the planning and training of different technicians, the experience and training of the observers and changes in the physiology of the volunteers. In order to minimize the effect of differences in knowledge and training of the technicians and observers in our study, all received training on image planning/analysis and completed written tests. Furthermore, a standardized imaging protocol was used at all three sites, but technicians were allowed to adjust the scanning parameters. Additionally, if two technicians performed the scanning, different levels of experience and planning styles resulted in different image planning at the same scanner. Due to the above listed reasons, the scans were of variable quality, which may have affected strain measurements. To monitor and reduce volunteer-related bias, volunteers were asked questions regarding their health, medications and smoking behavior before every scan and height, weight, blood pressure and heart frequency were monitored. Volunteers with new onset of disease or new intake of medication would have been excluded, but the impact of changes in factors such as weight and smoking behavior on strain measurements were not ruled out. In addition, it was not possible to keep the time difference between the scans at the three sites consistent, so we could not eliminate changes in myocardial function associated with timing of the scans. However, previous literature studying temporal variability of T_1 - and T_2 mapping in volunteers after approximately 90 days [32]

and 4D flow in 10 volunteers with a difference of one year between scans [33] reported no significant differences or significant agreement of results, indicating that myocardial function in healthy volunteers should be stable over a certain time period up to 1 year. Furthermore, the volunteers were also scanned at different time-points during the day, allowing for short-term differences in loading conditions to possibly affect strain results. Nevertheless, we only observed minor changes in volunteer characteristics, vital parameters and CMR-parameters, so we assume that myocardial function was stable in our group of volunteers during the course of the study.

The good to excellent test-retest reproducibility of averaged scans before and after the break and between single scans observed in our group of volunteers, regardless of MRI scanner used, matches the excellent test-retest reproducibility Giusca et al. reported in fSENC scans of eleven healthy subjects and seven patients with heart failure repeated 63 days apart [2]. These results also suggest that effects of short-term differences in myocardial function relating to loading conditions, stroke volume and heart frequency are minimal in volunteers. Furthermore, the very good to excellent intra- and inter-observer reproducibility we reported agrees with previous studies investigating fSENC [2, 15] as well.

When comparing CMR techniques to measure strain, obstacles preventing broad clinical use are centered around the long acquisition and post-processing time, especially concerning myocardial tagging [15, 34]. Due to the fast image acquisition without the need for breath-holds, fSENC could be a potential alternative to tagging. Strain measurements using fSENC have already been shown to be valuable to detect hypertrophic cardiomyopathy when EF is preserved [35], right-ventricular dysfunction due to pulmonary hypertension [36] and diastolic dysfunction in patients with type II diabetes mellitus [37]. Furthermore, fSENC reliably identifies myocardial regions affected by coronary artery disease and infarction [38] and reliably estimates LV-volumes and EF in patients with coronary artery disease, as shown by a recent study from our group [39].

Clinical implications

Our results suggest that an average bias of 0.01% to 1.88% strain (< 1.24% for GLS and < 1.88% for GCS) should be taken into account when comparing fSENC results of healthy individuals acquired using different scanners. This implies that a strain difference of below 2% on average may represent normal variability in the measurement and not necessarily a decrease or increase in myocardial function, if scanning is performed using different scanners. The limits of agreement indicate that strain results from different scanners should not be used totally interchangeably. Larger studies

are needed for further validation in order to facilitate the planning and comparison of multi-center studies, which are needed for standardization of strain measurements and to determine inter-vendor agreement in patients. Furthermore, technical differences between different scanners and imaging sequences should be assessed.

Limitations

Our study group is composed of a relatively small sample size of healthy young volunteers, in order to eliminate the influence of pathologies on strain measurements. Hence, it is important to conduct further studies to assess inter-vendor agreement in a larger study cohort and in patients. Furthermore, in-vitro scanning was performed using different phantoms, at different sites than where the volunteers were scanned and with different number of repeats per site. Unfortunately, multiple scans at site II had to be excluded from further strain analysis due to technical complications that similarly occur in the clinical routine, such as a defect optical fiber cable (preventing one volunteer from being scanned) and a malfunctioning body coil, resulting in artifacts during four GLS and five GCS scans. Additionally, we only focused on fSENC in this study and did not include conventional tagging, the gold standard for strain measurements, since fSENC had previously been validated against tagging [15]. Similarly, we did not evaluate other techniques for measuring strain. Nevertheless, it would be interesting to examine the impact of different MRI scanners on other CMR techniques used to determine strain, including tagging.

Conclusion

We found good inter-vendor agreement of strain measurements acquired with the fSENC technique at 3 T using MRI scanners from three major vendors with small biases, but considerable limits of agreement and a significant difference in strain results. Test-retest reproducibility between repeated scans was very high, regardless of the scanner chosen. Moreover, reproducibility of strain measurements was good to excellent, independent of the employed MR-platform. fSENC can be considered a reliable technique and suitable for strain measurements at different centers and, with further development, has the potential to improve diagnostics and therapy in heart failure patients. Our results might help to interpret strain assessed by fSENC at different sites using MRI scanners from different vendors.

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Compliance with ethical standards

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Lebenslauf

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

Komplette Publikationsliste

Artikel in wissenschaftlichen Fachzeitschriften (Peer-Review)

Demir A, Wiesemann S, Erley J, Schmitter S, Trauzeddel RF, Pieske B, Hansmann J, Kelle S, Schulz-Menger J. Traveling Volunteers: A Multi-Vendor, Multi-Center Study on Reproducibility and Comparability of 4D Flow Derived Aortic Hemodynamics in Cardiovascular Magnetic Resonance. *J Magn Reson Imaging*. 2022;55(1):211-22.

Journal Impact Factor (2020): 4,813

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Artikel in weiteren Zeitschriften

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